

A concise synthesis of carolacton

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1. Biological Supporting Information

1.1 Bacterial Strains and Culture Conditions

Streptococcus mutans wild-type strain UA159 was provided by Dr. Bettina Buttaro from Temple University Medical School, Philadelphia, PA. Bacteria were routinely maintained on Todd-Hewitt (TH) agar plates and liquid cultures were grown in Todd-Hewitt broth (THB). For growth of biofilms, THB was supplemented with 3 mM sucrose. Incubation was stagnant at 37 °C. Minimum inhibitory concentration (MIC) assays were incubated microaerophilically for approximately 16 hours in a 5% CO₂ atmosphere. Biofilms for imaging were incubated in an anaerobic vessel for approximately 20 hours.

1.2 Minimum Inhibitory Concentration Assay

MIC data was obtained using 96-well microtiter plates with a final well volume of 202 μL . Stock solutions of compounds were made in DMSO, and the final DMSO concentration in each well did not exceed 5%. The serial two-fold dilution method was used for dosing of the compounds. Inhibition of growth was determined visually by the presence of turbidity within the wells.

1.3 Cultivation of Biofilms for Confocal Microscopy Imaging

Biofilms were grown on ethanol soaked coverslips placed in each well of a 24-well plate with a final well volume of 1.04 mL. DMSO solutions of test compounds were added to the wells concurrently

with media and inoculum, and the DMSO concentration in each well did not exceed 2.5%. Biofilms were grown anaerobically for ~20-24 hours, at which point the media was removed from the well and the biofilms were washed once with phosphate buffered saline (PBS). Coverslips were then removed and placed over the wells of 8-well microscope slides containing 10 μ L of BacLight LIVE/DEAD stain. Images of biofilms were then obtained using the Leica Sp5 confocal microscope at the Confocal Microscopy Core at Temple University Medical School under the guidance of Dr. Bettina Buttaro.

2. Synthesis Supporting Information

2.1 Instrumentation and General Notes

^1H NMR and ^{13}C NMR spectra were recorded using the following spectrometers: Bruker Avance 500 (500/125 MHz), Bruker Avance 400 (400/100 MHz), or an Agilent DD2 400 (400/100 MHz). Chemical shifts are quoted in ppm relative to tetramethylsilane and with the indicated solvent as an internal referenceⁱ. The following abbreviations are used to describe signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), dt (doublet of triplets) etc. COSY, HMQC, and DEPT experiments were used when appropriate to aid structure assignment. Diastereotopic protons are labeled as H^a-X and H^b-X and imply no particular stereochemistry. Compounds were numbered according to their names as indicated in their structures.

Accurate mass spectra were recorded on a Waters Synapt G1 qTOF spectrometer equipped with a Waters Acquity UPLC (fitted with a BEH C18 Column, 130Å, 1.7 μ m, 2.1 \times 50 mm). Positive electrospray was used for ionization unless otherwise indicated.

Infrared spectra were obtained using a Thermo Nicolet 6700 FTIR spectrometer fitted with a diamond ATR. The spectra of solids were recorded using a thin film of the neat product whereas the spectra of oils were recorded using a thin liquid film of the product indicated by the bracketed solvent.

Optical rotations were measured in a 100 mm length cell using a Perkin Elmer 341 Polarimeter fitted with a sodium source lamp and a Glan-Taylor polarizer.

ⁱ The following values were used for $^1\text{H}/^{13}\text{C}$ NMR spectra, respectively: 7.26/77.16 ppm in CDCl_3 , 7.16/128.06 ppm in C_6D_6 , and 4.87/49.0 ppm in CD_3OD .

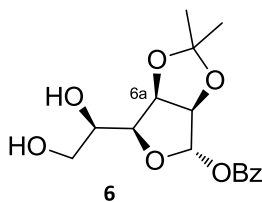
Melting points were recorded using a digital Stanford Research Systems OptiMelt automated melting point system. The reported values are an average of duplicate measurements which were taken by slowly increasing the temperature from 25 °C at a rate of 2.5 °C per min.

Analytical thin-layer chromatography was carried out on SiliCycle glass-backed extra hard layer 60Å plates (20 × 20 cm particle, 250 µm thickness), using either aqueous potassium permanganate or aqueous cerium ammonium molybdate stains to aid visualization.

Flash column chromatography was carried out following the general principles of Still (W.C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923) using SiliaFlash P60 silica (40-63 µm particle size, 230-400 mesh, SiliCycle). Preparative HPLC was performed on a Gilson HPLC consisting of a 215 liquid handler, 305/305 pump modules, and a 155 UV/VIS detector, all operating under control of Gilson's Trilution software. A Waters Sunfire silica column (10×250 mm, 5µm particle size) was used for purifications described herein.

Non-aqueous reactions were carried out under an atmosphere of nitrogen, in flame-dried glassware, using solvents dried by passage through activated alumina as described by Bergman and Grubbs (P. J. Alaimo, D.W. Peters, J. Arnold and R.G. Bergman, *J. Chem. Educ.*, **2001**, *78*, 64; A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R.K. Rosen and F. J. Timmers, *Organometallics*, **1996**, *15*, 151) or obtained by distillation when more appropriate. Bases such as triethylamine, pyridine, and diisopropylethylamine (Hünig's base) were freshly distilled from CaH₂ prior to use. Brine refers to a saturated solution of sodium chloride and pH 2 sulfate buffer refers to an aqueous solution made of 1 M sodium bisulfate and 1 M sodium sulfate mixed in 1:1 v/v ratio.

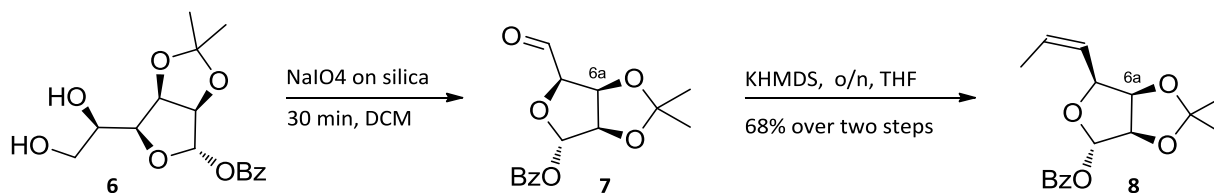
2.2 Experimental Procedures and Data



(3aR,4S,6S,6aR)-6-((R)-1,2-Dihydroxyethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl benzoate (6)

Based on the literature procedure by Fleet et al.¹: (3aR,4S,6S,6aR)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl benzoate (14.8 g, 40.6 mmol) was suspended

in a mixture of glacial acetic acid (225 mL) and water (25 mL). The reaction mixture (suspension turns into a clear solution) was heated at 30 °C (oil bath set to 35 °C) for 20 h, allowed to cool to room temperature and then concentrated under reduced pressure. Residual solvent was then co-eluted with toluene (3 × 100 mL) *in vacuo* to give the title compound **6** as a clumpy white solid (13.0 g, 99%); R_f 0.47 (9:1 CH₂Cl₂:MeOH); $[\alpha]_D^{20}$ -42.7 (c = 1.0 in CHCl₃); $[\alpha]_D^{20}$ -52.3 (c = 1.0 in EtOH) {lit.² ent-**6** $[\alpha]_D^{25}$ +91 (c = 1.2 in EtOH)}; m.p. 166-169 °C (lit.² ent-**6** 174-175 °C); ν_{\max} (neat)/cm⁻¹ 3478 (O-H), 3334 (br, O-H), 3015, 2991, 2941, 2885, 1716 (C=O), 1602, 1456, 1401, 1373, 1320, 1291, 1258, 1248, 1211, 1184, 1164, 1119, 1093, 1064, 1050, 1025, 996, 948, 895, 859, 837, 827, 765, 712, 685, 627, 616, 601, 511; δ_H (500 MHz, CDCl₃) 8.03-7.97 (m, 2H, Ph), 7.60-7.55 (m, 1H, Ph), 7.46-7.41 (m, 2H, Ph), 6.42 (s, 1H, H-4), 4.91 (dd, J = 5.9, 3.3 Hz, 1H, H-6a), 4.89 (d, J = 5.9 Hz, 1H, H-3a), 4.25 (dd, J = 7.1, 3.3 Hz, 1H, H-6), 4.13 (dddd, J = 7.1, 5.0, 3.6, 2.6 Hz, 1H, CHOH), 3.84 (ddd, J = 11.5, 6.3, 3.6 Hz, 1H, CHHOH), 3.76 (ddd, J = 11.5, 6.3, 5.0 Hz, 1H, CHHOH), 2.98 (d, J = 2.6 Hz, 1H, CHOH), 2.37 (t, J = 6.3 Hz, 1H, CH₂OH), 1.51 (s, 3H, C(CH₃)(CH₃)), 1.34 (s, 3H, C(CH₃)(CH₃)); δ_C (125 MHz, CDCl₃) 165.1 (CO), 133.7 (Ph), 129.9 (Ph), 129.5 (Ph), 128.6 (Ph), 113.6 (C(CH₃)₂), 101.1 (C-4), 85.8 (C-3a), 82.6 (C-6), 79.6 (C-6a), 70.9 (CHOH), 63.2 (CH₂OH), 26.1 (C(CH₃)(CH₃)), 24.8 (C(CH₃)(CH₃)); Accurate mass (ES⁺): Found 347.1092 (-4.3 ppm), C₁₆H₂₀O₇Na (M+Na⁺) requires 347.1107;



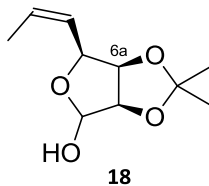
(3aR,4S,6R,6aR)-6-Formyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (7)

(3aR,4S,6S,6aR)-2,2-Dimethyl-6-((*Z*)-prop-1-en-1-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (8)

According to the procedure by Shing et al.³ Sodium periodate (8.00 g, 37.4 mmol) was suspended in water (16.0 mL) and heated with a heat-gun until a clear solution was obtained. Silica (32.0 g) was then added portion-wise with vigorous swirling until a free flowing powder was obtained. The silica was dried *in vacuo* for a few hours and the resulting powder (51.5 g) was stored at room temperature.

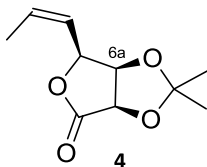
To a solution of (3aR,4S,6S,6aR)-6-((*R*)-1,2-dihydroxyethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (**6**) (1.00 g, 3.08 mmol) in dichloromethane (100 mL), sodium periodate

on silica (8.56 g, 6.16 mmol) was added. The suspension was then stirred at room temperature for 30 min, filtered through a sinter funnel and eluted with a mixture of dichloromethane and diethyl ether (approx. 150 mL of a 1:1 mixture). The solvent was then removed *in vacuo* to give the crude (3aR,4S,6R,6aR)-6-formyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (**7**) as a clear oil (foams when placed under vacuum); δ_{H} (400 MHz, CDCl_3) 9.67 (d, $J = 1.5$ Hz, 1H, CHO), 8.05-7.94 (m, 2H, Ar), 7.65-7.55 (m, 1H, Ar), 7.53-7.39 (m, 2H, Ar), 6.56 (s, 1H), 5.22 (dd, $J = 5.8$, 4.2 Hz, 1H), 4.94 (d, $J = 5.8$ Hz, 1H), 4.56 (dd, $J = 4.2$, 1.5 Hz, 1H), 1.50 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); To a suspension of ethyltriphenylphosphonium iodide (1.67 g, 4.02 mmol) in tetrahydrofuran (30 mL) at room temperature, a solution of KHMDS (4.00 mL, 4.00 mmol, 1 M in tetrahydrofuran) was added. After 2 h 15 min the red/orange suspension was cooled to -78°C and stirred for a further 2 h. A solution of freshly prepared (3aR,4S,6R,6aR)-6-formyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (**7**) (assumed 0.90 g, 3.08 mmol) in tetrahydrofuran (10 mL, 2×5 mL wash) was then added *via* cannula. The light orange suspension was allowed to warm to room temperature overnight (19 h). A saturated aqueous solution of ammonium chloride (100 mL) was then added followed by water (50 mL) and ethyl acetate (150 mL). The aqueous layer was extracted with ethyl acetate (3×150 mL) and the organic layers combined, dried (MgSO_4) and concentrated under reduced pressure. Purification by flash column chromatography (loaded in dichloromethane and eluted with 6:1 \rightarrow 3:1 Hexanes:EtOAc) gave (3aR,4S,6S,6aR)-2,2-dimethyl-6-((*Z*)-prop-1-en-1-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (**8**) (0.636 g, 68%) as a slightly yellow solid; R_f 0.57 (3:1 Hexanes:EtOAc); $[\alpha]_{\text{D}}^{20} +18.6$ ($c = 1.0$ in CHCl_3); m.p. $73-75^\circ\text{C}$; ν_{max} (neat)/ cm^{-1} 3046, 2999, 2939, 2883, 1725 (C=O), 1451, 1381, 1370, 1286, 1255, 1207, 1165, 1138, 1119, 1085, 1062, 1046, 1023, 982, 950, 892, 947, 891, 859, 844, 825, 764, 705, 684, 666, 631, 615, 589, 513; δ_{H} (400 MHz, CDCl_3) 8.06-8.00 (m, 2H, Ph), 7.62-7.55 (m, 1H, Ph), 7.49-7.41 (m, 2H, Ph), 6.41 (s, 1H, H-4), 5.84 (dq, $J = 11.1$, 6.9, 1.2 Hz, 1H, $\text{CH}=\text{CHCH}_3$), 5.67 (ddq, $J = 11.1$, 8.3, 1.8 Hz, 1H, $\text{CH}=\text{CHCH}_3$), 5.00 (dd, $J = 8.3$, 3.6 Hz, 1H, H-6), 4.90 (d, $J = 5.8$ Hz, 1H, H-3a), 4.82 (dd, $J = 5.8$, 3.6, Hz, 1H, H-6a), 1.74 (dd, $J = 6.9$, 1.8 Hz, 3H, $\text{CH}=\text{CHCH}_3$), 1.54 (q, $J = 0.6$ Hz, 3H, $\text{C}(\text{CH}_3)(\text{CH}_3)$), 1.36 (q, $J = 0.6$ Hz, 3H, $\text{C}(\text{CH}_3)(\text{CH}_3)$); δ_{C} (125 MHz, CDCl_3) 164.9 (CO), 133.2 (Ph), 129.6 ($\text{CH}=\text{CHCH}_3$ & Ph), 129.6 (Ph), 128.3 (Ph), 123.9 ($\text{CH}=\text{CHCH}_3$), 112.9 ($\text{C}(\text{CH}_3)_2$), 101.3 (C-4), 85.4 (C-3a), 80.8 (C-6a), 77.7 (C-6), 26.0 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 24.8 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 13.7 ($\text{CH}=\text{CHCH}_3$); Accurate mass (ES^+): Found 327.1199 (-2.8 ppm), $\text{C}_{17}\text{H}_{20}\text{O}_5\text{Na}$ ($\text{M}+\text{Na}^+$) requires 327.1208;



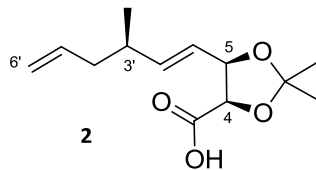
(3aR,6S,6aR)-2,2-Dimethyl-6-((Z)-prop-1-en-1-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (18**)**

To a solution of (3aR,4S,6S,6aR)-2,2-dimethyl-6-((Z)-prop-1-en-1-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl benzoate (**8**) (1.56 g, 5.12 mmol) in tetrahydrofuran (10 mL) at 0 °C, an aqueous solution of sodium hydroxide (0.25 g, 6.25 mmol, 2.5 M) was added followed by 1,4-dioxane (10 mL). The yellow solution was allowed to warm to room temperature and stirred until the starting material was fully converted by TLC (typically within 24-48 h). Water (30 mL) and diethyl ether (30 mL) were then added and the aqueous layer extracted with diethyl ether (5 × 50 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure to give the title compound **18** as a clear colorless oil which solidified to a white solid in the freezer overnight (1.04 g, *quant.*); *R*_f 0.25 (3:1 Hexanes:EtOAc); [α]_D²⁰ +58.3 (c = 1.0 in CHCl₃); m.p. 33-35 °C; ν_{max} (neat)/cm⁻¹ 3393-3338 (m, O-H), 3033, 2983, 2941, 1443, 1378, 1349, 1313, 1283, 1273, 1249, 1208, 1164, 1145, 1093, 1082, 1049, 1007, 977, 958, 942, 824, 911, 891, 851, 820, 771, 731, 692, 677, 638, 565, 516; δ_H (500 MHz, CDCl₃) 5.81 (dq, *J* = 11.0, 6.9, 1.0 Hz, 1H, CH=CHCH₃), 5.62 (ddq, *J* = 11.0, 8.6, 1.8 Hz, 1H, CH=CHCH₃), 5.39 (d, *J* = 2.4 Hz, 1H, H-4), 4.98 (ddt, *J* = 8.6, 3.8, 1.0 Hz, 1H, H-6), 4.70 (dd, *J* = 5.8, 3.8 Hz, 1H, H-6a), 4.63 (d, *J* = 5.8 Hz, 1H, H-3a), 3.02 (d, *J* = 2.4 Hz, 1H, OH), 1.73 (dd, *J* = 6.9, 1.8 Hz, 3H, CH=CHCH₃), 1.47 (s, 3H, C(CH₃)(CH₃)), 1.31 (s, 3H, C(CH₃)(CH₃)); δ_C (125 MHz, CDCl₃) 129.8 (CH=CHCH₃), 124.3 (CH=CHCH₃), 112.6 (C(CH₃)₂), 101.1 (C-4), 86.0 (C-3a), 81.4 (C-6a), 75.5 (C-6), 26.2 (C(CH₃)(CH₃)), 24.9 (C(CH₃)(CH₃)), 13.9 (CH=CHCH₃); Accurate mass (ES⁺): Found 223.0953 (3.1 ppm), C₁₀H₁₆O₄Na (M+Na⁺) requires 223.0946.



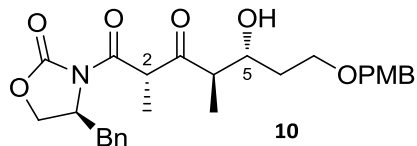
(3aR,6S,6aR)-2,2-Dimethyl-6-((Z)-prop-1-en-1-yl)dihydrofuro[3,4-d][1,3]dioxol-4-one (4)

To a solution of oxalyl chloride (3.40 mL, 40.2 mmol) in dichloromethane (200 mL) at $-78\text{ }^{\circ}\text{C}$, dimethyl sulfoxide (11.0 mL, 155 mmol) was added *via* syringe and the clear reaction mixture stirred for 1 h 20 min. A solution of (3aR,6S,6aR)-2,2-dimethyl-6-((Z)-prop-1-en-1-yl)tetrahydrofuro[3,4-d][1,3]dioxol-4-ol (**18**) (3.78 g, 18.9 mmol) in dichloromethane (50 mL, $2 \times 10\text{ mL}$ wash) at $-78\text{ }^{\circ}\text{C}$ was then added *via* cannula and the reaction mixture stirred for a further 2 h 30 min at $-78\text{ }^{\circ}\text{C}$. Triethylamine (15.0 mL, 108 mmol) was added and the reaction mixture stirred in the presence of the cooling bath for 3 h and then at room temperature for a further 1 h. The reaction mixture was then sequentially washed with aqueous hydrochloric acid (0.5 M, 200 mL) and a 50% saturated aqueous sodium bicarbonate solution (200 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound **4** as a white solid (3.66 g, 98%); R_f 0.22 (3:1 Hexanes:EtOAc); $[\alpha]_{\text{D}}^{20} -66.8$ ($c = 1.0$ in CHCl_3) {lit.⁴ ent-**4** $[\alpha]_{\text{D}} +62.1$ ($c = 0.985$ in CHCl_3)}; m.p. $103\text{--}104\text{ }^{\circ}\text{C}$ (lit.⁴ ent-**4** $107\text{--}108\text{ }^{\circ}\text{C}$); $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3037, 2987, 2932, 1770 (CO), 1664, 1460, 1374, 1355, 1326, 1276, 1258, 1216, 1204, 1186, 1157, 1137, 1100, 1079, 1047, 1002, 982, 960, 930, 909, 894, 869, 806, 790, 771, 747, 737, 685, 636, 584, 569, 550, 506; δ_{H} (500 MHz, CDCl_3) 5.93 (dq, $J = 10.8, 7.0, 1.2$ Hz, 1H, $\text{CH}=\text{CHCH}_3$), 5.66 (ddq, $J = 10.8, 8.7, 1.8$ Hz, 1H, $\text{CH}=\text{CHCH}_3$), 5.28 (ddd, $J = 8.7, 3.6, 1.2$ Hz, 1H, H-6), 4.38 (d, $J = 5.3$ Hz, 1H, H-3a), 4.76 (dd, $J = 5.3, 3.6$ Hz, 1H, H-6a), 1.76 (dd, $J = 7.0, 1.8$ Hz, 3H, $\text{CH}=\text{CHCH}_3$), 1.47 (s, 3H, $\text{C}(\text{CH}_3)(\text{CH}_3)$), 1.38 (s, 3H, $\text{C}(\text{CH}_3)(\text{CH}_3)$); δ_{C} (125 MHz, CDCl_3) 174.2 (CO), 132.5 ($\text{CH}=\text{CHCH}_3$), 122.3 ($\text{CH}=\text{CHCH}_3$), 114.1 ($\text{C}(\text{CH}_3)_2$), 77.8 (C-6a), 76.3 (C-3a), 74.6 (C-6), 26.9 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 25.9 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 13.8 ($\text{CH}=\text{CHCH}_3$); Accurate mass (ES^+): Found 221.0799 (4.1 ppm), $\text{C}_{10}\text{H}_{14}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}^+$) requires 221.0790. Data in accordance with the literature for the enantiomer.⁴



(4*R*,5*R*)-2,2-Dimethyl-5-((*R*,*E*)-3-methylhexa-1,5-dien-1-yl)-1,3-dioxolane-4-carboxylic acid (2**)**

A solution of copper(I) bromide dimethyl sulfide complex (0.311 g, 1.51 mmol) in a mixture of tetrahydrofuran (10.0 mL) and dimethyl sulfide (2.00 mL) was cooled to -50 °C. Upon addition of an allyl magnesium bromide solution (2.20 mL, approx 3.63 mmol, approx 1.65 M in diethyl ether) the clear colorless solution turned dark red. The reaction mixture was then stirred for 15 min at -50 °C before the addition of (3*aR*,6*S*,6*aR*)-2,2-dimethyl-6-((*Z*)-prop-1-en-1-yl)dihydrofuro[3,4-*d*][1,3]-dioxol-4(3*aH*)-one (**4**) (0.2 g, 1 mmol) in tetrahydrofuran (2 mL, 2 × 1 mL wash). The dark black reaction mixture was allowed to warm to -15 °C over a period of 2 h and then quenched with water (10 mL) and a saturated solution of bicarb (2 mL). The organic layer was then extracted with a 50% saturated bicarb solution (2 × 10 mL) and the combined aqueous layers acidified with a pH2 sulfate buffer and extracted with diethyl ether (30 mL) followed by ethyl acetate (10 mL). The organic layers were then combined, dried (MgSO₄) and concentrated under reduced pressure. Purification by flash column chromatography (9:1 CH₂Cl₂:MeOH) gave the title compound **2** as a colorless oil (0.146 g, 60%); *R_f* 0.52 (9:1 CH₂Cl₂:MeOH); [α]_D²⁰ -53.5 (c = 1.0 in CHCl₃); ν_{max}/cm⁻¹ (neat) 3072, 2980, 2962, 2929, 2872, 1727 (C=O), 1663, 1641, 1456, 1438, 1373, 1258, 1215, 1162, 1090, 1037, 992, 972, 912, 875, 841, 833, 788, 714, 666, 626, 511; δ_H (500 MHz, CDCl₃) 10.28 (br s, 1H, CO₂H), 5.83 (ddd, *J* = 15.5, 7.1, 1.0 Hz, 1H, H-2'), 5.72 (ddt, *J* = 16.9, 10.3, 7.0 Hz, 1H, H-5'), 5.36 (ddd, *J* = 15.5, 7.9, 1.3 Hz, 1H, H-1'), 5.00 (ddt, *J* = 16.9, 2.1, 1.3 Hz, 1H, H'-6'), 4.99 (ddt, *J* = 10.3, 2.1, 1.3 Hz, 1H, H''-6'), 4.81 (ddd, *J* = 7.9, 7.3, 1.0 Hz, 1H, H-5), 4.63 (d, *J* = 7.3 Hz, 1H, H-4), 2.25 (dtqd, *J* = 7.1, 7.0, 6.8, 1.3 Hz, 1H, H-3'), 2.10 (dtt, *J* = 13.8, 7.0, 1.3 Hz, 1H, H'-4'), 2.00 (dtt, *J* = 13.8, 7.0, 1.3 Hz, 1H, H''-4'), 1.61 (s, 3H, C(CH₃)), 1.40 (s, 3H, C(CH₃)), 0.97 (d, *J* = 6.8 Hz, 3H, CH₃); δ_C (125 MHz, CDCl₃) 175.0 (CO), 142.5 (C-2'), 136.6 (C-5'), 122.0 (C-1'), 116.3 (C-6'), 111.3 (C(CH₃)₂), 78.8 (C-5), 77.6 (C-4), 40.8 (C-4'), 36.1 (C-3'), 27.0 (C(CH₃)), 25.5 (C(CH₃)), 19.5 (CH₃); Accurate mass (ES⁺): Found 263.1271 (4.6 ppm), C₁₃H₂₀O₄Na (M+Na⁺) requires 263.1259.

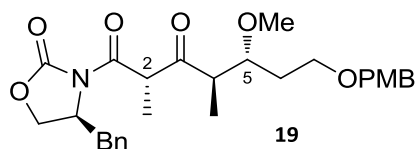


(2*S*,4*R*,5*R*)-1-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2,4-dimethylheptane-1,3-dione (10**)**

According to modified procedure by Evans et al.⁵: (*S*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-2-methylpentane-1,3-dione (7.50 g, 25.9 mmol) was dissolved in diethyl ether (150 mL) and cooled to 0 °C. (*c*-Hex)₂BCl (7.00 mL, 31.9 mmol) was added *via* syringe. *N,N*-Dimethylethylamine (3.80 mL, 35.1 mmol) was then added and the yellow suspension stirred for 1 h 40 min in the presence of the ice/water bath. The bright yellow suspension was cooled to -78 °C and a solution of 3-((4-methoxybenzyl)oxy)propanal (6.10 g, 31.4 mmol) in diethyl ether (20 mL, 2 × 10 mL wash) was added *via* cannula. The reaction mixture was stirred for 3 h then warmed to 0 °C and stirred for a further 15 min. pH 7.7 buffer (25 mL) was added followed by methanol (75 mL) and a mixture of H₂O₂ (35% in water, 25 mL) and methanol (50 mL). The slightly yellow clear solution was stirred at 0 °C for 40 min. A saturated aqueous solution of ammonium chloride (250 mL) was then added followed by ethyl acetate (200 mL). The aqueous layer was extracted with ethyl acetate (200 mL) and the organic layers combined, dried (MgSO₄) and concentrated under reduced pressure. Purification by flash column chromatography (4:1→2:1→1:1 Hexanes:EtOAc) gave the title compound **10** as a clear colorless oil (d.r 5:1ⁱⁱ, 10.1 g, 81%); R_f 0.41 (1:1 Hexanes:EtOAc); [α]_D²⁰ +62.4 (c = 1.0 in CHCl₃); ν_{max}/cm⁻¹ (thin film, CH₂Cl₂) 3495-3461 (m, O-H), 2980-2830 (m, C-H), 1776 (C=O), 1716 (C=O), 1693 (C=O), 1612, 1513, 1455, 1386, 1357, 1302, 1245, 1212, 1175, 1114, 1084, 1031, 1005, 984, 821, 755, 733, 701, 637, 569; δ_H (500 MHz, CDCl₃) 7.36-7.31 (m, 2H, Ar), 7.30-7.27 (m, 1H, Ar), 7.25-7.17 (m, 4H, Ar), 6.89-6.83 (m, 2H, Ar), 4.88 (q, *J* = 7.3 Hz, 1H, H-2), 4.73 (ddt, *J* = 9.6, 7.8, 3.1 Hz, 1H, CH₂CHN), 4.44 (d, *J* = 11.5 Hz, 1H, OCHHAr), 4.42 (d, *J* = 11.5 Hz, 1H, OCHHAr), 4.21 (dd, *J* = 9.1, 7.8 Hz, 1H, CHCHHO), 4.16 (dd, *J* = 9.1, 3.1 Hz, 1H, CHCHHO), 3.95 (ddt, *J* = 9.7, 7.1, 2.8 Hz, 1H, H-5), 3.80 (s, 3H, OCH₃), 3.70 (ddd, *J* = 9.3, 6.0, 4.5 Hz, 1H, H^β-7), 3.62 (ddd, *J* = 9.3, 8.2, 4.2 Hz, 1H, H^γ-7), 3.30 (d, *J* = 2.8 Hz, 1H, OH), 3.29 (dd, *J* = 13.4, 3.1 Hz, 1H, CHCHHPh), 2.84 (p, *J* = 7.1 Hz, 1H, H-4), 2.77 (dd, *J* = 13.4, 9.6 Hz, 1H, CHCHHPh), 1.81 (dddd, *J* = 14.4, 6.0, 4.2, 2.8 Hz, 1H, H^β-6), 1.69 (dddd, *J* = 14.4, 9.7, 8.2, 4.5 Hz, 1H, H^γ-6),

ⁱⁱ Reported NMR values are of the major diastereoisomer

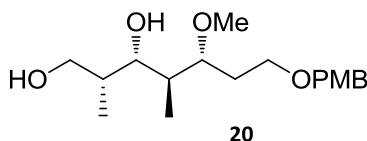
1.42 (d, $J = 7.3$ Hz, 3H, CH₃), 1.16 (d, $J = 7.1$ Hz, 3H, CH₃); δ_c (125 MHz, CDCl₃) 211.0 (CO), 170.9 (CO), 159.5 (CO), 153.6 (Ar), 135.3 (Ar), 130.0 (Ar), 129.6 (Ar), 129.5 (Ar), 129.1 (Ar), 127.5 (Ar), 114.0 (Ar), 73.5 (C-5), 73.2 (OCH₂Ar), 68.9 (C-7), 66.5 (CHCH₂O), 55.5 (OCH₃ or CH₂CHN), 55.4 (OCH₃ or CH₂CHN), 52.8 (C-2), 50.1 (C-4), 38.1 (CHCH₂Ph), 33.5 (C-6), 13.6 (CH₃), 12.9 (CH₃); Accurate mass (ES⁺): Found 506.2132 (-4.5 ppm), C₂₇H₃₃NO₇Na (M+Na⁺) requires 506.2155.



(2*S*,4*R*,5*R*)-1-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-methoxy-7-((4-methoxybenzyl)oxy)-2,4-dimethylheptane-1,3-dione (19)

To a solution of (2*S*,4*R*,5*R*)-1-((*S*)-4-benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-7-((4-methoxybenzyl)oxy)-2,4-dimethylheptane-1,3-dione (**10**) (4.09 g, 8.47 mmol) in dichloromethane (60 mL), proton sponge (3.70 g, 17.3 mmol) was added followed by trimethyloxonium tetrafluoroborate (2.51 g, 17.0 mmol). The orange suspension was stirred at room temperature overnight and then diluted with a mixture of hexanes and ethyl acetate (1:1, 200 mL). The resulting suspension was filtered through a plug of celite eluting with a mixture hexanes and ethyl acetate (1:1, approx. 400 mL). The solvent was then removed *in vacuo* and the crude orange oil purified by flash column chromatography (5:1→1:1 Hexanes:EtOAc) to give the title compound **19** as a clear colorless oil (d.r 6:1, 3.07 g, 73%); A small amount of the product was purified by HPLC (continuous gradient 1:1→0:1 Hexanes:Ethyl acetate) for characterization; R_f 0.62 (1:1 Hexanes:EtOAc); $[\alpha]_D^{20} +58.0$ ($c = 1.0$ in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (thin film, CH₂Cl₂) 2992, 2938, 2862, 2826, 1776 (C=O), 1715 (C=O), 1694 (C=O), 1612, 1513, 1454, 1386, 1356, 1301, 1244, 1211, 1175, 1085, 1032, 1000, 956, 919, 820, 761, 735, 702, 637, 594, 570; δ_H (400 MHz, CDCl₃) 7.28-7.23 (m, 2H, Ar), 7.22-7.16 (m, 3H, Ar), 7.14-7.10 (m, 2H, Ar), 6.82-6.77 (m, 2H, Ar), 4.76 (q, $J = 7.2$ Hz, 1H, H-2), 4.65 (dddd, $J = 9.7, 7.8, 3.4$ Hz, 1H, CH₂CHN), 4.37 (d, $J = 11.6$ Hz, 1H, OCHHAr), 4.34 (d, $J = 11.6$ Hz, 1H, OCHHAr), 4.13 (dd, $J = 9.1, 7.8$ Hz, 1H, CHCHHO), 4.08 (dd, $J = 9.1, 2.8$ Hz, 1H, CHCHHO), 3.72 (s, 3H, OCH₃), 3.49-3.44 (m, 3H, H-5 & H-7), 3.22 (dd, $J = 13.4, 3.4$ Hz, 1H, CHCHHPh), 3.15 (s, 3H, OCH₃), 2.90 (dq, $J = 8.4, 6.9$ Hz, 1H, H-4), 2.69 (dd, $J = 13.4, 9.7$ Hz, 1H, CHCHHPh), 1.85 (dtd, $J = 14.5, 7.2, 3.2$ Hz, 1H, H^p-6), 1.56 (ddt, $J = 14.5, 7.5, 5.8$ Hz, 1H, H^p-6), 1.38 (d, $J = 7.2$ Hz, 3H, CHCH₃), 1.02 (d, $J = 6.9$ Hz, 3H, CHCH₃); δ_c (100 MHz, CDCl₃) 210.2 (CO), 171.0 (CO), 159.3 (CO), 153.5 (Ar), 135.3 (Ar), 130.7 (Ar), 129.6 (Ar), 129.3 (Ar), 129.1 (Ar), 127.5 (Ar), 113.9 (Ar),

80.5 (C-5), 72.7 (OCH₂Ar), 66.5 (C-7 or CHCH₂O), 66.0 (C-7 or CHCH₂O), 58.6 (OCH₃), 55.5 (OCH₃), 55.4 (CH₂CHN), 53.1 (C-2), 48.7 (C-4), 38.1 (CHCH₂Ph), 31.2 (C-6), 13.4 (CHCH₃), 12.7 (CHCH₃); Accurate mass (ES⁺): Found 520.2286 (-4.8 ppm), C₂₈H₃₅NO₇Na (M+Na⁺) requires 520.2311.



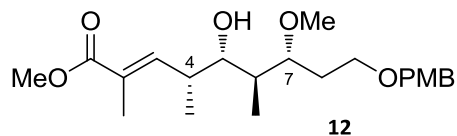
(2*R*,3*S*,4*S*,5*R*)-5-Methoxy-7-((4-methoxybenzyl)oxy)-2,4-dimethylheptane-1,3-diol (20**)**

(2*S*,4*R*,5*R*)-1-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-methoxy-7-((4-methoxybenzyl)oxy)-2,4-dimethylheptane-1,3-dione (**19**) (0.362 g, 0.72 mmol) was dissolved in diethyl ether (25 mL). Ethanol (0.14 mL, 2.40 mmol) was added and the clear solution cooled to -26 °C. A solution of lithium borohydride in tetrahydrofuran (2 M, 1.70 mL, 3.40 mmol) was then added and the solution was allowed to warm to -15 °C over a period of 20 min.ⁱⁱⁱ Water (10 mL) was then carefully added the resulting biphasic solution stirred at room temperature for 10 min. An aqueous solution of sodium hydroxide (3 M, 1.00 mL, 3.00 mmol) was then added and the biphasic solution vigorously stirred for a further 15 min. The aqueous layer was extracted with diethyl ether (4 × 30 mL) and the organic layers combined, dried (MgSO₄) and concentrated under reduced pressure. Purification by flash column chromatography (3:1→1:1→1:3→1:6 Hexanes:Ethyl acetate) gave the title compound **20** as a clear colorless oil (d.r.^{iv} 12:1, 0.207 g, 88%); A small amount of the product was purified by HPLC (continuous gradient 1:3→0:1 Hexanes:Ethyl acetate) for characterization; R_f 0.34 (3:1 EtOAc:Hexanes); [α]_D²⁰ -7.8 (c = 0.17 in CHCl₃); ν_{max}/cm⁻¹ (thin film, CHCl₃) 3404 (br, O-H), 2959-2871 (m, C-H), 1612, 1586, 1556, 1513, 1463, 1441, 1413, 1378, 1358, 1302, 1247, 1174, 1155, 1086, 1034, 981, 925, 885, 849, 820, 757, 706, 631, 585, 511; δ_H (400 MHz, CD₃OD) 7.29-7.23 (m, 2H, Ar), 6.91-6.85 (m, 2H, Ar), 4.46 (d, *J* = 11.3 Hz, 1H, OCHHAr), 4.39 (d, *J* = 11.3 Hz, 1H, OCHHAr), 3.77 (s, 3H, OCH₃), 3.69 (ddd, *J* = 10.3, 3.8, 2.2 Hz, 1H, H-5), 3.61-3.51 (m, 4H, H-3 & H-7 & H^β-1), 3.47 (dd, *J* = 10.5, 6.1 Hz, 1H, H^β-1), 3.29 (s, 3H, OCH₃), 2.06 (dq, *J* = 10.6, 6.9, 3.8 Hz, 1H, H-4), 1.87-1.77 (m, 2H, H-2 & H^β-6), 1.55 (ddt, *J* = 14.2, 10.4, 5.3 Hz, 1H, H^β-6), 0.84

ⁱⁱⁱ The solution which was cloudy at first then turned clear with a small sticky white precipitate. Manual swirling was occasionally carried out to aid the mechanical stirring.

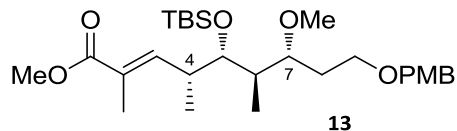
^{iv} Minor diastereoisomer originating from the minor product of the previous aldol reaction

(d, $J = 6.9$ Hz, 3H, CH₃), 0.74 (d, $J = 6.9$ Hz, 3H, CH₃); δ_c (100 MHz, CD₃OD) 160.9 (Ar), 131.6 (Ar), 130.7 (Ar), 114.7 (Ar), 80.0 (C-5), 73.7 (OCH₂Ar), 73.0 (C-3), 68.4 (C-7), 66.6 (C-1), 57.2 (OCH₃), 55.7 (OCH₃), 38.6 (C-2), 38.1 (C-4), 30.2 (C-6), 10.2 (CH₃), 9.1 (CH₃); Accurate mass (ES⁺): Found 349.1976 (3.4 ppm), C₁₈H₃₀O₅Na (M+Na⁺) requires 349.1991.



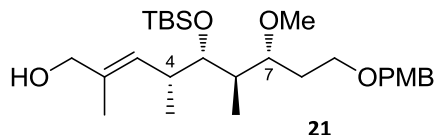
(4*R*,5*S*,6*S*,7*R*,*E*)-Methyl 5-hydroxy-7-methoxy-9-((4-methoxybenzyl)oxy)-2,4,6-trimethylnon-2-enoate (12**)**

A mixture of (2*R*,3*S*,4*S*,5*R*)-5-methoxy-7-((4-methoxybenzyl)oxy)-2,4-dimethylheptane-1,3-diol (**20**) (0.45 g, 1.38 mmol), (diacetoxyiodo)benzene (0.511 g, 1.59 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (0.022 g, 0.138 mmol) in dichloromethane (25 mL) was stirred at room temperature for 7 h. (Carbethoxymethylidene)triphenylphosphorane (1.45 g, 4.16 mmol) was then added and the reaction mixture (clear yellow solution) was stirred at room temperature for a further 18 h. The reaction mixture was then concentrated under reduced pressure and the residue purified by flash column chromatography (loaded in neat dichloromethane and eluted with 3:1 Hexanes:EtOAc) to give the title compound **12** as a colorless oil (0.436 g, 80%); R_f 0.56 (1:1 Hexanes:EtOAc); $[\alpha]_D^{20}$ -8.5 ($c = 1.0$ in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ (thin film, CH₂Cl₂) 3473 (O-H), 2966-2835 (C-H), 1709 (C=O), 1647, 1613, 1513, 1457, 1437, 1301, 1245, 1173, 1085, 1034, 987, 964, 821, 752, 733, 702, 563, 515; δ_H (500 MHz, CDCl₃) 7.26-7.22 (m, 2H, Ar), 6.89-6.86 (m, 2H, Ar), 6.84 (dq, $J = 9.8, 1.5$ Hz, 1H, H-3), 4.45 (d, $J = 11.5$ Hz, 1H, OCHHAr), 4.42 (d, $J = 11.5$ Hz, 1H, OCHHAr), 3.80 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.57-3.51 (m, 2H, H-9), 3.46-3.42 (m, 1H, H-7), 3.41 (dd, $J = 8.4, 3.6$ Hz, 1H, H-5), 3.31 (s, 3H, OCH₃), 2.69 (dq, $J = 9.8, 6.8, 3.6$ Hz, 1H, H-4), 1.98-1.88 (m, 2H, H⁸ & H-6), 1.85 (d, $J = 1.5$ Hz, 3H, C=CCH₃), 1.69 (dddd, $J = 14.8, 6.5, 5.5, 5.0$ Hz, 1H, H⁸), 1.01 (d, $J = 6.8$ Hz, 3H, CH₃), 0.85 (d, $J = 6.9$ Hz, 3H, CH₃); δ_c (125 MHz, CDCl₃) 168.9 (CO), 159.4, 146.0 (C-3), 130.5, 129.4 (Ar), 126.4, 113.9 (Ar), 82.1 (C-7), 77.1 (C-5), 72.9 (OCH₂Ar), 67.0 (C-9), 57.4 (OCH₃), 55.4 (OCH₃), 51.8 (OCH₃), 38.6 (C-6), 35.8 (C-4), 31.1 (C-8), 12.7 (CH₃), 12.6 (CH₃), 12.4 (CH₃); Accurate mass (ES⁺): Found 417.2245 (-1.9 ppm), C₂₂H₃₄O₆Na (M+Na⁺) requires 418.2253.



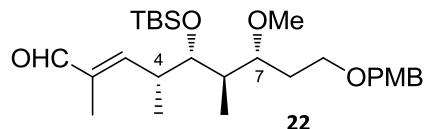
(4*R*,5*S*,6*R*,7*R*,*E*)-Methyl 5-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-9-((4-methoxybenzyl)oxy)-2,4,6-trimethylnon-2-enoate (13**)**

To a solution of (4*R*,5*S*,6*S*,7*R*,*E*)-methyl 5-hydroxy-7-methoxy-9-((4-methoxybenzyl)oxy)-2,4,6-trimethylnon-2-enoate (**12**) (0.427 g, 1.08 mmol) in dichloromethane (10 mL) at 0 °C, 2,6-lutidine (0.35 mL, 3.02 mmol) was added *via* syringe followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.35 mL, 1.52 mmol). The clear reaction mixture was stirred in the presence of the cooling bath for 3 h. A 50% saturated aqueous ammonium chloride solution (20 mL) was then added followed by dichloromethane (20 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the organic layers combined, dried (Na₂SO₄) and concentrated under reduced pressure. Purification by flash column chromatography (3:1, Hexanes:EtOAc) gave the title compound **13** as a clear colorless oil (0.53 g, 96%); *R_f* 0.34 (6:1 Hexanes:EtOAc); [α]_D²⁰ +13.8 (c = 1.0 in CHCl₃); ν_{max}/cm⁻¹ (thin film, CH₂Cl₂) 2953, 2929, 2888, 2865, 1714 (C=O), 1649, 1614, 1513, 1463, 1436, 1293, 1246, 1171, 1087, 1034, 1005, 834, 773, 750, 670, 570, 514; δ_H (400 MHz, CDCl₃) 7.29-7.19 (m, 2H, Ar), 6.89-6.83 (m, 2H, Ar), 6.70 (dq, *J* = 10.2, 1.5 Hz, 1H, H-3), 4.44 (d, *J* = 11.5 Hz, 1H, OCHHAr), 4.40 (d, *J* = 11.5 Hz, 1H, OCHHAr), 3.80 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃), 3.68 (dd, *J* = 6.0, 4.9 Hz, 1H, H-5), 3.55-3.51 (m, 2H, H-9), 3.32-3.27 (m, 1H, H-7), 3.24 (s, 3H, OCH₃), 2.70 (dq, *J* = 10.2, 6.7, 6.0 Hz, 1H, H-4), 1.95-1.84 (m, 2H, H-6 & H^β-8), 1.83 (d, *J* = 1.5 Hz, 3H, C=CCH₃), 1.68-1.57 (m, 1H, H^γ-8), 0.99 (d, *J* = 6.7 Hz, 3H, CH₃), 0.91 (s, 9H, C(CH₃)₃), 0.85 (d, *J* = 7.4 Hz, 3H, CH₃), 0.05 (s, 3H, SiCH₃), 0.03 (s, 3H, SiCH₃); δ_C (125 MHz, CDCl₃) 168.9 (CO), 159.2, 146.6 (C-3), 130.9, 129.3 (Ar), 125.8, 113.8 (Ar), 78.8 (C-7), 76.2 (C-5), 72.8 (OCH₂Ar), 66.7 (C-9), 56.6 (OCH₃), 55.4 (OCH₃), 51.8 (OCH₃), 41.1 (C-6), 36.6 (C-4), 30.5 (C-8), 26.3 (C(CH₃)₃), 18.5 (C(CH₃)₃), 16.0 (CH₃), 12.5 (C=CCH₃), 11.5 (CH₃), -3.7 (Si(CH₃)), -4.0 (Si(CH₃)); Accurate mass (ES⁺): Found 531.3107 (-2.1 ppm), C₂₈H₄₈O₆NaSi (M+Na⁺) requires 531.3118.



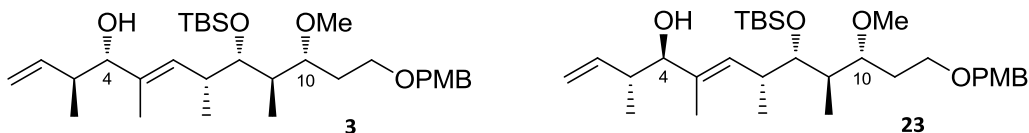
(4*R*,5*S*,6*R*,7*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-9-((4-methoxybenzyl)oxy)-2,4,6-trimethylnon-2-en-1-ol (21**)**

To a solution of (4*R*,5*S*,6*R*,7*R*,*E*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-9-((4-methoxybenzyl)oxy)-2,4,6-trimethylnon-2-enoate (**13**) (0.44 g, 0.87 mmol) in tetrahydrofuran (10 mL) at 0 °C, lithium aluminum hydride powder (0.09 g, 2.58 mmol) was added and the suspension stirred in the presence of the cooling bath for 1 h. The reaction mixture was then quenched with a few drops of water and saturated ammonium chloride. A saturated solution of Rochelle's salt (30 mL) was then added followed by ethyl acetate (30 mL) and the biphasic mixture was stirred for 5 h. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the organic layers combined, dried (MgSO₄) and concentrated under reduced pressure to give the title compound **21** as a clear colorless oil (0.418 g, 99%); *R_f* 0.26 (3:1 Hexanes:EtOAc); [α]_D²⁰ +10.8 (*c* = 1.0 in CHCl₃); *v*_{max}/cm⁻¹ (thin film, CH₂Cl₂) 3441 (O-H), 2955-2889 (C-H), 1613, 1587, 1513, 1473, 1463, 1394, 1361, 1302, 1247, 1173, 1086, 1034, 1005, 869, 833, 807, 772, 737, 674, 572; δ_H (500 MHz, CDCl₃) 7.23-7.19 (m, 2H, Ar), 6.85-6.80 (m, 2H, Ar), 5.29 (dq, *J* = 9.8, 1.3 Hz, 1H, H-3), 4.40 (d, *J* = 11.5 Hz, 1H, OCHHAr), 4.37 (d, *J* = 11.5 Hz, 1H, OCHHAr), 3.93-3.88 (m, 2H, H-1), 3.75 (s, 3H, OCH₃), 3.53 (dd, *J* = 6.2, 5.0 Hz, 1H, H-5), 3.51-3.47 (m, 2H, H-9), 3.40 (ddd, *J* = 9.0, 6.1, 2.7 Hz, 1H, H-7), 3.20 (s, 3H, OCH₃), 2.55 (dq, *J* = 9.8, 6.7, 6.2 Hz, 1H, H-4), 1.90 (dq, *J* = 6.1, 7.1, 5.0 Hz, 1H, H-6), 1.82 (dtd, *J* = 14.4, 7.6, 2.7 Hz, 1H, H^β-8), 1.78-1.73 (m, 1H), 1.60 (d, *J* = 1.3 Hz, 3H, C=CCH₃), 1.54 (ddt, *J* = 14.4, 9.0, 5.7 Hz, 1H, H^α-8), 0.91 (d, *J* = 6.7 Hz, 3H, CH₃), 0.87 (s, 9H, C(CH₃)₃), 0.81 (d, *J* = 7.1 Hz, 3H, CH₃), 0.00 (s, 6H, Si(CH₃)₂); δ_C (125 MHz, CDCl₃) 159.2, 133.1, 130.8, 130.7 (C-3), 129.4 (Ar), 113.8 (Ar), 78.4 (C-7), 77.4 (C-5), 72.7 (OCH₂Ar), 69.0 (C-1), 66.9 (C-9), 56.6 (OCH₃), 55.4 (OCH₃), 40.9 (C-6), 35.4 (C-4), 30.8 (C-8), 26.3 (C(CH₃)₃), 18.5 (C(CH₃)₃), 17.0 (CH₃), 13.9 (C=CCH₃), 11.3 (CH₃), -3.7 (Si(CH₃)₂), -3.7 (Si(CH₃)₂); Accurate mass (ES⁺): Found 503.3166 (-0.6 ppm), C₂₇H₄₈O₅NaSi (M+Na⁺) requires 503.3169.



(4*R*,5*S*,6*R*,7*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-9-((4-methoxybenzyl)oxy)-2,4,6-trimethylnon-2-enal (22**)**

A solution of (4*R*,5*S*,6*R*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-9-((4-methoxybenzyl)oxy)-2,4,6-trimethylnon-2-en-1-ol (**21**) (0.179 g, 0.372 mmol) in dichloromethane (6 mL) was cooled to 0 °C. Dess-Martin periodinane (0.190 g, 0.448 mmol) was added and the white milky suspension stirred in the presence of the cooling bath overnight. A solution of sodium thiosulfate (1.00 g) in saturated aqueous sodium bicarbonate (10 mL) was then added followed by water (5 mL) and diethyl ether (20 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL) and the organic layers combined, dried (MgSO₄) and concentrated under reduced pressure to give the title compound **22** as a slightly yellow oil (0.19 g, *quant.*); *R*_f 0.28 (6:1 Hexanes:EtOAc); [α]_D²⁰ +1.8 (*c* = 1.0 in CHCl₃); ν_{max}/cm⁻¹ (thin film, CH₂Cl₂) 2955-2856 (C-H), 1687 (C=O), 1641, 1613, 1513, 1463, 1361, 1302, 1247, 1209, 1173, 1087, 1034, 833, 772, 731, 674, 570, 512; δ_H (500 MHz, CDCl₃) 9.39 (s, 1H, CHO), 7.26-7.22 (m, 2H, Ar), 6.89-6.84 (m, 2H, Ar), 6.44 (dq, *J* = 10.0, 1.3 Hz, 1H, H-3), 4.43 (d, *J* = 11.5 Hz, 1H, OCHHAr), 4.40 (d, *J* = 11.5 Hz, 1H, OCHHAr), 3.80 (s, 3H, OCH₃), 3.74 (dd, *J* = 5.6, 4.9 Hz, 1H, H-5), 3.53-3.50 (m, 2H, H-9), 3.29 (ddd, *J* = 7.5, 6.7, 3.0 Hz, 1H, H-7), 3.22 (s, 3H, OCH₃), 2.93 (dq, *J* = 10.0, 6.7, 5.6 Hz, 1H, H-4), 1.94 (qdd, *J* = 7.2, 6.7, 4.9 Hz, 1H, H-6), 1.88 (dtd, *J* = 14.4, 7.5, 3.0 Hz, 1H, H^β-8), 1.75 (d, *J* = 1.3 Hz, 3H, C=CCH₃), 1.63 (dddd, *J* = 14.4, 7.5, 6.5, 5.5 Hz, 1H, H^γ-8), 1.06 (d, *J* = 6.7 Hz, 3H, CH₃), 0.92 (s, 9H, C(CH₃)₃), 0.89 (d, *J* = 7.2 Hz, 3H, CH₃), 0.05 (s, 6H, Si(CH₃)₂); δ_C (125 MHz, CDCl₃) 195.7, 195.6, 159.3, 158.8, 137.4, 130.8, 129.4, 113.9, 78.9, 75.9, 72.9, 66.5, 56.5, 55.4, 41.3, 36.8, 30.6, 26.4, 26.3, 18.5, 15.8, 11.7, 9.4, -3.7, -3.8; Accurate mass (ES⁺): Found 501.2991 (-4.2 ppm), C₂₇H₄₆O₅NaSi (M+Na⁺) requires 501.3012.

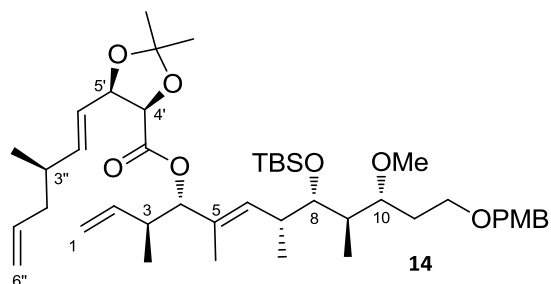


(3*S*,4*S*,7*R*,8*S*,9*R*,10*R*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-10-methoxy-12-((4-methoxybenzyl)oxy)-3,5,7,9-tetramethyldodeca-1,5-dien-4-ol (3**)**

(3*R*,4*R*,7*R*,8*S*,9*R*,10*R*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-10-methoxy-12-((4-methoxybenzyl)oxy)-3,5,7,9-tetramethyldodeca-1,5-dien-4-ol (23**)**

To a solution of aldehyde **22** (0.10 g, 0.209 mmol) in dichloromethane (4 mL), (*R,R*)-trans *EZ*-crotylMix (0.7 g) was added and the suspension stirred at room temperature for 40 h. The reaction mixture was then diluted with diethyl ether (50 mL) and 50% saturated aqueous hydrochloric acid solution (50 mL). The aqueous layer was then extracted with diethyl ether (3 × 350 mL) and the organic layers combined, dried (MgSO₄) and flushed through a short plug of celite eluting with diethyl ether. The solvent was removed *in vacuo* and the residual clear oil was purification by flash column chromatography (6:1→3:1→1:1 Hexanes:EtOAc) to give the title compound (**3**) as a clear oil (51 mg, 51%); *R_f* 0.47 (3:1 Hexanes:EtOAc); [α]_D²⁰ +1.3 (c = 2.0 in CHCl₃); ν_{max}/cm⁻¹ (thin film, CH₂Cl₂) 3461 (O-H), 2957, 2929, 2897, 2884, 2856, 1634, 1613, 1587, 1513, 1475, 1463, 1362, 1302, 1247, 1173, 1087, 1035, 1005, 939, 911, 833, 804, 772, 736, 704, 675, 570, 514; δ_H (500 MHz, CDCl₃) 7.28-7.23 (m, 2H, Ar), 6.89-6.84 (m, 2H, Ar), 5.74 (ddd, *J* = 17.2, 10.4, 8.1 Hz, 1H, H-2), 5.38 (dq, *J* = 9.9, 1.3, 0.7 Hz, 1H, H-6), 5.14 (ddd, *J* = 17.2, 1.8, 1.0 Hz, 1H, H¹-1), 5.13 (ddd, *J* = 10.4, 1.8, 0.6 Hz, 1H, H²-1), 4.44 (d, *J* = 11.5 Hz, 1H, OCHHAr), 4.41 (d, *J* = 11.5 Hz, 1H, OCHHAr), 3.80 (s, 3H, OCH₃), 3.63 (d, *J* = 8.1 Hz, 1H, H-4), 3.57-3.51 (m, 3H, H-8 & H-12), 3.42 (ddd, *J* = 8.5, 6.8, 2.9 Hz, 1H, H-10), 3.27 (s, 3H, OCH₃), 2.65 (dq, *J* = 9.9, 6.8, 5.7 Hz, 1H, H-7), 2.38-2.31 (m, 1H, H-3), 1.94-1.84 (m, 2H, H-9 & H²-11), 1.77 (br s, 1H, OH), 1.64-1.57 (m, 1H, H²-11), 1.61 (d, *J* = 1.3 Hz, 3H, C=CCH₃), 0.96 (d, *J* = 6.8 Hz, 3H, CH₃), 0.91 (d, *J* = 6.8 Hz, 3H, CH₃), 0.91 (s, 9H, C(CH₃)₃), 0.85 (d, *J* = 7.2 Hz, 3H, CH₃), 0.06 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃); δ_C (125 MHz, CDCl₃) 159.2 (Ar), 141.0 (C-2), 133.5, 133.2 (C-6), 130.9, 129.4 (Ar), 116.4 (C-1), 113.9 (Ar), 81.2 (C-4), 78.7 (C-10), 77.4, 72.8 (OCH₂Ar), 66.9, 56.8 (OCH₃), 55.4 (OCH₃), 42.2 (C-3), 41.2 (C-9), 35.7 (C-7), 30.8 (C-11), 26.3 (C(CH₃)₃), 18.5 (C(CH₃)₃), 17.1 (CH₃), 17.1 (CH₃), 11.9 (CH₃), 11.8 (CH₃), -3.6 (Si(CH₃)), -3.7 (Si(CH₃)); Accurate mass (ES⁺): Found 557.3641 (0.5 ppm), C₃₁H₅₄O₅NaSi (M+Na⁺) requires 557.3638. Further elution of the column gave (3*R*,4*R*,7*R*,8*S*,9*R*,10*R*,*E*)-8-((*tert*-butyldimethylsilyl)oxy)-10-methoxy-12-((4-methoxybenzyl)oxy)-3,5,7,9-tetramethyldodeca-1,5-dien-

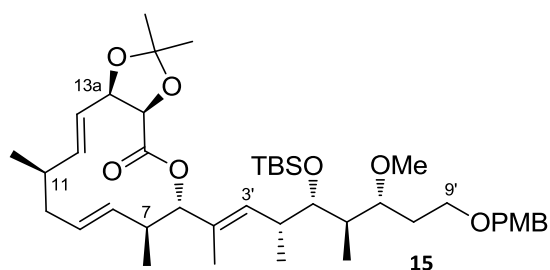
4-ol (**23**) as a clear colorless oil (11 mg, 100%); R_f 0.37 (3:1 Hexanes:EtOAc); $[\alpha]_D^{20} +4.8$ ($c = 0.34$ in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film, CDCl_3) 3469 (O-H), 2957, 2930, 2901, 2881, 2856, 1638, 1613, 1587, 1513, 1475, 1462, 1393, 1362, 1302, 1249, 1201, 1173, 1091, 1036, 1005, 935, 912, 858, 835, 774, 677, 637, 563, 510; δ_{H} (400 MHz, CDCl_3) 7.27-7.23 (m, 2H, Ar), 6.89-6.84 (m, 2H, Ar), 5.74 (ddd, $J = 17.3, 10.2, 8.3$ Hz, 1H, H-2), 5.32-5.27 (m, 1H, H-6), 5.15 (ddd, $J = 17.2, 1.9, 1.0$ Hz, 1H, H[']-1), 5.12 (ddd, $J = 10.2, 1.9, 0.6$ Hz, 1H, H^{''}-1), 4.44 (d, $J = 11.5$, 1H, OCHHAr), 4.40 (d, $J = 11.5$ Hz, 1H, OCHHAr), 3.80 (s, 3H, OCH₃), 3.63-3.50 (m, 4H, H-8 & H-10 & H-12), 3.49-3.41 (m, 1H, H-4), 3.26 (s, 3H, OCH₃), 2.68-2.57 (m, 1H, H-7), 2.35-2.23 (m, 1H, H-3), 2.00-1.81 (m, 2H, H[']-11 & H-9), 1.72-1.53 (m, 2H, H^{''}-11 & OH), 1.60 (d, $J = 1.4$ Hz, 3H, C=CCH₃), 0.93 (d, $J = 6.7$ Hz, 3H, CH₃), 0.91 (s, 9H, C(CH₃)₃), 0.85 (d, $J = 7.3$ Hz, 3H, CH₃), 0.85 (d, $J = 6.8$ Hz, 3H, CH₃), 0.06 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃); δ_{C} (100 MHz, CDCl_3) 159.2, 141.7 (C-2), 133.7 (C-6), 133.2, 130.8, 129.5 (Ar), 116.3 (C-1), 113.8 (Ar), 81.9, 78.5, 77.4, 72.8 (OCH₂Ar), 66.9, 56.7 (OCH₃), 55.4 (OCH₃), 42.3 (C-3), 41.0, 35.4 (C-7), 30.8 (C-11), 26.4 (C(CH₃)₃), 18.6, 17.0 (CH₃), 16.9 (CH₃), 11.4 (CH₃), 10.9 (CH₃), -3.6 (Si(CH₃)₂).



(4*R*,5*R*)-(3*S*,4*S*,7*R*,8*S*,9*R*,10*R*,*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-10-methoxy-12-((4-methoxybenzyl)oxy)-3,5,7,9-tetramethyldodeca-1,5-dien-4-yl 2,2-dimethyl-5-((*R*,*E*)-3-methylhexa-1,5-dien-1-yl)-1,3-dioxolane-4-carboxylate (14**)**

To a mixture of acid **2** (58.0 mg, 0.241 mmol), 4-(dimethylamino)pyridine (66.0 mg, 0.54 mmol) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (41.0 mg, 0.214 mmol) a solution of alcohol **3** (57.0 mg, 0.107 mmol) in dichloromethane (1 mL, 2 × 0.5 mL wash) was added *via* syringe. The clear colorless solution was sparged with nitrogen for a few minute and then stirred at room temperature overnight (14 h). A 50 % saturated solution of ammonium chloride (10 mL) was added to the yellow solution followed by dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography

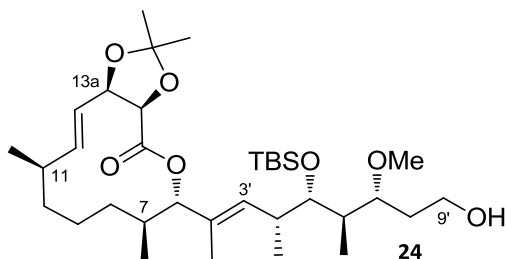
(9:1 Hexanes:EtOAc) gave the title compound **14** as a clear colorless oil (80 mg, 99%); R_f 0.41 (6:1 Hexanes:EtOAc); $[\alpha]_D^{20}$ -17.7 ($c = 0.83$ in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film, CH_2Cl_2) 2956-2856 (C-H), 1757 (C=O), 1731 (C=O), 1642, 1614, 1513, 1462, 1380, 1361, 1302, 1247, 1218, 1182, 1172, 1086, 1036, 1004, 973, 914, 877, 834, 773, 737, 704, 674, 511; δ_{H} (500 MHz, CDCl_3) 7.27-7.23 (m, 2H, Ar), 6.88-6.84 (m, 2H, Ar), 5.84-5.67 (m, 3H, H-2 & H-5'' & H-2''), 5.44 (dq, $J = 9.8, 1.3$ Hz, 1H, H-6), 5.31 (ddd, $J = 15.4, 8.2, 1.1$ Hz, 1H, H-1''), 5.07-4.93 (m, 5H, H-6'' & H-1 & H-4), 4.71 (ddd, $J = 8.2, 6.9, 0.8$ Hz, 1H, H-5'), 4.54 (d, $J = 6.9$ Hz, 1H, H-4'), 4.44 (d, $J = 11.4$ Hz, 1H, OCHHAr), 4.40 (d, $J = 11.4$ Hz, 1H, OCHHAr), 3.80 (s, 3H, OCH₃), 3.56-3.51 (m, 3H, H-8 & H-12), 3.39 (ddd, $J = 8.2, 6.7, 2.9$ Hz, 1H, H-10), 3.26 (s, 3H, OCH₃), 2.64 (ddq, $J = 12.6, 9.8, 6.7$ Hz, 1H, H-7), 2.56-2.46 (m, 1H, H-3), 2.26-2.17 (m, 1H, H-3''), 2.12 (dtt, $J = 14.0, 6.4, 1.4$ Hz, 1H, H'-4'') 1.98 (dtt, $J = 14.0, 7.4, 1.2$ Hz, 1H, H''-4''), 1.92-1.84 (m, 2H, H'-11 & H-9), 1.62 (d, $J = 1.3$ Hz, 3H, C=CCH₃), 1.61 (s, 3H, CH₃), 1.61-1.59 (m, 1H, H''-11), 1.38 (s, 3H, CH₃), 0.96 (d, $J = 6.7$ Hz, 3H, CH₃), 0.93 (d, $J = 7.2$ Hz, 3H, CH₃) 0.91 (s, 9H, C(CH₃)₃) 0.91 (d, $J = 6.6$ Hz, 3H, CH₃), 0.84 (d, $J = 7.1$ Hz, 3H, CH₃), 0.06 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃); δ_{C} (125 MHz, CDCl_3) 168.8 (CO), 159.2 (CO), 143.0, 140.2, 136.7, 135.6 (C-6), 130.9, 130.1, 129.4 (Ar), 122.4 (C-1''), 116.3 (CH=CH₂), 115.5 (CH=CH₂), 113.8 (Ar), 110.8 (C(CH₃)₂), 84.0 (C-4), 79.3 (C-5'), 78.7 (C-10), 78.3 (C-4'), 77.6 (C-8), 72.8 (OCH₂Ar), 66.9 (C-12), 56.9 (OCH₃), 55.4 (OCH₃), 41.0 (C-4'' or C-9), 40.9 (C-4'' or C-9), 40.1 (C-3), 36.3 (C-3''), 36.0 (C-7), 30.9 (C-11), 27.2 (CH₃), 26.4 (C(CH₃)₃), 25.9 (CH₃), 19.6 (CH₃), 18.6 (C(CH₃)₃), 17.1 (CH₃), 16.8 (CH₃), 12.3 (CH₃), 12.2 (CH₃), -3.6 (Si(CH₃)₃), -3.7 (Si(CH₃)₃); Accurate mass (ES⁺): Found 779.4881 (-1.7 ppm), C₄₄H₇₂O₈NaSi (M+Na⁺) requires 779.4894.



(3a*R*,6*S*,7*S*,8*E*,11*R*,12*E*,13a*R*)-6-((4*R*,5*S*,6*R*,7*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-9-((4-methoxybenzyl)oxy)-4,6-dimethylnon-2-en-2-yl)-2,2,7,11-tetramethyl-6,7,10,11-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one (15)

(4*R*,5*R*)-(3*S*,4*S*,7*R*,8*S*,9*R*,10*R*,*E*)-8-((*tert*-butyldimethylsilyl)oxy)-10-methoxy-12-((4-methoxybenzyl)oxy)-3,5,7,9-tetramethyldodeca-1,5-dien-4-yl 2,2-dimethyl-5-((*R*,*E*)-3-methylhexa-1,5-dien-1-yl)-1,3-dioxolane-4-carboxylate (**14**) (49.0 mg, 0.065 mmol) was dissolved in dichloromethane (12 mL).

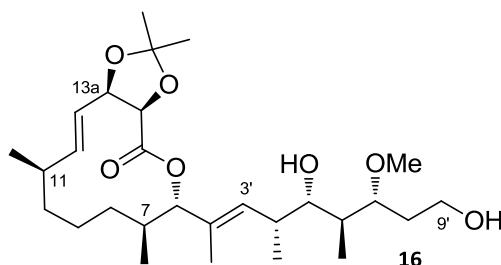
Grubbs 2nd generation catalyst (3.00 mg, 0.004 mmol) was added and the reddish reaction mixture stirred overnight (17 h) The reaction mixture was then poured into a 50:50 (v/v) mixture of water and 30% hydrogen peroxide (40 mL) at 0 °C and diluted with dichloromethane (20 mL). The biphasic solution was stirred for 1 h. The aqueous layer was then extracted with dichloromethane (3 × 40 mL) and the organic layers combined, dried (Na₂SO₄) and concentrated under reduced pressure. Purification by flash column chromatography (9:1 Hexanes:EtOAc) gave the title compound **15** as a clear colorless oil (36 mg, 76%); R_f 0.37 (6:1 Hexanes:EtOAc); [α]_D²⁰ -23.7 (c = 0.67 in CHCl₃); ν_{max}/cm⁻¹ (thin film, CH₂Cl₂) 2955, 2930, 2856, 1747, 1613, 1585, 1513, 1461, 1381, 1370, 1302, 1248, 1217, 1182, 1083, 1035, 1001, 968, 937, 874, 862, 834, 773, 736, 703, 672, 576, 511; δ_H (400 MHz, CDCl₃) 7.26-7.22 (m, 2H, Ar), 6.88-6.84 (m, 2H, Ar), 5.47 (ddd, J = 15.6, 6.9, 1.1 Hz, 1H, H-12), 5.44 (dq, J = 9.8, 1.3 Hz, 1H, H-3^o), 5.25 (ddd, J = 15.6, 7.1, 1.1 Hz, 1H, H-13), 5.18-5.09 (m, 2H, H-8 & H-9), 5.05 (d, J = 10.9 Hz, 1H, H-6), 4.72 (ddd, J = 7.1, 6.7, 1.1 Hz, 1H, H-13a), 4.47 (d, J = 6.7 Hz, 1H, H-3a), 4.43 (d, J = 11.5 Hz, 1H, OCHHAr), 4.39 (d, J = 11.5 Hz, 1H, OCHHAr), 3.80 (s, 3H, OCH₃), 3.56-3.48 (m, 3H, H-5' & H-9'), 3.42-3.35 (m, 1H, H-7'), 3.26 (s, 3H, OCH₃), 2.68-2.56 (m, 1H, H-4'), 2.45-2.36 (m, 1H, H-7), 2.29-2.18 (m, 2H, H-11 & H'-10), 2.01-1.92 (m, 1H, H'-10), 1.92-1.82 (m, 2H, H-6' & H'-8'), 1.69 (s, 3H, CH₃), 1.65-1.58 (m, 1H, H'-8'), 1.58 (d, J = 1.3 Hz, 3H, CH=CCH₃), 1.40 (s, 3H, CH₃), 1.06 (d, J = 6.6 Hz, 3H, CH₃), 0.91 (d, J = 6.7 Hz, 3H, CH₃), 0.90 (s, 9H, C(CH₃)₃) 0.83 (d, J = 7.1 Hz, 3H, CH₃) 0.82 (d, J = 6.9 Hz, 3H, CH₃), 0.06 (s, 3H, SiCH₃), 0.02 (s, 3H, SiCH₃); δ_C (100 MHz, CDCl₃) 169.7 (CO), 159.2, 138.9 (C-12), 136.4 (C-3^o), 134.7 (C-8 or C-9), 130.9, 130.6 (C-8 or C-9), 130.1, 129.4 (Ar), 123.7 (C-13), 113.9 (Ar), 111.0 (C(CH₃)(CH₃)), 84.5 (C-6), 78.9 (C-13a or C-7'), 78.8 (C-13a or C-7'), 78.5 (C-3a), 77.6 (C-5'), 72.8 (OCH₂Ar), 66.9 (C-9'), 56.9 (OCH₃), 55.4 (OCH₃), 41.2 (C-6'), 39.9 (C-7), 38.8 (C-10), 36.1 (C-4' & C-11), 30.9 (C-8'), 27.0 (C(CH₃)(CH₃)), 26.4 (C(CH₃)₃), 26.0 (C(CH₃)(CH₃)), 21.1 (CH₃), 18.5, 18.0 (CH₃), 17.0 (CH₃), 12.3 (CH₃), 11.7 (CH=CCH₃), -3.6 (Si(CH₃)), -3.7 (Si(CH₃)). Accurate mass (ES⁺): Found 751.4576 (-0.7 ppm), C₄₂H₆₈O₈NaSi (M+Na⁺) requires 751.4581.



(3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-6-((4*R*,5*S*,6*R*,7*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-9-hydroxy-7-methoxy-4,6-dimethylnon-2-en-2-yl)-2,2,7,11-tetramethyl-6,7,8,9,10,11-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one (24)

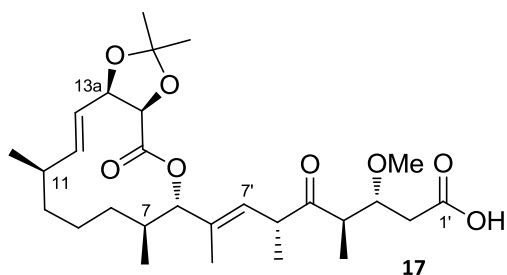
To a solution of macrocycle **15** (24.0 mg, 0.03 mmol) in the ethanol (3 mL), 5% palladium on carbon (1.00 mg) was added and the suspension was stirred under an atmosphere of hydrogen (using a single balloon) for 1 h 40 min. The reaction mixture was then passed through a plug of silica and eluted with ethyl acetate (approx. 25 mL). The solvent was removed under reduced pressure to give a clear colorless oil (which contained significant amount of starting material by NMR). The above sequence was repeated twice more using the residual oil and reaction times between 1 h and 1 h 20 min. The final crude oil was then purified by flash column chromatography (7:1→1:1 Hexanes:EtOAc) to give the title compound **24** as a clear colorless oil (14 mg, 70%); R_f 0.27 (3:1 Hexanes:EtOAc); $[\alpha]_D^{20}$ -57.4 ($c = 0.58$ in CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film, CHCl_3) 3534 (O-H), 2956-2848 (m, C-H), 1750 (C=O), 1475, 1460, 1380, 1251, 1184, 1083, 1033, 1005, 975, 948, 873, 834, 804, 753, 666, 618, 576, 510; δ_{H} (500 MHz, CDCl_3) 5.66 (ddd, $J = 15.5, 8.9, 1.4$ Hz, 1H, H-12), 5.54 (dd, $J = 15.5, 4.7$ Hz, 1H, H-13), 5.44 (dq, $J = 9.9, 1.3$ Hz, 1H, H-3'), 4.96 (d, $J = 11.4$ Hz, 1H, H-6), 4.82 (ddd, $J = 6.7, 4.7, 1.4$ Hz, 1H, H-13a), 4.55 (d, $J = 6.7$ Hz, 1H, H-3a), 3.77 (ddd, $J = 11.0, 7.2, 4.1$ Hz, 1H, H^{2-9'}), 3.71 (ddd, $J = 11.0, 6.8, 4.4$ Hz, 1H, H^{2-9'}), 3.54 (ddd, $J = 7.9, 6.5, 3.0$ Hz, 1H, H-7'), 3.47 (dd, $J = 6.0, 4.5$ Hz, 1H, H-5'), 3.33-3.31 (m, 1H), 3.31 (s, 3H, OCH_3), 2.61 (dq, $J = 9.9, 6.8, 6.0$ Hz, 1H, H-4'), 2.38-2.27 (m, 1H, H-11), 2.10-2.01 (m, 1H, H-6'), 2.01-1.95 (m, 1H), 1.87-1.79 (m, 1H), 1.78-1.72 (m, 1H), 1.70 (s, 3H, CH_3), 1.63-1.57 (m, 2H), 1.56 (d, $J = 1.3$ Hz, 3H, $\text{CH}=\text{CCH}_3$), 1.40 (s, 3H, CH_3), 1.39-1.30 (m, 2H), 1.30-1.27 (m, 2H), 0.98 (d, $J = 6.5$ Hz, 3H, CH_3), 0.92 (d, $J = 6.8$ Hz, 3H, CH_3), 0.91 (s, 9H, $\text{C}(\text{CH}_3)_3$), 0.83 (d, $J = 7.2$ Hz, 3H, CH_3), 0.78 (d, $J = 6.9$ Hz, 3H, CH_3), 0.07 (s, 3H, SiCH_3), 0.03 (s, 3H, SiCH_3); δ_{C} (125 MHz, CDCl_3) 169.1 (CO), 136.4 (C-12), 135.6 (C-3'), 131.2, 122.3 (C-13), 110.9 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 82.9 (C-6), 81.9 (C-7'), 78.5 (C-3a), 78.1 (C-5'), 77.5 (C-13a), 61.2 (C-9'), 56.3 (OCH_3), 39.5 (C-6'), 36.5 (C-4'), 35.7 (C-11), 33.8, 32.7 (C-7), 31.5, 29.4, 27.1 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 26.4 ($\text{C}(\text{CH}_3)_3$), 26.0 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 20.8, 18.6, 18.0, 17.3,

16.2, 12.4, 12.0, -3.5 (Si(CH₃)), -3.6 (Si(CH₃)); Accurate mass (ES⁺): Found 633.4134 (-2.3 ppm), C₃₄H₆₂O₇NaSi (M+Na⁺) requires 633.4163.



(3a*R*,6*S*,7*S*,11*R*,13a*R*,*E*)-6-((4*R*,5*S*,6*S*,7*R*,*E*)-5,9-Dihydroxy-7-methoxy-4,6-dimethylnon-2-en-2-yl)-2,2,7,11-tetramethyl-6,7,8,9,10,11-hexahydro-3a*H*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-4(13a*H*)-one (16)

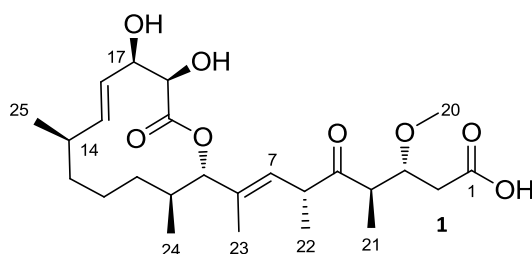
Alcohol **24** (14.0 mg, 0.023 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to 0 °C. A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 0.15 mL, 0.15 mmol) was added and the clear reaction mixture stirred at room temperature for 12 h. The reaction mixture was then concentrated under reduced pressure and purified by two rounds of flash column chromatography (3:1→1:1→1:3 Hexanes:EtOAc) to give the title compound **16** as a clear colorless oil (11 mg, 96%); *R_f* 0.22 (2:1 EtOAc:Hexanes); [α]_D²⁰ -74.5 (c = 0.67 in CHCl₃); ν_{max}/cm⁻¹ (thin film, CHCl₃) 3391 (br s, O-H), 2963-2819 (m, C-H), 1750 (C=O), 1675, 1456, 1379, 1250, 1238, 1222, 1185, 1152, 1123, 1086, 1050, 1005, 977, 943, 927, 874, 782, 731, 617; δ_H (500 MHz, CDCl₃) 5.65 (ddd, *J* = 15.5, 9.0, 1.4 Hz, 1H, H-12), 5.45 (dd, *J* = 15.5, 4.7 Hz, 1H, H-13), 5.50 (dq, *J* = 9.0, 1.4 Hz, 1H, H-3'), 4.96 (d, *J* = 11.4 Hz, 1H, H-6), 4.83 (ddd, *J* = 6.7, 4.7, 1.4 Hz, 1H, H-13a), 4.56 (d, *J* = 6.7 Hz, 1H, H-3a), 3.78-3.75 (m, 2H, H-9'), 3.64 (ddd, *J* = 8.3, 5.1, 3.1 Hz, 1H, H-7'), 3.35 (s, 3H, OCH₃), 3.26 (dd, *J* = 8.7, 3.5 Hz, 1H, H-5'), 2.63-2.52 (m, 1H, H-4'), 2.40-2.28 (m, 1H, H-11), 2.29-2.10 (m, 2H), 2.05-1.95 (m, 2H, H-6' & H-7), 1.81-1.73 (m, 2H), 1.70 (s, 3H, CH₃), 1.69-1.57 (m, 2H), 1.56 (d, *J* = 1.4 Hz, 3H, CH=CCH₃), 1.41 (s, 3H, CH₃), 1.38-1.29 (m, 2H), 1.29-1.20 (m, 2H), 0.98 (d, *J* = 6.6 Hz, 3H, CH₃), 0.96 (d, *J* = 6.8 Hz, 3H, CH₃), 0.83 (d, *J* = 7.0 Hz, 3H, CH₃), 0.77 (d, *J* = 7.0 Hz, 3H, CH₃); δ_C (125 MHz, CDCl₃) 169.2 (CO), 136.3 (C-12), 134.7 (C-3'), 132.1, 122.3 (C-13), 111.0 (C(CH₃)(CH₃)), 82.9 (C-6 or C-7'), 82.8 (C-6 or C-7'), 78.6 (C-3a), 77.5 (C-5' & C-13a), 61.4 (C-9'), 56.9 (OCH₃), 37.1 (C-6'), 35.7 (C-11), 34.8 (C-4'), 33.8, 32.6 (C-7), 31.7, 29.3, 27.0 (CH₃), 26.0 (CH₃), 20.8 (CH₃), 17.9, 16.2 (CH₃), 12.9 (CH₃), 12.0 (CH₃), 11.5 (CH₃); Accurate mass (ES⁺): Found 519.3295 (-0.6 ppm), C₂₈H₄₈O₇Na (M+Na⁺) requires 519.3298.



(3*R*,4*R*,6*R*,*E*)-3-Methoxy-4,6-dimethyl-5-oxo-8-((3*aR*,6*S*,7*S*,11*R*,13*aR*,*E*)-2,2,7,11-tetramethyl-4-oxo-4,6,7,8,9,10,11,13*a*-octahydro-3*aH*-[1,3]dioxolo[4,5-*c*][1]oxacyclododecin-6-yl)non-7-enoic acid (17)

To a solution of oxalyl chloride (0.025 mL, 0.295 mmol) in dichloromethane (3 mL) at -78°C dimethyl sulfoxide (0.05 mL, 0.704 mmol) was added *via* syringe. The clear reaction mixture was stirred for 30 min and then a solution of diol **16** (0.008 g, 0.016 mmol) in dichloromethane (1 mL, 2×1 mL wash) at -78°C was then added *via* cannula. The reaction mixture was stirred for 1 h 30 min at -78°C . Triethylamine (0.1 mL, 0.717 mmol) was added and the reaction mixture stirred in the presence of the cooling bath for 1 h 15 min and then at -25°C for 30 min. An aqueous solution of hydrochloric acid (0.5 M, 15 mL) was then added followed by dichloromethane (10 mL). The organic layer was washed with a 50% saturated aqueous solution of sodium bicarbonate (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The clear oil (9 mg) was then dissolved in *tert*-butanol (2 mL) and a solution of 2-methyl-2-butene (in tetrahydrofuran, 2 M, 0.3 mL, 0.6 mmol) was added *via* syringe. A mixture of sodium dihydrogen phosphate monohydrate (0.023 g, 0.167 mmol) and sodium chlorite (0.010g, 0.088 mmol) in water (2 mL) was then added dropwise over a period of approx. 5 min and the reaction mixture stirred at room temperature for 2 h 50 min. A saturated solution of brine (20 mL) was then added followed by diethyl ether (20 mL). The aqueous layer was extracted with diethyl ether (3×20 mL) and the organic layers combined, dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound **17** as colorless oil (8.4 mg, *quant.*); δ_{H} (500 MHz, CDCl_3) R_f 0.56 (9:1 CH_2Cl_2 :MeOH); $[\alpha]_{\text{D}}^{20}$ -165.0 ($c = 0.7$ in CH_2Cl_2) {lit.⁶ $[\alpha]_{\text{D}}^{24}$ -196.9 ($c = 1.0$ in CH_2Cl_2)}; $\nu_{\text{max}}/\text{cm}^{-1}$ (thin film, CH_2Cl_2) 2958-2848 (m, C-H), 1748 (C=O), 1713 (C=O), 1456, 1378, 1283, 1251, 1238, 1217, 1180, 1123, 1084, 1013, 977, 953, 874, 792, 724, 661, 618, 577, 515, 543; δ_{H} (500 MHz, CDCl_3) 5.66 (ddd, $J = 15.5, 8.9, 1.4$ Hz, 1H, H-12), 5.54 (dd, $J = 15.5, 4.7$ Hz, 1H, H-13), 5.33 (dq, $J = 10.0, 1.4$ Hz, 1H, H-7'), 4.98 (d, $J = 11.4$ Hz, 1H, H-6), 4.83 (ddd, $J = 6.7, 4.7, 1.4$ Hz, 1H, H-13a), 4.57 (d $J = 6.7$ Hz, 1H, H-3a), 3.75 (ddd, $J = 8.3, 6.3, 4.0$ Hz, 1H, H-3'), 3.48 (dq, $J = 10.0, 6.7$ Hz, 1H, H-6'), 3.31 (s, 3H, OCH_3),

2.99 (dq, $J = 8.3, 6.9$ Hz, 1H, H-4'), 2.64 (dd, $J = 15.8, 4.0$ Hz, 1H, H'-2'), 2.44 (dd, $J = 15.8, 6.3$ Hz, 1H, H''-2'), 2.38-2.28 (m, 1H, H-11), 2.09-1.98 (m, 1H, H-7), 1.82-1.72 (m, 1H), 1.70 (s, 3H, CH₃), 1.65 (d, $J = 1.4$ Hz, 3H, CH=CCH₃), 1.41 (s, 3H, CH₃), 1.39-1.31 (m, 3H), 1.28-1.20 (m, 2H), 1.12 (d, $J = 6.7$ Hz, 3H, CH₃), 0.98 (d, $J = 6.6$ Hz, 3H, CH₃), 0.93 (d, $J = 6.9$ Hz, 3H, CH₃), 0.91-0.86 (m, 1H), 0.75 (d, $J = 7.0$ Hz, 3H, CH₃); δ_c (125 MHz, CDCl₃) 213.2 (CO), 175.3 (CO), 169.1 (CO), 136.4 (C-12), 135.4, 129.7 (C-7'), 122.3 (C-13), 111.0 (C(CH₃)(CH₃)), 82.4 (C-6), 80.0 (C-3'), 78.5 (C-3a), 77.5 (C-13a), 58.3 (OCH₃), 47.5 (C-6' & C-4'), 35.9 (C-2'), 35.7 (C-11), 33.8, 32.6 (C-7), 29.3, 27.0 (CH₃), 26.0 (CH₃), 20.8 (CH₃), 17.9, 15.8 (CH₃), 15.7 (CH₃), 12.9 (CH₃), 12.0 (CH₃); Accurate mass (ES⁺): Found 526.3355 (-4.7 ppm), C₂₈H₄₈NO₈ (M+NH₄⁺) requires 526.3380. Data is in accordance with the literature.⁶



Carolacton (1)

To a solution of acid **17** (0.004 g, 0.008 mmol) in acetonitrile (1.5 mL) a 70% hydrogen fluoride in pyridine solution (3.0 μ L) was added followed by water (2.0 μ L). The reaction mixture was stirred at room temperature for 18 h 40 min and then concentrated under reduced pressure to give carolacton (**1**) as a clear colorless oil (0.004 g, *quant.*) See Table 1 (page 24) for the ¹³C NMR data and Table 2 (page 25) for the ¹H NMR data. R_f 0.46 (10:1 CH₂Cl₂:MeOH); $[\alpha]_D^{20}$ -160.8 (c = 0.34 in CH₂Cl₂) {lit.⁶ $[\alpha]_D^{20}$ -188 (c = 0.85 in CH₂Cl₂)}; $\nu_{\max}/\text{cm}^{-1}$ (CH₂Cl₂) 3480 (br, O-H), 2962, 2929, 2860, 1756-1691 (br s, C=O), 1454, 1375, 1262, 1193, 1126, 1086, 1011, 976, 950, 873, 837, 734, 702, 681, 610, 536; Accurate mass (ES⁺): Found 491.2624 (0.6 ppm), C₂₅H₄₀O₈Na (M+Na⁺) requires 491.2621.

Table 1: Comparison of the ^{13}C NMR data (in CDCl_3) for synthetic carolacton reported here with the synthetic carolacton reported by Kirschning and Schmidt⁶ and the isolated natural product reported by Muller *et al.*⁷

#	δ_{C} Synthetic 1 (125 MHz)/ppm	δ_{C} Kirschning 1 (100 MHz)/ppm	$\delta_{\text{C}}^{\text{v}}$ Natural 1 (150 MHz)/ppm
1	174.32	174.85	175.70
2	35.64	35.64	35.97
3	80.12	80.09	80.22
4	47.55	47.57	47.43
5	213.24	213.28	213.45
6	47.41	47.35	47.56
7	129.61	129.63	129.52
8	135.84	135.83	135.96
9	83.46	83.47	83.41
10	33.44	33.37	33.49
11	28.57	28.50	28.53
12	19.03	18.95	18.97
13	34.56	34.53	34.55
14	35.86	35.82	35.82
15	134.71	134.69	134.61
16	125.56	125.53	125.57
17	73.10	73.09	73.08
18	73.71	73.70	73.82
19	172.02	172.07	172.07
20	58.26	58.26	58.17
21	12.97	12.97	12.93
22	15.47	15.46	15.43
23	13.02	12.99	13.11
24	15.58	15.55	15.43
25	21.78	21.79	21.80

^v The ^{13}C NMR shifts reported by Muller *et al.* were referenced with the CDCl_3 signal set to 77.0 ppm.⁷ The values shown in Table 1 were obtained by the addition of 0.16 ppm to the reported values.

Table 2: Comparison of the ^1H NMR data (in CDCl_3) for synthetic carolacton reported here with the synthetic carolacton reported by Kirschning and Schmidt⁶ and the isolated natural product reported by Muller *et al.*⁷

#	δ_{H} Synthetic 1 (500 MHz)/ppm	δ_{H} Kirschning 1 (400 MHz)/ppm	δ_{H} Natural 1 (600 MHz)/ppm
1	N/A	N/A	N/A
2	2.66 (dd, $J = 15.6, 4.1$) 2.45 (dd, $J = 15.6, 5.8$)	2.66 (dd, $J = 15.7, 4.1$) 2.45 (dd, $J = 15.7, 5.8$)	2.66 (dd, $J = 15.7, 4.2$) 2.44 (dd, $J = 15.7, 5.9$)
3	3.75 (ddd, $J = 8.5, 5.8, 4.1$)	3.74 (ddd, $J = 8.5, 5.8, 4.1$)	3.74 (ddd, $J = 8.5, 5.9, 4.2$)
4	2.98 (dq, $J = 8.5, 6.9$)	2.98 (dq, $J = 8.5, 6.8$)	2.99 (dq, $J = 8.5, 6.9$)
5	N/A	N/A	N/A
6	3.49 (dq, $J = 10.2, 6.7$)	3.49 (dq, $J = 10.2, 6.7$)	3.49 (dq, $J = 10.2, 6.8$)
7	5.36 (dq, $J = 10.2, 1.3$)	5.36 (dd, $J = 10.2, 1.4$)	5.37 (dd, $J = 10.2, 1.5$ br)
8	N/A	N/A	N/A
9	4.76 (d, $J = 11.3$)	4.77 (d, $J = 11.3$)	4.75 (d, $J = 11.3$)
10	2.10-1.99 (m)	2.05 (m)	2.05 (tt, $J = 11.5, 7.0, 2.6$)
11	1.81-1.72 (m) 0.99-0.91 (m)	1.75 (m, H_a) 0.99 (m, H_b)	1.76 (tt, $J = 13.5, 4.0$) 0.99 (m)
12	1.32-1.21 (m) 0.93-0.89 (m)	1.34-1.21 (m, 2H)	1.26 (m) 0.99 (m)
13	1.43-1.34 (m) 1.32-1.21 (m)	1.38 (m, H_a) 1.34-1.21 (m, H_b)	1.38 (tt, $J = 12.8, 4.0$) 1.26 (m)
14	2.38-2.25 (m)	2.32 (m)	2.32 (dddq, $J = 11.1, 9.8, 4.5, 6.6$)
15	5.45 (ddd, $J = 15.4, 9.7, 2.0$)	5.45 (ddd, $J = 15.4, 9.6, 1.9$)	5.46 (ddd, $J = 15.5, 9.8, 1.9$)
16	5.53 (dd, $J = 15.4, 2.2$)	5.53 (dd, $J = 15.4, 2.4$)	5.53 (dd, $J = 15.5, 2.5$)
17	4.49 (ddd, $J = 3.6, 2.2, 2.0$)	4.49 (dd, $J = 3.7, 1.8$)	4.49 (dt, $J = 3.4, 2.5$)
18	4.18 (d, $J = 3.6$)	4.18 (d, $J = 3.7$)	4.17 (d, $J = 3.4$)
19	N/A	N/A	N/A
20	3.32 (s)	3.32 (s)	3.31 (s)
21	0.93 (d, $J = 6.9$)	0.93 (d, $J = 6.8$)	0.94 (d, $J = 6.8/7$)
22	1.11 (d, $J = 6.7$)	1.11 (d, $J = 6.7$)	1.11 (d, $J = 6.6$)
23	1.71 (d, $J = 1.3$)	1.71 (d, $J = 1.4$)	1.71 (d, $J = 1.1$)
24	0.77 (d, $J = 7.0$)	0.77 (d, $J = 6.8$)	0.77 (d, $J = 7$)
25	0.98 (d, $J = 6.5$)	0.98 (d, $J = 6.5$)	0.98 (d, $J = 6.6$)

2.3 References

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