A Diversity-Oriented Synthesis Approach to Macrocycles via Oxidative Ring Expansion

Felix Kopp,[1,2] Christopher F. Stratton,[1,3] Lakshmi B. Akella,[4] and Derek S. Tan*[,2,3]

[1]*These authors contributed equally to this work.*

[2]*Molecular Pharmacology & Chemistry Program,*
[3]*Tri-Institutional Training Program in Chemical Biology,*
and Tri-Institutional Research Program,
Memorial Sloan–Kettering Cancer Center
1275 York Avenue, Box 422, New York, New York 10065

and

[4]*Chemical Biology Platform*
Broad Institute of MIT and Harvard
7 Cambridge Center, Cambridge, MA 02142 USA

Supplementary Information

I. Supplementary Results

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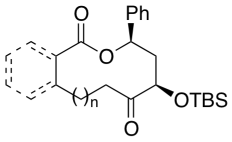
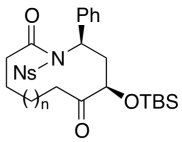
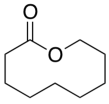
I. Supplementary Results



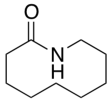
15a–f



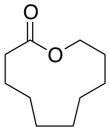
16a–c



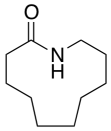
702 results
mostly fused rings
15 actual macrolides
0 natural products
15 library members
(14 *lactones from Amos Smith*)



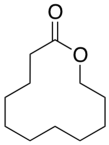
2386 results
mostly fused rings
0 actual macrolactams
0 natural products
0 library members



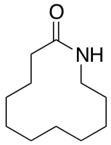
46 results
mostly fused rings
4 actual macrolides
0 natural products
4 library members
(4 *lactones from Amos Smith*)



607 results
mostly fused rings
0 actual macrolactams
0 natural products
0 library members

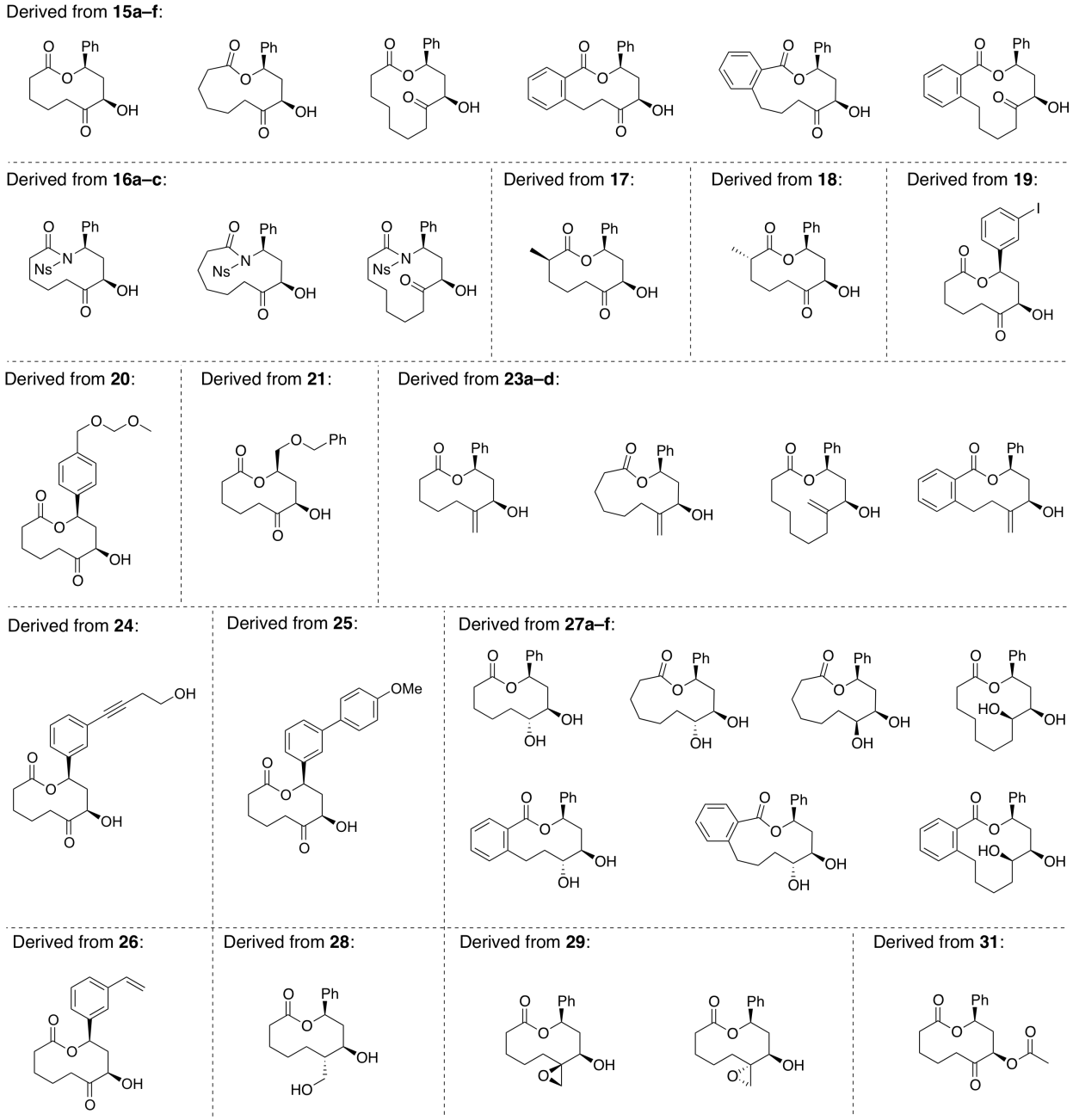


16 results
mostly fused rings
2 actual macrolides
0 natural products
2 library members
(2 *lactones from Amos Smith*)

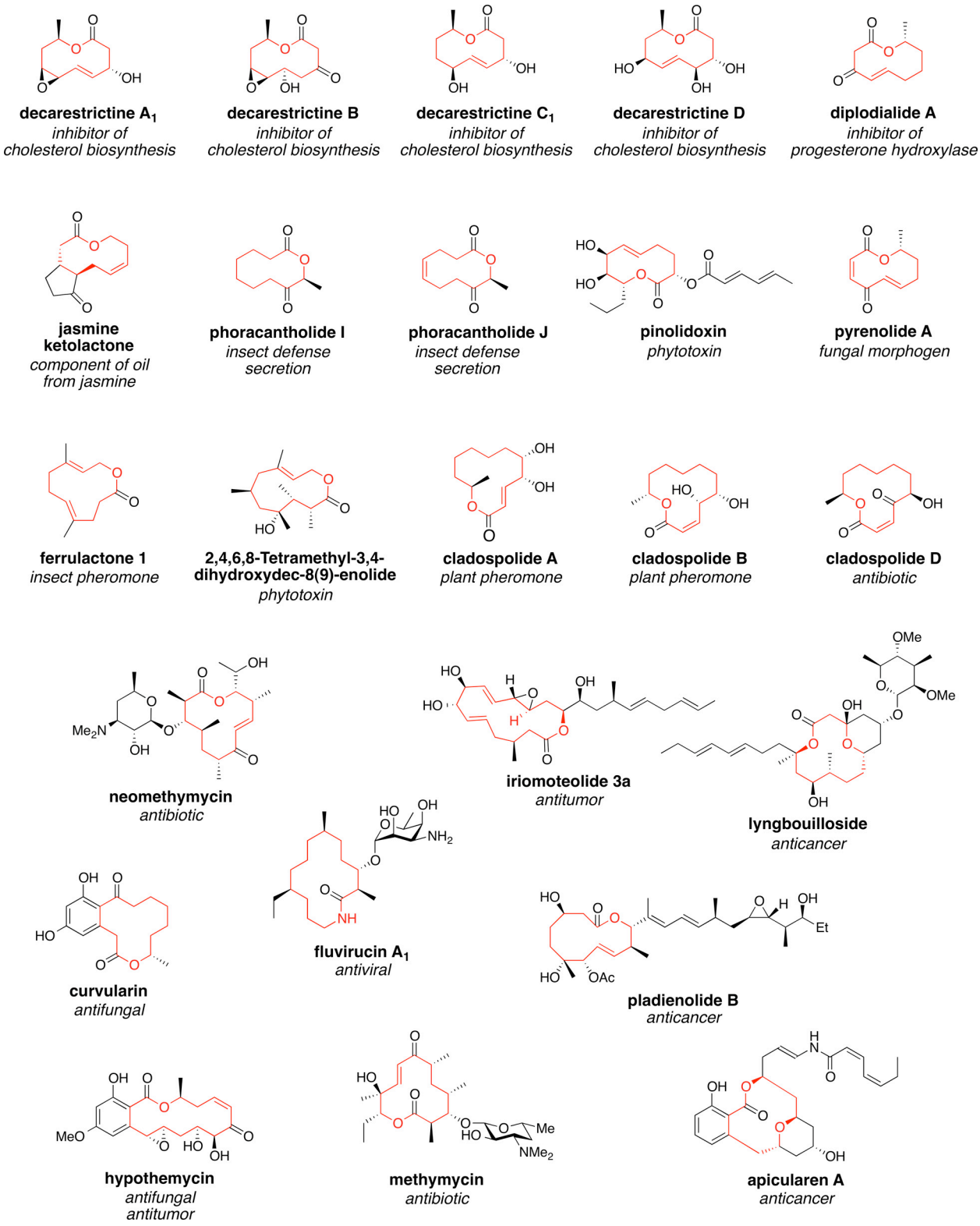


512 results
mostly fused rings
0 actual macrolactams
0 natural products
0 library members

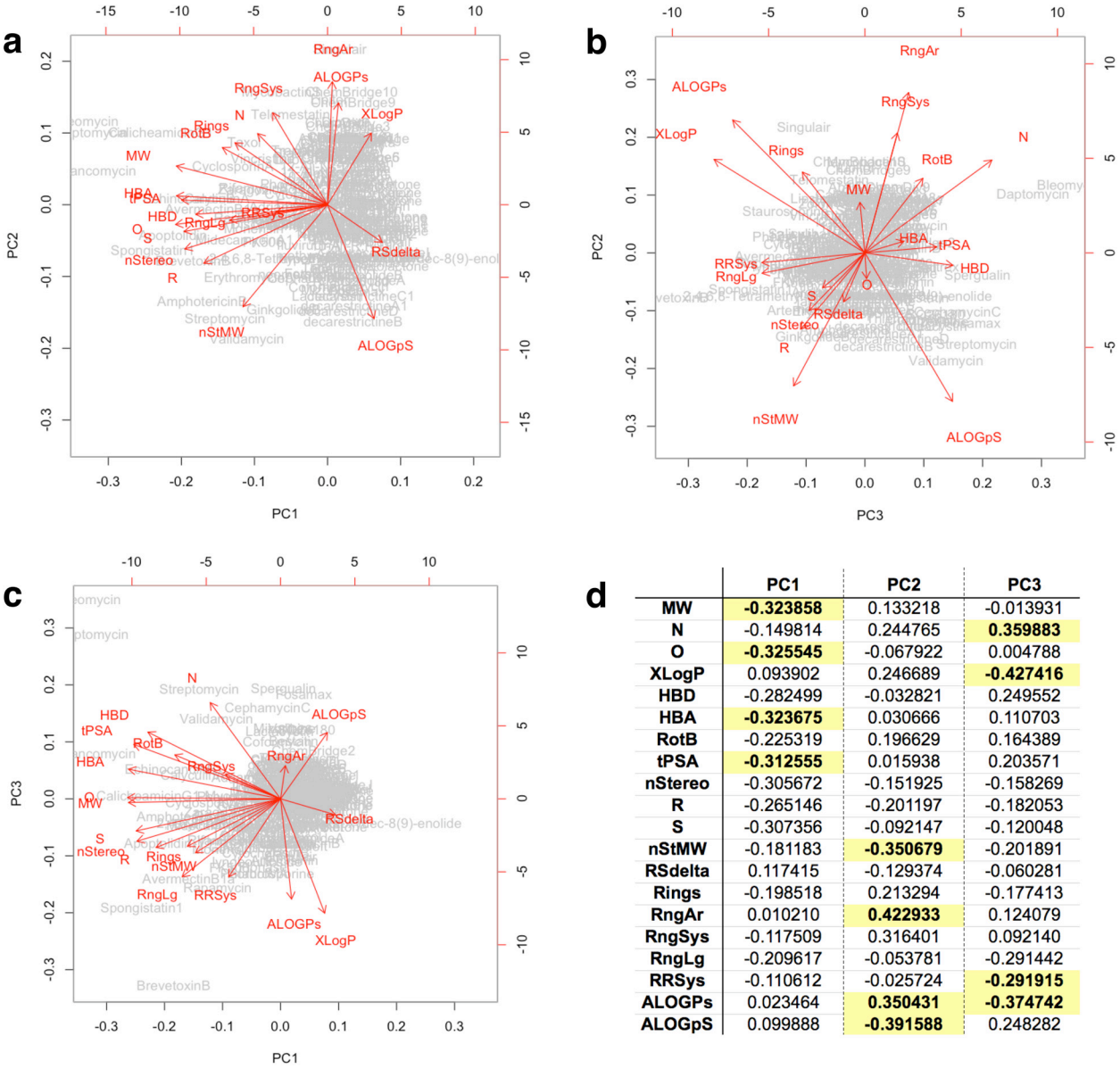
Supplementary Figure 1. Results of PubChem substructure searches for core scaffolds in the macrocycle library. Substructure searches of the PubChem database for the core scaffolds of macrolactones **15a–f** and macrolactams **16a–c** were carried out using the substructure search function at http://pubchem.ncbi.nlm.nih.gov/. (Select “Chemical structure search”, followed by the “Substructure/ Superstructure” tab). SMILES codes were entered for each scaffold to be searched and the results restricted to compounds in the MLSMR (Filters: Data source: From = MLSMR). Search results included non-macrocyclic structures, such as fused ring systems having the same skeletal outline, which were then excluded by manual inspection.



Supplementary Figure 2. Macrocycle library used in PCA and PMI analyses. The 32 structures are derived from **15a–f**, **16a–c**, **17–21**, **23a–d, 24–26, 27a–f**, **28**, **29**, and **31**, via *in silico* desilylation as necessary.

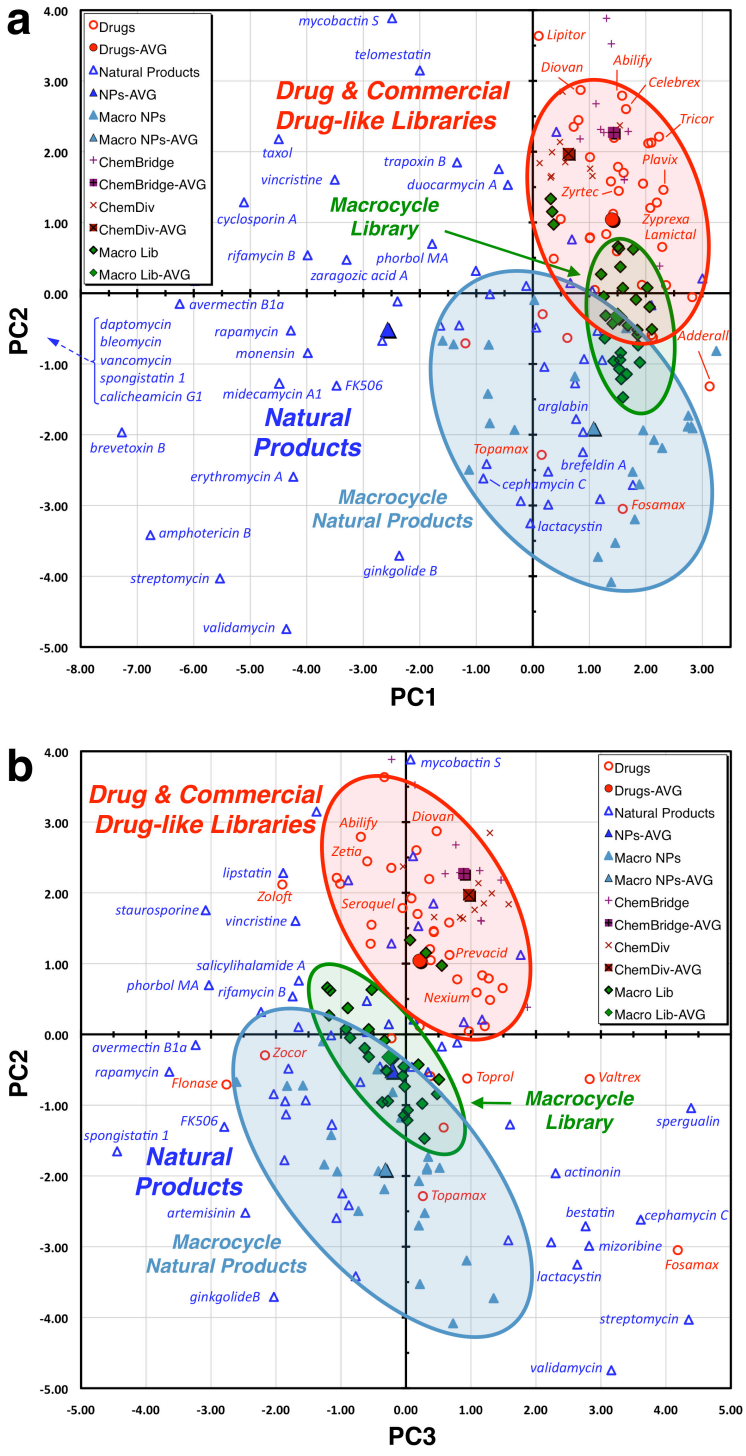


Supplementary Figure 3. Macrocyclic natural products used in PCA and PMI analyses. Set of 24 macrocyclic natural products with diverse chemical structures and biological activities.

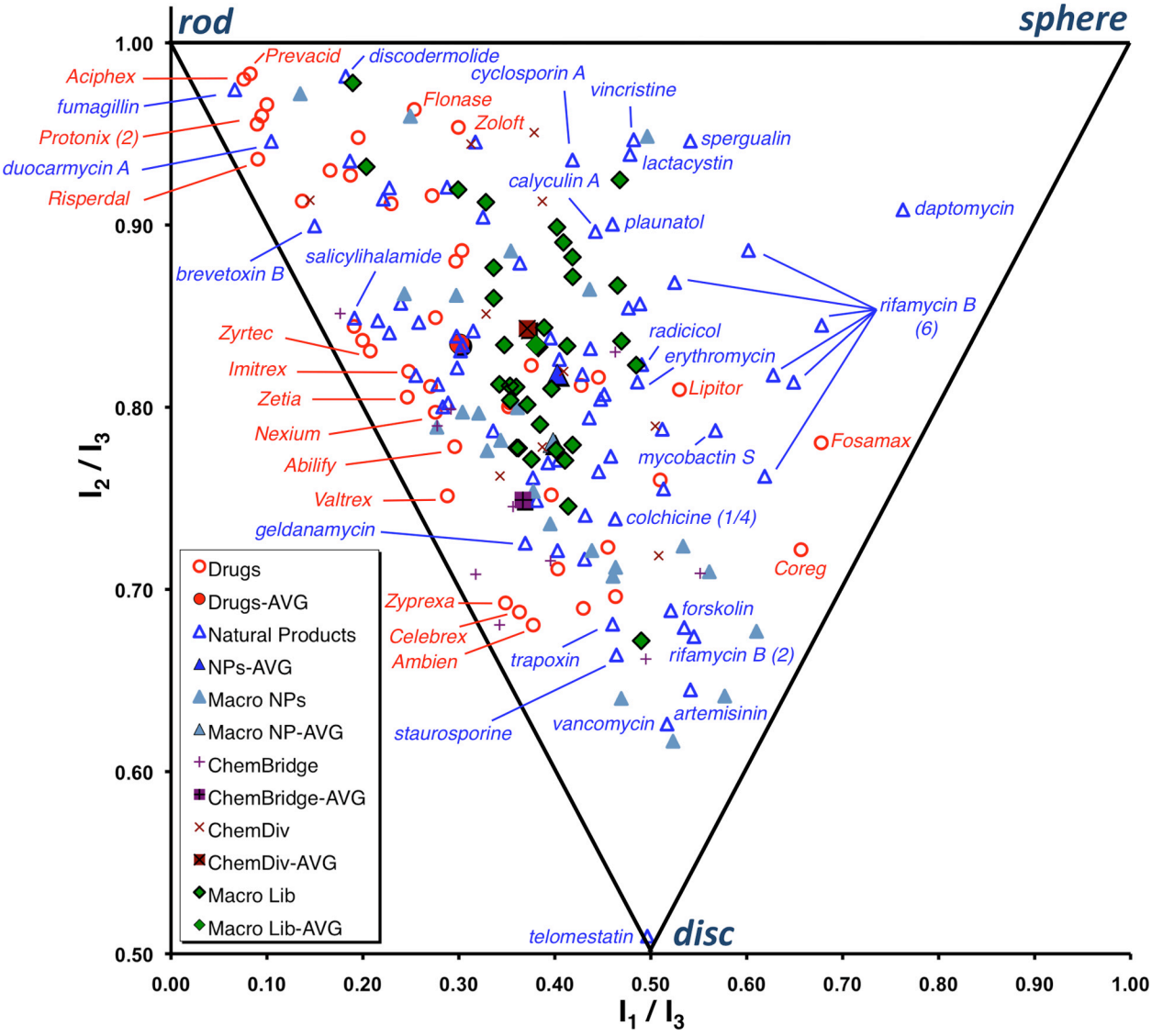


	PC1	PC2	PC3
MW	**-0.323858**	0.133218	-0.013931
N	-0.149814	0.244765	**0.359883**
O	**-0.325545**	-0.067922	0.004788
XLogP	0.093902	0.246689	**-0.427416**
HBD	-0.282499	-0.032821	0.249552
HBA	**-0.323675**	0.030666	0.110703
RotB	-0.225319	0.196629	0.164389
tPSA	**-0.312555**	0.015938	0.203571
nStereo	-0.305672	-0.151925	-0.158269
R	-0.265146	-0.201197	-0.182053
S	-0.307356	-0.092147	-0.120048
nStMW	-0.181183	**-0.350679**	-0.201891
RSdelta	0.117415	-0.129374	-0.060281
Rings	-0.198518	0.213294	-0.177413
RngAr	0.010210	**0.422933**	0.124079
RngSys	-0.117509	0.316401	0.092140
RngLg	-0.209617	-0.053781	-0.291442
RRSys	-0.110612	-0.025724	**-0.291915**
ALOGPs	0.023464	**0.350431**	**-0.374742**
ALOGpS	0.099888	**-0.391588**	0.248282

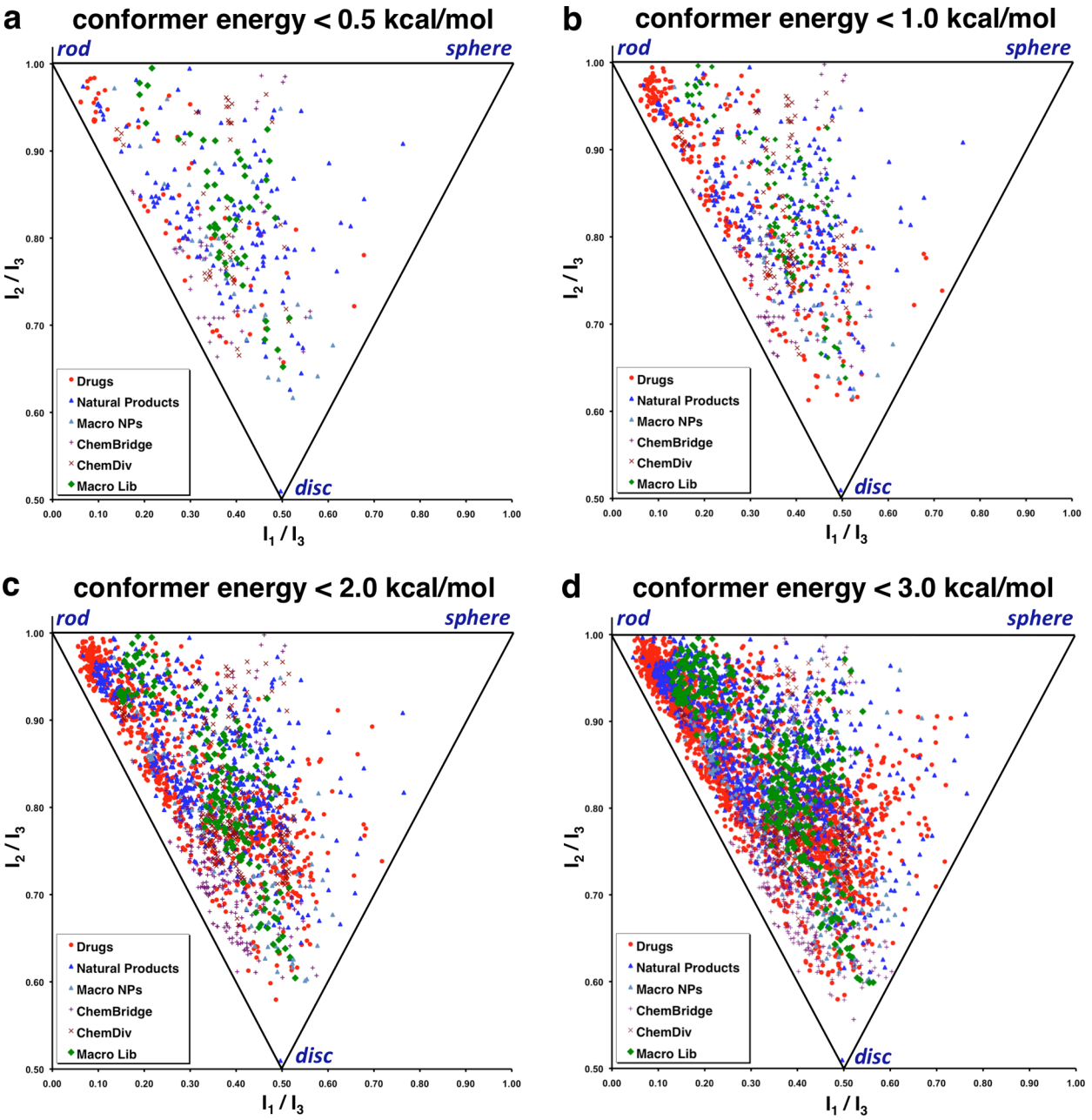
Supplementary Figure 4. Biplots and component loadings for PCA of macrocycle library with macrocyclic natural products and established reference sets. The biplots for **(a)** PC1 vs. PC2, **(b)** PC3 vs. PC2, and **(c)** PC1 vs. PC3, and component loadings **(d)** of the 20 original structural and physicochemical descriptors on the first three principal components indicate the influence of each structural and physicochemical descriptor upon the positioning of compounds in the PCA plots (**Fig. 4a–c** and **Supplementary Fig. 5**). The four most influential parameters on each principal component are highlighted (yellow).



Supplementary Figure 5. PCA of macrocycle library members with macrocyclic natural products and established reference sets. PCA of 20 structural and physicochemical parameters was carried out for the 32 macrocycle library members from **Supplementary Fig. 2** (Macro Lib), the 24 macrocyclic natural products from **Supplementary Fig. 3** (Macro NPs), 40 top-selling brand name drugs (Drugs), 60 diverse natural products (Natural Products/NPs), and 20 ChemBridge and ChemDiv drug-like library members. **(a)** Expanded version of PC1 vs. PC2 PCA plot in **Fig. 4a** of the manuscript with representative drug and natural product reference compounds labeled. **(b)** Expanded version of PC3 vs. PC2 PCA plot in **Fig. 4b** of the manuscript. See **Section I** for full details.



Supplementary Figure 6. PMI plot of macrocycle library, macrocyclic natural products, and established reference sets. Expanded version of PMI plot in **Fig. 4d** of the manuscript showing lowest energy conformations of the 32 macrocycle library members from **Supplementary Fig. 2** (Macro Lib), the 24 macrocyclic natural products from **Supplementary Fig. 3** (Macro NPs), 40 top-selling brand name drugs (Drugs), 60 diverse natural products (Natural Products/NPs), and 20 ChemBridge and ChemDiv drug-like library members. Representative drug and natural product reference compounds labeled. See **Section I** for full details.



Supplementary Figure 7. PMI plots of macrocycle library, macrocyclic natural products, and established reference sets displaying conformers at increasing energy level cutoffs. Conformers are shown for the 32 macrocycle library members from **Supplementary Fig. 2** (Macro Lib), the 24 macrocyclic natural products from **Supplementary Fig. 3** (Macro NPs), 40 top-selling brand name drugs (Drugs), 60 diverse natural products (Natural Products), and 20 ChemBridge and ChemDiv drug-like library members at energy level cutoffs of **(a)** <0.5 kcal/mol, **(b)** <1.0 kcal/mol, **(c)** <2.0 kcal/mol, or **(d)** <3.0 kcal/mol above the lowest energy conformer for each structure (*cf.* **Fig. 4d** of the manuscript). See **Section I** for full details.

II. Supplementary Methods

A. Materials and Methods

Reagents were obtained from Aldrich Chemical (www.sigma-aldrich.com) or Acros Organics (www.fishersci.com) and used without further purification. Optima grade solvents were obtained from Fisher Scientific (www.fishersci.com), degassed with Ar, and purified on a solvent drying system as described,[1] unless otherwise indicated. Diisopropylamine (*i*-Pr_2NH) was obtained from Aldrich in SureSeal bottles. Trimethylchlorosilane was obtained from Acros and used without further purification. Acetyl chloride was dried over P_2O_5, distilled under reduced pressure and stored under Ar. Acetic anhydride was obtained from Acros and used without further purification. *n*-Butyllithium was titrated against menthol in the presence of 1,10-phenanthroline as described.[2]

All reactions were performed in flame-dried glassware under positive Ar pressure with magnetic stirring unless otherwise noted. Rubber septa and syringes were used for the transfer of liquid reagents and solutions. Syringes were purged with argon prior to use. Cold baths were generated as follows: 0 °C, wet ice/water; –20 °C, dry ice/carbon tetrachloride monitored with a thermometer; –44 °C, dry ice/CH_3CN; –63 °C, dry ice/chloroform; –78 °C, dry ice/acetone; –100 °C, dry ice/Et_2O. Slow additions in macrocyclization reactions were carried out using KD Scientific KDS100 or KDS200 syringe pumps.

TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$), cerium ammonium molybdenate (CAM), phosphomolybdic acid (PMA), iodine (I_2), or *p*-anisaldehyde. Silica flash chromatography was performed on E. Merck 230–400 mesh silica gel 60.

Melting point determinations were performed on a Stanford Research Systems MPA100 OptiMelt Melting Point apparatus and are uncorrected (benzoic acid, lit.: 121.5 °C, found: 117.6–119.9 °C). IR spectra were recorded on a Bruker Optics Tensor 27 FTIR spectrometer with peaks reported in cm^{-1}. NMR spectra were recorded on Bruker Avance II 500, Avance II 600, or DRX500 instruments at 24 °C in $CDCl_3$ unless otherwise indicated. Spectra were processed using Bruker TopSpin or nucleomatica iNMR (www.inmr.net) software, and chemical shifts are expressed in ppm relative to TMS (^1H, 0 ppm) or solvent signals: $CDCl_3$ (^1H, 7.26; ^{13}C, 77.0 ppm), C_6D_6 (^1H, 7.16 ppm; ^{13}C, 128.0 ppm), toluene-d_8 (^1H, 2.08 ppm; ^{13}C, 20.4 ppm), or DMSO-d_6 (^1H, 2.50 ppm; ^{13}C, 39.5); coupling constants are expressed in Hz. Mass spectra were obtained at the MSKCC Analytical Core Facility on a Waters 3100 mass spectrometer by electrospray (ESI) ionization. X-ray crystallographic analysis was carried out at the University of Toledo Instrumentation Center (http://www.utoledo.edu/nsm/ic/index.html) on a Siemens Smart CCD System.

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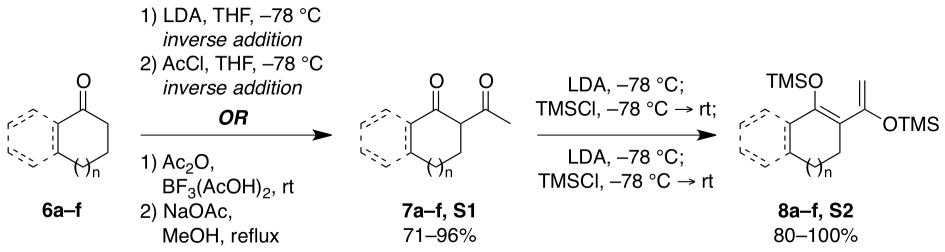
[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996,** *15*, 1518.
[2] Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503.

B. SYNTHESIS OF BIS(TRIMETHYLSILOXY)DIENES (8, S2)



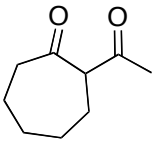
Supplementary Figure 8. Synthesis of bis(trimethylsiloxy)dienes 8. The 1,3-diketones **7** were synthesized using acylation protocols reported by Seebach (aliphatic backbones)[3] or Deshpande (benzannulated),[4] or were commercially available (**7a**,**d**). Bis(trimethylsiloxy)dienes **8** were then synthesized by successive treatment of 1,3-diketones **7** with LDA and trimethylchlorosilane at –78 °C.[5] In the case of **8f**, TMSOTf was substituted for trimethylchlorosilane.

1. SYNTHESIS OF 1,3-DIKETONES (7)

a. General protocol for α-acylation of aliphatic cyclic ketones (Seebach)[3]

In a roundbottom flask, *n*-butyllithium (1.60 M in hexanes, 1.10 equiv) was cooled to –78 °C. Diisopropylamine (1.12 equiv) was added dropwise and, subsequently, THF was added to reach a final concentration of *ca*. 1.0 M. After stirring for 40 min at –78 °C, a solution of the cyclic ketone **6** (1.00 equiv) in THF (0.67 M) was added slowly through a Teflon cannula. The resulting mixture was stirred for 1 h at –78 °C, then added slowly via cannula to a roundbottom flask containing a precooled (–78 °C) solution of acetyl chloride (1.20 equiv) in THF (1.20 M). The reactions were judged complete after 1 h by TLC and were quenched with satd aq NH_4Cl at –78 °C. The reaction mixture was warmed to rt and extracted with EtOAc (3×). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (hexanes/EtOAc) afforded the 1,3-diketone **7** in ≥90% purity, as judged by ^{1}H-NMR. The main impurity was the corresponding *O*-acylation product, observed in the ^{1}H- and ^{13}C-NMR spectra, which did not affect the subsequent transformation to bis(trimethylsiloxy)dienes (**8**), and was separable at that stage.

Acetylcyclohexanone (7a). Commercially available.



2-Acetylcycloheptanone (7b). Synthesized from cycloheptanone (561 mg, 5.00 mmol) and acetyl chloride (0.43 mL, 6.0 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc) afforded **7b** as a colorless oil that solidified upon storage at –20 °C (596 mg, 77%).

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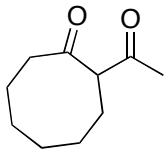
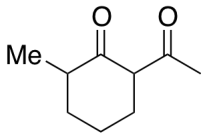
[3] Seebach, D.; Weller, T.; Protschuk, G.; Beck, A. K.; Hoekstra, M. S. *Helv. Chim. Acta* **1981**, *64*, 763.
[4] Patil, M. L.; Borate, H. B.; Ponde, D. E.; Deshpande, V. H. *Tetrahedron* **2002**, *58*, 6615.
[5] Sestelo, J. P.; del Mar Real, M.; Sarandeses, L. A. *J. Org. Chem.* **2001**, *66*, 1395.

TLC: R_f 0.50 (4:1 hexanes/EtOAc). **mp** = 30.0–32.4 °C. **IR** (NaCl, film): 2925 (s, C–H st), 2853 (m, C–H st), 1602 (vs, br, C=O st, C=C st), 1442 (m), 1283 (m), 1205 (w), 986 (m), 967 (m), 832 (w), 773 (w). **^{1}H-NMR** (500 MHz): δ 16.46 (s, 1H), 2.55–2.52 (m, 2H), 2.38–2.36 (m, 2H), 2.11 (s, 3H), 1.77–1.67 (m, 4H), 1.58 (m, 2H). **^{13}C-NMR** (125 MHz): δ 200.4, 185.6, 111.8, 40.5, 31.7, 28.8, 26.9, 24.8, 22.2. **ESI-MS** *m/z* (rel int): (pos) 177.1 ([M+Na]$^+$, 100), 155.1 ([M+H]$^+$, 70); (neg) 153.0 ([M–H]$^-$, 50); 113.0 (100).



2-Acetylcyclooctanone (7c). Synthesized from cyclooctanone (6.30 g, 49.9 mmol) and acetyl chloride (4.30 mL, 60.0 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc) afforded **7c** as a colorless oil that solidified upon storage at –20 °C (6.39 g, 76%).

TLC: R_f 0.55 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2926 (s, C–H st), 2855 (m, C–H st), 1595 (vs, br, C=O st, C=C st), 1472 (m), 1451 (m), 1418 (m), 1279 (m), 1171 (w), 1089 (w), 990 (m), 955 (w), 890 (w), 850 (w). **^{1}H-NMR** (500 MHz): δ 16.71 (s, 1H), 2.49–2.46 (m, 2H), 2.43–2.40 (m, 2H), 2.16 (s, 3H), 1.78–1.73 (m, 2H), 1.60–1.45 (m, 6H). **^{13}C-NMR** (125 MHz): 193.4, 192.3, 109.3, 35.3, 30.2, 28.8, 26.5, 25.8, 25.3, 23.8. **ESI-MS** *m/z* (rel int): (pos) 359.1 ([2M+Na]$^+$, 20), 232.0 (38), 191.0 ([M+Na]$^+$, 100), 169.1 ([M+H]$^+$, 5); (neg) 167.0 ([M–H]$^-$, 100).



2-acetyl-6-methylcyclohexanone[6] (S1). Synthesized from 2-methylcyclohexanone (560 mg, 5.00 mmol) and acetyl chloride (0.424 mL, 6.00 mmol). Purification by silica flash chromatography (19:1 hexanes/EtOAc 0.5 vol% Et_3N) afforded **S1** as a colorless oil (547 mg, 71%). All characterization data were in agreement with literature precedent.[6]

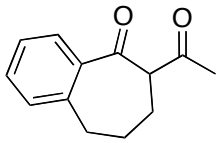
b. General protocol for α-acylation of benzannulated cyclic ketones (Deshpande)[4]

In a roundbottom flask, the cyclic ketone **6** was dissolved in acetic anhydride (1.80 mL/mmol substrate) under Ar. $BF_3(AcOH)_2$ (4.00 equiv) was added dropwise and the reaction was stirred at rt for 4.5 h. The reaction mixture was poured onto ice and stirred until the solution reached rt. The mixture was then extracted with EtOAc (3×) and the combined organic extracts were concentrated by rotary evaporation. The crude product was dissolved in MeOH (10.0 mL/mmol substrate) and sat aq NaOAc (7.00 mL/mmol substrate), and the mixture was heated to reflux with stirring for 2.5 h. The reaction was then cooled to rt and MeOH was removed by rotary

[6] Kopka, I; Rathke, M. W. J. Org. Chem. 1981, 46, 3771.

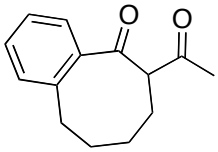
evaporation. The crude product was extracted with EtOAc (3×) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (hexanes/EtOAc) afforded the 1,3-diketone **7**.

2-Acetyltetralone (7d). Commercially available.



6-Acetyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (2-acetylbenzosuberone, 7e). Synthesized from benzosuberone (500 mg, 3.12 mmol) and acetic anhydride (5.62 mL, as solvent). Purification by silica flash chromatography (19:1 hexanes/EtOAc) afforded **7e** as a light yellow oil that solidified upon storage at –20 °C (mp < rt) (606 mg, 96%).

TLC: R_f 0.53 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2934 (m, C–H st), 2859 (w, C–H st), 1606 (vs, br, C=O st), 1560 (s, C=C st), 1454 (m), 1420 (m), 1296 (s), 1202 (w), 1181 (w), 1162 (w), 968 (m), 766 (m). **^{1}H-NMR** (500 MHz): δ 16.42 (s, 1H), 7.62 (dd, 1H, J = 7.5, 1.5), 7.39 (ddd, 1H, J = 7.5, 7.4, 1.5), 7.34 (ddd, 1H, J = 7.4, 7.5, 1.3), 7.20 (d, 1H, J = 7.4), 2.69 (t, 2H, J = 6.9), 2.25 (s, 3H), 2.16 (t, 2H, J = 6.9), 2.02 (quint, 2H, J = 6.9). **^{13}C-NMR** (125 MHz): δ 190.3, 188.2, 139.9, 137.5, 131.1, 128.8, 127.6, 126.7, 109.6, 31.2, 31.1, 23.8, 23.0. **ESI-MS** *m/z* (rel int): (pos) 427.1 ($[2M+Na]^+$, 23), 225.0 ($[M+Na]^+$, 100), 203.1 ($[M+H]^+$, 9); (neg) 201.0 ($[M+H]^-$, 100).



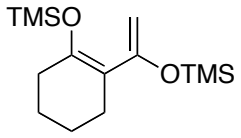
6-Acetyl-7,8,9,10-tetrahydrobenzo[8]annulen-5(6*H*)-one (2-acetylbenzocyclooctanone, 7f). Synthesized from 7,8,9,10-tetrahydrobenzo[8]annulen-5(6*H*)-one (100 mg, 0.574 mmol) and acetic anhydride (1.00 mL). Purification by silica flash chromatography (19:1 hexanes/EtOAc) afforded **7f** as a crystalline, colorless solid (111 mg, 90%).

TLC: R_f 0.77 (4:1 hexanes/EtOAc). **mp** = 62.8–68.4 ºC. **IR** (NaCl, film): 2932 (s, C–H st), 2854 (w, C–H st), 1608/1583/1559 (vs, br, C=O st, C=C st), 1449 (m), 1399 (m), 1355 (m), 1290 (m), 1203 (w), 1188 (w), 1156 (w), 1094 (w), 1018 (w), 982 (m, br), 931 (w), 874 (w), 784 (m), 769 (m), 753 (s). **^{1}H-NMR** (500 MHz): δ 16.3 (s, 1H), 7.39 (m, 2H), 7.28–7.23 (m, 2H), 2.83 (dd, 1H, J = 13.5, 8.4), 2.59 (dd, 1H, J = 13.5, 11.5), 2.46 (dd, 1H, J = 15.5, 7.9), 2.29 (s, 3H), 2.09 (m, 1H), 1.95–1.92 (m, 1H), 1.73 (dd, 1H, J = 15.5, 10.8), 1.47–1.41 (m, 2H). **^{13}C-NMR** (125 MHz): δ 198.3, 181.9, 141.5, 135.4, 130.5, 129.9, 127.3, 126.1, 112.7, 32.9, 28.6, 27.8, 25.8, 25.1. **ESI-MS** *m/z* (rel int): (pos) 239.0 ($[M+Na]^+$, 100), 216.9 ($[M+H]^+$, 5).

2. SYNTHESIS OF BIS(TRIMETHYLSILOXY)DIENES (8, S2)

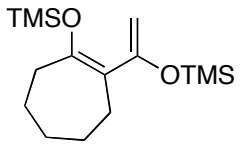
General protocol for synthesis of bis(trimethylsiloxy)dienes[5]

In a roundbottom flask, *n*-butyllithium (1.60 M in hexanes, 1.10 equiv) was cooled to –78 °C. Diisopropylamine (1.12 equiv) was added dropwise and, subsequently, THF was added to reach a final concentration of *ca*. 1.0 M. After stirring for 40 min at –78 °C, the resulting suspension was removed from the cooling bath (upon warming slightly, a clear solution is formed) and subsequently transferred slowly via cannula to a roundbottom flask containing a precooled (–78 °C) solution of the 1,3-diketone **7** (1.00 equiv) in THF (0.20 M). The resulting mixture was stirred for 1 h at –78 °C. Neat trimethylchlorosilane (TMSCl) (1.50 equiv) was added and the mixture was allowed to warm to rt (*ca*. 0.5 h) and stirred for an additional 1.5 h (the solution became turbid at this point in most cases). The reaction mixture was recooled to –78 °C and a 1.0 M solution of LDA (prepared as described above) was added slowly at –78 °C via cannula. The resulting mixture was stirred for 1 h at –78 °C. Neat trimethylchlorosilane (1.50 equiv) was added and the mixture was allowed to warm to rt (*ca*. 0.5 h) and stirred for an additional 1.5 h. The solvent was removed by rotary evaporation and the crude product was taken up in a small amount of hexanes. Purification by filtration through a short column of basic aluminum oxide (99:1 hexanes/EtOAc) afforded the bis(trimethylsiloxy)diene **8** as colorless to yellow oil that can be stored neat at –20 °C for several weeks without significant degradation.



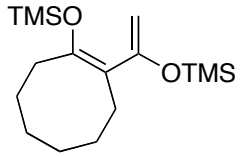
Trimethyl(1-(2-(trimethylsilyloxy)cyclohex-1-enyl)vinyloxy)silane (8a). Synthesized from 2-acetyltetralone **7a** (2.10 g, 15.0 mmol) and TMSCl (2 × 2.84 mL, 22.5 mmol). Purification by filtration through basic aluminum oxide (99:1 hexanes/EtOAc) afforded **8a** as a slightly yellow liquid (4.27 g, quant).

IR (NaCl, film): 2960 (m, C–H st), 2935 (m, C–H st), 2862 (w), 2843 (w), 1650 (m, C=C st), 1612 (w, C=C st), 1364 (w), 1290 (m), 1254 (s, $SiMe_3$ δ sy), 1206 (s), 1150 (m), 1080 (w), 1047 (w), 1016 (m), 928 (s), 870 (s), 846 (vs, br, $SiMe_3$, γ), 754 (m). **^{1}H-NMR** (500 MHz): δ 4.52 (s, 1H), 4.35 (s, 1H), 2.14–2.07 (m, 4H), 1.63 (m, 2H), 1.56–1.53 (m, 2H), 0.19 (s, 9H), 0.18 (s, 9H). **^{13}C-NMR** (125 MHz): δ 155.1, 147.2, 114.4, 94.1, 31.4, 26.5, 23.3, 22.9, 1.11, 0.3. **ESI-MS** *m/z* (rel int): (pos) 307.1 ($[M+Na]^+$, 100), 213.1 ($[M–TMS+H]^+$, 28); (neg) 211.0 ($[M–TMS]^-$, 100), 283.0 ($[M–H]^-$, 22).



Trimethyl(1-(2-(trimethylsilyloxy)cyclohept-1-enyl)vinyloxy)silane (8b). Synthesized from 2-acetylcycloheptanone **7b** (2.31 g, 15.0 mmol) and TMSCl (2 × 2.84 mL, 22.0 mmol). Purification by filtration through basic aluminum oxide (99:1 hexanes/EtOAc) afforded **8b** as a pale yellow oil (4.51 g, quant).

IR (NaCl, film): 2958 (m, C–H st), 2923 (s, C–H st), 2851 (m, C–H st), 1643 (m, C=C st), 1611 (m, C=C st), 1449 (w), 1300 (m), 1252 (s, $SiMe_3$ δ sy), 1223 (s), 1194 (m), 1146 (m), 1040 (m), 1015 (m), 936 (m), 892 (s), 843 (vs, br, $SiMe_3$, γ). **^{1}H-NMR** (500 MHz): δ 4.38 (s, 1H), 4.29 (s, 1H), 2.30 (m, 2H), 2.16 (m, 2H), 1.69 (m, 2H), 1.56–1.48 (m, 4H), 0.19 (s, 9H), 0.18 (s, 9H). **^{13}C-NMR** (125 MHz): δ 155.5, 152.7, 119.6, 93.7, 36.2, 32.2, 28.8, 27.1, 25.1, 1.0, 0.4. **ESI-MS** *m/z* (rel int): (pos) 321.08 ($[M+Na]^+$, 100), 299 ($[M+H]^+$, 40), 249.3 ($[M–TMS+Na]^+$, 66), 227.2 ($[M–TMS+H]^+$, 52); (neg) 297.2 ($[M–H]^–$, 28), 225.2 ($[M–TMS]^–$, 25), 169.0 (100).



Trimethyl(1-(2-(trimethylsilyloxy)cyclooct-1-enyl)vinyloxy)silane (8c). Synthesized from 2-acetylcyclooctanone **7c** (1.68 g, 10.0 mmol) and TMSCl (2 × 1.90 mL, 15.0 mmol). Purification by filtration through basic aluminum oxide (99:1 hexanes/EtOAc) afforded **8c** as a pale yellow liquid (2.91 g, 93%).

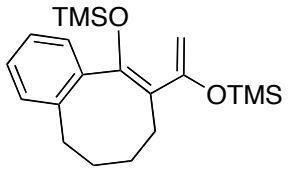
IR (NaCl, film): 2959 (w), 2927 (m, C–H st), 2854 (w), 1644 (m, C=C st), 1613 (m, C=C st), 1306 (m), 1253 (s, $SiMe_3$ δ sy), 1221 (s), 1199 (m), 1130 (m), 1036 (m), 1015 (s), 978 (s), 845 (vs, br, $SiMe_3$, γ). **^{1}H-NMR** (500 MHz): δ 4.43 (s, 1H), 4.35 (s, 1H), 2.27–2.24 (m, 2H), 2.19–2.17 (m, 2H), 1.63 (m, 2H), 1.55–1.47 (m, 6H), 0.21 (s, 9H), 0.18 (s, 9H). **^{13}C-NMR** (125 MHz): δ 154.7, 149.2, 116.7, 94.4, 32.8, 30.1, 28.6, 27.8, 26.9, 26.5, 1.1, 0.4. **ESI-MS** *m/z* (rel int): (pos) 335.3 ($[M+Na]^+$, 28), 313.3 ($[M+H]^+$, 30), 241.1 ($[M–TMS+H]^+$, 100); (neg) 311.2 ($[M–H]^–$, 18), 239.3 ($[M–TMS]^–$, 18), 113 (100).

Trimethyl(1-(1-(trimethylsilyloxy)-3,4-dihydronaphthalen-2-yl)vinyloxy)silane (8d). Synthesized from 2-acetyl-α-tetralone **7d** (2.82 g, 15.0 mmol) and TMSCl (2 × 2.84 mL, 22.0 mmol). Purification by filtration through basic aluminum oxide (99:1 hexanes/EtOAc) afforded **8d** as a yellow oil (4.70 g, 94%).

IR (NaCl, film): 2958 (m, C–H st), 2895 (w, C–H st), 2838 (w), 1694 (w), 1665 (w), 1611 (m, C=C st), 1302 (s), 1259 (vs, $SiMe_3$ δ sy), 1208 (w), 1153 (s), 1084 (w), 1018 (s), 920 (s), 849 (vs, br, $SiMe_3$, γ), 760 (s). **^{1}H-NMR** (500 MHz): δ 7.45 (d, 1H, J = 7.6), 7.22–7.11 (m, 3H), 4.83 (s, 1H), 4.54 (s, 1H), 2.74 (t, 2H, J = 7.7), 2.46 (t, 2H, J = 7.7), 0.26 (s, 9H), 0.22 (s, 9H). **^{13}C-NMR** (125 MHz): δ 154.0, 145.1, 137.3, 134.7, 127.3, 126.7, 126.1, 123.4, 117.9, 96.3, 28.4, 25.0, 0.9, 0.4. **ESI-MS** *m/z* (rel int): (pos) 355.3 ($[M+Na]^+$, 100), 261 ($[M–TMS+H]^–$, 57).

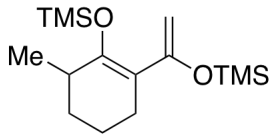
Trimethyl(1-(9-(trimethylsilyloxy)-6,7-dihydro-5*H*-benzo[7]annulen-8-yl)vinyloxy)silane (8e). Synthesized from 2-acetylbenzosuberone **7e** (1.10 g, 5.44 mmol) and TMSCl (2 × 1.03 mL, 8.12 mmol). Purification by filtration through basic aluminum oxide (99:1 hexanes/EtOAc) afforded **8e** as a yellow oil (1.74 g, 92%).

IR (NaCl, film): 3066 (w), 3020 (w), 2958 (m, C–H st), 2935 (m, C–H st), 2857 (w, C–H st), 1618 (m, C=C st), 1601 (m), 1449 (w), 1312 (w), 1277 (m), 1251 (s, $SiMe_3$ δ sy), 1200 (w), 1187 (w), 1147 (m), 1122 (w), 1089 (w), 1019 (m), 1009 (m), 889 (s), 874 (s), 843 (vs, br, $SiMe_3$, γ). **^{1}H-NMR** (500 MHz): δ 7.42 (dd, 1H, *J* = 7.5, 1.4), 7.23–7.19 (m, 2H), 7.15 (dd, 1H, *J* = 7.2, 1.3), 4.82 (s, 1H), 4.49 (s, 1H), 2.60 (t, 2H, *J* = 7.0), 2.07 (quint, 2H, *J* = 7.0), 1.89 (t, 2H, *J* = 7.0), 0.25 (s, 9H), 0.02 (s, 9H). **^{13}C-NMR** (125 MHz): δ 154.6, 146.7, 140.3, 139.7, 139.3, 128.5, 128.0, 127.9, 125.8, 118.8, 94.9, 34.7, 32.3, 26.0, 0.9, 0.4. **ESI-MS** *m/z* (rel int): (pos) 369.3 ($[M+Na]^+$, 100), 275.3 ($[M–TMS+2H]^+$, 43); (neg) 345.0 ($[M–H]^-$, 8), 273 ($[M–TMS]^-$, 100), 201 (54), 169 ($[M–2TMS+H]^-$, 80).



Trimethyl(1-(5-(trimethylsilyloxy)-7,8,9,10-tetrahydrobenzo[8]annulen-6-yl)vinyloxy)silane (8f). Synthesized by a modified version of the general protocol using TMSOTf. In a 50 mL roundbottom flask, *n*-butyllithium (1.59 M in hexanes, 1.44 mL, 2.29 mmol, 1.10 equiv) was cooled to –78 °C. Diisopropylamine (0.35 mL, 2.50 mmol 1.20 equiv) was added dropwise and, subsequently, Et_2O (0.50 mL) was added. After stirring for 40 min at –78 °C, a solution of 2-acetylbenzocyclooctanone **7f** (450 mg, 2.10 mmol, 1.00 equiv) in Et_2O (10.5 mL) was added slowly via Teflon cannula. The resulting slurry was stirred for 1 h at –78 °C, then trimethylsilyl trifluoromethanesulfonate (0.79 mL, 4.41 mmol, 2.10 equiv) was added neat via syringe. The mixture was allowed to warm to rt and stirred for an additional 1 h. Et_3N (2.20 mL, 15.8 mmol, 7.50 equiv) was added, followed by hexanes (*ca*. 15.0 mL). The resulting slurry was filtered twice through a plug of celite (hexanes) and concentrated by rotary evaporation. Drying under high vacuum afforded **8f** as a yellow liquid (739 mg, 98%).

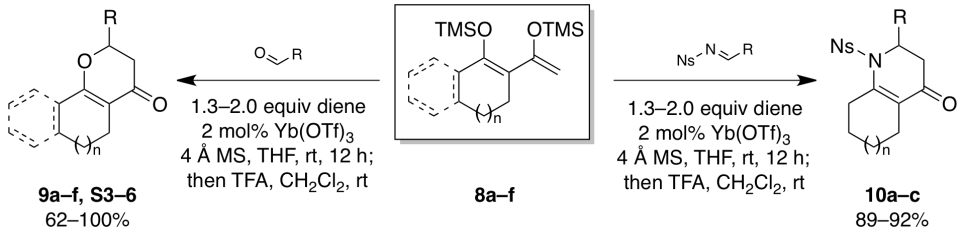
IR (NaCl, film): 2957 (m, C–H st), 2928 (m C–H st), 2856 (w, C–H st), 1626 (m, br, C=C st), 1487 (w), 1449 (w), 1305 (m), 1275 (m), 1252 (s, $SiMe_3$ δ sy), 1185 (m), 1149 (m), 1094 (m), 1016 (m), 884 (s), 844 (vs, br, $SiMe_3$, γ), 761 (m). **^{1}H-NMR** (500 MHz): δ 7.33 (d, 1H, *J* = 7.6), 7.25–7.14 (m, 3H), 4.61 (s, 1H), 4.52 (s, 1H), 2.78 (dd, 1H, *J* = 12.6, 8.2), 2.67 (t, 1H, *J* = 12.3), 2.32 (dd, 1H, *J* = 13.7, 8.2), 2.04–2.00 (m, 1H), 1.65–1.61 (m, 1H), 1.47–1.26 (m, 3H), 0.22 (s, 9H), –0.05 (s, 9H). **^{13}C-NMR** (125 MHz): δ 154.7, 145.8, 142.3, 137.2, 129.5, 128.6, 128.6, 125.3, 120.3, 95.7, 33.4, 29.0, 27.6, 24.9, 1.1, 0.3. **ESI-MS** *m/z* (rel int): (pos) 383.4 ($[M+Na]^+$, 9), 361.5 ($[M+H]^+$, 45), 329.4 (58), 289.3 ($[M–TMS+H]^+$, 100).



Trimethyl((1-(3-methyl-2-((trimethylsilyl)oxy)cyclohexyl)vinyl)oxy)silane (S2). Synthesized from 2-acetyl-6-methylcyclohexanone **S1** (285 mg, 1.85 mmol) and TMSCl (2 × 0.354 mL, 2.78 mmol). Purification by filtration through basic aluminum oxide (99:1 hexanes/EtOAc) afforded **S2** as a pale yellow oil (439 mg, 80%).

IR (NaCl, film): 2959 (s, C–H st), 2933 (s), 2858 (m, C–H st), 1643 (s), 1613 (s), 1457 (w), 1407 (w), 1374 (w), 1355 (w), 1340 (w), 1286 (s), 1252 (vs), 1224 (m), 1210 (m), 1186 (s), 1174 (s), 1147 (s), 1115 (w), 1086 (w), 1068 (w), 1015 (s), 974 (w), 919 (s), 844 (vs), 752 (m). **^{1}H-NMR** (500 MHz): δ 4.44 (s, 1H), 4.32 (s, 1H), 2.20–2.13 (m, 2H), 2.07–2.02 (m, 1H), 1.74 (dddt, 1H, *J* = 12.6, 9.5, 6.2, 3.1), 1.64–1.55 (m, 1H), 1.48 (ttd, 1H, *J* = 10.5, 5.3, 2.5), 1.39 (dddd, 1H, *J* = 11.8, 8.7, 5.4, 3.0), 1.08 (d, 3H, *J* = 7.0), 0.18 (d, 18H, *J* = 8.6). **^{13}C-NMR** (125 MHz): δ 155.4, 150.7, 115.0, 94.1, 34.7, 31.4, 27.2, 19.8, 19.0, 0.86, 0.26. **ESI-MS** *m/z* (rel int): (pos) 227.3 ($[M–TMS+H]^+$, 100), 299.2 ($[M+H]^+$, 25).

C. SYNTHESIS OF DIHYDROPYRONES AND DIHYDROPYRIDONES (9, 10, S3–6)



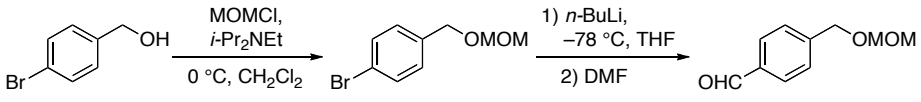
9a–f, S3–6
62–100%

8a–f

10a–c
89–92%

Supplementary Figure 9. Synthesis of dihydropyrones 9, S3–6 and dihydropyridones 10. The bis-(trimethylsiloxy)dienes **8** were reacted with various dienophiles using $Yb(OTf)_3$ as a Lewis acid catalyst; the inclusion of molecular sieves is essential for efficient reaction. Treatment with TFA/CH_2Cl_2 then cyclizes the primary Mukaiyama aldol adduct (the linear intermediate was isolated and characterized by ^{1}H-NMR and MS in the case of **9a**) and removes remaining TMS groups. In the presence of acid-labile functionalities, TFA can be replaced by formic acid.

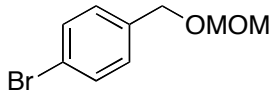
1. SYNTHESIS OF DIENOPHILES



quant

80%

Supplementary Figure 10. Synthesis of 4-([methoxymethoxy]methyl)benzaldehyde. 4-Bromobenzylic alcohol was MOM-protected using standard literature conditions.[7] The crude product was then treated with *n*-butyllithium at –78 °C, and the resulting aryl lithium reagent was reacted with *N,N*-dimethylformamide to give the desired aldehyde after aqueous workup.

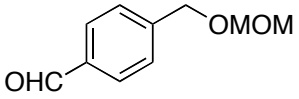


1-Bromo-4-((methoxymethoxy)methyl)benzene. In a 25 mL roundbottom flask, 4-bromobenzyl alcohol (374 mg, 2.00 mmol) was dissolved in diisopropylethyl amine (8.00 mL) and CH_2Cl_2 (2.00 mL). The solution was cooled to 0 °C and chloro(methoxy)methane (1.52 mL, 20.0 mmol, 10.0 equiv) was added slowly over 10 min. After stirring for 1 h at 0 °C, TLC analysis of a reaction aliquot indicated full conversion. Satd aq $NaHCO_3$ was added to quench excess chloro(methoxy)methane. Satd aq NH_4Cl was added and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with water (2×) and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The crude residue was redissolved in a small volume of hexanes and filtered through a pad of celite. Removal of the solvent by rotary evaporation afforded the crude product as a light brown-orange, slightly volatile liquid that displays a characteristic scent (461 mg, quant). The crude product was sufficiently pure, as judged by NMR, for use in the next step without further purification.

TLC: R_f 0.42 (9:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.48 (d, 2H, J = 8.3), 7.23 (d, 2H, J = 8.3), 4.69 (s, 2H), 4.54 (s, 2H), 3.40 (s, 3H). **^{13}C-NMR** (125 MHz): δ 136.9, 131.7, 129.6,

[7] Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

121.7, 95.9, 68.6, 55.6. The ^{1}H- and ^{13}C-NMR data are in accordance with those reported in the literature.[8]



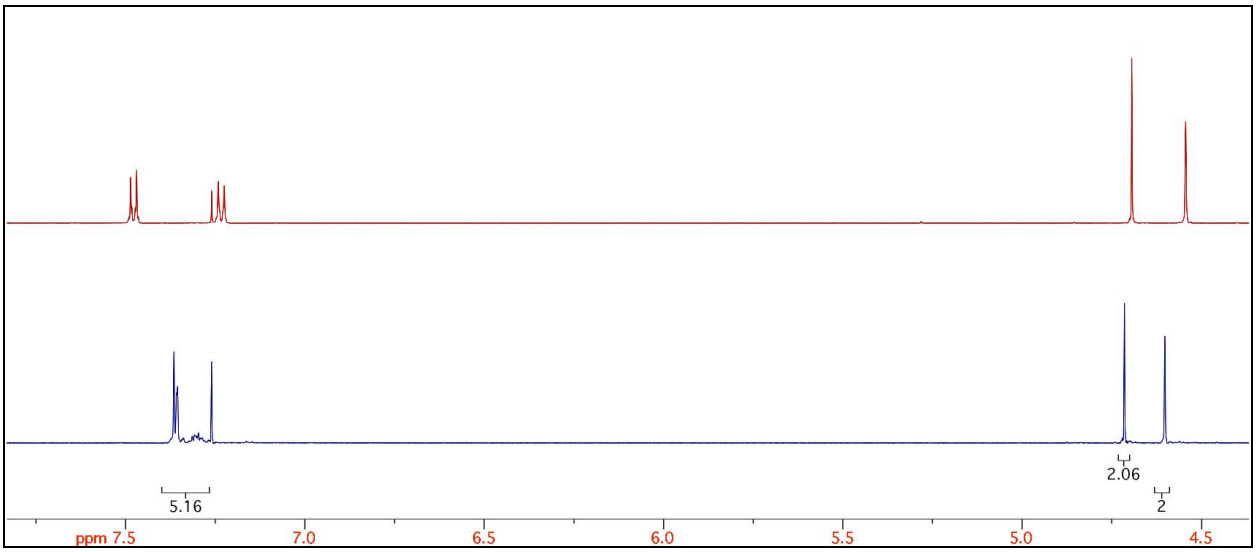
4-((Methoxymethoxy)methyl)benzaldehyde. In a 50 mL roundbottom flask, 1-bromo-4-([methoxymethoxy]methyl)benzene (878 mg, 3.80 mmol) was dissolved in THF (7.60 mL) and the resulting solution was cooled to –78 °C. *n*-Butyllithium (1.56 M in hexanes, 2.68 mL, 4.18 mmol, 1.10 equiv) was added dropwise over 20 min. The bromine/lithium exchange was generally complete after 30–40 min as indicated by ^{1}H-NMR analysis (see below) of reaction aliquots (quench with satd aq NH_4Cl, extract with Et_2O, dry ($MgSO_4$), concentrate by rotary evaporation; high vacuum is to be avoided due to the considerable volatility of ([methoxymethoxy]methyl)benzene). Subsequently, DMF (0.50 mL, excess) was added neat in one portion. After 1 h at –78 °C, TLC analysis of reaction aliquots (workup as described above) indicated full conversion. Satd aq NH_4Cl and water (1:1, v/v) was added at –78 °C and the resulting mixture was warmed to rt and extracted with EtOAc (2×). The combined organic extracts were washed with water (2×) and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (short column, 9:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded 4-([methoxymethoxy]methyl)benzaldehyde as a colorless liquid (546 mg, 80%).

NOTE: The product is easily oxidized in air and should be stored under Ar atmosphere at low temperature.

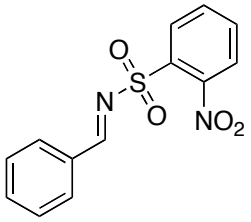
TLC: R_f 0.27 (9:1 hexanes/EtOAc, double elution). **^{1}H-NMR** (500 MHz): δ 10.01 (s, 1H), 7.87 (d, 2H, J = 8.1), 7.53 (d, 2H, J = 8.1), 4.74 (s, 2H), 4.68 (s, 2H), 3.42 (s, 3H). **^{13}C-NMR** (125 MHz): δ 192.0, 145.2, 135.9, 130.0, 128.0, 96.2, 68.7, 55.7. The ^{1}H-NMR data are in accordance with those reported in the literature.[9]

[8] Chen, D.-W.; Beuscher, A. E. IV; Stevens, R. C.; Wirsching, P.; Lerner, R. A.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 1725.

[9] Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *673*, 656.



Monitoring of bromine/lithium exchange by ^{1}H-NMR in $CDCl_3$. The ^{1}H-NMR spectrum of a reaction aliquot, quenched after 40 min at –78 °C (black, lower trace), shows no remaining starting bromide (brown, top trace).



***N*-Benzylidene-2-nitrobenzenesulfonamide.** Synthesized as previously described.[10] Toluene (35.0 mL) and benzaldehyde (738 mg, 6.95 mmol, 1.10 equiv) were added to a 35 mL roundbottom flask containing activated 4 Å molecular sieves and *p*-nitrobenzenesulfonamide (1.28 g, 6.33 mmol, 1.00 equiv). Amberlyst 15 resin (catalytic) was then added and the mixture was heated at reflux for 20 h under a Dean–Stark trap. The mixture was cooled to rt and filtered through a pad of celite. The pad was washed with additional toluene and the filtrate was concentrated by rotary evaporation to afford a light tan solid. The solid was washed with hexanes, then placed under high vacuum for 1 h to afford *N*-benzylidene-2-nitrobenzene-sulfonamide as a light tan solid (1.36 g, 74%).

mp = 125.2–129.3 ºC. **^{1}H-NMR** (500 MHz): δ 9.09 (s, 1H), 8.40 (d, 1H, *J* = 6.9), 8.00 (d, 2H, *J* = 6.9), 7.83–7.79 (m, 3H), 7.67 (t, 1H, *J* = 7.4), 7.53 (t, 2H, *J* = 7.7). **^{13}C-NMR** (125 MHz): δ 174.1, 148.8, 136.0, 134.9, 132.9, 132.4, 132.1, 129.6, 125.1. **ESI-MS** *m/z* (rel int): (neg) 291 ($[M+H]^+$, 10), 313 ($[M+Na]^+$, 95), 345 ($[M+Na]^+$, 100).

[10] Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701.

2. SYNTHESIS OF DIHYDROPYRONES AND DIHYDROPYRIDONES (9, 10, S3–6)

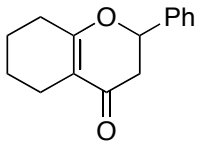
General protocol for Yb(OTf)$_3$-catalyzed Diels–Alder reactions

Freshly ground molecular sieves were extensively pre-dried in a round bottom flask under high vacuum using a Bunsen burner flame. A high temperature is maintained over a period of 30 min by heating until Na^+ is emitted from the glass surface, giving the blue gas flame a yellow color, but not beyond this temperature. ***CAUTION***: Overheating or maintaining this temperature for extended periods may cause the flask to melt or implode! Use of a blast shield is recommended. After cooling, the molecular sieves are stored under Ar.

The 4 Å molecular sieves prepared above (660 mg/mmol dienophile) were placed in a roundbottom flask, and flame dried under high vacuum. After cooling to rt, THF (3.0 mL/mmol dienophile) was added, followed by the bis(trimethylsiloxy)diene **8a–f** (1.05–2.00 equiv) and the dienophile (1.00 equiv). Neat Yb(OTf)$_3$ (2.0 mol%) was added, the flask was sealed with a glass stopper, and the mixture was stirred overnight at rt. TLC analysis of a reaction aliquot (diluted with EtOAc) indicated complete consumption of the dienophile and formation of the intermediate Mukaiyama aldol product. The reaction mixture was then filtered through a pad of celite and the pad was rinsed thoroughly with EtOAc and CH_2Cl_2. The solvents were then removed by rotary evaporation.

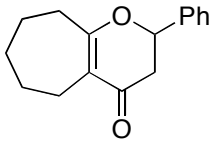
NOTE: In cases where the Mukaiyama addition step proceeded slugglishly, it was found that using CH_2Cl_2 as the solvent in place of THF increased the speed of the reaction. For reactions that worked well in THF, the use of CH_2Cl_2 was associated with the formation of trace side products. Thus, it is recommended to use CH_2Cl_2 only in the case of sluggish reactions or in the event of solubility issues.

The resulting residue was dissolved in CH_2Cl_2 (9.5 mL/mmol dienophile) in an Ar-flushed roundbottom flask. TFA (0.5 mL/mmol dienophile) was added and the mixture was stirred at rt for *ca*. 30 min, after which the reaction was judged complete by TLC in most cases. (Some substrates (for example from the benzannulated series) may require longer reaction times; reaction intermediates may be detected by TLC, but disappear over time; in some cases they were indentified as the TMS-deprotected Mukaiyama adducts befor cyclodehydration). The reaction was quenched with satd aq $NaHCO_3$ and the mixture was stirred vigorously for 20 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (hexanes/EtOAc) afforded the dihydropyrone **9a–f** or dihydropyridone **10a–c**.



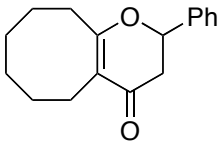
2-Phenyl-5,6,7,8-tetrahydro-2*H*-chromen-4(3*H*)-one (9a). Synthesized from bis(trimethylsiloxy)diene **8a** (1.48 g, 5.20 mmol) and benzaldehyde (424 mg, 4.00 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 10:1) afforded **9a** as a pale yellow, crystalline solid (800 mg, 88%).

TLC: R_f 0.16 (10:1 hexanes/EtOAc). **mp** = 50.4–54.5 °C. **IR** (NaCl, film): 2934 (m, C–H st), 2857 (w, C–H st), 1663 (vs, C=O st), 1615 (vs, C=C st), 1452 (w), 1406 (s), 1300 (m), 1192 (m), 1147 (s), 1002 (m), 973 (m), 911 (m), 760 (m), 701 (m). **^{1}H-NMR** (500 MHz): δ 7.43–7.35 (m, 5H), 5.34 (dd, 1H, *J* = 14.5, 3.4), 2.86 (dd, 1H, *J* = 16.8, 14.5), 2.63 (dd, 1H, *J* = 16.8, 3.4), 2.42–2.18 (m, 4H), 1.85–1.73 (m, 2H), 1.68–1.60 (m, 1H), 1.56–1.48 (m, 1H). **^{13}C-NMR** (125 MHz): δ 192.0, 171.5, 138.9, 128.9, 128.7, 126.2, 112.6, 80.0, 43.2, 28.8, 22.2, 22.0, 20.9 **ESI-MS** *m/z* (rel int): (pos) 479.4 ([2M+Na]$^+$, 100), 251.2 ([M+Na]$^+$, 48), 229.2 ([M+H]$^+$, 49).



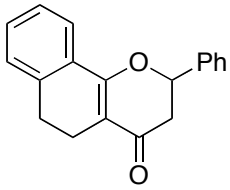
2-Phenyl-2,3,6,7,8,9-hexahydrocyclohepta[*b*]pyran-4(5*H*)-one (9b). Synthesized from bis(trimethylsiloxy)diene **8b** (894 mg, 3.00 mmol) and benzaldehyde (212 mg, 2.00 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc) afforded **9b** as colorless, crystalline solid (464 mg, 96%).

TLC: R_f 0.21 (10:1 hexanes/EtOAc). **mp** = 55.8–58.2 °C. **IR** (NaCl, film): 2921 (m, C–H st), 2798 (w, C–H st), 1658 (vs, C=O st), 1605 (vs, C=C st), 1444 (m), 1399 (s), 1360 (m), 1331 (m), 1225 (m), 1159 (m), 1125 (s), 1000 (w), 891 (w). **^{1}H-NMR** (500 MHz): δ 7.41–7.35 (m, 5H), 5.31 (dd, 1H, *J* = 14.5, 3.4), 2.81 (dd, 1H, *J* = 16.7, 14.5), 2.61 (dd, 1H, *J* = 16.7, 3.4), 2.58–2.46 (m, 3H), 2.42 (ddd, 1H, *J* = 15.1, 9.2, 2.1), 1.79–1.61 (m, 4H), 1.57–1.46 (m, 2H). **^{13}C-NMR** (125 MHz): δ 191.0, 177.1, 138.8, 128.9, 128.8, 126.2, 116.9, 80.2, 42.4, 35.1, 31.9, 27.1, 25.1, 22.1. **ESI-MS** *m/z* (rel int): (pos) 507.2 ([2M+Na]$^+$, 100), 265.04 ([M+Na]$^+$, 10), 243.1([M+H]$^+$, 10); (neg) 241.0 ([M–H]$^-$, 85).



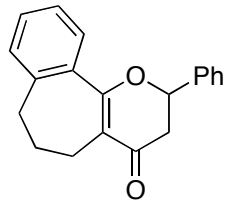
2-Phenyl-5,6,7,8,9,10-hexahydro-2*H*-cycloocta[*b*]pyran-4(3*H*)-one (9c). Synthesized from bis(trimethylsiloxy)diene **8c** (312 mg, 1.00 mmol) and benzaldehyde (53.0 mg, 0.499 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc) afforded **9c** as a colorless oil (128 mg, quant).

TLC: R_f 0.26 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 3064 (w), 3034 (w), 3009 (w), 2925 (vs, C–H st), 2853 (s, C–H st), 1661 (vs, C=O st), 1609 (vs, C=C st), 1498 (w), 1455 (m), 1395 (s), 1360 (m), 1328 (m), 1223 (m), 1194 (m), 1169 (m), 1125 (s), 1085 (s), 1031 (w), 998 (m), 959 (w), 875 (m), 759 (s). **^{1}H-NMR** (500 MHz): δ 7.42–7.35 (m, 5H), 5.32 (dd, 1H, *J* = 14.2, 3.4), 2.82 (dd, 1H, *J* = 16.7, 14.2), 2.64 (dd, 1H, *J* = 16.7, 3.4), 2.53–2.48 (m, 3H), 2.37 (ddd, 1H, *J* = 13.9, 8.9, 4.7), 1.82–1.75 (m, 1 H), 1.73–1.66 (m, 1 H), 1.63–1.39 (m, 6H). **^{13}C-NMR** (125 MHz): δ 191.2, 173.6, 138.7, 128.8, 128.5, 126.1, 114.0, 79.7, 42.8, 31.7, 29.9, 28.7, 26.5, 26.4, 22.4. **ESI-MS** *m/z* (rel int): (pos) 791 ([3M+Na]$^+$, 24), 535 ([2M+Na]$^+$, 100), 311.0 ([M+Na]$^+$, 10), 257.1 ([M+H]$^+$, 100); (neg) 255.1 ([M–H]$^-$, 100).



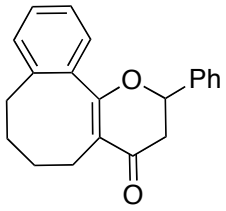
2-Phenyl-5,6-dihydro-2*H*-benzo[*h*]chromen-4(3*H*)-one (9d). Synthesized from bis(trimethylsiloxy)diene **8d** (166 mg, 0.499 mmol) and benzaldehyde (27.0 mg, 0.254 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc) afforded **9d** as a colorless, crystalline solid (59.0 mg, 84%).

TLC: R_f 0.16 (10:1 hexanes/EtOAc). **mp** = 120.8–121.7 °C. **IR** (NaCl, film): 3064 (w), 2941 (w, C–H st), 2895 (w, C–H st), 2845 (w, C–H st), 1656 (vs, C=O st), 1611 (s, C=C st), 1563 (s), 1451 (w), 1403 (vs), 1319 (m), 1259 (w), 1158 (m), 1110 (m), 1064 (w), 1029 (w), 954 (w), 919 (w), 870 (w). **^{1}H-NMR** (500 MHz): δ 7.76–7.75 (m, 1H), 7.51–7.34 (m, 6H), 7.28–7.21 (m, 2H), 5.55 (dd, 1H, *J* = 14.2, 3.4), 2.98 (dd, 1H, *J* = 16.8, 14.2), 2.86 (m, 2H), 2.79 (dd, 1H, *J* = 16.8, 3.4), 2.71–2.64 (m, 2H). **^{13}C-NMR** (125 MHz): δ 191.6, 164.2, 140.3, 138.9, 131.2, 129.4, 129.0, 128.8, 128.0, 126.8, 126.2, 124.5, 111.1, 80.3, 43.2, 27.7, 18.8. **ESI-MS** *m/z* (rel int): (pos) 575.4 ($[2M+Na]^+$, 55), 299.2 ($[M+Na]^+$, 52), 277.3 ($[M+H]^+$, 100).

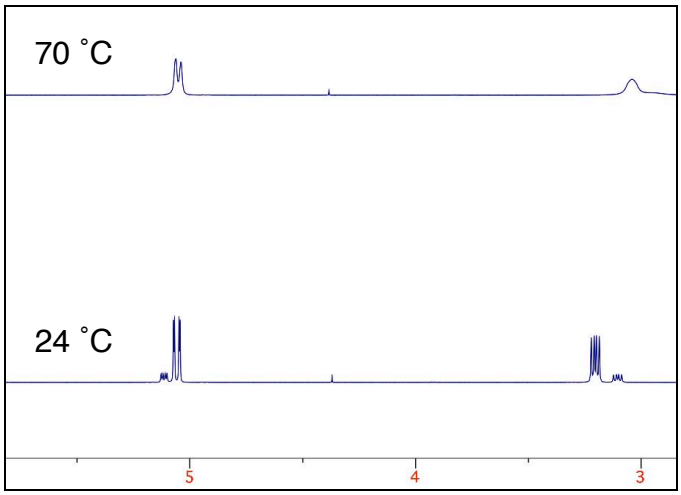


[8.9]-*Benzo*-2-phenyl-2,3,5,6,7-pentahydrocyclohepta[*b*]pyran-4(5*H*)-one (9e). Synthesized from bis(trimethylsiloxy)diene **8e** (173 mg, 0.499 mmol) and benzaldehyde (27.0 mg, 0.254 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 10:1) afforded **9e** as an off-white solid (55.1 mg, 74%).

TLC: R_f 0.19 (10:1 hexanes/EtOAc). **mp** = 106.8–107.9 °C. **IR** (NaCl, film): 3090 (w), 2931 (m, C–H st), 2857 (w, C–H st), 1659 (vs, C=O st), 1607 (s, C=C st), 1584 (s), 1567 (m), 1448 (w), 1394 (vs), 1331 (m), 1272 (m), 1238 (w), 1214 (w), 1198 (w), 1147 (s), 1111 (w), 1063 (w), 989 (w), 903 (w), 759 (m). **^{1}H-NMR** (500 MHz): δ 7.61 (dd, 1H, *J* = 7.7, 1.3), 7.49–7.36 (m, 6H), 7.29 (m, 2H), 5.57 (dd, 1H, *J* = 14.3, 3.2), 3.05 (dd, 1H, *J* = 16.8, 14.3), 2.80–2.74 (m, 2H), 2.66 (dd, 2H, *J* = 8.7, 5.4), 2.22–2.09 (m, 2H), 1.73 (ddd, 1H, *J* = 13.7, 11.3, 7.4). **^{13}C-NMR** (125 MHz): δ 191.6, 168.2, 142.4, 138.8, 134.7, 130.9, 129.6, 128.9, 128.8, 127.9, 126.5, 126.3, 115.3, 80.6, 43.2, 33.5, 32.4, 19.6. **ESI-MS** *m/z* (rel int): (pos) 291.0 ($[2M+Na]^+$, 45), 313 ($[M+Na]^+$, 100), 291.2 ($[M+H]^+$, 85).



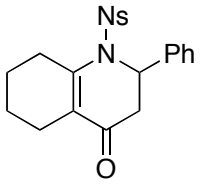
[9.10]-*Benzo*-2-Phenyl-2,3,5,6,7,8-hexahydrocycloocta[*b*]pyran-4(5*H*)-one (9f). Synthesized from bis(trimethylsiloxy)diene **8f** (271 mg, 0.75 mmol) and benzaldehyde (53.1 mg, 0.50 mmol). DCM was used as a solvent. Cyclization to the final product (TFA, CH_2Cl_2, rt) required 12 h. Purification by silica flash chromatography (10:1 hexanes/EtOAc) afforded **9f** as yellow resin that partially crystallized by time (139 mg, 91%).



^{1}H-NMR signals of 9f in toluene-d_8 at ambient and elevated temperature.

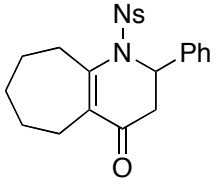
The ^{1}H- and ^{13}C-NMR spectra of **9f** exhibit two sets of signals at rt (5:1 ratio by ^{1}H-NMR), presumed to arise from atropisomers that do not interconvert rapidly on the NMR timescale at rt. The signals converge to a single set of peaks at higher temperatures in NMR experiments in toluene-d_8. The major set of ^{1}H- and ^{13}C-NMR signals at 25 °C are reported below.

TLC: R_f 0.19 (10:1 hexanes/EtOAc). **mp** = 75.6–77.5 °C. **IR** (NaCl, film): 3063 (w), 3019 (w), 2928 (m, C–H st), 2855 (w, C–H st), 1663 (vs, C=O st), 1611 (vs, C=C st), 1590 (s, C=C st), 1491 (w), 1451 (m), 1383 (vs), 1327 (m), 1283 (w), 1235 (w), 1183 (w), 1142 (s), 1100 (m), 1080 (w), 1064 (w), 1003 (m), 982 (w), 974 (w), 891 (w), 759 (s), 743 (m), 719 (w). **^{1}H-NMR** (500 MHz, toluene-d_8, 25 °C, main set of signals): δ 7.30 (dd, 1H, J = 7.9, 1.3), 7.11–7.02 (m, 5H), 6.98–6.95 (m, 3H), 5.01 (dd, 1H, J = 14.8, 2.9), 3.15 (dd, 1H, J = 13.6, 7.7), 2.65–2.58 (m, 2H), 2.48–2.44 (m, 2H), 1.86–1.82 (m, 1H), 1.76–1.71 (m, 1H), 1.43 (qd, 1H, J = 12.8, 4.9), 1.27–1.16 (m, 2H). **^{13}C-NMR** (125 MHz): δ 192.2, 167.6, 143.3, 138.7, 132.9, 130.9, 130.2, 128.8, 128.7, 128.3, 126.2, 125.7, 116.9, 80.9, 43.6, 33.4, 28.6, 25.1, 23.4. **ESI-MS** *m/z* (rel int): (pos) 327.1 ($[M+Na]^+$, 100), 305 ($[M+H]^+$, 5); (neg) 303.1 ($[M–H]^-$, 100).



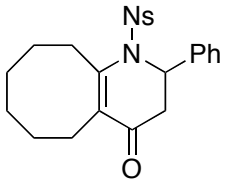
1-(2-Nitrophenylsulfonyl)-2-phenyl-2,3,5,6,7,8-hexahydroquinolin-4(1*H*)-one (10a). Synthesized from bis(trimethylsiloxy)diene **8a** (193 mg, 0.678 mmol) and *N*-benzylidene-2-nitrobenzenesulfonamide (100 mg, 0.344 mmol). Purification by silica flash chromatography (35:1 $CHCl_3$/EtOAc) afforded **10a** as light yellow foam (128.5 mg, 92%).

TLC: R_f 0.11 (2:1 hexanes/EtOAc). **IR** (NaCl, film): 3095 (w), 3068 (w), 3032 (w), 2943 (s, C–H st), 2866 (m, C–H st), 1671 (vs, C=O st), 1606 (s), 1546 (vs, N=O st), 1500 (m), 1452 (m), 1441 (m), 1377 (vs, S=O st), 1293 (m), 1174 (vs, S=O st), 1137 (vs, S=O st), 1046 (s), 1001 (m), 974 (m), 914 (s), 854 (m), 781 (s), 741 (vs). **^{1}H-NMR** (500 MHz): δ 8.12 (dd, 1H, J = 7.8, 1.3), 7.82–7.72 (m, 3H), 7.34–7.27 (m, 5H), 5.73 (dd, 1H, J = 5.8, 1.7), 2.94 (m, 2H), 2.75 (dd, 1H, J = 17.7, 5.8), 2.31 (m, 2H), 2.07–2.01 (m, 1H), 1.73 (m, 1H), 1.59–1.47 (m, 2H), 1.39 (m, 1H). **^{13}C-NMR** (125 MHz): δ 192.1, 150.2, 148.0, 137.4, 134.8, 133.3, 132.4, 131.0, 128.7, 128.1, 126.6, 125.0, 124.8, 59.3, 40.1, 31.6, 22.5, 22.1, 21.1. **ESI-MS** *m/z* (rel int): (pos) 435 ($[M+Na]^+$, 100), 413 ($[M+H]^+$, 25).



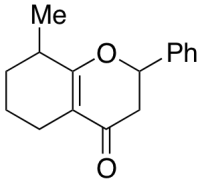
1-(2-Nitrophenylsulfonyl)-2-phenyl-2,3,6,7,8,9-hexahydro-1*H*-cyclohepta[*b*]pyridin-4(5*H*)-one (10b). Synthesized from bis(trimethylsiloxy)diene **8b** (203 mg, 0.680 mmol) and *N*-benzylidene-2-nitrobenzenesulfonamide (100 mg, 0.344 mmol). Purification by silica flash chromatography (35:1 $CHCl_3$/EtOAc) afforded **10b** as light yellow foam (131.0 mg, 91%).

TLC: R_f 0.18 (2:1 hexanes/EtOAc). **IR** (NaCl, film): 3092 (w), 3066 (w), 2924 (m, C–H st), 2853 (m, C–H st), 1664 (s, C=O st), 1603 (m), 1544 (vs, N=O st), 1450 (m), 1440 (m), 1375 (vs, S=O st), 1298 (m), 1171 (s), 1146 (m), 1131 (m), 1058 (w), 1021 (m), 1004 (w), 912 (w), 852 (w), 733 (s). **^{1}H-NMR** (500 MHz): δ 8.10 (dd, 1H, J = 7.8, 1.4), 7.81 (td, 1H, J = 7.7, 1.4), 7.76–7.71 (m, 2H), 7.32 (m, 5H), 5.66 (dd, 1H, J = 5.7, 1.1), 2.88 (dd, 1H, J = 18.1, 1.1), 2.79 (dd, 1H, J = 14.76, 9.35), 2.72–2.66 (m, 2H), 2.55 (dd, 1H, J = 14.5, 9.6), 2.32 (dd, 1H, J = 14.5, 9.3), 1.73–1.66 (m, 1H), 1.59–1.49 (m, 2H), 1.43–1.35 (m, 1H), 1.21–1.05 (m, 2H). **^{13}C-NMR** (125 MHz): δ 191.6, 155.1, 148.2, 137.4, 134.9, 132.9, 132.2, 131.9, 131.1, 128.7, 128.3, 127.2, 124.9, 58.9, 38.9, 35.9, 31.9, 25.4, 24.1, 23.6. **ESI-MS** *m/z* (rel int): (pos) 449 ($[M+Na]^+$, 100), 427 ($[M+H]^+$, 25).



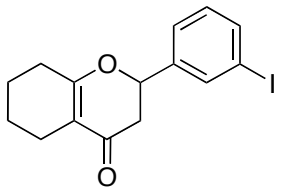
1-(2-Nitrophenylsulfonyl)-2-phenyl-2,3,5,6,7,8,9,10-octahydrocycloocta[*b*]pyridin-4(1*H*)-one (10c). Synthesized from bis(trimethylsiloxy)diene **8c** (213 mg, 0.681 mmol) and *N*-benzylidene-2-nitrobenzenesulfonamide (100 mg, 0.344 mmol). Purification by silica flash chromatography (35:1 $CHCl_3$/EtOAc) afforded **10c** as light yellow foam (133 mg, 89%).

TLC: R_f 0.32 (1:1 hexanes/EtOAc). **IR** (NaCl, film): 2922 (m, C–H st), 2851 (w, C–H st), 1665 (s, C=O st), 1591 (m), 1545 (vs, N=O st), 1498 (w), 1472 (w), 1450 (m), 1442 (m), 1376 (vs, S=O st), 1306 (m), 1280 (w), 1172 (s, S=O st), 1140 (m), 1123 (s), 1102 (w), 1046 (w), 982 (m), 971 (m), 945 (w), 912 (m), 779 (m), 732 (s). **^{1}H-NMR** (500 MHz): δ 8.11 (dd, 1H, J = 7.9, 1.3), 7.83–7.72 (m, 3H), 7.40–7.29 (m, 5H), 5.77 (d, 1H, J = 3.5), 3.20 (dt, 1H, J = 14.2, 4.3), 2.96 (dd, 1H, J = 17.9, 3.5), 2.88 (ddd, 1H, J = 12.9, 5.3, 2.9), 2.70–2.65 (m, 2H), 2.01 (t, 1H, J = 12.9), 1.62–1.51 (m, 2H), 1.37–1.30 (m, 1H), 1.07–0.85 (m, 4H), 0.15–0.07 (m, 1H). **^{13}C-NMR** (125 MHz): δ 191.8, 152.6, 148.3, 137.3, 134.9, 133.0, 132.3, 131.0, 129.2, 128.6, 127.9, 124.9, 58.5, 38.4, 30.9, 30.1, 28.4, 26.3, 24.9, 24.0; 1C-Ar not observed. **ESI-MS** *m/z* (rel int): (pos) 463 ($[M+Na]^+$, 100).



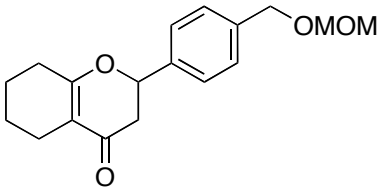
8-Methyl-2-phenyl-5,6,7,8-tetrahydro-2*H*-chromen-4(3*H*)-one (S3). Synthesized from bis(trimethylsiloxy)diene **S2** (400 mg, 1.34 mmol) and benzaldehyde (95.0 mg, 0.895 mmol). Purification by silica flash chromatography (9:1 hexanes/EtOAc) afforded **S3** as light yellow solid (203 mg, 94%, 1.3:1.0 dr).

TLC: R_f 0.31 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2933 (s, C–H st), 2855 (m, C–H st), 1663 (vs, C=O st), 1607 (vs, C=C st), 1498 (w), 1454 (m), 1401 (s), 1369 (m), 1301 (m), 1288 (m), 1250 (w), 1217 (w), 1149 (s), 1066 (w), 994 (w), 901 (w), 759 (m). **^{1}H-NMR** (500 MHz): δ 7.43–7.34 (m, 5H-major, 5H-minor), 5.31 (td, 1H-major, 1H-minor, J = 14.6, 3.3), 2.82 (ddd, 1H-major, 1H-minor, J = 21.7, 16.8, 14.5), 2.64 (td, 1H-major, 1H-minor, J = 16.4, 3.3), 2.55–2.46 (m, 1H-major, 1H-minor), 2.44–2.33 (m, 1H-major, 1H-minor), 2.25–2.16 (m, 1H-major, 1H-minor), 1.95–1.89 (m, 1H-minor), 1.84–1.75 (m, 1H-major, 1H-minor), 1.67–1.61 (m, 1H-major, 1H-minor), 1.58–1.52 (m, 1H-major), 1.52–1.45 (m, 1H-minor), 1.41–1.34 (m, 1H-major), 1.23 (d, 3H-major, J = 7.0), 1.20 (d, 3H-minor, J = 7.2). **^{13}C-NMR** (125 MHz): δ 192.4, 192.3, 174.5, 174.3, 139.2, 139.0, 128.7, 128.6, 128.4, 126.0, 125.9, 112.1, 112.0, 79.8, 79.7, 43.3, 43.0, 33.9, 32.7, 31.4, 30.2, 21.5, 21.3, 20.4, 18.7, 18.4, 18.0. **ESI-MS** *m/z* (rel int): (pos) 243.1 ($[M+H]^+$, 100), 265.1 ($[M+Na]^+$, 30), 507.4 ($[2M+Na]^+$, 66).



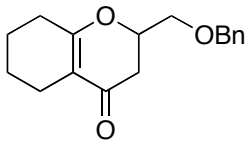
2-(3-Iodophenyl)-5,6,7,8-tetrahydro-2*H*-chromen-4(3*H*)-one (S4). Synthesized from bis(trimethylsiloxy)diene **8a** (568 mg, 2.00 mmol) and 3-iodobenzaldehyde (232 mg, 1.00 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc) afforded **S4** as a reddish brown solid (313 mg, 88%).

TLC: R_f 0.13 (10:1 hexanes/EtOAc). **mp** = 102.5–103.2 °C. **IR** (NaCl, film): 3060 (w), 3012 (w), 2936 (m, C–H st), 2861 (w, C–H st), 1729 (w), 1662 (s, C=O st), 1611 (vs, C=C st), 1566 (m), 1408 (s), 1354 (m), 1301 (m), 1214 (m), 1193 (m), 1148 (s), 1066 (m), 1033 (m), 995 (m), 974 (m), 920 (w). **^{1}H-NMR** (500 MHz): δ 7.78 (s, 1H), 7.70 (d, 1H, J = 7.8), 7.34 (d, 1H, J = 7.8), 7.14 (t, 1H, J = 7.8), 5.27 (dd, 1H, J = 14.4, 3.4), 2.80 (dd, 1H, J = 16.7, 14.4), 2.62 (dd, 1H, J = 16.7, 3.4), 2.41–2.17 (m, 4H), 1.85–1.73 (m, 2H), 1.67–1.62 (m, 1H), 1.55–1.50 (m, 1H). **^{13}C-NMR** (125 MHz): δ 191.5, 171.3, 141.2, 137.8, 135.2, 130.6, 125.4, 112.8, 94.7, 79.0, 43.2, 28.8, 22.2, 22.0, 20.9. **ESI-MS** *m/z* (rel int): (pos) 731.1 ([2M+Na]$^+$, 100), 377.0 ([M+Na]$^+$, 61), 355.0 ([M+H]$^+$, 35); (neg) 371.1 ([M+OH]$^-$, 57), 353.0 ([M–H]$^-$, 100).



2-(4-((Methoxymethoxy)methyl)phenyl)-5,6,7,8-tetrahydro-2*H*-chromen-4(3*H*)-one (S5). Synthesized from bis(trimethylsiloxy)diene **8a** (284 mg, 1.00 mmol, 2.00 equiv) and 4-([methoxymethoxy]methyl)benzaldehyde (90.0 mg, 0.499 mmol, 1.00 equiv). Due to the instability of the MOM group towards TFA, formic acid (0.250 mL) in CH_2Cl_2 (4.75 mL; 5% v/v) was used instead to induce cyclodehydration over *ca*. 6 h. The remaining workup was performed according to the general protocol. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **S5** as a yellow resin (93.0 mg, 62%).

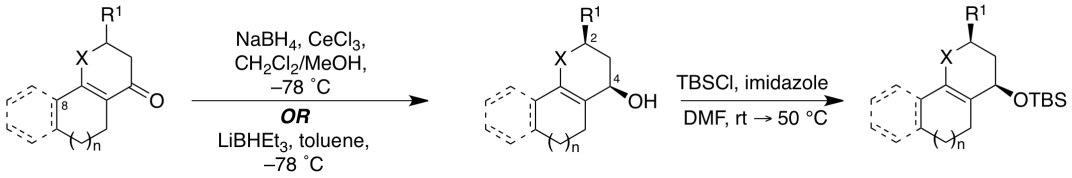
TLC: R_f 0.63 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2932 (m, C–H st), 2886 (m, C–H st), 2858 (m, C–H st), 2824 (m, C–H st), 1664 (s, C=O st), 1616 (vs, C=C st), 1406 (s), 1300 (m), 1256 (w), 1218 (w), 1191 (m), 1148 (s, C–O/Si–O st), 1103 (m), 1047 (s, C–O/Si–O st), 1020 (w), 971 (w), 915 (w), 818 (m, Si–C st), 748 (w, Si–C st). **^{1}H-NMR** (500 MHz): δ 7.33 (s, 4H), 5.27 (dd, 1H, J = 14.4, 3.4), 4.64 (s, 2H), 4.54 (s, 2H), 3.35–3.34 (m, 3H), 2.78 (dd, 1H, J = 16.8, 14.4), 2.55 (dd, 1H, J = 16.8, 3.4), 2.33–2.11 (m, 4H), 1.77–1.66 (m, 2H), 1.61–1.54 (m, 1H), 1.49–1.41 (m, 1H). **^{13}C-NMR** (125 MHz): δ 192.0, 171.5, 138.6, 138.3, 128.3, 126.4, 112.6, 95.9, 79.8, 68.8, 55.5, 43.2, 28.8, 22.2, 22.0, 20.9. **ESI-MS** *m/z* (rel int): (pos) 627.1 ([2M+Na]$^+$, 48), 416.1 (80), 359.0 (75), 324.9 ([M+Na]$^+$, 100), 497.3 ([M+H]$^+$, 19); (neg) 301.1 ([M–H]$^-$, 100).



2-(Benzyloxymethyl)-5,6,7,8-tetrahydro-2*H*-chromen-4(3*H*)-one (S6). Synthesized from bis-(trimethylsiloxy)diene **8a** (369 mg, 1.30 mmol) and freshly distilled benzyloxyacetaldehyde (132 mg, 0.88 mmol). (***NOTE:*** The quality of this aldehyde, even in newly opened commercial bottles, is highly variable; the use of freshly distilled reagent is strongly recommended.) Purification by silica flash chromatography (10:1 hexanes/EtOAc) afforded **S6** as a colorless, crystalline solid (192 mg, 71%).

TLC: R_f 0.03 (10:1 hexanes/EtOAc). **mp** = 56.0–58.3 °C. **IR** (NaCl, film): 2933 (m, C–H st), 2860 (w, C–H st), 1663 (s, C=O st), 1615 (C=C st), 1452 (w), 1407 (m), 1353 (w), 1302 (m), 1201 (m), 1157 (m), 1122 (m, br), 1044 (w), 738 (w). **^{1}H-NMR** (500 MHz): δ 7.38–7.29 (m, 5H), 4.61 (q, 2H, J = 11.1), 4.50 (ddt, 1H, J = 14.3, 4.9, 3.6), 3.70–3.64 (m, 2H), 2.69 (dd, 1H, J = 16.8, 14.3), 2.38 (dd, 1H, J = 16.8, 3.6), 2.34–2.13 (m, 4H), 1.81–1.67 (m, 2H), 1.64–1.56 (m, 1H), 1.52–1.44 (m, 1H). **^{13}C-NMR** (125 MHz, acetone-d_6): δ 191.3, 170.7, 139.4, 129.1, 128.4, 128.3, 112.3, 78.1, 73.7, 72.0, 38.6, 29.0, 22.9, 22.6, 21.5. **ESI-MS** *m/z* (rel int): (pos) 567.3 ($[2M+Na]^+$, 100), 545.3 ($[2M+H]^+$, 32), 295.0 ($[M+Na]^+$, 52), 273.0 ($[M+H]^+$, 98); (neg) 271.0 ($[M–H]^-$, 11).

D. SYNTHESIS OF TBS-PROTECTED ALCOHOLS (13, 14, S11–15)



9a–f (X = O)
10a–c (X = NNs)
S3 (X = O, n = 1, R^1 = Ph; 8-*R*/*S*-methyl)

S4 (X = O, n = 1, R^1 = 3-I-Ph)
S5 (X = O, n = 1, R^1 = 4-(MOMOCH$_2$)Ph)
S6 (X = O, n = 1, R^1 = CH$_2$OBn)

11a–f, 85–100%, ≥98:2 dr
12a–c, 87–89%, ≥98:2 dr
S7, 100%, ≥98:2 dr at C2/C4

S8, 99%, ≥98:2 dr
S9, 98%, ≥98:2 dr
S10, 100%, 90:10 dr

13a–f, 77–92%
14a–c, 89–92%
S11, 80% (8-*R*-Methyl)
S12, 74% (8-*S*-Methyl)
S13, 82%
S14, 75%
S15, 74%

Supplementary Figure 11. Synthesis of TBS-protected alcohols 11, 12, S11–15. The Diels–Alder condensation products **9, 10, S3–6** were reduced diastereoselectively using either modified Luche conditions (**9, S3–6**) or Super-Hydride (**10**) to afford alcohols **11**, **12**, **S7–10**. The crude alcohols were characterized by ^{1}H-NMR, ^{13}C-NMR, and MS. Relative stereochemistry at C2 and C4 was confirmed by NOESY experiments with **11a** (X = O, n = 1) and **12a** (X = NNs, n = 1), and assigned to other products by analogy. Silylation of the crude alcohols then afforded ring expansion substrates **13**, **14**, **S11–15**.

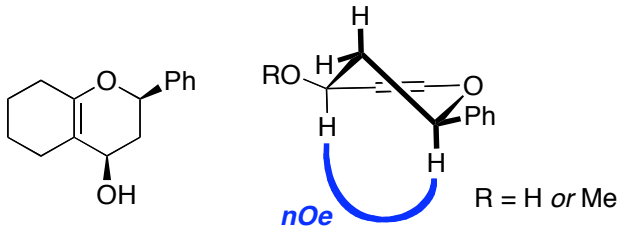
1. DIASTEREOSELECTIVE REDUCTION OF DIHYDROPYRONES (9, S3–6)

General protocol for low-temperature Luche reduction[11]

In a roundbottom flask, the dihydropyrone **9** or **S3–6** was dissolved in CH_2Cl_2 (4.60 mL/mmol, 0.22 M solution) and cooled to –78 °C. A freshly prepared solution of anhyd cerium (III) chloride in MeOH (*ca*. 0.40 M, 3.0 equiv) was added slowly and the mixture was stirred at –78 °C for 20 min. Neat $NaBH_4$ (1.50 equiv) was added in one portion and the mixture was stirred at –78 °C until TLC analysis of a reaction aliquot (add to a solution of one drop of 1,3-propanediol in EtOAc, wash with satd aq NH_4Cl) indicated completion of the reaction (usually 2 h). 1,3-Propanediol (1.5–2.0 equiv) was added and the mixture was allowed to warm to rt and stirred for an additional 15 min. After recooling to –78 °C, satd aq NH_4Cl was added and the mixture was warmed to rt. Water (*ca*. 40 mL/mmol) and EtOAc (*ca*. 40 mL/mmol) were added and the mixture was shaken thoroughly in a separatory funnel. The layers were separated and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to afford the crude alcohol **11** or **S7–10**, which was dried under high vacuum and used in the next reaction without further purification.

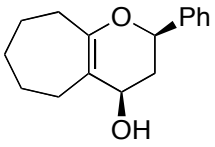
NOTE: The reaction proved very sensitive to the quality of reagents, and the use of freshly prepared $CeCl_3$ solution and a newly opened bottle of $NaBH_4$ is strongly recommended. Workup with 1,3-propanediol serves to break up boron–oxygen aggregates that may hinder reaction completion and/or are sensitive to reoxidation during workup.

[11] For diastereoselective Luche reductions at low temperatures, see: (a) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 1609.



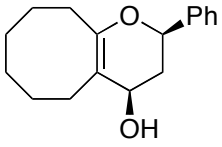
***cis*-2-Phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-ol (11a).** Synthesized from dihydropyrone **9a** (627 mg, 2.74 mmol). Crude **11a** was obtained as a white solid (635 mg, quant, ≥98:2 dr).

TLC: R_f 0.21 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 3324 (m, br, O–H st), 2927 (s, C–H st), 2857 (m, C–H st), 2841 (m, C–H st), 1681 (m, C=C st), 1496 (w), 1449 (w), 1367 (w), 1340 (w), 1310 (w), 1271 (w), 1226 (m), 1149 (s, C–O/C–OH st), 1068 (m), 1048 (m), 1024 (m), 966 (w), 895 (w) 879 (w). **^{1}H-NMR** (500 MHz): δ 7.38–7.28 (m, 5H), 4.95 (dd, 1H, *J* = 10.9, 2.2), 4.35–4.33 (m, 1H), 2.41 (ddd, 1H, *J* = 13.4, 6.7, 2.2), 2.28–2.26 (m, 1H), 2.12–2.04 (m, 3H), 1.97–1.93 (m, 1H), 1.78–1.72 (m, 2H), 1.67–1.60 (m, 1H), 1.57–1.52 (m, 1H), 1.22 (d, 1H, *J* = 5.3). **^{13}C-NMR** (125 MHz): δ 149.4, 141.0, 128.5, 127.7, 126.0, 108.0, 75.8, 66.7, 40.4, 27.3, 24.1, 22.8, 22.7. **ESI-MS** *m/z* (rel int): (pos) 253.1 ([M+Na]$^+$, 87), 213.1 ([M–H_2O+H]$^+$; (neg) 459.4 ([2M–H]$^-$, 53), 229.0 ([M–H]$^-$, 15).



***cis*-2-Phenyl-2,3,4,5,6,7,8,9-octahydrocyclohepta[*b*]pyran-4-ol (11b).** Synthesized from dihydropyrone **9b** (46.6 mg, 0.190 mmol). Crude **11b** was obtained as a white solid (50.0 mg, quant, ≥98:2 dr).

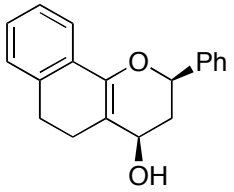
TLC: R_f 0.36 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.23–7.19 (m, 4H), 7.16–7.12 (m, 1H), 4.79 (dd, 1H, *J* = 10.5, 2.5), 4.19 (q, 1H, *J* = 7.2), 2.22 (ddd, 1H, *J* = 13.5, 7.2, 2.5), 2.17–2.14 (m, 2H), 2.12–1.99 (m, 2H), 1.93–1.87 (m, 1H), 1.64–1.42 (m, 5H), 1.37–1.31 (m, 1H), 0.93 (d, 1H, *J* = 8.5). **^{13}C-NMR** (125 MHz): δ 155.3, 141.0, 128.5, 127.7, 126.0, 112.3, 75.8, 67.5, 40.0, 33.2, 31.8, 27.9, 27.3, 25.5. **ESI-MS** *m/z* (rel int): (pos) 511.3 ([2M+Na]$^+$, 16), 493.3 ([2M–H_2O+Na]$^+$, 24), 267.1 ([M+Na]$^+$, 86), 227.1 ([M–H_2O+H]$^+$, 100); (neg) 487.3 ([2M–H]$^-$, 100), 243.0 ([M–H]$^-$, 11).



***cis*-2-Phenyl-3,4,5,6,7,8,9,10-octahydro-2*H*-cycloocta[*b*]pyran-4-ol (11c).** Synthesized from dihydropyrone **9c** (51.0 mg, 0.20 mmol). Crude **11c** was obtained as a white solid (43.7 mg, 85%, ≥98:2 dr).

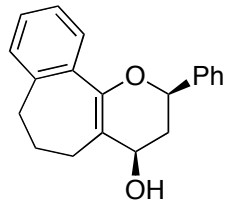
TLC: R_f 0.34 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.39–7.35 (m, 4H), 7.31–7.28 (m, 1H), 4.95 (dd, 1H, *J* = 10.6, 2.3), 4.40 (q, 1H, *J* = 7.6), 2.42–2.34 (m, 3H), 2.21–2.15 (m, 2H),

2.12–2.04 (m, 1H), 1.72–1.46 (m, 8H), 1.11 (d, 1H, J = 8.3). **^{13}C-NMR** (125 MHz): δ 152.3, 141.2, 128.6, 127.9, 126.0, 109.7, 76.2, 65.5, 40.5, 30.3, 30.1, 28.9, 26.9, 26.6, 25.3. **ESI-MS** m/z (rel int): (pos) 281.2 ([M+Na]$^+$, 100), 521.3 ([2M–H_2O+Na]$^+$, 13).



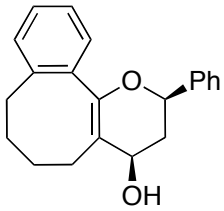
***cis*-2-Phenyl-3,4,5,6-tetrahydro-2*H*-benzo[*h*]chromen-4-ol (11d).** Synthesized from dihydropyrone **9d** (970 mg, 3.51 mmol). Crude **11d** was obtained as a white solid (977 mg, quant, ≥98:2 dr).

TLC: R_f 0.27 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.59–7.57 (m, 1H), 7.46 (d, 2H, J = 7.3), 7.40 (t, 2H, J = 7.3), 7.33 (t, 1H, J = 7.3), 7.22–7.18 (m, 2H), 7.16–7.13 (m, 1H), 5.20 (dd, 1H, J = 10.5, 2.2), 4.57 (q, 1H, J = 8.1), 2.91–2.80 (m, 2H), 2.64–2.53 (m, 2H), 2.34 (dt, 1H, J = 15.8, 7.9), 2.19 (ddd, 1H, J = 13.5, 10.5, 8.1), 1.27 (d, 1H, J = 8.1). **^{13}C-NMR** (125 MHz): δ 146.3, 141.0, 136.7, 131.1, 128.7, 128.0, 127.9, 127.2, 126.4, 126.0, 122.0, 110.8, 76.1, 66.3, 40.3, 28.3, 22.7. **ESI-MS** m/z (rel int): (pos) 301.2 ([M+Na]$^+$, 100), 283.2 ([M–H_2O+Na]$^+$, 76), 261.3 ([M–H_2O+H]$^+$, 64).



[8.9]-Benzo-*cis*-2-phenyl-2,3,4,5,6,7-hexahydrocyclohepta[*b*]pyran-4-ol (11e). Synthesized from dihydropyrone **9e** (210 mg, 0.72 mmol). Crude **11e** was obtained as a white solid (220 mg, quant, ≥98:2 dr).

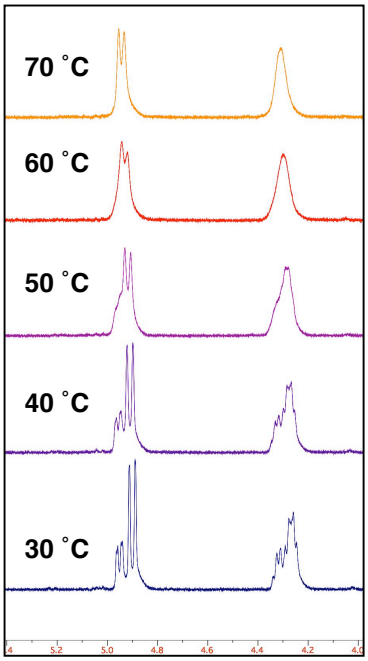
TLC: R_f 0.33 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.54–7.52 (m, 1H), 7.45 (d, 2H, J = 7.6), 7.38 (t, 2H, J = 7.6), 7.33–7.21 (m, 7H), 5.20 (dd, 1H, J = 10.7, 1.9), 4.60 (q, 1H, J = 7.8), 2.76–2.72 (m, 1H), 2.68–2.63 (m, 1H), 2.54 (ddd, 1H, J = 13.5, 6.7, 1.9), 2.26–2.10 (m, 4H), 1.91–1.87 (m, 1H). **^{13}C-NMR** (125 MHz): δ 148.5, 141.4, 140.9, 136.1, 129.1, 128.7, 128.5, 128.4, 128.0, 127.1, 126.2, 126.2, 113.9, 76.8, 67.9, 35.5, 32.7, 24.8. **ESI-MS** m/z (rel int): (pos) 607.5 ([2M+Na]$^+$, 5), 315.3 ([M+Na]$^+$, 46).



[9.10]-Benzo-*cis*-2-Phenyl-3,4,5,6,7,8,-hexahydro-2*H*-cycloocta[*b*]pyran-4-ol (11f). Synthesized from dihydropyrone **9f** (100 mg, 0.330 mmol). Crude **11f** was obtained as a white solid (95.0 mg, 94%, ≥98:2 dr, see below).

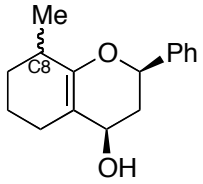
The ^{1}H- and ^{13}C-NMR spectra of **11f** exhibit two sets of signals at rt (variable ratio in crude product), presumed to arise from atropisomers that do not interconvert rapidly on the NMR timescale at rt. The signals converge to a single set of peaks at higher temperatures in NMR experiments in toluene-d_8, and the diastereoselectivity is, thus, assumed to be ≥98:2 dr.

Both sets of ^{1}H- and ^{13}C-NMR signals at 25 °C are reported below as assignment to individual atropisomers was not possible for all peaks. ^{1}H-NMR integrals are normalized using the benzylic proton of the minor isomer as standard for 1H and are reported to one decimal place.



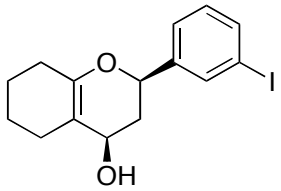
^{1}H-NMR signals of 11f in toluene-d_8 at various temperatures.

TLC: R_f 0.16 (10:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.56 (d, 1.1H, J = 7.2), 7.49 (d, 2.1H, J = 7.6), 7.47–7.34 (m, 9.7H), 7.31–7.22 (m, 9.6H), 7.17 (t, 1.3H, J = 7.3), 5.31 (dd, 1.0H, J = 7.7, 3.6), 5.20 (dd, 1.4H, J = 11.5, 1.6), 4.65 (q, 1.4H, J = 8.2), 4.53 (q, 1.0H, J = 7.5), 2.87–2.77 (m, 3.9H), 2.65 (t, 1.1H, J = 12.2), 2.56–2.39 (m, 4.6H), 2.31 (dd, 1.4H, J = 13.7, 8.2), 2.27–2.20 (m, 1.4H), 2.10–2.05 (m, 2.4H), 1.83–1.78 (m, 1.5H), 1.75–1.57 (m, 4.1H), 1.52–1.29 (m, 5.9H), 1.09 (d, 0.9H, J = 9.3). **^{13}C-NMR** (150 MHz, DMSO-d_6): δ 147.1, 146.8, 142.2, 141.7, 141.6, 141.3, 135.3, 134.3, 129.2, 129.1, 128.6, 128.5, 128.3, 127.6, 127.5, 127.2, 126.1, 125.9, 125.4, 125.1, 115.3, 114.7, 77.1, 76.0, 67.8, 62.4, 40.6, 40.4, 33.0, 32.4, 29.2, 29.0, 28.5, 25.3, 24.5, 23.6. **ESI-MS** *m/z* (rel int): (pos) 329.4 ($[M+Na]^+$, 100), 289.3 ($[M–H_2O]^+$, 57), 305.4 ($[M–H]^-$, 20).



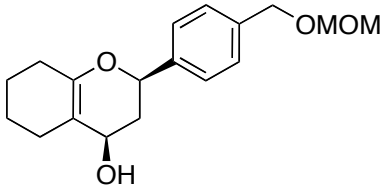
(2*R*,4R*,8RS*)-8-Methyl-2-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-ol (S7). Synthesized from dihydropyrone **S3** (50 mg, 0.21 mmol). Crude **S7** was obtained as a white solid (50 mg, quant., 1.3:1.0 dr at C8).

TLC: R_f 0.21 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.38–7.34 (m, 4H-major, 4H-minor), 7.31–7.27 (m, 1H-major, 1H-minor), 4.91 (ddd, 1H-major, 1H-minor, *J* = 11.2, 5.7, 2.3), 4.37 (dq, 1H-major, 1H-minor, *J* = 23.0, 7.6), 2.41 (dddd, 1H-major, 1H-minor, *J* = 18.2, 13.4, 6.8, 2.2), 2.35–2.23 (m, 2H-major, 2H-minor), 2.06 (ddd, 1H-major, *J* = 13.3, 10.9, 8.6), 1.98–1.91 (m, 1H-major, 2H-minor), 1.87–1.72 (m, 2H-major, 1H-minor), 1.69–1.60 (m, 1H-major, 1H-minor), 1.53–1.46 (m, 1H-major, 1H-minor), 1.34 (dddd, 1H-minor, *J* = 12.9, 11.0, 8.4, 2.6), 1.27 (d, 1H-major, *J* = 7.6), 1.22 (d, 1H-minor, *J* = 7.8), 1.15 (d, 3H-major, *J* = 6.8), 1.09 (d, 3H-minor, J = 7.0). **^{13}C-NMR** (125 MHz): δ 153.1, 152.9, 141.6, 141.2, 129.0, 128.5, 127.7, 127.6, 126.0, 125.8, 107.7, 107.6, 75.7, 75.6, 67.2, 66.9, 41.1, 40.3, 32.5, 32.1, 31.2, 30.7, 24.9, 24.7, 21.3, 19.2, 18.8, 18.7. **ESI-MS** *m/z* (rel int): (pos) 227.1 ([M–H_2O+H]$^+$, 100), 511.5 ([2M+Na]$^+$, 10).



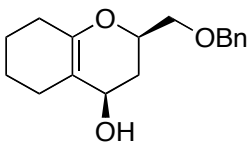
***cis*-2-(3-Iodophenyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-ol (S8).** Synthesized from dihydropyrone **S4** (425 mg, 1.20 mmol). Crude **S8** was obtained as a white solid (419 mg, 99%, ≥98:2 dr).

TLC: R_f 0.32 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.73 (s, 1H), 7.63 (d, 1H, *J* = 7.8), 7.32 (d, 1H, *J* = 7.8), 7.09 (t, 1H, *J* = 7.8), 4.87 (dd, 1H, *J* = 11.2, 2.0), 4.36 (q, 1H, *J* = 7.4), 2.39 (ddd, 1H, *J* = 13.3, 6.7, 2.1), 2.30–2.24 (m, 1H), 2.15–1.92 (m, 4H), 1.78–1.72 (m, 2H), 1.65–1.59 (m, 1H), 1.56–1.51 (m, 1H), 1.23 (d, 1H, *J* = 7.4). **^{13}C-NMR** (125 MHz): δ 149.4, 143.6, 137.0, 135.2, 130.4, 125.4, 108.4, 94.6, 75.2, 66.7, 40.7, 27.4, 24.2, 22.9, 22.8(5). **ESI-MS** *m/z* (rel int): (pos) 395.2 ([M+K]$^+$, 80), 379.2 ([M+Na]$^+$, 47).



***cis*-2-(4-((*tert*-Butyldiphenylsilyloxy)methyl)phenyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-ol (S9).** Synthesized from dihydropyrone **S5** (104 mg, 0.344 mmol). Crude **S9** was obtained as a white solid (102 mg, 98%, ≥98:2 dr).

TLC: R_f 0.41 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.40–7.33 (m, 4H), 4.95 (dd, 1H, *J* = 10.9, 2.3), 4.73–4.68 (m, 2H), 4.63–4.57 (m, 2H), 4.34 (t, 1H, *J* = 7.1), 3.41 (s, 3H), 2.39 (ddd, 1H, *J* = 13.4, 7.1, 2.3), 2.30–2.24 (m, 1H), 2.15–2.03 (m, 3H), 1.97–1.92 (m, 1H), 1.77–1.70 (m, 2H), 1.67–1.59 (m, 1H), 1.57–1.49 (m, 1H). **^{13}C-NMR** (125 MHz): δ 149.5, 140.7, 137.6, 128.2, 126.3, 108.3, 95.8, 75.7, 69.0, 66.8, 55.5, 40.5, 27.5, 24.3, 22.9, 22.9. **ESI-MS** *m/z* (rel int): (neg) 607.2 ([2M–H]$^-$, 100); (pos) 327.0 ([M+Na]$^+$, 100).



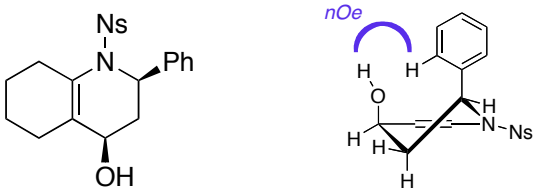
***cis*-2-(Benzyloxymethyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-ol (S10).** Synthesized from dihydropyrone **S6** (45.0 mg, 0.165 mmol). Crude **S10** was obtained as colorless oil (45.0 mg, quant, 90:10 dr).

TLC: R_f 0.18 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.36–7.26 (m, 5H), 4.60–4.56 (m, 2H), 4.13 (m, 2H), 3.64 (dd, 1H, *J* = 10.4, 5.5), 3.57 (dd, 1H, *J* = 10.4, 4.2), 2.28–2.03 (m, 4H), 1.90–1.86 (m, 1H), 1.79 (ddd, 1H, *J* = 13.5, 9.1, 7.5), 1.71–1.50 (m, 4H). **^{13}C-NMR** (125 MHz): δ 148.7, 138.1, 128.4, 127.7 (presumably 2 carbons overlapping), 107.6, 73.5, 72.7, 72.4, 65.2, 35.0, 27.4, 24.5, 22.9, 22.8. **ESI-MS** *m/z* (rel int): (pos) 297.0 ([M+Na]$^+$, 100), 279.1 ([M–H_2O+Na]$^+$, 25), 257.0 ([M–H_2O+H]$^+$, 45); (neg) 273.3 ([M–H]$^-$, 65).

2. DIASTEREOSELECTIVE REDUCTION OF DIHYDROPYRIDONES (10)

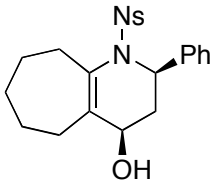
General protocol for Super-Hydride reduction

In a roundbottom flask, dihydropyridone **10** was dissolved in toluene (0.20 M solution) and cooled to –78 ºC. A solution of $LiEt_3BH$ (1.0 M in THF, 1.50 equiv) was added dropwise and the resulting solution was allowed to stir at –78 ºC until the reaction was complete as judged by TLC analysis (*ca.* 40 min). The reaction was quenched with satd aq NH_4Cl at –78 ºC, allowed to warm to rt, and extracted with EtOAc (3×). The combined organic extracts were concentrated by rotary evaporation. The crude product was dissolved in THF (1.0 mL/80 mg) at rt and an equal volume of 1 N NaOH was added to the solution. The mixture was stirred at rt for 10 min, after which the solution was diluted with satd aq NH_4Cl and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated by rotary evaporation to afford crude alcohol **12**, which was used in the next reaction without further purification.



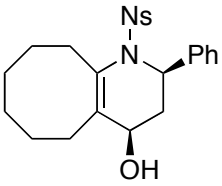
***cis*-1-(2-Nitrophenylsulfonyl)-2-phenyl-1,2,3,4,5,6,7,8-octahydroquinolin-4-ol (12a).** Synthesized from dihydropyridone **10a** (80.0 mg, 0.194 mmol). Crude **12a** was obtained as a light yellow foam (71.5 mg, 89%, ≥98:2 dr).

TLC: R_f 0.38 (2:1 EtOAc/hexanes). **IR** (NaCl, film): 3442 (s, br, O–H st), 3092 (w), 3064 (w), 3029 (w), 2934 (m, C–H st), 2856 (m, C–H st), 1662 (w), 1544 (vs, N=O st), 1496 (w), 1449 (m), 1439 (m), 1372 (s, S=O st), 1170 (s, S=O st), 1090 (w), 1053 (m), 985 (w), 952 (w), 909 (w), 851 (w), 739 (m), 729 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 8.02 (dd, 1H, J = 7.7, 1.6), 7.72–7.63 (m, 3H), 7.35–7.26 (m, 5H), 5.59 (t, 1H, J = 3.8), 3.67–3.64 (m, 1H), 2.86–2.80 (m, 1H), 2.52 (ddd, 1H, J = 14.8, 3.8, 2.5), 2.41–2.37 (m, 1H), 2.32–2.21 (m, 2H), 2.00–1.96 (m, 1H), 1.85–1.80 (m, 1H), 1.66 (td, 2H, J = 8.2, 4.1), 1.57–1.53 (m, 1H), 0.69 (d, 1H, J = 10.2). **^{13}C-NMR** (125 MHz): δ 148.0, 139.3, 133.8, 133.8, 131.8, 130.8, 130.3, 128.8, 128.0, 127.9, 127.3, 126.3, 124.5, 65.1, 56.0, 37.6, 30.2, 26.7, 23.6, 22.0. **ESI-MS** *m/z* (rel int): (pos) 297 ($[M+H]^+$, 100), 319 ($[M+Na]^+$, 20); (neg) 295 ($[M–H]^-$, 100).



***cis*-1-(2-Nitrophenylsulfonyl)-2-phenyl-1,2,3,4,5,6,7,8,9-nonahydroquinolin-4-ol (12b).** Synthesized from dihydropyridone **10b** (118 mg, 0.277 mmol). Crude **12b** was obtained as a light yellow foam (104 mg, 88%, ≥98:2 dr).

TLC: R_f 0.40 (2:1 EtOAc/hexanes). **^{1}H-NMR** (500 MHz): δ 8.05 (dd, 1H, J = 7.8, 1.4), 7.74–7.65 (m, 3H), 7.38–7.31 (m, 4H), 7.25–7.22 (m, 1H), 5.51 (dd, 1H, J = 5.3, 3.0), 3.71 (dd, 1H, J = 10.3, 5.8), 2.76–2.56 (m, 3H), 2.38 (ddd, 1H, J = 15.1, 8.0, 1.8), 2.21–2.10 (m, 2H), 1.90–1.83 (m, 1H), 1.78–1.69 (m, 1H), 1.68–1.56 (m, 2H), 1.51–1.42 (m, 2H), 0.65 (d, 1H, J = 10.3). **^{13}C-NMR** (125 MHz): δ 148.1, 138.7, 135.2, 133.9, 133.8, 133.7, 131.7, 130.9, 128.7, 127.3, 126.5, 124.5, 65.5, 55.0, 36.7, 34.7, 32.0, 30.5, 26.5, 25.4. **ESI-MS** *m/z* (rel int): (pos) 411 ($[M–H_2O+H]^+$, 25), 450 ($[M+Na]^+$, 100).



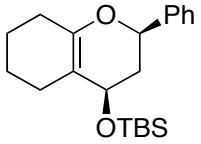
***cis*-1-(2-Nitrophenylsulfonyl)-2-phenyl-1,2,3,4,5,6,7,8-octahydroquinolin-4-ol (12c).** Synthesized from dihydropyridone **10c** (95.0 mg, 0.216 mmol). Crude **12c** was obtained as a light yellow foam (83.2 mg, 87%, ≥98:2 dr).

TLC: R_f 0.43 (2:1 EtOAc/hexanes). **^{1}H-NMR** (500 MHz): δ 8.00 (dd, 1H, *J* = 7.8, 1.3), 7.73–7.63 (m, 3H), 7.41 (d, 2H, *J* = 7.9), 7.32 (t, 2H, *J* = 7.7), 7.24 (t, 1H, *J* = 6.6), 5.56 (t, 1H, *J* = 5.4), 3.78–3.74 (m, 1H), 2.92–2.86 (m, 1H), 2.59 (ddt, 1H, *J* = 12.2, 8.3, 4.0), 2.49 (dt, 1H, *J* = 14.4, 4.4), 2.43–2.33 (m, 2H), 2.24 (dddd, 1H, *J* = 13.6, 8.2, 4.7, 3.5), 1.74–1.61 (m, 3H), 1.52–1.36 (m, 4H), 1.21–1.15 (m, 1H), 1.00 (d, 1H, *J* = 8.9). **^{13}C-NMR** (125 MHz): δ 148.1, 139.5, 133.9, 132.5, 132.2, 131.5, 130.8, 128.6, 128.1, 127.4, 126.8, 124.3, 65.1, 55.8, 38.0, 30.5, 30.1, 29.0, 28.0, 26.2, 26.1. **ESI-MS** *m/z* (rel int): (pos) 425 ($[M–H_2O+H]^+$, 10), 465 ($[M+Na]^+$, 100).

3. TBS PROTECTION OF ALCOHOLS (13, 14, S11–15)

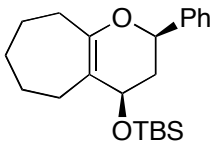
General protocol for TBS protection

The crude alcohol **11**, **12**, or **S7–10** was placed in a roundbottom flask. In a separate flask, *tert*-butyldimethylchlorosilane (TBSCl, 1.2 equiv) and imidazole (2.5 equiv) were dissolved in DMF (*ca*. 3.00 mL/mmol alcohol). The resulting solution was added to the alcohol flask and the mixture was stirred at 50 ºC (unless otherwise noted) until full conversion as judged by TLC (aliquots quenched with satd aq $NaHCO_3$, extracted with EtOAc). The mixture was cooled to rt and satd aq $NaHCO_3$ was added with stirring. After stirring for at least 10 min at rt, EtOAc was added, the layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (hexanes/EtOAc, 0.5 vol% Et_3N) afforded the TBS-protected alcohol **13**, **14**, or **S11–15**.



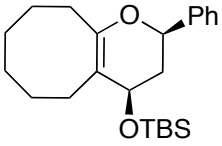
***tert*-Butyldimethyl-(*cis*-2-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-yloxy) silane (13a).** Synthesized from crude alcohol **11a** (633 mg, 2.75 mmol) and TBSCl (497 mg, 3.30 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **13a** as a colorless solid (875 mg, 92%).

TLC: R_f 0.73 (10:1 hexanes/EtOAc). **mp** 61.1–63.4 °C. **IR** (NaCl, film): 2950 (s, C–H st), 2929 (s, C–H st), 2888 (m, C–H st), 2856 (s, C–H st), 1684 (m, C=C st), 1472 (w), 1380 (m), 1254 (s, Si-Me δ sy), 1228 (m), 1176 (s), 1087 (vs, Si–O st), 1065 (vs, Si–O st), 1008 (m), 971 (w), 904 (m), 835 (vs, Si–C st), 774 (s, Si–C st), 759 (m), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.35 (m, 4H), 7.29–7.26 (m, 1H), 4.84 (dd, 1H, *J* = 12.3, 1.4), 4.48–4.45 (m, 1H), 2.29–2.15 (m, 2H), 2.11–1.97 (m, 3H), 1.85–1.79 (m, 1H), 1.76–1.68 (m, 2H), 1.68–1.43 (m, 2H), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H). **^{13}C-NMR** (125 MHz): δ 149.2, 141.6, 128.7, 128.0, 126.4, 108.7, 76.5, 67.8, 41.5, 27.6, 26.0, 24.6, 23.0, 22.9, 18.4, –4.1, –4.6. **ESI-MS** *m/z* (rel int): (pos) 467.0 ($[M+Na]^+$, 100).



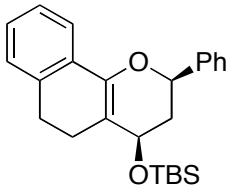
***tert*-Butyldimethyl(*cis*-2-phenyl-2,3,4,5,6,7,8,9-octahydrocyclohepta[*b*]pyran-4-yloxy)-silane (13b).** Synthesized from crude alcohol **11b** (341 mg, 1.40 mmol) and TBSCl (253 mg, 1.68 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **13b** as a colorless oil (414 mg, 81%).

TLC: R_f 0.82 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2951 (s, C–H st), 2926 (s, C–H st), 2854 (s, C–H st), 1676 (m, C=C st), 1472 (w), 1446 (w), 1379 (w), 1361 (w), 1247 (s, Si-Me δ sy), 1172 (s, C–O/Si–O st), 1151 (s, C–O/Si–O st), 1154 (m, C–O/Si–O st), 1100 (s, C–O/Si–O st), 987 (m), 965 (m), 938 (m), 899 (m), 858 (m), 836 (vs, Si–C st), 774 (s, Si–C st), 757 (m), 697 (m). **^{1}H-NMR** (500 MHz): δ 7.42–7.37 (m, 4H), 7.32 (m, 1H), 4.84 (dd, 1H, J = 12.4, 1.9), 4.52 (t, 1H, J = 8.8), 2.31–2.16 (m, 4H), 2.09 (ddd, 1H, J = 15.0, 8.1, 2.7), 2.01 (ddd, 1H, J = 13.1, 12.4, 8.8), 1.82–1.53 (m, 6H), 0.91 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H). **^{13}C-NMR** (125 MHz): δ 155.0, 141.6, 128.6, 127.9, 126.4, 112.8, 76.7, 68.3, 41.1, 33.3, 32.0, 27.6, 27.2, 26.0, 25.7, 18.3, –3.9, –4.7. **ESI-MS** *m/z* (rel int): (pos) 381.2 ($[M+Na]^+$, 100), 227 ($[M–TBSOH+H]^+$, 70).



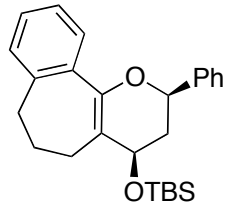
***tert*-Butyldimethyl(*cis*-2-phenyl-3,4,5,6,7,8,9,10-octahydro-2*H*-cycloocta[*b*]pyran-4-yloxy)-silane (13c).** Synthesized from crude alcohol **11c** (225 mg, 0.870 mmol) and TBSCl (158 mg, 1.00 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **13c** as a colorless solid (298 mg, 92%).

TLC: R_f 0.83 (10:1 hexanes/EtOAc). **mp** = 39.1–41.2 °C. **IR** (NaCl, film): 2952 (s, C–H st), 2927 (vs, C–H st), 2854 (s, C–H st), 1673 (m, C=C st), 1496 (w), 1463 (m), 1362 (m), 1254 (s, Si-Me δ sy), 1181 (m), 1167 (m, C–O/Si–O st), 1128 (m, C–O/Si–O st), 1074 (vs, br, C–O/Si–O st), 953 (m), 930 (m), 886 (m), 836 (s, Si–C st), 782 (m), 755 (m), 697 (m). **^{1}H-NMR** (500 MHz): δ 7.40–7.28 (m, 5H), 4.84 (dd, 1H, J = 12.3, 1.8), 4.55 (dd, 1H, J = 9.5, 6.9), 2.39–2.32 (m, 2H), 2.23–2.12 (m, 3H), 2.09–2.02 (m, 1H), 1.71–1.41 (m, 8H), 0.90 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H). **^{13}C-NMR** (125 MHz): δ 152.0, 141.8, 128.6, 127.9, 126.3, 109.8, 76.8, 66.2, 41.4, 30.5, 29.8, 29.0, 27.1, 26.7, 26.0, 24.7, 18.3, –4.2, –4.7. **ESI-MS** *m/z* (rel int): (pos) 395.3 ($[M+Na]^+$, 100), 241.1 ($[M–TBSOH+H]^+$, 47).



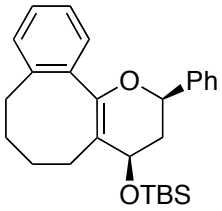
***tert*-Butyldimethyl(*cis*-2-phenyl-3,4,5,6-tetrahydro-2*H*-benzo[*h*]chromen-4-yloxy)silane (13d).** Synthesized from crude alcohol **11d** (975 mg, 3.51 mmol) and TBSCl (633 mg, 4.20 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **13d** as a colorless solid (1.18 g, 86%).

TLC: R_f 0.74 (10:1 hexanes/EtOAc). **mp** = 107.9–110.9 °C. **IR** (NaCl, film): 2954 (s, C–H st), 2928 (s, C–H st), 2887 (m, C–H st), 2856 (s, C–H st), 1656 (m, C=C st), 1493 (w), 1470 (w), 1457 (w), 1360 (m), 1355 (m), 1290 (m), 1254 (m, Si-Me δ sy), 1150 (m), 1095 (vs, C–O/Si–O st), 1067 (s, C–O/Si–O st), 958 (m), 897 (m), 836 (vs, Si–C st), 763 (m, Si–C st), 733 (w), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.52–7.47 (m, 3H), 7.41 (t, 2H, *J* = 7.4), 7.34 (t, 1H, *J* = 7.4), 7.16–7.10 (m, 3H), 5.06 (dd, 1H, *J* = 12.5, 1.6), 4.72 (t, 1H, *J* = 8.1), 2.83 (t, 2H, *J* = 8.0), 2.56 (dt, 1H, *J* = 16.0, 8.0), 2.32 (ddd, 1H, *J* = 13.0, 6.8, 1.6), 2.23 (dt, 1H, *J* = 16.0, 8.0), 2.13 (td, 1H, *J* = 12.5, 9.5), 0.91 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H). **^{13}C-NMR** (125 MHz): δ 146.1, 141.6, 136.4, 131.5, 128.6, 128.0, 127.5, 127.0, 126.3, 121.8, 111.5, 76.7, 67.2, 41.2, 28.2, 26.0, 22.8, 18.3, –4.0, –4.6. **ESI-MS** *m/z* (rel int): (pos) 415.2 ([M+Na]$^+$, 100), 261.0 ([M–TBSOH+H]$^+$, 83).



***tert*-Butyldimethyl([8.9]-benzo-*cis*-2-phenyl-2,3,4,5,6,7-hexahydrocyclohepta[*b*]pyran-4-yloxy)silane (13e).** Synthesized from crude alcohol **11e** (200 mg, 0.680 mmol) and TBSCl (124 mg, 0.820 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **13e** as a colorless oil that solidified upon storage at –20 °C (217 mg, 77%).

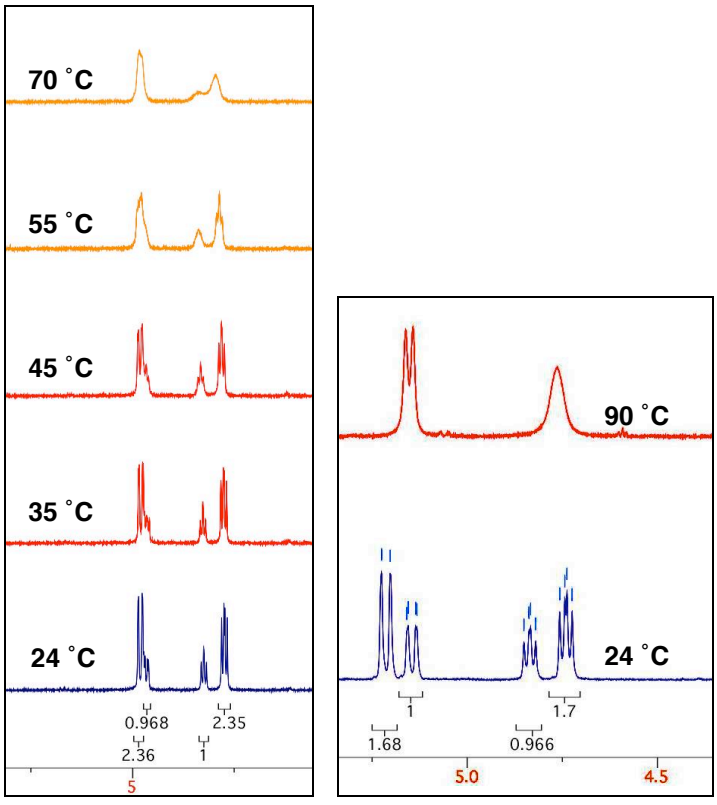
TLC: R_f 0.76 (10:1 hexanes/EtOAc). **mp** = 113.7–116.5 °C. **IR** (NaCl, film): 2951 (m, C–H st), 2929 (m, C–H st), 2855 (m, C–H st), 1651 (w, C=C st), 1455 (w), 1361 (m), 1348 (m), 1283 (m), 1251 (m, Si-Me δ sy), 1134 (m), 1090 (m, C–O/Si–O st), 1061 (vs, C–O/Si–O st), 1009 (w), 978 (w), 931 (m), 897 (m), 836 (vs, Si–C st), 768 (s, Si–C st), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.49–7.45 (m, 3H), 7.38 (t, 2H, *J* = 7.4), 7.32 (t, 1H, *J* = 7.4), 7.24–7.21 (m, 3H), 5.11 (dd, 1H, *J* = 12.1, 1.6), 4.70 (dd, 1H, *J* = 9.4, 7.0), 2.81 (ddd, 1H, *J* = 12.9, 11.2, 7.8), 2.62 (ddd, 1H, *J* = 12.9, 6.5, 2.6), 2.32 (ddd, 1H, *J* = 13.1, 7.0, 1.6), 2.28–2.17 (m, 2H), 2.12–2.02 (m, 2H), 1.77 (td, 1H, *J* = 12.6, 6.8), 0.94 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H). **^{13}C-NMR** (125 MHz): δ 148.5, 141.6, 141.4, 136.5, 129.0, 128.6, 128.0, 128.0, 127.1, 126.4, 126.0, 114.5, 77.2, 68.5, 41.2, 35.3, 32.7, 26.0, 24.8, 18.2, –3.9, –4.6. **ESI-MS** *m/z* (rel int): (pos) 429.4 ([M+Na]$^+$, 45), 297.3 ([M–TBSOH+Na]$^+$, 100), 275.3 ([M–TBSOH+H]$^+$, 30).



***tert*-Butyldimethyl([9.10]-benzo-*cis*-2-phenyl-3,4,5,6,7,8,-hexahydro-2*H*-cycloocta[*b*]pyran-4-yloxy)silane (13f).** Synthesized from crude alcohol **11f** (49.5 mg, 0.160 mmol) and TBSCl (29.3 mg, 0.194 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **13f** as a colorless solid (53.7 mg, 80%).

The ^{1}H- and ^{13}C-NMR spectra of **13f** exhibit two sets of signals at rt (variable ratio in crude product), presumed to arise from atropisomers that do not interconvert rapidly on the NMR timescale at rt. The signals converge to a single set of peaks at higher temperatures in NMR experiments in toluene-d_8.

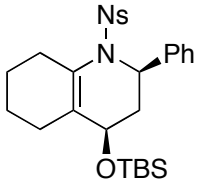
Both sets of ^{1}H- and ^{13}C-NMR signals at 25 °C are reported below as assignment to individual atropisomers was not possible for all peaks. ^{1}H-NMR integrals are normalized using the benzylic proton of the minor isomer as standard for 1H and are reported to one decimal place.



^{1}H-NMR signals of 13f in toluene-d_8 (left) and DMSO-d_6 (right) at various temperatures.

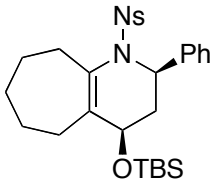
TLC: R_f 0.16 (10:1 hexanes/EtOAc). **mp** = 104.1–106.3 °C. **IR** (NaCl, film): 3063 (w), 3030 (w), 2953 (m, C–H st), 2928 (s, C–H st), 2856 (m, C–H st), 1663 (w, C=C st), 1452 (w), 1362

(w), 1281 (w), 1256 (m, Si-Me δ sy), 1177 (w), 1149 (w), 1126 (m), 1093 (m), 1069 (s), 1031 (w), 1007 (w), 953 (m), 900 (m), 838 (s, Si–C st), 761 (m), 699 (m). **^{1}H-NMR** (500 MHz, DMSO-d_6): δ 7.46–7.13 (m, 25.1H), 5.21 (d, 1.7H, J = 11.7), 5.15 (dd, 1.0H, J = 11.5, 1.9), 4.84 (dd, 1.0H, J = 8.8, 6.7), 4.74 (dd, 1.7H, J = 9.6, 6.8), 2.79 (m, 2.7H), 2.66–2.59 (m, 2.7H), 2.45 (dd, 1.1H, J = 13.8, 8.2), 2.28 (m, 2.8H), 2.17 (dd, 1.8H, J = 13.6, 7.6), 2.08–1.98 (m, 5.6H), 1.71–1.59 (m, 4.4H), 1.41–1.13 (m, 7.4H), 0.89 (s, 15.4H), 0.83 (s, 9.5H), 0.12 (s, 4.9H), 0.11 (s, 5.2H), 0.09 (s, 3.0H), 0.07 (s, 2.9H). **^{13}C-NMR** (125 MHz, DMSO-d_6): δ 147.8, 147.3, 142.1, 141.7, 141.4, 141.0, 135.1, 134.1, 129.3, 129.1, 128.8, 128.5, 128.4, 128.3, 128.3, 127.8, 127.6, 127.2, 126.2, 126.0, 125.4, 125.2, 114.0, 113.4, 76.9, 75.6, 69.6, 64.2, 40.7, 40.2, 32.9, 32.6, 29.1, 30.0, 28.3, 26.0, 25.8, 25.7, 24.4, 23.6, 17.7, –4.4, –4.5, –4.9, –5.1 (41 of 42 possible signals were observed). **ESI-MS** *m/z* (rel int): (pos) 443.1 ([M+Na]$^+$, 72), 289 ([M–TBSOH+H]$^+$, 100).



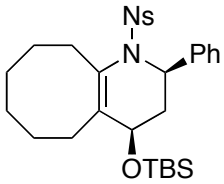
***cis*-4-(*tert*-Butyldimethylsilyloxy)-1-(2-nitrophenylsulfonyl)-2-phenyl-1,2,3,4,5,6,7,8-octahydroquinoline (14a).** Synthesized from crude alcohol **12a** (71.5 mg, 0.173 mmol) and TBSCl (58.2 mg, 0.386 mmol). Purification by silica flash chromatography (6:1 hexanes/EtOAc, 1 vol% Et_3N) afforded **14a** as white solid (81.0 mg, 89%).

TLC: R_f 0.29 (4:1 hexanes/EtOAc). **mp** = 122.4–125.5 ºC. **IR** (NaCl, film): 2932 (s, C–H st), 2886 (m, C–H st), 2857 (s, C–H st), 1546 (vs, N=O st), 1496 (w), 1471 (m), 1461 (m), 1449 (m), 1439 (m), 1373 (vs, N=O st), 1257 (m, Si–Me), 1221(w), 1203 (w), 1172 (s, Si–O), 1143 (s, S=O st), 1125 (s, Si–O), 1089 (s), 1066 (s), 1002 (w), 956 (m), 911 (s), 868 (s), 852 (s), 838 (s), 776 (s), 734 (s), 700 (m), 655 (m). **^{1}H-NMR** (500 MHz): δ 7.87 (dd, 1H, J = 7.9, 1.3), 7.68 (td, 1H, J = 7.7, 1.4), 7.61 (td, 1H, J = 7.7, 1.3), 7.57 (dd, 1H, J = 7.8, 1.3), 7.33–7.27 (m, 4H), 7.23–7.20 (m, 1H), 5.35 (t, 1H, J = 8.0), 3.56–3.50 (m, 1H), 2.78 (tdd, 1H, J = 11.5, 5.7, 2.8), 2.58 (ddd, 1H, J = 13.2, 8.0, 5.2), 2.38–2.28 (m, 1H), 2.11–2.07 (m, 1H), 1.99–1.92 (m, 2H), 1.82–1.76 (m, 1H), 1.72–1.52 (m, 3H), 0.73 (s, 9H), –0.16 (s, 3H), –0.21 (s, 3H). **^{13}C-NMR** (125 MHz): δ 147.9, 142.4, 138.3, 133.6, 132.3, 131.0, 130.8, 128.5, 128.3, 127.2, 126.8, 123.7, 66.2, 57.1, 42.9, 30.4, 25.7, 24.8, 23.3, 22.2, 18.0, –4.8, –5.3. **ESI-MS** *m/z* (rel int): (pos) 551 ([M+Na]$^+$, 100), 1080 ([2M+H+Na]$^+$, 20).



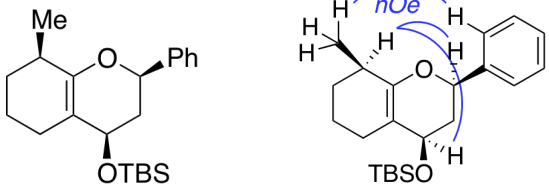
***cis*-4-(*tert*-Butyldimethylsilyloxy)-1-(2-nitrophenylsulfonyl)-2-phenyl-2,3,4,5,6,7,8,9-nonahydroquinoline (14b).** Synthesized from crude alcohol **12b** (104 mg, 0.243 mmol) and TBSCl (83.0 mg, 0.551 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 1 vol% Et_3N) afforded **14b** as light yellow solid (120 mg, 91%).

TLC: R_f 0.39 (4:1 hexanes/EtOAc). **mp** = 130.2–135.3 ºC. **IR** (NaCl, film): 2952 (m, C–H st), 2928 (s, C–H st), 2855 (m, C–H st), 1588 (w), 1546 (vs, N=O st), 1495 (w), 1471 (w), 1461 (w), 1449 (w), 1439 (w), 1372 (s, N=O st), 1257 (m, Si–Me), 1173 (m, S=O st), 1145 (w, Si–O), 1122 (m, Si–O), 1067 (m), 977 (w), 954 (w), 896 (w), 882 (w), 852 (m), 838 (m), 775 (m), 740 (w), 669 (w). **^{1}H-NMR** (500 MHz): δ 7.94 (dd, 1H, *J* = 7.9, 1.3), 7.69 (td, 1H, *J* = 7.7, 1.4), 7.63 (td, 1H, *J* = 7.7, 1.3), 7.58 (dd, 1H, *J* = 7.8, 1.3), 7.37 (d, 2H, *J* = 7.4), 7.31–7.28 (m, 2H), 7.24–7.21 (m, 1H), 5.33 (t, 1H, *J* = 7.8), 3.47 (t, 1H, *J* = 6.7), 2.70 (dd, 1H, *J* = 15.5, 9.4), 2.58–2.51 (m, 2H), 2.38 (dd, 1H, *J* = 15.2, 7.8), 2.22–2.17 (m, 1H), 1.97 (ddd, 1H, *J* = 13.3, 7.8, 6.7), 1.80 (qd, 1H, *J* = 8.4, 3.5), 1.70–1.62 (m, 2H), 1.56–1.42 (m, 3H), 0.75 (s, 9H), –0.16 (s, 3H), –0.19 (s, 3H). **^{13}C-NMR** (125 MHz): δ 148.0, 143.2, 142.0, 133.6, 133.1, 132.4, 131.0, 130.9, 128.3, 127.2, 127.0, 123.8, 66.2, 56.4, 42.2, 35.5, 31.9, 26.9, 26.2, 25.8, 25.7, 18.0, –4.7, –5.3. **ESI-MS** *m/z* (rel int): (pos) 565 ([M+Na]$^+$, 100).



4-(*tert*-Butyldimethylsilyloxy)-1-(2-nitrophenylsulfonyl)-2-phenyl-1,2,3,4,5,6,7,8,9,10-decahydrocycloocta[*b*]pyridine (14c). Synthesized from crude alcohol **12c** (83.2 mg, 0.188 mmol) and TBSCl (65.0 mg, 0.431 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 1 vol% Et_3N) afforded **14c** as a light yellow solid (97.1 mg, 92%).

TLC: R_f 0.40 (2:1 EtOAc/hexanes). **mp** = 127.1–131.4 ºC. **IR** (NaCl, film): 2951 (m, C–H st), 2928 (s, C–H st), 2855 (m, C–H st), 1546 (vs, N=O st), 1496 (w), 1463 (m), 1373 (s, N=O st), 1256 (m, Si-Me), 1174 (m, S=O st), 1132 (m, Si–O), 1096 (m), 1068 (m), 1033 (w), 1005 (w), 980 (w), 948 (w), 910 (w), 880 (w), 853 (m), 837 (m), 776 (m), 773 (m). **^{1}H-NMR** (500 MHz): δ 7.84 (d, 1H, *J* = 7.7), 7.67 (d, 1H, *J* = 7.5), 7.58 (dd, 2H, *J* = 24.8, 7.7), 7.46 (d, 2H, *J* = 7.5), 7.31 (t, 2H, *J* = 7.4), 7.24 (d, 1H, *J* = 7.4), 5.40 (t, 1H, *J* = 8.4), 3.49 (dd, 1H, *J* = 9.5, 4.4), 2.92 (d, 1H, *J* = 14.6), 2.66–2.61 (m, 1H), 2.53–2.48 (m, 1H), 2.28–2.21 (m, 2H), 1.98 (q, 1H, *J* = 10.7), 1.59–1.49 (m, 3H), 1.36–1.24 (m, 5H), 0.81 (s, 9H), –0.12 (s, 3H), –0.25 (s, 3H). **^{13}C-NMR** (125 MHz): δ 148.0, 142.3, 142.0, 133.6, 131.5, 131.3, 130.6, 130.3, 128.3, 127.3, 127.1, 123.6, 67.1, 56.6, 43.0, 31.0, 30.0, 29.2, 26.6, 26.5, 26.3, 25.7, 17.9, –4.7, –5.3. **ESI-MS** *m/z* (rel int): (pos) 557 ([M+H]$^+$, 10), 579 ([M+Na]$^+$, 100); (neg) 591 ([M+Cl]$^-$, 100).

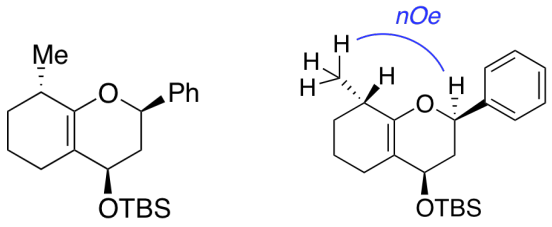


***tert*-butyldimethyl(((2*R*,4R*,8R**)-8-methyl-2-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-yl)oxy)silane (S11).** Synthesized from crude alcohol **S7** (50.0 mg, 0.206 mmol, 1.3:1.0 mixture of diastereomers at C8) and TBSCl (61.8 mg, 0.412 mmol). Purification by preparative thin

layer chromatography (130:1 hexanes/EtOAc; 6 elutions) afforded **S11** as a white solid (33.4 mg, 80%; based on a 1.3:1.0 mixture of diastereomers of alcohol **S7**).

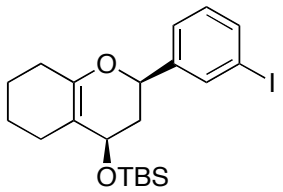
The stereochemical configuration of **S11** was confirmed unambiguously by x-ray crystallographic analysis of a p-bromobenzoate derivative **17´** of the corresponding ring expansion product **17** (see below).

TLC: R_f 0.48 (130:1 hexanes/EtOAc; 3 elutions). **IR** (NaCl, film): 2955 (s, C–H st), 2929 (s, C–H st), 2887 (m, C–H st), 2856 (s, C–H st), 1674 (m, C=C st), 1603 (w), 1496 (w), 1471 (m), 1461 (m), 1454 (m), 1348 (m), 1254 (s, Si-Me δ sy), 1235 (m), 1152 (s), 1110 (s), 1089 (vs, C–O/Si–O st), 1070 (vs, C–O/Si–O st), 1049 (m), 935 (s), 903 (m), 835 (vs, Si–C st), 774 (s, Si–C st). **^{1}H-NMR** (500 MHz): δ 7.38–7.34 (m, 4H), 7.29 (dd, 1H, J = 5.9, 2.8), 4.85 (dd, 1H, J = 12.6, 1.9), 4.50–4.47 (m, 1H), 2.30–2.24 (m, 2H), 2.18 (ddd, 1H, J = 13.1, 6.7, 1.9), 1.96 (td, 1H, J = 12.6, 9.7), 1.86–1.72 (m, 3H), 1.51–1.43 (m, 1H), 1.38–1.31 (m, 1H), 1.13 (d, 3H, J = 6.8), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR** (125 MHz): δ 152.0, 142.1, 128.4, 127.6, 125.9, 108.3, 75.9, 67.9, 41.8, 32.5, 32.1, 25.9, 25.3, 21.5, 18.5, 18.3, –4.2, –4.7. **ESI-MS** *m/z* (rel int): (pos) 227.2 ([M–TBSOH+H]$^+$, 30), 249.1 ([M–TBSOH+Na]$^+$, 100), 381.3 ([M+Na]$^+$, 95).



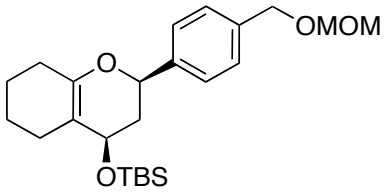
***tert*-butyldimethyl(((2*R**,4*R**,8*S**)-8-methyl-2-phenyl-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-yl)oxy)silane (S12).** Synthesized from crude alcohol **S7** (50.0 mg, 0.206 mmol, 1.3:1.0 mixture of diastereomers) and TBSCl (61.8 mg, 0.412 mmol). Purification by preparative thin layer chromatography (130:1 hexanes/EtOAc; 6 elutions) afforded **S12** as a white solid (23.7 mg, 74%; based on a 1.3:1.0 mixture of diastereomers of alcohol **S7**).

TLC: R_f 0.35 (130:1 hexanes/EtOAc; 3 elutions). **IR** (NaCl, film): 2955 (s, C–H st), 2929 (s, C–H st), 2886 (m, C–H st), 2857 (s, C–H st), 1679 (m, C=C st), 1497 (w), 1471 (m), 1462 (m), 1454 (m), 1348 (m), 1253 (s, Si-Me δ sy), 1229 (m), 1147 (s), 1087 (vs, C–O/Si–O st), 1070 (vs, C–O/Si–O st), 1043 (m), 932 (m), 903 (m), 835 (vs, Si–C st), 774 (m, Si–C st). **^{1}H-NMR** (500 MHz): δ 7.40–7.35 (m, 4H), 7.30 (ddt, 1H, J = 7.2, 2.0, 2.5), 4.80 (dd, 1H, J = 12.4, 1.6), 4.48 (dd, 1H, J = 8.8, 7.6), 2.29–2.20 (m, 3H), 2.03 (td, 1H, J = 12.7, 9.6), 1.85–1.74 (m, 2H), 1.64–1.57 (m, 2H), 1.46 (dquintet, 1H, J = 10.4, 3.4), 1.05 (d, 3H, J = 7.0), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR** (125 MHz): δ 152.8, 141.6, 128.5, 127.8, 126.2, 108.0, 76.3, 67.8, 41.3, 31.0, 30.3, 25.9, 25.1, 18.9, 18.8, 18.2, –4.3, –4.8. **ESI-MS** *m/z* (rel int): (pos) 227.2 ([M–TBSOH+H]$^+$, 30), 381.3 ([M+Na]$^+$, 95).



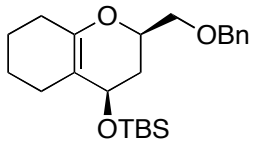
***tert*-Butyl(*cis*-2-(3-iodophenyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-yloxy)dimethylsilane (S13).** Synthesized from crude alcohol **S8** (419 mg, 1.17 mmol) and TBSCl (217 mg, 1.44 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc 0.5 vol% Et_3N) afforded **S13** as a colorless oil (482 mg, 82%).

TLC: R_f 0.73 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2950 (m, C–H st), 2928 (s, C–H st), 2888 (m, C–H st), 2855 (m, C–H st), 1685 (m, C=C st), 1593 (w), 1566 (w), 1472 (m), 1379 (w), 1360 (m), 1254 (m, Si-Me δ sy), 1227 (m), 1151 (m), 1085 (s, C–O/Si–O st), 1066 (vs, C–O/Si–O st), 1007 (w), 971 (w), 938 (w), 906 (w), 837 (vs, Si–C st), 776 (s, Si–C st), 718 (w). **^{1}H-NMR** (500 MHz): δ 7.73 (t, 1H, *J* = 1.6), 7.63 (ddd, 1H, *J* = 7.8, 1.6, 1.1), 7.33 (d, 1H, *J* = 7.8), 7.09 (t, 1H, *J* = 7.8), 4.79 (dd, 1H, *J* = 12.3, 1.9), 4.44 (m, 1H), 2.28–2.22 (m, 1H), 2.17 (ddd, 1H, *J* = 13.2, 6.8, 1.9), 2.12–1.95 (m, 3H), 1.85–1.80 (m, 1H), 1.76–1.71 (m, 2H), 1.66–1.58 (m, 1H), 1.52–1.44 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR** (125 MHz): δ 148.9, 144.0, 137.0, 135.4, 130.4, 125.6, 108.9, 94.6, 75.6, 67.4, 41.4, 27.5, 26.0, 24.6, 22.9, 22.8, 18.3, –4.1, –4.7. **ESI-MS** *m/z* (rel int): (pos) 493.2 ($[M+Na]^+$, 100), 339.2 ($[M–TBSOH+H]^+$, 11).



***tert*-Butyl(*cis*-2-(4-((methoxymethoxy)methyl)phenyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-yloxy)dimethylsilane (S14).** Synthesized from crude alcohol **S9** (100 mg, 0.330 mmol) and TBSCl (59.0 mg, 0.391 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **S14** as colorless oil that solidified upon storage at –20 °C (103 mg, 75%).

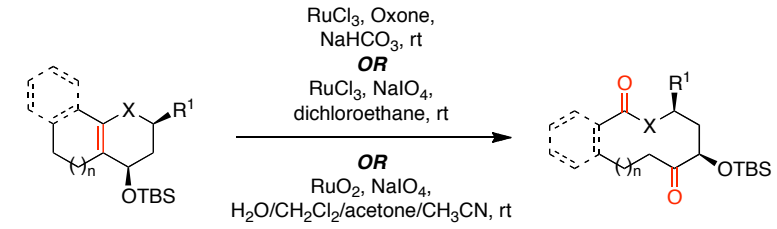
TLC: R_f 0.47 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2948 (m, C–H st), 2929 (s, C–H st), 2886 (m, C–H, st), 2856 (m, C–H, st), 1471 (w), 1463 (w), 1382 (w), 1361 (m), 1255 (m, Si-Me δ sy), 1151 (m), 1228 (m), 1150 (s, C–O/Si–O st), 1086 (s, C–O/Si–O st), 1064 (vs, C–O/Si–O st), 1050 (vs, C–O/Si–O st), 1007 (m), 971 (w), 911 (m), 911 (m), 895 (m), 836 (s, Si–C st), 775 (m). **^{1}H-NMR** (500 MHz): δ 7.38–7.34 (m, 4H), 4.86 (dd, 1H, *J* = 12.4, 1.9), 4.70 (s, 2H), 4.59 (s, 2H), 4.49–4.45 (m, 1H), 3.41 (s, 3H), 2.30–2.23 (m, 1H), 2.19 (ddd, 1H, *J* = 13.2, 6.9, 1.9), 2.11–2.00 (m, 3H), 1.86–1.82 (m, 1H), 1.77–1.71 (m, 2H), 1.66–1.59 (m, 1H), 1.52–1.44 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR** (125 MHz): δ 137.7, 128.2, 126.5, 108.7, 95.7, 76.2, 69.0, 67.7, 55.5, 41.6, 27.6, 26.0, 24.6, 23.0, 22.9, 18.4, –4.1, –4.7. **ESI-MS** *m/z* (rel int): (pos) 441.1 ($[M+Na]^+$, 100).



(*cis*-2-(Benzyloxymethyl)-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-yloxy)(*tert*-butyl)dimethylsilane (S15). Synthesized from crude alcohol **S10** (50.1 mg, 0.183 mmol) and TBSCl (32.6 mg, 0.216 mmol). Purification by silica flash chromatography (99:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **S15** as a colorless oil (52.0 mg, 74%). The product decomposes slowly over time and must be stored frozen in benzene; for best results in the subsequent ring expansion reaction, **S15** should be used immediately after purification.

TLC: R_f 0.45 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2929 (vs, C–H st), 2887 (m, C–H st), 2857 (s, C–H st), 1683 (m, C=C st), 1472 (w), 1455 (w), 1384 (w), 1361 (w), 1347 (w), 1321 (w), 1254 (m, Si-Me δ sy), 1152 (m), 1084 (s, C–O/Si–O st), 1065 (s, C–O/Si–O st), 1001 (m), 892 (m), 880 (m), 836 (s, Si–C st), 774 (s, Si–C st), 734 (m), 697 (m). **^{1}H-NMR** (500 MHz): δ 7.36–7.27 (m, 5H), 4.62–4.56 (m, 2H), 4.24–4.21 (m, 1H), 4.10 (dddd, 1H, *J* = 10.3, 6.5, 4.1, 2.5), 3.68 (dd, 1H, *J* = 10.4, 6.5), 3.48 (dd, 1H, *J* = 10.4, 4.1), 2.27–2.19 (m, 1H), 2.08–2.01 (m, 3H), 1.78–1.44 (m, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR** (125 MHz): δ 148.1, 138.5, 128.5, 127.9, 127.7, 108.3, 73.5, 73.1, 72.5, 66.4, 35.6, 27.6, 26.0, 24.9, 23.0, 22.9, 18.3, –4.55, –4.28. **ESI-MS** *m/z* (rel int): (pos) 406.3 ($[M+NH_4]^+$, 55), 256.9 ($[M–TBSOH+H]^+$, 100); (neg) 255.2 ($[M–TBSOH–H]^-$, 35).

E. RING EXPANSION TO MACROLACTONES AND MACROLACTAMS (15–21)



13a–f, (X = O)
14a–c, (X = NNs)
S11 (X = O, n = 1, R^1 = Ph, *R*-8-Methyl)
S12 (X = O, n = 1, R^1 = Ph, *S*-8-Methyl)
S13 (X = O, n = 1, R^1 = 3-I-Ph)
S14 (X = O, n = 1, R^1 = 4-($MOMOCH_2$)Ph)
S15 (X = O, n = 1, R^1 = CH_2OBn)

15a–f, 56–77%
16a–c, 65–68%
17, 69%
18, 60%
19, 70%
20, 71%
21, 55%

Supplementary Figure 12. Oxidative ring expansions of the TBS-protected alcohols 13, 14, and S11–15. Three related protocols, all employing RuO_4 as the active species,[12] were used to access the corresponding macrolactones and macrolactams **15–21**.

NOTE: Due to their biphasic character, all of the oxidation reactions require vigorous stirring to assure sufficient dispersion of the layers. Insufficient mixing can result in more sluggish reactions and/or lower yields. Furthermore, the catalyst stock solution should always be freshly prepared right before use.

General protocol for oxidative ring expansion using $RuCl_3$ with $NaIO_4$ as a stoichiometric oxidant (Protocol A)[12a,b]

TBS-protected alcohol **13a–c** was dissolved in 1,2-dichloroethane (5.50 mL/mmol substrate). Water (4.50 mL/mmol) was added, followed by a solution of $RuCl_3$ (0.035 M in water, 3.5 mol%). Neat $NaIO_4$ (2.00 equiv) was added in one portion, and the resulting biphasic mixture was stirred until the reaction was complete as judged by TLC analysis (aliquots quenched with satd aq $Na_2S_2O_3$, extracted with EtOAc). Satd aq $Na_2S_2O_3$ was added and the resulting mixture was stirred for 10 min, then extracted with CH_2Cl_2 (5×). The combined organic extracts were washed with water and brine, and dried ($MgSO_4$). To the dessicant slurry, a spatula of celite was added and the mixture was agitated for 5 min. The suspension was then filtered through a plug of celite and the solvents were removed by rotary evaporation. Purification by silica flash chromatography (hexanes/EtOAc, 0.5 vol% Et_3N) afforded the macrolactone **15a–c**.

General protocol for oxidative ring expansion using $RuCl_3$ with Oxone as a stoichiometric oxidant (Protocol B)[12a,b]

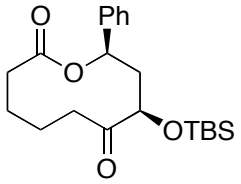
TBS-protected alcohol **13d–f** or **S11–15** was dissolved in acetonitrile (16.0 mL/mmol). Water (10.0 mL/mmol substrate) was added, resulting in the precipitation of substrate from the solution in most cases. $RuCl_3$ (0.035 M in water, 3.5 mol%) was added and, after stirring for several minutes, the starting material partially redissolved. A solid mixture of Oxone (1.50 equiv) and

[12] (a) Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814. (b) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (c) Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* **1985**, *50*, 4980. (d) Rincon, S.; del Río, R. E.; Sandoval-Ramírez, J.; Meza-Reyes, S.; Montiel-Smith, S.; Fernández, M. A.; Farfán, N.; Santillan, R. *Tetrahedron*, **2006**, *62*, 2594.

$NaHCO_3$ (4.60 equiv, 1.02 equiv relative to Oxone protons) was then added in portions. The mixture was stirred until the reaction was complete as judged by TLC analysis (aliquots quenched with satd aq $Na_2S_2O_3$, extracted with EtOAc). Satd aq $Na_2S_2O_3$ was added, and the resulting mixture was stirred for 10 min, then extracted with EtOAc (3×). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (hexanes/EtOAc, 0.5 vol% Et_3N) afforded the macrolactone **15d–f** or **17–21**.

General protocol for oxidative ring expansion using RuO_2 with $NaIO_4$ as a stoichiometric oxidant (Protocol C)[12c,d]

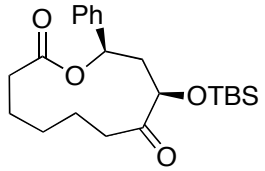
TBS-protected alcohol **14a–c** was dissolved in CH_2Cl_2 (14.0 mL/mmol). Acetonitrile (6.00 mL/mmol substrate) and acetone (6.00 mL/mmol substrate) were added. In a separate flask, $NaIO_4$ (3.00 equiv) was dissolved in H_2O (5.3 mL/mmol substrate) and RuO_2 (17 mol%) was added. The activated catalyst was then added to the solution of TBS-protected alcohol in two portions over 5 min and stirred at until the reaction was complete as judged by TLC analysis (*ca*. 40 min). Satd aq $Na_2S_2O_3$ was added and the resulting mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered over a pad of celite covered by a thin layer of activated charcoal. The filtrate was concentrated by rotary evaporation. Purification by silica flash chromatography (hexanes/EtOAc) afforded the macrolactam **16a–c**.



***cis*-8-(*tert*-Butyldimethylsilyloxy)-10-phenyloxecane-2,7-dione (15a).** Synthesized according to Protocol A from TBS-protected alcohol **13a** (38.0 mg, 0.110 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **15a** as a colorless solid (31.5 mg, 71%).

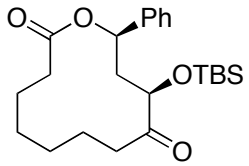
A yield of 82% was also obtained using Protocol B.

TLC: R_f 0.22 (10:1 hexanes/EtOAc). **mp** = 66.1–67.4 °C. **IR** (NaCl, film): 2932 (s, C–H st), 2892 (m, C–H st), 2858 (m, C–H st), 1736 (vs, C=O st, shoulder visible), 1462 (w), 1415 (w), 1363 (w), 1250 (s, Si-Me δ sy), 1232 (s, Si-Me δ sy), 1162 (m), 1116 (m), 1088 (m, Si–O st), 1055 (m), 1018 (m), 947 (w), 837 (m, Si–C st), 778 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.36–7.26 (m, 5H), 5.86 (dd, 1H, J = 10.7, 2.4), 4.27 (dd, 1H, J = 9.6, 4.9), 2.75 (ddd, 1H, J = 18.3, 7.9, 2.4), 2.60–2.43 (m, 3H), 2.29 (ddd, 1H, J = 17.4, 12.8, 2.4), 2.22 (ddd, 1H, J = 14.3, 4.9, 2.4), 2.08–2.01 (m, 1H), 1.94 (qd, 1H, J = 12.8, 2.2), 1.77–1.65 (m, 2H), 0.83 (s, 9H), 0.01 (s, 3H), –0.01 (s, 3H). **^{13}C-NMR** (125 MHz): δ 210.9, 171.9, 139.7, 128.7, 128.3, 126.5, 77.0, 72.3, 43.3, 38.3, 35.2, 25.8, 22.2, 22.2, 18.2, –4.8, –4.9. **ESI-MS** *m/z* (rel int): (pos) 399.1 ($[M+Na]^+$, 100); (neg) 375.2 ($[M–H]^-$, 100).



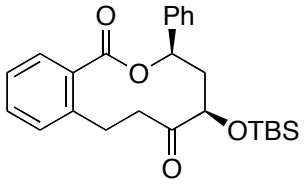
***cis*-9-(*tert*-Butyldimethylsilyloxy)-11-phenyloxacycloundecane-2,8-dione (15b).** Synthesized according to Protocol A from TBS-protected alcohol **13b** (40.0 mg, 0.112 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **15b** as a colorless oil (30.7 mg, 70%).

TLC: R_f 0.27 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2954 (s, C–H st), 2930 (s, C–H st), 2884 (m, C–H st), 2857 (m, C–H st), 1741 (vs, C=O st), 1715 (s, C=O st), 1463 (w), 1363 (w), 1335 (w), 1253 (s, Si-Me δ sy), 1238 (s, Si-Me δ sy), 1190 (w), 1143 (m), 1088 (s, C–O/Si–O st), 1041 (m, C–O/Si–O st), 993 (m), 888 (m), 857 (m), 838 (s, Si–C st), 811 (w), 779 (s, Si–C st), 763 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.33–7.26 (m, 5H), 5.61 (dd, 1H, J = 10.3, 1.0), 4.20 (dd, 1H, J = 9.3, 6.1), 3.12 (ddd, 1H, J = 18.9, 11.3, 3.6), 2.47–2.55 (m, 2H), 2.33–2.38 (m, 1H), 2.21–2.13 (m, 2H), 1.91–1.84 (m, 1H), 1.80–1.66 (m, 2H), 1.59–1.47 (m, 2H), 1.38–1.32 (m, 1H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). **^{13}C-NMR** (125 MHz): δ 211.4, 171.7, 141.2, 128.7, 128.1, 126.1, 77.8, 72.5, 43.1, 36.2, 33.2, 25.8, 24.8, 21.1, 20.4, 18.2, –4.8, –4.9. **ESI-MS** *m/z* (rel int): (pos) 413.2 ($[M+Na]^+$, 35), 408.3 ($[M+NH_4]^+$, 89), 391.2 ($[M+H]^+$, 100); (neg) 389.3 ($[M–H]^-$, 28).



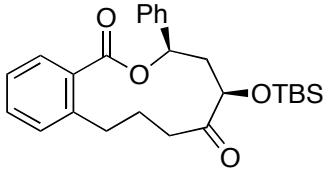
***cis*-10-(*tert*-Butyldimethylsilyloxy)-12-phenyloxacyclododecane-2,9-dione (15c).** Synthesized according to Protocol A from TBS-protected alcohol **13c** (41.0 mg, 0.110 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **15c** as a colorless oil that solidified upon storage at –20 °C (31.5 mg, 71%).

TLC: R_f 0.42 (10:1 hexanes/EtOAc). **mp** = 53.9–57.0 °C. **IR** (NaCl, film): 2952 (m, C–H st), 2931 (s, C–H st), 2857 (m, C–H st), 1734 (vs, C=O st, shoulder at *ca*. 1720), 1461 (w), 1361 (w), 1254 (s, Si-Me δ sy), 1143 (m), 1098 (s, C–O/Si–O st), 1077 (s, C–O/Si–O st), 1010 (w), 982 (w), 935 (w), 838 (s, Si–C st), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.33–7.31 (m, 4H), 7.28–7.26 (m, 1H), 5.77 (dd, 1H, J = 10.8, 2.0), 4.25 (dd, 1H, J = 9.5, 3.8), 2.78–2.70 (m, 2H), 2.55 (ddd, 1H, J = 18.2, 9.5, 2.9), 2.32 (ddd, 1H, J = 13.0, 10.1, 3.7), 2.21 (ddd, 1H, J = 14.0, 7.2, 3.7), 1.93–1.37 (m, 8H), 1.29–1.20 (m, 1H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). **^{13}C-NMR** (125 MHz): δ 209.3, 172.9, 141.4, 128.7, 128.1, 126.3, 77.0, 73.5, 41.3, 37.0, 34.0, 25.8, 25.6, 25.2, 23.1, 20.0, 18.1, –4.6, –4.7. **ESI-MS** *m/z* (rel int): (pos) 427.2 ($[M+Na]^+$, 63), 422.2 ($[M+NH_4]^+$, 100), 405.2 ($[M+H]^+$, 75); (neg) 403.1 ($[M–H]^-$, 25).



***cis*-5-(*tert*-Butyldimethylsilyloxy)-3-phenyl-4,5,7,8-tetrahydro-1*H*-benzo[*c*]oxecine-1,6(3*H*)-dione (15d).** Synthesized according to Protocol B from TBS-protected alcohol **13d** (500 mg, 1.27 mmol), except that 3.0 equiv of Oxone and 9.2 equiv of $NaHCO_3$ were used. Purification by silica flash chromatography (10:1 hexanes/ EtOAc, 0.5 vol% Et_3N) afforded **15d** as a colorless solid (302 mg, 56%).

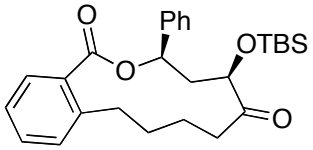
TLC: R_f 0.21 (10:1 hexanes/EtOAc). **mp** = 121.3–121.8 °C. **IR** (NaCl, film): 2953 (m, C–H st), 2928 (m, C–H st), 2885 (m, C–H st), 2856 (m, C–H st), 1721 (vs, C=O st, shoulder at 1710), 1602 (w), 1497 (w), 1449 (w), 1361 (w), 1289 (m), 1263 (vs, Si-Me δ sy), 1116 (s, C–O/Si–O st), 1102 (s, C–O/Si–O st), 1050 (w), 939 (w), 866 (m), 837 (s, Si–C st), 780 (m, Si–C st), 754 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 8.03 (dd, 1H, *J* = 7.8, 1.5), 7.48 (td, 1H, *J* = 7.5, 1.5), 7.41–7.39 (m, 2H), 7.36–7.27 (m, 5H), 6.05 (dd, 1H, *J* = 7.8, 4.8), 4.28 (dd, 1H, *J* = 8.1, 5.0), 4.13 (ddd, 1H, *J* = 13.5, 12.3, 3.6), 3.51 (ddd, 1H, *J* = 12.0, 6.0, 3.6), 2.99 (ddd, 1H, *J* = 13.5, 6.0, 4.3), 2.65–2.58 (m, 2H), 2.17 (td, 1H, *J* = 12.0, 4.3), 0.83 (s, 9H), 0.01 (s, 3H), –0.07 (s, 3H). **^{13}C-NMR** (125 MHz): δ 212.7, 166.4, 141.9, 140.3, 133.3, 132.2, 132.2, 129.1, 128.7, 127.9, 127.3, 126.0, 77.8, 72.4, 42.3, 38.6, 34.6, 25.8, 18.2, –4.8, –5.1. **ESI-MS** *m/z* (rel int): (pos) 447.2 ($[M+Na]^+$, 100), 442.3 ($[M+NH_4]^+$, 76), 425.3 ($[M+H]^+$, 23); (neg) 423.5 ($[M–H]^-$, 90).



***cis*-5-(*tert*-Butyldimethylsilyloxy)-3-phenyl-4,5,8,9-tetrahydrobenzo[*c*][1]oxacycloundecine-1,6(3*H*,7*H*)-dione (15e).** Synthesized according to Protocol B from TBS-protected alcohol **13e** (100 mg, 0.246 mmol), except that 2.7 equiv of Oxone and 8.5 equiv of $NaHCO_3$ were used. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **15e** as a colorless solid (74.3 mg, 69%).

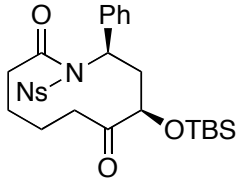
TLC: R_f 0.65 (10:1 hexanes/EtOAc). **mp** = 92.0–93.8 °C. **IR** (NaCl, film): 2953 (m, C–H st), 2929 (m, C–H st), 2884 (w, C–H st), 2856 (m, C–H st), 1710 (C=O st, shoulder at *ca*. 1740), 1617 (w), 1496 (w), 1471 (w), 1461 (w), 1447 (w), 1362 (m), 1330 (m), 1262 (vs, Si-Me δ sy), 1114 (s, C–O/Si–O st), 1104 (s, C–O/Si–O st), 1082 (s, C–O/Si–O st), 1050 (m), 1014 (w), 965 (w), 913 (w), 876 (m), 836 (s, Si–C st), 778 (m, Si–C st), 752 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.60 (dd, 1H, *J* = 7.8, 1.2), 7.42 (td, 1H, *J* = 7.5, 1.4), 7.35–7.32 (m, 4H), 7.28–7.25 (m, 2H), 7.23 (td, 1H, *J* = 7.5, 1.2), 5.98 (dd, 1H, *J* = 8.8, 4.2), 4.34 (dd, 1H, *J* = 8.3, 4.5), 3.04 (dt, 1H, *J* = 13.9, 5.3), 2.92 (ddd, 1H, *J* = 17.8, 10.5, 3.3), 2.81 (ddd, 1H, *J* = 13.9, 9.7, 4.3), 2.57 (dt, 1H, *J* = 14.8, 8.8), 2.48–2.39 (m, 2H), 2.04–2.10 (m, 2H), 0.80 (s, 9H), –0.01 (s, 3H), –0.06 (s, 3H). **^{13}C-NMR** (125 MHz): δ 212.5, 168.2, 141.8, 141.0, 131.9, 131.7, 131.2, 130.0,

128.7, 127.9, 126.2, 126.0, 76.5, 74.4, 42.6, 36.4, 31.8, 25.8, 25.4, 18.2, –4.8, –4.9. **ESI-MS** *m/z* (rel int): (pos) 477.2 ($[M+K]^+$, 3), 461.2 ($[M+Na]^+$, 100); (neg) 437.1 ($[M–H]^-$, 75).



***cis*-5-(*tert*-Butyldimethylsilyloxy)-3-phenyl-4,5,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclo-dodecine-1,6(3*H*)-dione (15f).** Synthesized according to Protocol B from TBS-protected alcohol **13f** (50.0 mg, 0.119 mmol), except that 3.0 equiv of Oxone and 9.2 equiv of $NaHCO_3$ were used. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **15f** as a colorless solid (31.6 mg, 59%).

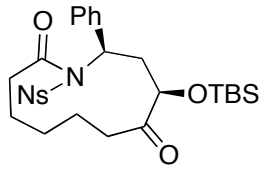
TLC: R_f 0.34 (10:1 hexanes/EtOAc). **mp** = 113.5–115.5°C. **IR** (NaCl, film): 2954 (m, C–H st), 2931 (m, C–H st), 2857 (m, C–H st), 1717 (vs, C=O st), 1651 (w), 1601 (w), 1559 (w), 1540 (w), 1458 (m), 1364 (w), 1335 (w), 1274 (m), 1250 (s, Si-Me δ sy), 1084 (s, C–O/Si–O st), 1050 (m, C–O/Si–O st), 976 (w), 930 (w), 878 (m), 837 (m), 779 (m, Si–C st), 752 (m, Si–C st). **^{1}H-NMR** (500 MHz): δ 7.63 (dd, 1H, *J* = 7.6, 1.3), 7.36 (td, 1H, *J* = 7.6, 1.3), 7.31–7.27 (m, 5H), 7.20 (d, 1H, *J* = 7.6), 7.16 (td, 1H, *J* = 7.6, 1.0), 5.94 (d, 1H, *J* = 9.8), 4.27 (dd, 1H, *J* = 10.5, 5.9), 3.57 (td, 1H, *J* = 11.8, 4.6), 3.14 (ddd, 1H, *J* = 19.6, 11.8, 3.9), 2.69–2.55 (m, 2H), 2.38 (td, 1H, *J* = 11.8, 7.2), 2.12 (dd, 1H, *J* = 15.2, 5.9), 2.04–1.98 (m, 1H), 1.69–1.62 (m, 2H), 1.50 (ddd, 1H, *J* = 14.4, 10.9, 3.8), 0.88 (s, 9H), 0.05 (s, 6H). **^{13}C-NMR** (125 MHz): δ 211.3, 168.3, 143.4, 141.9, 132.1, 132.0, 130.7, 130.5, 128.9, 128.0, 126.1, 125.8, 78.5, 73.9, 43.6, 33.0, 32.3, 30.3, 25.8, 20.7, 18.1, –4.8, –4.9. **ESI-MS** *m/z* (rel int): (pos) 475.5 ($[M+Na]^+$, 100); (neg) 452 ($[M–H]^-$, 50).



***cis*-8-(*tert*-Butyldimethylsilyloxy)-1-(2-nitrophenylsulfonyl)-10-phenylazecane-2,7-dione (16a).** Synthesized according to Protocol C from TBS-protected alcohol **14a** (20 mg, 0.038 mmol). Purification by silica flash chromatography (6:1 hexanes/EtOAc) afforded **16a** as white solid (14.5 mg, 68%).

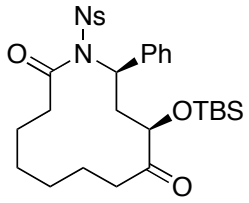
TLC: R_f 0.10 (4:1 hexanes/EtOAc). **mp** = 147.2–149.5 ºC. **IR** (NaCl, film): 2954 (m, C–H st), 2930 (m, C–H st), 2894 (w), 2858 (m), 1718 (s, C=O st), 1593 (w), 1544 (vs, N=O st), 1496 (w), 1442 (m), 1370 (vs, N=O st), 1256 (w, Si-Me), 1192 (m, S=O st), 1123 (m, Si–O), 1079 (m), 1025 (w), 979 (w), 963 (w), 941 (w), 911 (w), 855 (m), 839 (m), 779 (m), 734 (s), 700 (m), 656 (m). **^{1}H-NMR** (500 MHz): δ 7.80 (d, 1H, *J* = 7.9), 7.56 (d, 1H, J = 7.9), 7.46 (t, 1H, *J* = 7.7), 7.31 (t, 1H, *J* = 7.7), 7.14 (d, 2H, *J* = 7.0), 6.97–6.93 (m, 3H), 5.33 (d, 1H, *J* = 11.5), 4.29 (dd, 1H, *J* = 11.3, 4.8), 3.26 (dt, 1H, *J* = 15.3, 11.5), 3.04 (dd, 1H, *J* = 16.4, 10.3), 2.81 (ddd, 2H, *J* = 35.2, 17.9, 9.8), 2.35 (dd, 1H, *J* = 19.3, 6.9), 2.14 (sextet, 2H, *J* = 11.9), 2.00–1.94 (m, 2H), 1.70–1.59 (m, 1H), 0.85 (s, 10H), 0.06 (s, 3H), 0.02 (s, 3H). **^{13}C-NMR** (125 MHz): δ 211.7,

177.2, 147.2, 139.6, 134.2, 133.1, 132.5, 131.9, 128.1, 127.4, 127.0, 124.9, 79.4, 62.5, 40.6, 39.9, 34.8, 25.6, 25.4, 21.3, 17.9, –5.0, –5.1. **ESI-MS** *m/z* (rel int): (pos) 583 ([M+Na]$^+$, 20); (neg) 559 ([M–H]$^-$, 45), 595 (100).



***cis*-9-(*tert*-Butyldimethylsilyloxy)-1-(2-nitrophenylsulfonyl)-11-phenylazacycloundecane-2,8-dione (16b).** Synthesized according to Protocol C from TBS-protected alcohol **14b** (20 mg, 0.037 mmol). Purification by silica flash chromatography (6:1 hexanes/EtOAc) afforded **16b** as a white resin (13.8 mg, 65%).

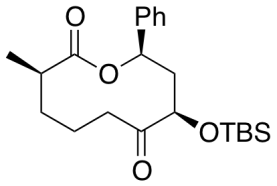
TLC: R_f 0.20 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2952 (m, C–H st), 2931 (m, C–H st), 2886 (w), 2857 (m), 1719 (s, C=O st), 1592 (w), 1545 (vs, N=O st), 1497 (w), 1463 (m), 1442 (m), 1370 (vs, N=O st), 1254 (w, Si-Me), 1178 (m, S=O st), 1121 (m, Si–O), 948 (w), 912 (w), 839 (m), 779 (m), 733 (m). **^{1}H-NMR** (500 MHz): δ 7.60 (dd, 1H, *J* = 8.0, 1.1), 7.55–7.51 (m, 2H), 7.34 (td, 1H, *J* = 7.7, 1.1), 7.25–7.24 (m, 2H), 7.12–7.07 (m, 3H), 5.29 (t, 1H, *J* = 6.4), 4.46–4.41 (m, 1H), 3.05–2.99 (m, 2H), 2.85–2.71 (m, 2H), 2.50–2.40 (m, 1H), 2.36–2.30 (m, 1H), 2.03–1.87 (m, 2H), 1.86–1.78 (m, 1H), 1.75–1.67 (m, 1H), 1.66–1.57 (m, 1H), 1.54–1.48 (m, 1H), 0.96 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H). **^{13}C-NMR** (125 MHz): δ 211.8, 176.0, 147.5, 134.3, 132.9, 131.9, 131.5, 128.2, 128.0, 127.8, 127.7, 124.7, 75.2, 58.4, 39.4, 38.2, 34.9, 26.2, 25.8, 22.8, 21.2, 18.2, –4.6, –5.0. **ESI-MS** *m/z* (rel int): (pos) 575 ([M+H]$^+$, 15), 597 ([M+Na]$^+$, 100); (neg) 573 ([M–H]$^-$, 100).



***cis*-10-(*tert*-Butyldimethylsilyloxy)-1-(2-nitrophenylsulfonyl)-12-phenylazacyclododecane-2,9-dione (16c).** Synthesized according to Protocol C from TBS-protected alcohol **14c** (20 mg, 0.036 mmol). Purification by silica flash chromatography (6:1 hexanes/EtOAc) afforded **16c** as a colorless oil (13.9 mg, 66%).

TLC: R_f 0.25 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2953 (m, C–H st), 2930 (m, C–H st), 2857 (m), 1719 (s, C=O st), 1544 (vs, N=O st), 1497 (w), 1464 (m), 1451 (m), 1441 (m), 1370 (vs, N=O st), 1255 (m, Si-Me), 1179 (m, S=O st), 1105 (m, Si–O), 945 (w), 917 (w), 852 (m), 778 (m), 740 (w), 732 (w). **^{1}H-NMR** (500 MHz): δ 7.60 (dd, 1H, *J* = 8.0, 1.3), 7.54 (td, 1H, *J* = 7.7, 1.3), 7.47–7.45 (m, 1H), 7.37–7.34 (m, 3H), 7.21–7.17 (m, 3H), 5.38 (t, 1H, *J* = 6.6), 4.21 (t, 1H, *J* = 6.4), 2.99 (ddd, 1H, *J* = 14.5, 8.3, 6.4), 2.89–2.76 (m, 3H), 2.62 (ddd, 1H, *J* = 14.7, 7.1, 5.9), 2.41 (ddd, 1H, *J* = 17.1, 6.9, 4.6), 1.93–1.85 (m, 1H), 1.81–1.72 (m, 2H), 1.68–1.60 (m, 2H), 1.48 (dq, 1H, *J* = 13.6, 6.6), 1.40–1.28 (m, 2H), 0.96 (s, 9H), 0.14 (s, 3H), 0.07 (s, 3H). **^{13}C-NMR** (125 MHz): δ 212.3, 175.7, 147.6, 136.7, 133.9, 133.3, 131.7, 131.4, 128.3, 128.3,

128.1, 124.4, 76.1, 60.4, 38.9, 37.9, 36.1, 26.3, 25.8, 25.3, 25.1, 22.2, 18.2, –4.61, –4.79. **ESI-MS** *m/z* (rel int): (pos) 611 ([M–H+Na]$^+$, 100); (neg) 589 ([M]$^-$, 100).

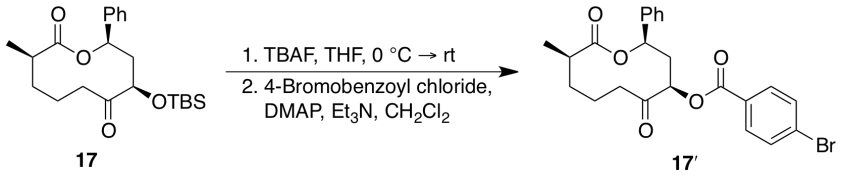


(3*R,8*R**,10*R**)-8-((*tert*-butyldimethylsilyl)oxy)-3-methyl-10-phenyloxecane-2,7-dione (17).** Synthesized according to Protocol B from TBS-protected alcohol **S11** (10 mg, 0.028 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **17** as a colorless oil (7.4 mg, 69%).

The stereochemical configuration of macrocycle **17** was confirmed unambiguously by x-ray crystallographic analysis of a *p*-bromobenzoate derivative **17´** (see below).

TLC: R_f 0.48 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.36–7.27 (m, 5H), 5.86 (dd, 1H, *J* = 11.0, 2.2), 4.30 (dd, 1H, *J* = 9.7, 4.9), 2.65–2.59 (m, 1H), 2.56–2.37 (m, 3H), 2.21 (ddd, 1H, *J* = 14.3, 4.9, 2.2), 2.11–2.04 (m, 1H), 1.95–1.87 (m, 1H), 1.74–1.67 (m, 1H), 1.54 (ddt, 1H, *J* = 11.7, 5.9, 2.9), 1.10 (d, 3H, *J* = 7.2), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). **^{13}C-NMR** (125 MHz): δ 210.4, 175.0, 139.8, 128.6, 128.1, 126.0, 76.6, 72.0, 43.7, 41.6, 38.3, 30.7, 25.7, 21.3, 19.8, 18.1, –4.8, –5.0. **ESI-MS** *m/z* (rel int): (pos) 413.3 ([M+Na]$^+$, 100), 803.6 ([2M+Na]$^+$, 75).

Derivatization of macrocycle 17 for x-ray crystallographic analysis

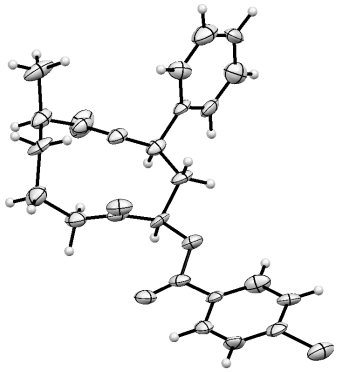


(2*R,4*R**,9*R**)-9-methyl-5,10-dioxo-2-phenyloxecan-4-yl 4-bromobenzoate (17´).** In a 4 mL vial equipped with a septum and magnetic stir bar, macrocycle **17** (7.4 mg, 0.019 mmol) was dissolved in THF (1.0 mL) under Ar and cooled to 0 °C. A 1:1 solution of TBAF and AcOH (40 μL, 0.038 mmol, 2.0 equiv.) was then added and the reaction was stirred at rt for 5 h. The reaction was diluted with sat aq $NaHCO_3$ and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to afford the crude alcohol that was used without further purification. In a 4 mL vial equipped with a septum and magnetic stir bar, the crude alcohol was dissolved in CH_2Cl_2 (1.0 mL) under Ar. To the solution was added Et_3N (5.3 μL, 0.038 mmol, 2.0 equiv.) and DMAP (cat.), and the mixture was cooled to 0 °C. A solution of 4-bromobenzoyl chloride (5.0 mg, 0.023 mmol, 1.2 equiv) in 100 μL CH_2Cl_2 was then added and the mixture was allowed to warm to rt overnight. The reaction was diluted with sat aq $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined

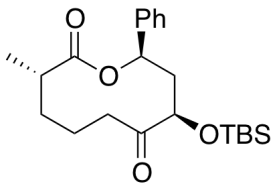
organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (10:1 hexanes/EtOAc with 0.5 vol% Et_3N) afforded *p*-bromobenzoate derivative **17´** as a white crystalline solid (6.0 mg, 68% over 2 steps), which was then recrystallized from CH_2Cl_2/toluene.

TLC: R_f 0.63 (1:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.64 (d, 2H, *J* = 8.5), 7.51 (d, 2H, *J* = 8.5), 7.39–7.33 (m, 5H), 6.06 (dd, 1H, *J* = 9.8, 2.6), 5.21 (dd, 1H, *J* = 9.8, 3.9), 2.77–2.70 (m, 3H), 2.61–2.57 (m, 1H), 2.45–2.38 (m, 1H), 2.32–2.24 (m, 1H), 2.10–2.02 (m, 1H), 1.53–1.50 (m, 2H), 1.16 (d, 3H, *J* = 7.1). **^{13}C-NMR** (125 MHz): δ 205.3, 175.4, 165.1, 139.3, 131.7, 131.3, 128.8, 128.6, 128.2, 127.9, 125.8, 76.7, 72.1, 41.2, 39.4, 38.0, 29.1, 21.5, 19.5. **ESI-MS** *m/z* (rel int): (pos) 481.2 ([M+Na]$^+$, 100), 483.1 ([M+2+Na]$^+$, 97).

X-ray crystallographic analysis of macrocycle *p*-bromobenzoate derivative 17´[13]



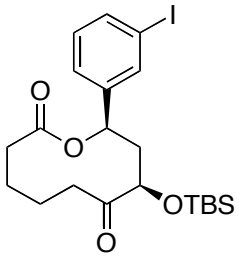
Molecules of $C_{23}H_{23}BrO_5$, crystallized in the space group $P2_1/c$ with unit cell dimensions a = 18.606(10) Å, b = 11.432(6) Å, c = 9.801(5) Å, β = 79.820(9) ° at 150 K. A crystal of 0.20 mm x 0.02 mm x 0.01 mm was measured using Mo K_α radiation, which resulted in diffraction data to a maximum of < 44° in 2θ. The structure solution confirmed the composition of $C_{23}H_{23}BrO_5$, and the structure refinement converged to R_1 = 7.97% and wR_2 (all data) = 22.57%. Both enantiomers C8-*R*,C13-*R*,C16-*R* and C8-*S*,C13-*S*,C16-*S* are present in the unit cell but due to symmetry elements, only one is shown in the structure solution.



(3*S,8*R**,10*R**)-8-((*tert*-butyldimethylsilyl)oxy)-3-methyl-10-phenyloxecane-2,7-dione (18).** Synthesized according to Protocol B from TBS-protected alcohol **S12** (10 mg, 0.28 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **18** as a colorless oil (6.5 mg, 60%).

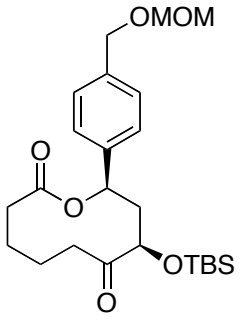
[13] CCDC 853922 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

TLC: R_f 0.45 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2953 (s, C–H st), 2929 (s, C–H st), 2886 (m, C–H st), 2856 (m, C–H st), 1731 (vs, C=O st), 1496 (w), 1462 (w), 1363 (w), 1333 (w), 1255 (m, Si-Me δ sy), 1221 (w, Si-Me δ sy), 1185 (m), 1091 (m, C–O/Si–O st), 1018 (m, C–O/Si–O st), 986 (w), 930 (w), 871 (m), 836 (s, Si–C st), 778 (s, Si–C st). **^{1}H-NMR** (500 MHz): δ 7.35–7.30 (m, 4H), 7.29–7.27 (m, 1H), 5.88 (dd, 1H, J = 10.9, 2.3), 4.29 (dd, 1H, J = 9.7, 4.6), 2.61–2.52 (m, 3H), 2.47–2.40 (m, 1H), 2.24–2.16 (m, 2H), 2.01–1.94 (m, 1H), 1.85–1.78 (m, 1H), 1.63–1.57 (m, 1H), 1.16 (d, 3H, J = 7.2), 0.83 (s, 9H), 0.02 (s, 3H), –0.01 (s, 3H). **^{13}C-NMR** (125 MHz): δ 210.3, 175.3, 139.7, 128.6, 128.2, 126.5, 76.5, 72.3, 43.4, 38.3, 37.1, 25.7, 18.2, 17.2, 14.6, –4.8, –5.0. **ESI-MS** *m/z* (rel int): (pos) 391.4 ([M+H$^+$], 10), 413.3 ([M+Na]$^+$, 100), 803.7 ([2M+Na]$^+$, 70).



***cis*-8-(*tert*-Butyldimethylsilyloxy)-10-(3-iodophenyl)oxecane-2,7-dione (19).** Synthesized according to Protocol B from TBS-protected alcohol **S13** (60.0 mg, 0.128 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **19** as colorless oil (44.9 mg, 70%).

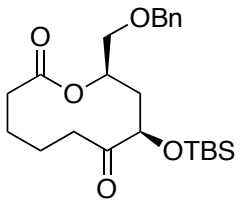
TLC: R_f 0.13 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2952 (s, C–H st), 2929 (s, C–H st), 2886 (m, C–H st), 2856 (m, C–H st), 1736 (vs, C=O st, shoulder at *ca*. 1710), 1592 (w), 1568 (w), 1472 (m), 1440 (w), 1425 (w), 1407 (w), 1362 (m), 1340 (w), 1253 (s, Si-Me δ sy), 1230 (s), 1167 (m), 1119 (m, C–O/Si–O st), 1091 (m, C–O/Si–O st), 1055 (m, C–O/Si–O st), 1026 (m), 1014 (m), 976 (m), 956 (w), 837 (vs, Si–C st), 779 (s, Si–C st), 733 (w). **^{1}H-NMR** (500 MHz): δ 7.67 (s, 1H), 7.61 (d, 1H, J = 7.9), 7.30 (d, 1H, J = 7.8), 7.06 (t, 1H, J = 7.8), 5.78 (dd, 1H, J = 10.0, 2.6), 4.25 (dd, 1H, J = 9.1, 4.8), 2.76 (dd, 1H, J = 18.9, 7.6), 2.55–2.39 (m, 3H), 2.34–2.23 (m, 2H), 2.07–1.89 (m, 2H), 1.78–1.67 (m, 2H), 0.81 (s, 9H), 0.01 (s, 3H), –0.03 (s, 3H). **^{13}C-NMR** (125 MHz): δ 210.8, 171.7, 142.0, 137.1, 135.2, 130.3, 125.7, 94.4, 76.7, 71.3, 42.8, 38.1, 35.1, 25.7, 22.1, 18.1, –4.9, –5.1. **ESI-MS** *m/z* (rel int): (pos) 525.1 ([M+Na]$^+$, 100); (neg) 501.0 ([M–H]$^-$, 23), 740.9 (100).



***cis*-8-(*tert*-Butyldimethylsilyloxy)-10-(4-((methoxymethoxy)methyl)phenyl)oxecane-2,7-dione (20).** Synthesized according to Protocol B from TBS-protected alcohol **S14** (14.7 mg,

0.0351 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **20** as a colorless oil (11.3 mg, 71%).

TLC: R_f 0.13 (9:1 hexanes/EtOAc). **IR** (NaCl, film): 3027 (w), 2953 (m. C–H st), 2931 (m, C–H st), 2887 (m, C–H st), 2859 (m, C–H st), 1736 (s, C=O st, shoulder at *ca*. 1715), 1474 (w), 1465 (w), 1442 (w), 1365 (w), 1256 (m, Si-Me δ sy) 1233 (m, Si-Me δ sy), 1169 (w), 1151 (m), 1106 (vs, C–O/Si–O st), 1051 (s, C–O/Si–O st) 1019 (m), 960 (w), 940 (w), 921 (w), 876 (m), 840 (s, Si–C st), 818 (w), 780 (m). **^{1}H-NMR** (500 MHz): δ 7.33 (s, 4H), 5.84 (dd, 1H, *J* = 10.6, 2.1), 4.69 (s, 2H), 4.57 (s, 2H), 4.27 (dd, 1H, *J* = 10.1, 4.9), 3.40 (s, 3H), 2.73 (ddd, 1H, *J* = 18.2, 7.9, 2.1), 2.55 (dt, 1H, *J* = 14.3, 10.1), 2.51–2.43 (m, 2H), 2.28 (ddd, 1H, *J* = 17.4, 12.7, 2.3), 2.08–2.02 (m, 1H), 1.97–1.89 (m, 1H), 1.76–1.64 (m, 2H), 0.83 (s, 9H), 0.01 (s, 3H), –0.01 (s, 3H). **^{13}C-NMR** (125 MHz): δ 210.9, 139.2, 138.1, 128.2, 126.7, 95.8, 72.1, 68.8, 55.5, 43.4, 38.4, 35.2, 25.8, 22.2, 18.2, –4.75, –4.88. **ESI-MS** *m/z* (rel int): (pos) 473.2 ([M+Na]$^+$, 100).

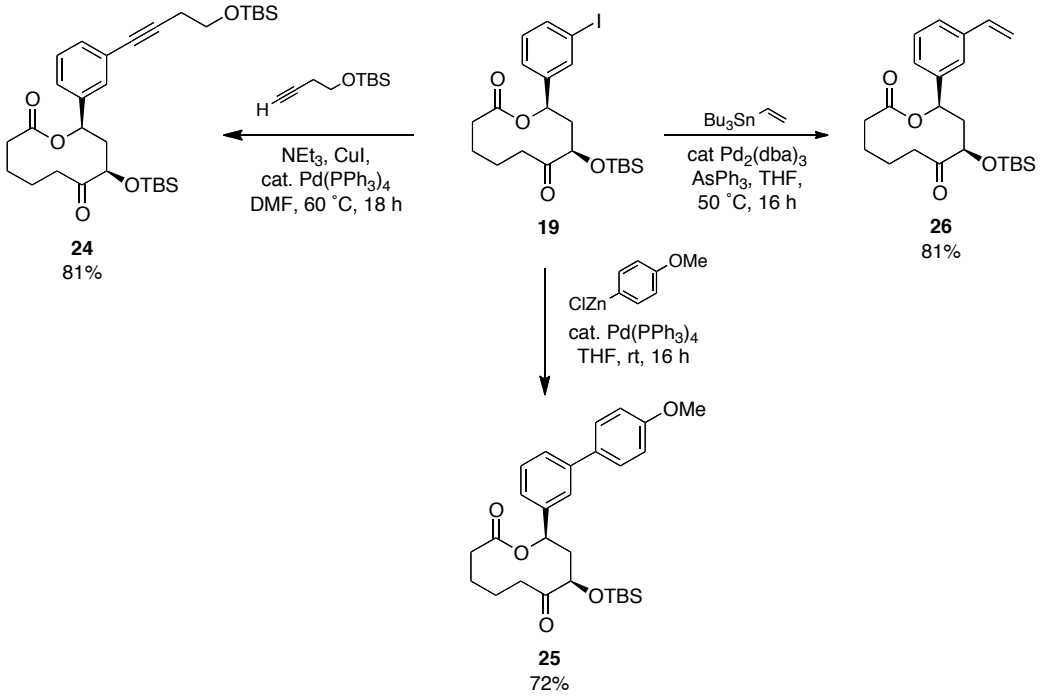


***cis*-10-(Benzyloxymethyl)-8-(*tert*-butyldimethylsilyloxy)oxecane-2,7-dione (21).** Synthesized by a modified version of Protocol B (10.5 mol% $RuCl_3$) from TBS-protected alcohol **S15** (15.0 mg, 0.0386 mmol). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **21** as colorless oil (8.9 mg, 55%).

TLC: R_f 0.30 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2954 (s, C–H st), 2931 (s, C–H st), 2886 (m, C–H st), 2858 (s, C–H st), 1734 (vs, C=O st, slight shoulder at *ca*. 1710), 1453 (w), 1456 (w), 1366 (m), 1278 (m), 1254 (s, Si-Me δ sy), 1239 (m), 1154 (m), 1126 (s, C–O/Si–O st), 1111 (s, C–O/Si–O st), 1073 (m, C–O/Si–O st), 1031 (m), 1008 (w), 963 (w), 937 (w), 890 (w), 839 (s), 815 (m), 782 (m), 740 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.35–7.27 (m, 5H), 5.12 (m, 1H), 4.56–4.50 (m, 2H), 4.18 (dd, 1H, *J* = 6.7, 3.9), 3.82 (dd, 1H, *J* = 10.8, 7.8), 3.53 (dd, 1H, *J* = 10.8, 4.0), 2.66–2.61 (m, 1H), 2.54–2.45 (m, 2H), 2.34 (ddd, 1H, *J* = 18.2, 10.0, 2.1), 2.26 (ddd, 1H, *J* = 17.2, 12.5, 2.1), 2.05–1.95 (m, 2H), 1.88 (q, 1H, *J* = 13.1), 1.73–1.61 (m, 2H), 0.88 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H). **^{13}C-NMR** (125 MHz): δ 210.4, 172.6, 138.0, 128.5, 127.8, 76.2, 73.3, 71.4, 37.0, 36.7, 35.1, 25.9, 22.3, 22.2, 18.3, –4.9, –5.2. **ESI-MS** *m/z* (rel int): (pos) 863.6 ([2M+Na]$^+$, 100), 443.3 ([M+Na]$^+$, 100), 421.3 ([M+H]$^+$, 12); (neg) 419.4 ([M–H]$^-$, 100).

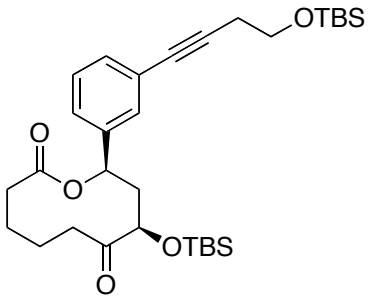
F. FUNCTIONALIZATION OF MACROCYCLIC SCAFFOLDS

1. CROSS-COUPLING REACTIONS OF IODIDE MACROCYCLE (19)



Supplementary Figure 13. Cross-coupling reactions of iodide macrocycle 19. Aryl iodide **19** underwent efficient Sonogashira, Negishi, and Stille cross-coupling reactions to introduce additional substituents. (dba = dibenzylideneacetone).

a. Sonogashira cross-coupling of iodide macrocycle 19

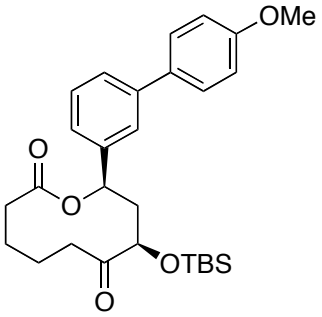


***cis*-8-(*tert*-Butyldimethylsilyloxy)-10-(3-(4-(*tert*-butyldimethylsilyloxy)but-1-ynyl)phenyl)-oxecane-2,7-dione (24).** In a 4 mL vial equipped with a septum and a magnetic stir bar, aryl iodide **19** (41.1 mg, 0.0818 mmol) was dissolved in DMF under Ar. Subsequently, CuI (6.2 mg, 0.033 mmol, 0.40 equiv), (but-3-ynyloxy)(*tert*-butyl)dimethylsilane (45.2 mg, 0.245 mmol, 3.00 equiv), and Et_3N (0.06 mL, 0.4 mmol, *ca*. 5 equiv) were added. The vial was purged with Ar and $Pd(PPh_3)_4$ (18.9 mg, 20.0 mol%) was added. The vial was purged again and sealed with a screw cap. The mixture was heated to 60 °C for 18 h until the reaction was complete as judged by TLC analysis (aliquots worked up with satd aq NH_4Cl/one drop NH_3/EtOAc, then eluted 5 times with 10:1 hexanes/EtOAc). The reaction mixture was poured into satd aq NH_4Cl, a small amount of NH_4OH was added, and the mixture was extracted with EtOAc (3×). The combined

organic extracts were washed with satd aq NH_4Cl and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **24** as a colorless oil (37.0 mg, 81%).

TLC: R_f 0.41 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2953 (m, C–H st), 2930 (s, C–H st), 2857 (m, C–H st), 1739 (s, shoulder at *ca*. 1710, C=O st), 1472 (w), 1463 (w), 1388 (w), 1362 (w), 1253 (s, Si-Me δ sy), 1230 (m), 1187 (w), 1108 (vs, C–O/Si–O st), 1056 (m, C–O/Si–O st), 1025 (w), 1011 (w), 958 (w), 837 (vs, Si–C st), 777 (vs, Si–C st). **^{1}H-NMR** (500 MHz): δ 7.36–7.37 (m, 1H), 7.28–7.33 (m, 1H), 7.25–7.24 (m, 2H), 5.80 (dd, 1H, *J* = 10.6, 2.5), 4.25 (dd, 1H, *J* = 9.5, 4.9), 3.82 (d, 2H, *J* = 14.2), 2.78–2.73 (m, 1H), 2.62 (d, 2H, *J* = 14.2), 2.54–2.41 (m, 3H), 2.29 (ddd, 1H, *J* = 17.5, 12.7, 2.4), 2.21 (ddd, 1H, *J* = 14.3, 4.9, 2.5), 2.06–1.88 (m, 2H), 1.78–1.66 (m, 2H), 0.92 (s, 9H), 0.82 (s, 9H), 0.10 (s, 6H), 0.01 (s, 3H), –0.02 (s, 3H). **^{13}C-NMR** (125 MHz): δ 211.0, 139.9, 129.5, 128.6, 125.9, 124.2, 87.8, 81.4, 71.8, 62.0, 43.2, 38.3, 35.2, 26.1, 25.8, 24.0, 22.32, 22.17, 18.5, 18.2, –4.78, –4.91, –5.07. **ESI-MS** *m/z* (rel int): (pos) 581.2 ($[M+Na]^+$, 100), 313.1 ($[M–TBSOH–TBS+H]^+$, 28); (neg) 557.2 ($[M–H]^-$, 100).

b. Negishi cross-coupling of iodide macrocycle 19



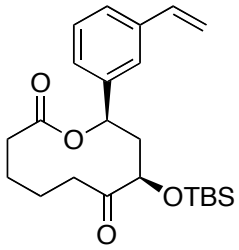
***cis*-8-(*tert*-Butyldimethylsilyloxy)-10-(4'-methoxybiphenyl-3-yl)oxecane-2,7-dione (25).** In a 4 mL vial equipped with a septum and a magnetic stir bar, aryl iodide **19** (35.0 mg, 0.070 mmol) was dissolved in THF under an Ar atmosphere. Subsequently, $Pd(PPh_3)_4$ (4.0 mg, 5.0 mol%) was added and the vial was purged with Ar. (4-Methoxyphenyl)zinc(II) chloride (0.36 M in THF, 1.5 equiv; prepared by lithiation of the corresponding bromide (–78 °C, THF, 30 min) and subsequent transmetalation with $ZnCl_2$ (1 M in THF, –78 °C → rt, 1 h; concentration determined iodometrically[14]) and sealed with a screw cap. The mixture was stirred at rt for 16 h until the reaction was complete as judged by TLC analysis (aliquot worked up with satd aq NH_4Cl/EtOAc). Satd aq NH_4Cl was added and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with satd aq NH_4Cl and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **25** as a colorless oil (24.0 mg, 72%).

TLC: R_f 0.24 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2952 (m, C–H st), 2930 (m, C–H st), 2856 (m, C–H st), 1732 (s, shoulder at *ca.* 1710, C=O st), 1518 (m), 1484 (w), 1471 (w), 1463 (w), 1440 (w), 1408 (w), 1362 (w), 1275 (m), 1248 (vs, Si-Me δ sy), 1233 (m), 1188 (m), 1167 (m), 1114 (m), 1090 (m), 1051 (m, C–O/Si–O st), 1029 (m), 957 (w), 939 (w), 910 (w), 883 (w), 836

[14] Krasovskiy, A.; Knochel, P *Synlett* **2006**, *5*, 890.

(s, Si–C st), 795 (m), 778 (m, Si–C st), 732 (w), 704 (w). **^{1}H-NMR** (500 MHz): δ 7.53–7.50 (m, 3H), 7.46 (dt, 1H, *J* = 7.7, 1.3), 7.38 (t, 1H, *J* = 7.7), 7.29 (dt, 1H, *J* = 7.7, 1.3), 7.00–6.97 (m, 2H), 5.91 (dd, 1H, *J* = 10.7, 2.3), 4.30 (dd, 1H, *J* = 9.6, 4.9), 3.86 (s, 3H), 2.78–2.73 (m, 1H), 2.62 (ddd, 1H, *J* = 14.3, 10.7, 9.6), 2.54–2.45 (m, 2H), 2.33–2.25 (m, 2H), 2.09–2.03 (m, 1H), 2.00–1.92 (m, 1H), 1.77–1.65 (m, 2H), 0.83 (s, 9H), 0.01 (s, 3H), –0.01 (s, 3H). **^{13}C-NMR** (125 MHz): δ 210.8, 171.9, 159.3, 141.2, 140.1, 133.4, 129.0, 128.3, 126.6, 124.8, 124.7, 114.3, 72.3, 55.4, 43.3, 38.3, 35.1, 29.7, 25.7, 22.1, 18.1, –4.87, –5.01 (the TBS protected carbinol overlaps with the $CDCl_3$ signal, but was identified by a HSQC experiment). **ESI-MS** *m/z* (rel int): (pos) 505.2 ($[M+Na]^+$, 100).

c. Stille cross-coupling*[15] *of iodide macrocycle 19



***cis*-8-(*tert*-Butyldimethylsilyloxy)-10-(3-vinylphenyl)oxecane-2,7-dione (26).** In a 4 mL vial equipped with a septum and a magnetic stir bar, aryl iodide **19** (22.3 mg, 0.0444 mmol) was dissolved in THF (0.28 mL) under Ar. $AsPh_3$ (1.1 mg, 8.0 mol%) was added, followed by $Pd_2(dba)_3$ (0.8 mg, 2 mol%). The vial was purged with Ar and the mixture stirred for 10 min at rt. Vinyltributyltin (*ca.* 13 μL, *ca.* 1.0 equiv) was added and the mixture was stirred for 16 h at rt, followed by 18 h at 50 °C to ensure full conversion (the starting material and the product have identical R_f values). The mixture was cooled to rt, satd aq NH_4Cl was added, and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with 1 M HCl, water, and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (hexanes/EtOAc, 10:1, 0.5 vol% Et_3N) afforded **26** as a pale yellow oil (14.5 mg, 81%, *ca.* 95% purity by ^{1}H NMR, with minor impurities observed in the aromatic region).

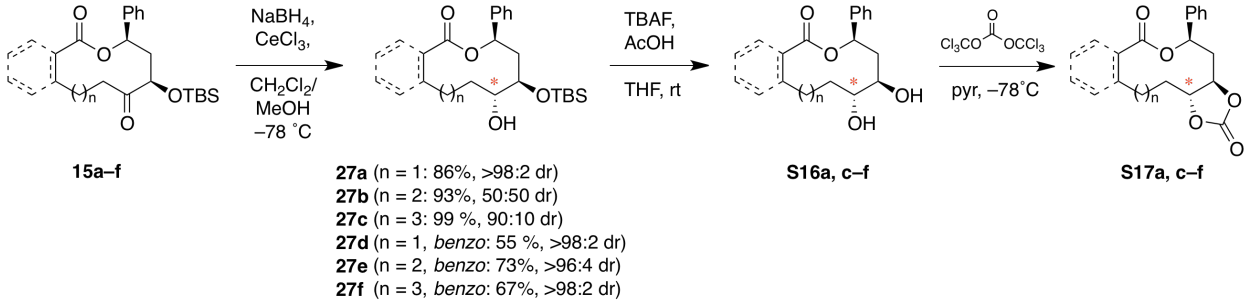
TLC: R_f 0.51 (4:1 hexanes/EtOAc). **IR** (NaCl, film): 2952 (m, C–H st), 2929 (m, C–H st), 2886 (w), 2857 (m, C–H st), 1735 (s, shoulder at *ca.* 1710, C=O st), 1518 (m), 1604 (w), 1471 (w), 1463 (w), 1442 (w), 1408 (w), 1363 (m), 1274 (m), 1253 (s, Si-Me δ sy), 1230 (s), 1166 (m), 1116 (m), 1090 (m), 1055 (m, C–O/Si–O st), 1026 (m), 958 (w), 907 (w), 838 (s, Si–C st), 802 (m), 778 (s, Si–C st), 713 (w). **^{1}H-NMR** (500 MHz): δ 7.36 (s, 1H), 7.33 (d, 1H, *J* = 7.6), 7.29 (t, 1H, *J* = 7.6), 7.24 (d, 1H, *J* = 7.6), 6.70 (dd, 1H, *J* = 17.5, 10.9), 5.85 (dd, 1H, *J* = 10.6, 2.2), 5.75 (d, 1H, *J* = 17.5), 5.27 (d, 1H, *J* = 10.9), 4.27 (dd, 1H, *J* = 9.8, 4.9), 2.75 (ddd, 1H, *J* = 18.3, 8.0, 1.9), 2.57 (ddd, 1H, *J* = 14.3, 10.6, 9.8), 2.53–2.43 (m, 2H), 2.32–2.20 (m, 2H), 2.08–2.02 (m, 1H), 1.99–1.91 (m, 1H), 1.77–1.66 (m, 2H), 0.83 (s, 9H), 0.01 (s, 3H), –0.01 (s, 3H). **^{13}C-NMR** (125 MHz): δ 210.9, 171.9, 140.0, 138.0, 136.6, 128.9, 126.1, 126.0, 124.4, 114.6, 72.2, 43.3, 38.4, 35.2, 25.8, 22.2, 18.2, –4.77, –4.91 (the TBS protected carbinol overlaps with

[15] For Ph_3As promoted Stille couplings, see: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

the $CDCl_3$ signal, but was identified by an HSQC experiment). **ESI-MS** *m/z* (rel int): (pos) 425.2 ($[M+Na]^+$, 100).

2. DIASTEREOSELECTIVE REDUCTIONS OF KETONE MACROCYCLES (15)

A variety of reduction conditions were investigated to effect stereoselective reduction of the ring ketone. While treatment with $NaBH_4$ resulted in no reaction, the more reactive L-Selectride tended to form very strong complexes with the resulting alcohol that complicated purification. However, the modified Luche conditions used in the reduction of the dihydropyrones (see SECTION D above) proved highly efficient and afforded the desired alcohols in good yield and excellent diastereoselectivity in most cases (**Supplementary Fig. 14**). Cerium chloride may facilitate reduction through activation of the ketone for the hydride attack.[16] Relative stereochemical configurations were determined by NOESY experiments on cyclic carbonate derivatives.



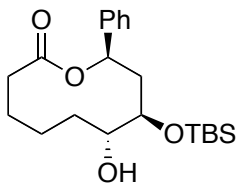
Supplementary Figure 14. Diastereoselective reductions of ketone macrocycles 15a–f. Cerium-mediated reduction of the ketone macrocycles **15a–f** afforded stereoselective access to alcohols **27a–f**. Relative stereochemical assignments were determined by deprotection of the TBS group and conversion of diols **S16a,c–f** to the corresponding cyclic carbonates (**S17a,c–f)**, followed by NOESY analysis. As reduction of macrocycle **15b** gave a 50:50 mixture of diastereomers (**27b**), the corresponding cyclic carbonate was not prepared for this scaffold.

a. General protocol for Luche reductions of ketone macrocycles 15a–f

In a roundbottom flask, ketone macrocycle **15** was dissolved in CH_2Cl_2 (4.6 mL/mmol substrate; 0.22 M) and cooled to –78 °C. A solution of anhyd $CeCl_3$ (*ca.* 0.40 M in anhyd MeOH, 3.00 equiv) was added slowly and the mixture was stirred at –78 °C for an additional 20 min. Neat $NaBH_4$ (1.50 equiv) was added in one portion and the mixture was stirred at –78 °C until the reaction was complete as judged by TLC analysis (usually 2 h; aliquots added to a solution of one drop of 1,3-propanediol in EtOAc, then washed with satd aq NH_4Cl). 1,3-propanediol (1.5–2.0 equiv) was added and the resulting mixture was allowed to warm to rt and stirred for an additional 15 min. After recooling to –78 °C, satd aq NH_4Cl was added, and the mixture was allowed to warm to rt. Water and EtOAc were added and the mixture was thoroughly shaken in a separatory funnel. The organic layer was washed with water and brine, dried ($MgSO_4$),

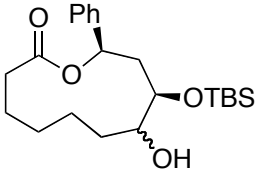
[16] For literature on cerium as an activator for carbonyls, see: a) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497; (b) Imamoto, T.; Sugiyura, Y.; Takiyama, N.; Hatojima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392; (c) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763; (d) Imamoto, T.; Sugiyura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography afforded alcohol macrocycle **27**.



(7*R,8*R**,10*R**)-8-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-10-phenyloxecan-2-one (27a).** Synthesized from macrocycle **15a** (150 mg, 0.398 mmol). ^{1}H-NMR analysis of the crude product indicated a single diastereomer (≥98:2 dr). Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **27a** as a white solid (127 mg, 84%, single isomer).

TLC: R_f 0.34 (4:1 hexanes/EtOAc). **mp** = 72.4–74.5 °C. **IR** (NaCl, film): 3552 (br, O–H st), 3090 (w), 3065 (w), 3034 (w), 2954 (s, C–H st), 2930 (s, C–H st), 2857 (m, C–H st), 1733 (vs, C=O st), 1497 (w), 1471 (w), 1462 (w), 1453 (w), 1362 (w), 1335 (w), 1261 (s, Si-Me δ sy), 1232 (m), 1156 (w), 1110 (m), 1088 (s, C–OH/C–O/Si–O st), 1075 (s, C–OH/C–O/Si–O st), 1055 (s, C–OH/C–O/Si–O st), 1033 (s, C–OH/C–O/Si–O st), 967 (w), 938 (m), 873 (m), 836 (s, C–Si st), 778 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.36–7.27 (m, 5H), 5.85 (dd, 1H, *J* = 10.2, 2.6), 3.98–3.95 (m, 1H), 3.63–3.60 (m, 1H), 2.84 (s, 1H), 2.58 (dt, 1H, *J* = 15.5, 4.3), 2.32–2.20 (m, 2H), 2.16–2.06 (m, 2H), 1.98–1.90 (m, 1H), 1.74–1.67 (m, 1H), 1.60–1.54 (m, 1H), 1.47–1.33 (m, 2H), 0.84 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H). **^{13}C-NMR** (125 MHz): δ 173.1, 140.5, 128.6, 128.0, 126.2, 74.1, 73.8, 71.9, 34.9, 32.0, 25.7, 24.4, 20.8, 18.0, –4.4, –5.0. **ESI-MS** *m/z* (rel int): (pos) 401.1 ($[M+Na]^+$, 100) (neg) 377.1 ($[M–H]^–$).

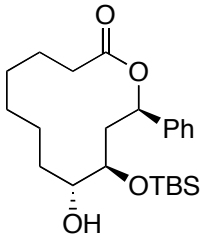


(9*R,11*R**)-9-(*tert*-Butyldimethylsilyloxy)-8-hydroxy-11-phenyloxacycloundecan-2-one (27b).** Synthesized from macrocycle **15b** (26.0 mg, 0.0666 mmol). ^{1}H-NMR analysis of the crude product indicated a 1:1 dr. Purification by silica flash chromatography (10:1→4:1 hexanes/EtOAc) afforded the individual isomers as colorless solids (**27b-1** = 11.7 mg, 45%; **27b-2** = 12.6 mg, 48%; relative stereochemistry not determined).

27b-1: TLC: R_f 0.55 (4:1 hexanes/EtOAc). **mp** = 94.3–97.2 °C. **IR** (NaCl, film): 3623 (w, O–H st), 3065 (w), 3033 (w), 3008 (w), 2954 (s, C–H st), 2930 (s, C–H st), 2903 (m, C–H st), 2857 (m, C–H st), 1730 (vs, C=O st), 1497 (w), 1453 (m), 1403 (w), 1359 (w), 1274 (w), 1253 (s, Si-Me δ sy), 1226 (m), 1215 (m), 1153 (m), 1073 (vs, C–OH/C–O/Si–O st), 1039 (m, C–OH/C–O/Si–O st), 996 (m), 936 (w), 867 (m), 836 (s, C–Si st), 810 (w), 878 (m), 761 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.37–7.28 (m, 5H), 6.27 (dd, 1H, *J* = 12.0, 2.1), 3.77 (ddd, 1H, *J* = 7.7, 5.8, 1.5), 3.63–3.59 (m, 1H), 2.68 (t, 1H, *J* = 2.0), 2.53 (ddd, 1H, *J* = 16.0, 7.5, 1.7), 2.30 (ddd, 1H, *J* = 15.9, 12.0, 5.8), 2.22 (ddd, 1H, *J* = 16.0, 11.7, 1.7), 2.15–2.06 (m, 1H), 1.95–1.85 (m, 2H), 1.74–1.57 (m, 4H), 1.52–1.46 (m, 1H), 1.15–1.08 (m, 1H), 0.92 (s, 9H), 0.21 (s, 3H),

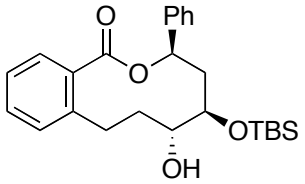
0.18 (s, 3H). **^{13}C-NMR** (125 MHz): δ 173.3, 140.6, 128.8, 128.3, 126.2, 74.56, 74.51, 72.7, 44.1, 35.7, 28.6, 27.9, 26.0, 20.7, 19.0, 18.1, –3.6, –4.6. **ESI-MS** *m/z* (rel int): (pos) 393.2 ([M+Na]$^+$, 100); (neg) 391.3 ([M–H]$^-$, 100).

27b-2: TLC: R_f 0.46 (4:1 hexanes/EtOAc). **mp** = 57.5–61.5 °C. **IR** (NaCl, film): 3500 (br, O–H st), 3089 (w), 3065 (w), 3034 (w), 2953 (s, C–H st), 2905 (s, C–H st), 2858 (s, C–H st), 1728 (vs, C=O st), 1495 (w), 1464 (m), 1387 (w), 1338 (w), 1307 (w), 1255 (s, Si-Me δ sy), 1228 (m), 1161 (w), 1122 (w), 1074 (s, C–OH/C–O/Si–O st), 1050 (s, C–OH/C–O/Si–O st), 996 (m), 960 (w), 924 (w), 903 (w), 869 (m), 836 (s, C–Si st), 778 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.35–7.28 (m, 5H), 6.10 (dd, 1H, *J* = 11.8, 1.1), 3.92 (dt, 1H, *J* = 6.1, 2.1), 3.62 (br d, 1H, *J* = 10.3), 2.74 (ddd, 1H, *J* = 16.0, 11.8, 6.1), 2.56–2.52 (m, 1H), 2.29 (s, 1H), 2.20–2.06 (m, 2H), 1.99–1.91 (m, 1H), 1.69 (d, 1H, *J* = 16.0), 1.64–1.56 (m, 3H), 1.52–1.42 (m, 3H), 1.22–1.13 (m, 1H), 0.90 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H). **^{13}C-NMR** (125 MHz): δ 74.8, 74.5, 73.6, 40.2, 35.7, 28.4, 28.0, 26.0, 21.7, 20.1, 18.1, –4.2, –4.6. **ESI-MS** *m/z* (rel int): (pos) 410.3 ([M+NH_4]$^+$, 100), 393.2 ([M+Na]$^+$, 97); (neg) 391.1 ([M–H]$^-$, 100).



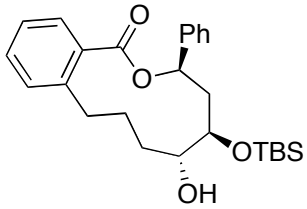
(10*R,12*R**)-10-(*tert*-Butyldimethylsilyloxy)-9-hydroxy-12-phenyloxacyclododecan-2-one (27c).** Synthesized from macrocycle **15c** (27.0 mg, 0.0667 mmol). ^{1}H-NMR analysis of the crude product indicated 90:10 dr. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded the major isomer **27c-1** (24.4 mg, 90%). The minor isomer (**27c-2**) was also isolated in low purity, but was identifiable by diagnostic signals in the NMR and mass spectra.

27c-1: **TLC**: R_f 0.70 (4:1 hexanes/EtOAc). **mp** = 65.6–67.5 °C). **IR** (NaCl, film): 3556 (w, O–H st), 3090 (w), 3065 (w), 3034 (w), 2950 (s, C–H st), 2932 (vs, C–H st), 2857 (m, C–H st), 1464 (w), 1403 (w), 1361 (w), 1254 (m, Si-Me δ sy), 1213 (w), 1175 (w, 1142 (m), 1105 (m), 1069 (s, C–OH/C–O/Si–O st), 1052 (s, C–OH/C–O/Si–O st), 1033 (m), 1005 (w), 957 (w), 935 (w), 885 (w), 837 (s, C–Si st), 776 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.36–7.27 (m, 5H), 5.97 (dd, 1H, *J* = 12.0, 2.1), 3.92–3.88 (m, 1H), 3.75 (d, 1H, *J* = 8.5), 2.60 (ddd, 1H, *J* = 15.1, 12.0, 8.5), 2.47 (ddd, 1H, *J* = 14.2, 10.7, 3.6), 2.35–2.30 (m, 2H), 1.86–1.80 (m, 1H), 1.72–1.45 (m, 8H), 1.42–1.36 (m, 2H), 1.28–1.23 (m, 1H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). **^{13}C-NMR** (125 MHz): 173.6, 140.9, 128.7, 128.2, 126.3, 75.3, 74.3, 71.0, 42.3, 33.4, 33.1, 25.9, 24.8, 23.9, 23.8, 22.1, 18.1, –4.0, –4.6. **ESI-MS** *m/z* (rel int): (pos) 424.3 ([M+NH_4]$^+$, 76), 407.2 ([M+H]$^+$, 100); (neg) 405.2 ([M–H]$^-$, 100).



(3*R,5*R**,6*R**)-5-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-3-phenyl-3,4,5,6,7,8-hexahydro-1*H*-benzo[*c*]oxecin-1-one (27d).** Synthesized from macrocycle **15d** (50.0 mg, 0.118 mmol). ^{1}H-NMR analysis of the crude product indicated a single diastereomer (≥98:2 dr). Purification by silica flash chromatography (2:1→1:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **27d** as a white solid (28.0 mg, 56%).

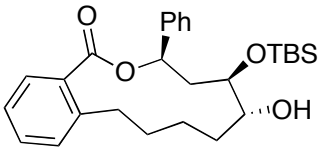
TLC: R_f 0.49 (4:1 hexanes/EtOAc). **mp** = 115.6–118.8 °C. **IR** (NaCl, film): 3580 (br, O–H st), 3089 (w), 3065 (w), 3032 (w), 2953 (m, C–H st), 2929 (m, C–H st), 2885 (w, C–H st), 2857 (m, C–H st), 1727 (vs, C=O st), 1603 (w), 1461 (w), 1451 (w), 1391 (w), 1362 (w), 1336 (w), 1283 (m), 1257 (s, Si-Me δ sy), 1131 (m), 1113 (w), 1070 (s, C–OH/C–O/Si–O st), 1055 (m, C–OH/C–O/Si–O st), 1029 (w), 1007 (w), 982 (w), 938 (w), 908 (w), 887 (m), 860 (m), 837 (s, C–Si st), 811 (w), 778 (m), 751 (m), 735 (m), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.48 (dd, 1H, *J* = 7.6, 1.0), 7.41–7.32 (m, 6H), 7.28 (d, 1H, *J* = 7.6), 7.24 (dd, 1H, *J* = 7.5, 0.9), 5.97 (dd, 1H, *J* = 11.9, 2.3), 4.05 (t, 1H, *J* = 7.7), 3.68 (t, 1H, *J* = 6.6), 2.87–2.80 (m, 2H), 2.72 (ddd, 1H, *J* = 13.6, 9.0, 4.3), 2.36 (ddd, 1H, *J* = 15.5, 11.9, 7.7), 2.30–2.25 (m, 1H), 2.19–2.12 (m, 1H), 1.95 (dd, 1H, *J* = 15.5, 2.3), 0.94 (s, 10H), 0.22 (s, 3H), 0.21 (s, 3H). **^{13}C-NMR** (125 MHz): δ 168.8, 141.5, 140.0, 133.2, 131.3, 130.7, 128.9, 128.4(3), 128.4(1), 126.3, 125.9, 77.1, 75.3, 73.8, 43.8, 33.0, 29.5, 25.9, 18.1, –3.7, –4.5. **ESI-MS** *m/z* (rel int): (pos) 449.1 ([M+Na]$^+$, 100); (neg) 425.1 ([M–H]$^-$, 100).



(3*R,5*R**)-5-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-3-phenyl-4,5,6,7,8,9-hexahydrobenzo-[*c*][1]oxacycloundecin-1(3*H*)-one (27e).** Synthesized from macrocycle **15e** (25.6 mg, 0.0584 mmol). ^{1}H-NMR analysis of the crude product indicated a 96:4 dr. Purification by silica flash chromatography (10:1→4:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **27e** as a colorless solid (18.6 mg, 73%; 96:4 mixture of isomers).

TLC: R_f 0.47 (4:1 hexanes/EtOAc, major diastereomer). **mp** = 140.1–142.0 °C. **IR** (NaCl, film): 3517 (br, O–H st), 3064 (w), 3032 (w), 2952 (m, C–H st), 2930 (m, C–H st), 2884 (w, C–H st), 2857 (m, C–H st), 1706 (s, C=O st), 1601 (w), 1497 (w), 1471 (w), 1462 (w), 1448 (w), 1407 (w), 1361 (w), 1312 (w), 1273 (s, Si-Me δ sy), 1250 (vs, Si-Me δ sy), 1123 (m), 1081 (s, C–OH/C–O/Si–O st), 1050 (s, C–OH/C–O/Si–O st), 1026 (m), 983 (w), 943 (w), 906 (w), 884 (w), 864 (w), 837 (s, C–Si st), 808 (w), 778 (m), 750 (m), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.96 (d, 1H, *J* = 7.7), 7.43–7.33 (m, 5H), 7.29–7.24 (m, 5H), 6.28 (dd, 1H, *J* = 11.5, 3.8), 4.05–3.96 (m, 2H), 3.66–3.61 (m, 1H), 2.99 (d, 1H, *J* = 5.8), 2.63–2.51 (m, 2H), 2.08 (dd, 1H, *J* = 15.4, 3.8), 1.91–1.97 (m, 1H), 1.72 (m, 2H), 1.69–1.77 (m, 1H), 0.91 (s, 9H), 0.20 (s, 3H), 0.13 (s,

3H). **^{13}C-NMR** (125 MHz): δ 168.4, 144.0, 140.7, 133.2, 132.7, 131.4, 129.4, 128.8, 128.1, 126.5, 126.2, 77.0, 73.4, 70.6, 44.7, 34.3, 33.0, 27.5, 25.9, 18.1, –3.8, –4.7. **ESI-MS** *m/z* (rel int): (pos) 463.1 ([M+Na]$^+$, 100) (neg) 439.1 ([M–H]$^-$, 100).

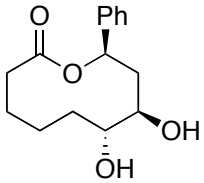


(3*R,5*R**,6*R**)-5-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-3-phenyl-3,4,5,6,7,8,9,10-octahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (27f).** Synthesized from macrocycle **15f** (10.3 mg, 0.0228 mmol). ^{1}H-NMR analysis of the crude product indicated a single diastereomer (≥98:2 dr). Purification by silica flash chromatography (first column: 10:1 hexanes/EtOAc, 0.5 vol% Et_3N; second column: 20:1→10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **27f** as a colorless resin (7.1 mg, 68%, >90% purity).

TLC: R_f 0.15 (20:1 hexanes/EtOAc). **IR** (NaCl, film): 3571 (br, O–H st), 3088 (w), 3065 (w), 3031 (w), 2951 (m, C–H st), 2929 vs, C–H st), 2856 (m, C–H st), 1710 (s, C=O st), 1601 (w), 1495 (w), 1461 (w), 1447 (w), 1389 (w), 1360 (w), 1311 (w), 1253 (vs, Si-Me δ sy), 1196 (w), 1124 (m), 1096 (s, C–OH/C–O/Si–O st), 1071 (s, C–OH/C–O/Si–O st), 1049 (m, C–OH/C–O/Si–O st), 1028 (m), 1007 (w), 973 (w), 936 (w), 909 (w), 865 (m), 836 (m, C–Si st), 808 (w), 778 (m), 748 (m), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.70 (dd, 1H, *J* = 7.8, 1.3), 7.42–7.20 (m, 8H), 6.27 (dd, 1H, *J* = 11.6, 2.0), 4.00 (dt, 1H, *J* = 7.2, 4.2), 3.64–3.61 (m, 1H), 3.34–3.28 (m, 1H), 2.75–2.70 (m, 1H), 2.56 (d, 1H, *J* = 3.5), 2.45 (ddd, 1H, *J* = 15.7, 11.6, 4.4), 1.92 (ddd, 1H, *J* = 15.7, 4.2, 2.0), 1.80–1.65 (m, 5H), 1.50–1.42 (m, 1H), 0.92 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H). **^{13}C-NMR** (125 MHz): δ 168.7, 143.4, 140.9, 132.0, 131.2, 130.8, 130.8, 128.8, 128.2, 126.1, 126.0, 75.6, 73.5, 73.4, 43.5, 31.9, 31.5, 29.2, 26.0, 21.8, 18.3, –3.7, –4.4. **ESI-MS** *m/z* (rel int): (pos) 477.0 ([M+Na]$^+$, 100) (neg) 453.2 ([M–H]$^-$, 100).

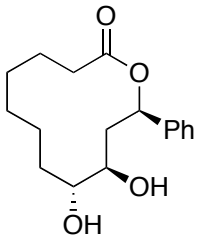
b. General protocol for deprotection of mono-TBS-protected diol macrocycles 27a,c–f

In a roundbottom flask, TBS-protected alcohol **27** was dissolved in THF (93.0 mL/mmol). A freshly prepared solution of TBAF and AcOH (*ca*. 1.0 M each in THF, 2.0 equiv) was added and the resulting solution was stirred at the temperature indicated below until the reaction was complete as judged by TLC analysis. The solvents were removed by rotary evaporation. Purification by silica flash chromatography afforded diol **S16**.



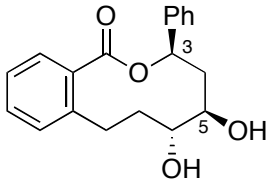
(7*R,8*R**,10*R**)-7,8-Dihydroxy-10-phenyloxecan-2-one (S16a).** Synthesized from TBS-protected alcohol **27a** (150 mg, 0.396 mmol). The reaction proceeded at rt in 1 h. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **S16a** as a white, crystalline solid (64.5 mg, 61%).

TLC: R_f 0.67 (EtOAc). **^{1}H-NMR** (500 MHz): δ 7.40–7.27 (m, 5H), 5.89 (dd, 1H, *J* = 8.4, 2.7), 4.00–3.96 (m, 1H), 3.60–3.56 (m, 1H), 2.63 (ddd, 1H, *J* = 15.2, 5.6, 2.7), 2.40–2.13 (m, 6H), 1.96–1.89 (m, 1H), 1.75–1.70 (m, 1H), 1.55–1.39 (m, 3H). **^{13}C-NMR** (125 MHz): δ 172.9, 140.2, 128.7, 128.0, 125.8, 73.8, 73.7, 72.6, 34.6, 31.9, 24.6, 20.8. **ESI-MS** *m/z* (rel int): (pos) 551.1 ([2M+Na]$^+$, 20), 287.1 ([M+Na]$^+$, 100); (neg) 527.2 ([2M–H]$^-$, 100), 263.0 ([M–H]$^-$, 50).



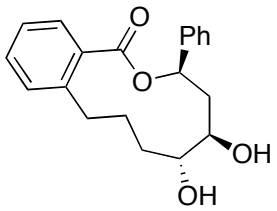
(9*R,10*R**,12*R**)-9,10-Dihydroxy-12-phenyloxacyclododecan-2-one (S16c).** Synthesized from TBS-protected alcohol **27c** (16.0 mg, 0.0393 mmol). The reaction proceeded at rt in 1 h. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **S16c** as a white solid (11.0 mg, 97%).

TLC: R_f 0.72 (EtOAc). **^{1}H-NMR** (500 MHz): δ 7.36–7.27 (m, 5H), 6.09 (dd, 1H, *J* = 11.3, 1.9), 3.84–3.82 (m, 1H), 3.68–3.65 (m, 1H), 2.63 (s, 1H), 2.44–2.27 (m, 4H), 1.87 (ddd, 1H, *J* = 15.0, 4.8, 1.9), 1.80–1.36 (m, 11H). **^{13}C-NMR** (125 MHz): δ 174.0, 140.5, 128.7, 128.2, 126.3, 74.5, 71.8, 71.5, 42.4, 34.0, 30.8, 25.03, 24.86, 24.0, 20.7. **ESI-MS** *m/z* (rel int): (pos) 315.3 ([M+Na]$^+$, 100); (neg) 291.3 ([M–H]$^-$, 100).



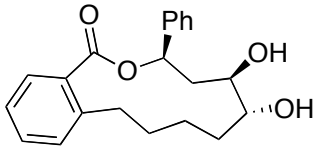
(3*R,5*R**,6*R**)-5,6-Dihydroxy-3-phenyl-3,4,5,6,7,8-hexahydro-1*H*-benzo[*c*]oxecin-1-one (S16d).** Synthesized from TBS-protected alcohol **27d** (14.3 mg, 0.335 mmol). The reaction proceeded at rt in 1.75 h. Filtration through a short plug of silica gel (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **S16d** as a white solid (11.2 mg, > quant, 80–85% purity). In addition to some aliphatic impurities, ^{1}H-NMR analysis revealed an impurity (*ca*. 5%) with signals that may correspond to the product of a transesterification involving the C5-alcohol. The diagnostic benzylic proton (C3) is observed at 5.1 ppm in this impurity. The diol was used in the next step without further purification.

TLC: R_f 0.66 (EtOAc). **^{1}H-NMR** (500 MHz): δ 7.53 (dd, 1H, *J* = 7.9, 1.4), 7.40 (td, 1H, *J* = 7.5, 1.4), 7.36–7.30 (m, 5H), 7.24–2.27 (m, 3H), 5.96 (dd, 1H, *J* = 11.8, 2.4), 4.08 (t, 1H, *J* = 8.0), 3.73 (ddd, 1H, *J* = 8.0, 5.8, 2.0), 2.88–2.82 (m, 1H), 2.75 (ddd, 1H, *J* = 13.4, 9.8, 3.3), 2.42–2.36 (m, 1H), 2.32 (ddd, 1H, *J* = 15.4, 11.8, 8.1), 2.22–2.15 (m, 1H), 2.10 (dd, 1H, *J* = 15.4, 2.4). **^{13}C-NMR** (125 MHz): δ 168.5, 141.5, 132.9, 131.5, 130.6, 129.0, 128.8, 128.4, 126.5, 126.0, 76.9, 76.3, 73.0, 42.7, 33.9, 29.6, 14.3. **ESI-MS** *m/z* (rel int): (pos) 647.1 ([2M+Na]$^+$, 25), 334.9 ([M+Na]$^+$, 100); (neg) 311.0 ([M–H]$^-$, 100).



(3*R,5*R**)-5,6-Dihydroxy-3-phenyl-4,5,6,7,8,9-hexahydrobenzo[*c*][1]oxacycloundecin-1(3*H*)-one (S16e).** Synthesized from TBS-protected alcohol **27e** (9.1 mg, 0.021 mmol). The reaction proceeded at rt in 1.75 h. Purification by silica flash chromatography (EtOAc) afforded **S16e** as a white solid (8.6 mg, > quant, 95:5 mixture of isomers, *ca*. 90% purity, containing traces of TBAF).

TLC: R_f 0.66 (EtOAc). **^{1}H-NMR** (500 MHz): δ 8.02 (dd, 1H, *J* = 7.8, 1.3), 7.46–7.35 (m, 5H), 7.31–7.27 (m, 3H), 6.37 (dd, 1H, *J* = 9.5, 3.4), 3.98 (ddd, *J* = 7.6, 4.7, 4.6, 1H), 3.86 (ddd, 1H, *J* = 7.6, 4.6, 3.3), 3.59 (ddd, 1H, *J* = 13.1, 7.6, 5.0), 2.75 (dt, 1H, *J* = 13.1, 7.6), 2.50 (ddd, 1H, *J* = 15.7, 9.5, 4.9), 2.26 (dd, 1H, *J* = 15.2, 3.2), 2.05–1.90 (m, 2H), 1.67–1.60 (m, 2H). **^{13}C-NMR** (125 MHz): δ 167.9, 144.0, 140.1, 133.0, 132.8, 131.7, 129.4, 128.9, 128.1, 126.5, 125.8, 76.2, 73.9, 72.1, 41.7, 34.9, 32.0, 26.9. **ESI-MS** *m/z* (rel int): (pos) 675.1 ($[2M+Na]^+$, 30), 349.0 ($[M+Na]^+$, 100); (neg) 324.9 ($[M–H]^-$, 100).



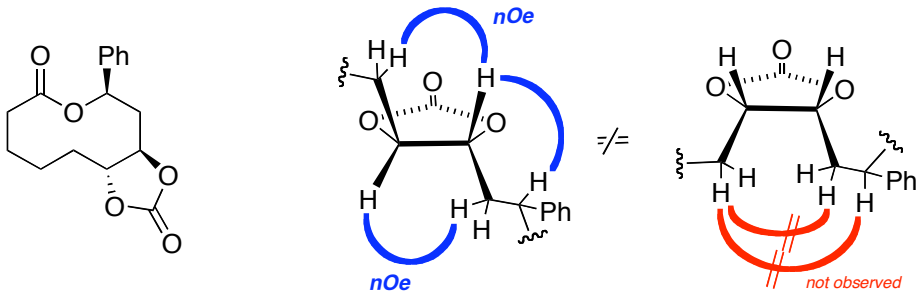
(3*R,5*R**,6*R**)-5,6-Dihydroxy-3-phenyl-3,4,5,6,7,8,9,10-octahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (S16f).** Synthesized from TBS-protected alcohol **27f** (7.0 mg, 0.015 mmol). TBAF was added at 0 °C and the resulting solution was stirred with warming to rt for 1 h. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **S16f** as a white solid (3.8 mg, 72%; 95:5 mixture of isomers, *ca*. 90% purity).

TLC: R_f 0.51 (EtOAc). **^{1}H-NMR** (500 MHz): δ 7.77 (dd, 1H, *J* = 7.8, 1.3), 7.44–7.22 (m, 8H), 6.30 (dd, 1H, *J* = 10.9, 1.9), 3.96–3.93 (m, 1H), 3.70–3.67 (m, 1H), 3.46 (ddd, 1H, *J* = 12.7, 10.0, 6.2), 2.66–2.60 (m, 2H), 2.41 (ddd, 1H, *J* = 15.6, 10.9, 2.6), 2.36 (s, 1H), 2.02 (ddd, 1H, *J* = 15.6, 6.1, 1.9), 1.89–1.66 (m, 6H), 1.49–1.41 (m, 1H). **^{13}C-NMR** (125 MHz): δ 168.6, 147.9, 143.2, 140.5, 132.2, 131.4, 131.2, 130.5, 128.8, 126.2, 126.0, 75.4, 73.8, 72.0, 41.9, 32.6, 32.0, 28.2, 21.6. **ESI-MS** *m/z* (rel int): (pos) 703.1 ($[2M+Na]^+$, 45), 363.0 ($[M+Na]^+$, 100); (neg) 679.2 ($[2M–H]^-$, 35), 339.0 ($[M–H]^-$, 100).

c. General protocol for synthesis of cyclic carbonates S17a,c–f and NOESY analysis

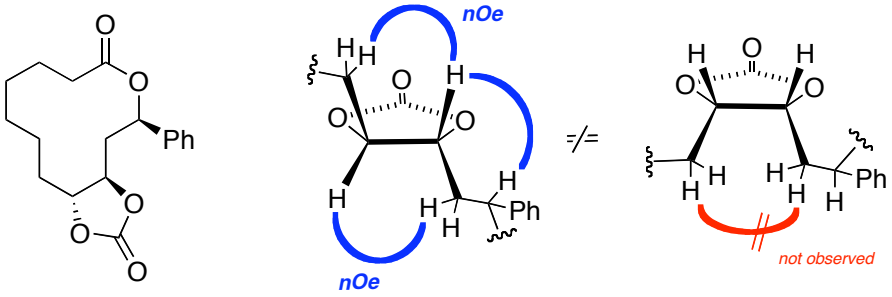
In a roundbottom flask or flame-dried 4 mL vial equipped with a septum cap, diol macrocycle **S16** was dissolved in CH_2Cl_2 (3.0 mL/mmol), and pyridine (6.0 equiv) was added. The resulting solution was cooled to –78 °C, and a solution of triphosgene (0.5 equiv) in CH_2Cl_2 (0.25 M) was added dropwise and the mixture was stirred at the temperature indicated below until the reaction

was complete as judged by TLC analysis. Satd aq NH_4Cl was added the mixture warmed to rt and extracted with EtOAc (3×). The combined organic extracts were washed with 1 M HCl, satd aq $NaHCO_3$, and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography carbonate **S17.**



(3a*R,5*R**,11a*R**)-5-Phenylhexahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxecine-2,7(8*H*)-dione (S17a).** Synthesized from diol macrocycle **S16a** (20.0 mg, 0.0757 mmol). The reaction proceeded at –78 °C in 4 h. Purification by silica flash chromatography (4:1 hexanes/EtOAc) afforded **S17a** as a white solid (12.0 mg, 54%).

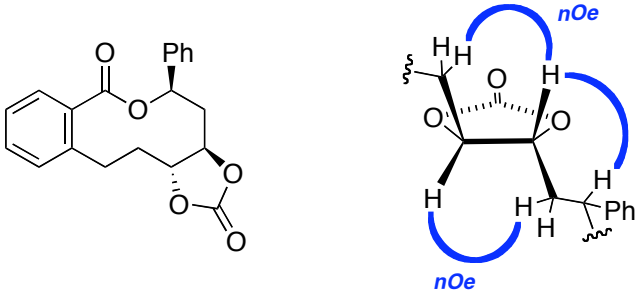
TLC: R_f 0.12 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.42–7.35 (m, 5H), 5.92 (dd, 1H, *J* = 8.6, 6.2), 4.86 (ddd, 1H, *J* = 7.6, 6.2, 3.3), 4.43 (td, 1H, *J* = 7.6, 5.9), 2.64 (ddd, 1H, *J* = 16.7, 4.9, 3.3), 2.48–2.54 (m, 2H), 2.29 (ddd, 1H, *J* = 16.7, 13.2, 3.2), 2.14–2.04 (m, 2H), 2.01–1.93 (m, 1H), 1.83–1.76 (m, 1H), 1.64 (ddt, 1H, *J* = 15.7, 12.3, 3.3), 1.57–1.48 (m, 1H). **^{13}C-NMR** (125 MHz): δ 154.1, 138.7, 129.0, 128.9, 126.3, 81.5, 80.7, 73.2, 40.8, 34.5, 31.6, 24.9, 20.0. **ESI-MS** *m/z* (rel int): (pos) 603.0 ($[2M+Na]^+$, 97), 312.9 ($[M+Na]^+$, 100).



(3a*R,5*R**,13a*R**)-5-Phenyloctahydro-3a*H*-[1,3]dioxolo[4,5-*d*][1]oxacyclododecine-2,7(8*H*)-dione (S17c).** Synthesized from diol macrocycle **S16c** (10.0 mg, 0.0342 mmol). After stirring for 2.75 h at –78 °C, the reaction was warmed to –20 °C and stirred at this temperature overnight to reach complete conversion. Purification by silica gel chromatography (4:1 hexanes/EtOAc) afforded **S17c** as a white solid (7.2 mg, 68%). Some aliphatic impurities remained, but did not affect NMR structure determination.

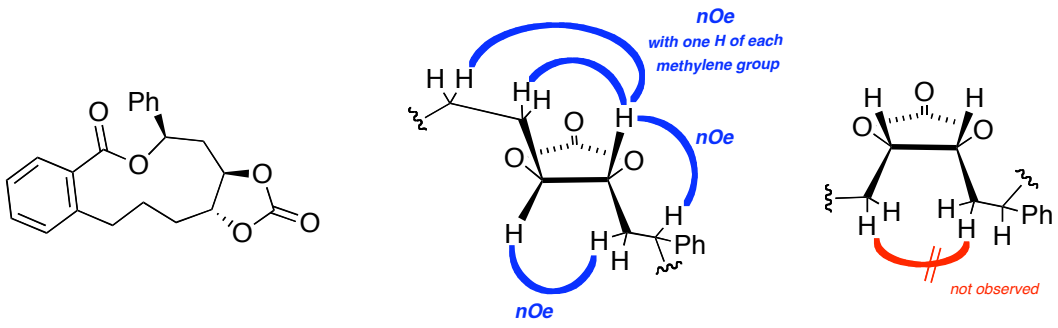
TLC: R_f 0.32 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.37–7.30 (m, 5H), 5.79 (d, 1H, *J* = 11.2), 4.81 (ddd, 1H, *J* = 8.8, 6.1, 2.6), 4.43 (ddd, 1H, *J* = 10.0, 6.1, 3.6), 2.56–2.44 (m, 2H), 2.36–2.28 (m, 2H), 1.94–1.84 (m, 2H), 1.76–1.66 (m, 2H), 1.62–1.41 (m, 6H). **^{13}C-NMR** (125 MHz): δ 172.7, 154.3, 140.1, 129.0, 128.7, 126.0, 81.1, 79.9, 73.5, 40.9, 32.5, 31.9, 23.8,

23.1, 22.6, 21.6. **ESI-MS** *m/z* (rel int): (pos) 659.6 ([2M+Na]$^+$, 50), 341.3 ([M+Na]$^+$, 100); (neg) 317.2 ([M–H]$^-$, 100).



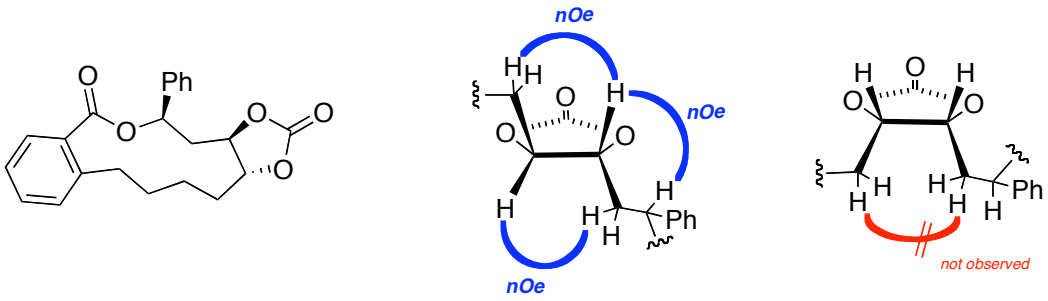
(3a*R,5*R**,11a*R**)-5-Phenylhexahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxecine-2,7(8*H*)-dione (S17d).** Synthesized from diol macrocycle **S16d** (11.2 mg, 0.0359 mmol). After the addition of triphosgene at –78 °C, the mixture was warmed to –20 °C and stirred for 12 h. TLC analysis showed considerable amounts of remaining starting material, thus, another portion of triphosgene (5.3 mg, 0.50 equiv) was added and the mixture was stirred at 0 °C for 2 d, after which TLC analysis showed full conversion of the starting material. Purification by silica flash chromatography (20:1→10:1→4:1 hexanes/EtOAc) afforded **S17d** as a white solid (5.4 mg, 44%, 85–90% purity)

TLC: R_f 0.21 (4:1 hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.48 (td, 1H, *J* = 7.5, 1.4), 7.43–7.36 (m, 7H), 7.30 (td, 1H, *J* = 7.5, 1.0), 5.94–5.91 (m, 1H), 4.87 (dt, 1H, *J* = 11.8, 3.6), 4.69–4.66 (m, 1H), 3.04 (ddd, 1H, *J* = 14.3, 5.3, 3.5), 2.60 (td, 1H, *J* = 14.3, 2.8), 2.48–2.40 (m, 3H), 2.12 (dddd, 1H, *J* = 14.1, 11.8, 5.3, 2.7). **^{13}C-NMR** (125 MHz): δ 167.9, 138.6, 138.1, 133.3, 131.5, 130.6, 129.1, 129.0, 127.3, 127.1, 126.0, 81.8, 79.9, 75.9, 40.8, 36.0, 28.8. **ESI-MS** *m/z* (rel int): (pos) 699.1 ([2M+Na]$^+$, 50), 360.9 ([M+Na]$^+$, 100); (neg) 555.2 (100), 337.0 ([M–H]$^-$, 39).



(3a*R,5*R**,14a*R**)-5-Phenyl-4,5,12,13,14,14a-hexahydrobenzo[*c*][1,3]dioxolo[4,5-*h*][1]oxacycloundecine-2,7(3a*H*)-dione (S17e).** Synthesized from diol macrocycle **S16e** (8.6 mg, 0.026 mmol). After the addition of triphosgene at –78 °C, the reaction mixture was warmed to –20 °C and stirred for 12 h. Satd aq $NaHCO_3$ was added and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (4:1 hexanes/EtOAc) afforded **S17e** as a white solid (5.7 mg, 62%, 85–90% purity)

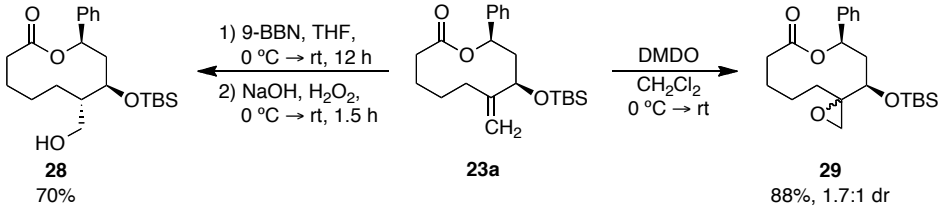
TLC: R_f 0.36 (4:1 hexanes/EtOAc, major diastereomer). **^{1}H-NMR** (500 MHz): δ 7.93 (dd, 1H, *J* = 7.8, 1.3), 7.47–7.24 (m, 8H), 6.15 (dd, 1H, *J* = 11.8, 4.1), 4.98 (dt, 1H, *J* = 11.0, 4.2), 4.64 (ddd, 1H, *J* = 9.4, 4.2, 1.0), 3.68–3.62 (m, 1H), 2.65–2.51 (m, 3H), 2.17–2.11 (m, 1H), 2.03–1.95 (m, 1H), 1.92–1.86 (m, 1H), 1.65–1.57 (m, 1H). **^{13}C-NMR** (125 MHz): δ 167.8, 154.0, 142.5, 139.7, 133.5, 133.2, 131.3, 129.0, 128.7, 128.6, 127.0, 125.9, 83.0, 79.1, 76.6, 43.8, 33.3, 32.6, 26.9. **ESI-MS** *m/z* (rel int): 375.2 ([M+Na]$^+$, 100); (neg) 387.4 ([M+Cl]$^-$, 100), 350.9 ([M–H]$^-$, 65).



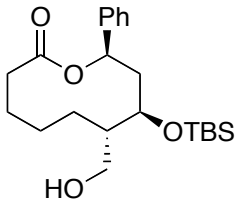
(3a*R,5*R**,15a*R**)-Phenyl-4,5,13,14,15,15a-hexahydro-3a*H*-benzo[*c*][1,3]dioxolo[4,5-*i*][1]-oxacyclododecine-2,7(12*H*)-dione (S17f).** Synthesized from diol macrocycle **S16f** (3.3 mg, 9.7 μmol). After the addition of triphosgene at –78 °C, the reaction mixture was warmed to –20 °C and stirred for 12 h. Satd aq $NaHCO_3$ was added and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (4:1 hexanes/EtOAc) afforded **S17f** as a colorless solid (3.1 mg, 87%, 85–90% purity; aliphatic impurities observed in ^{1}H- and ^{13}C-NMR spectra)

TLC: R_f 0.13 (10:1 hexanes/EtOAc, double elution). **^{1}H-NMR** (500 MHz): δ 7.50–7.39 (m, 6H), 7.32–7.23 (m, 8H), 6.20 (dd, 1H, *J* = 10.8, 1.8), 4.55 (ddd, 1H, *J* = 9.6, 8.0, 3.7), 4.44–4.40 (m, 1H), 3.18 (ddd, 1H, *J* = 14.0, 10.0, 5.9), 2.80 (dt, 1H, *J* = 14.0, 5.1), 2.59–2.47 (m, 2H), 1.83–1.68 (m, 5H), 1.00–0.94 (m, 1H). **^{13}C-NMR** (125 MHz): δ 168.6, 154.2, 140.4, 139.6, 132.9, 131.5, 130.2, 129.2, 129.0, 127.9, 126.2, 125.9, 84.3, 81.1, 73.6, 40.6, 31.3, 29.1, 28.3, 23.6. **ESI-MS** *m/z* (rel int): 389.2 ([M+Na]$^+$, 100).

3. Hydroboration–Oxidation and Epoxidation of Methylenated Macrocycle (23a)

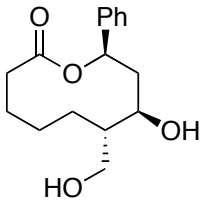


Supplementary Figure 15. Epoxidation and hydroboration–oxidation of methylenated macrocycle 23a. The olefin of macrocycle **23a** (synthesized as described in SECTION G below) was functionalized by stereoselective hydroboration–oxidation with 9-BBN and $NaOH/H_2O_2$ to afford primary alcohol **28** or epoxidation with DMDO to afford spiroepoxide **29**. The relative stereochemistry of **28** was determined by NOESY analysis of the corresponding cyclic carbonate (**28´b**), prepared as follows: **28** → **28´a** (TBAF, THF, 0 °C → rt, 12 h) → **28´b** (CDI, DMAP, CH_2Cl_2, rt, 2 h).



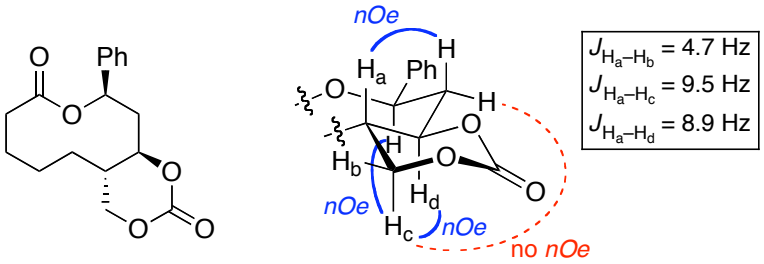
(8*R,10*R**)-8-(*tert*-Butyldimethylsilyloxy)-7-(hydroxymethyl)-10-phenyloxecan-2-one (28).** In a flame-dried, Ar-flushed 4 mL vial equipped with stir bar and septum cap, methylenated macrocycle **23a** (20 mg, 0.054 mmol) was dissolved in THF (0.50 mL) and cooled to 0 ºC. 9-BBN (0.5 M in THF; 0.20 mL, 0.096 mmol, 1.8 equiv) was added via syringe, and the mixture was allowed to warm to rt, then stirred overnight. The reaction was cooled to 0 ºC and 6 N NaOH (54 μL, 0.032 mmol, 6.0 equiv) was added, followed by 30% H_2O_2 (54 μL, 1 mL/mmol substrate). The reaction was warmed to rt and stirred for 1.5 h. The reaction was diluted with water and the aqueous phase was extracted with Et_2O (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (6:1 hexanes/EtOAc; 0.5 vol% Et_3N) afforded **28** as a light yellow oil (14.7 mg, 70%; ≥98:2 dr).

TLC: R_f 0.28 (4:1 Hexanes/EtOAc). **IR** (NaCl, film): 3549 (m, O–H st), 3467 (m, O–H st), 2953 (s, C–H st), 2930 (vs, C–H st), 2883 (m, C–H st), 2858 (m, C–H st), 1732 (vs, C=O st), 1497 (w), 1471 (w), 1463 (w), 1407 (w), 1389 (w), 1362 (w), 1336 (w), 1252 (vs, Si-Me), 1234 (m), 1213 (w), 1156 (m), 1112 (m), 1061 (s), 1027 (s), 1004 (m), 935 (m), 867 (m), 837 (s), 776 (s), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.35 (d, 4H, *J* = 4.2,), 7.30 (dt, 1H, *J* = 8.4, 4.2), 5.89 (dd, 1H, *J* = 11.6, 2.4), 3.71 (ddd, 1H, *J* = 9.7, 5.7, 2.0), 3.62–3.50 (m, 2H), 3.15 (dd, 1H, *J* = 10.2, 3.0), 2.60–2.56 (m, 1H), 2.46 (ddd, 1H, *J* = 14.5, 11.6, 9.8), 2.35–2.29 (m, 1H), 2.24–2.10 (m, 2H), 2.04–1.99 (m, 1H), 1.74–1.62 (m, 2H), 1.55–1.46 (m, 1H), 1.43–1.36 (m, 1H), 1.26–1.17 (m, 1H), 1.07 (ddt, 1H, *J* = 14.9, 11.6, 3.2), 0.88 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H). **^{13}C-NMR** (125 MHz): δ 173.2, 140.5, 128.6, 128.0, 126.1, 74.3, 65.1, 47.5, 44.4, 35.1, 27.5, 25.8, 25.4, 22.7, 20.4, 17.9, -4.6, -4.9. **ESI-MS** *m/z* (rel int): (pos) 415 ($[M+Na]^+$, 100).



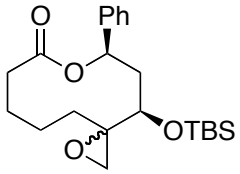
(7*S,8*R**,10*R**)-8-Hydroxy-7-(hydroxymethyl)-10-phenyloxecan-2-one (28´a).** In a 10 mL roundbottom flask, TBS-protected alcohol **28** (72.0 mg, 0.183 mmol) was dissolved in THF (2.5 mL) and the resulting solution was cooled to 0 °C. TBAF (1.0 M in THF, 0.275 mL, 0.275 mmol, 1.5 equiv) was added dropwise and the reaction mixture was warmed to rt over 3 h. The reaction was diluted with satd aq NH_4Cl and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (1:1 hexanes/EtOAc) afforded **28´a** as a clear oil (40 mg, 79%).

TLC: R_f 0.15 (1:1 Hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.37 (dt, 4H, J = 17.6, 8.3), 7.28 (t, 1H, J = 8.3), 5.93 (t, 1H, J = 5.2), 3.74–3.71 (m, 2H), 3.62–3.58 (m, 1H), 2.64–2.58 (m, 1H), 2.32 (d, 2H, J = 5.2), 2.25–2.18 (m, 3H), 1.71–1.62 (m, 2H), 1.48–1.45 (m, 1H), 1.22–1.19 (m, 1H), 1.06-1.00 (m, 1H). **^{13}C-NMR** (125 MHz): δ 174.3, 141.5, 129.9, 129.1, 127.0, 77.3, 75.1, 66.4, 45.1, 44.2, 36.1, 31.5, 26.7, 21.7. **ESI-MS** *m/z* (rel int): (pos) 301 ([M+Na]$^+$, 100); (neg) 277 ([M–H]$^-$, 100).



(4a*S,11*R**,12a*R**)-11-Phenyloctahydro-[1,3]dioxino[4,5-*d*]oxecine-2,9(11*H*)-dione (28´b).** In a 25 mL roundbottom flask, diol **28´a** (2.0 mg, 7.2 μmol) was dissolved in CH_2Cl_2 (1.0 mL). To this solution, 1,1´-carbonyldiimidazole (2.4 mg, 14.4 μmol, 2 equiv) and DMAP (cat.) were added sequentially and the reaction was allowed to stir for 2.5 h at rt. The reaction was diluted with sat aq NH_4Cl and the solution was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (1:1 hexanes/EtOAc) afforded **28´b** as a colorless film (1.5 mg, 68%).

TLC: R_f 0.41 (1:2 Hexanes/EtOAc). **^{1}H-NMR** (500 MHz): δ 7.38–7.34 (m, 4H), 7.31 (ddd, 1H, J = 9.0, 5.8, 2.7), 5.90 (dd, 1H, J = 9.8, 3.1), 4.34 (td, 1H, J = 8.9, 3.5), 4.28 (dd, 1H, J = 10.8, 4.7), 3.95 (dd, 1H, J = 10.8, 9.5), 2.64 (ddd, 1H, J = 15.8, 4.8, 3.3), 2.53 (dddd, 1H, J = 11.8, 9.3, 6.8, 2.3), 2.49–2.41 (m, 2H), 2.26 (ddd, 1H, J = 15.8, 12.8, 2.9), 2.20–2.10 (m, 1H), 1.76–1.64 (m, 2H), 1.61–1.55 (m, 1H), 1.46 (dtd, 1H, J = 15.5, 7.8, 3.5), 1.37–1.29 (m, 1H). **^{13}C-NMR** (125 MHz): δ 173.1, 150.6, 139.7, 129.3, 129.0, 126.5, 84.0, 73.9, 69.9, 36.1, 35.1, 26.5, 25.9, 20.9, **ESI-MS** *m/z* (rel int): (pos) 327 ([M+Na]$^+$, 100).

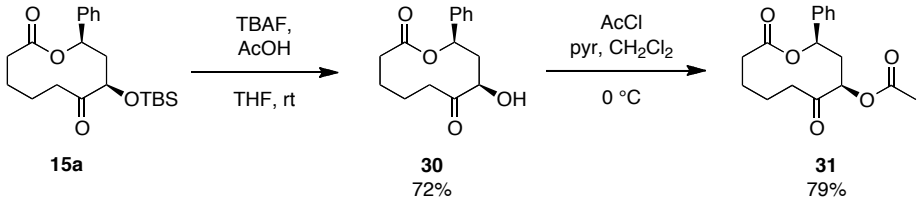


(4*R,6*R**)-4-(*tert*-Butyldimethylsilyloxy)-6-phenyl-1,7-dioxaspiro[2.9]dodecan-8-one (29).** In a flame-dried, Ar-flushed 4 mL vial equipped with stir bar and septum cap, methylenated macrocycle **23a** (5.0 mg, 0.013 mmol) was dissolved in CH_2Cl_2 (0.50 mL) and cooled to 0 ºC. DMDO (0.073 M in acetone; 0.28 mL, 0.024 mmol, 1.8 equiv) was added via syringe, and the mixture was allowed to warm to rt, then stirred at rt for 4 h, after which TLC analysis revealed the appearance of a new spot, as well as unreacted starting material. Thus, the solution was cooled to 0 ºC and additional DMDO (0.073 M in acetone; 0.28 mL, 0.024 mmol, 1.8 equiv) was

added via syringe, and the mixture was allowed to warm to rt overnight, then concentrated by rotary evaporation. Purification by silica flash chromatography (15:1 hexanes/EtOAc; 0.5 vol% Et_3N) afforded **29** as a colorless film (4.6 mg, 88%; 1.7:1 dr).

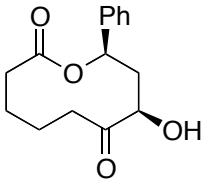
TLC: R_f 0.42 (4:1 Hexanes/EtOAc). **IR** (NaCl, film): 2953 (s, C–H st), 2928 (vs, C–H st), 2886 (m, C–H st), 2856 (m, C–H st), 1733 (vs, C=O st), 1496 (w), 1472 (w), 1461 (w), 1348 (w), 1251 (vs, Si-Me), 1217 (s), 1159 (w), 1141 (w), 1090 (s), 1060 (s), 1026 (m), 956 (w), 900 (w), 867 (m), 837 (s), 777 (s), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.40–7.39 (m, 2H-major, 2H-minor), 7.37–7.33 (m, 2H-major, 2H-minor), 7.31–7.28 (m, 1H-major, 1H-minor), 5.88–5.84 (m, 1H-major, 1H-minor), 3.66–3.59 (m, 1H-major), 3.54–3.50 (m, 1H-minor), 2.83–2.77 (m, 2H-major), 2.61–2.50 (m, 2H-major, 4H-minor), 2.43–2.37 (m, 1H-minor), 2.30–2.20 (m, 3H-minor), 2.17–2.06 (m, 2H-major), 2.02–1.80 (m, 3H-major, 1H-minor), 1.77-1.62 (m, 2H-major, 2H-minor), 1.24–1.14 (m, 1H-major), 1.08–0.98 (m, 1H-minor), 0.87 (s, 9H-major), 0.84 (s, 9H-minor), 0.08 (s, 3H-major), 0.03 (s, 3H-major), 0.02 (s, 3H-minor), 0.01 (s, 3H-minor). **^{13}C-NMR** (125 MHz): δ 172.7, 172.6, 140.9, 140.3, 128.6, 128.5, 128.2, 127.9, 126.4, 126.3, 75.7, 72.9, 72.5, 62.0, 58.9, 50.6, 49.5, 41.9, 41.6, 35.6, 35.4, 28.2, 27.2, 25.7, 25.6, 24.9, 24.2, 22.3, 21.0, 18.1, 17.9, –4.6, –4.7, –4.8, –5.1. **ESI-MS** *m/z* (rel int): (pos) 413 ([M+Na]$^+$, 100). The ratio of diastereomers was determined based on the ^{1}H-NMR signals for the carbinol protons of the TBS-protected alcohol: 3.66–3.59 (m, 1H-major) and 3.54–3.50 (m, 1H-minor).

4. Deprotection and acylation of TBS-protected alcohol macrocycle (15a)



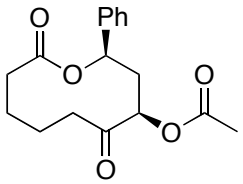
15a **30** 72% **31** 79%

Supplementary Figure 16. Deprotection and acylation of the TBS-protected alcohol in macrocycle 15a. TBS-protected alcohol **15a** was deprotected to unveil the secondary alcohol, which could then be acylated efficiently.



***cis*-8-Hydroxy-10-phenyloxecane-2,7-dione (30).** TBS-protected alcohol **15a** (20.0 mg, 0.396 mmol) was dissolved in THF (5.0 mL), and a freshly prepared solution of TBAF and AcOH (*ca.* 1.0 M each in THF, 0.11 mL, 2.0 equiv) was added and the resulting solution was allowed to stir at rt for 3.5 h. The solvents were removed by rotary evaporation. Purification by silica flash chromatography (2:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **30** as a colorless oil that solidified over time (10.0 mg, 72%).

TLC: R_f 0.36 (1:1 hexanes/EtOAc). **IR** (NaCl, film): 3436 (br, O–H st), 3064 (w), 3033 (w), 2930 (m, C–H st), 2874 (m, C–H st), 1721 (s, C=O st), 1603 (w), 1496 (w), 1451 (w), 1421 (w), 1370 (w), 1336 (w), 1311 (w), 1296 (m), 1252 (m), 1231 (w), 1168 (m), 1102 (w), 1046 (m, C–OH/C–O st), 1020 (m), 956 (w), 935 (w), 862 (m), 840 (w), 810 (w). **^{1}H-NMR** (500 MHz): δ 7.36–7.27 (m, 5H), 5.97 (dd, 1H, J = 7.5, 3.3), 4.27 (td, 1H, J = 7.5, 4.1), 2.95 (d, 1H, J = 7.5), 2.71 (ddd, 1H, J = 18.4, 13.1, 3.3), 2.63–2.55 (m, 2H), 2.47–2.32 (m, 3H), 2.28–2.11 (m, 2H), 1.69–1.64 (m, 1H), 1.55–1.48 (m, 1H). **^{13}C-NMR** (125 MHz): δ 211.1, 172.5, 139.4, 128.6, 128.0, 125.9, 74.9, 72.8, 42.3, 37.0, 34.6, 22.4, 20.5. **ESI-MS** *m/z* (rel int): (pos) 285.0 ($[M+Na]^+$, 100), 547.3 ($[2M+Na]^+$, 25) (neg) 261.2 ($[M–H]^-$, 15), 297.2 ($[M+Cl]^-$, 100), 559.5 ($[2M+Cl]^-$, 30).



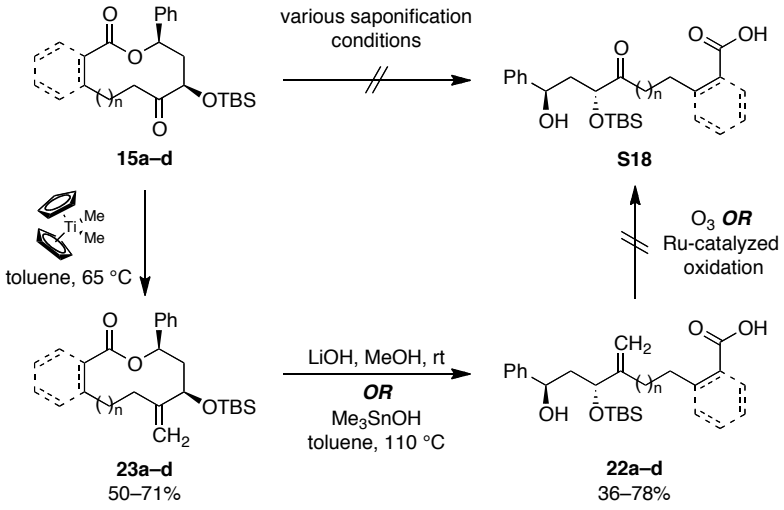
***cis*-5,10-Dioxo-2-phenyloxecan-4-yl acetate (31).** Macrocyclic alcohol **30** (21.5 mg, 0.082 mmol) was dissolved in pyridine (0.50 mL) and CH_2Cl_2 (0.50 mL) and cooled to 0 °C. Acetyl chloride (0.06 mL, *ca*. 10 equiv) was added dropwise; at the end of the addition, rapid formation of a white precipitate was observed and the reaction was complete as judged by TLC analysis (aliquot worked up with satd aq $NaHCO_3$/EtOAc). Satd aq $NaHCO_3$ was added, followed by water to dissolve the precipitate, and the mixture was extracted with EtOAc (3×). The combined organic extracts were washed with water (2×), satd aq NH_4Cl, and brine, dried ($MgSO_4$) and concentrated by rotary evaporation. Purification by silica flash chromatography (10:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **31** as a white, crystalline solid (19.6 mg, 79%).

TLC: R_f 0.64 (1:1 hexanes/EtOAc). **IR** (NaCl, film): 2932 (w, C–H st), 1729 (vs, shoulder at *ca*. 1740, C=O st), 1452 (w), 1438 (w), 1426 (w), 1372 (w), 1274 (m), 1238 (s, Si-Me δ sy), 1166 (m), 1051 (m, C–O/Si–O st), 1027 (m), 960 (w), 937 (w), 913 (w), 901 (w), 841 (w), 809 (w), 762 (w), 700 (m). **^{1}H-NMR** (500 MHz): δ 7.35–7.30 (m, 5H), 5.96 (dd, 1H, J = 11.4, 2.3), 4.95 (dd, 1H, J = 11.0, 3.6), 2.75–2.60 (m, 3H), 2.53 (ddd, 1H, J = 16.6, 5.9, 2.5), 2.30–2.17 (m, 3H), 2.14–2.03 (m, 1H), 2.01 (s, 3H), 1.60 (m, 1H, J = 5.6, 2.8), 1.50–1.42 (m, 1H). **^{13}C-NMR** (125 MHz): δ 206.7, 172.6, 170.5, 139.1, 128.8, 128.6, 126.4, 76.4, 72.7, 39.7, 38.9, 34.6, 22.3, 20.5, 20.4. **ESI-MS** *m/z* (rel int): (pos) 631.2 ($[M+2Na]^+$, 95), 327.1 ($[M+Na]^+$, 100), 309.1 ($[M–O+Na]^+$, 93).

G. SYNTHESIS OF RELATED SECO-ACIDS (22a–d, S22)

1. SYNTHESIS OF *SECO*-ACIDS (22a–d)

Attempts to saponify macrolactones **15a–d** directly to **S18** using various literature procedures literature (*e.g.*, LiOH, NaOH) proved unsuccessful, as either no reaction or decomposition occurred (**Supplementary Fig. 17**). Presuming that the reactivity of the α-siloxy ketones was the origin of these problems, the ketones were olefinated using Petasis' reagent (for some substrates, partial olefination of the ester function was observed as a side reaction). Subsequent hydrolysis using either LiOH in MeOH or Me_3SnOH in toluene afforded the *seco*-acid cyclization precursors **22a–d**. Consistent with our inability to access **S18** by saponification of **15a–d**, numerous attempts at oxidative cleavage of the methylene group of **22a–d** also failed; ozonolysis resulted in the formation of at least three side products and the desired *seco*-acid could not be successfully isolated from the crude mixture; ruthenium-catalyzed oxidation protocols led to complex mixtures. Thus, we presume **S18** to be inherently unstable, making direct macrocyclization to **15a–d** unfeasible.



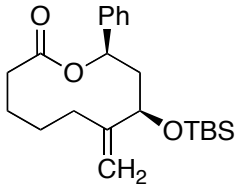
Supplementary Figure 17. Synthesis of methylenated *seco*-acids 22a–d as substrates for macrocyclization. The linear cyclization precursors **22a–d** were synthesized methylenation of the macrocyclic ketone and subsequent saponification. Attempts to access the corresponding ketone **S18** remained unsuccessful.

a. General protocol for Petasis olefination of macrocyclic ketones 15a–d[17]

In a flame-dried, Ar-flushed vial (small scale) or sealed tube (large scale), equipped with a stir bar and a septum, macrocyclic ketone **15** was dissolved in a solution of dimethyl titanocene (Cp_2TiMe_2) in toluene prepared by Howell's protocol[18] (*ca.* 0.4–0.6 M; concentration determined by ^{1}H-NMR analysis; 2.5 equiv). The septum was replaced by a screw cap (vial) or Teflon stopper (sealed tube), respectively. ***NOTE:*** The tube **must** be sealed tightly, as a loss in internal pressure may lead to a much lower conversion! The tube was heated at 65 °C for at least 12 h.

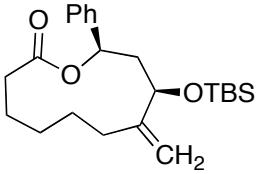
[17] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
[18] Blauvelt, M. L.; Howell, A. R. *J. Org. Chem.* **2008**, *73*, 517.

The progress of the reaction was monitored by TLC analysis of small reaction aliquots (removed from the reaction vessel under Ar stream after temporarily cooling to rt). After the reaction had reached sufficient conversion (traces of the starting material were visible, as well as the presumably doubly olefinated product at higher R_f), the reaction solution was transferred into a roundbottom flask with rinsing with excess CH_2Cl_2, such that the final solution contains toluene and CH_2Cl_2 in at least a 1:10 ratio. Flash grade silica gel was then added, leading to evolution of gas, and the solvents are subsequently removed by rotary evaporation. The resulting yellow-orange powder was dry-loaded directly onto column for purification by silica flash chromatography (hexanes/EtOAc) to afford methylenated macrocycle **23**.



***cis*-8-(*tert*-Butyldimethylsilyloxy)-7-methylene-10-phenyloxecan-2-one (23a).** Synthesized from macrocyclic ketone **15a** (204 mg, 0.542 mmol). Purification by silica flash chromatography (20:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **23a** as colorless solid (111 mg, 55%).

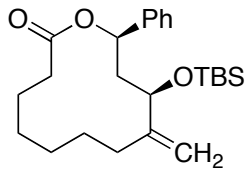
TLC: R_f 0.47 (10:1 hexanes/EtOAc). **mp** = 55.7–58.4 °C. **IR** (NaCl, film): 2952 (s, C–H st), 2929 (s, C–H st), 2894 (m, C–H st), 2856 (s, C–H st), 1733 (C=O st), 1495 (w), 1471 (w), 1460 (w), 1361 (w), 1349 (w), 1251 (s, Si-Me δ sy), 1212 (m), 1146 (w), 1089 (m, C–O/Si–O st), 1059 (vs, C–O/Si–O st), 1023 (m), 1006 (w), 946 (w), 896 (m), 880 (m), 835 (s, C–Si st), 777 (m), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.37–7.32 (m, 4H), 7.29–7.27 (m, 1H), 5.75 (d, 1H, J = 10.8), 5.17 (s, 1H), 4.92 (s, 1H), 4.18 (dd, 1H, J = 10.2, 4.7), 2.51–2.43 (m, 2H), 2.35–2.28 (m, 1H), 2.24–2.17 (m, 1H), 2.11–1.95 (m, 4H), 1.70–1.63 (m, 2H), 0.84 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). **^{13}C-NMR** (125 MHz, C_6D_6): δ 171.7, 150.9, 141.1, 128.5, 128.3, 126.7, 109.4, 76.8, 72.5, 45.2, 35.5, 29.3, 25.7, 24.7, 22.4, 18.1, –4.8, –5.2. **ESI-MS** *m/z* (rel int): (pos) 397.2 ($[M+Na]^+$, 95), 375.2 ($[M+H]^+$, 90), 243.0 ($[M–TBSOH+H]^+$, 100).



***cis*-9-(*tert*-Butyldimethylsilyloxy)-8-methylene-11-phenyloxacycloundecan-2-one (23b).** Synthesized from macrocycle **15b** (80.0 mg, 0.205 mmol). Purification by silica flash chromatography (20:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **23b** as slightly yellow oil (43.2 mg, 55%).

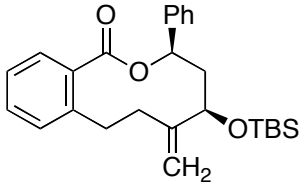
TLC: R_f 0.62 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2951 (s, C–H st), 2930 (s, C–H st), 2856 (m, C–H st), 1734 (vs, C=O st), 1648 (w, C=C st), 1461 (m), 1389 (w), 1361 (m), 1334 (m), 1252 (vs, Si-Me δ sy), 1160 (m), 1148 (m), 1099 (m, C–O/Si–O st), 1070 (s, C–O/Si–O st), 1044

(s, C–O/Si–O st), 1014 (m), 969 (w), 903 (w), 872 (m), 836 (s, C–Si st), 776 (s, C–Si st), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.36–7.26 (m, 5H), 5.68 (dd, 1H, *J* = 10.6, 0.7), 5.10 (s, 1H), 4.77 (s, 1H), 4.31 (dd, 1H, *J* = 8.4, 4.9), 2.53–2.41 (m, 3H), 2.18–2.07 (m, 2H), 1.99–1.89 (m, 2H), 1.67–1.51 (m, 4H), 1.36–1.34 (m, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). **^{13}C-NMR** (125 MHz): δ 172.6, 149.4, 141.7, 128.7, 128.0, 126.2, 110.9, 76.2, 73.8, 44.5, 36.3, 26.0, 25.8, 25.3, 23.9, 20.8, 18.3, –4.63, –4.80. **ESI-MS** *m/z* (rel int): (pos) 427.0 ([M+K]$^+$, 60), 411.1 ([M+Na]$^+$, 100); (neg) 387.1 ([M–H]$^-$, 100).



***cis*-10-(*tert*-Butyldimethylsilyloxy)-9-methylene-12-phenyloxacyclododecan-2-one (23c).** Synthesized from macrocycle **15c** (120 mg, 0.297 mmol). Purification by silica flash chromatography (20:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **23c** as colorless oil (60.4 mg, 50%).

TLC: R_f 0.72 (10:1 hexanes/EtOAc). **IR** (NaCl, film): 2952 (s, C–H st), 2931 (s, C–H st), 2857 (m, C–H st), 1734 (vs, C=O st), 1654 (w), 1463 (m), 1389 (w), 1361 (m), 1333 (m), 1250 (s, Si-Me δ sy), 1179 (m), 1154 (m), 1137 (m), 1102 (m, C–O/Si–O st), 1069 (s, C–O/Si–O st), 1055 (s, C–O/Si–O st), 1037 (m, C–O/Si–O st), 987 (m), 904 (m), 871 (m), 836 (s, C–Si st), 775 (s, C–Si st), 698 (m). **^{1}H-NMR** (500 MHz): δ 7.35–7.26 (m, 7H), 5.82 (dd, 1H, *J* = 9.8, 1.5), 5.11 (s, 1H), 4.83 (s, 1H), 4.22 (t, 1H, *J* = 5.9), 2.41 (ddd, 1H, *J* = 15.3, 9.7, 6.0), 2.36–2.26 (m, 3H), 2.05 (ddd, 1H, *J* = 14.9, 9.3, 6.0), 1.90 (ddd, 1H, *J* = 15.2, 5.9, 1.5), 1.83–1.35 (m, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H). **^{13}C-NMR** (125 MHz): δ 173.3, 150.2, 141.9, 128.7, 127.9, 126.1, 111.7, 74.3, 74.1, 45.7, 34.9, 29.9, 26.7, 26.0, 25.7, 25.0, 22.9, 18.3, –4.3, –4.8. **ESI-MS** *m/z* (rel int): (pos) 443.1 ([M+NH_4+Na]$^+$, 40), 425.1 ([M+Na]$^+$, 100); (neg) 401.1 ([M–H]$^-$, 60).



***cis*-5-(*tert*-Butyldimethylsilyloxy)-6-methylene-3-phenyl-3,4,5,6,7,8-hexahydro-1*H*-benzo-[*c*]oxecin-1-one (23d).** Synthesized from macrocycle **15d** (100 mg, 0.236 mmol). Purification by silica flash chromatography (20:1 hexanes/EtOAc, 0.5 vol% Et_3N) afforded **23d** as pale yellow solid (70.4 mg, 71%).

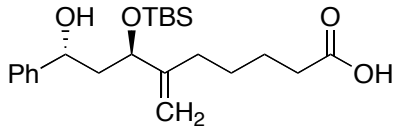
TLC: R_f 0.70 (10:1 hexanes/EtOAc). **mp** = 99.6–100.1 °C. **IR** (NaCl, film): 2953 (m, C–H st), 2929 (m, C–H st), 2883 (w), 2856 (m, C–H st), 1714 (vs, C=O st), 1603 (w), 1471 (w), 1449 (w), 1331 (w), 1289 (m), 1265 vs, Si-Me δ sy), 1252 (m, Si-Me δ sy), 1126 (s, C–O/Si–O st), 1071 (s, C–O/Si–O st), 1053 (s, C–O/Si–O st), 1025 (m, C–O/Si–O st), 1004 (m), 958 (w), 936 (w), 881 (m), 816 (s, C–Si st), 777 (m), 754 (m), 703 (s). **^{1}H-NMR** (500 MHz): δ 7.94 (dd, 1H, *J* = 7.6, 1.3), 7.47–7.44 (m, 3H), 7.36 (t, 2H, *J* = 7.6), 7.31–7.25 (m, 6H), 5.89 (d, 1H, *J* = 11.3), 4.87 (s, 1H), 4.40 (dd, 1H, *J* = 10.9, 5.2), 4.12 (s, 1H), 4.05 (td, 1H, *J* = 13.2, 4.1), 2.96 (dt, 1H, *J* =

13.2, 4.1), 2.77 (dt, 1H, *J* = 13.2, 4.4), 2.61 (ddd, 1H, *J* = 14.4, 11.5, 10.9), 2.12 (dd, 1H, *J* = 14.4, 5.2), 1.99 (td, 1H, *J* = 13.2, 4.4), 0.87 (s, 9H), 0.04 (s, 3H), –0.01 (s, 3H). **^{13}C-NMR** (125 MHz): δ 168.6, 147.3, 143.1, 140.5, 132.9, 132.2, 131.5, 130.7, 128.8, 128.2, 126.6, 126.6, 117.9, 77.9, 73.8, 43.7, 36.2, 30.7, 25.9, 18.3, –4.6, –4.9. **ESI-MS** *m/z* (rel int): (pos) 445.5 ([M+Na]$^+$, 100).

b. General protocol for saponification of macrolactones 23a–d using LiOH in MeOH

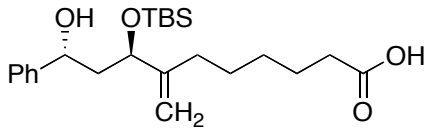
Macrocycle **23** was dissolved in MeOH (25 mL/mmol, 0.04 M solution) at rt. LiOH (35 equiv) was added neat in 5–6 portions over 5–10 min at rt. The reaction mixture was stirred at rt for 6–18 h. Progress of the reaction was monitored by TLC analysis (aliquots worked up with 1.0 M HCl/EtOAc). After the reaction was complete, the mixture was cooled to 0 °C and satd aq NH_4Cl was added, followed by 1.0 M HCl. The still-cool mixture was extracted with EtOAc (5×). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to *ca.* 1/5th of their original volume by rotary evaporation. An approximately equal volume of cyclohexane was added to remove azeotropically any trace AcOH contaminants from the EtOAc, and all solvents were removed by rotary evaporation. The crude residue was dried under high vacuum and immediately purified by silica flash chromatography to afford *seco*-acid **22**.

NOTE: *seco*-Acids **22** appear to be sensitive to overly acidic conditions, leading to decomposition and/or silyl migration. Avoid generating and/or storing concentrated solutions that may contain traces of AcOH (occasional contaminants from EtOAc) or other acids. For the same reason, CH_2Cl_2/MeOH eluent mixtures are recommended for silica flash chromatography instead of hexanes/EtOAc/AcOH mixtures, although the latter were used successfully in some cases.



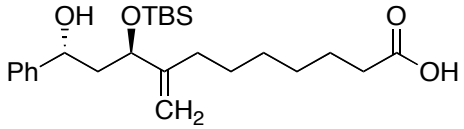
***trans*-7-(*tert*-Butyldimethylsilyloxy)-9-hydroxy-6-methylene-9-phenylnonanoic acid (22a).** Synthesized from macrocyclic olefin **23a** (74.8 mg, 0.200 mmol). Purification by silica flash chromatography (19:1 CH_2Cl_2/MeOH) afforded **22a** as colorless solid (48.9 mg, 62%).

TLC: R_f 0.37 (19:1 CH_2Cl_2/MeOH). **mp** = 75.1–79.1 °C. **IR** (NaCl, film) 3406 (br, O–H st), 3137 (br, O–H st), 3085 (w), 3064 (w), 3030 (w), 2952 (s, C–H st), 2929 (m, C–H st), 2894 (m, C–H st), 2857 (m, C–H st), 1710 (vs, C=O st), 1462 (w), 1410 (w), 1390 (w), 1361 (w), 1253 (s, Si-Me δ sy), 1195 (w), 1092 (m, C–OH/C–O/Si–O st), 1059 (s, C–OH/C–O/Si–O st), 981 (w), 901 (m), 835 (vs, C–Si st), 777 (m), 699 (m). **^{1}H-NMR** (500 MHz): δ 7.35–7.31 (m, 4H), 7.27–7.23 (m, 1H), 5.21 (s, 1H), 4.97 (s, 1H), 4.89 (dd, 1H, *J* = 10.0, 2.2), 4.42 (t, 1H, *J* = 4.4), 2.39 (t, 2H, *J* = 7.4), 2.13–2.06 (m, 1H), 2.02–1.91 (m, 2H), 1.86 (ddd, 1H, *J* = 14.5, 5.6, 2.2), 1.72–1.65 (m, 2H), 1.60–1.51 (m, 2H), 0.11 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR** (125 MHz): δ 177.4, 149.7, 145.0, 128.5, 127.3, 125.8, 110.6, 74.2, 71.1, 44.6, 33.6, 31.7, 27.4, 26.0, 24.7, 18.4, –4.6, –5.2. **ESI-MS** *m/z* (rel int): (pos) 415.0 ([M+Na]$^+$, 100); (neg) 783.4 ([2M–H]$^-$, 61), 391.1 ([M–H]$^-$, 100).



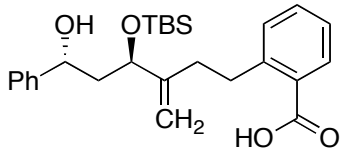
***trans*-8-(*tert*-Butyldimethylsilyloxy)-10-hydroxy-7-methylene-10-phenyldecanoic acid (22b).** Synthesized from macrocyclic olefin **23b** (35.0 mg, 0.0901 mmol). Purification by silica flash chromatography (1:1 hexanes/EtOAc, 1.0 vol% AcOH) afforded **22b** as colorless oil (28.0 mg, 78%).

TLC: R_f 0.36 (19:1 CH_2Cl_2/MeOH). **IR** (NaCl, film): 3400 (br, O–H st), 3159 (br, O–H st), 385 (w), 3064 (w), 3029 (w), 2951 (s, C–H st), 2929 (vs, C–H st), 2857 (s, C–H st), 1710 (vs, C=O st), 1648 (w), 1462 (m), 1410 (m), 1361 (w), 1253 (s, Si-Me δ sy), 1194 (m), 1093 (s, C–OH/C–O/Si–O st), 1059 (s, C–OH/C–O/Si–O st), 1005 (w), 982 (m), 939 (w), 900 (m), 835 (s, C–Si st), 778 (m, C–Si st), 757 (m), 699 (s). **^{1}H-NMR** (500 MHz): δ 7.35–7.31 (m, 4H), 7.25–7.22 (m, 1H), 5.21 (s, 1H), 4.96 (s, 1H), 4.90 (dd, 1H, J = 9.9, 2.1), 4.42 (t, 1H, J = 4.4), 2.36 (t, 2H, J = 7.5), 2.10–2.04 (m, 1H), 1.98–1.91 (m, 2H), 1.85 (ddd, 1H, J = 14.5, 5.6, 2.1), 1.66 (quintet, 2H, J = 7.5), 1.56–1.44 (m, 2H), 1.43–1.35 (m, 2H), 1.26 (s, 1H), 0.95 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR** (125 MHz): 179.4, 149.9, 144.9, 128.5, 127.3, 125.8, 110.4, 74.2, 71.1, 44.4, 34.1, 32.0, 29.1, 27.7, 26.0, 24.7, 18.3, –4.6, –5.2. **ESI-MS** *m/z* (rel int): (pos) 429.4 ([M+Na]$^+$, 100); (neg) 405.3 ([M–H]$^-$, 100).



***trans*-9-(*tert*-Butyldimethylsilyloxy)-11-hydroxy-8-methylene-11-phenylundecanoic acid (22c).** Synthesized from macrocyclic olefin **23c** (32.1 mg, 0.0798 mmol). Purification by silica flash chromatography (19:1 CH_2Cl_2/MeOH) afforded **22c** as colorless oil (12.0 mg, 36%).

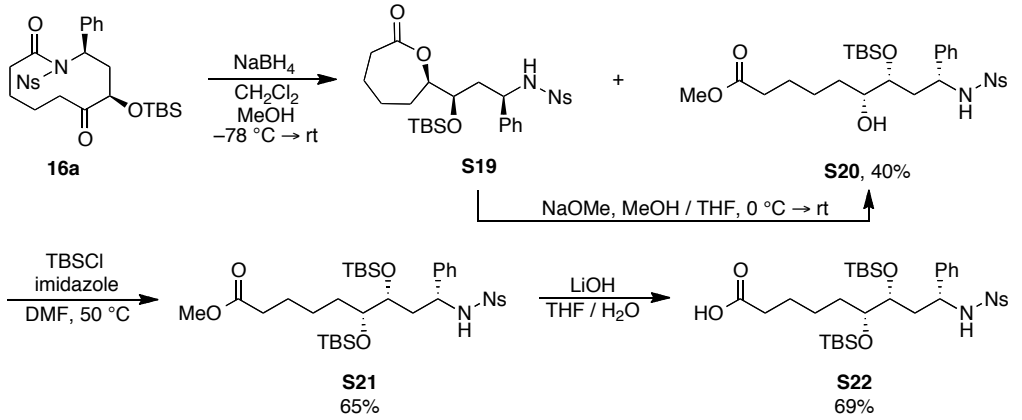
TLC: R_f 0.31 (19:1 CH_2Cl_2/MeOH). **IR** (NaCl, film): 3398 (br, O–H st), 3169 (br, O–H st), 3085 (w), 3064 (w), 3030 (w), 2949 (s, C–H st), 2929 (vs, C–H st), 2856 (s, C–H st), 1710 (s, C=O st), 1462 (w), 1409 (w), 1390 (w), 1361 (w), 1252 (m, Si-Me δ sy), 1219 (w), 1082 (m, C–OH/C–O/Si–O st), 1060 (m, C–OH/C–O/Si–O st), 983 (w), 901 (w), 835 (s, C–Si st), 776 (s, C–Si st). **^{1}H-NMR** (500 MHz): δ 7.36–7.31 (m, 4H), 7.26–7.22 (m, 1H), 5.20 (s, 1H), 4.96 (s, 1H), 4.90 (dd, 1H, J = 10.0, 2.2), 4.42 (t, 1H, J = 4.2), 2.35 (t, 2H, J = 7.3), 2.06 (ddd, 1H, J = 15.6, 9.2, 6.6), 1.94 (m, 2H, J = 4.0), 1.85 (ddd, 1H, J = 14.5, 5.4, 2.2), 1.65 (quintet, 2H, J = 7.3), 1.54–1.43 (m, 2H), 1.37–1.31 (m, 4H), 0.95 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H). **^{13}C-NMR** (125 MHz): δ 177.8, 150.0, 145.0, 128.5, 127.3, 125.8, 110.3, 74.3, 71.1, 44.4, 33.8, 32.1, 29.3, 29.0, 27.8, 26.0, 24.8, 18.4, –4.6, –5.2. **ESI-MS** *m/z* (rel int): (pos) 443.0 ([M+Na]$^+$, 100); (neg) 419.1 ([M–H]$^-$, 100).



2-(*trans*-4-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-3-methylene-6-phenylhexyl)benzoic acid (22d). In a flame-dried, Ar-flushed 4 mL vial equipped with a stir bar and a septum cap, macrocyclic olefin **23d** (20.8 mg, 0.0492 mmol) was dissolved in toluene (0.20 mL; 0.25 M solution) at rt. Trimethyltin hydroxide (178.0 mg, 0.980 mmol, 20.0 equiv) was added neat, and the tube was sealed with a screw cap and heated to 110 °C for 12 h. The reaction was monitored by TLC analysis (aliquots worked up with 1.0 M HCl/EtOAc). After the reaction was complete, the mixture was cooled to 0 °C and satd aq NH_4Cl was added, followed by 1.0 M HCl. The still-cool mixture was extracted with EtOAc (5×), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to *ca*. 1/5 of their volume by rotary evaporation. An approximately equal volume cyclohexane was added and all solvents were removed by rotary evaporation. Purification by silica flash chromatography (40:1 CH_2Cl_2/MeOH) afforded **22d** as colorless oil (13.2 mg, 60%).

TLC: R_f 0.28 (19:1 CH_2Cl_2/MeOH). **IR** (NaCl, film): 3408 (br, O–H st), 3144 (br, O–H st), 3064 (w), 3028 (w), 2954 (s, C–H st), 2929 (s, C–H st), 2892 (m, C–H st), 2857 (m, C–H st), 2647 (w), 1693 (vs, C=O st), 1650 (w), 1602 (w), 1576 (w), 1491 (w), 1454 (w), 1405 (w), 1389 (w), 1299 (m), 1256 (s, Si-Me δ sy), 1135 (w), 1086 (s, C–OH/C–O/Si–O st), 1061 (s, C–OH/C–O/Si–O st), 972 (w), 901 (m), 835 (vs, C–Si st), 777 (m, C–Si st), 750 (m), 700 (m). **^{1}H-NMR** (500 MHz): δ 7.99 (d 1H, J = 7.5,), 7.48 (td, 1H, J = 7.5, 0.9), 7.34 (m, 2H), 7.31–7.27 (m, 4H), 7.20 (t, 1H, J = 7.5), 5.28 (s, 1H), 5.08 (s, 1H), 4.95 (dd, 1H, J = 10.3, 1.8), 4.58–4.56 (m, 1H), 3.32 (td, 1H, J = 12.1, 4.3), 3.02 (td, 1H, J = 12.1, 5.4), 2.38 (td, 1H, J = 13.2, 5.4), 2.27 (td, 1H, J = 13.2, 4.3), 2.01 (ddd, 1H, J = 14.5, 10.3, 3.7), 1.88 (ddd, 1H, J = 14.5, 6.1, 1.8), 1.26 (s, 1H), 0.97 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H). **^{13}C-NMR** (125 MHz): δ 171.7, 150.1, 145.1, 144.9, 133.1, 132.0, 131.3, 128.4, 128.2, 127.3, 126.4, 125.8, 110.7, 73.4, 71.3, 44.9, 34.9, 34.1, 26.0, 18.4, –4.5, –5.1. **ESI-MS** *m/z* (rel int): (pos) 903.9 ($[2M+Na]^+$, 25), 463.4 ($[M+Na]^+$, 100); (neg) 879.8 ($[2M–H]^-$, 12), 439.5 ($[M– H]^-$, 100).

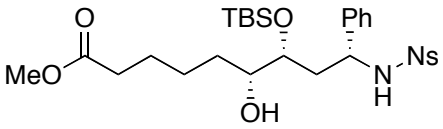
2. SYNTHESIS OF LINEAR *N*-NOSYL AMINO ACID (S22)



Supplementary Figure 18. Synthesis of *N*-nosyl amino acid S22. Exposure of *N*-nosyl-protected macrolactam **16a** to $NaBH_4$ in CH_2Cl_2 / MeOH resulted in a mixture of products, including lactone **S19** and methyl ester **S20**. Presumably, reduction of the ketone of **16a** is followed by a transannular lactonization event to yield lactone **S19**, which then undergoes methanolysis to afford methyl ester **S20**. Treatment of the crude mixture with NaOMe in MeOH / THF converts lactone **S19** to methyl ester **S20**, which is then TBS protected to give **S21**. Exposure of methyl ester **S21** to LiOH then affords *N*-nosyl-protected amino acid **S22**, which is the then used as the precursor for macrocyclization.

The attempted direct hydrolysis of macrolactam **16a** using reagents such as LiOH and NaOH led to complex mixtures. We suspected the sensitive ketone functionality of **16a** played a role in complicating the saponification reaction and, thus, we attempted an analogous ketone methylenation approach as was used in the macrolactone series above. Unfortunately, repeated attempts at methylenation (*e.g.*, Petasis, Tebbe, Wittig) of the ketone of **16a** resulted only in decomposition of the starting material. This may result from side reactions of the activated carbonyl in the *N*-nosylamide moiety.

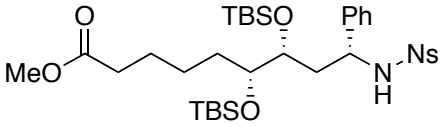
Interestingly, treatment of macrolactam **16a** with $NaBH_4$ in CH_2Cl_2/MeOH resulted in a mixture of products, including caprolactone **S19** and methyl ester **S20** (**Supplementary Fig. 18**). Presumably, macrolactam **16a** undergoes $NaBH_4$ reduction followed by transesterification to yield lactone **S19**, which can then undergo methanolysis to afford methyl ester **S20**. Notably, lactone **S19** was converged to methyl ester **S20** by treatment of the crude mixture with NaOMe/MeOH in THF. Methyl ester **S20** was then converted to the *N*-nosyl amino acid **S22** as a substrate for macrocyclization experiments in SECTION H below.



(6*R,7*R**,9*R**)-Methyl-7-(*tert*-butyldimethylsilyloxy)-6-hydroxy-9-(2-nitrophenylsulfonamido)-9-phenylnonanoate (S20).** In a flame-dried, Ar-flushed 4 mL vial equipped with stir bar and septum cap, macrolactam **16a** (40 mg, 0.071 mmol) was dissolved in CH_2Cl_2 (0.30 mL) and MeOH (0.30 mL). The solution was cooled to –78 ºC and $NaBH_4$ (3.0 mg, 0.079 mmol, 1.1 equiv) was added as a solid. The reaction was allowed to warm rt and stirred for 12 h, after which the majority of macrolactam **16a** had been consumed and several new spots were observed

by TLC analysis. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to afford a mixture of lactone **S19** and methyl ester **S20**. The crude product was dissolved in THF (1 mL) and cooled to 0 ºC. NaOMe (0.5 M in MeOH, 1 mL, 0.5 mmol, 7 equiv) was added and the reaction was warmed to rt and stirred for 12 h. Satd aq NH_4Cl was added at rt, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by preparative TLC (4:1 hexanes/EtOAc) afforded **S20** as a clear oil (16.9 mg, 40%).

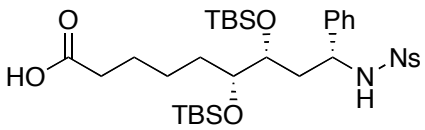
TLC: R_f 0.23 (2:1 Hexanes/EtOAc). **IR** (NaCl, film): 3433 (br, s, O–H), 3091 (w), 3078 (w), 3029 (w), 2952 (s, C–H st), 2930 (s, C–H st), 2899 (m, C–H st), 2857 (m), 1735 (s, C=O st), 1595 (w), 1541 (vs, N=O st), 1459 (w), 1440 (w), 1413 (w), 1361 (m), 1257 (m, Si–Me), 1168 (vs, S=O st), 1125 (w), 1092 (m), 1075 (m), 836 (m), 778 (m), 741 (m), 730 (m), 701 (m). **^{1}H-NMR** (500 MHz): δ 7.66 (dd, 1H, J = 7.9, 1.1), 7.51–7.45 (m, 2H), 7.29 (td, 1H, J = 7.7, 1.1), 7.03 (tt, 5H, J = 6.0, 3.0), 6.02 (d, 1H, J = 8.5), 4.65 (td, 1H, J = 8.5, 5.4), 3.73–3.70 (m, 1H), 3.66 (s, 3H), 3.54–3.50 (m, 1H), 2.31 (t, 2H, J = 7.5), 2.20 (ddd, 1H, J = 14.4, 9.5, 4.9), 1.96 (d, 1H, J = 7.0), 1.81–1.76 (m, 1H), 1.68–1.57 (m, 2H), 1.52–1.27 (m, 4H), 0.93 (s, 9H), 0.16 (s, 3H), 0.05 (s, 3H). **^{13}C-NMR** (125 MHz): δ 174.1, 147.2, 140.2, 134.6, 132.7, 132.3, 130.8, 128.5, 127.8, 126.5, 124.7, 73.1, 72.0, 56.6, 51.5, 41.4, 34.0, 32.6, 26.0, 25.6, 24.9, 18.2, –4.3, –4.4. **ESI-MS** *m/z* (rel int): (pos) 617 ($[M+H]^+$, 100); (neg) 593 ($[M–H]^-$, 100).



(6*R,7*R**,9*R**)-Methyl-6,7-bis(*tert*-butyldimethylsilyloxy)-9-(2-nitrophenylsulfonamido)-9-phenylnonanoate (S21).** In a flame-dried, Ar-flushed 4 mL vial equipped with stir bar and septum cap, alcohol **S20** (16.0 mg, 0.0269 mmol) was dissolved in DMF (0.25 mL). To this solution was added imidazole (9.5 mg, 0.14 mmol, 5.0 equiv), then TBSCl (8.1 mg, 0.054 mmol, 2.0 equiv), and the reaction mixture was stirred for 12 h at 50 ºC. The reaction was cooled to rt, quenched with satd aq $NaHCO_3$, and extracted with EtOAc (3×). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (6:1 hexanes/EtOAc) afforded **S21** as a clear oil (12.4 mg, 65%).

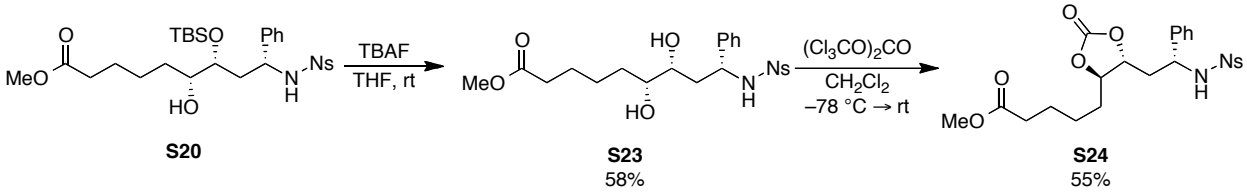
TLC: R_f 0.60 (2:1 Hexanes/EtOAc). **IR** (NaCl, film): 3360 (m, N-H), 2952 (s, C–H st), 2930 (s, C–H st), 2893 (m, C–H st), 2857 (s, C–H st), 1739 (s, C=O st), 1542 (vs, N=O st), 1495 (w), 1471 (m), 1460 (m), 1441 (m), 1411 (s), 1361 (s), 1258 (s, Si-Me), 1171 (vs, S=O st), 1096 (s, Si–O), 1075 (m), 939 (w), 920 (w), 835 (vs), 806 (m), 777 (vs), 741 (m), 731 (m), 700 (s). **^{1}H-NMR** (500 MHz): δ 7.64 (dd, 1H, J = 8.3, 0.9), 7.43 (t, 2H, J = 7.5), 7.21 (td, 1H, J = 7.5, 0.9), 7.03–6.95 (m, 5H), 5.73 (d, 1H, J = 9.6), 4.69 (ddd, 1H, J = 11.8, 9.6, 2.3), 4.03 (dd, 1H, J = 9.9, 4.8), 3.63–3.61 (m, 4H), 2.27 (t, 2H, J = 7.5), 2.10 (dd, 1H, J = 14.0, 11.8), 1.65–1.55 (m, 4H), 1.54–1.44 (m, 1H), 1.17–1.12 (m, 2H), 0.97 (d, 18H, J = 4.4), 0.31 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.08 (s, 3H). **^{13}C-NMR** (125 MHz): δ 174.1, 147.2, 140.7, 134.8, 132.4, 132.2, 130.6, 128.3, 127.5, 126.3, 124.6, 74.3, 71.2, 56.6, 51.5, 39.1, 34.0, 29.5, 26.2, 26.0, 25.9,

25.2, 18.1, 18.1, –3.9, –3.9, –4.5, –4.6. **ESI-MS** *m/z* (rel int): (pos) 717.5 ([M+Na]$^+$, 100), 319 ([M+Na]$^+$, 20); (neg) 295 ([M–H]$^-$, 100).

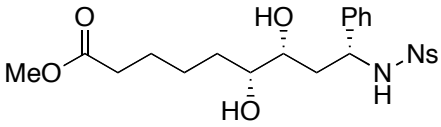


(6*R,7*R**,9*R**)-6,7-Bis(*tert*-butyldimethylsilyloxy)-9-(2-nitrophenylsulfonamido)-9-phenylnonanoic acid (S22).** In a 4 mL vial equipped with a stir bar, methyl ester **S21** (5.9 mg, 0.0083 mmol) was dissolved in THF (0.75 mL) and water (0.75 mL). LiOH (1.0 mg, 0.042 mmol, 5.0 equiv) was added and the reaction mixture was stirred at rt for 4.5 h. Satd aq NH_4Cl was added and the mixture was stirred for an additional 10 min. The reaction was extracted with EtOAc (3×) and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (3:1 hexanes/EtOAc) afforded **S22** as a colorless film (4.0 mg, 69%).

TLC: R_f 0.32 (2:1 Hexanes/EtOAc). **IR** (NaCl, film): 3359 (N-H), 2952 (s, C–H st), 2929 (s, C–H st), 2896 (m), 2856 (m), 1710 (s, C=O st), 1541 (s, N=O st), 1459 (w), 1411 (m), 1360 (m), 1258 (m, Si-Me), 1170 (s, S=O st), 1094 (s, Si–O), 913 (s), 834 (s), 805 (w), 777 (s), 743 (vs), 700 (w), 656 (w), 629 (w). **^{1}H-NMR** (500 MHz): δ 7.64 (dd, 1H, *J* = 8.3, 1.2), 7.44–7.41 (m, 2H), 7.23–7.20 (m, 1H), 6.99–6.96 (m, 5H), 5.74 (d, 1H, *J* = 9.7), 4.69 (ddd, 1H, *J* = 11.7, 9.7, 2.2), 4.03 (dd, 1H, *J* = 9.4, 4.5), 3.63 (ddd, 1H, *J* = 9.7, 4.5, 2.0), 2.32 (t, 2H, *J* = 7.4), 2.10 (dd, 1H, *J* = 13.9, 11.7), 1.65–1.45 (m, 5H), 1.35–1.20 (d, 2H, *J* = 0.7), 0.97 (d, 18H, *J* = 3.7), 0.31 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.08 (s, 3H). **^{13}C-NMR** (125 MHz): δ 175.6, 147.2, 140.7, 134.8, 132.4, 132.2, 130.6, 128.3, 127.5, 126.3, 124.6, 74.3, 71.2, 56.6, 39.1, 29.7, 29.5, 26.2, 26.0, 25.9, 24.9, 18.1, 1.1, –3.8, –3.9, –4.5, –4.7. **ESI-MS** *m/z* (rel int): (pos) 717.5 ([M+Na]$^+$, 100), 733.4 ([M+K]$^+$, 10); (neg) 693.4 ([M–H]$^-$, 100).



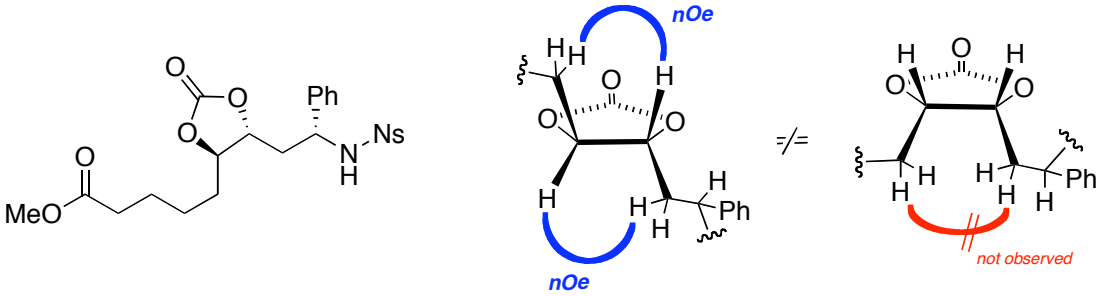
Supplementary Figure 19. Assignment of relative stereochemistry of diol S20. The relative stereochemistry of diol **S20**, generated via $NaBH_4$ reduction of macrolactam **16a**, was determined via NOESY experiments on corresponding cyclic carbonate derivative (**S24**).



(6*R,7*R**,9*R**)-Methyl-6,7-dihydroxy-9-(2-nitrophenylsulfonamido)-9-phenylnonanoate (S23).** In a 4 mL vial equipped with stir bar and septum, TBS-protected alcohol **S20** (4.9 mg, 0.0082 mmol) was dissolved in THF (1.0 mL) and the mixture was cooled to 0 °C. TBAF (0.1 M in THF, 0.25 mL, 0.025 mmol, 3.0 equiv) was added and the reaction mixture was

allowed to warm to rt and stirred for 6 h. Satd aq $NaHCO_3$ was added and the mixture was stirred for an additional 10 min, then extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (1:1 hexanes/EtOAc) afforded **S23** as a colorless film (2.3 mg, 58%).

TLC: R_f 0.15 (1:1 Hexanes/EtOAc). **IR** (NaCl, film): 3511 (s, br, O–H st), 3332 (s, br), 3098 (w), 3067 (w), 3029 (w), 3003 (w), 2945 (s, C–H st), 2864 (m, C–H st), 1724 (s, C=O st), 1593 (w), 1540 (vs, N=O st), 1495 (w), 1455 (m), 1440 (m), 1416 (m), 1361 (s, N=O st), 1166 (vs, S=O st), 1062 (m), 914 (w), 854 (w), 783 (w), 733 (m), 703 (m). **^{1}H-NMR** (500 MHz): δ 7.74 (dd, 1H, J = 7.9, 1.4), 7.71 (dd, 1H, J = 7.9, 1.2), 7.54 (td, 1H, J = 7.7, 1.4), 7.43 (td, 1H, J = 7.7, 1.3), 7.06 (dd, 5H, J = 3.7, 1.4), 6.57 (d, 1H, J = 9.1), 4.86 (td, 1H, J = 9.1, 3.5), 3.73–3.69 (m, 1H), 3.67 (s, 3H), 3.45–3.41 (m, 1H), 2.74 (d, J = 4.9, 1H), 2.32 (td, 2H, J = 7.3, 1.4), 2.07 (d, 1H, J = 5.5,), 2.00–1.95 (m, 1H), 1.90–1.85 (m, 1H), 1.67–1.59 (m, 2H), 1.49–1.33 (m, 4H). **^{13}C-NMR** (125 MHz): δ 174.2, 147.3, 139.7, 134.6, 133.0, 132.5, 130.8, 128.4, 127.6, 126.4, 124.9, 74.2, 70.8, 56.7, 51.6, 40.3, 33.9, 32.9, 24.9, 24.7. **ESI-MS** *m/z* (rel int): (pos) 502.9 ($[M+Na]^+$, 100); (neg) 479.1 ($[M–H]^-$, 100).



Methyl 5-((4*R,5*R**)-5-((*R**)-2-(2-nitrophenylsulfonamido)-2-phenylethyl)-2-oxo-1,3-dioxolan-4-yl)pentanoate (S24).** In a flame-dried, Ar-flushed 4 mL vial equipped with a stir bar and septum, diol **S23** (11.3 mg, 0.024 mmol) was dissolved in CH_2Cl_2 (2.00 mL) and cooled to –78 °C. Pyridine (11 μL, 0.14 mmol, 6.0 equiv) and triphosgene (3.5 mg, 0.012 mmol, 0.5 equiv) were added, and the mixture was allowed to warm to rt and stirred for 4 h. Satd aq NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (3:1 hexanes/EtOAc) afforded **S24** as a colorless film (4.1 mg, 55%).

TLC: R_f 0.38 (1:1 Hexanes/EtOAc). **IR** (NaCl, film): 3097 (w), 3071 (w), 3028 (w), 2956 (m, C–H st), 2931 (m, C–H st), 2871 (w), 1797 (vs, C=O st), 1730 (vs, C=O st), 1541 (vs, N=O st), 1458 (m), 1441 (m), 1418 (m), 1364 (s, N=O st), 1287 (m), 1169 (vs), 1126 (m), 1061 (s), 912 (w), 854 (w), 776 (w), 731 (w), 702 (w). **^{1}H-NMR** (600 MHz): δ 7.82 (dd, 1H, J = 7.9, 1.3), 7.68 (dd, 1H, J = 7.9, 1.1), 7.55 (td, 1H, J = 7.7, 1.3), 7.49 (td, 1H, J = 7.7, 1.2), 7.08–7.05 (m, 5H), 6.11 (d, 1H, J = 10.1), 4.77 (td, 1H, J = 10.1, 2.9), 4.65 (ddd, 1H, J = 9.8, 6.7, 2.7), 4.29 (q, 1H, J = 6.7), 3.73 (s, 3H), 2.43–2.34 (m, 2H), 2.26 (ddd, 1H, J = 14.5, 11.3, 2.9), 2.10 (ddd, 1H, J = 14.5, 10.5, 3.6), 1.88–1.82 (m, 1H), 1.78–1.64 (m, 3H), 1.50–1.42 (m, 1H), 1.33–1.27 (m, 1H). **^{13}C-NMR** (125 MHz): δ 173.9, 154.9, 147.2, 138.7, 134.1, 133.3, 132.7, 131.1, 128.8,

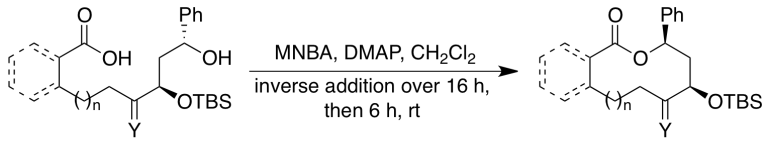
128.3, 126.0, 125.0, 81.3, 78.1, 55.9, 51.8, 42.0, 33.5, 33.1, 24.0, 23.9. **ESI-MS** *m/z* (rel int): (pos) 503 ($[M+Na]^+$, 100); (neg) 479 ($[M–H]^–$, 100).

H. MACROCYCLIZATION EXPERIMENTS WITH RELATED *SECO*-ACIDS

To evaluate the efficiency of our ring expansion approach compared to classical macrocyclizations, we investigated macrolactonization and macrolactamization reactions of the related *seco*-acids and amino acids. The *seco*-acid (**22a–d**) and amino acid (**S22**) substrates were accessed from the macrocyclic ring expansion products **15a–d** and **16a**, as described in SECTION G above.

1. MACROLACTONIZATION OF SECO-ACIDS (22a–d) WITH THE SHIINA MNBA REAGENT[19]

Macrolactonization according to the Shiina protocol was used in attempts to cyclize *seco*-acids **22**. As a positive control, one example from the original publication was reproduced successfully.[19a]



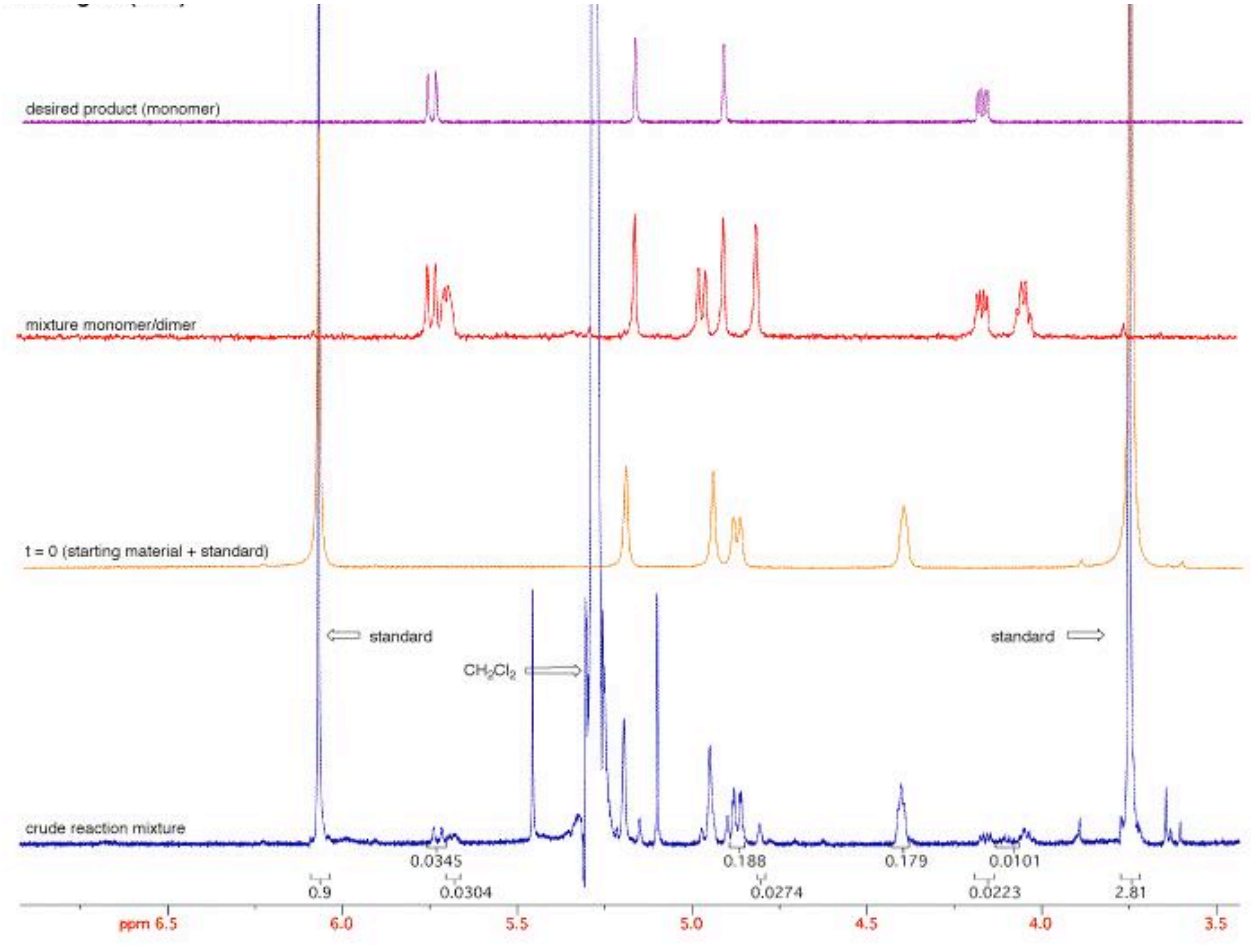
22a–d **23a–d**

Supplementary Figure 20. MNBA-mediated macrolactonizations of *seco*-acids 24. The *seco*-acids **22a–d** were subjected to Shiina macrolactonization conditions using MNBA and DMAP. The reactions were monitored by ^{1}H-NMR versus an internal standard (see **Supplementary Fig. 21** below). (MNBA = 6-methyl-2-nitrobenzoic anhydride; DMAP = 4-dimethylaminopyridine.)

General protocol for ^{1}H-NMR monitored macrolactonizations of seco-acids 24

In a roundbottom flask (fitted with a Teflon tubing Ar inlet to avoid leeching of plasticizers that interfere with ^{1}H-NMR analysis into the sample), *seco*-acid **22** and 1,3,5-trimethoxybenzene (1.00 equiv, ^{1}H-NMR internal standard) were dissolved in $CDCl_3$ and a t = 0 ^{1}H-NMR spectrum was recorded to account for any inaccuracies in weighing small quantities. The $CDCl_3$ was carefully removed by rotary evaporation (≥200 mTorr, 25 °C), and the residue was redissolved in CH_2Cl_2 (400 mL/mmol substrate, 2.50 mM), then added via syringe pump over 16 h to a solution of MNBA (6-methyl-2-nitrobenzoic anhydride; 1.20 equiv) and DMAP (dimethylaminopyridine; 2.40 equiv) in CH_2Cl_2 (497 mL/mmol MNBA) with vigorous stirring at rt. The resulting mixture was stirred at rt for an additional 6 h. Satd aq NH_4Cl was added and the mixture was stirred vigorously for at least 15 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried ($MgSO_4$), filtered, and carefully concentrated by rotary evaporation (≥ 200 mTorr, 25 °C). The residue was immediately redissolved in $CDCl_3$ and analyzed by ^{1}H-NMR.

[19] (a) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535; (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822.

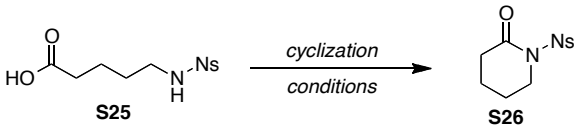


Supplementary Figure 21. Monitoring of macrocyclization experiments by ^{1}H-NMR. Example of ^{1}H-NMR spectra for the conversion of *seco*-acid **22a** to macrolactone **23a**. The desired monomeric macrocyclic product **23a** (top), a mixed fraction containing authentic samples of monomeric and dimeric macrocyclic products (second), the starting material **22a** and internal standard 1,3,5-trimethoxybenzene at t = 0 (third), and the crude reaction mixture (bottom). While some signals in the crude reaction mixture overlap with the CH_2Cl_2 solvent signal, there are sufficient isolated signals to identify and quantify all components of the reaction mixture.

2. Macrolactamization of *N*-nosyl amino acid (S22) with DCC or HATU

a. Control experiments confirming the suitability of N-nosyl-protected amines as nucleophiles in lactamization reactions

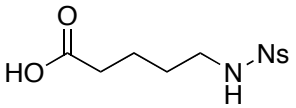
To validate *N*-nosyl amines as competent nucleophiles in both DCC- and HATU-mediated cyclization reactions, positive control experiments were carried out using *N*-nosyl-5-aminovaleric acid (**S19**). This substrate was converted efficiently to *N*-nosyl-valerolactam (**S20**) upon exposure to DCC (with 4-pyrrolidinopyridine) or HATU (with either Et_3N or DBU).



S25 **S26**

method	cyclization conditions	yield (%)
A	DCC, 4-PPy, CH_2Cl_2, rt	81
B	HATU, DBU, DMF, rt	75
C	HATU, Et_3N, DMF, rt	79

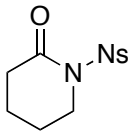
Supplementary Figure 22. Positive control experiments demonstrating cyclization of *N*-nosyl-5-aminovaleric acid (S25). *N*-nosyl amines were validated as competent nucleophiles for HATU- and DCC-mediated cyclizations through the conversion of *N*-nosyl-5-aminovaleric acid **S25** to *N*-nosyl valerolactam **S26**. (HATU = 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium; 4-PPy = 4-pyrrolidinopyridine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.)



5-(2-Nitrophenylsulfonamido)pentanoic acid (S25). In a 15 mL roundbottom flask, *N*-nosyl valerolactam[20] **S26** (200 mg, 0.704 mmol) was dissolved in THF (10.0 mL). 2.0 M KOH (2.1 mL, 4.2 mmol, 6.0 equiv) was added and the mixture was heated to 60 °C for 1 h. The reaction was cooled to rt and 1.0 M HCl (8.0 mL) was added. The resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (9:1 CH_2Cl_2/MeOH) afforded **S25** as a white solid (189 mg, 89%).

TLC: R_f 0.45 (9:1 CH_2Cl_2/MeOH). **mp** = 79.9–81.3 ºC. **IR** (NaCl, film): 3333 (m, br, N-H), 3099 (w), 2943 (m), 1707 (s, C=O st), 1540 (vs, N=O st), 1414 (m), 1363 (s), 1340 (s, N=O st), 1164 (vs, S=O st), 1126 (w), 854 (w), 783 (w), 740 (m), 731 (m), 655 (m). **^{1}H-NMR** (500 MHz): δ 8.07 (dt, 1H, *J* = 5.9, 3.4), 7.81 (ddq, 3H, *J* = 17.5, 6.4, 3.4), 3.06 (t, 2H, *J* = 6.7), 2.25 (t, 2H, *J* = 7.1), 1.61–1.50 (m, 4H). **^{13}C-NMR** (125 MHz): δ 177.2, 149.6, 134.9, 134.8, 133.5, 131.4, 125.8, 43.9, 34.2, 30.2, 22.9. **ESI-MS** *m/z* (rel int): (pos) 325 ($[M+Na]^+$, 50), 627 ($[2M+Na]^+$, 100); (neg) 301 ($[M–H]^-$, 100), 301 ($[M+Cl]^-$, 40), 603 ($[2M–H]^-$, 40).

[20] Grant, T. N.; Benson, C. L.; West, F. G. *Org. Lett.* **2008**, *10*, 3985.



1-(2-Nitrobenzenesulfonyl)piperidin-2-one (S26)[20]

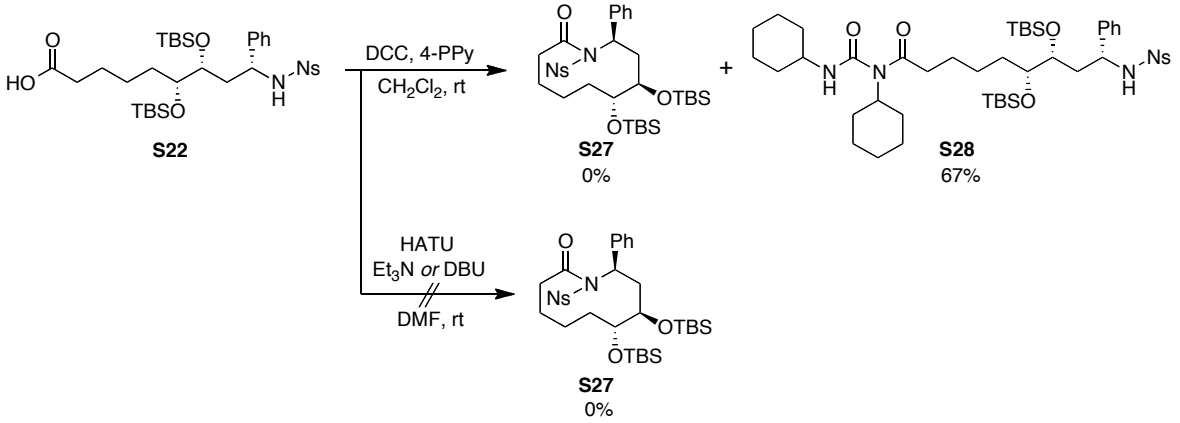
Method A (DCC, 4-PPy):[21] In a 10 mL roundbottom flask, *N*-nosyl amino acid **S25** (10 mg, 0.033 mmol) was dissolved in CH_2Cl_2 (3.3 mL). 4-Pyrrolidinopyridine (0.50 mg, 0.040 mmol, 0.10 equiv) and DCC (7.5 mg, 0.036 mmol, 1.1 equiv) were added and the mixture was stirred at rt for 15 h, after which nearly full conversion of the starting material was observed by TLC analysis. Satd aq $NaHCO_3$ was added and the resulting mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (CH_2Cl_2) afforded lactam **S26** as a white solid (7.6 mg, 81%). All characterization data were in agreement with literature precedent.[20]

Method B (HATU, DBU): In a 10 mL round bottom flask, *N*-nosyl amino acid **S25** (5.0 mg, 0.017 mmol) was dissolved in DMF (8.3 mL). DBU (5.0 μL, 0.033 mmol, 2.0 equiv) and HATU (12.6 mg, 0.033 mmol, 2.0 equiv) were added and the mixture was stirred at rt for 12 h. Water was added and the resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (CH_2Cl_2) afforded lactam **S26** as a white solid (3.5 mg, 75%). All characterization data were in agreement with literature precedent.[20]

Method C (HATU, Et_3N): In a 25 mL round bottom flask, *N*-nosyl amino acid **S25** (5.0 mg, 0.017 mmol) was dissolved in DMF (8.3 mL). Et_3N (3.4 mg, 0.033 mmol, 2.0 equiv) and HATU (12.6 mg, 0.033 mmol, 2.0 equiv) were added and the mixture was stirred at rt for 12 h. Water was added and the resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (CH_2Cl_2) afforded lactam **S26** as a white solid (3.7 mg, 79%). All characterization data were in agreement with literature precedent.[20]

[21] Tanner, D.; Somfai, P. *Tetrahedron*, **1988**, *44*, 613.

b. Attempted macrolactamizations of N-nosyl amino acid S22

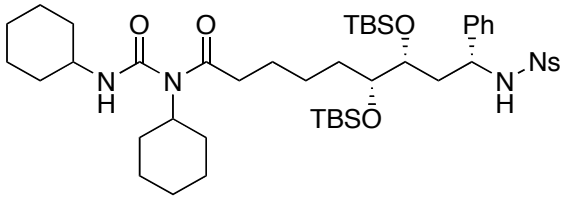


Supplementary Figure 23. Attempted macrolactamization of *N*-nosyl amino acid S22. Reaction of *N*-nosyl amino acid **S22** with DCC led only to the *N*-acyl urea **S28** instead of the desired macrolactam **S27**. Exposure of **S22** to HATU led to an intractable mixture of products. (Ns = 2-nitrobenzenesulfonyl; 4-PPy = 4-pyrrolidinopyridine; HATU = 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.)

Attempted macrolactamization of N-nosyl amino acid S22 using Method A (DCC, 4-PPy)

Macrolactamization of *N*-nosyl-protected amino acid **S22** was attempted using a procedure identical to that reported by Tanner and coworkers for the cyclization of *N*-tosyl-protected amino acids in the synthesis of 4–9-membered ring lactams.[21]

In a flame-dried, Ar-flushed 4 mL vial equipped with a magnetic stir bar and septum, *N*-nosyl amino acid **S22** (6.6 mg, 9.5 μmol) was dissolved in CH_2Cl_2 (1.0 mL). DCC (2.1 mg, 10 μmol, 1.1 equiv) and 4-pyrrolidinopyridine (0.14 mg, 0.95 μmol, 0.1 equiv) were added and the reaction was stirred for 20 h, after which TLC analysis indicated that the majority of starting material had been consumed and a single streaky spot had appeared. Sat aq $NaHCO_3$ was added and the resulting mixture was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Purification by silica flash chromatography (4:1 hexanes/EtOAc) afforded a linear compound (5.7 mg, 67%) presumed based on NMR and MS analysis to be *N*-acyl urea **S28**, formed by isomerization of the corresponding *O*-acyl isourea initially formed in the activation of amino acid **S22** by DCC.[22]



(6*R,7*R**,9*R**)-6,7-Bis(*tert*-butyldimethylsilyloxy)-*N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-9-(2-nitrophenylsulfonamido)-9-phenylnonanamide (S28).** **TLC**: R_f 0.35 (4:1 hexanes/

[22] (a) Kurzer, F.; Douraghi–Zadeh, K. *Chem. Rev.* **1967**, *67*, 107. (b) Neises, B.; Steglich, W. *Angew. Chem. Intl. Ed.* **1978**, *17*, 522. (c) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

EtOAc). **IR** (NaCl, film): 2951 (m), 2930 (m), 2857 (m), 1710 (s), 1693 (s), 1681 (s), 1660 (s), 1643 (vs), 1545 (vs, N=O st), 1412 (m), 1362 (m), 1261 (m), 1233 (s), 1172 (vs, S=O st), 1097 (m), 1077 (m), 920 (w), 855 (m), 778 (m). **^{1}H-NMR** (500 MHz): δ 7.64 (dd, 1H, *J* = 8.2, 1.2), 7.44–7.41 (m, 2H), 7.22 (td, 1H, *J* = 7.7, 1.1), 7.01–6.96 (m, 5H), 5.74 (d, 1H, *J* = 9.7), 4.72–4.67 (m, 1H), 4.03 (dd, 1H, *J* = 9.8, 4.6), 3.88–3.81 (m, 1H), 3.69–3.61 (m, 2H), 2.39–2.36 (m, 2H), 2.10 (dd, 1H, *J* = 14.0, 11.8), 1.96–1.88 (m, 4H), 1.81–1.51 (m, 17H), 1.37–1.12 (m, 13H), 0.97 (d, 18H, *J* = 5.9), 0.30 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.09 (s, 3H). **^{13}C-NMR** (125 MHz): δ154.1, 147.2, 140.7, 134.8, 132.4, 132.2, 130.6, 128.3, 127.5, 126.4, 124.6, 74.4, 71.2, 56.6, 49.6, 39.0, 35.9, 32.8, 30.9, 29.7, 26.4, 26.0, 25.9, 25.7, 25.5, 25.3, 24.7, 18.0, 1.0, –3.9, –3.9, –4.5, –4.6. **ESI-MS** *m/z* (rel int): (pos) 924 ([M+Na]$^+$, 100); (neg) 900 ([M–H]$^-$, 100).

Attempted macrolactamization of N-nosyl amino acid S22 using Method B (HATU, DBU)

To investigate a more active acylation reagent, we attempted macrolactamization using HATU and DBU.

In a flame-dried, Ar-flushed 4 mL vial equipped with a magnetic stir bar and septum, *N*-nosyl amino acid **S22** (0.5 mg, 0.7 μmol) was dissolved in DMF (0.36 mL). DBU (0.22 mg, 1.4 μmol, 2.0 equiv) and HATU (0.54 mg, 1.4 μmol, 2.0 equiv) were added and the reaction was stirred overnight at rt, after which TLC analysis indicated complete consumption of the starting material and the appearance of multiple streaky, low-running spots. Satd aq NH_4Cl was added and the resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. ^{1}H-NMR analysis of the crude product revealed an intractable mixture with no identifiable signals. ESI-MS analysis of the crude product did not produce peaks with identifiable *m/z*.

Attempted macrolactamization of N-nosyl amino acid S22 using Method C (HATU, Et$_3$N)

We suspected that the strong basicity of DBU may have contributed to degradation of starting material or product in the attempted HATU-mediated macrolactamization of *N*-nosyl amino acid **S22** above. Thus, we attempted the same reaction with Et_3N.

In a flame-dried, Ar-flushed 4 mL vial equipped with a magnetic stir bar and septum, *N*-nosyl amino acid **S22** (5.0 mg, 0.007 mmol) was dissolved in DMF (3.5 mL). Et_3N (2.2 mg, 0.014 mmol, 2.0 equiv) and HATU (5.3 mg, 0.014 mmol, 2.0 equiv) were added and the mixture was stirred at rt for 12 h, after which TLC analysis indicated full conversion of the starting material to a single new spot. Water was added and the resulting mixture was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The crude product was purified by silica flash chromatography (4:1 hexanes/EtOAc). ^{1}H-NMR analysis of the isolated material revealed an intractable mixture, containing more than one compound, which could not be identified. ESI-MS analysis of this material did not produce peaks with identifiable *m/z*.

I. CHEMINFORMATIC ANALYSIS OF MACROCYCLES

1. PRINCIPAL COMPONENT ANALYSIS

To generate the plots shown in **Fig. 4a–c** of the manuscript and **Supplementary Fig. 5**, a total of 176 compounds (**Supplementary Table 1**) were compared by principal component analysis (PCA):[23]

- 40 top selling brand-name small molecule drugs by revenue in 2006[24] (**Supp. Fig. 24**)
- 10 drug-like pyrrazolecarboxamides in the MLSMR from ChemBridge[23c] (**Supp. Fig. 25**)
- 10 drug-like dihydrotriazolopyrimidines in the MLSMR from Chem Div[23c] (**Supp. Fig. 25**)
- 60 natural products with diverse structures[23c] (**Supp. Fig. 26**)
- 24 macrocycle natural products (**Supp. Fig. 3**)
- 32 macrocycle library members (**Supp. Fig. 2**)

The 32 macrocycle library members were derived from **15a–f**, **16a–c**, **17–21**, **23a–d**, **24–26**, **27a–f**, **28**, **29**, and **31** via *in silico* desilylation as necessary (**Supplementary Fig. 2**).

A set of 20 physicochemical properties (**Supplementary Table 2**) for all 144 or 176 compounds, respectively, was obtained from PubChem and/or calculated using free online cheminformatics tools (Molinspiration[25], VCCLab[26]), ChemDraw and manual inspection.[23c] These properties were selected based on several criteria. First, Lipinski parameters[27] (MW $\leq$ 500, logP $\leq$ 5, HBA $\leq$ 10, HBD $\leq$ 5) and Veber parameters[28] (RotB $\leq$ 10, tPSA $\leq$ 140 Å^2) have been correlated with oral bioavailability. While oral bioavailability is not an immediate goal of most academic screening campaigns, some attention to these parameters is useful to the extent that they correlate partially to cell permeability,[28] which is relevant to the utility of new chemical probes discovered from library screening. Second, Tetko's calculated logS aqueous solubility (ALOGpS)[29] was included since compound solubility is critical in screening and is often problematic for commercial drug-like libraries. Third, several stereochemical parameters (nStereo, R, S, nStMW, RSdelta) were included as a first-order approximation of three-dimensional complexity, and to enable the differentiation of enantiomeric structures. Indeed, the number of stereogenic centers is a key distinguishing factor between synthetic drugs and natural products,[30] and has recently been

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[23] (a) Moura-Letts, G.; DiBlasi, C. M.; Bauer, R. A.; Tan, D. S. *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 6745–6750. (b) Bauer, R. A.; DiBlasi, C. M.; Tan, D. S. *Org. Lett.* **2010**, *12*, 2084–2087, (c) For a full discussion, see: Bauer, R. A.; Wurst, J. M.; Tan, D. S. *Curr. Opin. Chem. Biol.* **2010**, *14*, 308–314.

[24] (a) Jón T. Njardarson Group Website – "Top 200 Brand-Name Drugs by Retail Dollars in 2006": http://cbc.arizona.edu/njardarson/group/sites/default/files/Top 200 Brand Name Drugs by Retail Dollars in 2006_0.pdf (b) Drug Topics Website – "Top 200 brand-name drugs by retail dollars in 2006": http://drugtopics.modernmedicine.com/drugtopics/Pharmacy+Facts+%26+Figures/Top-200-brand-name-drugs-by-retail-dollars-in-2006/ArticleStandard/Article/detail/405100?contextCategoryId=7604

[25] MolInspiration – free on-line cheminformatics tool; http://www.molinspiration.com/cgi-bin/properties

[26] (a) Tetko, I. V., Virtual Computational Chemistry Laboratory; http://www.vcclab.org/lab/alogps/ (b) Tetko, I.V.; Tanchuk, V.Y.; Kasheva, T.N.; Villa, A.E.P. *J Chem Inf Comput Sci* **2001**, *41*, 246–252.

[27] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25.

[28] Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. *J. Med. Chem.* **2002**, *45*, 2615–2623.

[29] Tetko, I. V.; Tanchuk, V. Y.; Kasheva, T. N.; Villa, A. E. P. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1488–1493.

[30] Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218–227.

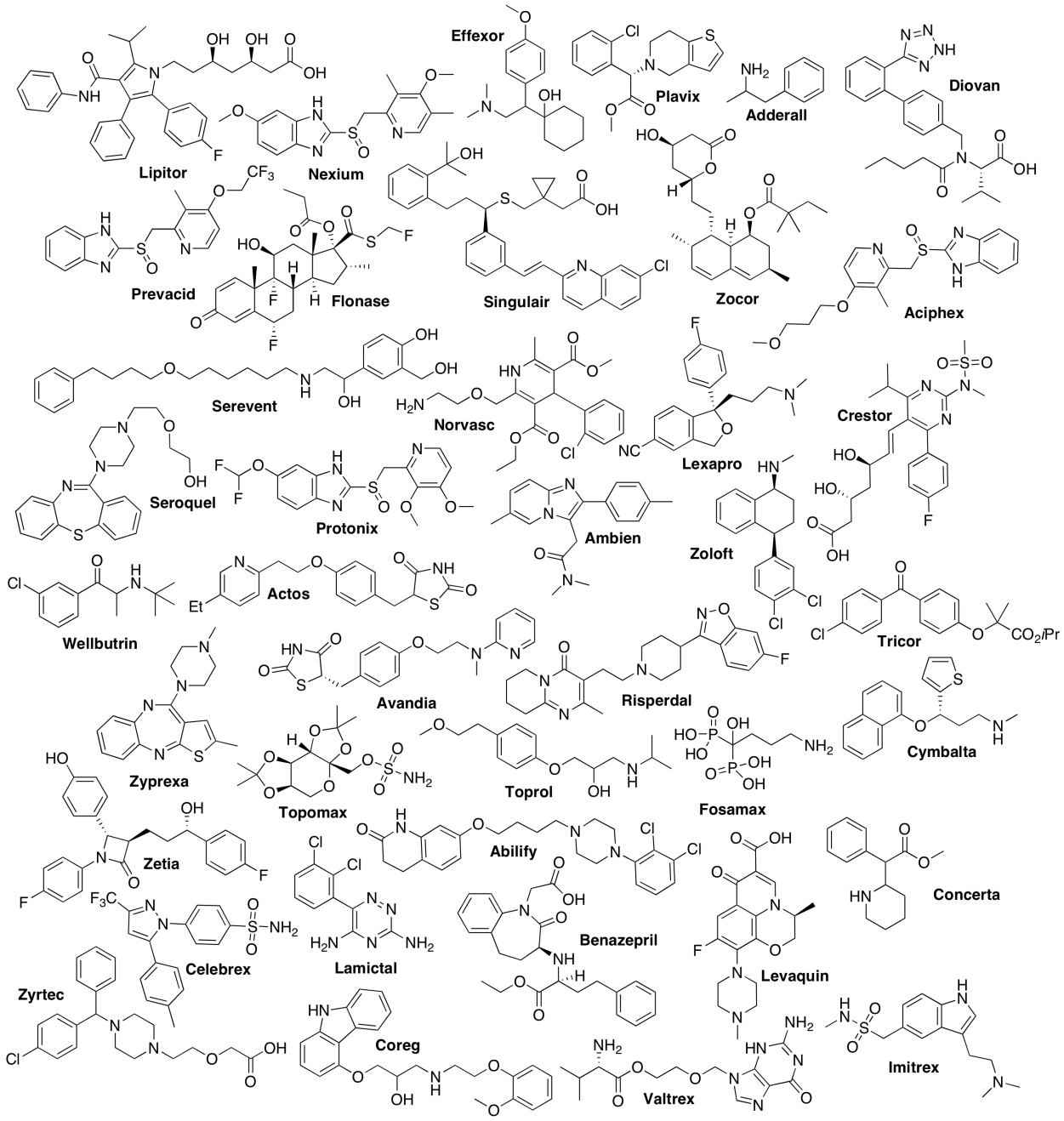
shown to impact protein binding selectivity and frequency.[31] Fourth, several additional parameters found previously to differentiate synthetic drugs and natural products were included.[30] Synthetic drugs tend to have higher nitrogen counts, while natural products tend to have higher oxygen counts (N,O). Natural products also tend to have fewer aromatic rings and more complex, fused ring systems (Rings, RngAr, RngSys, RngLg, RRSys). While analyses using larger compound datasets and parameter lists are possible, we believe that there is limited additional value to such an analysis in the context of library planning.

These data were assembled in a Microsoft Excel spreadsheet (*Supplementary Dataset 1 PCA.xls*) and average values for each parameter were calculated within each compound series. This hypothetical average molecule for each compound series was also included in the PCA analysis (**Supplementary Table 3**).

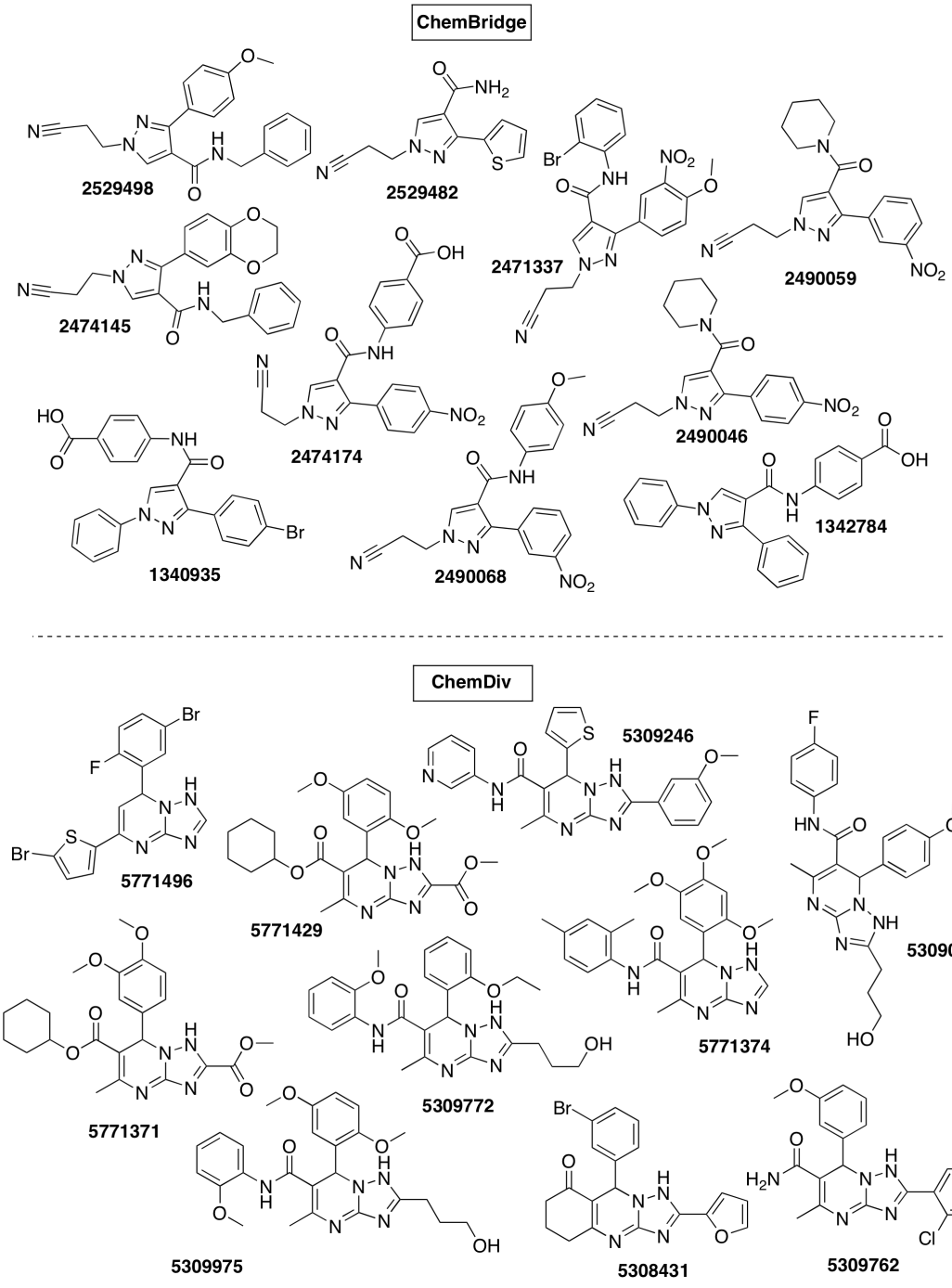
[31] Clemons, P. A.; Bodycombe, N. E.; Carrinski, H. A.; Wilson, J. A.; Shamji, A. F.; Wagner, B. K.; Koehler, A. N.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 18787–18792.

Supplementary Table 1. Compounds used in principal component analysis.

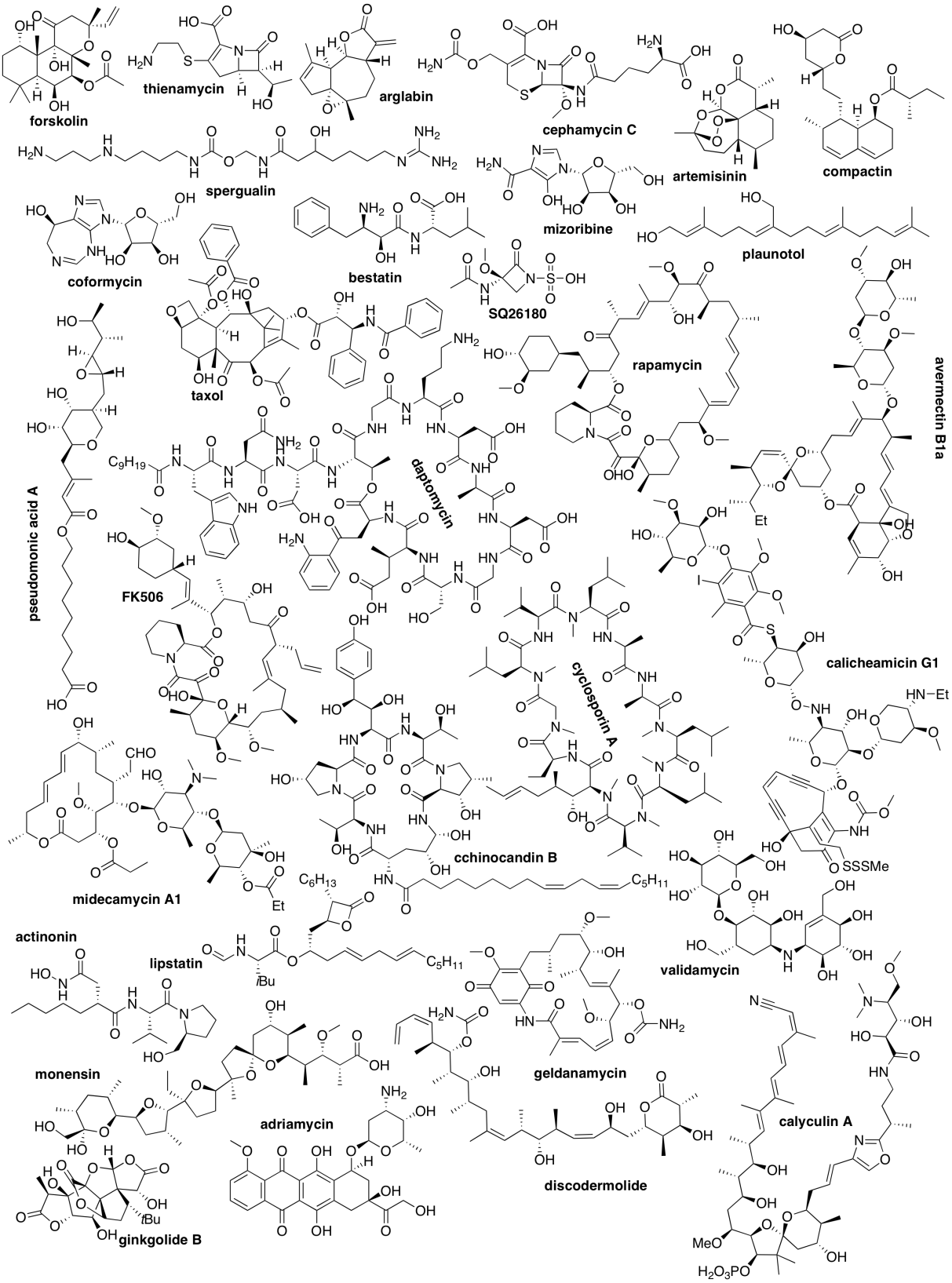
Series	Compounds			
Best-Selling Brand Name Drugs (40 entries)	Lipitor	Lexapro	Topamax	Coreg
	Nexium	Seroquel	Toprol	Valtrex
	Prevacid	Protonix	Zetia	Adderall
	Flonase	Ambien	Fosamax	Aciphex
	Serevent	Actos	Abilify	Cymbalta
	Singulair	Zoloft	Levaquin	Crestor
	Effexor	Wellbutrin	Lamictal	Diovan
	Plavix	Avandia	Celebrex	Tricor
	Zocor	Risperdal	Benazepril	Concerta
	Norvasc	Zyprexa	Zyrtec	Imitrex
ChemBridge Library (10 entries)	*PubChem Compound CIDs:*	5771429	5309975	5308431
		5771374	5309772	5309246
	5771496	5771371	5309762	5309020
ChemDiv Library (10 entries)	*PubChem Compound CIDs:*	2529482	2474145	2490046
		2474174	1340935	2490068
	2529498	2471337	2490059	1342784
Natural Products (60 entries)	cephamycinC	mizoribine	coformycin	compactin
	spergualin	SQ26180	arglabin	artemisinin
	forskolin	thienamycin	bestatin	plaunotol
	daptomycin	validamycin	midecamycin A_1	rapamycin
	echinocandinB	avermectin B1a	taxol	FK506
	calicheamicin g1	cyclosporin A	pseudomonic acid A	lipstatin
	geldanamycin	trapoxin B	talaromycin B	bleomycin
	actinonin	vincristine	spongistatin 1	brefeldin A
	discodermolide	colchicine	radicicol	cytochalasin B
	monensin	trichostatin	salicylihalamide A	epothilone A
	calyculin A	fumagillin	brevetoxin B	apoptolidin
	amphotericin B	staurosporine	rifamycin B	lactacystin
	adriamycin	erythromycin A	quinine	duocarmycin A
	ginkgolide B	streptomycin	mycobactin S	zaragozic Acid A
	phorbol MA	penicillin G	telomestatin	vancomycin
Macrocycle Natural Products (24 entries)	decarestrictine A_1	decarestrictine B	decarestrictine C_1	decarestrictine D
	diplodialide A	jasmine ketolactone	phoracantholide I	phoracantholide J
	pinolidoxin	pyrenolide A	ferrulactone 1	2,4,6,8-Tetramethyl-3,4-dihydroxydec-8(9)-enolide
	apicularen A	cladospolide A	cladospolide B	cladospolide D
	curvularin	lyngbouilloside	methymycin	neomethymycin
	pladienolide B	fluvirucin A_1	hypothemycin	iriomoteolide 3a
Macrocycle Library (32 entries)	*Derived from:*	**15a,b,c,d,e,f**	**23a,b,c,d**	**28**
		16a,b,c	**24–26**	**29**
		17–21	**27a,b,c,d,e,f**	**31**



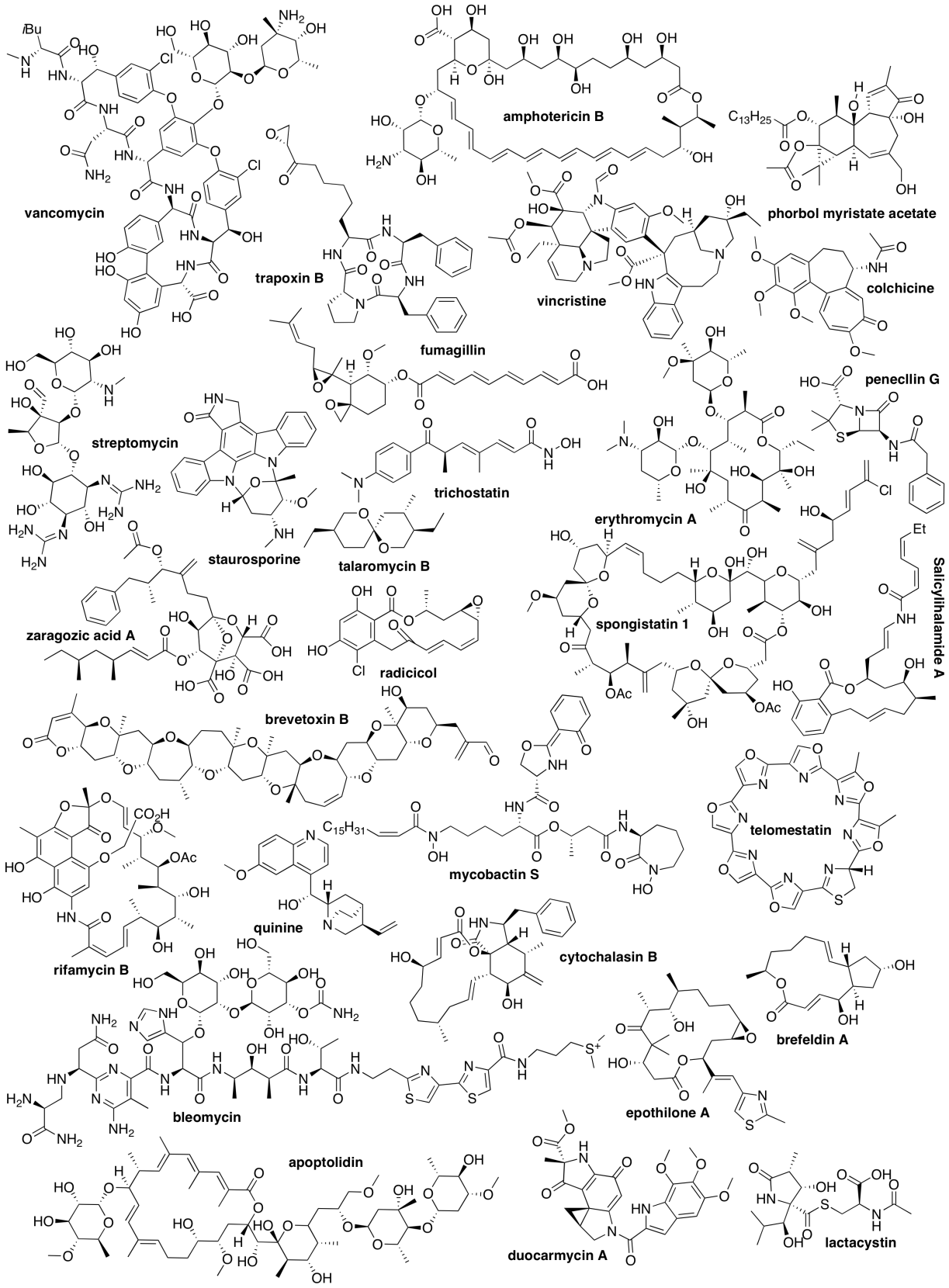
Supplementary Figure 24. Brand name drug reference set for PCA (40 structures)[22].



Supplementary Figure 25. ChemBridge and ChemDiv drug-like library reference sets for PCA.



Supplementary Figure 26. Natural product reference set for PCA (60 structures) (*continued on next page*).



Supplementary Figure 26 (continued). Natural product reference set for PCA (60 structures).

Supplementary Table 2. Structural and physicochemical parameters used in PCA.

Parameter	Description	Method of Determination
MW	molecular weight	ChemDraw Analysis Window
N	number of nitrogens	ChemDraw Analysis Window
O	number of oxygens	ChemDraw Analysis Window
XlogP	calc *n*-octanol/water partition coefficient	http://www.vcclab.org
HBD	number of hydrogen bond donors	http://www.molinspiration.com
HBA	number of hydrogen bond acceptors	http://www.molinspiration.com
RotB	number of rotatable bonds	http://www.molinspiration.com
tPSA	topological polar surface area	http://www.molinspiration.com
ALOGPs	calc *n*-octanol/water partition coeff (alt)	http://www.vcclab.org
ALOGpS	calculated aqueous solubility	http://www.vcclab.org
nStereo	number of stereocenters	http://www.molinspiration.com
R	number of R stereocenters	ChemDraw Show Stereochemistry
S	number of S stereocenters	ChemDraw Show Stereochemistry
RSdelta	*R – S*	Microsoft Excel
nStMW	*nStereo ÷ MW* (stereochemical density)	Microsoft Excel
Rings	number of rings	Manual inspection
RngAr	number of aromatic rings	Manual inspection
RngSys	number of ring systems	Manual inspection
RngLg	number of atoms in largest ring outline	Manual inspection
RRSys	*Rings ÷ RngSys* (ring complexity)	Microsoft Excel

Supplementary Table 3. Average structural and physicochemical parameters by compound series.
† = nStMW × 1000 for clarity

	Drugs	NPs	ChemBrg	ChemDiv	Macro NP	Macro Lib
MW	361	629	381	446	303	316
N	2.2	2.6	4.3	4.7	0.2	0.2
O	2.9	9.7	3.1	3.4	4.8	4.3
XLogP	2.7	1.5	2.9	1.8	2.0	3.0
HBD	1.5	4.9	1.1	1.9	1.7	1.3
HBA	5.4	10.8	5.9	7.7	5.0	4.5
RotB	6.3	9.7	5.3	6.1	2.0	1.7
tPSA	69	183	103	94	77	70.9
ALOGPs	2.8	2.1	3.3	2.7	1.8	2.1
ALOGpS	-3.9	-3.8	-4.0	-3.8	-2.4	-3.2
nStereo	1.4	9.1	0.0	1.0	4.4	2.4
R	0.6	4.1	0.0	0.5	2.2	1.2
S	0.8	5.0	0.0	0.5	2.3	1.2
nStMW†	3.7	13.9	0.0	2.2	13.1	7.8
RSdelta	-0.2	-0.9	0.0	0.0	-0.1	0.0
Rings	2.9	3.8	3.2	4.2	1.6	2.4
RngAr	2.1	1.0	2.9	2.9	0.1	1.3
RngSys	2.1	2.0	3.1	3.1	1.2	2.1
RngLg	8.4	15.8	6.3	9.4	12.3	11.6
RRSys	1.4	2.3	1.0	1.4	1.4	1.1

To provide a visual representation of the position of each compound in chemical space, we then carried out principal component analysis with the "R" open source statistical computing package[32] to reduce the 20-dimensional vector corresponding to each compound to a 2-dimensional vector, with minimal loss of information. The detailed protocol is as follows:

1) In MS Excel, a "Raw" worksheet was created with compounds in rows and physicochemical descriptors in columns. Note that compound names must not have spaces or other punctuation.
2) Mean values were calculated for individual compound categories (*e.g.*, for "Drugs", "Natural Products", etc.). In addition, mean and standard deviation values were calculated for each column.
3) A "Norm" worksheet was created and mean-centered, standardized values were generated for each column using the equation:

normval = (val – Column Mean) / Column Standard Deviation

4) With the upper left cell blank (R requires this to recognize a header row), the Number format was designated for all data columns to 4 decimal places.
5) The Excel workbook was saved.
6) The "Norm" worksheet was saved as "Data.txt" (Text–Tab Delimited) on the Desktop (Mac).
7) The Excel workbook was closed and the changes discarded.
8) The "R" open source computing package was opened and the following commands were entered:

```
9)  R> read.table("~/Desktop/Data.txt") -> a          # read data into dataframe a
10) R> prcomp(a) -> b                                 # PCA of dataframe a, results to b
11) R> summary(b)                                     # prints summary of %contributions
12) R> b                                              # prints the rotation (loading) matrix
13) R> biplot(b, choices = c(1,2), col = c("gray", "red"))   # Biplot of scores and eigenvectors for
                                                              PC1 vs PC2
14) R> biplot(b, choices = c(1,3), col = c("gray", "red"))   # Biplot of scores and eigenvectors for
                                                              PC1 vs PC3
15) R> biplot(b, choices = c(3,2), col = c("gray", "red"))   # Biplot of scores and eigenvectors for
                                                              PC3 vs PC2
16) R> b$x                                            # prints the rotated data (scores)
```

17) This final command prints the rotated data (scores) and the first section of the data was selected and copied (PC1–PC10, without top headers).
18) These results were pasted into a MS Word text file and the font changed to Courier 5 pt.
19) This MS Word file was Saved as... "Scores.txt" (Text Only with Line Breaks)
20) Excel was opened again and the scores were imported by selecting "Get External Data" in the Data menu, then "Import from Text file".
21) The "Fixed" width button was left checked and dividers were adjusted, making sure to include minus signs in the second column (PC1) rather than the first (compound names).
22) This data file was imported into a new Excel worksheet "Scores".
23) The first four columns (compound names, PC1, PC2, and PC3) where copied into a new worksheet "PCA", and the Number format was designated to 3 decimal places.
24) Each group of compounds was then sorted in order of ascending PC1 to facilitate its location on the PCA plot.
25) With the PC1 and PC2 columns selected, the Scatter XY plot was selected in the Chart Wizard.
26) Series information for each set of compounds, *e.g.* Drugs, AVG Drug, etc., was entered and the chart formatted as desired.
27) Steps 25) and 26) were repeated to generate plots of PC1 vs PC3 and PC3 vs PC2.

[32] The R Project for Statistical Computing; http://www.r-project.org/

PCA PLOT OF MACROCYCLE LIBRARY WITH MACROCYCLIC NATURAL PRODUCTS AND ESTABLISHED REFERENCE SETS

Following PCA, the 32 macrocycle library members, 24 macrocyclic natural products, and our established reference sets[23] were plotted on newly generated, unitless, orthogonal axes (principal components) that are based on linear combinations of the original 20 parameters (**Fig. 4a–c** of the manuscript, **Supplementary Fig. 5**, and *Supplementary Information Fig 4.xls*). Summary information from R is shown in **Supplementary Table 4**.

Supplementary Table 4. Standard deviation and percent contribution for each principal component in PCA plot of macrocycle library (R Summary).

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
Standard deviation	2.929	1.858	1.699	1.343	1.080	0.823	0.639	0.503	0.450	0.391
Proportion of Variance	0.429	0.173	0.144	0.090	0.058	0.034	0.020	0.013	0.010	0.008
Cumulative Proportion	0.429	0.602	0.746	0.836	0.894	0.928	0.949	0.961	0.971	0.979

These data indicate that >90% of the variance in the complete 20-dimensional dataset is accounted for by the first six principal components (PC1–PC6), due to correlations between some of the original 20 parameters. For visualization purposes, the first three principal components (PC1–PC3) were used to generate the plots shown in **Fig. 4a–c** of the manuscript. Together, these three principal components account for 74.6% of the variance in the complete dataset, with individual contributions of 42.9%, 17.3%, and 14.4%, respectively (**Supplementary Table 4**).

The Biplot() function in R was then used to display the loadings of the original 20 parameters on 2-dimensional principal component plots (**Supplementary Fig. 4**). These data indicate that O, MW, HBA, tPSA have the largest loadings on PC1 and shift compounds to the left in the PC1 vs. PC2 (**Supplementary Fig. 4a**) and PC1 vs. PC3 (**Supplementary Fig. 4c**) plots. The descriptors with the largest loadings on PC2 are RngAr and ALOGPs, which shift compounds to the top of the PC1 vs. PC2 and PC3 vs. PC2 (**Supplementary Fig. 4b**) plots, as well as nStMW and ALOGpS, which shift compounds to the bottom of the PC1 vs. PC2 and PC3 vs. PC2 plots. The descriptors with the largest loading on PC3 are XlogP, ALOGPs, and RRSys, which shift compounds in the negative direction along PC3, as well as N, which shifts compounds in the positive direction along PC3.

2. PRINCIPAL MOMENT OF INERTIA CALCULATIONS

Minimum energy conformers for each compound were generated by executing the stochastic conformational search algorithm, a variant of the random incremental pulse search (RIPS) method,[33] as implemented in the MOE molecular modeling software package.[34] The Merck Molecular Force Field (MMFF94) combined with the generalized Born (GB) solvation model of

[33] Ferguson, D. M.; Raber, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4371–4378.
[34] (a) MOE 2009.10; Chemical Computing Group: 1010 Sherbrooke St. W, Suite 910, Montreal, Quebec, Canada H3A 2R7. http://www.chemcomp.com (b) Chen, I.-J.; Foloppe, N. *J. Chem. Inf. Model.* **2008**, *48*, 1773–1791.

aqueous solvation were used. Conformational sampling of the potential energy surface was ensured by setting two key parameters, **maxConfs** (maximum number of conformations) and **Failure Limit** (number of failures in which no new conformations are generated after a specified number of consecutive attempts), to values established previously as being effective for the analysis of macrocycle libraries (further increases to these parameters do not result in the identification of additional conformers).[35] The computational job was carried out on a Linux cluster as a batch job. To consider biologically-relevant conformational space, all conformations within 3 kcal/mol of the minimum energy conformation were recorded. A conformation was considered as duplicate if the RMSD value was <0.15 Å upon superposition.

The parameters used for conformer generation are listed below:

maxConfs: 10000 (maximum number of conformations; default is 250)

RMSD ≤ 0.15 (threshold to check for duplicates)

Failure Limit: 100 (number of attempts to generate a new conformation above the RMSD threshold prior to terminating the search; default is 30)

Energy cutoff: 7 kcal/mol

Iteration limit: 10000 (number of attempts to generate a new conformation)

MM Iteration limit: 500 (maximum number of energy minimization steps performed for each conformer energy minimization search)

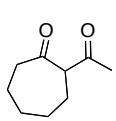
Upon completion of the job, three-dimensional descriptors, the three principal moments of inertia (Ixx, Iyy, Izz) and normalized principal moments of inertia, npr1 (Ixx/Izz) and npr2 (Iyy/Izz) were calculated. The npr1 and npr2 calculation is scripted in MOE.

Following the PMI analysis, the normalized PMI ratios were plotted for the 32 macrocycle library members, 24 macrocyclic natural products, and our established reference sets[23] on a triangular graph, with the vertices (0,1), (0.5,0.5), and (1,1) representing a perfect rod, disc, and sphere, respectively.[36] These data were assembled in a Microsoft Excel spreadsheet (*Supplementary Dataset 2 PMI.xls*). This provides a chemically intuitive, visual representation of the three-dimensional shape of each molecule. For ease of visualization, lowest energy conformers are plotted in **Fig. 4d** of the manuscript, while collections of conformers up to 3 kcal/mol above the lowest energy conformer are plotted in **Supplementary Fig. 7**.

[35] Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D.; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962–16976.

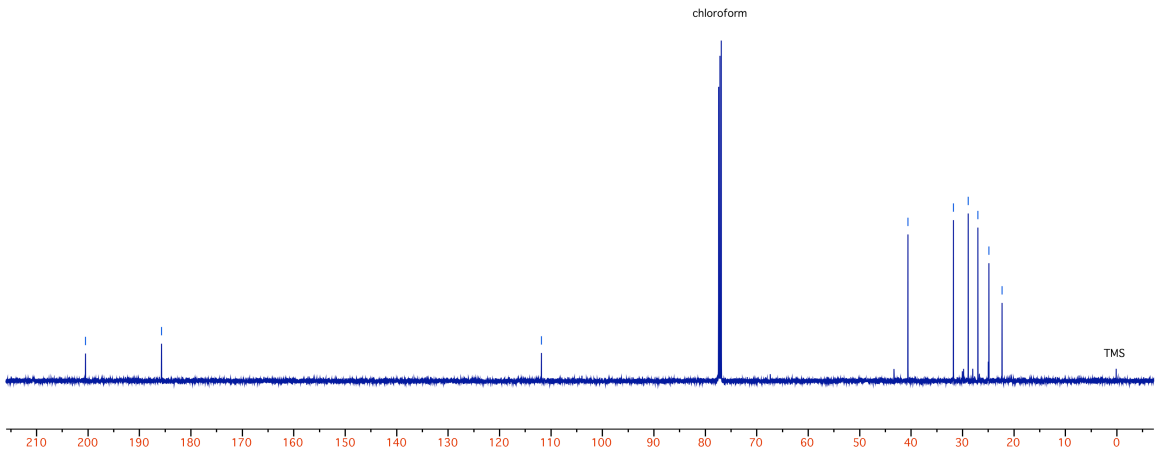
[36] Sauer, W. H. B.; Schwarz, M. K. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 987–1003.

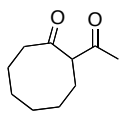
J. ^{1}H-NMR AND ^{13}C-NMR SPECTRA



7b

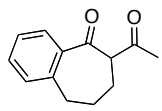
chloroform
TMS
0.92
2.02
3
6.18
2
2.01
ppm 17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
200.492
185.710
111.860
40.621
31.777
28.906
27.026
24.883
22.326


chloroform
TMS
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



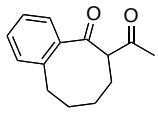
7c

TMS
chloroform
0.957
1.92
3.06
6.17
1.96
ppm 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
193.394
192.251
109.338
chloroform
35.305
30.207
28.775
26.453
25.836
25.287
23.751
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



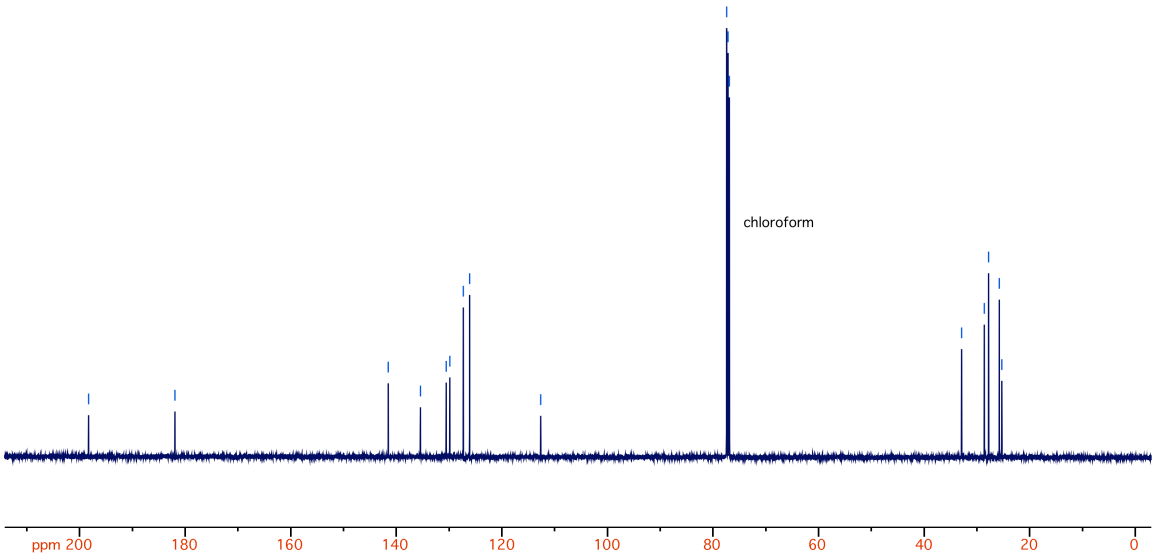
7e

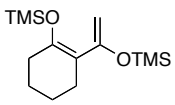
enol
chloroform
TMS
0.66
1
1.05
1.02
1.04
2.16
2.18
3.13
2.2
190.345
188.190
139.888
137.513
131.075
128.842
127.563
126.700
109.593
31.317
31.049
23.809
22.985
chloroform
TMS



7f

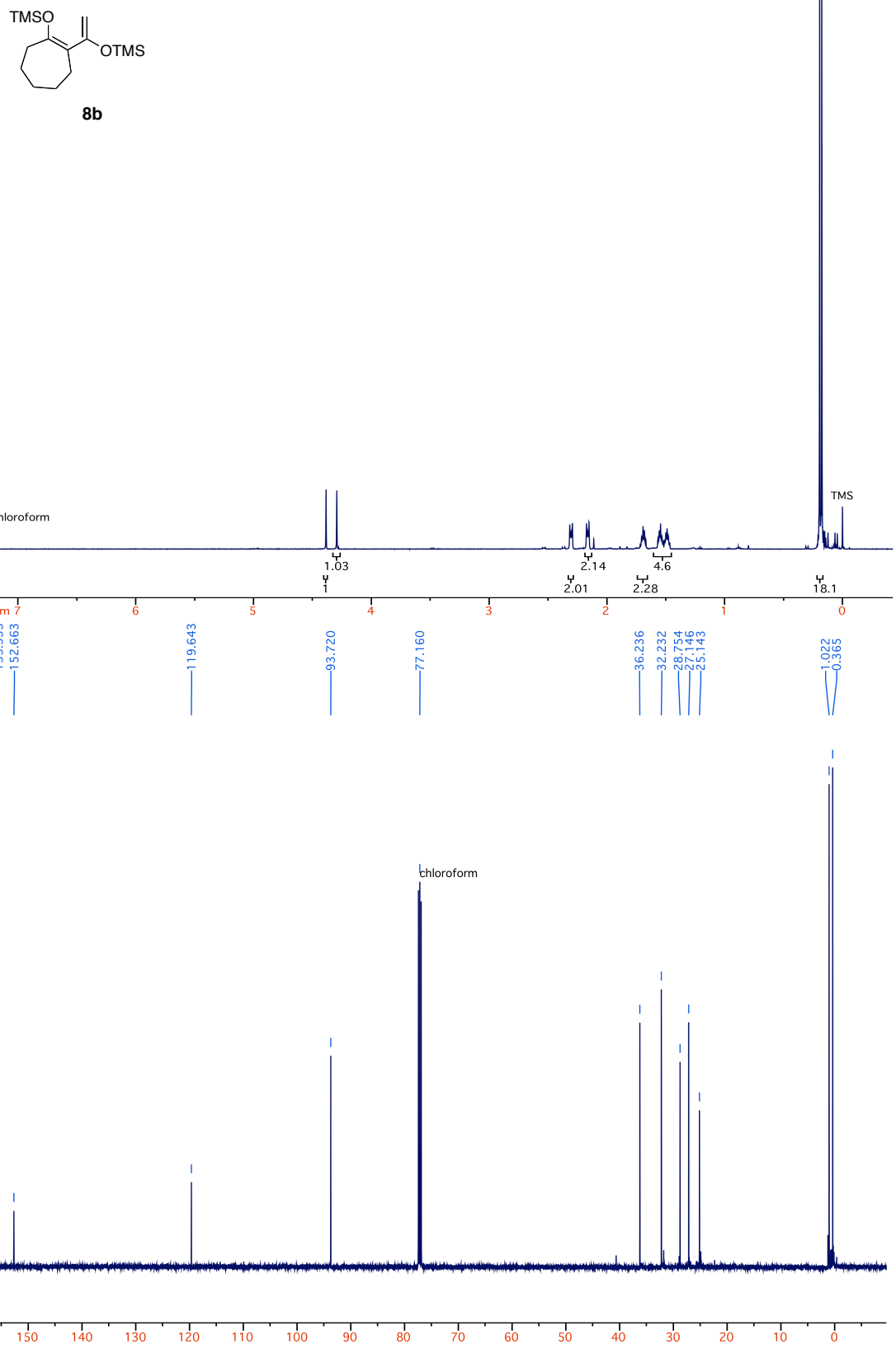
chloroform
16.3 ppm, enol signal
2.4
1.85
0.966
1.88
198.299
181.943
141.533
135.426
130.546
129.864
127.308
126.115
112.650
77.414
77.160
76.905
32.902
28.605
27.796
25.764
25.287

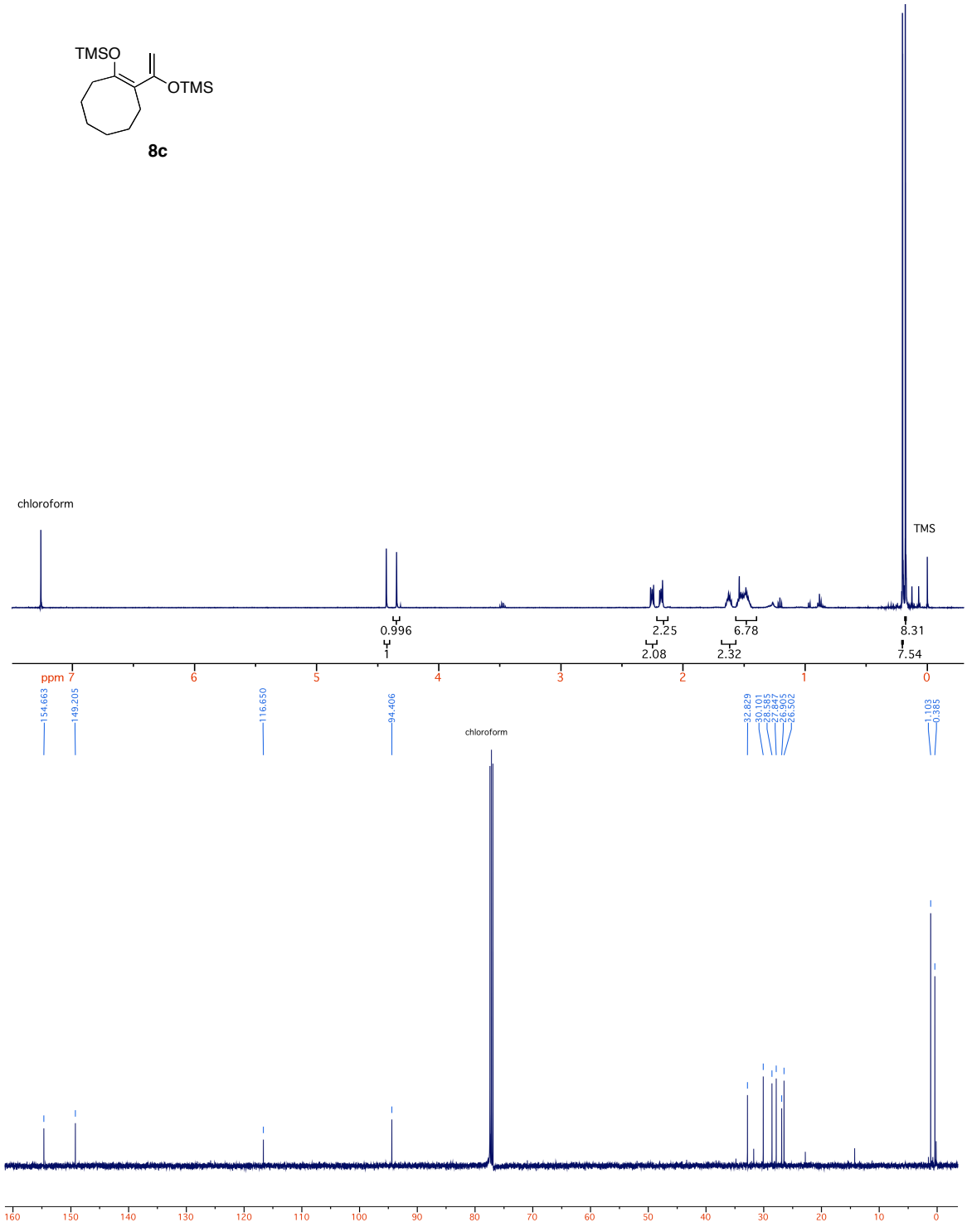

chloroform

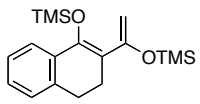

TMSO
OTMS

8a

chloroform
TMS
1
0.99
4.34
2.14
2.21
9.12
9.14
ppm 8
7
6
5
4
3
2
1
0
155.098
147.223
114.436
94.084
31.362
26.500
23.314
23.370
1.114
0.000
0.325
chloroform
60
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

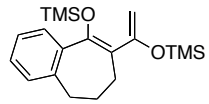

TMSO
OTMS
8b
chloroform
TMS
1.03
2.14
4.6
1
2.01
2.28
18.1
ppm 7
6
5
4
3
2
1
0
155.533
152.663
119.643
93.720
77.160
36.236
32.232
28.754
27.146
25.143
1.022
0.365
chloroform
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TMSO
OTMS
8c
chloroform
TMS
0.996
2.25
6.78
8.31
1
2.08
2.32
7.54
ppm 7
6
5
4
3
2
1
0
154.663
149.205
116.650
94.406
chloroform
32.829
30.101
28.155
27.847
26.905
26.502
1.103
0.385
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TMSO
OTMS

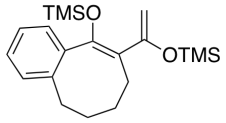
8d

3.17
1.03
2.15
9.34
1
1.02
2.16
9
ppm 7
6
5
4
3
2
1
0
154.037
145.112
137.239
134.672
127.343
127.224
126.140
123.392
117.852
96.296
28.442
25.018
0.935
0.401
chloroform
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TMSO
OTMS

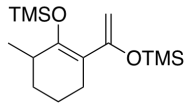
8e

chloroform
TMS
2.1
0.888
1.01
0.96
1
2.05
2.09
2.07
8.87
8.91
ppm 7
6
5
4
3
2
1
0
154.580
146.725
140.325
139.689
128.548
127.961
127.890
125.797
118.842
94.940
chloroform
34.667
32.252
25.962
0.940
0.436
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TMSO
OTMS

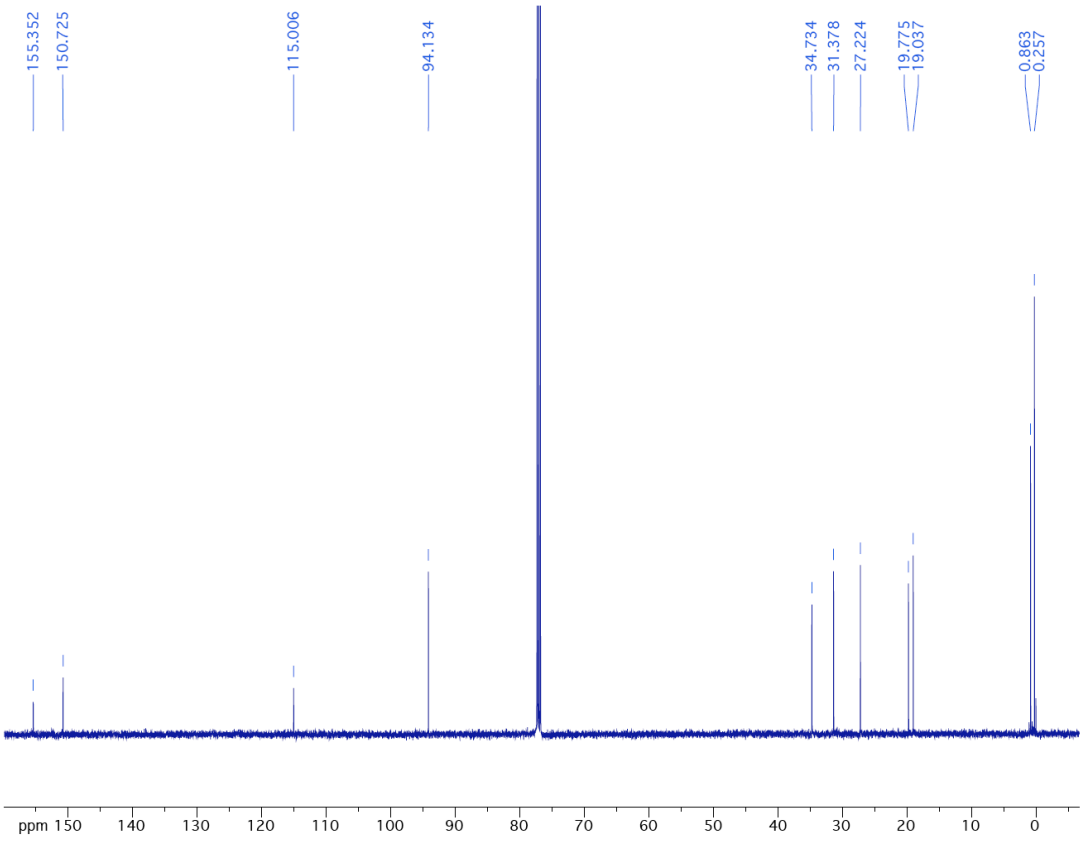
8f

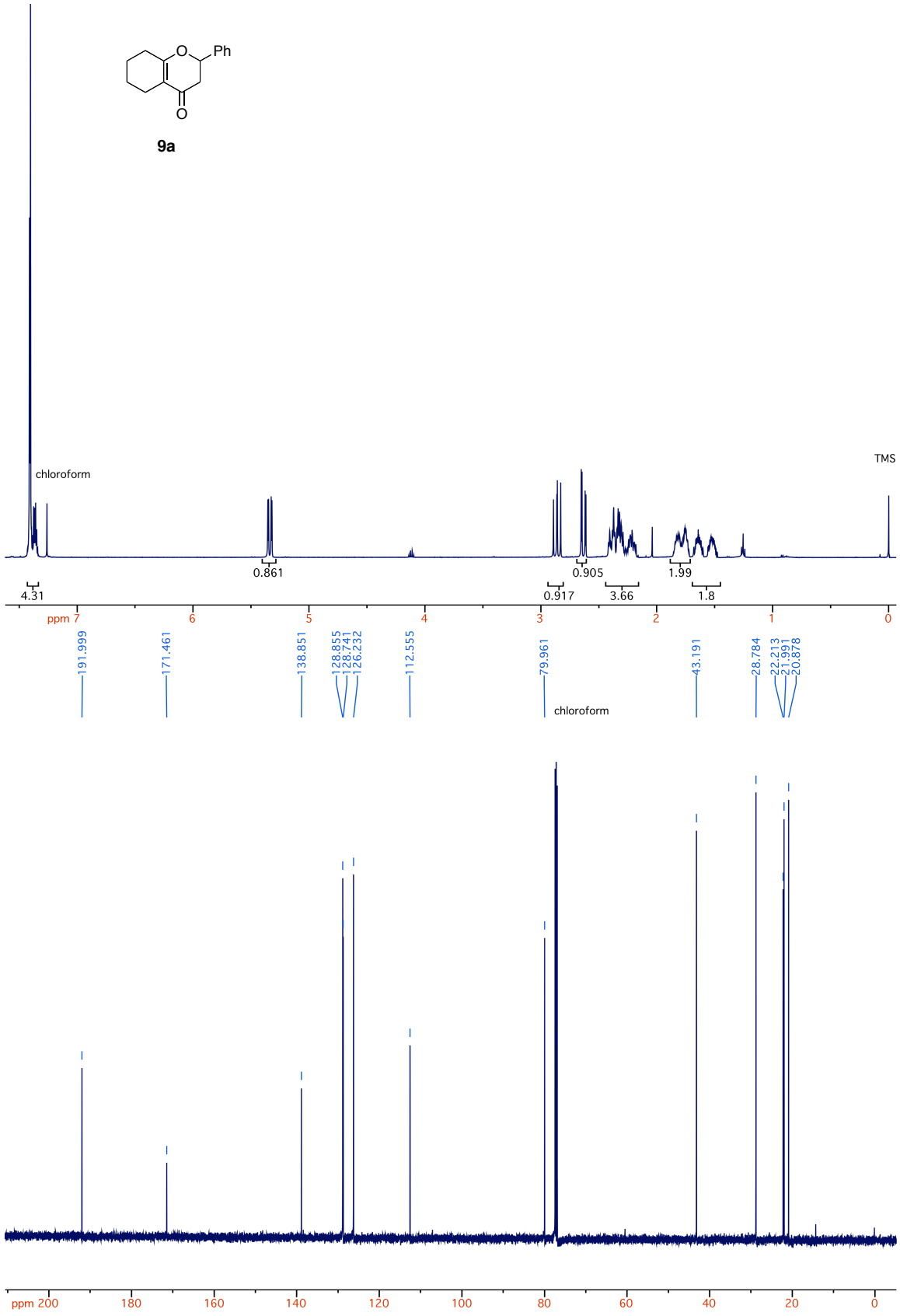
chloroform
0.911
0.985
2.07
1.01
1.01
1.12
1.04
1.17
1.11
1.11
4.53
9
9.04
ppm 7
6
5
4
3
2
1
0
154.733
145.837
142.317
137.223
129.549
128.679
128.660
125.323
120.300
95.742
33.434
29.007
27.591
24.921
1.051
0.344
chloroform
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

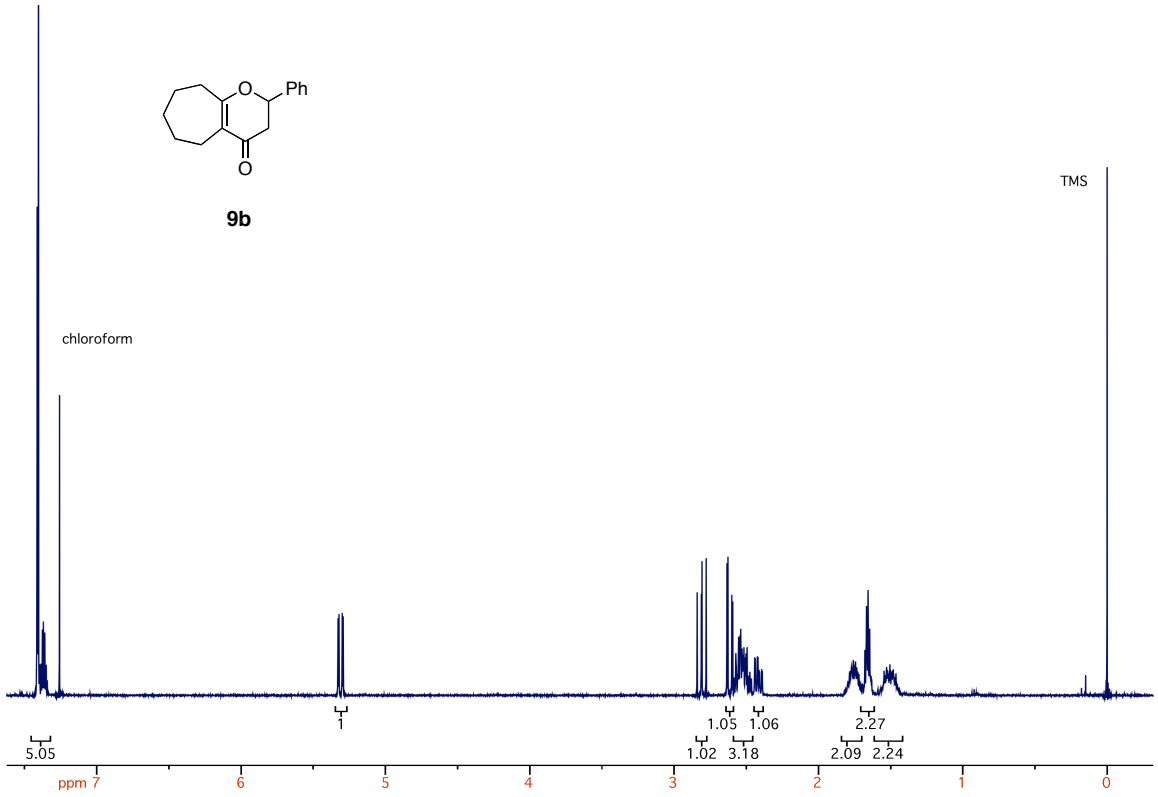

TMSO
OTMS

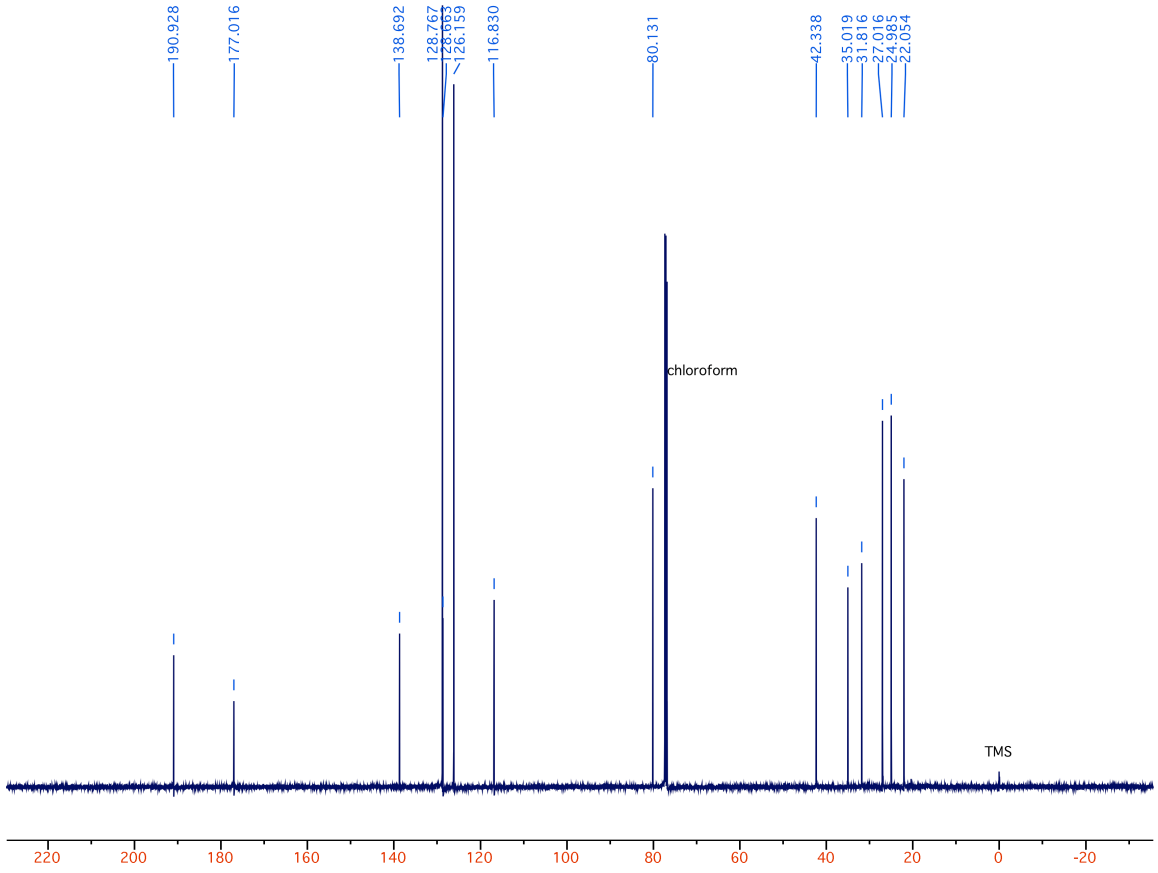
S2

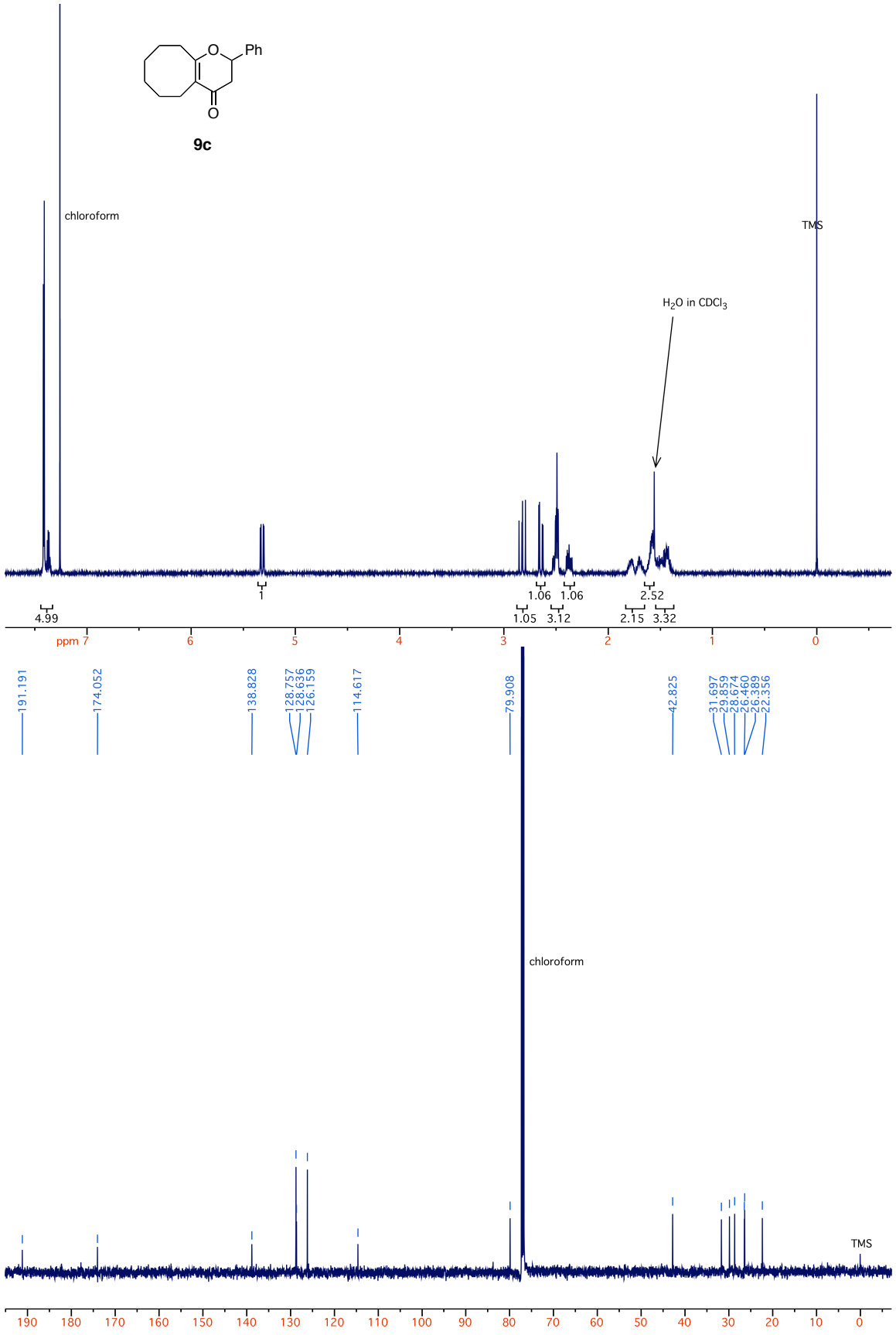
1
1.09
1.07
1.02
17.7
1
2.03
1.02
1.04
3.04
ppm 7
6
5
4
3
2
1
0

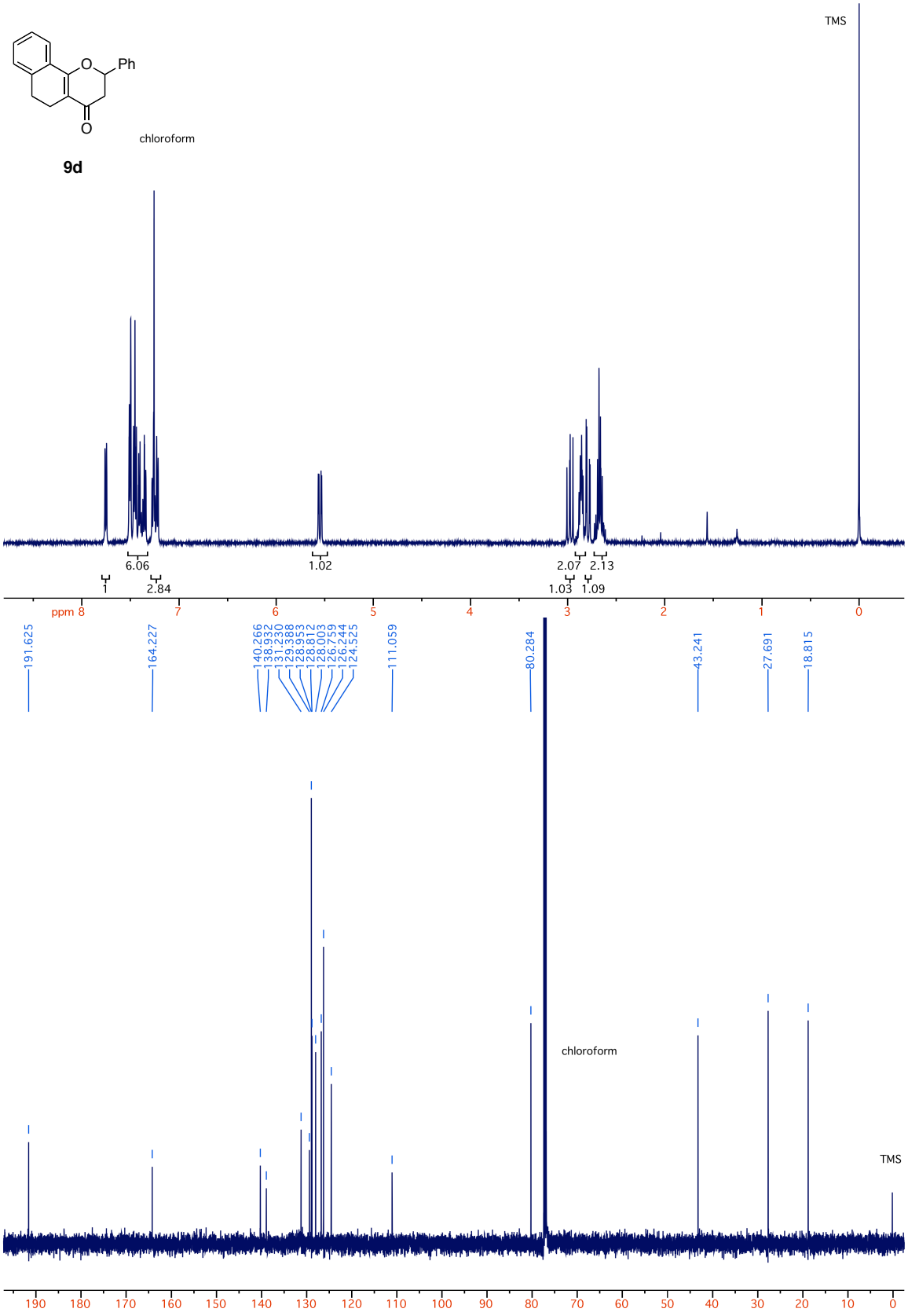

155.352
150.725
115.006
94.134
34.734
31.378
27.224
19.775
19.037
0.863
0.257
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

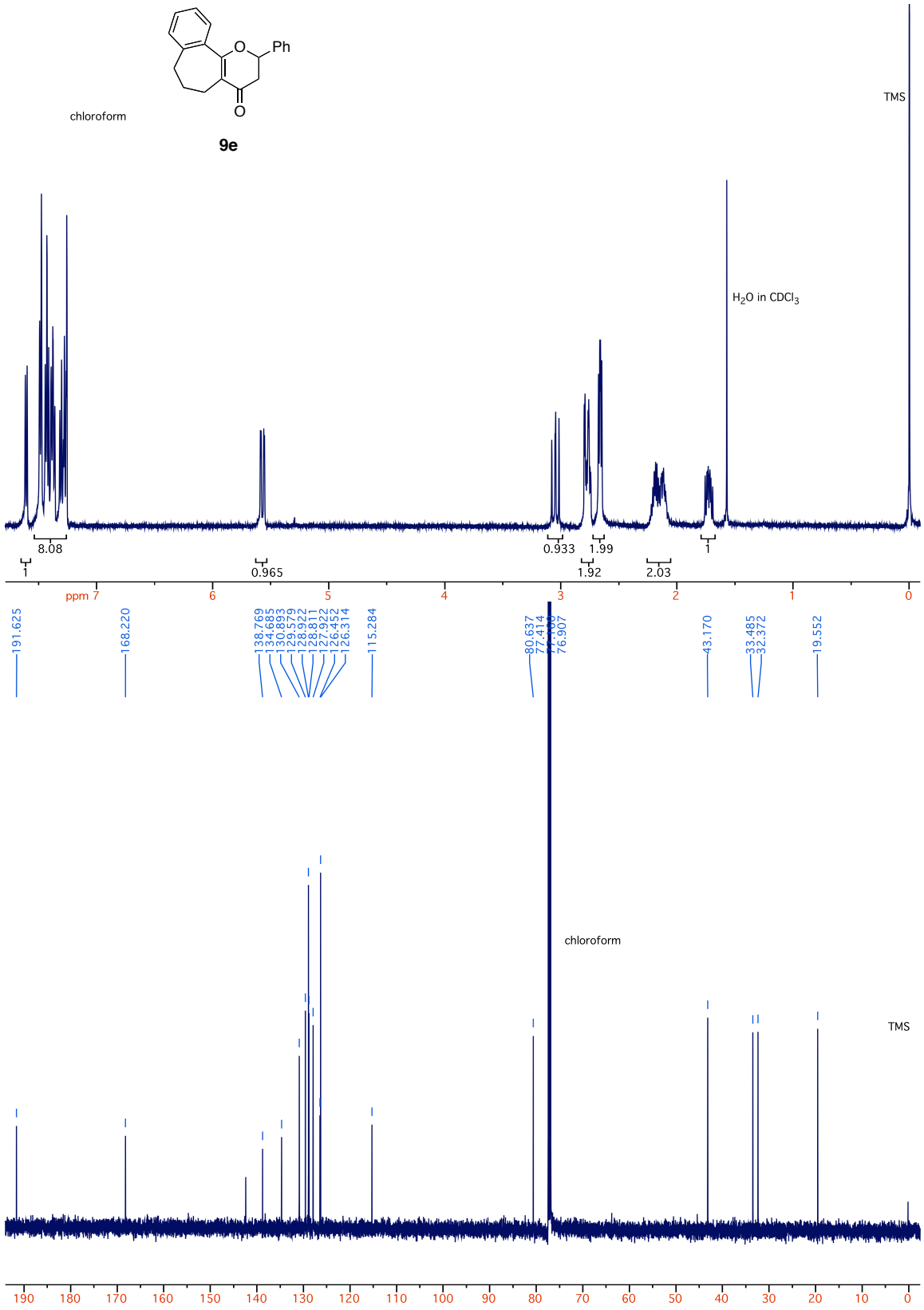

O
Ph
O
9a
chloroform
TMS
0.861
0.905
1.99
4.31
0.917
3.66
1.8
ppm 7
6
5
4
3
2
1
0
191.999
171.461
138.851
128.855
128.741
126.232
112.555
79.961
chloroform
43.191
28.784
22.213
21.991
20.878
ppm 200
180
160
140
120
100
80
60
40
20
0

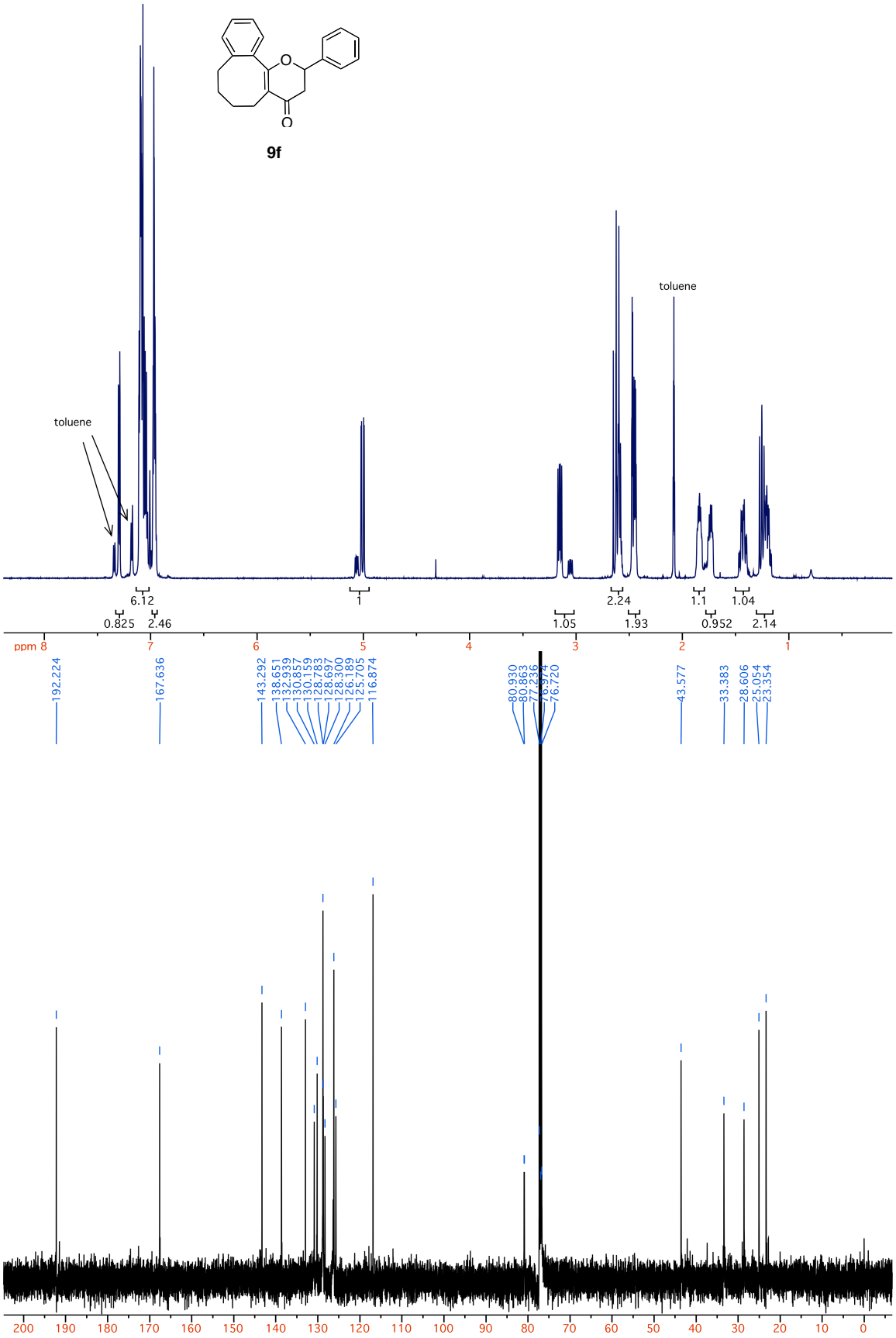

O
Ph
O
9b
TMS
chloroform
1
1.05
1.06
2.27
5.05
1.02
3.18
2.09
2.24
ppm 7
6
5
4
3
2
1
0

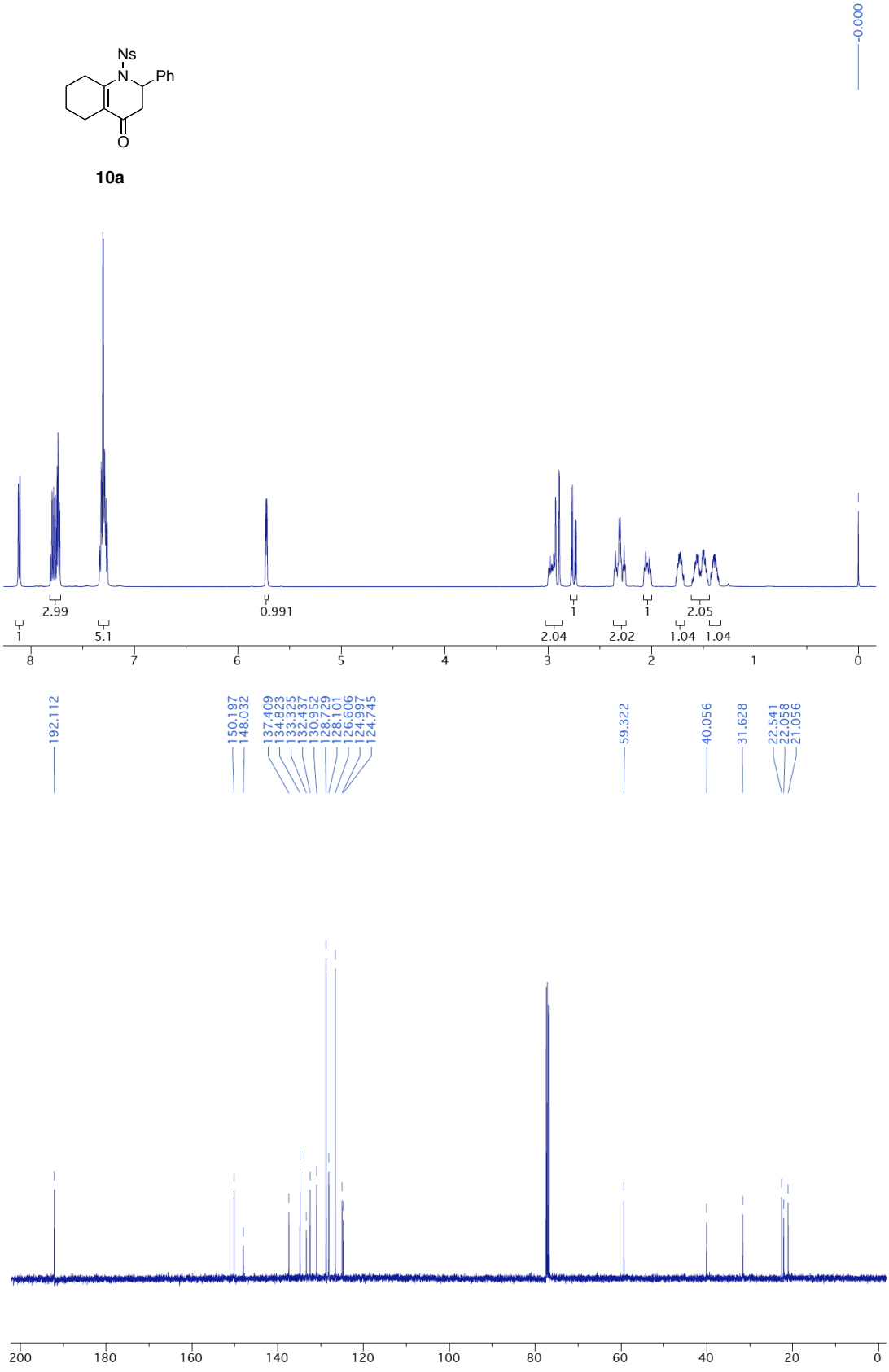

190.928
177.016
138.692
128.767
128.063
126.159
116.830
80.131
42.338
35.019
31.816
27.016
24.985
22.054
chloroform
TMS
220
200
180
160
140
120
100
80
60
40
20
0
-20

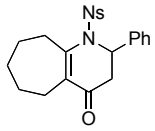

O
Ph
O
9c
chloroform
TMS
H2O in CDCl3
4.99
1
1.05
1.06
3.12
1.06
2.15
2.52
3.32
ppm 7
6
5
4
3
2
1
0
191.191
174.052
138.828
128.757
128.636
126.159
114.617
79.908
42.825
31.697
29.859
28.674
26.460
26.389
22.356
chloroform
TMS
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Ph
O
O
chloroform
9d
TMS
6.06
1.02
2.07
2.13
1
2.84
1.03
1.09
ppm 8
7
6
5
4
3
2
1
0
191.625
164.227
140.266
138.932
131.230
129.388
128.953
128.812
128.003
126.759
126.244
124.525
111.059
80.284
43.241
27.691
18.815
chloroform
TMS
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

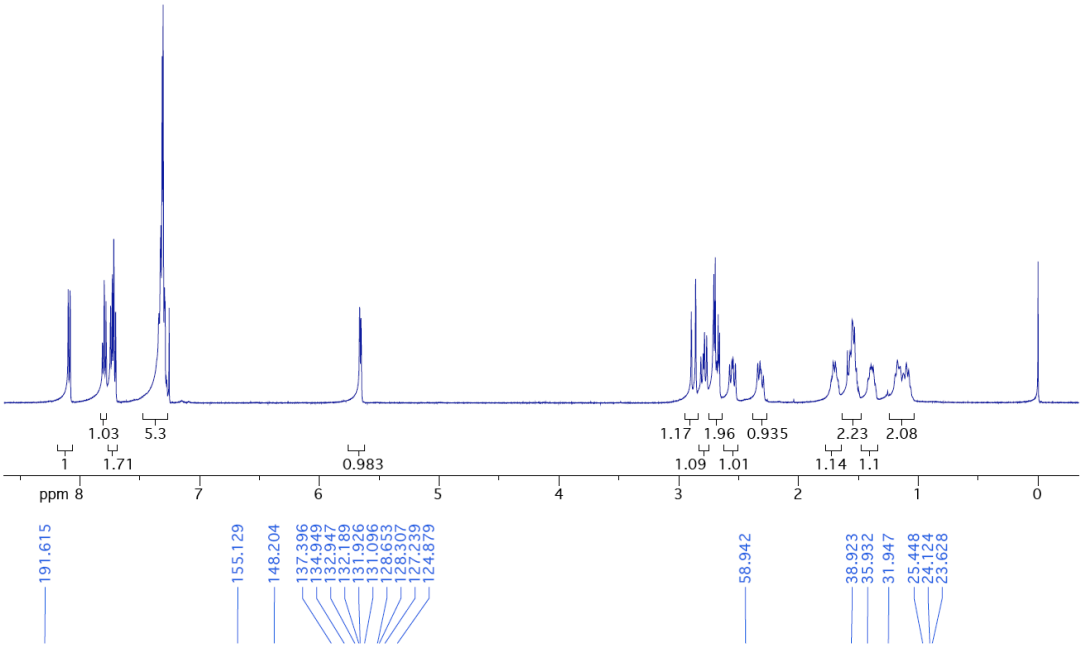

O
Ph
O
chloroform
9e
TMS
H2O in CDCl3
8.08
0.933
1.99
1
1
0.965
1.92
2.03
ppm 7
6
5
4
3
2
1
0
191.625
168.220
138.769
134.685
130.883
130.579
128.922
128.811
127.922
126.452
126.314
115.284
80.637
77.414
77.188
76.907
43.170
33.485
32.372
19.552
chloroform
TMS
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


9f
toluene
toluene
6.12
0.825
2.46
1
1.05
2.24
1.93
1.1
0.952
1.04
2.14
ppm 8
7
6
5
4
3
2
1
192.224
167.636
143.292
138.651
132.939
130.857
130.159
128.783
128.697
128.300
126.189
125.705
116.874
80.930
80.863
77.636
76.974
76.720
43.577
33.383
28.606
25.054
23.354
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

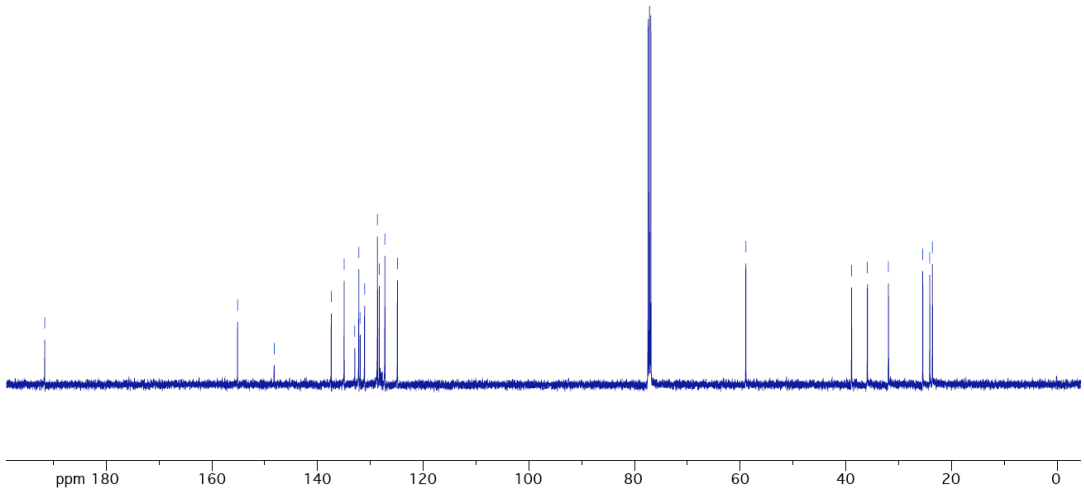

Ns
N
Ph
O
10a
0.000
2.99
0.991
1
1
2.05
1
5.1
2.04
2.02
1.04
1.04
192.112
150.197
148.032
137.409
134.823
133.335
132.437
130.932
128.729
128.101
126.666
124.997
124.745
59.322
40.056
31.628
22.541
22.058
21.056

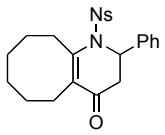

Ns
N
Ph
O

10b

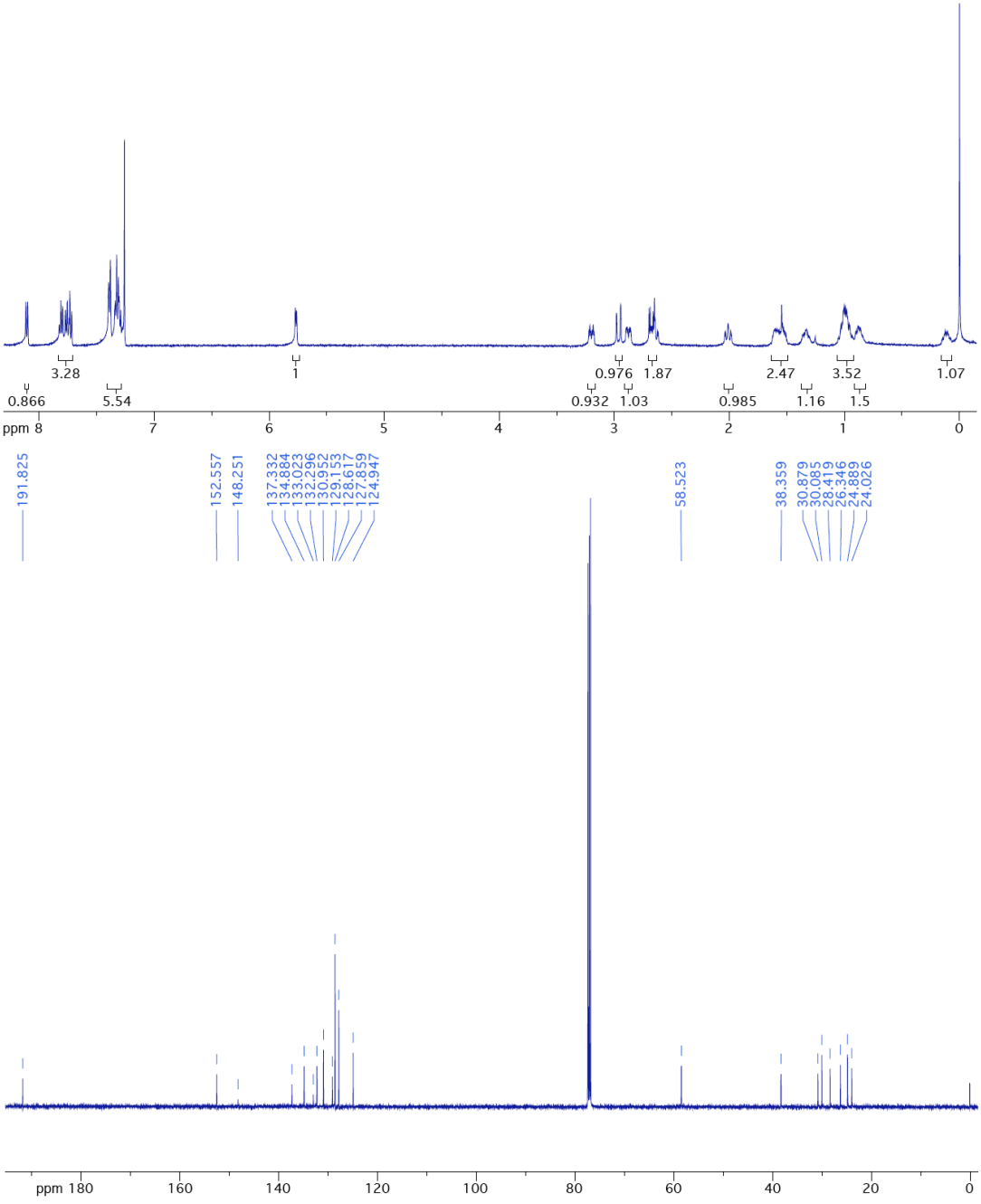

1.03
5.3
1
1.71
0.983
1.17
1.96
0.935
2.23
2.08
1.09
1.01
1.14
1.1
ppm 8
7
6
5
4
3
2
1
0

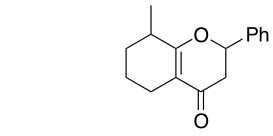
191.615
155.129
148.204
137.396
134.949
132.947
132.189
131.926
131.096
128.653
128.307
127.239
124.879
58.942
38.923
35.932
31.947
25.448
24.124
23.628


ppm 180
160
140
120
100
80
60
40
20
0


Ns
N
Ph
O

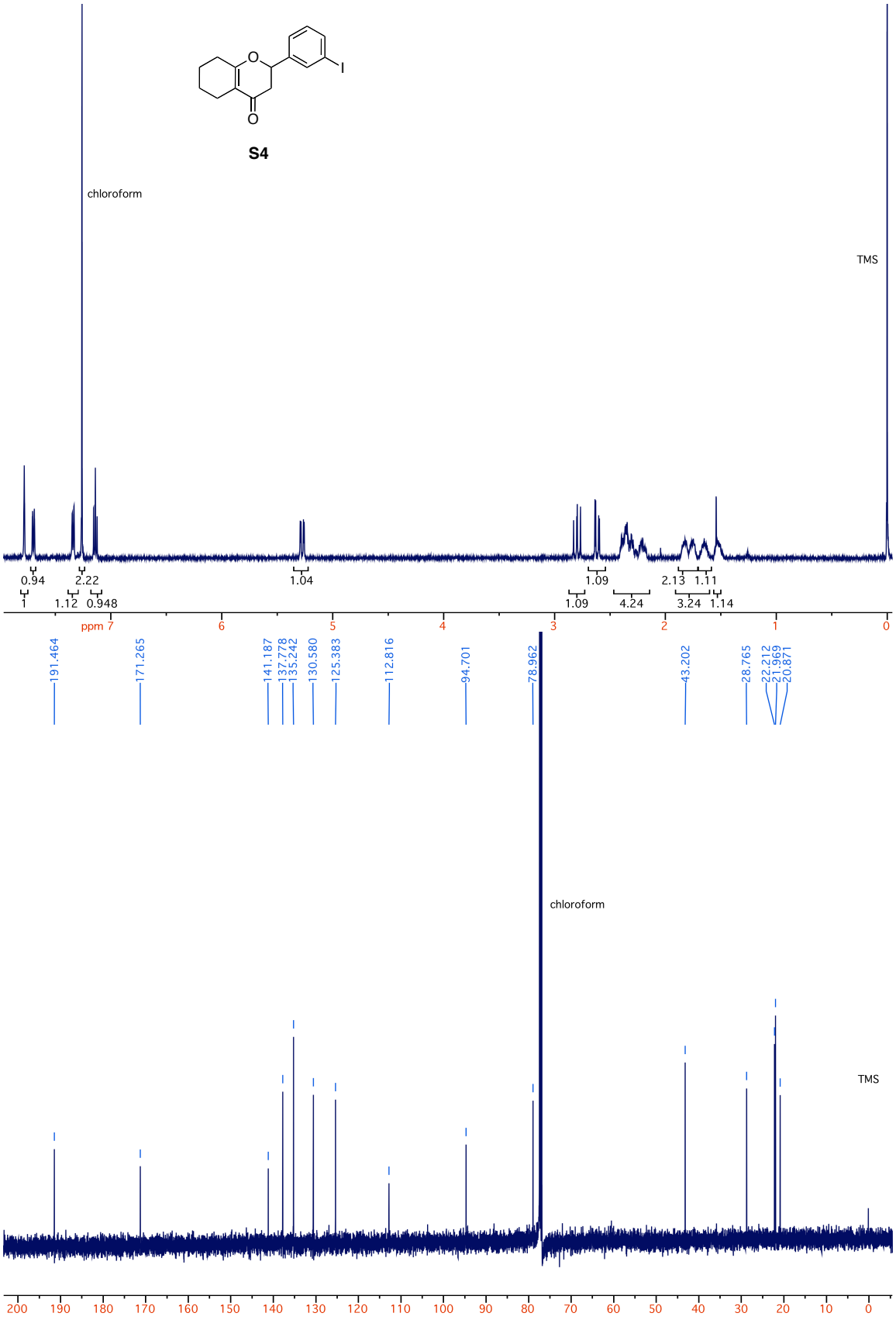
10c

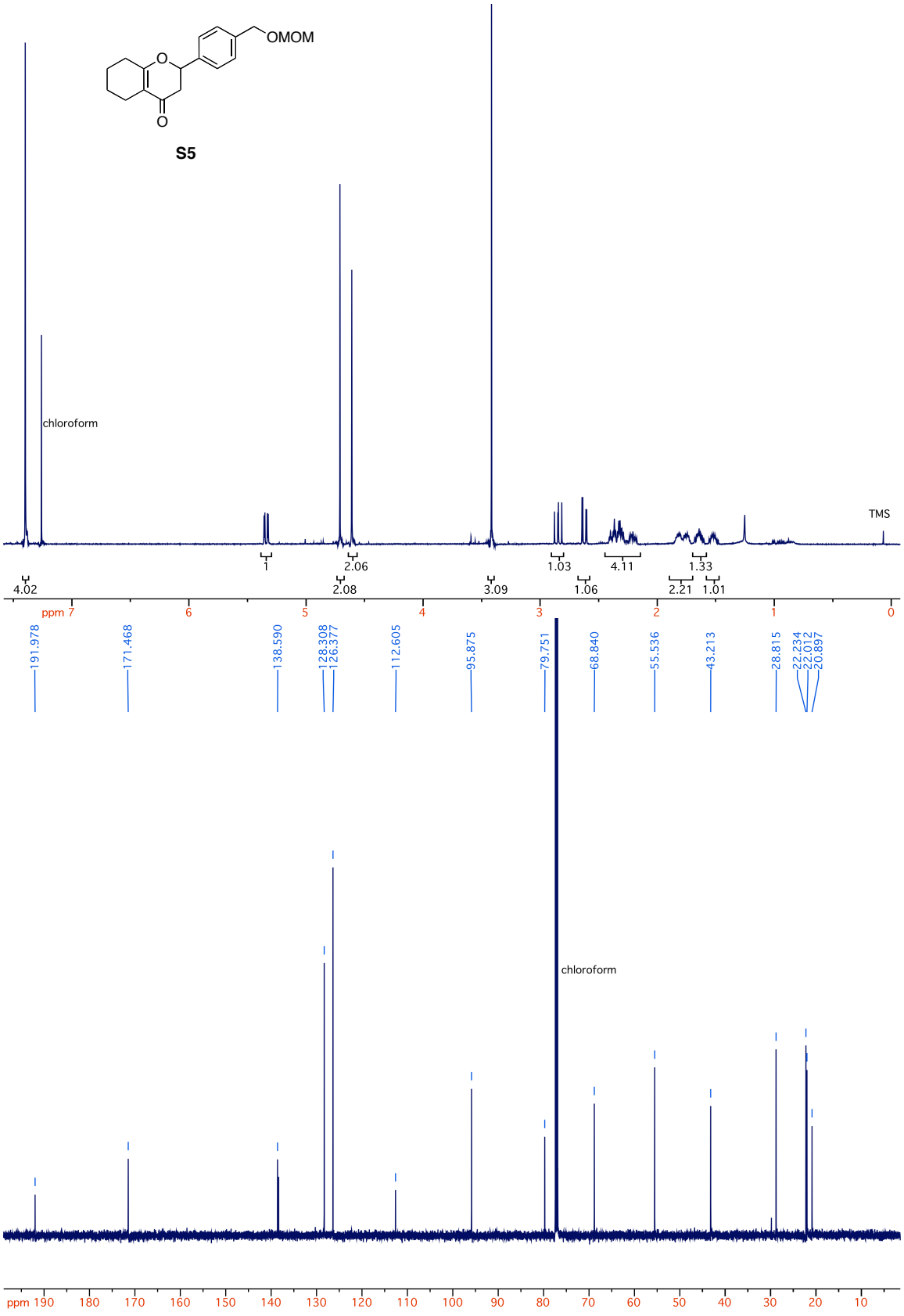

3.28
1
0.976
1.87
2.47
3.52
1.07
0.866
5.54
0.932
1.03
0.985
1.16
1.5
ppm 8
7
6
5
4
3
2
1
0
191.825
152.557
148.251
137.332
134.884
133.023
132.296
130.952
129.153
128.617
127.859
124.947
58.523
38.359
30.879
30.085
28.419
26.346
24.889
24.026
ppm 180
160
140
120
100
80
60
40
20
0

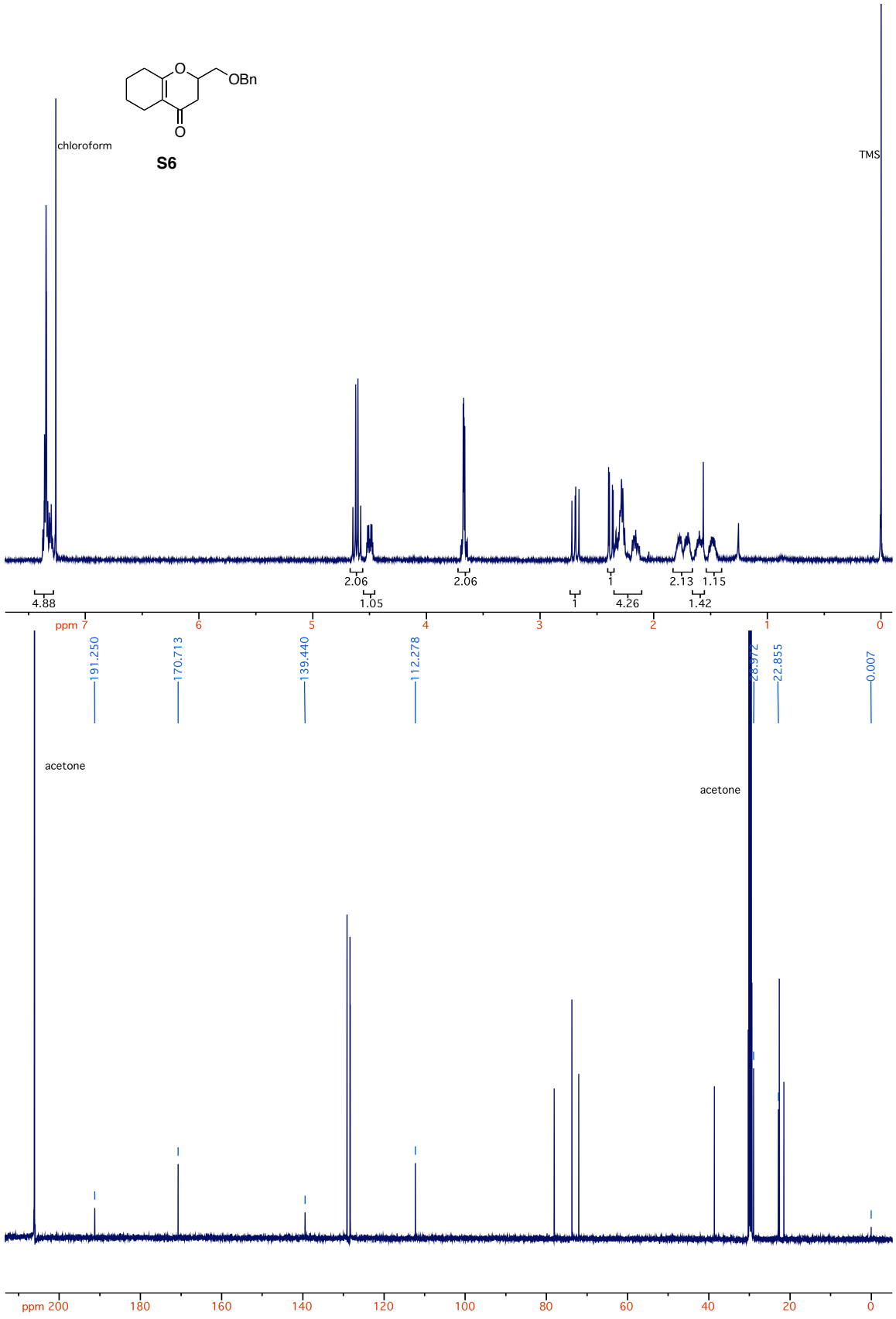

O
Ph
O

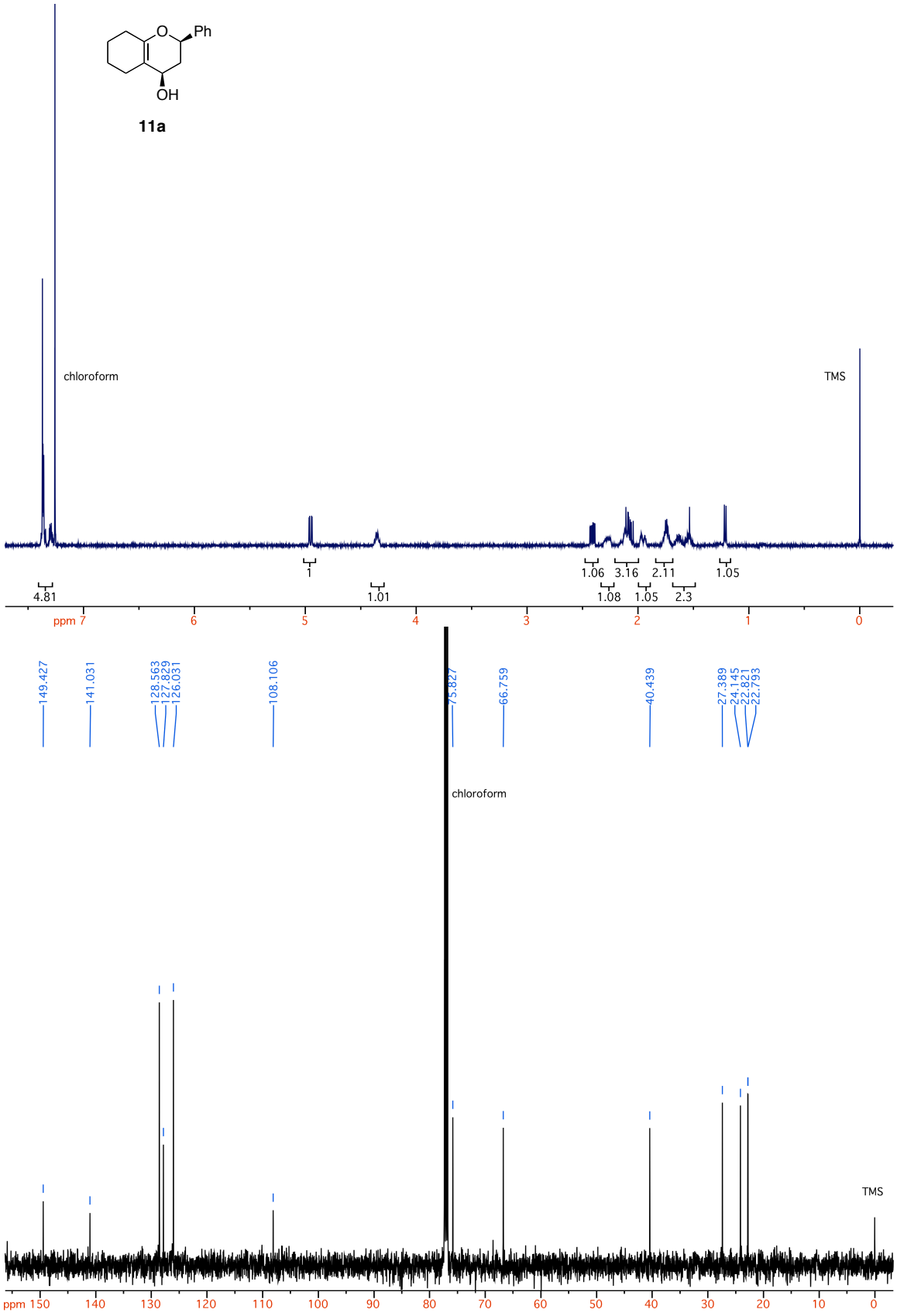
S3

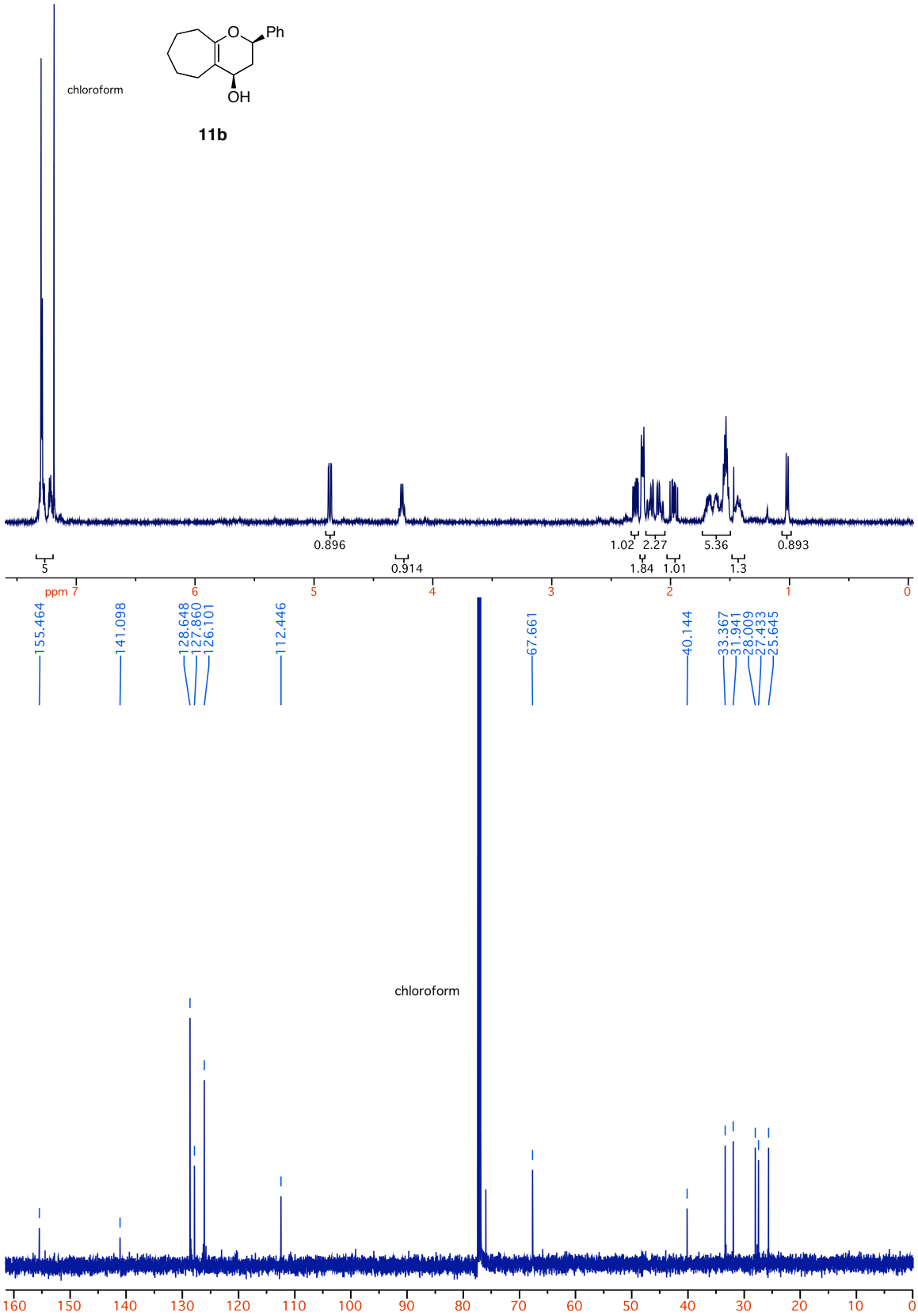
2.07
10.4
2.19 2.22 1.18 1.99 1.15 3.49
2.17 2.13 2.19 2.19 2.19 1.21 2.98
ppm 7 6 5 4 3 2 1 0
192.395 192.296 174.491 174.341 139.198 138.956 128.746 128.561 128.433 126.049 125.872 112.058 111.994 79.773 79.555 43.329 42.986 33.879 32.685 31.406 30.210 21.526 21.349 20.427 18.696 18.437 18.017
00 180 160 140 120 100 80 60 40 20 0

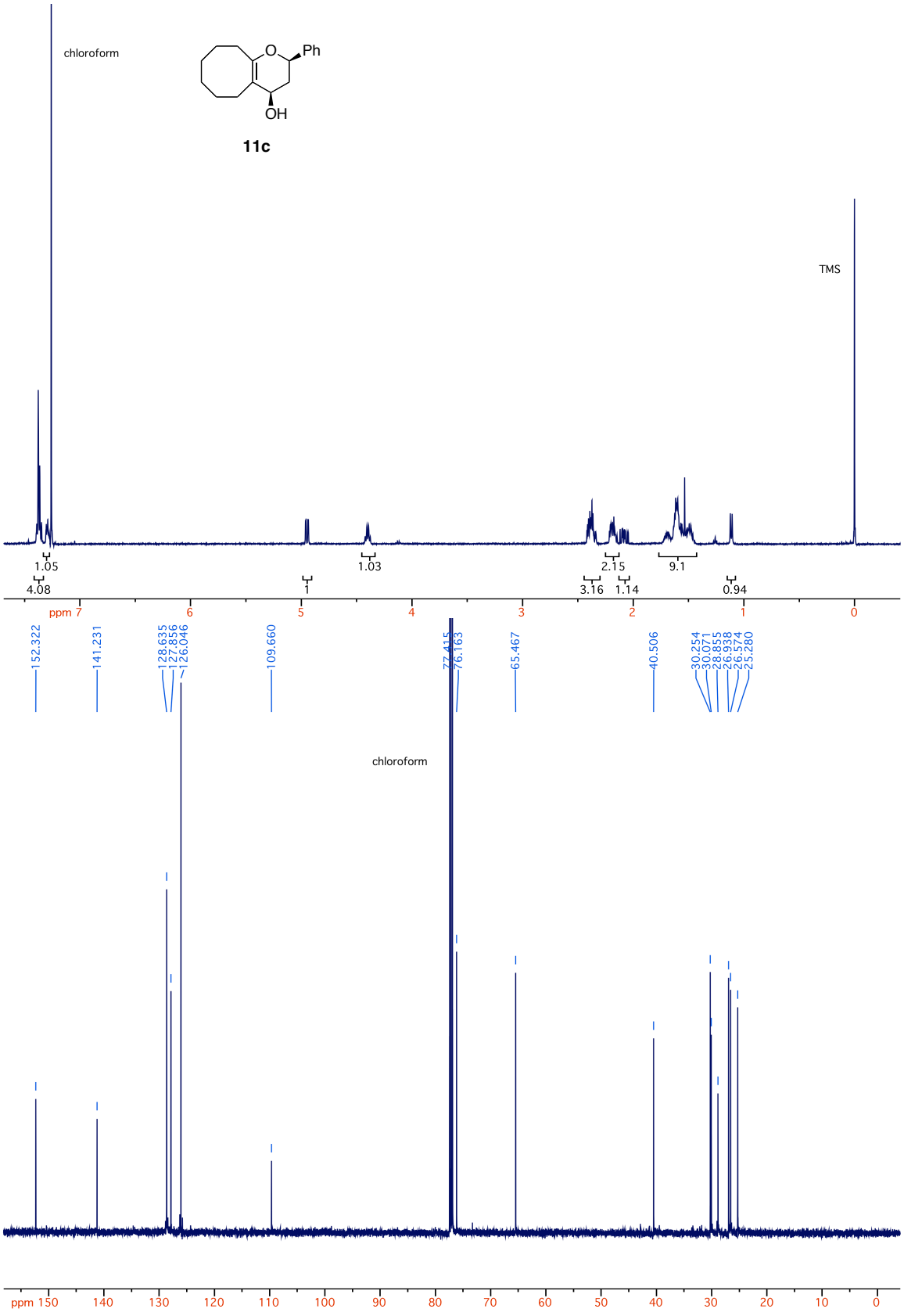

S4
chloroform
TMS
0.94
2.22
1.04
1.09
2.13
1.11
1
1.12
0.948
1.09
4.24
3.24
1.14
ppm 7
6
5
4
3
2
1
0
191.464
171.265
141.187
137.778
135.242
130.580
125.383
112.816
94.701
78.962
43.202
28.765
22.212
21.969
20.871
chloroform
TMS
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

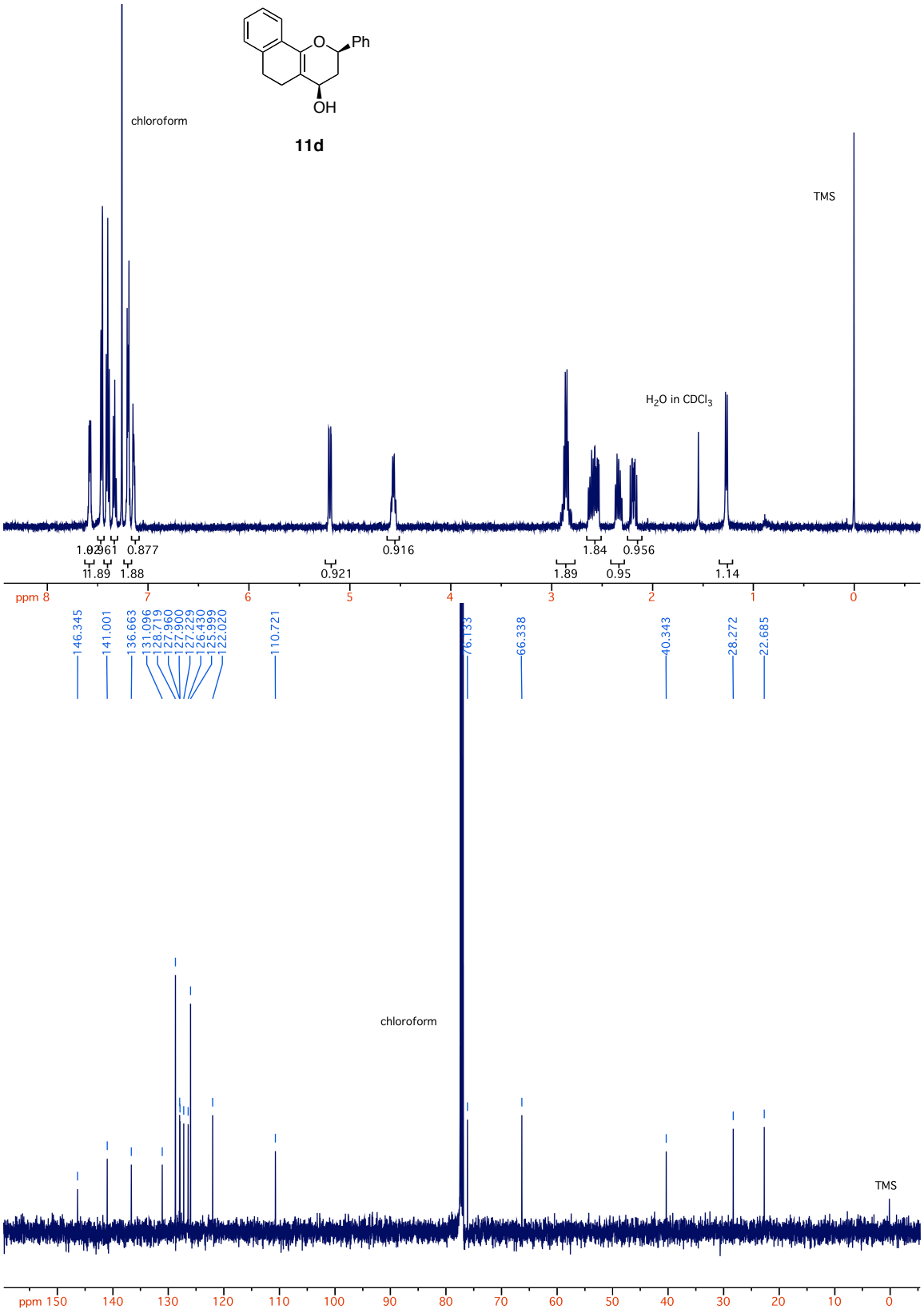

OMOM
O
O
S5
chloroform
TMS
1
2.06
1.03
4.11
1.33
4.02
2.08
3.09
1.06
2.21
1.01
ppm 7
6
5
4
3
2
1
0
191.978
171.468
138.590
128.308
126.377
112.605
95.875
79.751
68.840
55.536
43.213
28.815
22.234
22.012
20.897
chloroform
ppm 190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

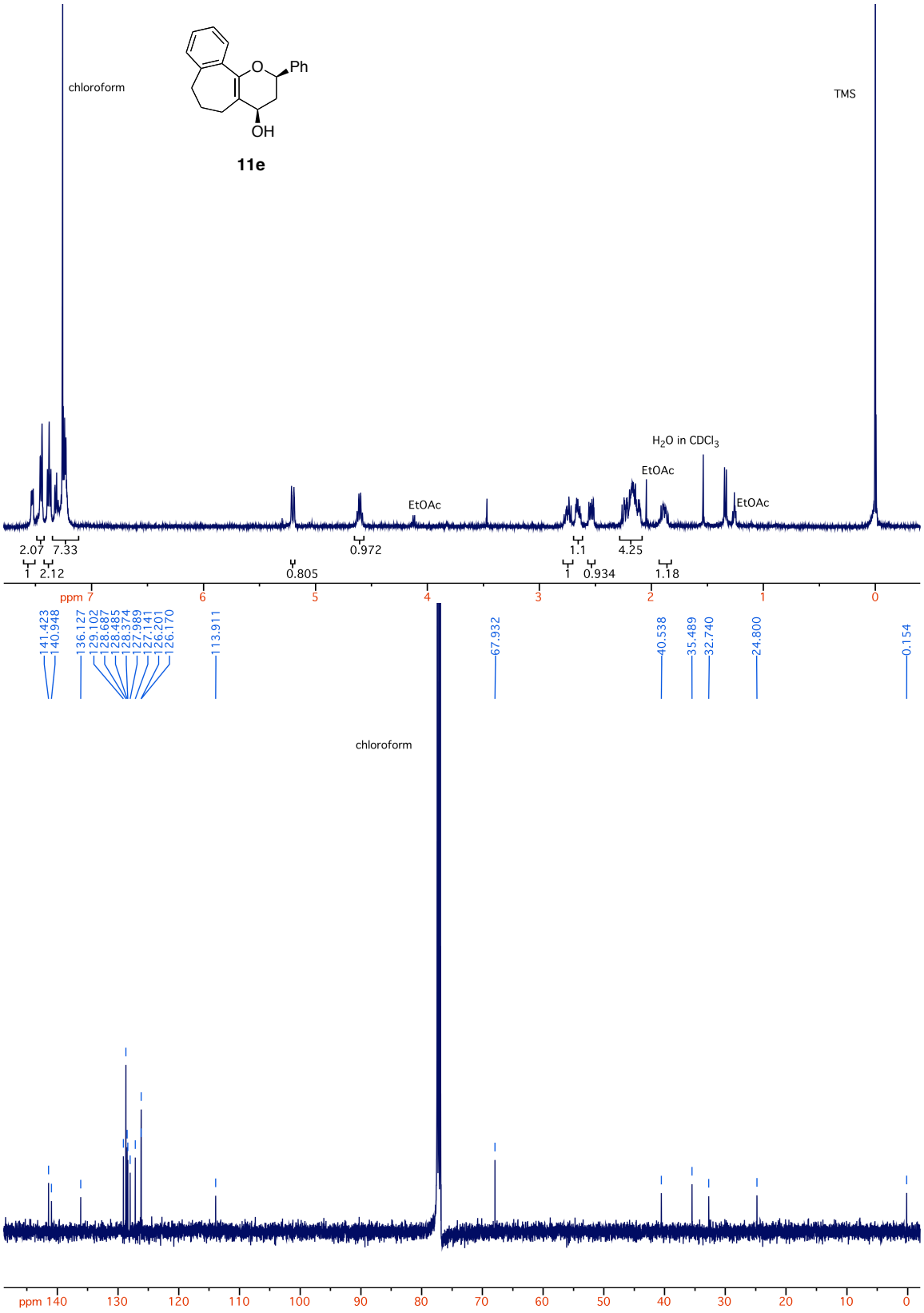

OBn
O
O
S6
chloroform
TMS
4.88
2.06
1.05
2.06
1
1
4.26
2.13
1.15
1.42
ppm 7
6
5
4
3
2
1
0
191.250
170.713
139.440
112.278
28.972
22.855
0.007
acetone
acetone
ppm 200
180
160
140
120
100
80
60
40
20
0

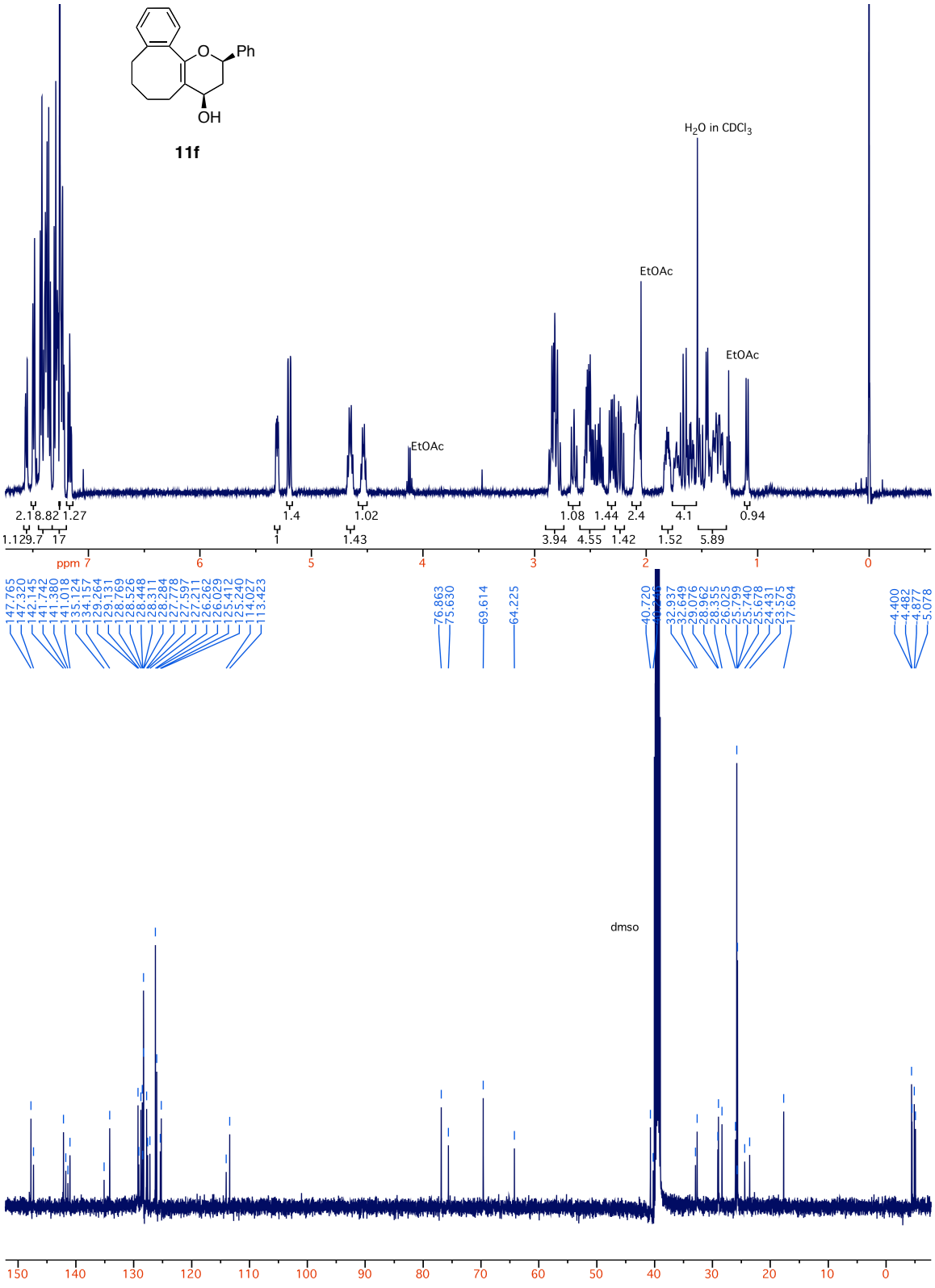

O
Ph
OH
11a
chloroform
TMS
4.81
1
1.01
1.06
3.16
2.11
1.05
1.08
1.05
2.3
ppm 7
6
5
4
3
2
1
0
149.427
141.031
128.563
127.829
126.031
108.106
75.827
66.759
40.439
27.389
24.145
22.821
22.793
chloroform
TMS
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

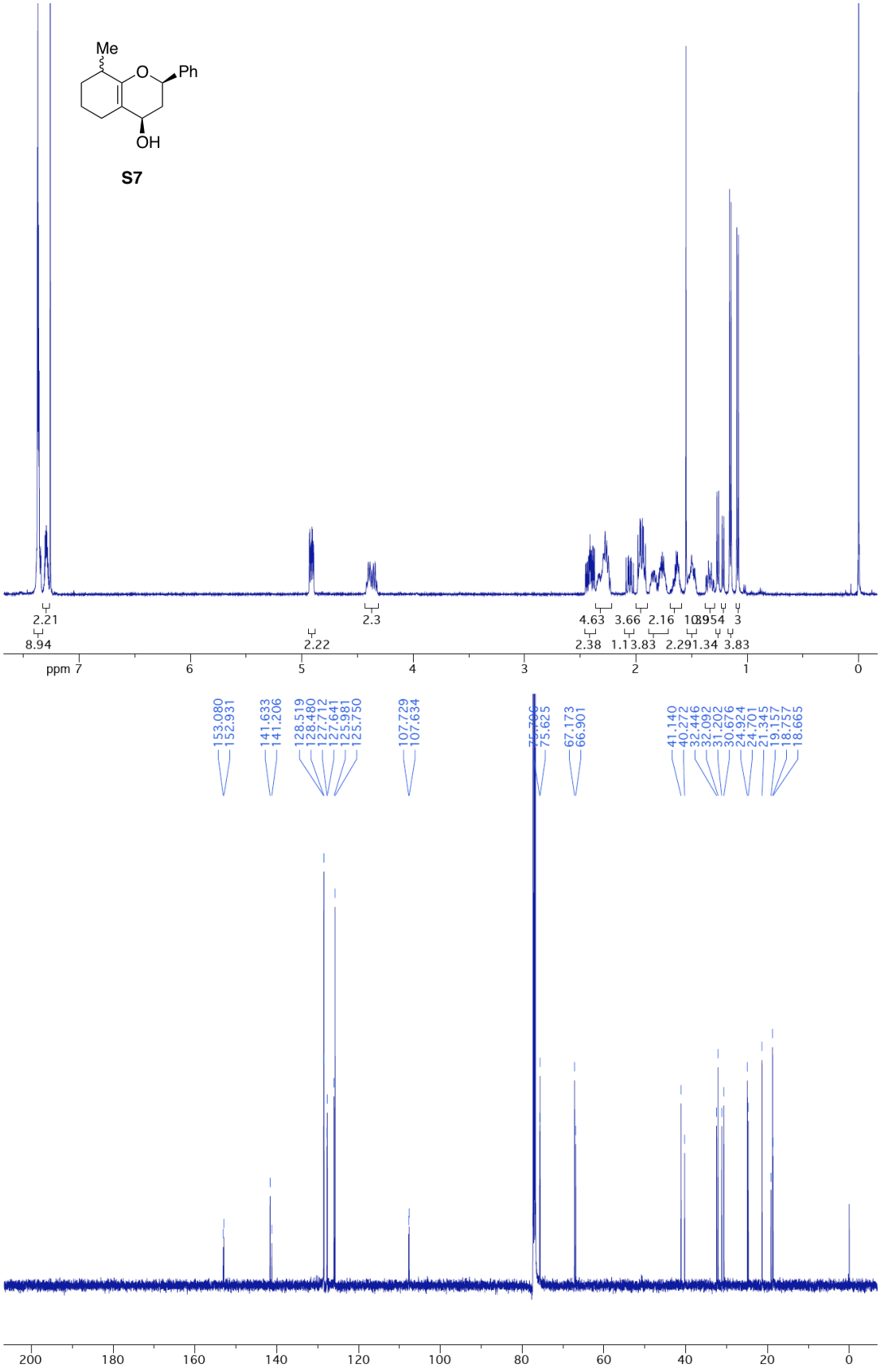

chloroform
O
Ph
OH
11b
0.896
0.914
1.02
2.27
1.84
1.01
5.36
1.3
0.893
5
ppm 7
6
5
4
3
2
1
0
155.464
141.098
128.648
127.860
126.101
112.446
67.661
40.144
33.367
31.941
28.009
27.433
25.645
chloroform
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

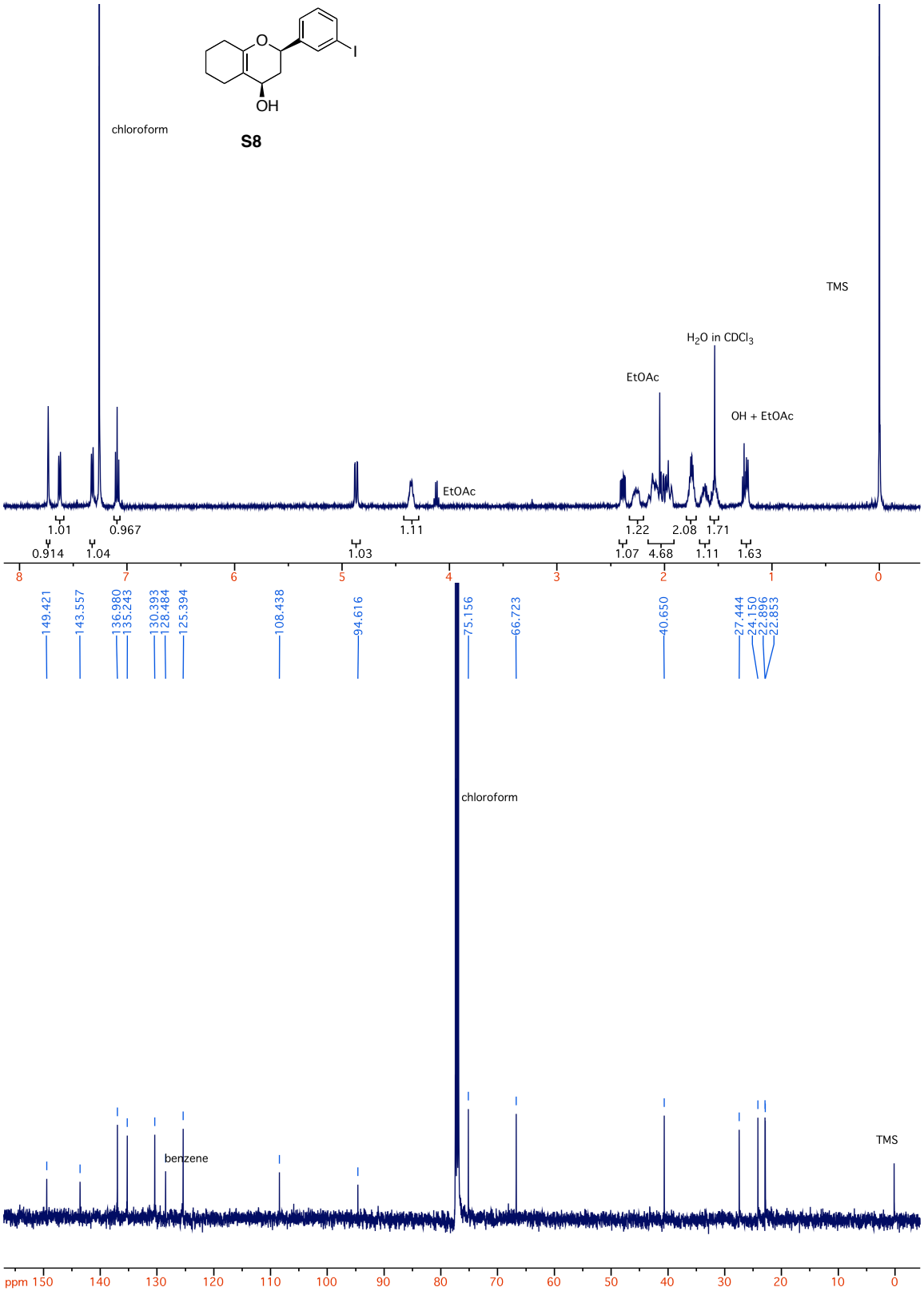

chloroform
O
Ph
OH
11c
TMS
1.05
4.08
1.03
1
2.15
3.16
1.14
9.1
0.94
ppm 7
6
5
4
3
2
1
0
152.322
141.231
128.635
127.856
126.046
109.660
77.415
76.163
65.467
40.506
30.254
30.071
28.855
26.938
26.574
25.280
chloroform
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

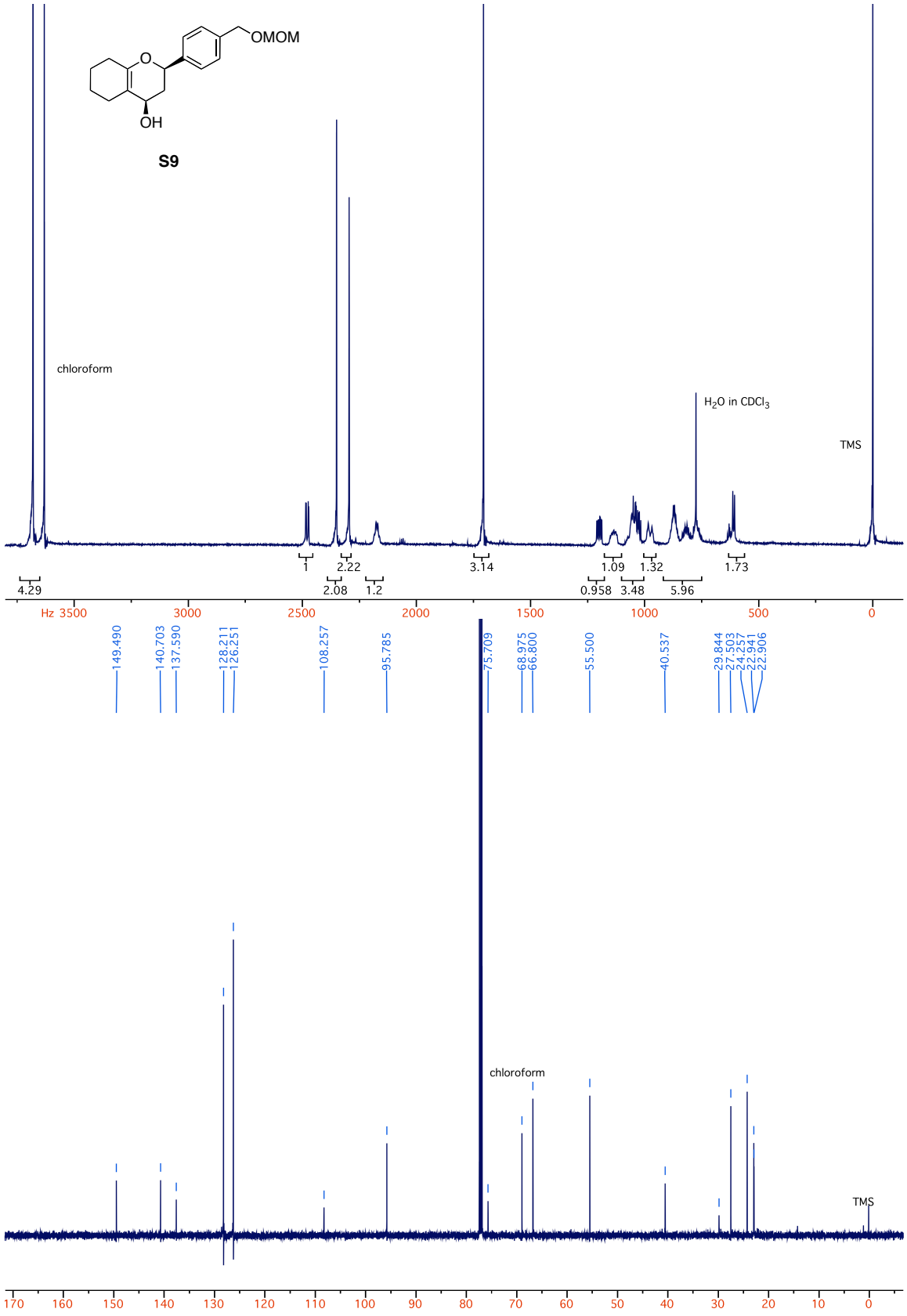

O
Ph
OH
11d
chloroform
TMS
H2O in CDCl3
1.02
2.61
0.877
11.89
1.88
0.921
0.916
1.84
0.956
1.89
0.95
1.14
ppm 8
7
6
5
4
3
2
1
0
146.345
141.001
136.663
131.096
128.719
127.960
127.920
127.290
126.430
125.999
122.020
110.721
76.133
66.338
40.343
28.272
22.685
chloroform
TMS
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

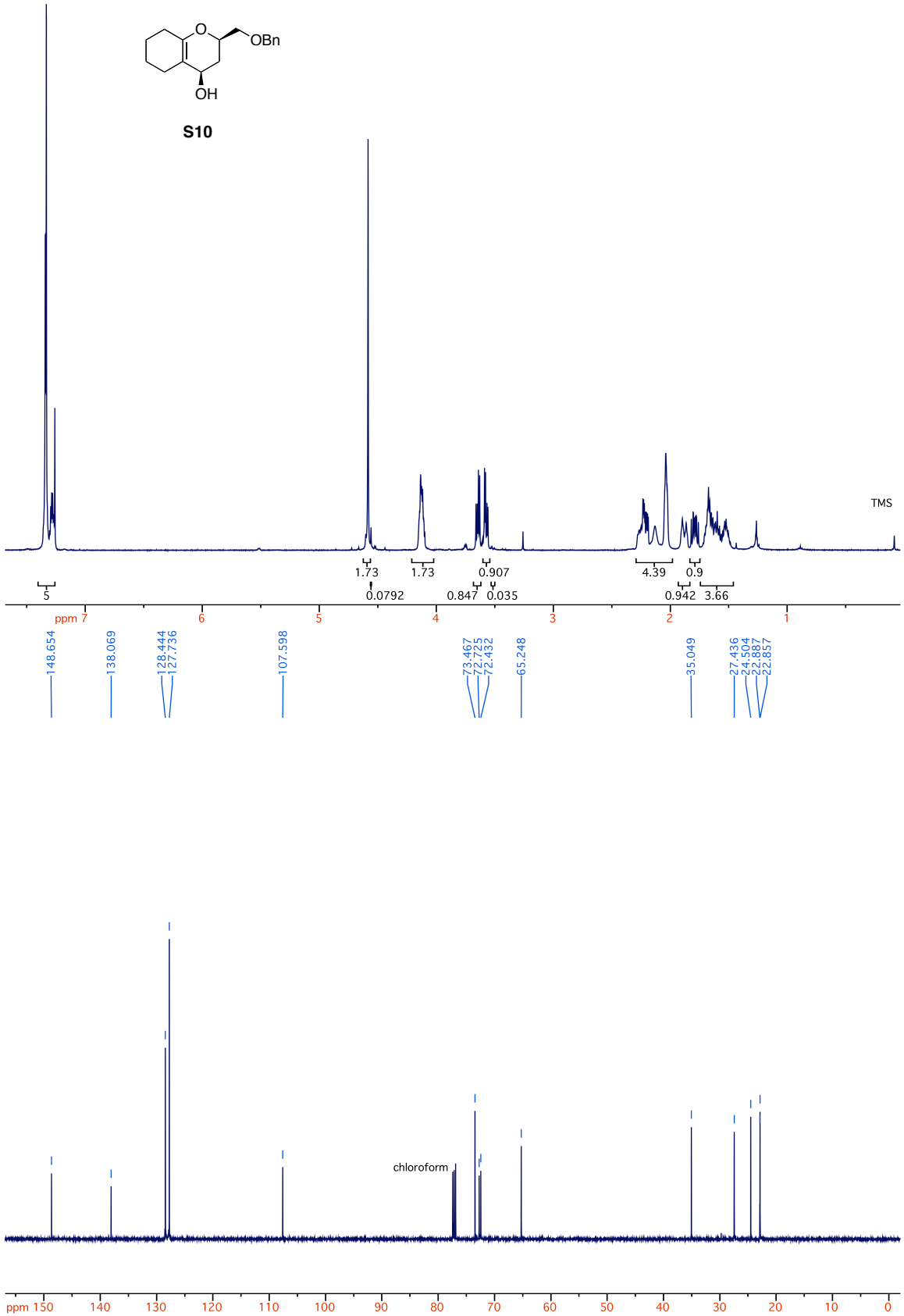

chloroform
O
Ph
OH
11e
TMS
H2O in CDCl3
EtOAc
EtOAc
EtOAc
2.07
7.33
0.972
1.1
4.25
1
2.12
0.805
1
0.934
1.18
ppm 7
6
5
4
3
2
1
0
141.423
140.948
136.127
129.102
128.687
128.485
128.374
127.989
127.141
126.201
126.170
113.911
67.932
40.538
35.489
32.740
24.800
0.154
chloroform
ppm 140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

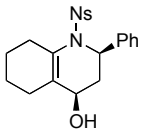

Ph
O
OH
11f
H2O in CDCl3
EtOAc
EtOAc
EtOAc
2.18.82 1.27
1.129.7 17
1.4
1
1.02
1.43
1.08 1.44 2.4
3.94 4.55 1.42
4.1
1.52
0.94
5.89
ppm 7
6
5
4
3
2
1
0
147.765
147.320
142.145
141.742
141.380
141.018
135.124
134.157
129.264
129.131
128.769
128.526
128.448
128.311
128.284
127.778
127.597
127.211
126.262
126.029
125.412
125.240
124.027
113.423
76.863
75.630
69.614
64.225
40.720
40.429
32.337
32.649
29.076
28.962
28.555
26.025
25.749
25.678
23.431
23.575
17.694
4.400
4.382
4.877
5.078
dmso
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Me
O
Ph
OH
S7
2.21
8.94
2.22
2.3
4.63
3.66
2.16
2.38
1.13
3.83
2.29
1.34
3.83
ppm 7
6
5
4
3
2
1
0
153.080
152.931
141.633
141.206
128.519
128.480
127.712
127.641
125.981
125.750
107.729
107.634
75.706
75.625
67.173
66.901
41.140
40.272
32.446
32.092
31.202
30.676
24.924
24.701
21.345
19.157
18.757
18.665
200
180
160
140
120
100
80
60
40
20
0

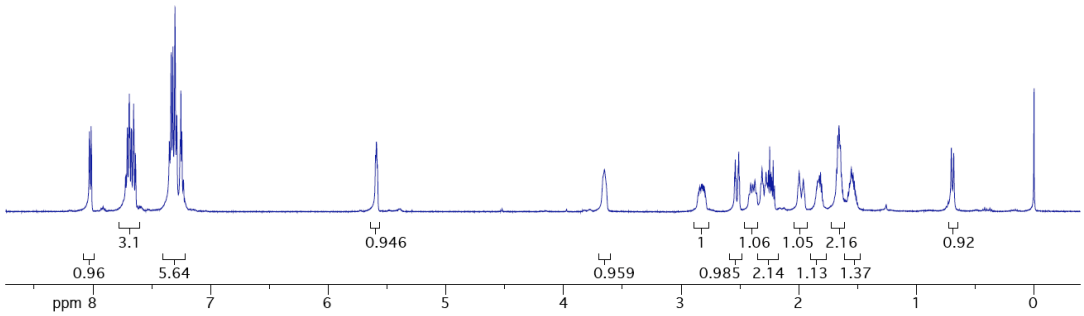

O
I
OH
S8
chloroform
TMS
H_2O in $CDCl_3$
EtOAc
OH + EtOAc
EtOAc
1.01
0.967
1.11
1.22
2.08
1.71
0.914
1.04
1.03
1.07
4.68
1.11
1.63
8
7
6
5
4
3
2
1
0
149.421
143.557
136.980
135.243
130.393
128.484
125.394
108.438
94.616
75.156
66.723
40.650
27.444
24.150
22.896
22.853
chloroform
benzene
TMS
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

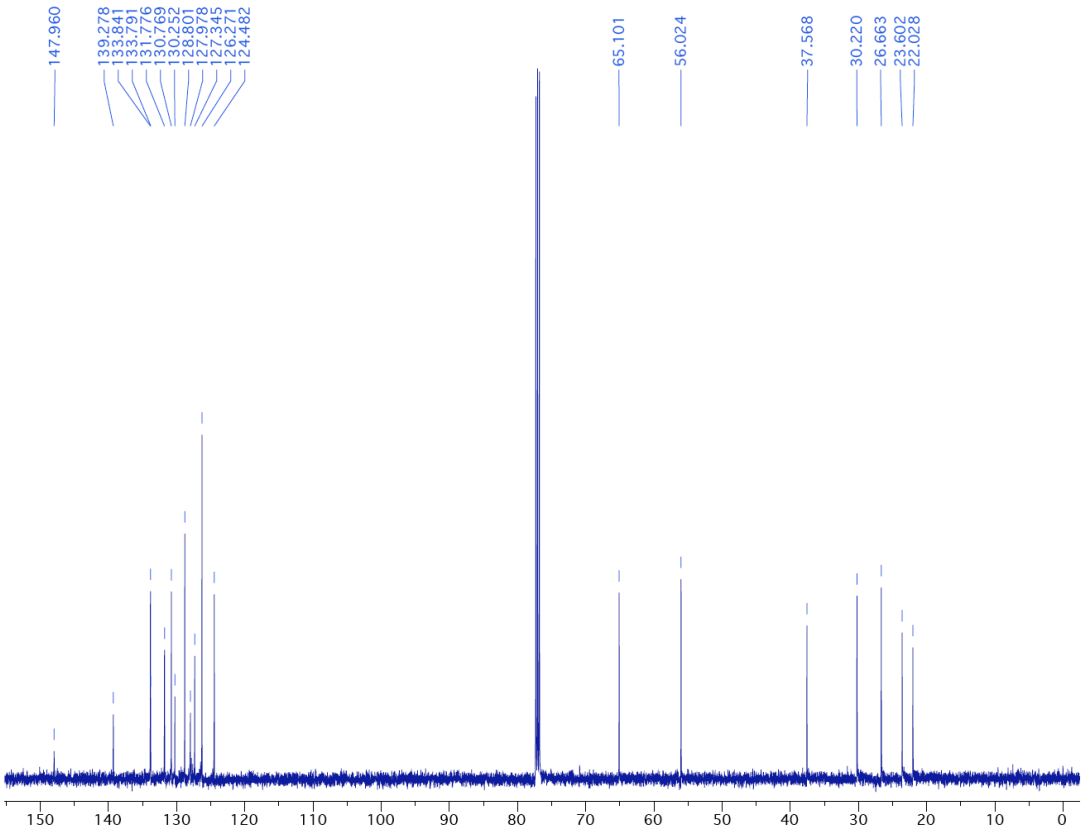

OMOM
O
OH
S9
chloroform
H2O in CDCl3
TMS
4.29
1
2.22
3.14
1.09
1.32
1.73
2.08
1.2
0.958
3.48
5.96
Hz 3500
3000
2500
2000
1500
1000
500
0
149.490
140.703
137.590
128.211
126.251
108.257
95.785
75.709
68.975
66.800
55.500
40.537
29.844
27.503
24.257
22.941
22.906
chloroform
TMS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

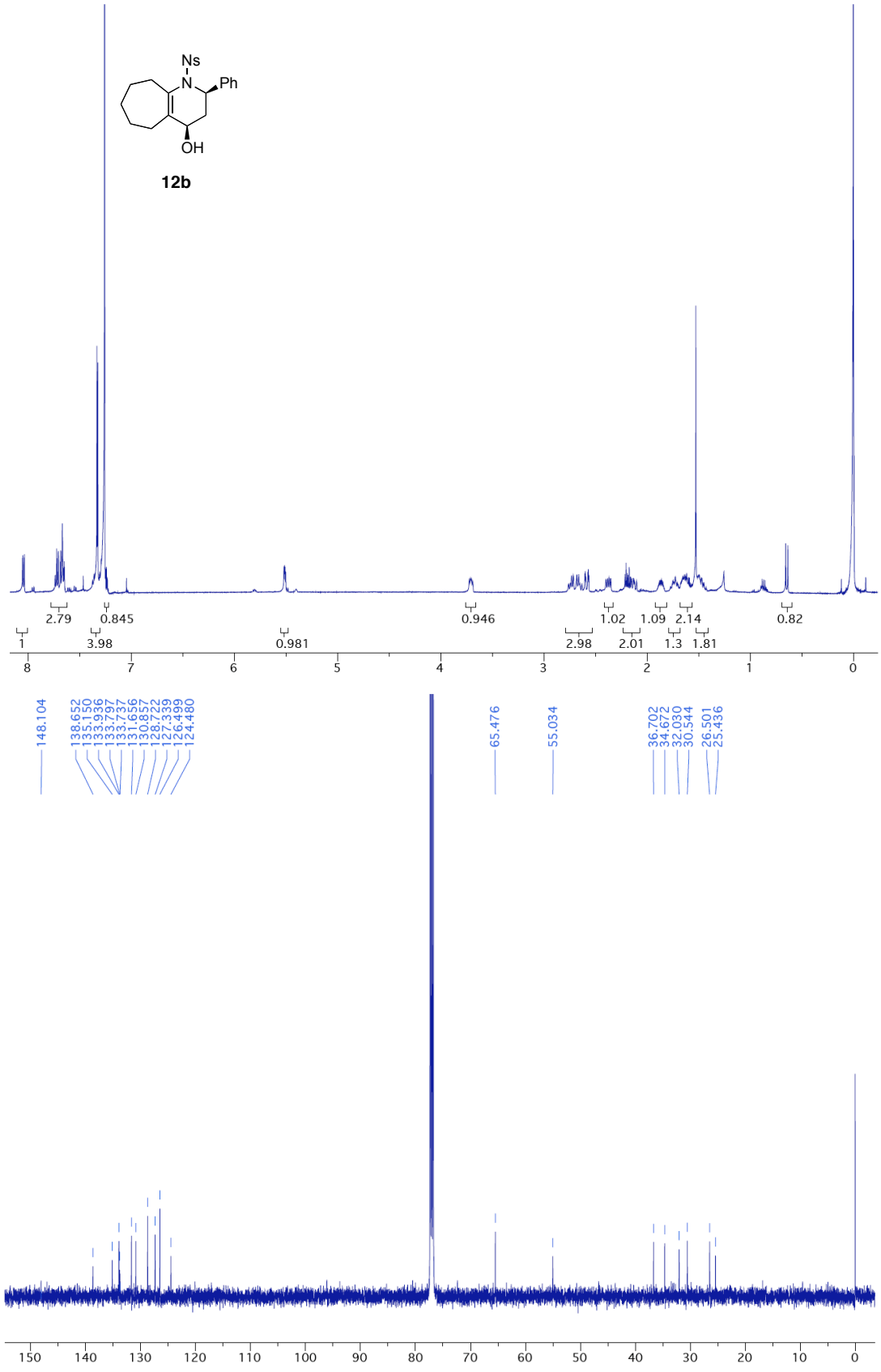

O
OBn
OH
S10
TMS
1.73
1.73
0.907
4.39
0.9
5
0.0792
0.847
0.035
0.942
3.66
ppm 7
6
5
4
3
2
1
148.654
138.069
128.444
127.736
107.598
73.467
72.725
72.432
65.248
35.049
27.436
24.504
22.887
22.857
chloroform
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

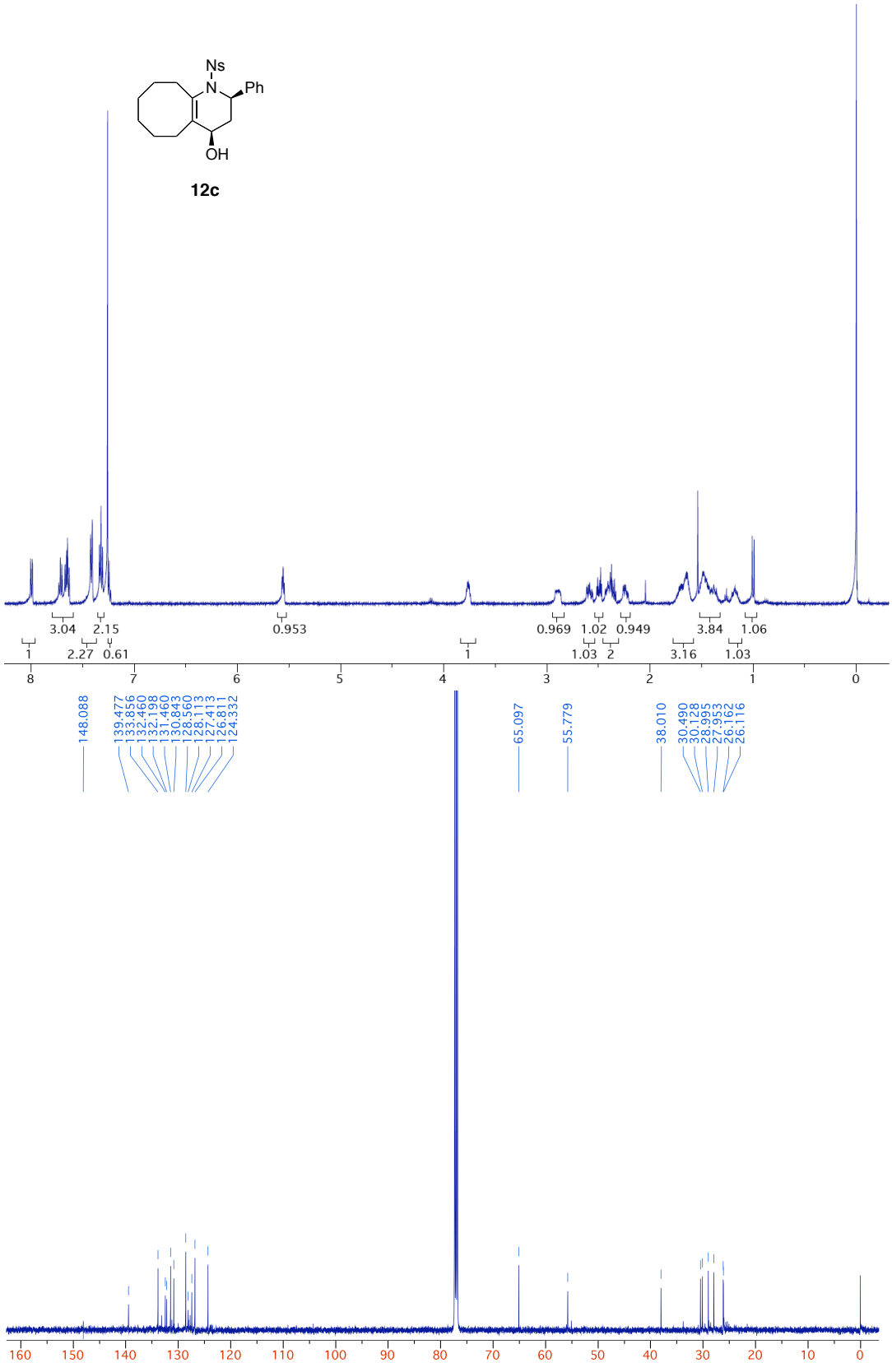

Ns
N
Ph
OH

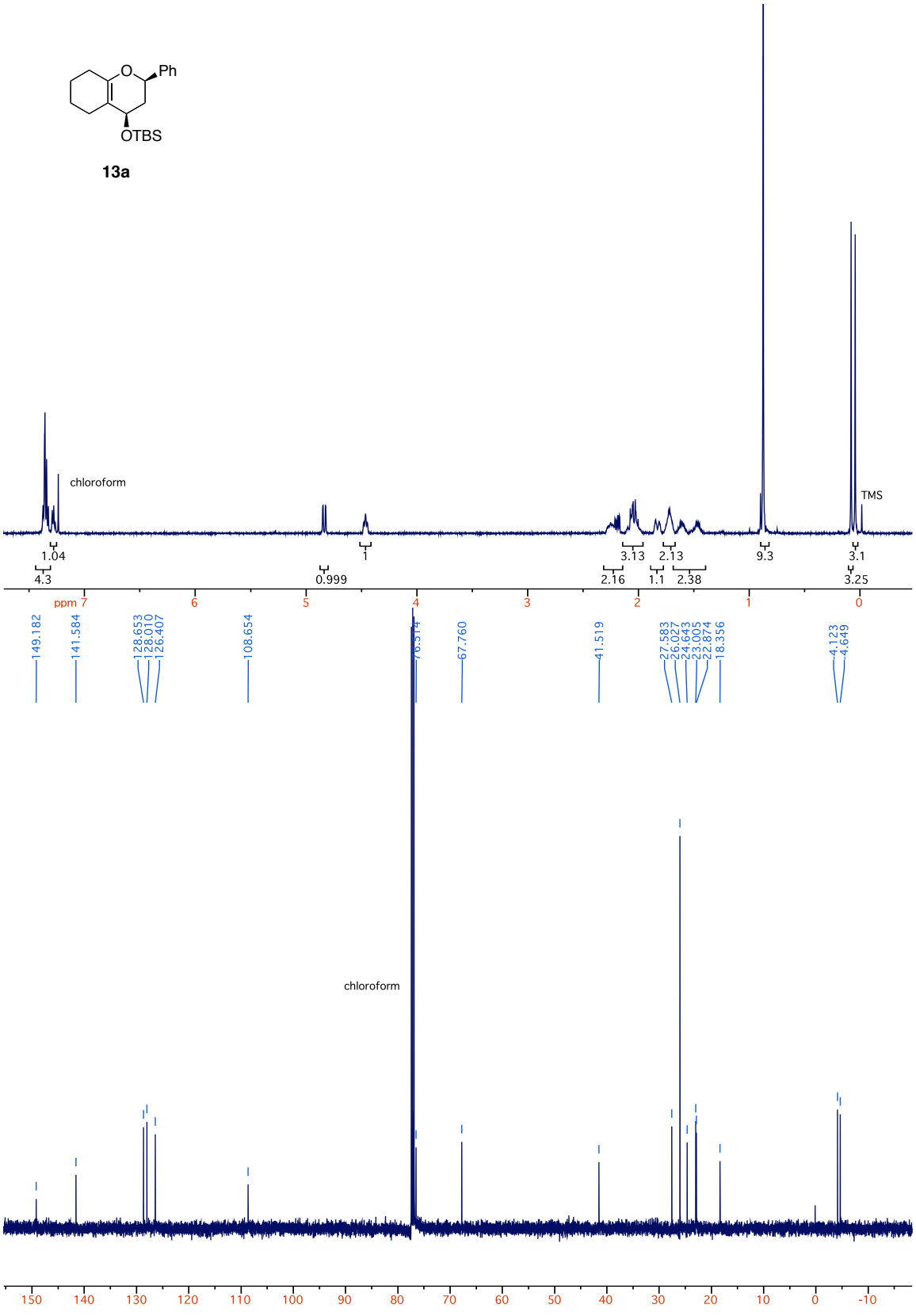
12a


3.1
0.946
1
1.06
1.05
2.16
0.92
0.96
5.64
0.959
0.985
2.14
1.13
1.37
ppm 8
7
6
5
4
3
2
1
0

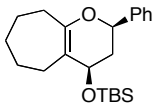

147.960
139.278
133.841
133.791
131.776
130.769
130.252
128.801
127.978
127.345
126.271
124.482
65.101
56.024
37.568
30.220
26.663
23.602
22.028
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Ns
N
Ph
OH
12b
2.79
0.845
0.946
1.02
1.09
2.14
0.82
1
3.98
0.981
2.98
2.01
1.3
1.81
8
7
6
5
4
3
2
1
0
148.104
138.652
135.150
133.936
133.797
133.737
131.656
130.857
129.722
127.339
126.499
124.480
65.476
55.034
36.702
34.672
32.030
30.544
26.501
25.436
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Ns
N
Ph
OH
12c
3.04
2.15
0.953
0.969
1.02
0.949
3.84
1.06
2.27
0.61
1.03
2
3.16
1.03
148.088
139.477
133.856
133.466
132.198
131.460
130.843
128.560
128.113
127.413
126.811
124.332
65.097
55.779
38.010
30.490
30.128
28.965
27.953
27.162
26.116

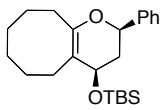

O
Ph
OTBS
chloroform
TMS
1.04
4.3
1
0.999
3.13
2.16
2.13
1.1
2.38
9.3
3.1
3.25
ppm 7
6
5
4
3
2
1
0
149.182
141.584
128.653
128.010
126.407
108.654
76.314
67.760
41.519
27.583
26.027
24.643
23.005
22.874
18.356
4.123
4.649
chloroform
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

13a


O
Ph
OTBS

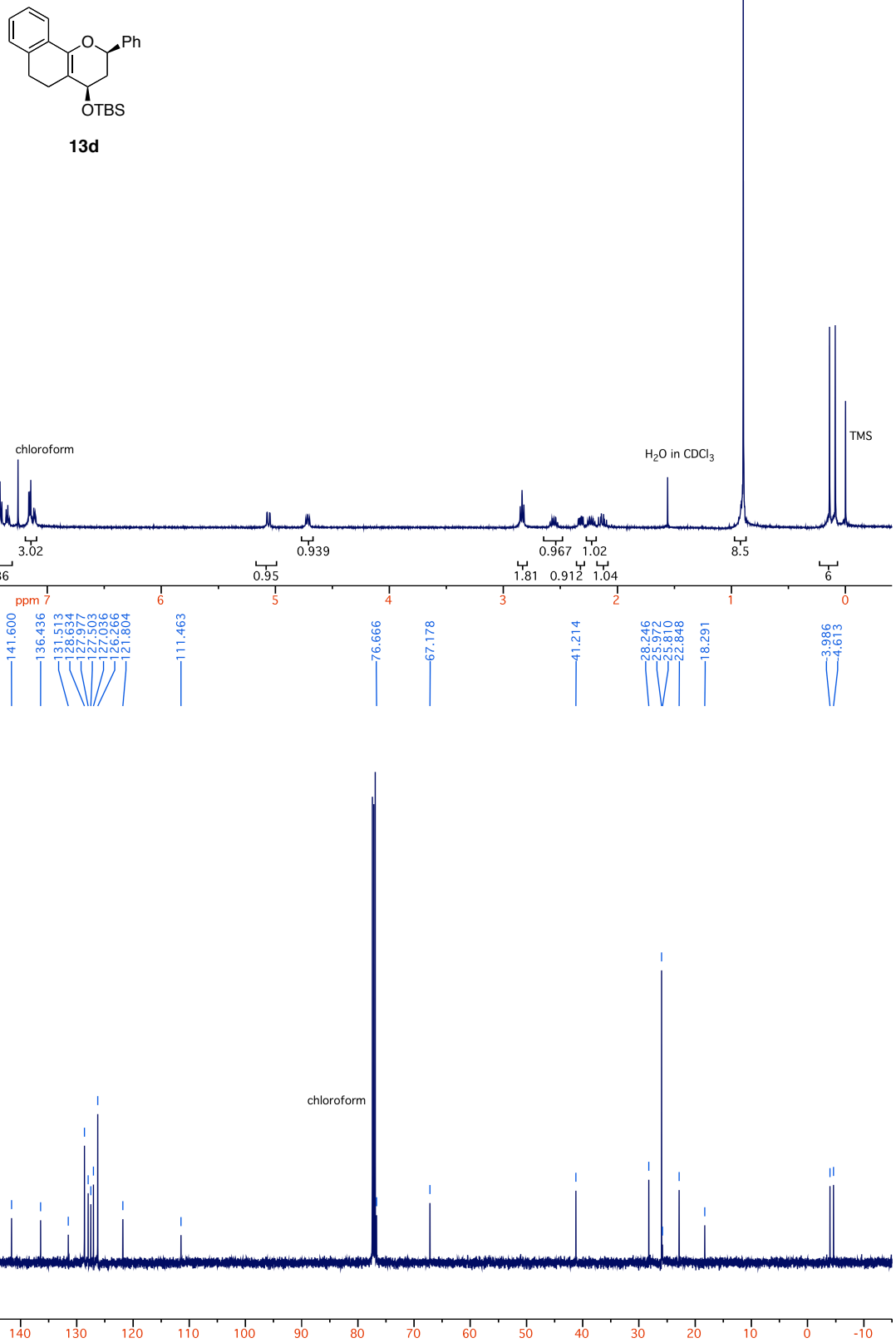
13b

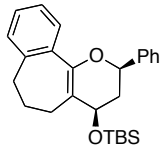
chloroform
CH2Cl2
TMS
0.883
4.24
0.952
0.947
0.979
6.19
4
0.97
8.68
2.92
2.84
154.975
141.628
128.598
127.920
126.363
112.754
68.342
41.055
33.281
32.027
27.649
27.175
26.011
25.667
18.277
3.864
4.723
chloroform


O
Ph
OTBS

13c

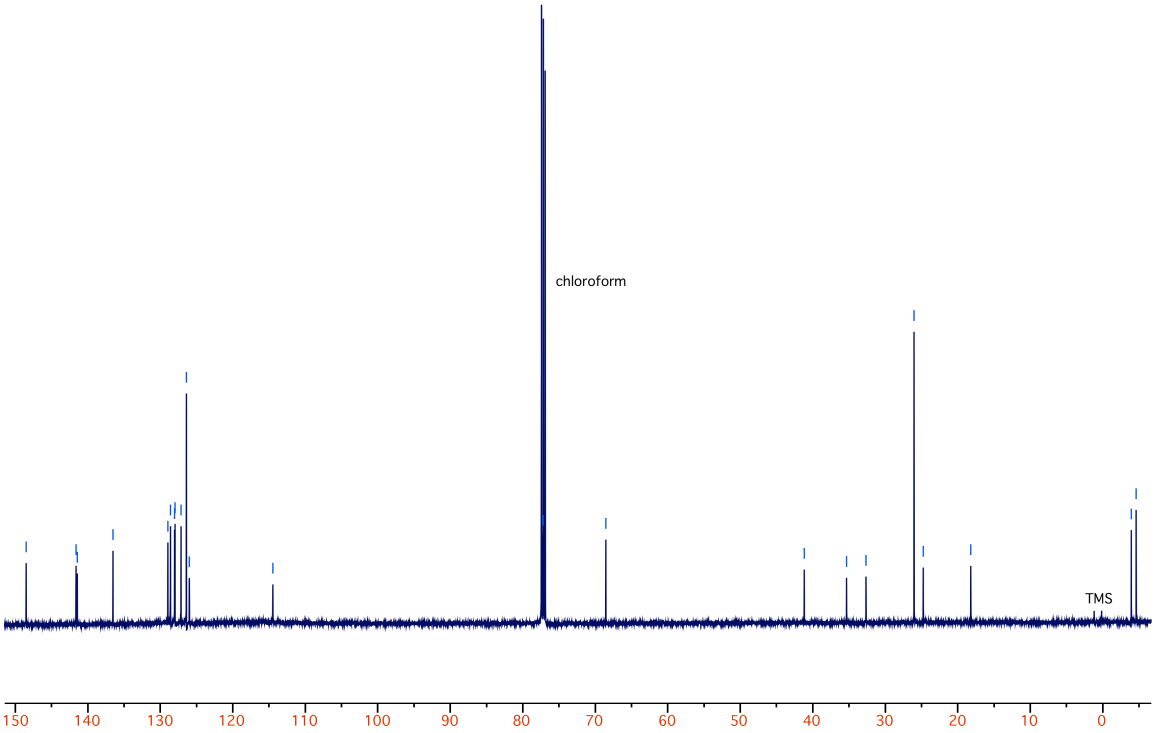
chloroform
0.937
0.92
1.92
1.08
2.88
8.35
8.72
3.03
2.91
5
ppm 7
6
5
4
3
2
1
0
151.983
141.787
128.627
127.933
126.292
109.817
66.164
41.441
30.478
29.776
29.099
28.968
27.684
26.030
24.691
18.276
4.163
4.696
chloroform
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

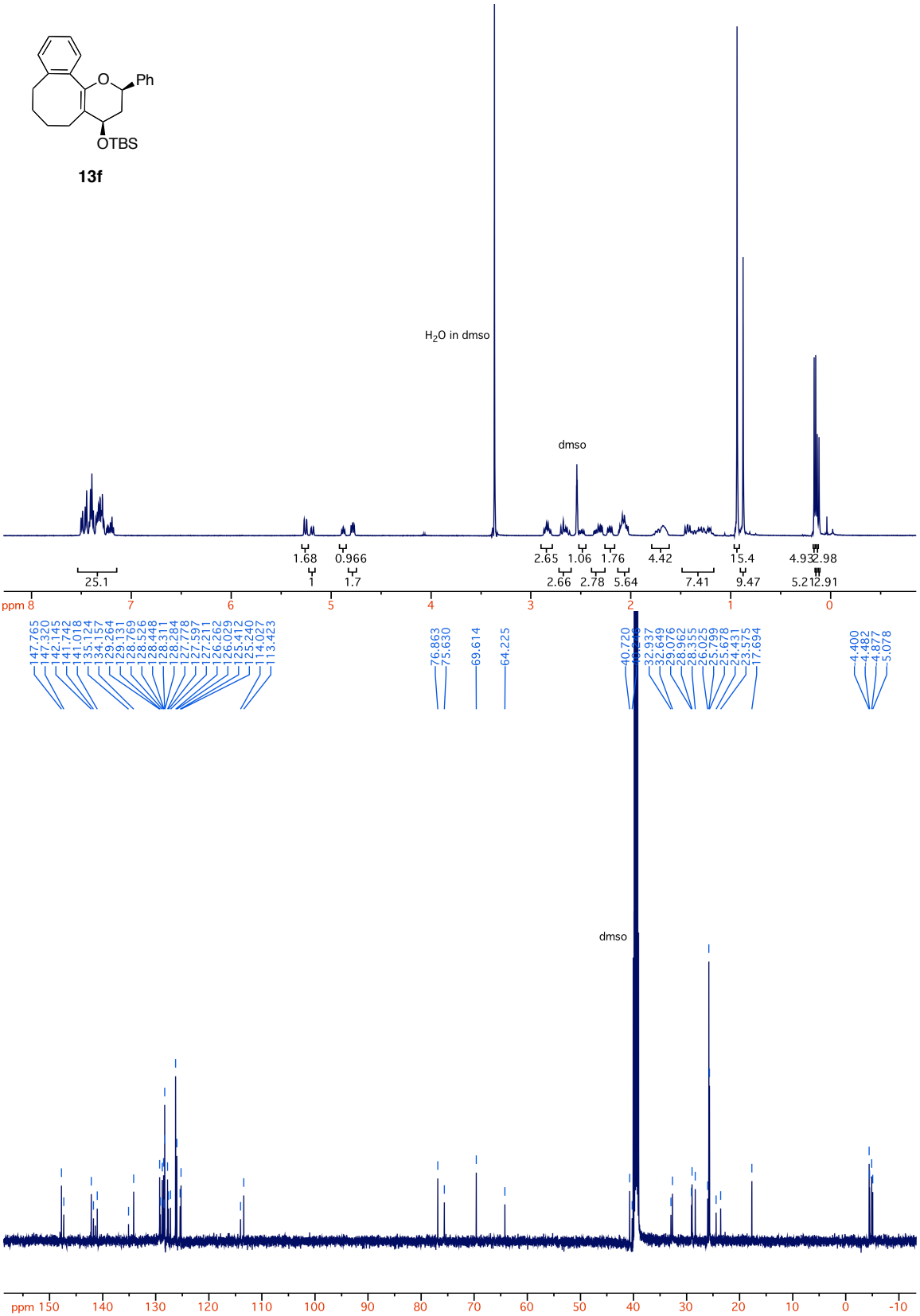

O
Ph
OTBS
13d
chloroform
H2O in CDCl3
TMS
3.02
0.939
0.967
1.02
8.5
5.86
0.95
1.81
0.912
1.04
6
ppm 7
6
5
4
3
2
1
0
146.079
141.600
136.436
131.513
128.634
127.977
127.503
127.036
126.266
121.804
111.463
76.666
67.178
41.214
28.246
25.977
25.810
22.848
18.291
3.986
4.613
chloroform
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

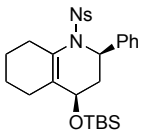

O
Ph
OTBS

13e

chloroform
TMS
2.05
3.08
1.01
1.02
4.13
9.17
3.12
3.05
1.02
1
1
1.09
1.02
3.05
ppm 7
6
5
4
3
2
1
0
148.499
141.616
141.445
136.522
128.951
128.592
128.032
127.961
127.132
126.394
125.994
114.466
77.202
68.540
41.168
35.335
32.657
26.028
24.756
18.206
3.940
4.607


chloroform
TMS
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

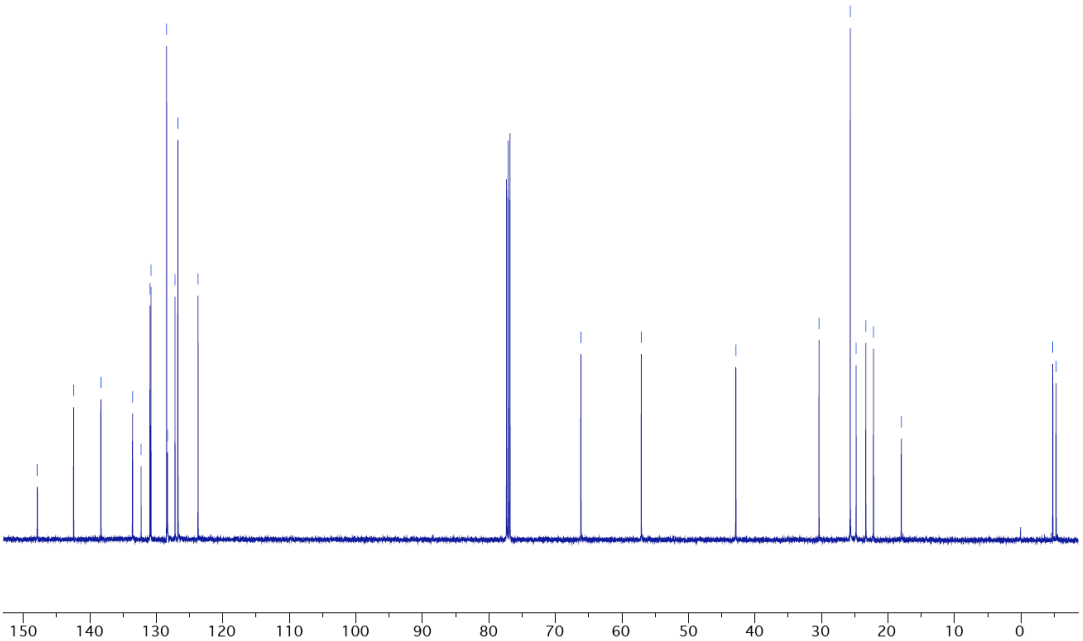

Ph
O
OTBS
13f
H2O in dmso
dmso
1.68
0.966
2.65
1.06
1.76
4.42
15.4
4.93
2.98
25.1
1
1.7
2.66
2.78
5.64
7.41
9.47
5.21
2.91
ppm 8
7
6
5
4
3
2
1
0
147.765
147.320
142.145
141.742
141.018
135.124
134.157
129.264
129.131
128.769
128.526
128.448
128.311
128.284
127.778
127.597
127.211
126.262
126.029
125.412
125.240
114.027
113.423
76.863
75.630
69.614
64.225
40.720
32.937
32.649
29.076
28.962
28.355
26.025
25.799
25.431
24.571
17.694
4.400
4.482
4.877
5.078
dmso
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

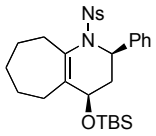

Ns
N
Ph
OTBS

14a

1.02 0.977 0.973
1 1.02 4.07
1.01
1.01
1.02 1.03 1.03
1.02 1.02 2.07 3.14
9.19
3.04
3.05
ppm 8 7 6 5 4 3 2 1 0

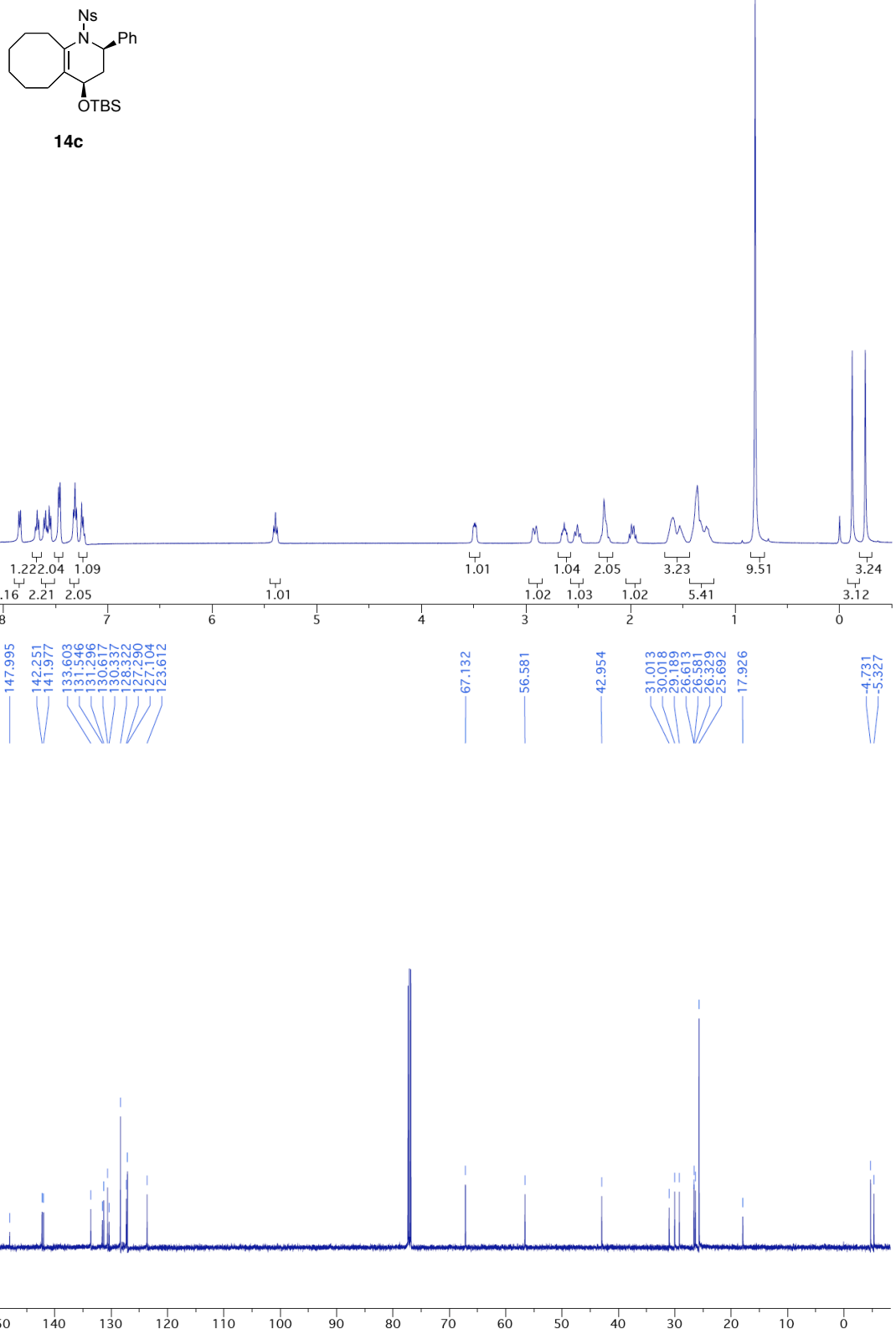

147.890
142.432
138.337
133.569
132.290
130.957
130.795
128.449
128.316
127.186
126.751
123.728
66.163
57.084
42.878
30.364
25.674
24.791
23.327
22.183
17.989
-4.769
-5.284

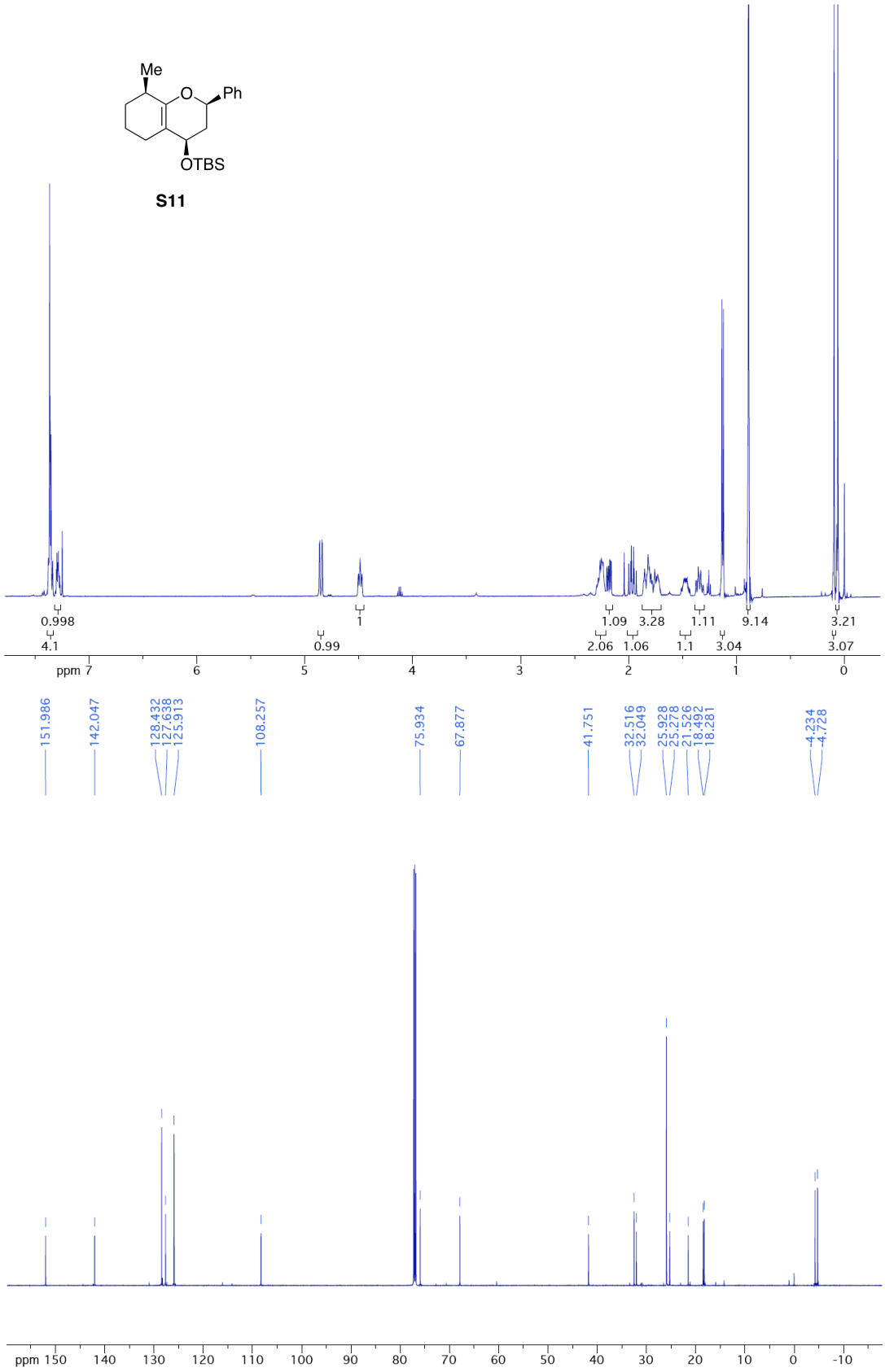

150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

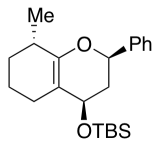

Ns
N
Ph
OTBS

14b

1.00 2.98 2.04
0.995
1.01 1.02 1.01 2.08
9.08
3.04
1 1.02 2.02 0.988
0.996
2.05 1.06 1.03 3.22
3
ppm 8 7 6 5 4 3 2 1 0
147.947
143.181
141.956
133.547
133.070
132.390
130.996
130.866
128.338
127.181
127.024
123.758
66.243
56.386
42.241
35.465
31.848
26.866
26.168
25.785
25.672
17.988
-4.708
-5.335
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Ns
N
Ph
OTBS
14c
1.22 2.04 1.09 1.01 1.04 2.05 3.23 9.51 3.24
1.16 2.21 2.05 1.01 1.02 1.03 1.02 5.41 3.12
8 7 6 5 4 3 2 1 0
147.995
142.251
141.977
133.603
131.546
131.296
130.617
130.337
128.322
127.290
127.104
123.612
67.132
56.581
42.954
31.013
30.018
29.189
26.613
26.581
26.329
25.692
17.926
-4.731
-5.327
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

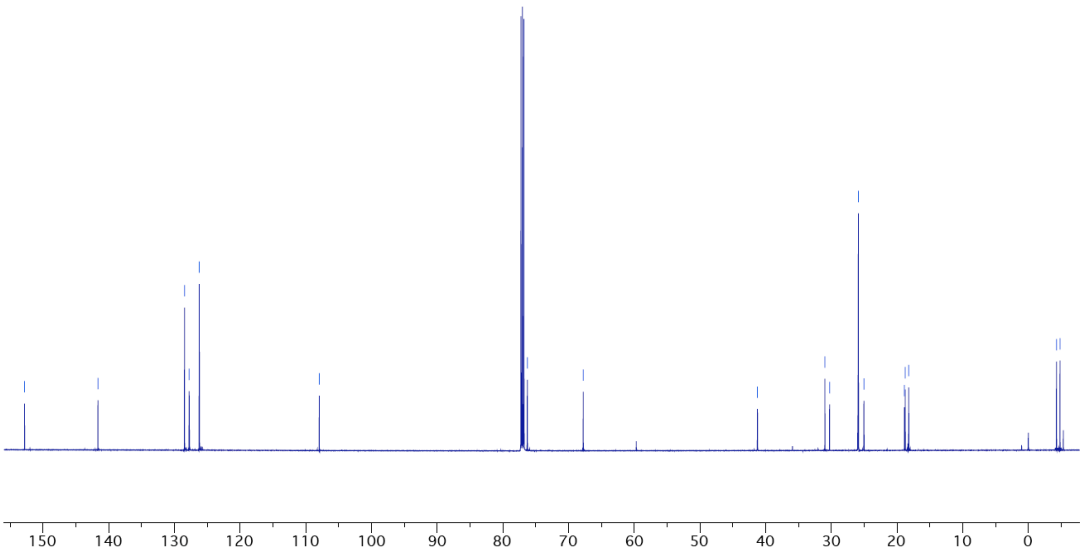

Me
O
Ph
OTBS
S11
0.998
4.1
1
0.99
1.09
3.28
2.06
1.06
1.11
1.1
9.14
3.04
3.21
3.07
ppm 7
6
5
4
3
2
1
0
151.986
142.047
128.432
127.638
125.913
108.257
75.934
67.877
41.751
32.516
32.049
25.928
25.278
21.526
18.492
18.281
-4.234
-4.728
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

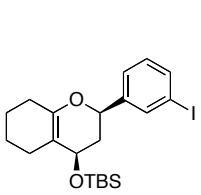

Me
O
Ph
OTBS

S12

1.03
4.3
1
1.09
1.06
3.24
2.12
2.19
1.11
3.06
10.3
3.12
3.13
ppm 7
6
5
4
3
2
1
0

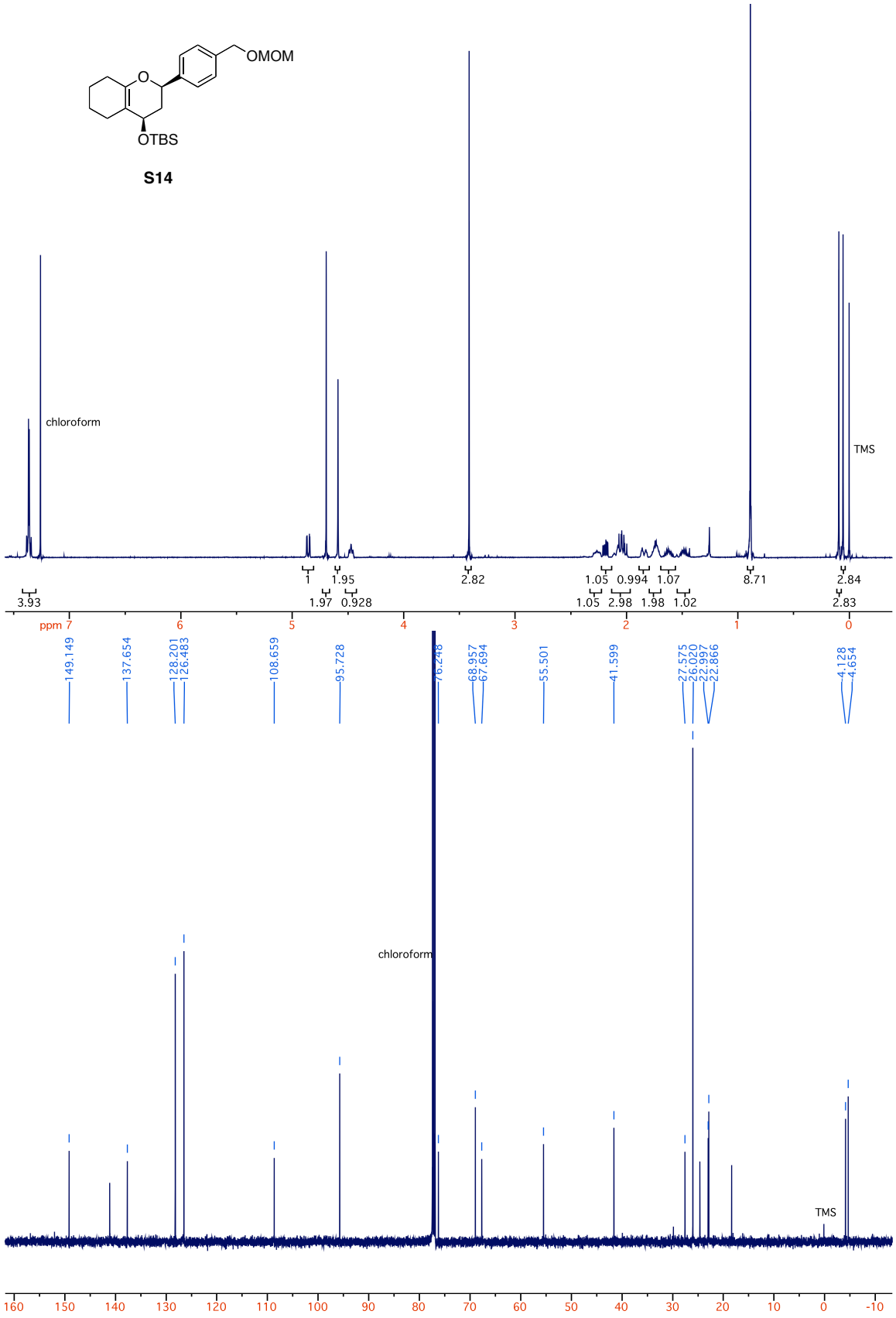
152.818
141.644
128.465
127.757
126.213
107.951
76.287
67.771
41.259
31.006
30.290
25.903
25.062
18.888
18.782
18.234
-4.247
-4.781

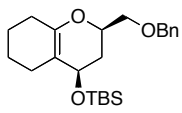

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
I
OTBS

S13

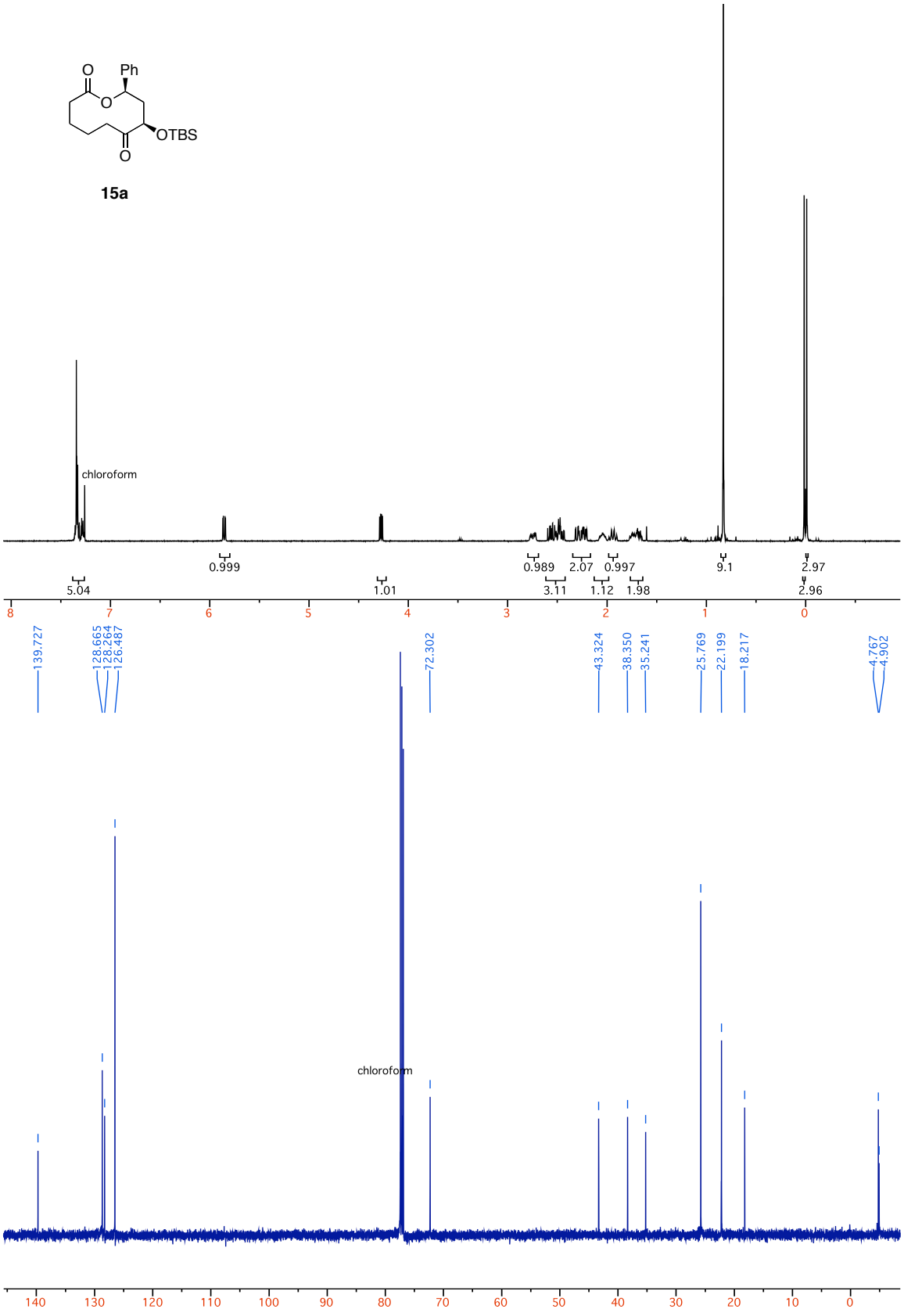
chloroform
TMS
0.943
0.987
0.97
1
1.02
2.61
2.99
0.949
1.01
0.967
0.966
3.08
2.15
9.48
3.26
8
7
6
5
4
3
2
1
0
148.883
143.970
136.983
135.428
130.383
125.569
108.908
94.552
75.565
67.407
41.433
27.492
26.006
24.601
22.943
22.832
18.322
4.112
4.658
chloroform
TMS
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

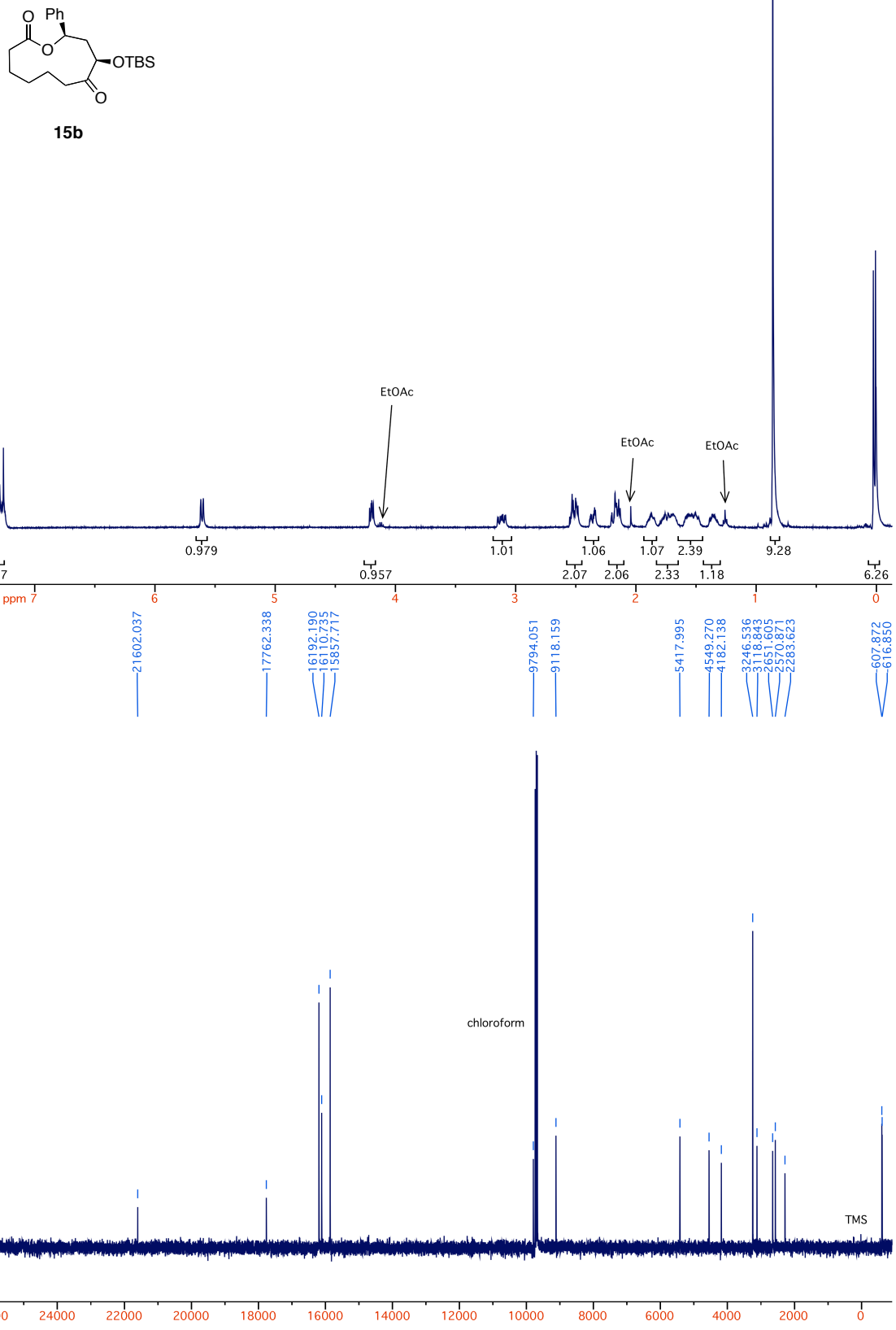

OMOM
O
OTBS
S14
chloroform
TMS
3.93
1
1.95
1.97
0.928
2.82
1.05
0.994
1.07
1.05
2.98
1.98
1.02
8.71
2.84
2.83
ppm 7
6
5
4
3
2
1
0
149.149
137.654
128.201
126.483
108.659
95.728
76.248
68.957
67.694
55.501
41.599
27.575
26.020
22.997
22.866
4.128
4.654
chloroform
TMS
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

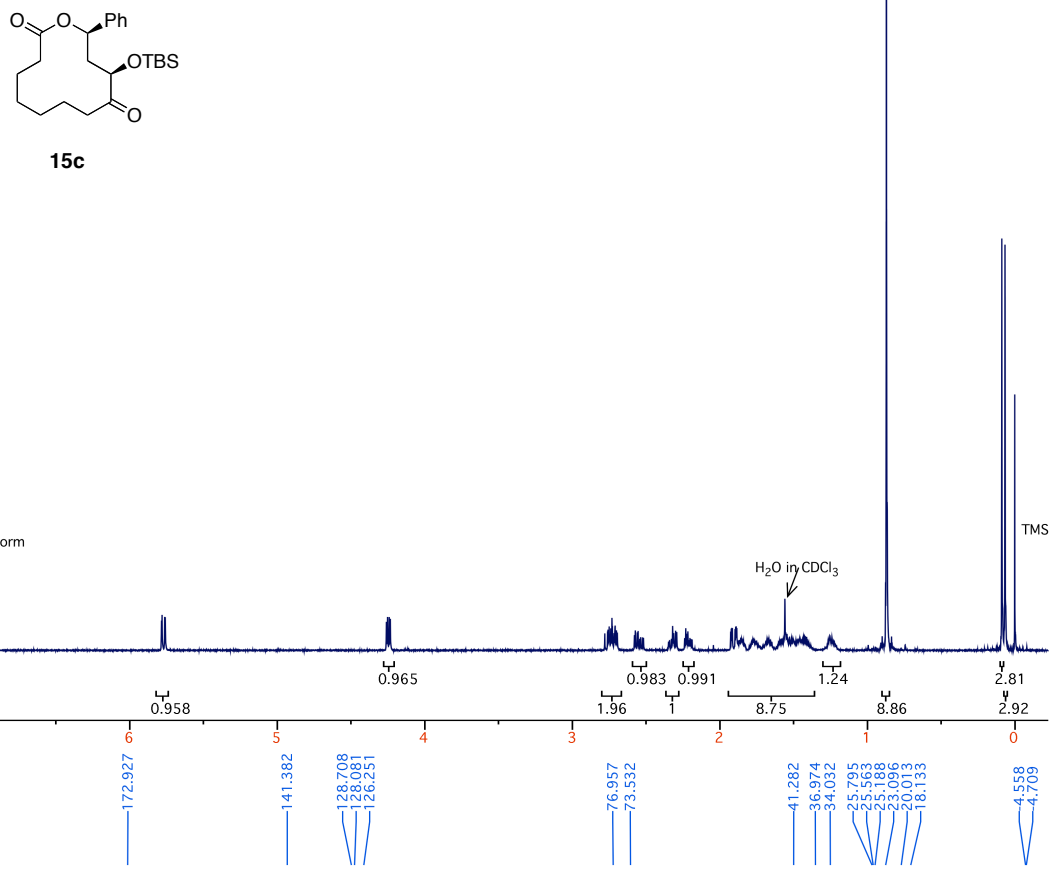

O
OBn
OTBS

S15

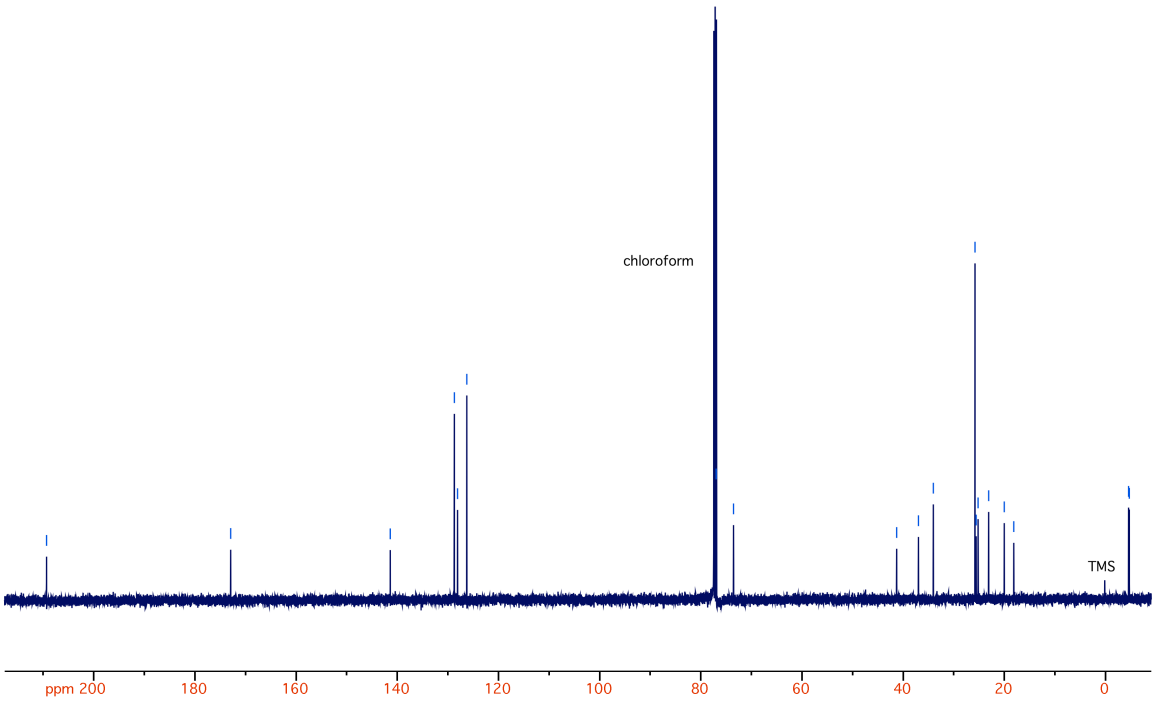
chloroform
TMS
2.06
1.02
1
3.07
9.22
2.82
5.04
0.996
1.02
1.15
6.95
3.14
ppm 7
6
5
4
3
2
1
0
148.063
138.461
128.495
127.950
127.737
108.260
73.518
73.146
72.384
66.415
35.648
27.554
26.027
24.946
23.015
22.924
18.305
4.123
4.649
chloroform
TMS
ppm 150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

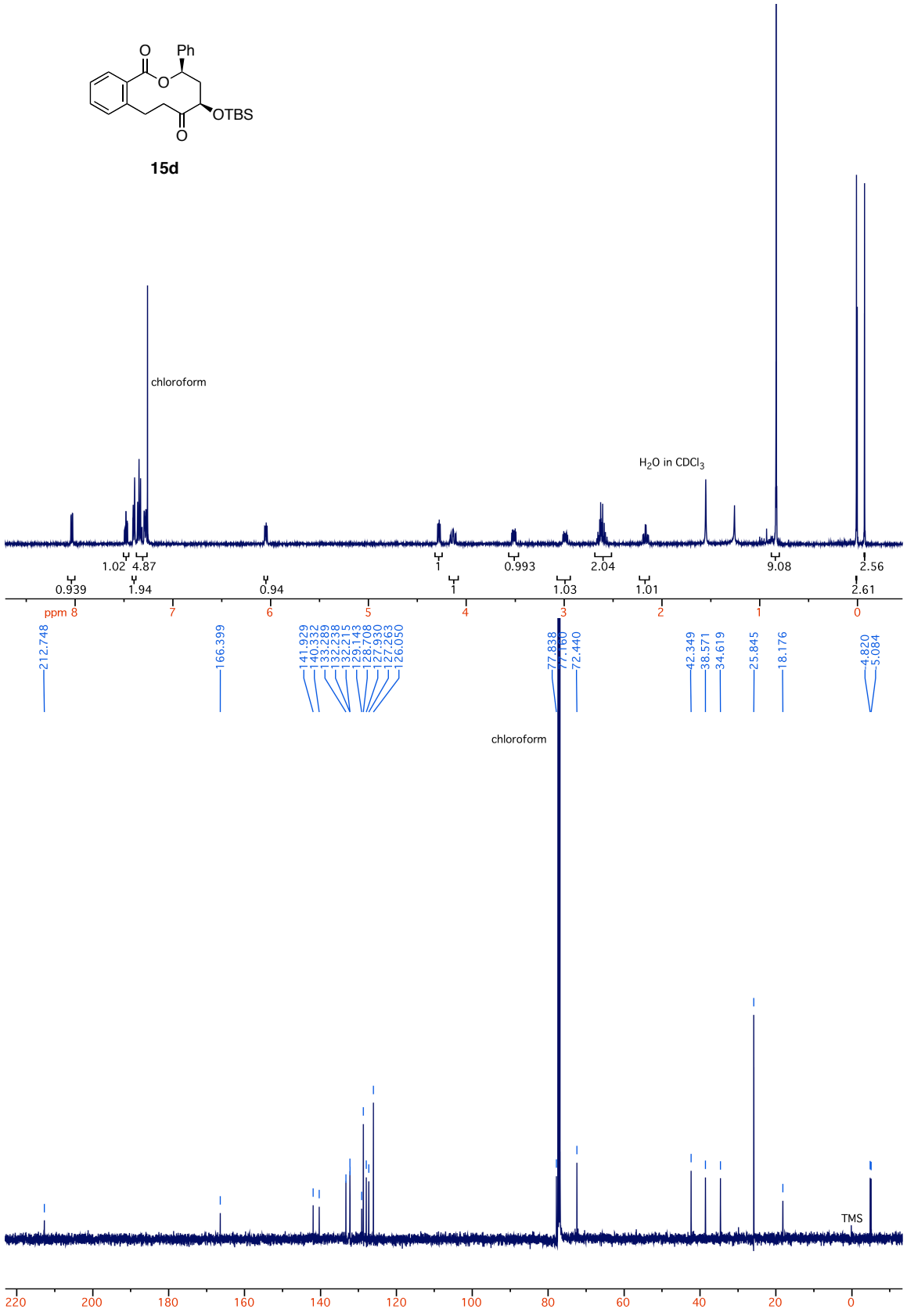

O
Ph
O
OTBS
O
15a
chloroform
0.999
1.01
0.989
2.07
0.997
9.1
2.97
5.04
3.11
1.12
1.98
2.96
8
7
6
5
4
3
2
1
0
139.727
128.665
128.264
126.487
72.302
43.324
38.350
35.241
25.769
22.199
18.217
4.767
4.902
chloroform
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

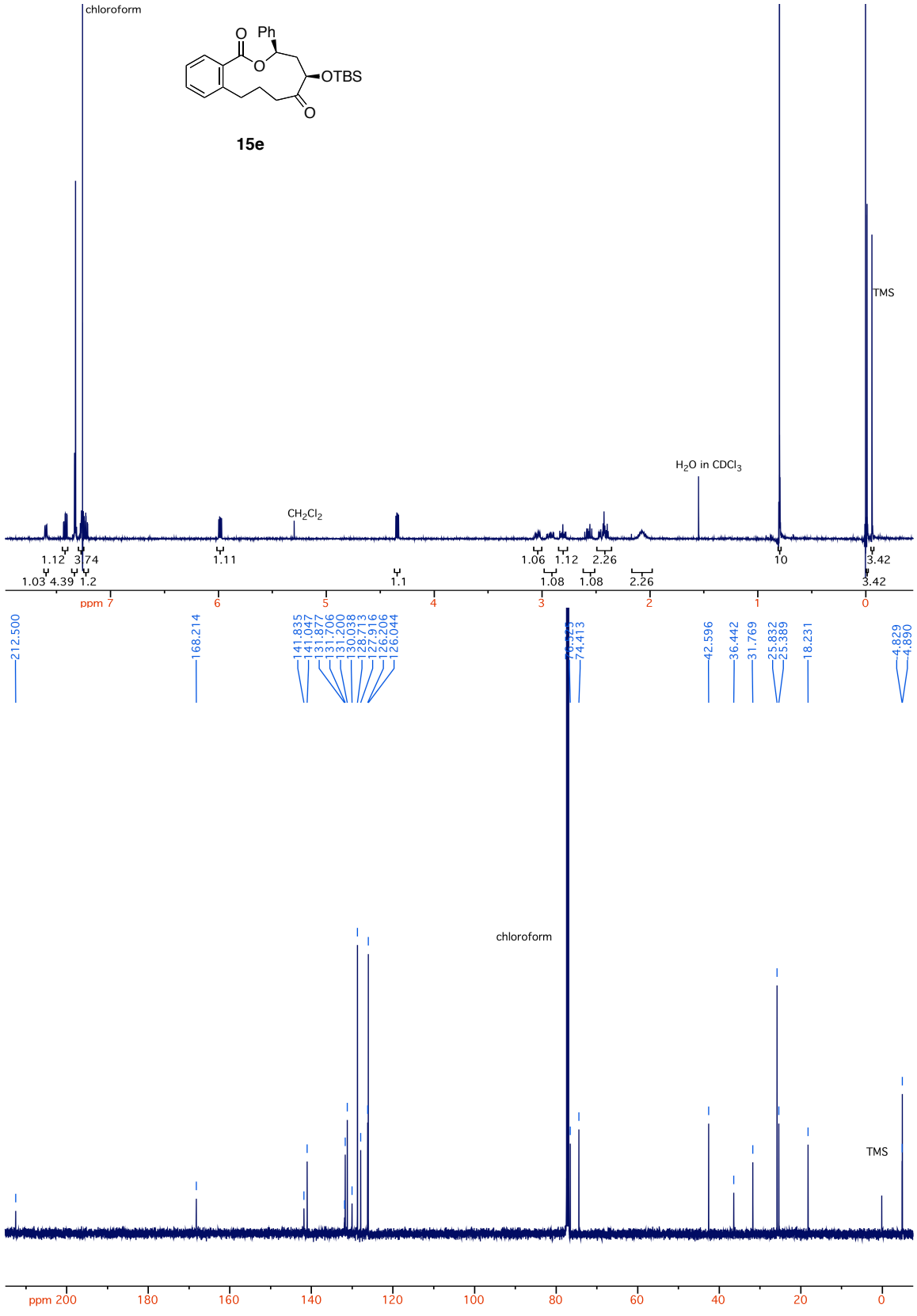

O
Ph
O
OTBS
O
15b
EtOAc
EtOAc
EtOAc
0.979
1.01
1.06
1.07
2.39
9.28
5.37
0.957
2.07
2.06
2.33
1.18
6.26
ppm 7
6
5
4
3
2
1
0
26594.938
21602.037
17762.338
16192.190
16110.735
15857.717
9794.051
9118.159
5417.995
4549.270
4182.138
3246.536
3118.843
2651.605
2570.871
2283.623
607.872
616.850
chloroform
TMS
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0

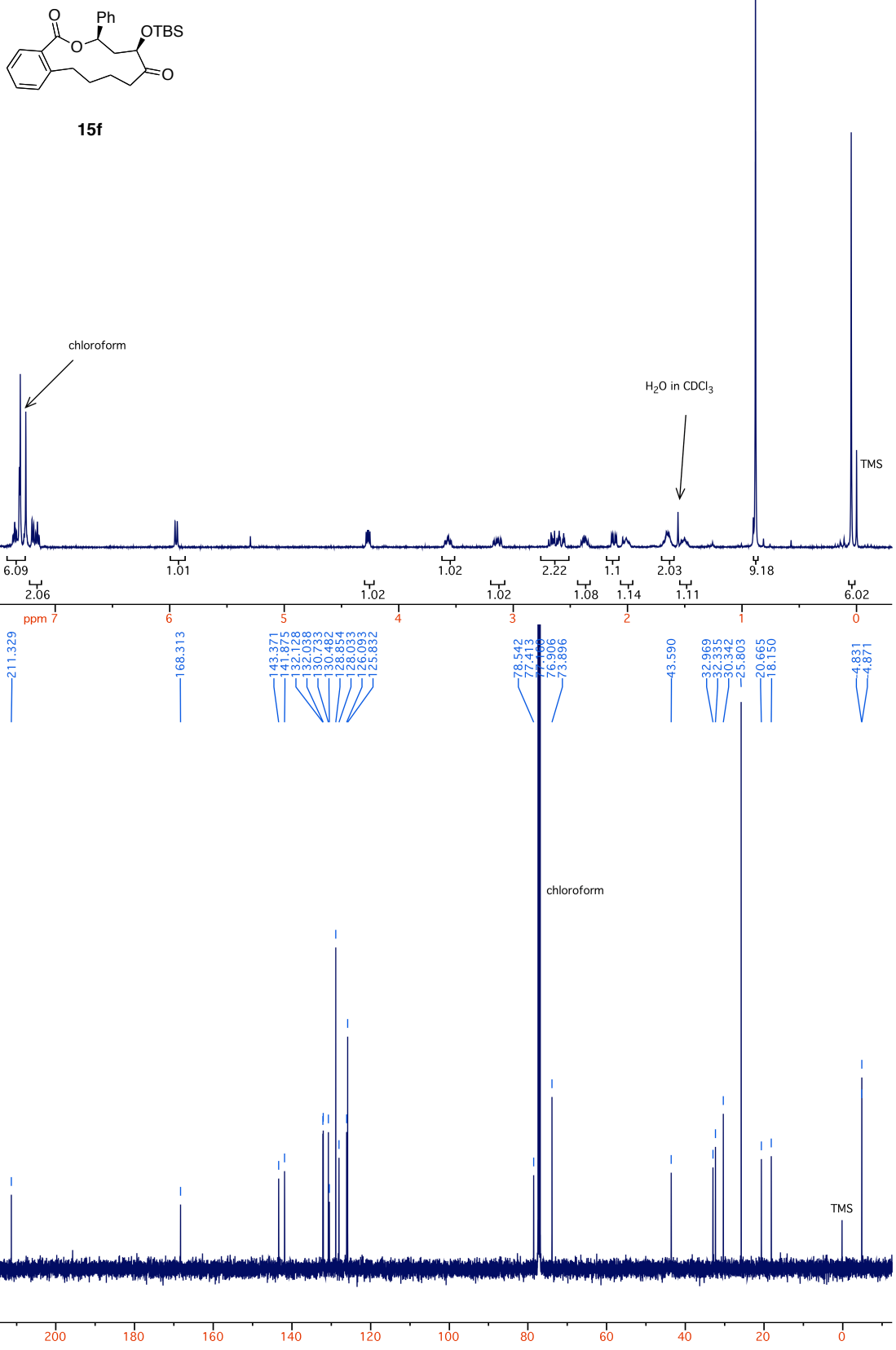

O
O
Ph
OTBS
O
chloroform
H2O in CDCl3
TMS
0.757
0.965
0.983
0.991
1.24
2.81
3.76
0.958
1.96
1
8.75
8.86
2.92
ppm 7
6
5
4
3
2
1
0
209.325
172.927
141.382
128.708
128.081
126.251
76.957
73.532
41.282
36.974
34.032
25.795
25.563
25.188
23.096
20.013
18.133
4.558
4.709

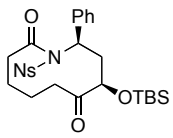
15c


chloroform
TMS
ppm 200
180
160
140
120
100
80
60
40
20
0


O
Ph
O
OTBS
O
15d
chloroform
H2O in CDCl3
1.02
4.87
1
0.993
2.04
9.08
2.56
0.939
1.94
0.94
1
1.03
1.01
2.61
ppm 8
7
6
5
4
3
2
1
0
212.748
166.399
141.929
140.332
133.289
132.238
132.215
129.143
128.708
127.930
127.263
126.050
77.838
77.160
72.440
42.349
38.571
34.619
25.845
18.176
4.820
5.084
chloroform
TMS
220
200
180
160
140
120
100
80
60
40
20
0

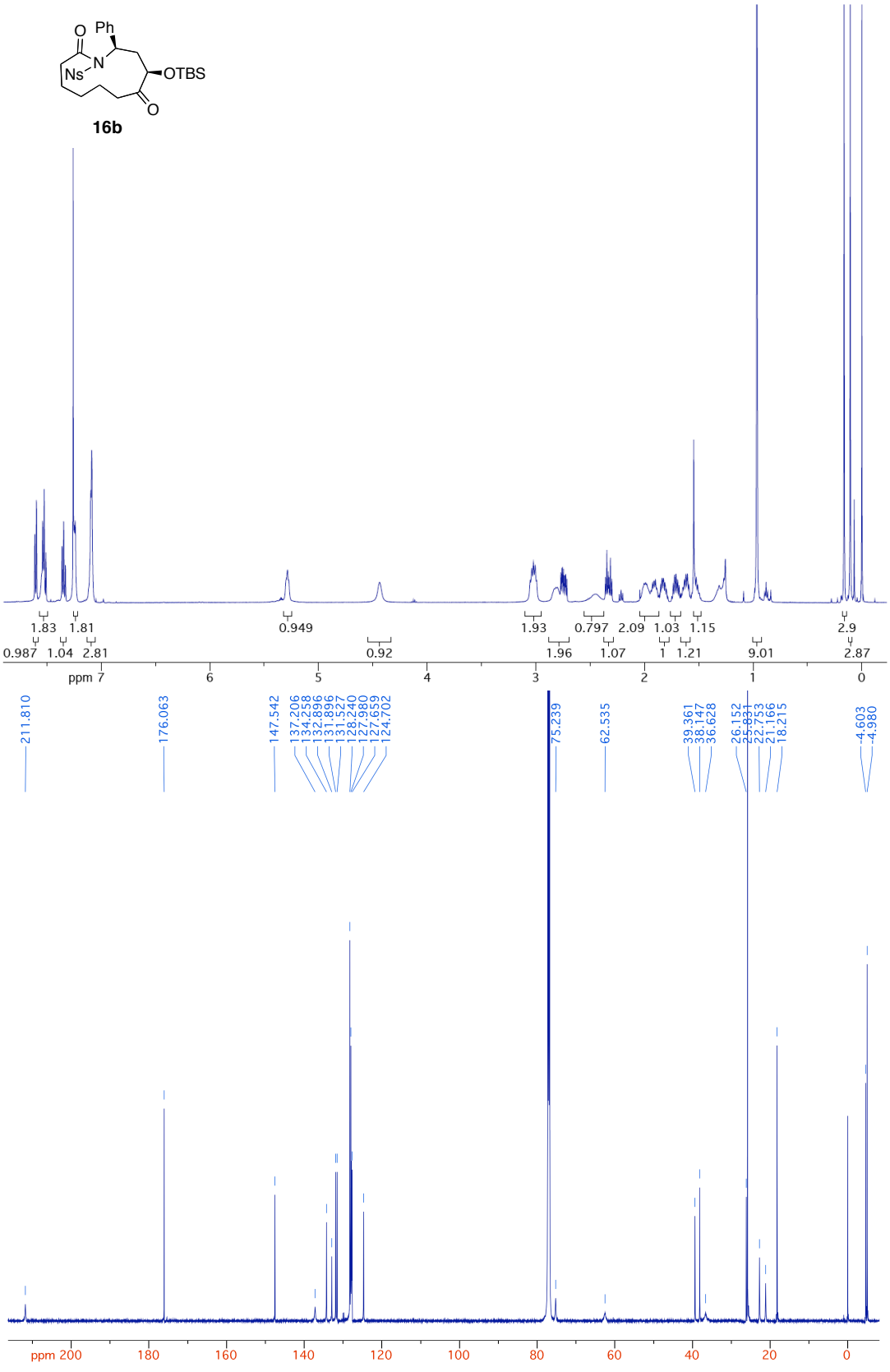

chloroform
O
Ph
O
OTBS
O
15e
TMS
H_2O in $CDCl_3$
CH_2Cl_2
1.12 3.74
1.03 4.39 1.2
1.11
1.1
1.06 1.12 2.26
1.08 1.08 2.26
10
3.42
3.42
ppm 7
6
5
4
3
2
1
0
212.500
168.214
141.835
141.047
131.877
131.706
131.200
130.038
128.713
127.916
126.206
126.044
77.423
74.413
42.596
36.442
31.769
25.832
25.389
18.231
4.829
4.890
chloroform
TMS
ppm 200
180
160
140
120
100
80
60
40
20
0

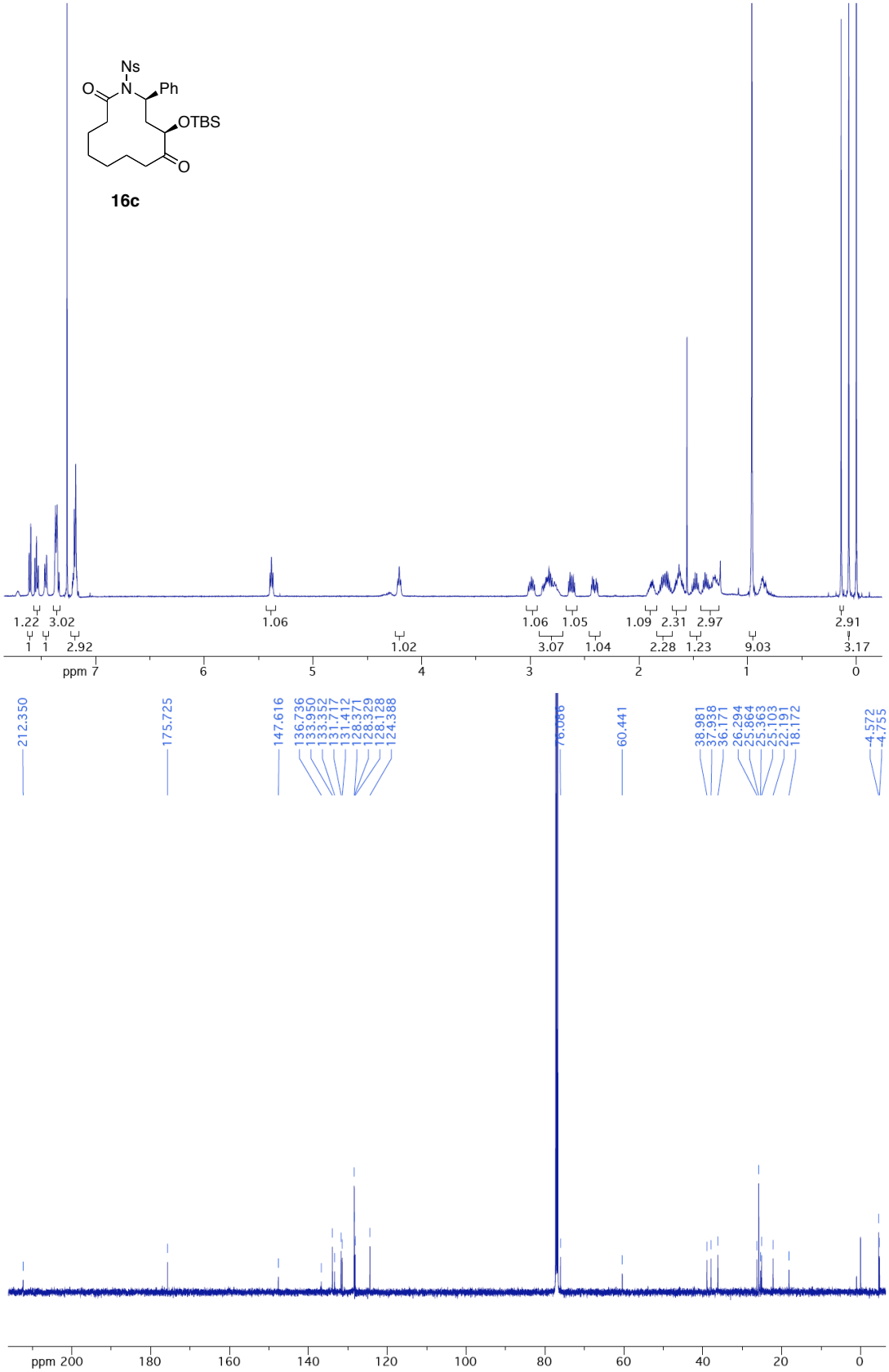

O
Ph
OTBS
O
O
15f
chloroform
H2O in CDCl3
TMS
6.09
1.01
1.02
2.22
1.1
2.03
9.18
1
2.06
1.02
1.02
1.08
1.14
1.11
6.02
ppm 7
6
5
4
3
2
1
0
211.329
168.313
143.371
141.875
141.128
132.058
130.733
130.482
128.854
128.033
126.093
125.832
78.542
77.413
77.166
76.906
73.896
43.590
32.969
32.335
30.345
30.342
25.803
20.665
18.150
4.831
4.871
chloroform
TMS
220
200
180
160
140
120
100
80
60
40
20
0

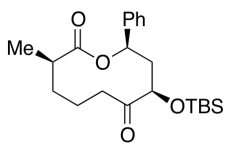

O
Ph
N
Ns
OTBS
O

16a

1.03 1.08 3.21
1.06
1.04
1.05 2.15
9.87
3.14
1 1.07 2.14
1.02
1.05 2.13
2.15 1.15
3.16
ppm 7 6 5 4 3 2 1 0
211.665
177.157
147.154
139.631
134.245
133.141
132.488
131.897
128.106
127.427
126.986
124.870
79.395
62.486
40.551
39.889
34.781
25.605
25.349
21.251
17.927
-4.951
-5.052
ppm 200 180 160 140 120 100 80 60 40 20 0

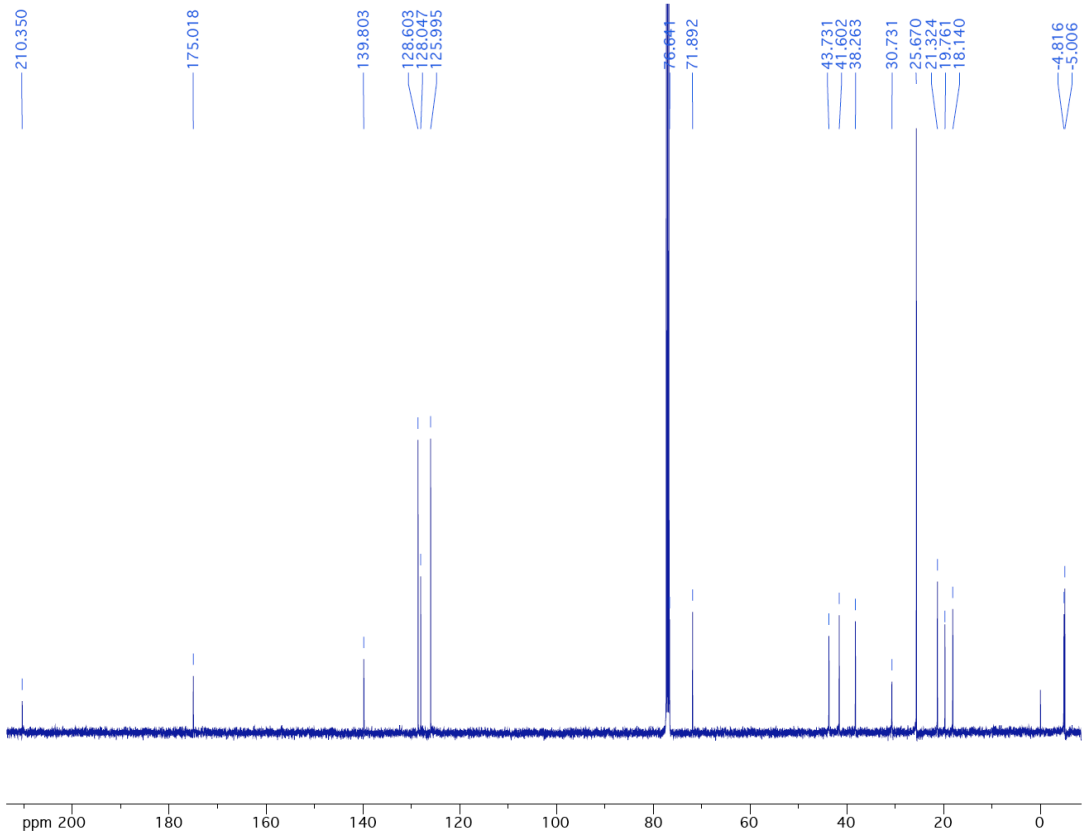

O
Ph
N
Ns
OTBS
O
16b
1.83
1.81
0.949
1.93
0.797
2.09
1.03
1.15
2.9
0.987
1.04
2.81
0.92
1.96
1.07
1
1.21
9.01
2.87
ppm 7
6
5
4
3
2
1
0
211.810
176.063
147.542
137.206
134.258
132.896
131.896
131.527
128.240
127.380
127.059
124.702
75.239
62.535
39.361
38.147
36.628
26.152
25.831
22.753
21.166
18.215
-4.603
-4.980
ppm 200
180
160
140
120
100
80
60
40
20
0

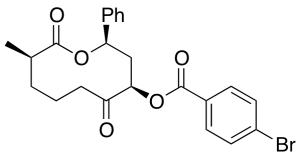

Ns
N
O
Ph
OTBS
O
16c
1.22 3.02 1.06 1.06 1.05 1.09 2.31 2.97 2.91
1 1 2.92 1.02 3.07 1.04 2.28 1.23 9.03 3.17
ppm 7 6 5 4 3 2 1 0
212.350
175.725
147.616
136.736
133.950
133.352
131.717
131.412
128.371
128.329
128.128
124.388
76.086
60.441
38.981
37.938
36.171
26.294
25.864
25.363
25.103
22.191
18.172
-4.572
-4.755
ppm 200 180 160 140 120 100 80 60 40 20 0


O
Ph
Me
O
OTBS
O

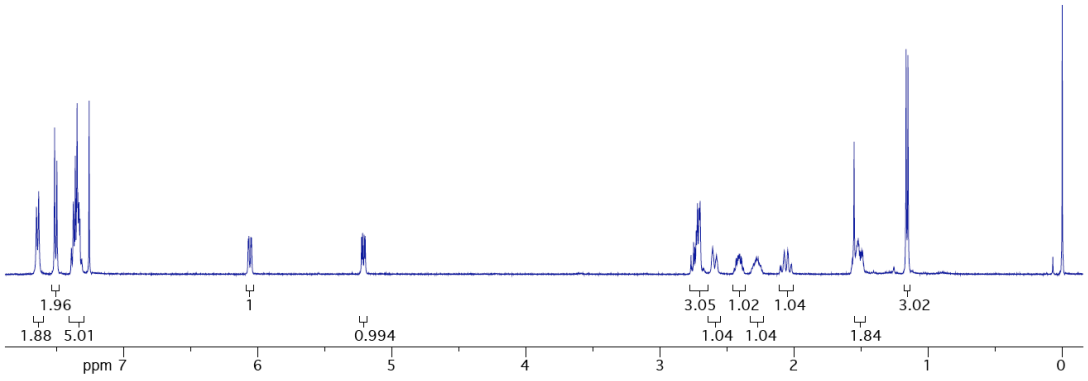
17

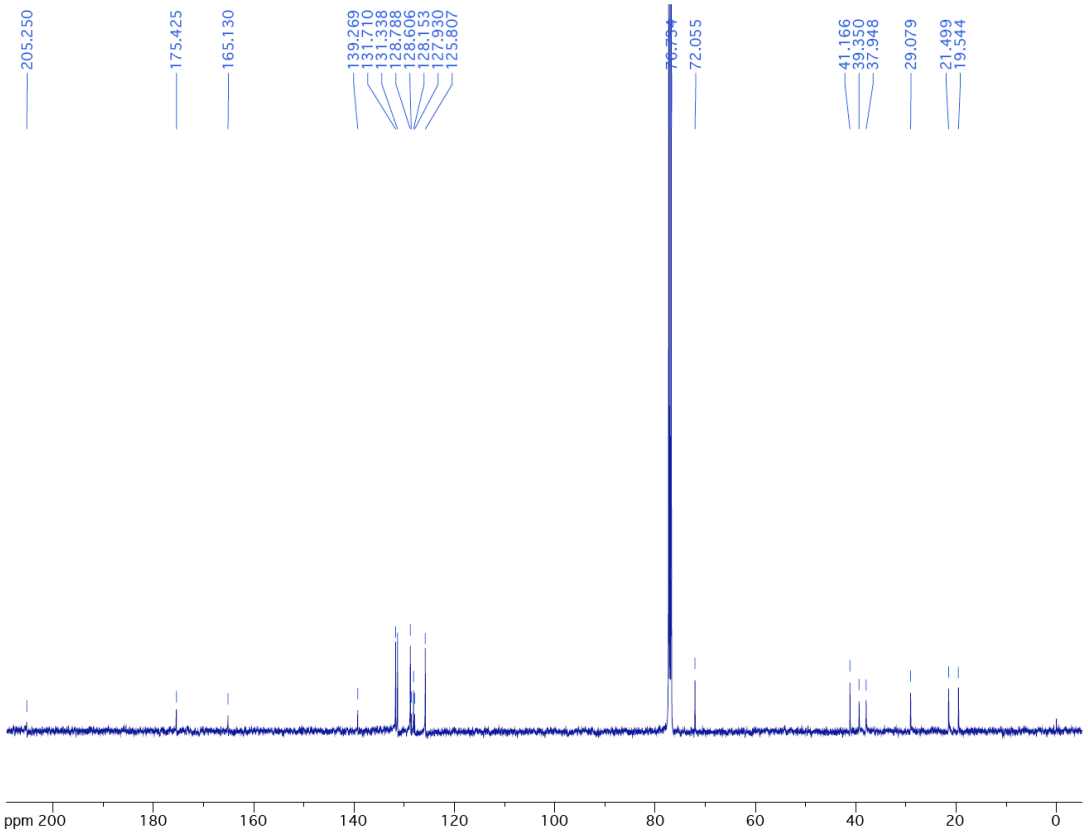
1
0.99
1.02
1.02
1.17
9.09
2.95
4.93
1.02
3.1
1.04
1.03
3.04
2.95
ppm 7
6
5
4
3
2
1
0

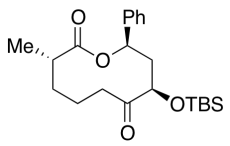

210.350
175.018
139.803
128.603
128.047
125.995
76.641
71.892
43.731
41.602
38.263
30.731
25.670
21.324
19.761
18.140
-4.816
-5.006
ppm 200
180
160
140
120
100
80
60
40
20
0


O
Ph
O
O
O
O
Br

17′

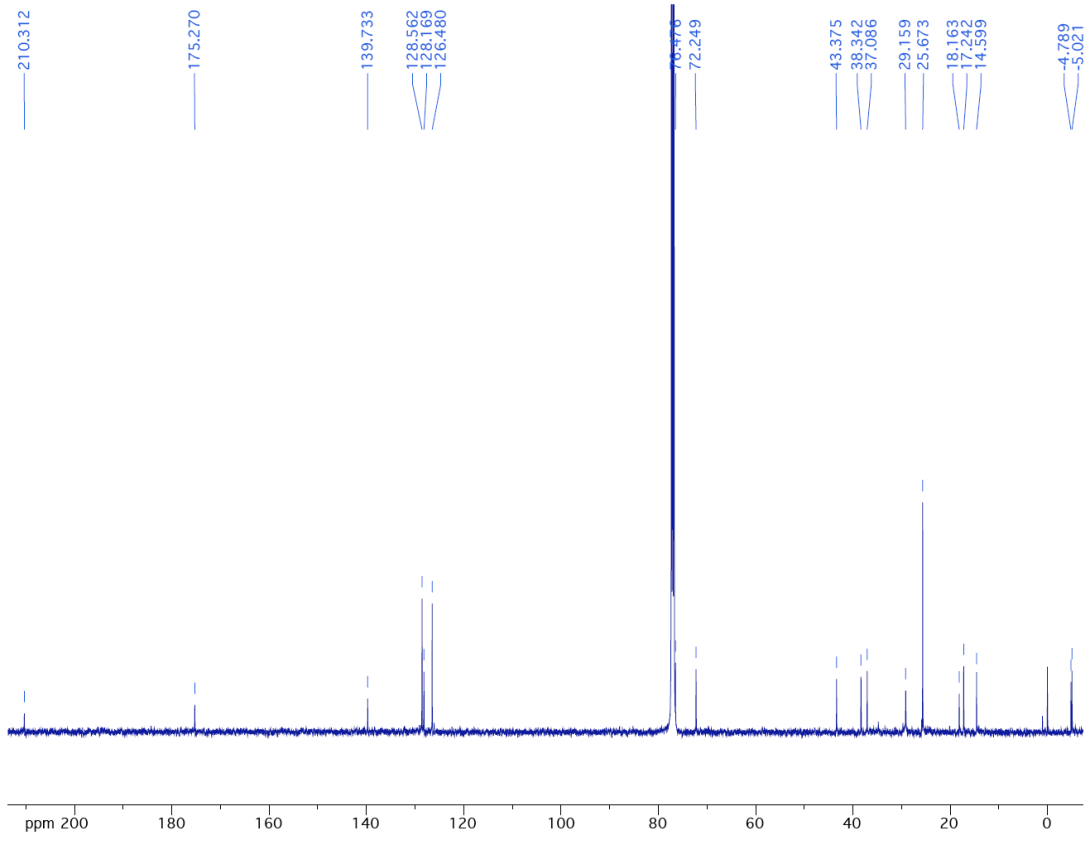

1.96
1.88
5.01
1
0.994
3.05
1.04
1.02
1.04
1.04
1.84
3.02
ppm 7
6
5
4
3
2
1
0

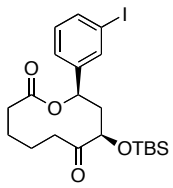

205.250
175.425
165.130
139.269
131.710
131.338
128.788
128.606
128.153
127.930
125.807
76.734
72.055
41.166
39.350
37.948
29.079
21.499
19.544
ppm 200
180
160
140
120
100
80
60
40
20
0


O
Ph
Me
O
OTBS
O

18

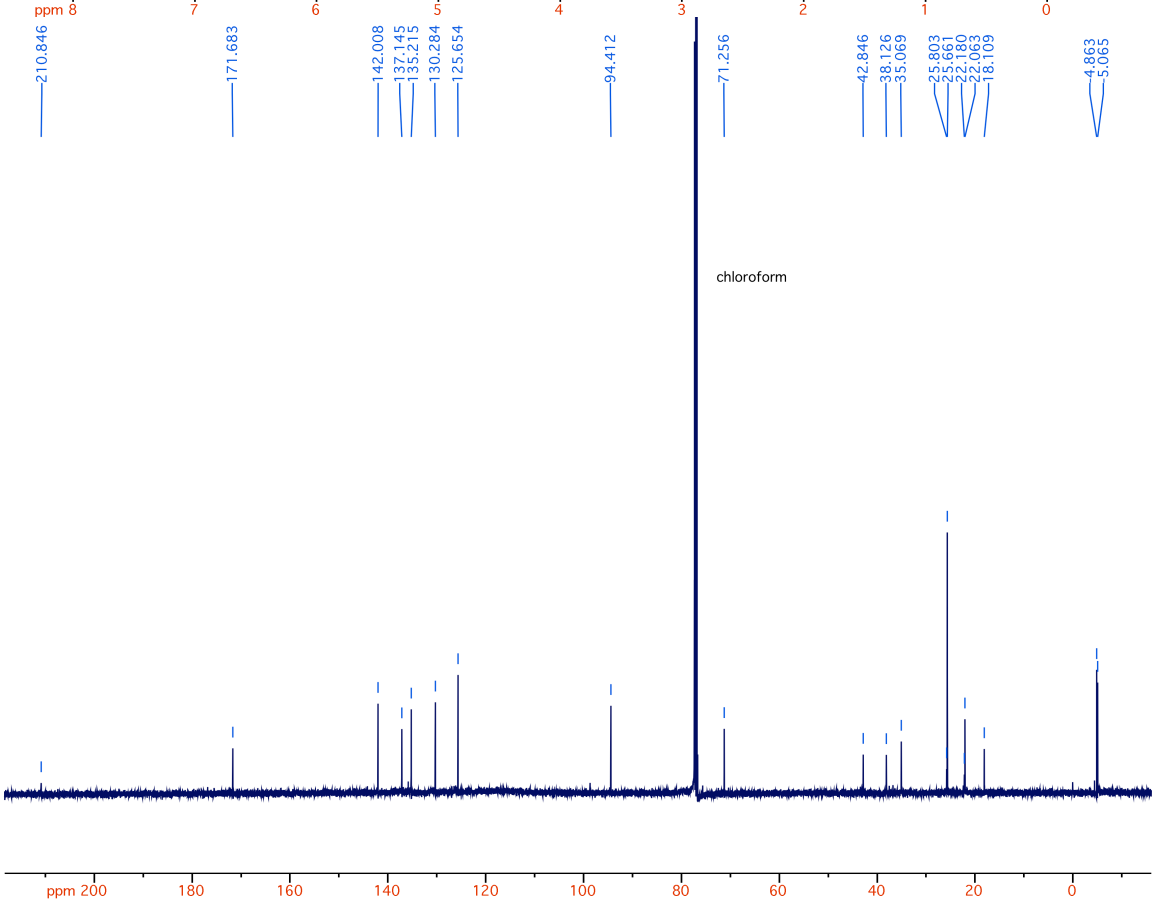
0.969
3.86
1.04
1
1.06
2.91
1.33
2.22
1.41
1.19
8.59
2.94
2.89
2.96
ppm 7
6
5
4
3
2
1
0

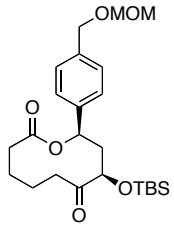

210.312
175.270
139.733
128.562
128.169
126.480
76.478
72.249
43.375
38.342
37.086
29.159
25.673
18.163
17.242
14.599
-4.789
-5.021
ppm 200
180
160
140
120
100
80
60
40
20
0


I
O
O
OTBS
O

19

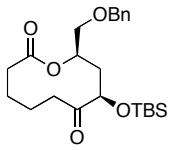
chloroform
H2O in CDCl3
0.954
1.02
1.05
3.24
1.14
2.17
3.16
1
1.06
1.03
1.01
2.15
1.1
9.37
3.11
ppm 8
7
6
5
4
3
2
1
0


210.846
171.683
142.008
137.145
135.215
130.284
125.654
94.412
71.256
42.846
38.126
35.069
25.803
25.661
22.180
22.063
18.109
4.863
5.065
chloroform
ppm 200
180
160
140
120
100
80
60
40
20
0


OMOM
O
O
OTBS
O

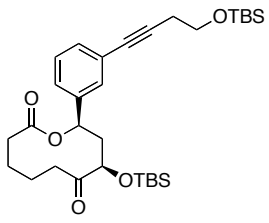
20

chloroform
H2O in CDCl3
1.04
2.08
3
1.08
1.06
1.06
2.1
2.92
4.15
2.05
1.05
1.01
2.1
1.04
1.06
9
3.16
ppm 7
6
5
4
3
2
1
0
210.855
171.945
139.168
138.076
128.158
126.652
95.796
77.414
77.160
76.905
72.116
68.824
55.508
43.367
38.400
35.226
25.765
22.185
18.223
4.748
4.884
chloroform
TMS
220
200
180
160
140
120
100
80
60
40
20
0


OBn
O
O
OTBS
O

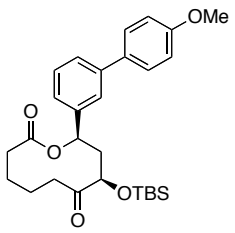
21

chloroform
1
0.988
0.996
2.04
2.05
2.27
2.76
5.95
2.02
0.993
0.956
2.12
1.15
8.89
3.16
8
7
6
5
4
3
2
1
0
210.431
172.554
138.155
128.525
127.813
77.413
77.160
76.907
73.287
71.437
37.006
36.646
35.133
25.865
22.254
22.165
18.274
4.801
5.114
chloroform
TMS
ppm 200
180
160
140
120
100
80
60
40
20
0


OTBS
O
O
OTBS
O

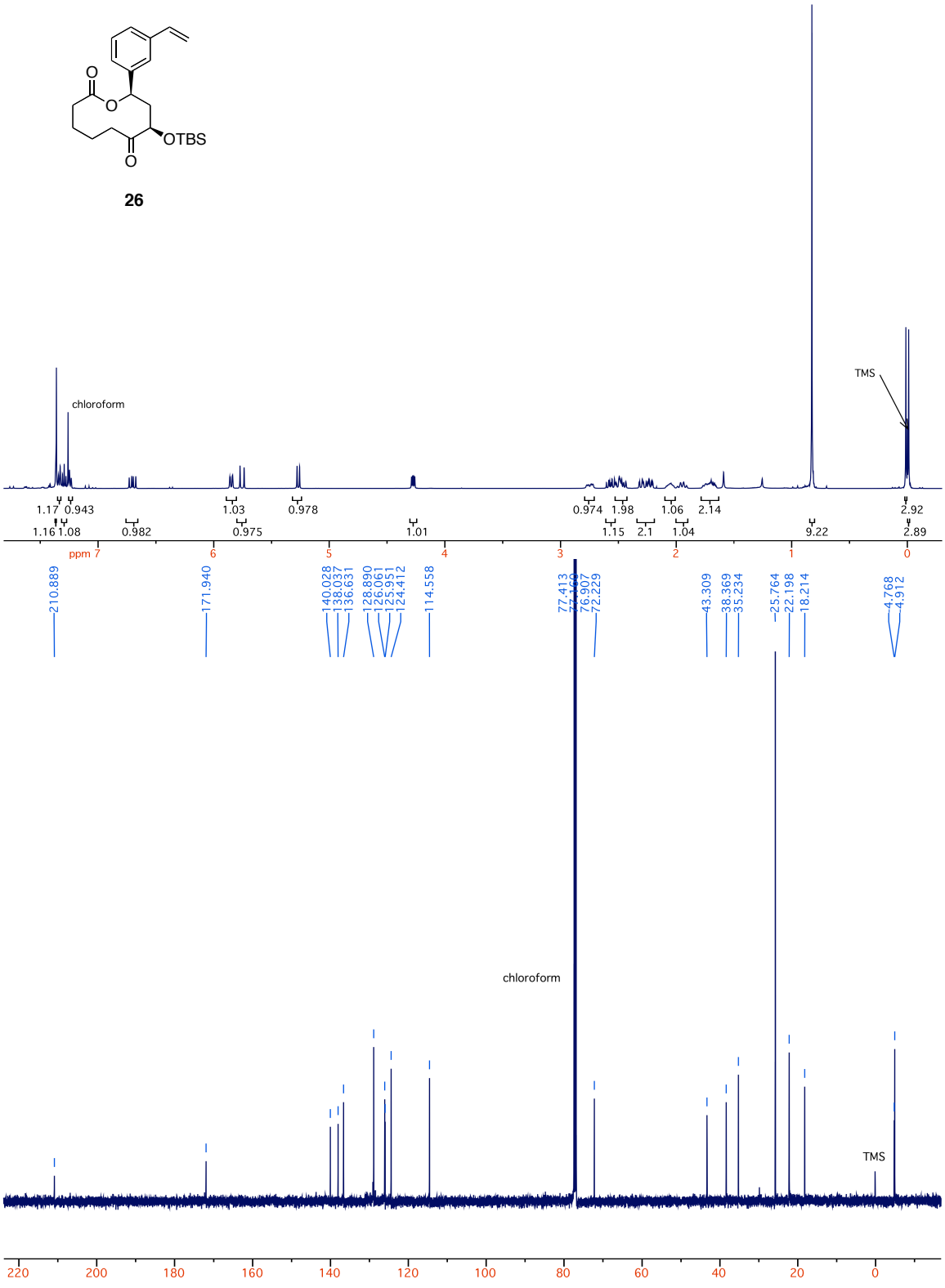
24

chloroform
0.954
1.02
2.08
2.04
1.05
2.11
8.81
5.78
2.97
1
2.07
1.02
0.926
3.18
1.05
2.09
9.19
2.85
ppm 7
6
5
4
3
2
1
0
210.950
171.819
139.874
131.344
129.532
128.572
125.872
124.225
87.788
81.378
77.414
76.905
71.835
62.049
43.183
38.301
35.226
26.067
25.766
23.964
22.315
22.165
18.525
18.211
-4.779
-4.910
-5.072
chloroform
20
200
180
160
140
120
100
80
60
40
20
0

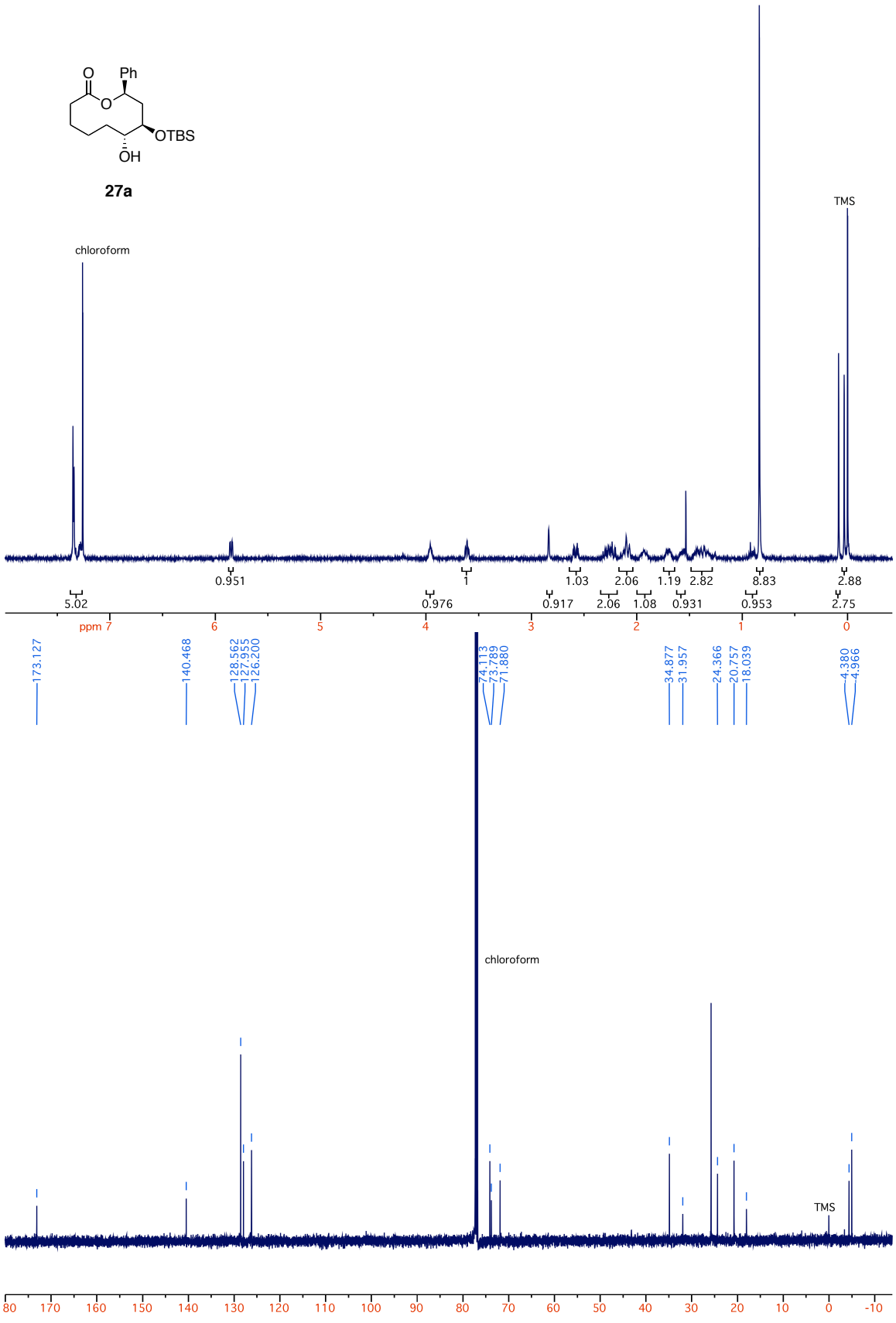

OMe
O
O
OTBS
O

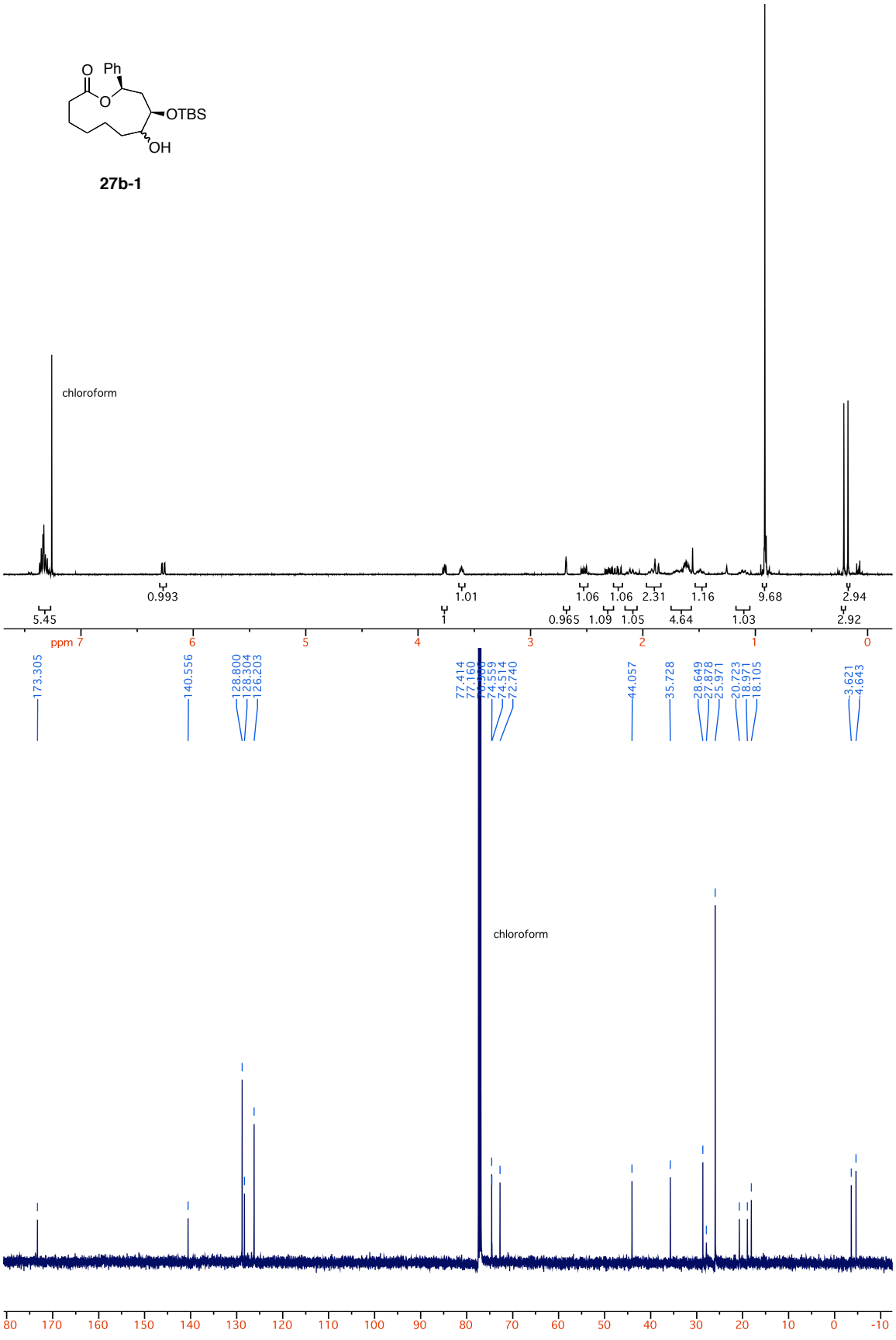
25

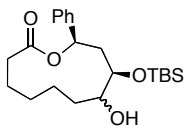
chloroform
TMS
1.01 1 1 2.99 1 2
2.99
1.03 2.03 1.03 0.97 2.04 1.07 2.16
9.26
2.79 2.8
ppm 7 6 5 4 3 2 1 0
210.779
171.871
159.335
141.242
140.100
133.409
128.972
128.264
126.596
124.788
124.719
114.276
77.305
76.798
72.260
55.399
43.304
38.269
35.145
29.737
25.659
22.107
18.115
4.869
5.011
chloroform
TMS
220 200 180 160 140 120 100 80 60 40 20 0


O
O
OTBS
O
chloroform
TMS
1.17 0.943
1.03
0.978
0.974 1.98
1.06 2.14
2.92
1.16 1.08
0.982
0.975
1.01
1.15 2.1
1.04
9.22
2.89
ppm 7
6
5
4
3
2
1
0
210.889
171.940
140.028
138.037
136.631
128.890
126.061
125.551
124.412
114.558
77.413
76.907
72.229
43.309
38.369
35.234
25.764
22.198
18.214
4.768
4.912
chloroform
TMS
220
200
180
160
140
120
100
80
60
40
20
0

26

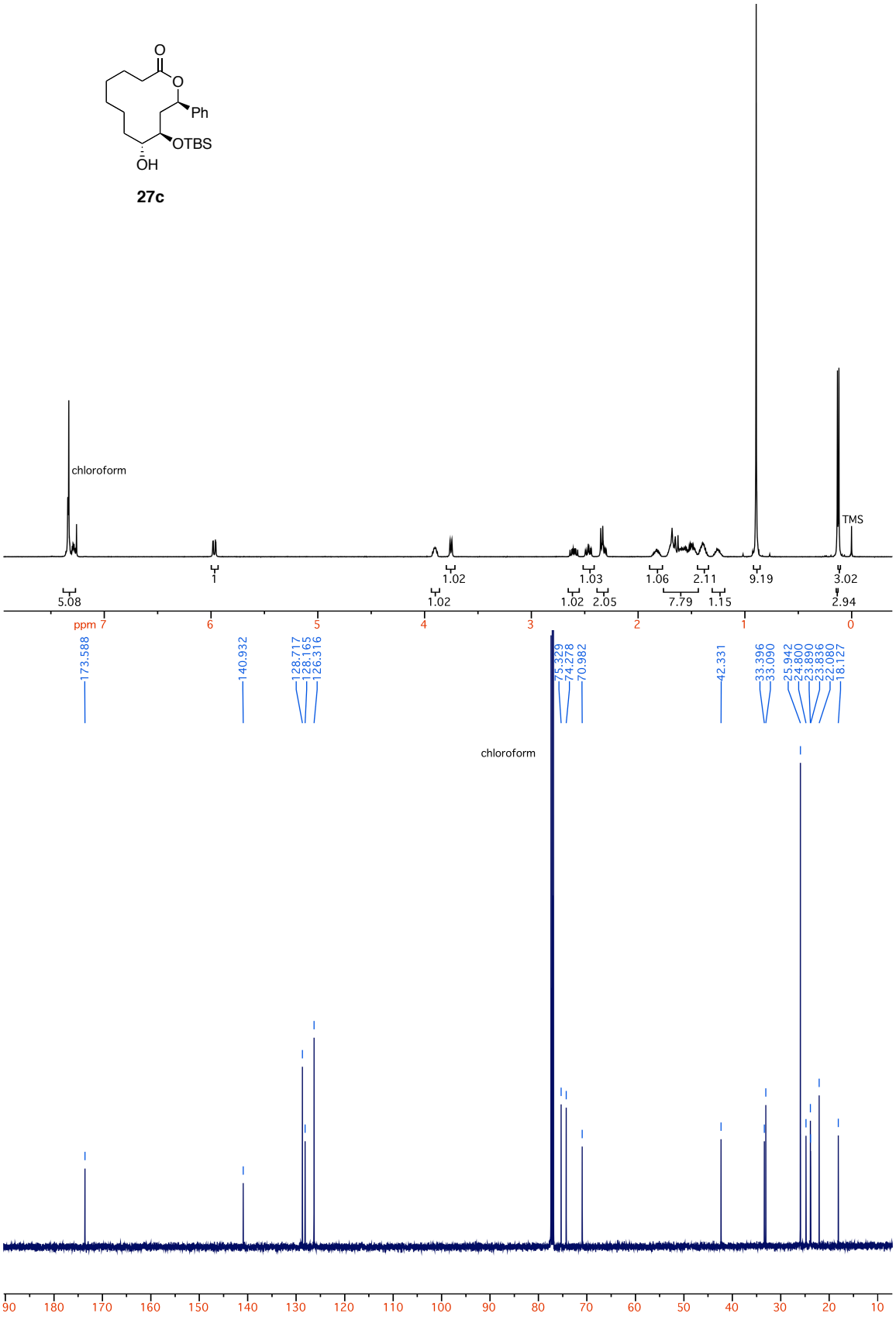

O
Ph
O
OTBS
OH
27a
TMS
chloroform
0.951
1
1.03
2.06
1.19
2.82
8.83
2.88
5.02
0.976
0.917
2.06
1.08
0.931
0.953
2.75
ppm 7
6
5
4
3
2
1
0
173.127
140.468
128.562
127.955
126.200
74.113
73.789
71.880
34.877
31.957
24.366
20.757
18.039
4.380
4.966
chloroform
TMS
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

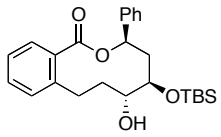

O
Ph
O
OTBS
OH
27b-1
chloroform
0.993
1.01
1.06
1.06
2.31
1.16
9.68
2.94
5.45
1
0.965
1.09
1.05
4.64
1.03
2.92
ppm 7
6
5
4
3
2
1
0
173.305
140.556
128.800
128.304
126.203
77.414
77.160
74.559
74.514
72.740
44.057
35.728
28.649
27.878
25.971
20.723
18.971
18.105
3.621
4.643
chloroform
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
Ph
O
OTBS
OH

27b-2

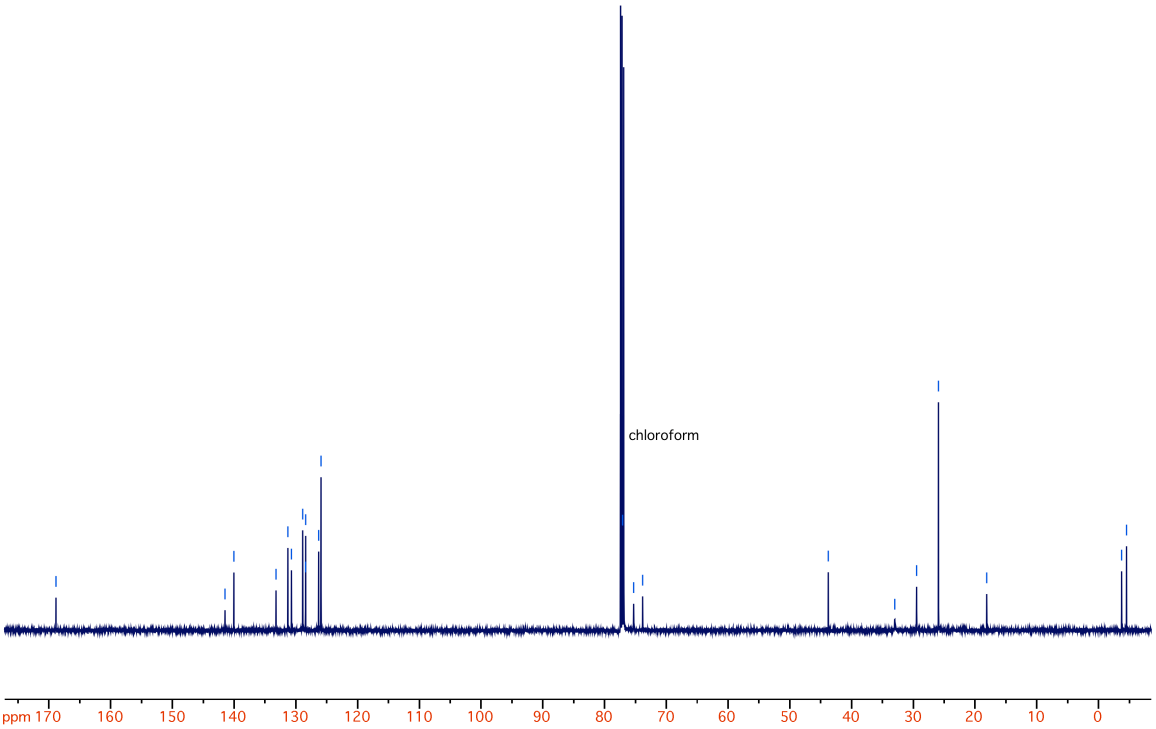
chloroform
0.946
1.02
1.04
2.12
1.18
3.11
9.22
2.98
5.02
1
1.02
0.965
1.11
2.54
1
2.97
ppm 7
6
5
4
3
2
1
0
172.883
140.795
128.602
128.089
126.157
77.677
77.353
73.442
40.082
35.553
28.224
27.876
27.735
25.815
21.569
19.950
17.962
4.322
4.738
chloroform
ppm 170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

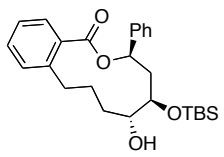

O
O
Ph
OTBS
OH
27c
chloroform
TMS
1
1.02
1.03
1.06
2.11
9.19
3.02
5.08
1.02
1.02
2.05
7.79
1.15
2.94
ppm 7
6
5
4
3
2
1
0
173.588
140.932
128.717
128.165
126.316
75.329
74.278
70.982
42.331
33.396
33.090
25.942
24.800
23.890
23.836
22.080
18.127
chloroform
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


O
Ph
O
OTBS
OH

27d

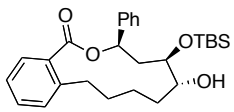
chloroform
6.47
0.833
1.08
2.15
1.07
1.08
9.6
3.09
1
1.18
1.03
1.06
1.09
1.1
1.06
3.04
ppm 7
6
5
4
3
2
1
0
168.849
141.475
140.035
133.211
131.290
130.715
128.891
128.429
126.306
125.921
77.081
75.292
73.833
43.767
33.001
29.465
25.924
18.108
3.738
4.537


chloroform
ppm 170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
Ph
O
OTBS
OH

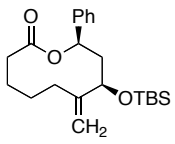
27e

chloroform
TMS
5.44
0.982
5.16
0.972
0.0361
1.97
0.974
1.04
2.01
1.07
1.03
2.14
1.22
9.22
3.19
2.9
ppm 8
7
6
5
4
3
2
1
0
168.445
144.017
140.666
133.167
132.674
131.377
129.363
128.796
128.148
126.492
126.159
77.382
73.406
70.605
44.653
34.296
33.013
27.537
25.927
18.115
3.847
4.658
chloroform
TMS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
Ph
OTBS
O
OH

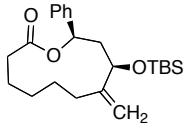
27f

chloroform
TMS
6.6
1
1.01
1
1.03
5.33
9.21
2.95
1
1.49
1.02
0.993
0.978
1.03
1.21
2.93
ppm 7
6
5
4
3
2
1
0
168.690
143.355
140.929
131.970
131.202
130.768
128.847
128.181
126.116
125.986
75.578
73.514
73.413
43.524
31.852
31.437
29.453
29.172
21.802
18.258
3.705
4.433
chloroform
TMS
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
Ph
O
OTBS
CH2

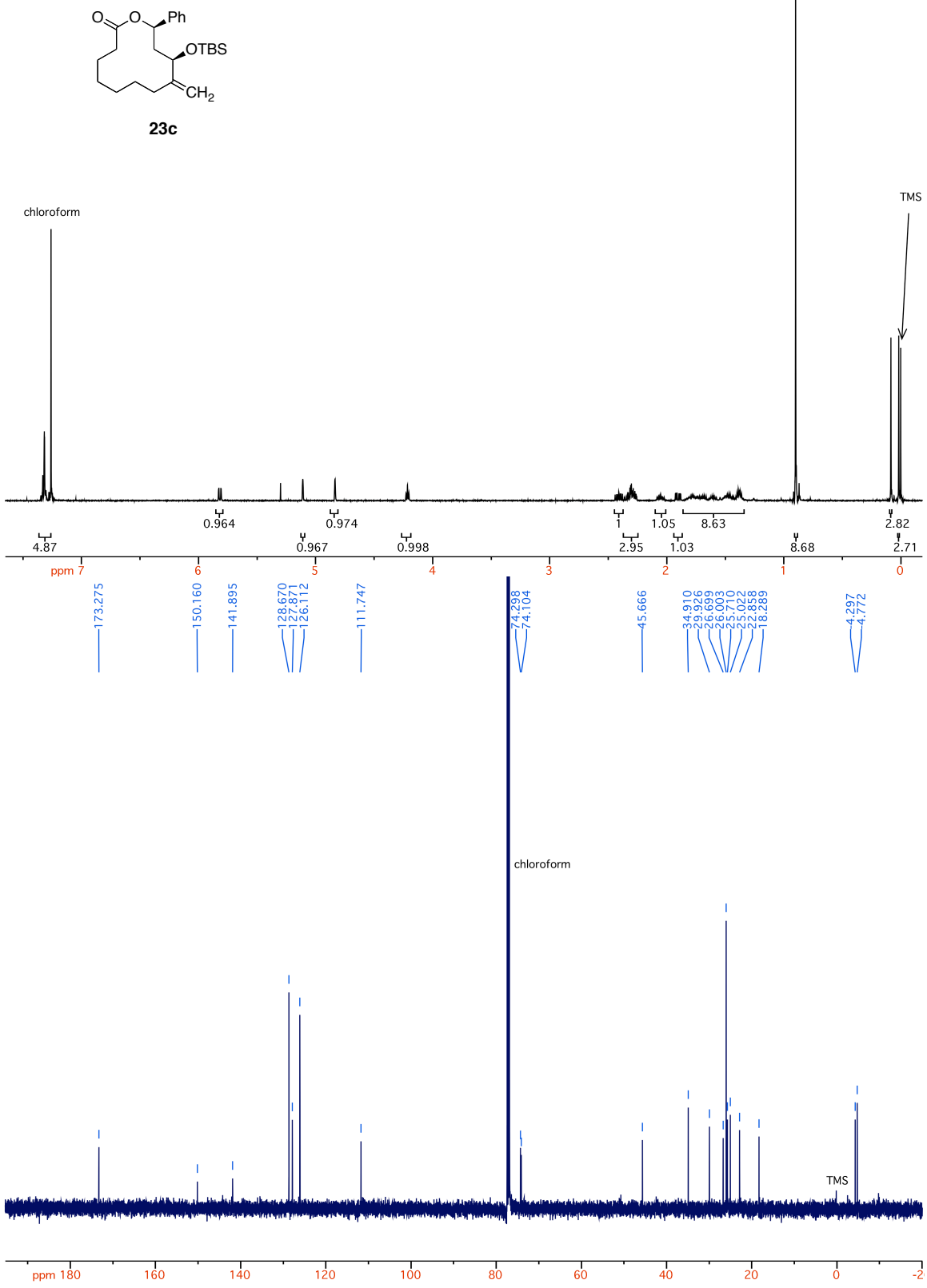
23a

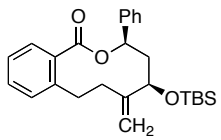
chloroform
TMS
1
1.01
2.02
1.05
2.03
2.53
4.91
0.998
1
1.03
4.18
9.18
2.42
ppm 7
6
5
4
3
2
1
0
171.722
150.729
141.124
128.531
128.230
126.710
109.395
76.846
72.454
45.235
35.534
29.272
25.726
24.707
22.390
18.053
4.830
5.244
benzene
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
Ph
O
OTBS
CH2

23b

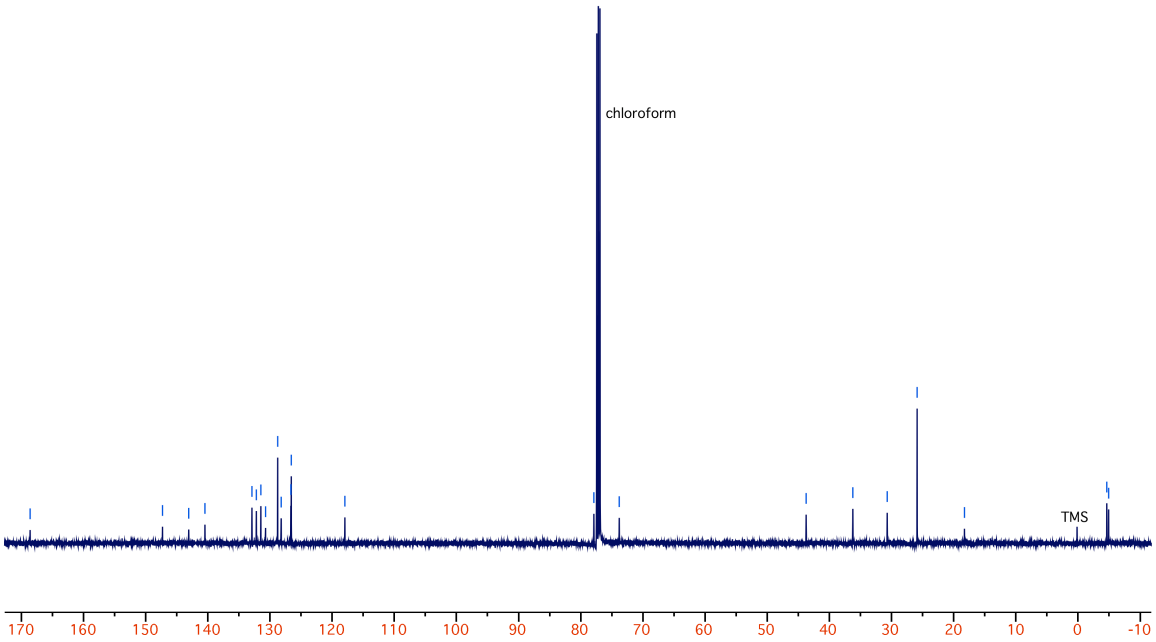
chloroform
TMS
0.996
3.11
3.19
2.99
1.09
5.19
1
1.03
1.17
1.49
ppm 7
6
5
4
3
2
1
0
172.585
149.378
141.675
128.674
127.966
126.226
110.895
76.173
73.816
44.482
36.289
25.950
25.757
25.347
23.865
20.777
18.273
4.627
4.802
chloroform
TMS
ppm 170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

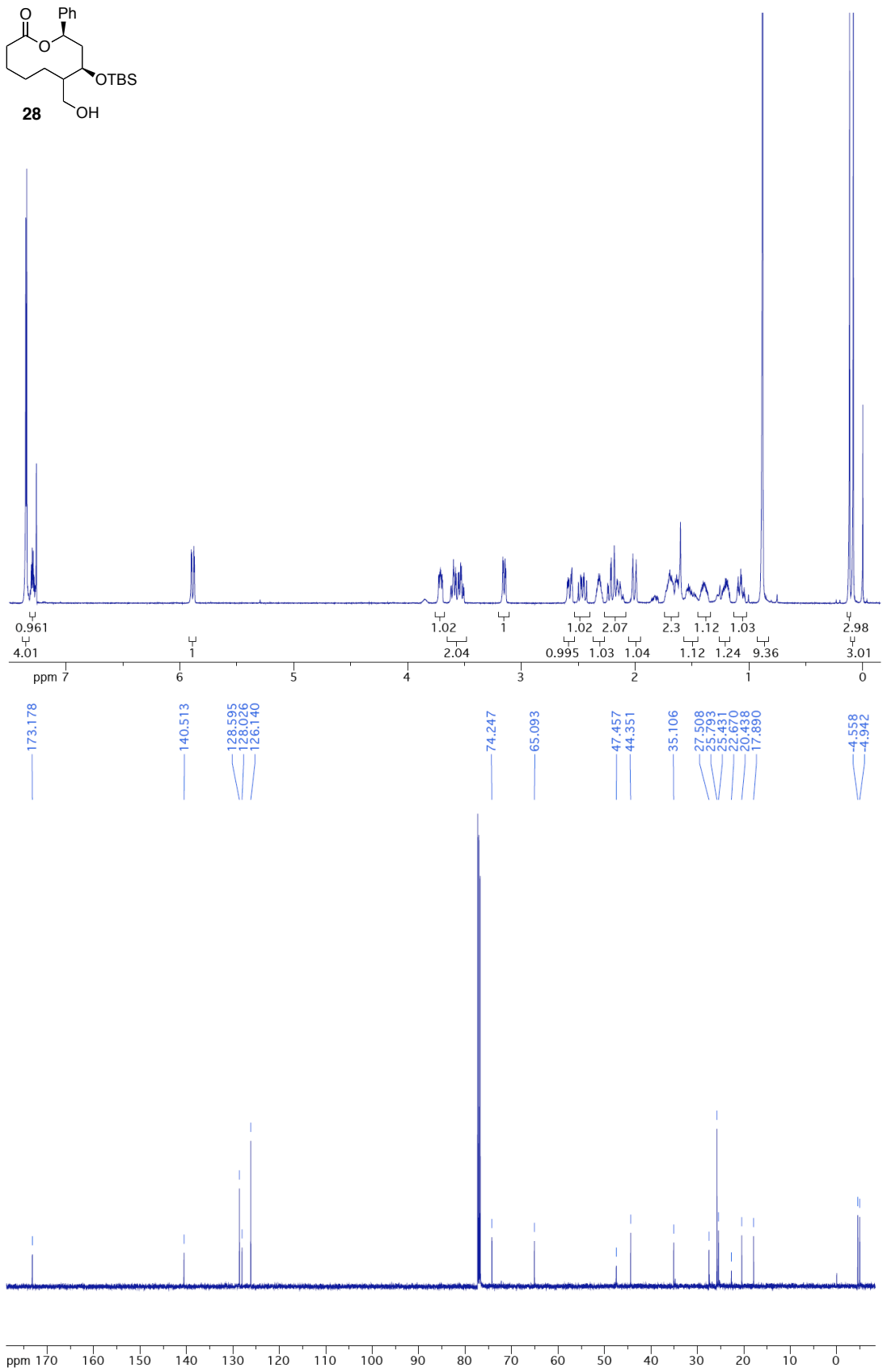

O
O
Ph
OTBS
CH2
23c
chloroform
TMS
0.964
0.974
1
1.05
8.63
2.82
4.87
0.967
0.998
2.95
1.03
8.68
2.71
ppm 7
6
5
4
3
2
1
0
173.275
150.160
141.895
128.670
127.871
126.112
111.747
74.298
74.104
45.666
34.910
29.326
26.699
26.003
25.710
25.022
22.558
18.289
4.297
4.772
chloroform
TMS
ppm 180
160
140
120
100
80
60
40
20
0
-2

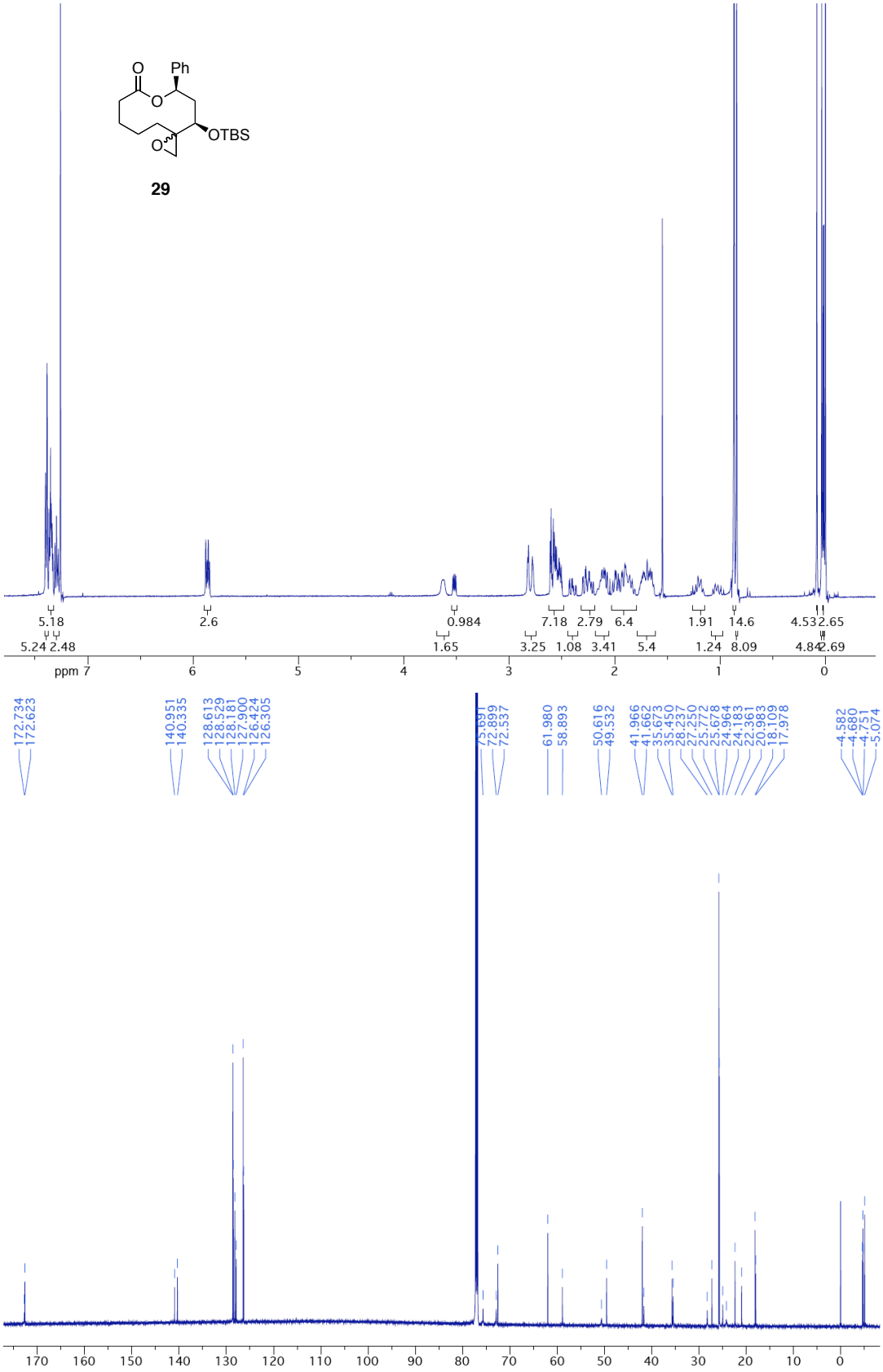

O
Ph
O
OTBS
CH2

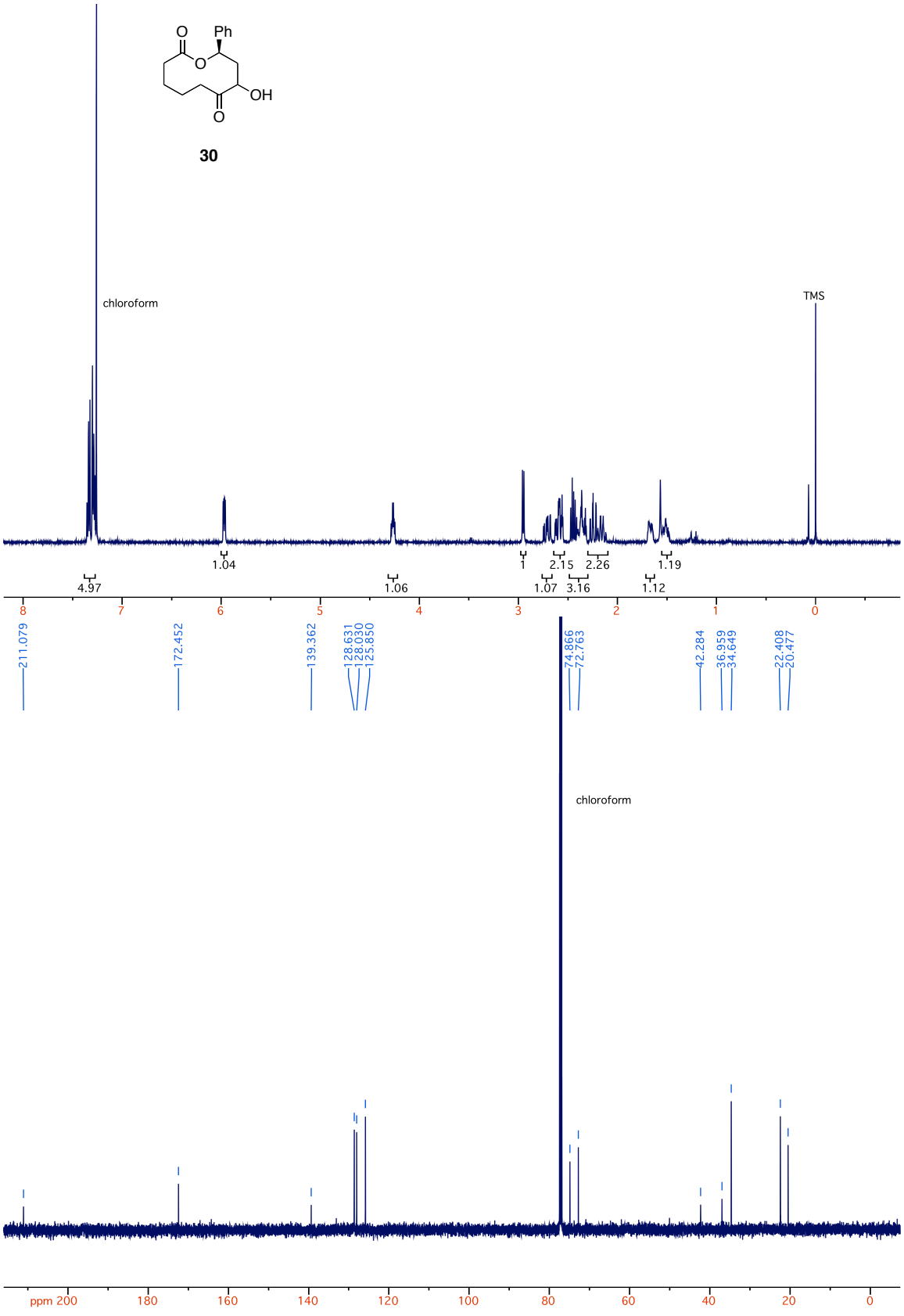
23d

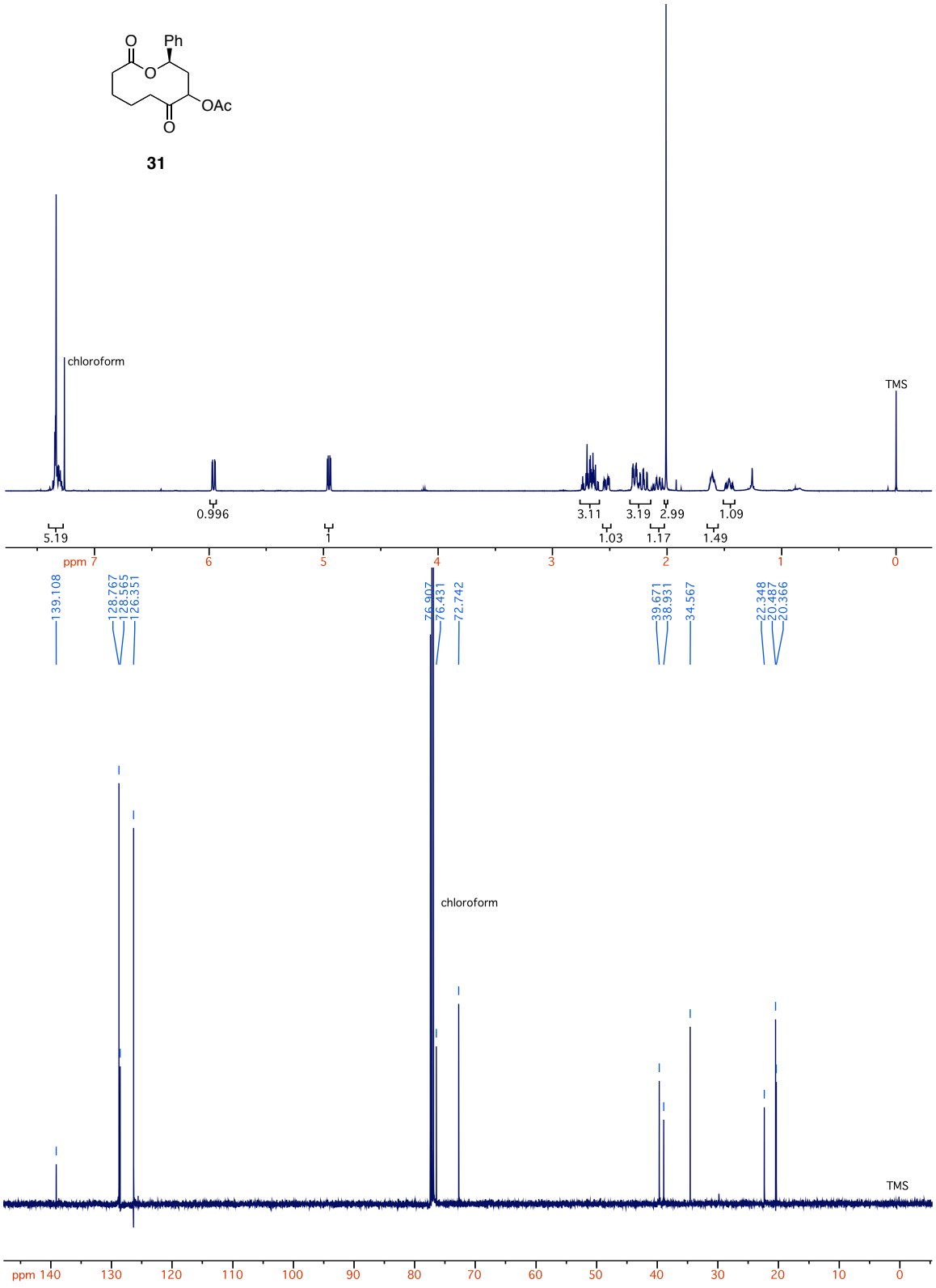
TMS
chloroform
H2O in CDCl3
2.74 5.73 1 1.07 0.998 1.05 1.03 2.54
0.895 1.82 1.03 1.04 1.12 1.05 1 8.51 2.68
8 7 6 5 4 3 2 1 0
168.583 147.282 143.069 140.458 132.896 132.190 131.461 130.703 128.751 128.190 126.638 126.567 117.945 77.889 73.807 43.735 36.226 30.693 25.882 18.265 4.630 4.933


chloroform
TMS
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

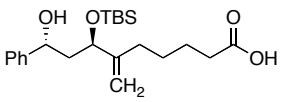

O
Ph
O
OTBS
OH
28
0.961
4.01
1
1.02
2.04
1
1.02
0.995
2.07
1.03
1.04
2.3
1.12
1.24
1.03
9.36
2.98
3.01
ppm 7
6
5
4
3
2
1
0
173.178
140.513
128.595
128.026
126.140
74.247
65.093
47.457
44.351
35.106
27.508
25.793
25.431
22.670
20.438
17.890
-4.558
-4.942
ppm 170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
Ph
O
OTBS
O
29
5.18
5.24 2.48
2.6
0.984
1.65
7.18 2.79 6.4
3.25 1.08 3.41 5.4
1.91 14.6
1.24 8.09
4.53 2.65
4.84 2.69
ppm 7
6
5
4
3
2
1
0
172.734
172.623
140.951
140.335
128.613
128.529
128.181
127.900
126.424
126.305
75.691
72.899
72.537
61.980
58.893
50.616
49.532
41.966
41.662
35.673
35.450
28.237
27.250
25.772
25.678
24.964
24.183
22.361
20.983
18.109
17.978
-4.582
-4.680
-4.751
-5.074
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
Ph
O
OH
O
30
chloroform
TMS
4.97
1.04
1.06
1
2.15
2.26
1.07
3.16
1.12
1.19
8
7
6
5
4
3
2
1
0
211.079
172.452
139.362
128.631
128.030
125.850
74.866
72.763
42.284
36.959
34.649
22.408
20.477
chloroform
ppm 200
180
160
140
120
100
80
60
40
20
0

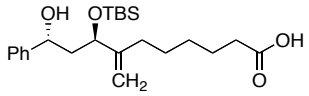

O
Ph
O
OAc
O
chloroform
TMS
0.996
3.11
3.19
2.99
1.09
5.19
1
1.03
1.17
1.49
ppm 7
6
5
4
3
2
1
0
139.108
128.767
128.565
126.351
76.907
76.431
72.742
39.671
38.931
34.567
22.348
20.487
20.366
chloroform
TMS
ppm 140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

31


OH
OTBS
O
Ph
OH
CH2

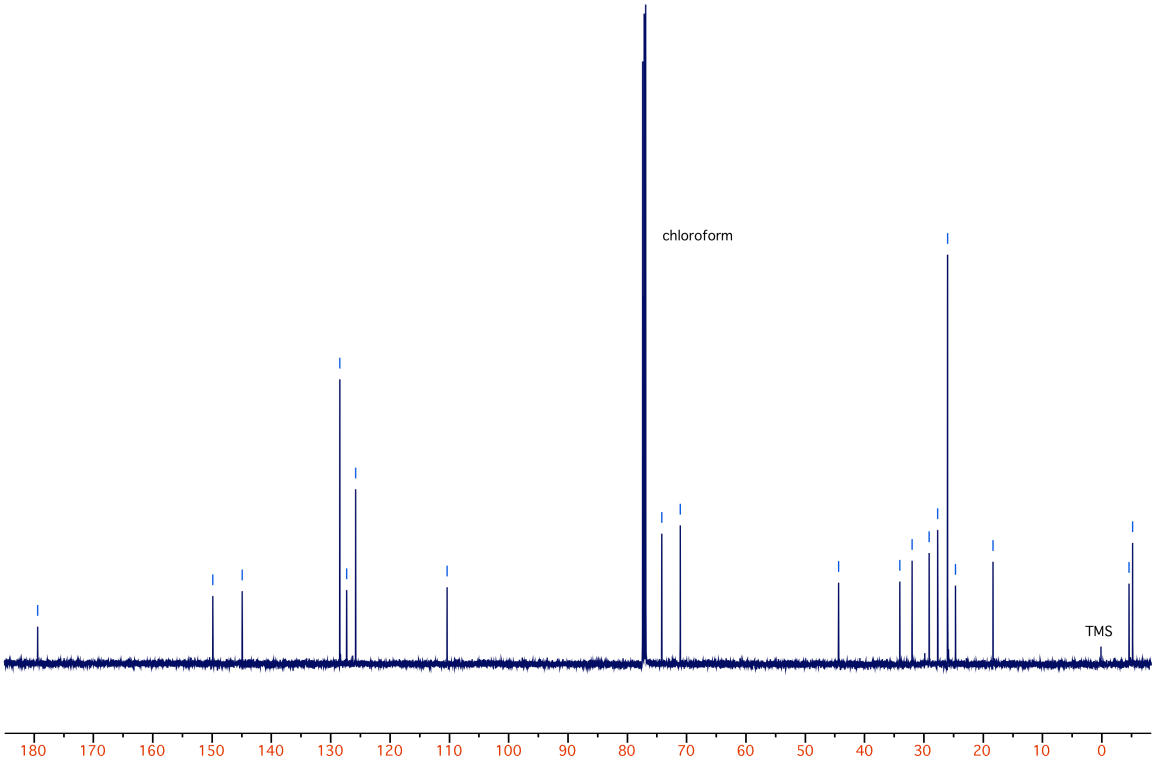
22a

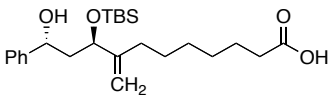
TMS
chloroform
0.278
4 0.988
1.02
0.983
1
1.03
1.92
2.12
2.17
1.07
1.04
2.17
8.92
2.92
2.74
ppm 7
6
5
4
3
2
1
0
177.447
149.695
145.011
128.501
127.343
125.807
110.552
74.222
71.060
44.570
33.621
31.696
27.402
26.018
24.719
18.357
4.565
5.165
chloroform
TMS
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


OH
OTBS
Ph
OH
CH2
O

22b

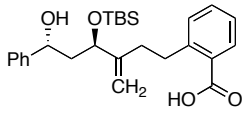
chloroform
DCM
TMS
0.0399
4.1
0.883
0.956
0.969
0.963
0.933
1.92
1.98
2
2.07
8.63
2.9
1.03
1
2.1
0.997
2.96
ppm 7
6
5
4
3
2
1
0
179.402
149.880
144.926
128.467
127.311
125.796
110.382
74.187
71.073
44.381
34.059
31.989
29.117
27.681
26.003
24.675
18.350
4.578
5.186


chloroform
TMS
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


OH
OTBS
O
Ph
OH
CH2

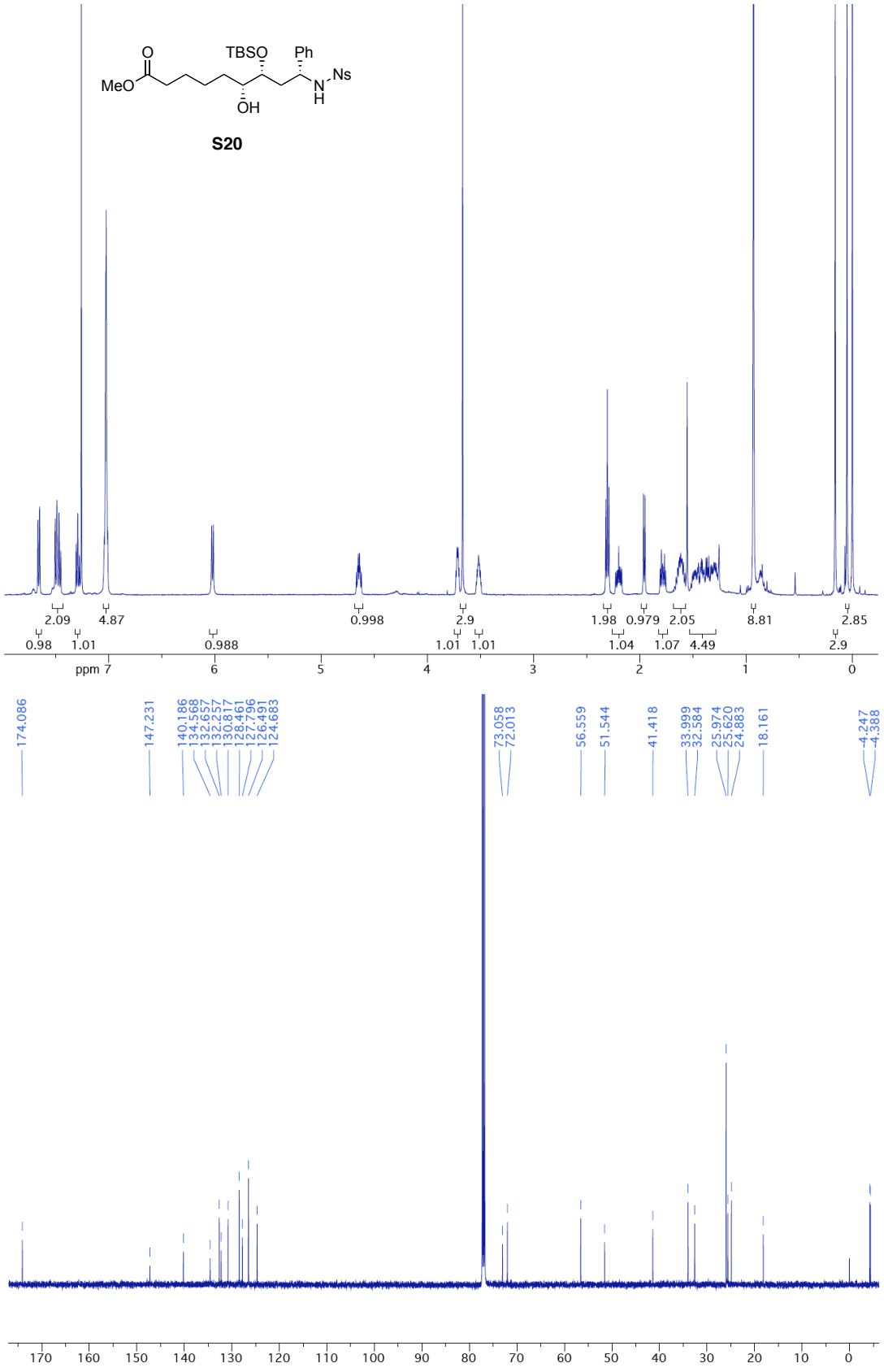
22c

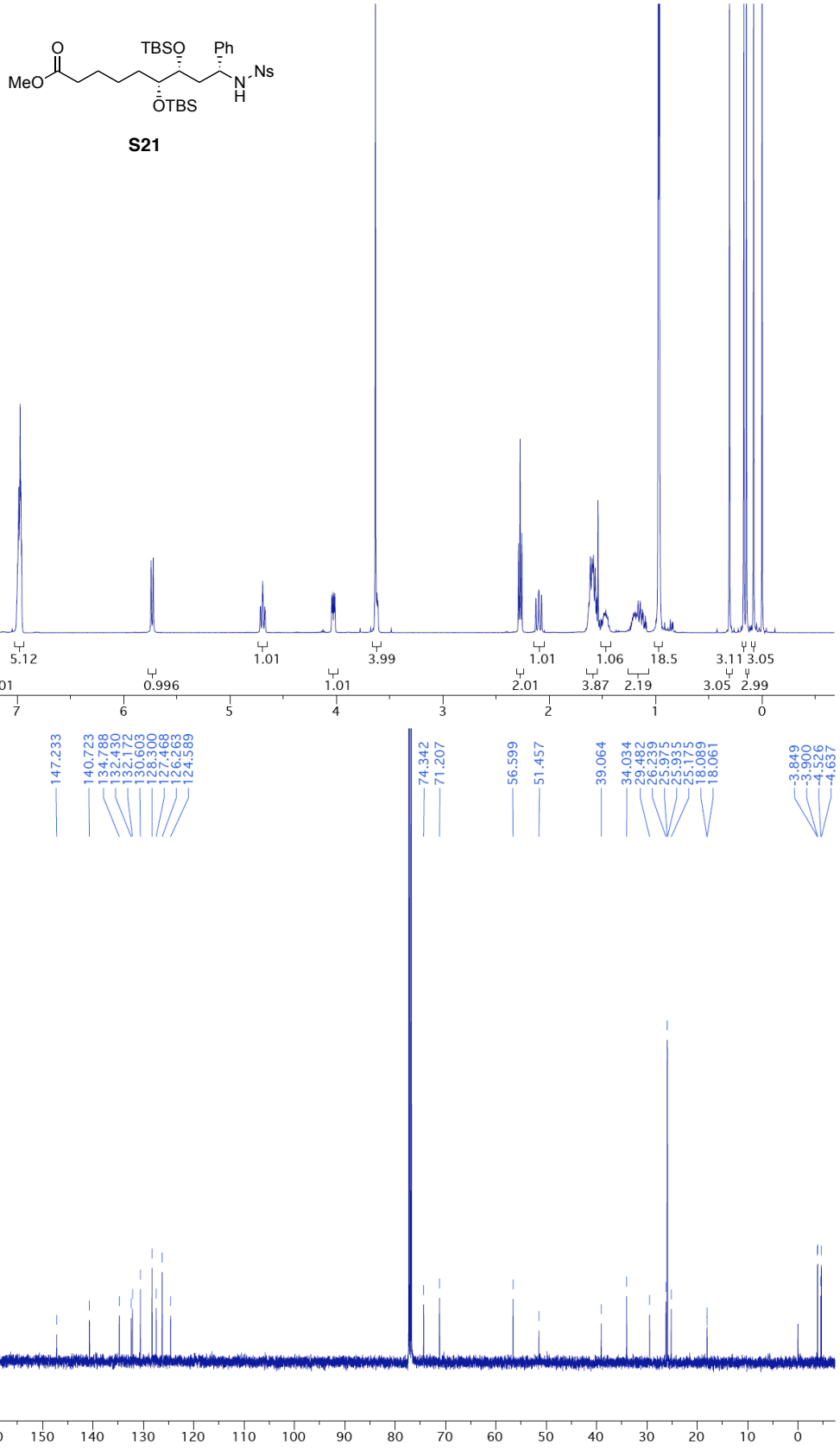
chloroform
TMS
6.7
3.82
1.02
1.01
1.06
1.1
1.96
1.11
2.01
1.03
2
2.1
3.95
0.483
8.6
2.83
2.94
ppm 7
6
5
4
3
2
1
0
177.813
150.013
144.996
128.473
127.305
125.810
110.291
77.414
77.160
76.906
74.251
71.079
44.358
33.821
32.150
29.273
29.044
27.805
26.013
24.789
18.360
4.571
5.186
chloroform
TMS
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20

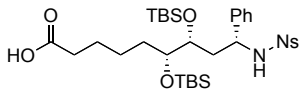

OH
OTBS
Ph
CH2
HO
O

22d

chloroform
DCM
TMS
1.05 4.32 0.965 2.04 0.906
0.974 0.972 0.975 0.977
0.964 0.964
1.01 1.03 0.994 0.985
1.02 8.85
2.88 2.97
ppm 8 7 6 5 4 3 2 1 0
171.691
150.094
145.050
144.901
133.119
131.959
131.341
128.440
128.155
127.257
126.398
125.787
110.749
73.362
71.289
44.902
34.915
34.146
26.047
18.375
4.485
5.142
chloroform
TMS
ppm 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

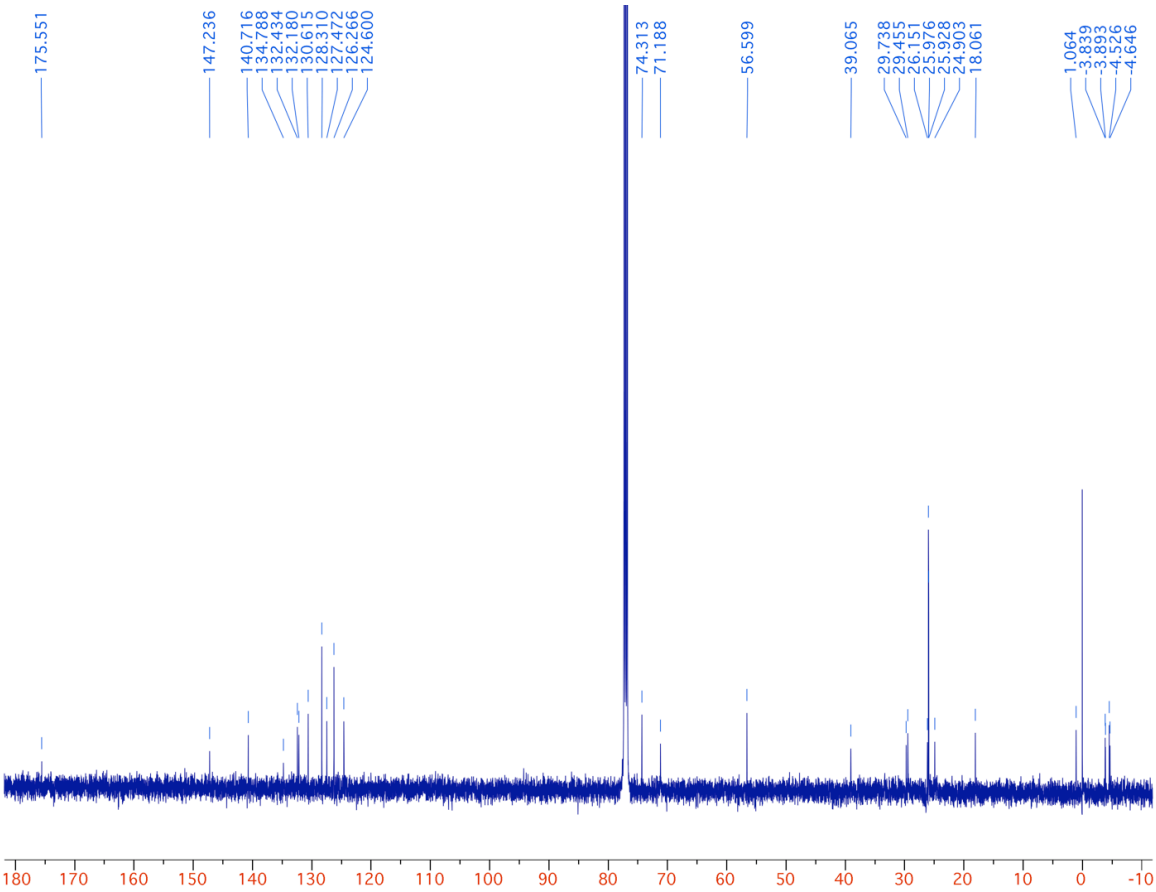

O
TBSO
Ph
MeO
Ns
N
H
OH
S20
2.09
4.87
0.998
2.9
1.98
0.979
2.05
8.81
2.85
0.98
1.01
0.988
1.01
1.01
1.04
1.07
4.49
2.9
ppm 7
6
5
4
3
2
1
0
174.086
147.231
140.186
134.568
132.657
132.257
130.817
128.461
127.796
126.491
124.683
73.058
72.013
56.559
51.544
41.418
33.999
32.584
25.974
25.620
24.883
18.161
-4.247
-4.388
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

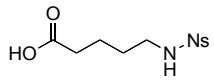

O
TBSO
Ph
MeO
Ns
N
H
OTBS
S21
2.03
5.12
1.01
3.99
1.01
1.06
18.5
3.11
3.05
0.992
1.01
0.996
1.01
2.01
3.87
2.19
3.05
2.99
8
7
6
5
4
3
2
1
0
174.096
147.233
140.723
134.788
132.430
132.172
130.603
128.300
127.468
126.263
124.589
74.342
71.207
56.599
51.457
39.064
34.034
29.482
26.239
25.975
25.935
25.175
18.089
18.061
-3.849
-3.900
-4.526
-4.637
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


O
HO
TBSO
Ph
N
H
Ns
OTBS

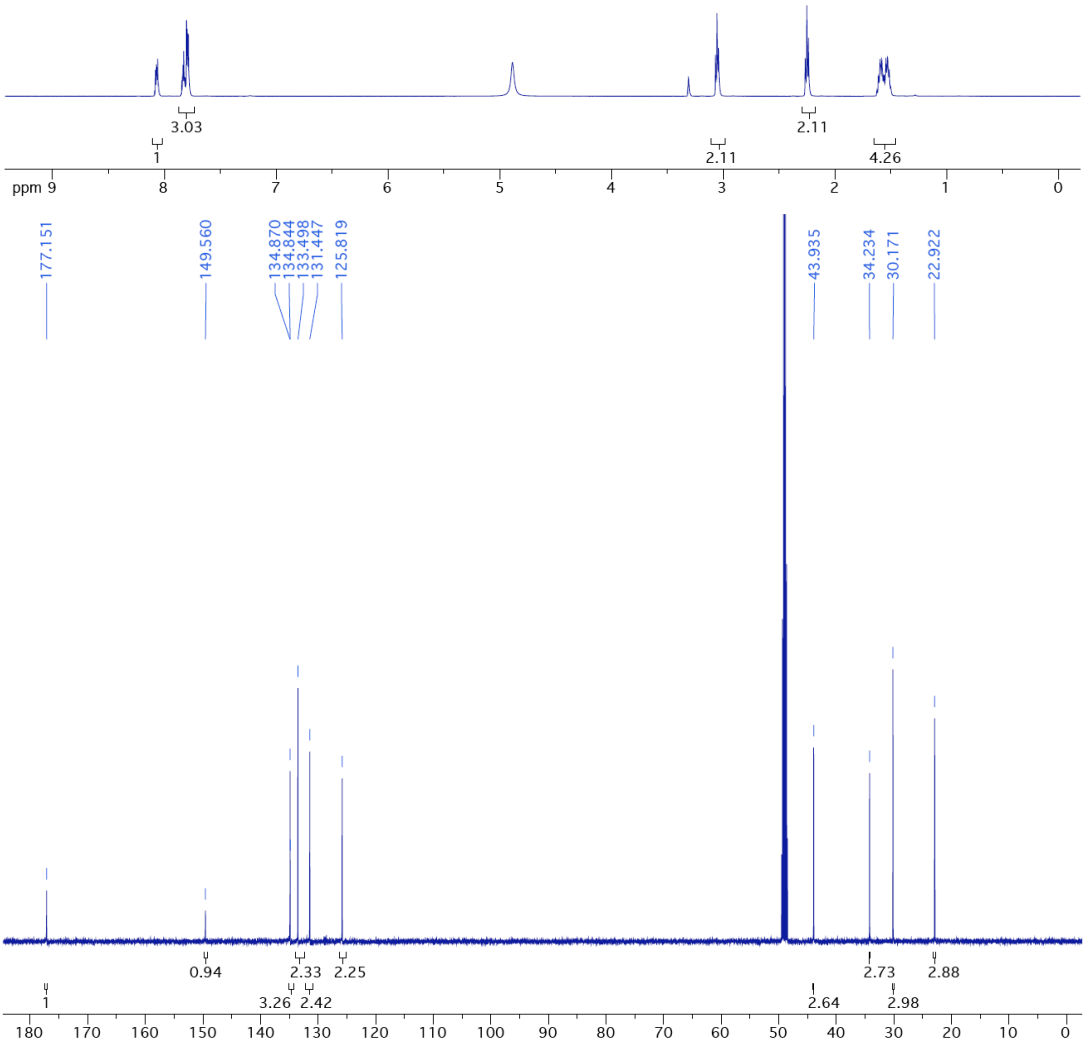
S22

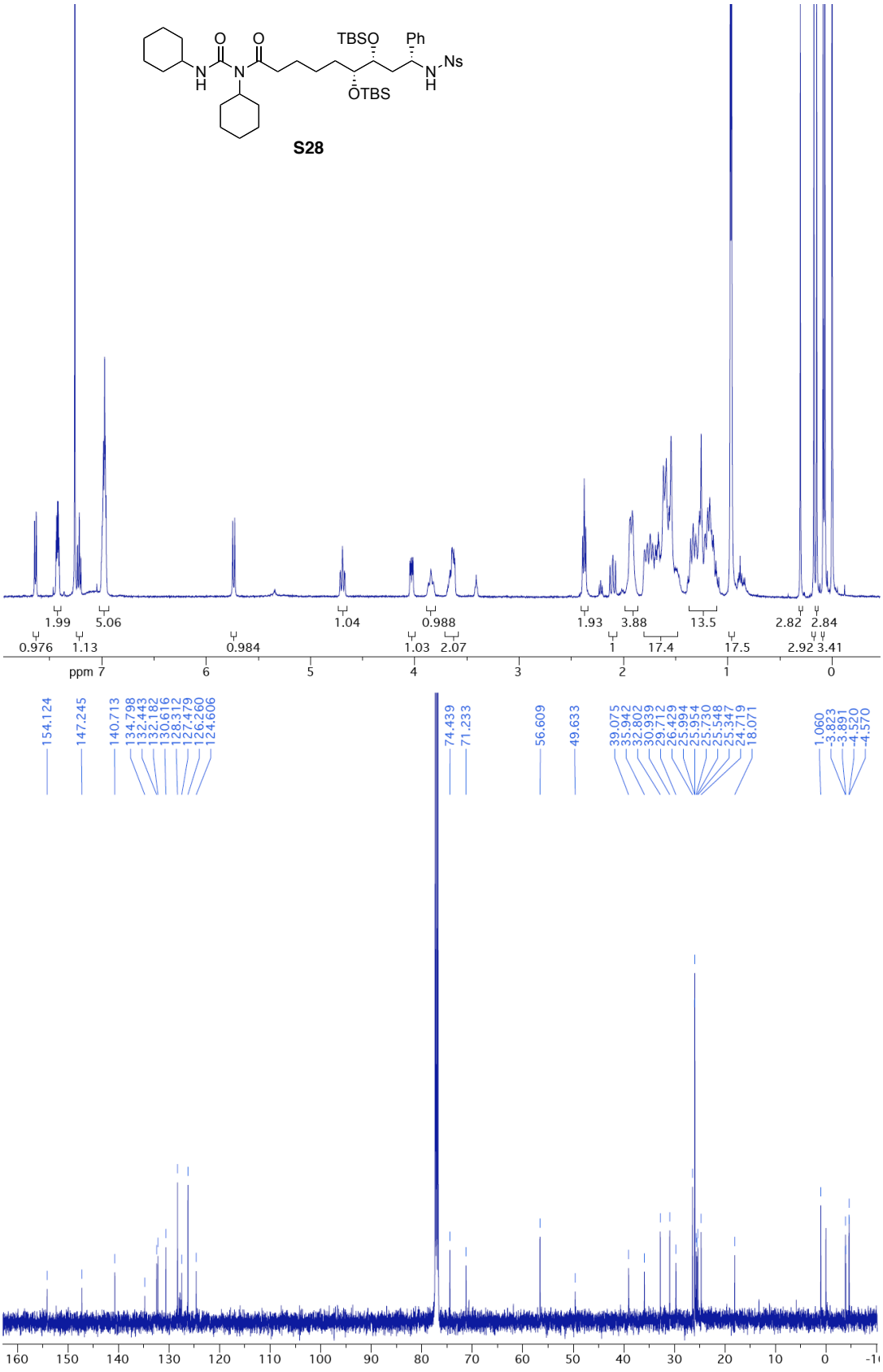
2.04
4.86
0.956
1.09
1.14
1.09
1.1
2.09
1.15
5.15
2.13
17.6
2.9
2.83
2.83
2.62
ppm 7
6
5
4
3
2
1
0


175.551
147.236
140.716
134.788
132.434
132.180
130.615
128.310
127.472
126.266
124.600
74.313
71.188
56.599
39.065
29.738
29.455
26.151
25.976
25.928
24.903
18.061
1.064
-3.839
-3.893
-4.526
-4.646
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


O
HO
N
H
Ns

S25


3.03
2.11
4.26
1
2.11
ppm 9
8
7
6
5
4
3
2
1
0
177.151
149.560
134.870
134.844
133.498
131.447
125.819
43.935
34.234
30.171
22.922
0.94
2.33
2.25
2.73
2.88
1
3.26
2.42
2.64
2.98
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


TBSO
Ph
Ns
OTBS
S28
1.99
5.06
1.04
0.988
1.93
3.88
13.5
2.82
2.84
0.976
1.13
0.984
1.03
2.07
1
17.4
17.5
2.92
3.41
ppm 7
6
5
4
3
2
1
0
154.124
147.245
140.713
134.798
132.443
132.182
130.616
128.312
127.479
126.260
124.606
74.439
71.233
56.609
49.633
39.075
35.942
32.802
30.939
29.712
26.429
25.994
25.954
25.730
25.548
25.347
24.719
18.071
1.060
-3.823
-3.891
-4.520
-4.570
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0