Strain-Release in C–H Bond Activation?

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For literature citations, footnotes, caption to Table I, as well as a description of experimental procedure and conditions used in determining relative oxidation rates, see the original paper. In den English text below, footnotes and citations are indicated in brackets, e.g.(2/1535), the meaning of which is: footnote (or citation) 2 on (Helvetica) page 1535.

On the relative rate of the oxidation of secondary alicyclic alcohols by chromic acid

J. Schreiber, A. Eschenmoser, Helv. Chim. Acta, 1955, *38*,1529-1536

About two decades ago, M.G. Vavon and coworkers (2/1529) while studying the effect of steric hindrance on the reactivity of secondary alcohols, observed for the first time that epimeric secondary cyclanols show a remarkable discrepancy in reactivity regarding their oxydation with chromic acid versus reactions such as acylations. Within the series of 2-alkyl-cyclohexanols, the cis isomers were found to be oxidized by chromic acid faster than the corresponding trans isomers, whereas the reaction rates for acylations and for the hydrolysis of respective esters are exactly inverse. Similar observations were made later by different authors in the steroid series (3/1529), where cholic acid stands for a classical example in as far as the reactivity of its three hydroxy groups in their oxidation with chromic acid decreases along the sequence C7>C12>C3, whereas the hydroxy group at position C3 is acylated most easily.

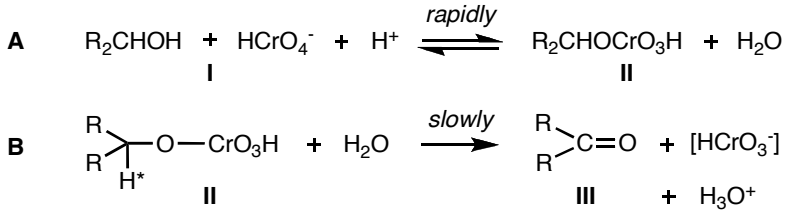
An interpretation of these notable facts has become possible only recently on the basis of conformational analysis (1/1530). D.R.H. Barton was able to summarize the known experimental data for chromic acid oxidation of alicyclic alcohols by the following general rule: *among two epimeric, secondary cyclanols the axial isomer is oxidized faster than the equatorial isomer.*

The theoretical interpretation put forward for this rule was based on Westheimer´s views on the mechanism of chromic acid oxidations. It was assumed that the difference in oxidation rates is due to the difference in steric hindrance toward proton abstraction by a base: in the case of the axial alcohol this abstraction is sterically less hindered because the carbinol hydrogen is equatorial, as compared to the equatorial alcohol where that carbinol hydrogen is axial. Since in our view the experimental facts can be interpreted in a different way and since a more detailed knowledge of this issue would be important from both a theoretical and an analytical point of

view, we conducted additional studies on this subject, the preliminary results of which we are presenting here.

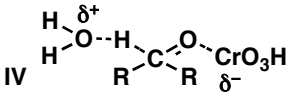
For the qualitative discussion of relative rates of chromic acid oxidation of secondary steroid alcohols we surmise that these cyclanols are oxidized by the same mechanism as 2-propanol. For this alcohol F.H. Westheimer and co-workers (2/1530) have shown that chromic acid oxidation in water or aqueous. acetic acid most likely proceeds according to scheme I → III via the chromic acid ester II, which solvolytically dissociates into acetone and an unstable CrIV-species. Because of the isotopic effect observed for the oxidation of 2-deutero-propan-2-ol it is certain that the cleavage of the C-H* bond of the carbinol group is the rate determining step of the reaction.

According to this scheme, the rate of oxidation with chromic acid of a given alcohol under the given reaction conditions depends on the position of the equilibrium A and on the rate of reaction B. The possibility that in the case of two epimeric cyclanols, such as two epimeric cholestanols the higher oxidation rate of the axial alcohol could be due to a corresponding difference in the position of the respective equilibria A can be excluded, since it is to be expected that in the case of the axial isomer this equilibrium is most likely even less in favor of the chromic acid ester than in the case of the equatorial alcohol, the ester group having a higher spatial requirement that the corresponding free hydroxyl groups.



The higher rate of decomposition of the axial chromic acid ester can formally be ascribed to different factors; besides the already mentioned difference in steric hindrance toward solvolytic elimination of the proton H*, what above all has also to be considered is the fact that the transformation of the tetrahedral ester group into the trigonal keto group is associated with a change in non-classical strain within the molecule, a change which in the case of the axial alcohol will be connected with a decrease of such strain. If the assumption applies, that strain release already operates in the rate determining formation of the transition state IV, then it can be anticipated solely from this point of view that a parallelism will exist between decomposition rate and non-classical strain of the chromic acid acid ester and, thus, a higher oxidation rate of

the axial alcohol (1/1531). Such a rate acceleration would be analogous to the kind of "steric acceleration" that has been proposed to operate in the solvolysis of highly branched tertiary alkyl chlorides (1/1532).



In order to obtain a preliminary qualitative answer to the question of whether and to what extent such a factor could be responsible for the rate differences observed for the oxidation of alicyclic alcohols, we determined under standardized reaction conditions relative rates of the chromic acid oxidation of a variety of secondary steroid alcohols, in particular hydroxy-cholestanes. The results obtained are summarized in Table I. The relative values k~ const. dCrIV/dt used for the equation k* = k (ROH)/ k (3β-hydroxy-cholestane) were determined graphically in each case by extrapolation to the start of the reaction. The sequence of k* values obtained in this way was found to be identical with the sequence of corresponding half-lives deduced from the empirical oxidation curves.

	β	α
a) 1-Oxy-cholestan	**k*** ca. 9,7	13,0
b) 2-Oxy-cholestan	20	1,3
c) 3-Oxy-cholestan	1,0	3,0
d) 4-Oxy-cholestan	35	2,0
e) 6-Oxy-cholestan	36	2,0
f) 7-Oxy-cholestan	3,3	12,3
g) 11-Oxy-cholestan	> 60	7,0

Table I.

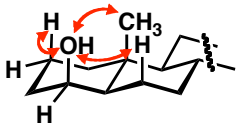
The obtained data fully corroborate the rule mentioned at the beginning, namely, that axial steroid alcohols are oxidized faster than their corresponding equatorial epimers.(Table I) Most notable is the fact that within the series of axial isomers very pronounced differences in oxidation rate are observed. *The observed sequence of these rates* is *not at all in accordance with the sequence one would expect if 'steric hindrance' to the abstraction of the equatorial hydrogen would be the responsible factor; the sequence is, however, fully consistent with the assumption that release of non-classical strain in the rate-determining step of the reaction is the dominant factor in determining relative oxidation rates.*

To illustrate this statement, Table II summarizes for each of the axial alcohols the steric interactions that are essential in this context and juxtaposes them with the corresponding relative oxidation rates. In estimating relative strain for the axial alcohols, emphasis is put on the interactions between the axial oxygen function and the axial substituent (H and CH3) at the γ-position, these refer the strain parameters that can be considered to be mainly responsible for the

relative thermodynamic instability of the axial position of the oxygen functionality; they are the parameters that vanish in forming the carbonyl group. (cf. Fig. 1 for 4β-oxy-cholestan (4/1533).

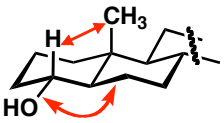
Axial alcohol	Strain parameters		k*
	1:3-CH(a):H(a)	1:3-CH(a):CH_3(a)	
3α-Oxy-cholestan	2	0	3,0
7α-Oxy-cholestan	3	0	12,3
1α-Oxy-cholestan	3	0	13,0
2β-Oxy-cholestan	1	1	20
4β-Oxy-cholestan	2	1	35
6β-Oxy-cholestan	2	1	36
11β-Oxy-allopr.	1	2	> 60

Table II.



2 X 1:3–OH(a):H(a)
1 X 1:3–OH(a):CH_3(a)

Fig. 1.



1 X 1:2–OH(e):R(e)
1 X 1:3–H(a):CH_3(a)

Fig. 2.

As expected, within the series of equatorial alcohols the differences in oxidation rates are not that distinctive and, therefore, they are less significant with regard to the question addressed. given the semi-quantitative character of the experimental observations. Nevertheless, Table III indicates that the same type of correlation between oxidation rate and non-classical strain seems to exist as in the series of the axial alcohols (1/1534) Above all, the data of the series convincingly corroborate the view that greater 'steric hindrance' towards abstraction of the axial hydrogen of the carbinol group is not responsible for lower oxidation rates (1/1535).

The observations discussed here have, from a kinetic point of view, the character of qualitative results that leave the discussion of various questions to be postponed until more quantitative data will be available. Especially the kinetic data of sterically strongly hindered axial alcohols such 11β-hydroxy-steroids deserve further study; furthermore, more precise information is desirable on the relative position of equilibria between esters and alcohols for axial and equatorial epimers, or the steric interactions between carbonyl oxygens and α-substituents in six-membered ring ketones...

Equatorial alcohol	Strain parameters (R=Alkyl)			k*
	1:2-OH(e):R^2	1:3-OH(e):R^3	1:3-H(a):CH_3(a)	
3β-Oxy-cholestan	0	0	0	1,0
2α-Oxy-cholestan	0	0	1	1,3
4α-Oxy-cholestan	1R(e)	0	1	2,0
6α-Oxy-cholestan	1R(e)	0	1	2,0
7β-Oxy-cholestan	1R(e)	1	0	3,3
11α-Oxy-allopr.	1R(e)	1	2	7,0
1β-Oxy-cholestan	2R(e + a)	1	0	9,7

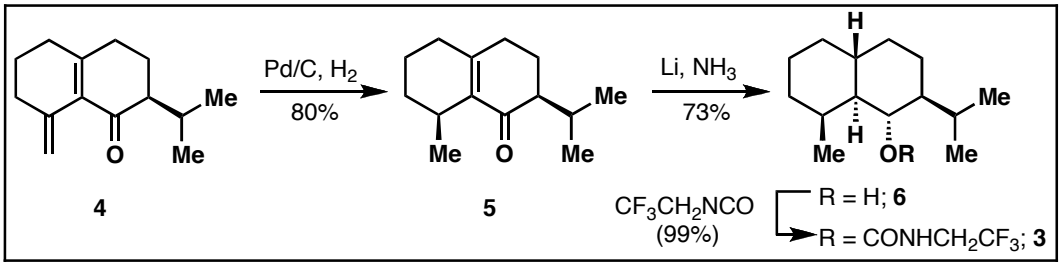
Table III.

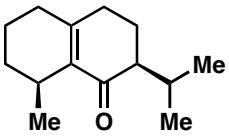
The results of this exploratory study allow us to postulate the follwing rule: *Under the reaction conditions described, the oxidation of a saturated secondary alcohol by chromic acid proceeds the faster the greater the decrease in non-classical strain in the transformation of the alcohol into the corresponding ketone* (2/1535). Apart from the interest in its theoretical aspects, this rule could prove useful for the determination of the constitution of alicyclic compounds in the sense that, based on oxidation rates of epimeric alcohols of unknown constitution measured under standardized conditions, it should be possible not only to determine their relative configuration, but also to gain clues about the constitutional surroundings of the oxygen functionality.

General Procedures.

All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions, unless otherwise noted. Dry dichloromethane (DCM), diethyl ether, and methanol (MeOH) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and *p*-anisaldehyde in ethanol/aqueous H_2SO_4/CH_3CO_2H and heat, Seebach's stain and heat, or *o*-vanillin in ethanol/aqueous H_2SO_4 and heat as developing agents. NMR spectra were recorded on a Bruker DRX 600, DRX 500, or AV 400 spectrometer and were calibrated using residual undeuterated solvent as an internal reference. The following abbreviations and combinations there of were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Perkin-Elmer Spetrum BX spectrometer. High resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points (m.p.) are uncorrected and were recorded on a Fisher-Johns 12-144 melting point apparatus.

Experimental Procedures.





5

Compound 5: Under hydrogen (1 atmosphere), a solution of compound **4**[1] (0.51 g, 2.5 mmol, 1.0 equiv.) in methanol (25 mL, 0.1 M) was stirred with palladium on carbon (10%, 0.27 g, 0.25 mmol, 0.1 equiv.) at room temperature for 15 minutes. The reaction mixture was filtered through a plug of silica gel topped with celite (EtOAc elute) to provide the crude material, which was purified by column chromatography (silica gel, gradient from 4:1 to 1:1 hexanes:benzene) to provide enone **5** (412.3 mg, 80%) along with its diastereomer **S1** (84.3 mg, 16%). Note: for the purpose of these studies, the above sequence started with racemic **4** as starting material.

Physical State: colorless oil

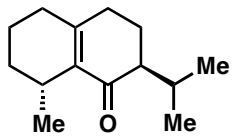
R_f: 0.5 (silica gel, benzene)

IR (film) ν_{max}: 2955, 2931, 2869, 1661, 1632, 1382 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): 2.81 (br, 1H), 2.22 − 2.32 (m, 2 H), 2.07 − 2.18 (m, 3 H), 1.89 − 1.99 (m, 2 H), 1.76 − 1.83 (m, 1 H), 1.65 − 1.74 (m, 1 H), 1.53 − 1.61 (m, 2 H), 1.47 − 1.51 (m, 1 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.7 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): 201.9, 154.9, 137.2, 52.9, 32.0, 30.0, 29.8, 26.7, 25.8, 22.8, 20.8, 20.4, 19.3, 18.0

HRMS (ESI): calcd. for $C_{14}H_{22}O$ [M+Na]$^+$: 229.1568; found: 229.1561.



S1

Physical State: colorless oil

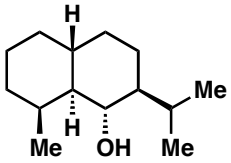
R_f: 0.8 (silica gel, benzene)

IR (film) ν_{max}: 2954, 2930, 1662, 1634, 1382 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): 2.77 (br, 1 H), 2.36 − 2.43 (m, 2 H), 2.14 − 2.30 (m, 4 H), 1.89 − 1.94 (m, 1 H), 1.50 − 1.74 (m, 5 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): 200.2, 154.6,137.0, 52.6, 31.7, 31.1,29.6, 25.9 (2 C), 23.0, 20.8, 19.8, 18.3,17.3

HRMS (ESI): calcd. for $C_{14}H_{22}O$ [M+Na]$^+$: 229.1568; found: 229.1559.



6

Compound 6: To a solution of compound **5** (320.4 mg, 1.56 mmol, 1.0 equiv.) and *tert*-butanol (1.5 mL, 15.6 mmol, 10.0 equiv.) in THF (5 mL, 0.3 M) at −78 °C was added liquid ammonia (*ca*. 20 mL). Lithium (*ca*. 2 g) was added in pieces until the blue color persisted, after which the mixture was stirred at −78 °C for 90 minutes. The blue color was dissipated by adding saturated aqueous ammonium chloride solution (20 mL). The ammonia was evaporated as the crude was warmed up to room temperature. The mixture was then extracted with ether (3 X 20 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography (silica gel, gradient from 4:1 to 1:2 hexanes:DCM) to provide alcohol **6** (239.7 mg, 73%) along with two minor diastereomers which

were not characterized. Crystallization of **6** from cyclohexane/Et_2O yielded colorless plates of suitable quality for X-Ray diffraction (CCDC# 743143).

Physical State: colorless plate (mp 30-32 °C)

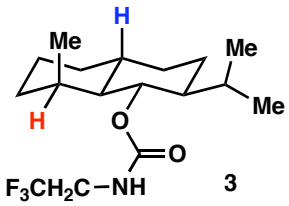
R_f: 0.50 (silica gel, 4:1 hexanes: Et2O)

IR (film) ν_{max}: 3316, 2955, 2918, 2860, 2847, 1457, 1447, 1382 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$): 3.20 (t, *J* = 9.9 Hz, 1 H), 2.22 − 2.25 (m, 1 H), 2.15 − 2.20 (m, 1 H), 1.54 − 1.63 (m, 4 H), 1.40 − 1.45 (m, 3 H), 1.34 (br, 1H), 1.17 − 1.24 (m, 2 H), 1.07 (dt, *J* = 4.0, 10.2 Hz, 1 H), 0.87 − 0.98 (m, 3 H), 0.92 (d, *J* = 7.2 Hz, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.79 (d, *J* = 7.0 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): 72.2, 52.7, 50.5, 34.5, 34.2, 34.0, 33.6, 27.3, 26.2, 22.7, 21.2, 20.2, 16.2, 12.8

HRMS (ESI): calcd. for $C_{14}H_{26}O$ $[M+H]^+$: 211.2062; found: 211.1938.



3

Compound 3: In a flame-dried round-bottom flask, compound **6** (165.7 mg, 0.79 mmol, 1.0 equiv.) was dissolved in DCM (4 mL, 0.2 M). DMAP (*ca*. 5 mg, catalytic) followed by pyridine (0.26 mL, 3.16 mmol, 4.0 equiv.) was added. A solution of trifluoroethyl isocyanate[1] in DCM (0.4 M, 2.0 mL, 1.0 equiv.) was added in one portion. The resulting colorless, homogeneous solution was stirred under nitrogen at room temperature for 1 hour. The solvent and pyridine was then removed by concentration *in vacuo*. The crude solid was filtered through a short silica plug eluting with DCM to provide carbamate **3** (261.8 mg, 99%).

Physical State: white solid (mp 108-110°C)

R_f: 0.85 (silica gel, DCM)

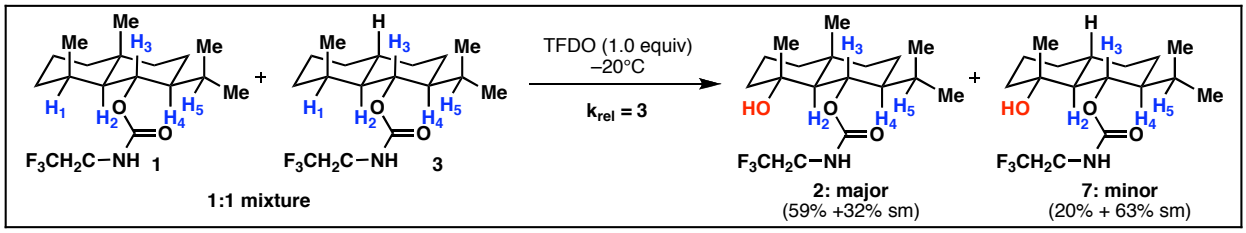
IR (film) ν_{max}: 3385, 2962, 2928, 2850, 1698, 1520, 1280, 1235, 1163 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$): 4.94 (br, 1 H), 4.60 (t, *J* = 10.2 Hz, 1 H), 3.73 – 3.84 (m, 2 H), 1.88 – 1.93 (m, 1 H), 1.27 – 1.76 (m, 12 H), 0.97 – 1.20 (m, 2 H), 0.92 (d, *J* = 7.2 Hz, 3 H), 0.88 (d, *J* = 7.0 Hz, 3 H), 0.82 (d, *J* = 6.9 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): 156.2, 124.4 (q, *J* = 279 Hz), 76.6, 51.0, 49.1, 42.6 (q, *J* = 35 Hz), 34.4, 34.1, 33.5, 33.4, 27.6, 26.3, 22.5, 21.2, 19.8, 16.1, 12.7

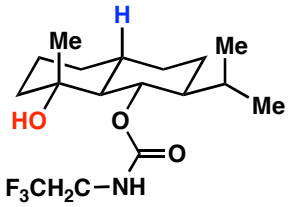
HRMS (ESI): calcd. for $C_{17}H_{28}F_3NO_2$ $[M+Na]^+$: 358.1970; found: 358.1955.

Studies on the rate of 1 and 3 in the C–H oxidation using TFDO:



A solution of compound **1** (19.7 mg, 0.056 mmol, 1.0 equiv.) and compound **3** (18.9 mg, 0.056 mmol, 1.0 equiv.) in DCM (0.56 mL, 0.1 M of **1** or **3**) was cooled in a methanol-ice bath (–20 °C). A freshly prepared solution of TFDO in trifluoroacetone (0.13 M, 0.43 mL, 1.0 equiv. of **1** or **3**, 0.5 equiv. of **1** and **3** combined) was added in one portion. The resulting colorless, homogeneous solution was stirred for an additional 30 minutes before Me_2S (0.1 mL) was added. The reaction mixture was warmed to room temperature and concentrated *in vacuo* to give a white foam, which was purified by column chromatography (silica gel, gradient from 9:1 to 3:1 hexanes:EtOAc) to provide two fractions. The less polar fraction consisted of a 1:2 mixture of **1**:**3** (18.1 mg, 32 % recovered **1**, 63 % recovered **3**), while the more polar fraction consisted of a

3:1 mixture of **2**:**7** (16.0 mg, 59 % of **2**, 20% of **7**). [Note: the ratios were determined by the integration of C_3–Hs of the ^{1}H spectrum (compound **1**: **δ** 4.89; compound **3**: **δ** 4.60; compound **7**: **δ** 4.81; compound **2**: **δ** 5.15)]. Compound **7** and compound **2** could be further separated by chromatography for a second time (silica gel, gradient from 4:1 to 2:1 hexanes:EtOAc). For the H^1, C^{13} data and X-ray of **2**, see reference 1.



7

Physical State: white solid (mp 137-139°C)

R_f: 0.50 (silica gel, 2:1 hexanes:EtOAc)

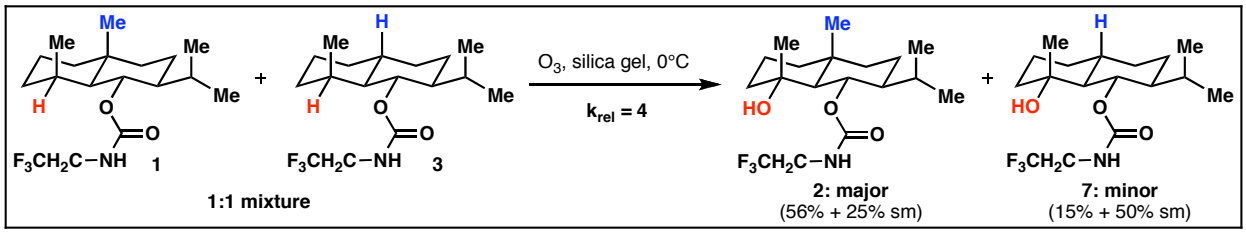
IR (film) ν_{max}: 2944, 1736, 1550, 1397, 1256, 1141 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): 5.21 (brs, 1 H), 4.81 (t, *J* = 8.6 Hz, 1 H), 3.76 – 3.88 (m, 2 H), 1.59 – 1.76 (m, 6 H), 1.42 – 1.46 (m, 3 H), 0.99 – 1.35 (m, 6 H), 1.27 (s, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): 155.8, 124.3 (q, *J* = 279 Hz), 77.5, 73.4, 56.1, 49.6, 43.2, 42.9 (q, *J* = 35 Hz), 39.2, 34.1, 33.6, 25.8, 23.0, 22.6, 22.0, 21.5, 16.2

HRMS (ESI): calcd. for $C_{17}H_{28}F_3O_3$ $[M+Na]^+$: 374.1919; found: 374.1899.

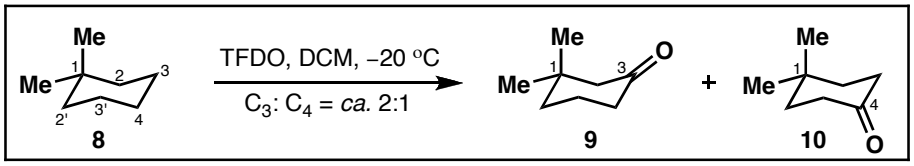
Studies on the rate of 1 and 3 in the C–H oxidation using Ozone-silica gel:



Compound **1** (6.8 mg, 0.019 mmol, 1.0 equiv.) and compound **3** (6.5 mg, 0.019 mmol, 1.0 equiv.) was evenly absorbed on silica gel (oven-dried, *ca*. 0.5 g, 2% w/w) and cooled to 0 °C. A steam of ozone was passed through the mixture at 0 °C for 30 minutes. The reaction mixture was

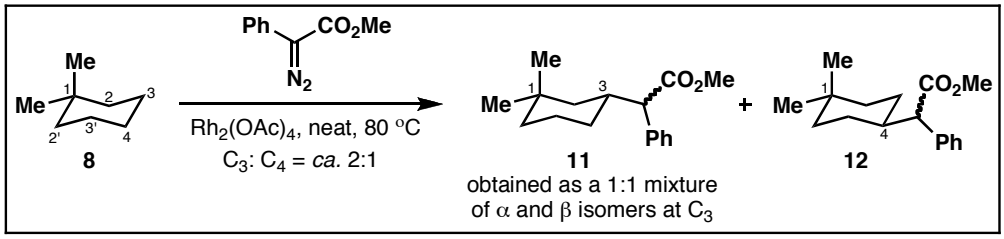
warmed to room temperature and eluted with EtOAc (20 mL). The solvent was removed by concentration *in vacuo*, and the resulting white foam was purified by column chromatography (silica gel, gradient from 9:1 to 3:1 hexanes:EtOAc) to provide two fractions. The less polar fraction consisted of a 1:2 mixture of **1**:**3** (5.1 mg, 25 % recovered **1**, 50 % recovered **3**), while the more polar fraction was collected and concentrated to yield a mixture as yellow foam. Chromatography for a second time (silica gel, gradient from 9:1 to 2:1 DCM:Et_2O) afforded a 4:1 mixture of **2**:**7** (5.0 mg, 56 % of **2**, 15 % of **7**). [Note: the ratios were determined by the integration of C_3–Hs of the ^{1}H spectrum (compound **1**: δ 4.89; compound **3**: δ 4.60; compound **7**: δ 4.81; compound **2**: δ 5.15).]

Studies on the rate of C-2, C-3 and C-4 of 1,1-dimethyl-cyclohexane in the C–H oxidation using TFDO:



A solution of 1,1-dimethyl-cyclohexane **8** (9.7 mg, 0.09 mmol, 1.0 equiv.) in DCM (0.9 mL, 0.1 M) was cooled in a methanol-ice bath (–20 °C). A freshly prepared solution of TFDO in trifluoroacetone (0.13 M, 0.69 mL, 1.0 equiv.) was added in one portion. The resulting colorless, homogeneous solution was stirred for an additional 30 minutes before Me_2S (0.1 mL) was added. The reaction mixture was warmed to room temperature and concentrated *in vacuo* to give a colorless oil (5.6 mg, *ca*. 50%, non-optimized). The 2:1 ratio of ketone **9** and **10** was determined by comparison of the crude H^1 spectrum to the literature report and the integration of the corresponding peaks. [2,3]

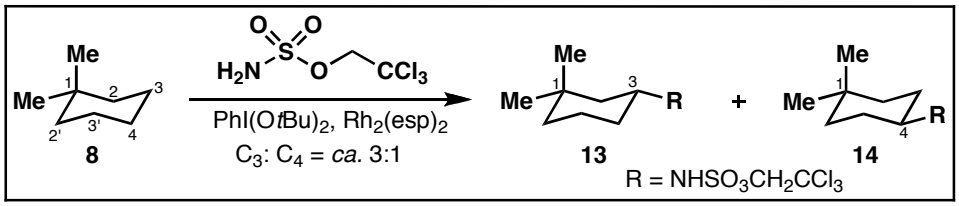
Studies on the rate of C-2, C-3 and C-4 of 1,1-dimethyl-cyclohexane in the C–H oxidation using carbene:



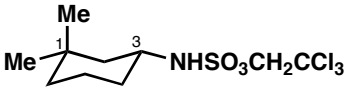
In a capped microwave vial, a mixture of 1,1-dimethyl-cyclohexane **8** (0.1 mL, excess) and $Rh_2(OAc)_4$ (12.4 mg, 0.03 mmol, 0.2 equiv.) was heated to 80 °C. To this green, homogeneous solution, methyl phenyldiazoacetate (24.7 mg, 0.14 mmol, 1.0 equiv.) in 1,1-dimethyl-cyclohexane **8** (0.1 mL) was added over 30 minutes. After addition, the resulting reaction crude was stirred for an additional 30 minutes before cooled to room temperature and concentrated *in vacuo* to give a dark red oil. Purification by column chromatography (silica gel, gradient from 9:1 to 4:1 hexanes:EtOAc) afforded **11** (α + β) and **12** as an inseparable mixture (14.6 mg, 41%, non-optimized). The 2:1 ratio of **11** (α:β = 1:1) and **12** was determined by the integration of C_3–H and C_4–H of the ^{1}H spectrum.

HRMS (ESI): calcd. for $C_{17}H_{24}O_2$ $[M+Na]^+$: 283.1674; found: 283.1661.

Studies on the rate of C-2, C-3 and C-4 of 1,1-dimethyl-cyclohexane in the C–H oxidation using nitrene:



A microwave vial was charged with 1,1-dimethyl-cyclohexane **8** (33.6 mg, 0.30 mmol, 5.0 equiv.), $Rh_2(esp)_2$ (2.2 mg, 3.0 μmol, 0.05 equiv.), $CCl_3CH_2OSO_2NH_2$ (13.5 mg, 0.06 mmol, 1.0 equiv.) and benzene (0.1 mL, 0.6 M of the sulfamate). To this green mixture was added 0.14 mL of a 2.0 M benzene solution of $PhI(OtBu)_2$ (48.8 mg, 0.12 mmol, 2.0 equiv.) via syringe pump over 1 hour. After addition, the resulting dark-red solution was stirred for an additional 30 minutes before concentrated *in vacuo* to give a dark red oil. The 3:1 ratio of **13** and **14** was determined by the integration of C_3–H and C_4–H of the crude ^1H spectrum. The mixture of diastereomers **13** and **14** was further separated by two consecutive preparative TLCs (silica gel, 6:1 Hexanes:EtOAc) in 37% overall yield (5.7 mg **13**, 1.7 mg **14**, non-optimized).



13

Physical State: colorless oil

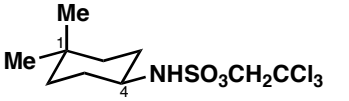
R_f: 0.45 (silica gel, 6:1 Hexanes:EtOAc)

IR (film) ν_{max}: 3681, 3297, 2950, 1453, 1365, 1183, 1051, 1017 cm^{-1}

^1H NMR (600 MHz, $CDCl_3$): 4.62 (s, 2H), 4.35 (brd, J = 7.7 Hz, 1H), 3.50 − 3.58 (m, 1 H), 2.15 − 2.20 (m, 1 H), 1.81 − 1.86 (m, 1 H), 1.61 − 1.66 (m, 1 H), 1.47 − 1.52 (m, 1 H), 1.33 − 1.37 (m, 1 H), 1.03 − 1.11 (m, 3 H), 0.95 (s, 3 H), 0.92 (s, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): 93.6, 78.2, 51.9, 46.7, 38.0, 34.0, 33.0, 32.1, 24.7, 21.3

HRMS (ESI): calcd. for $C_{10}H_{18}Cl_3NO_3S$ $[M+Na]^+$: 359.9971; found: 359.9960.



14

Physical State: colorless oil

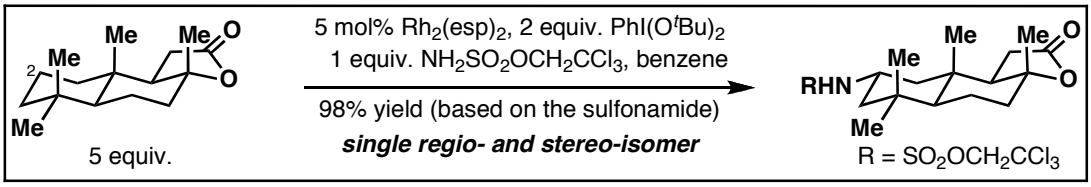
R_f: 0.48 (silica gel, 6:1 Hexanes:EtOAc)

IR (film) ν_{max}: 3681, 3300, 2924, 2854, 1453, 1365, 1184, 1168, 1017 cm^{-1}

^{1}H NMR (600 MHz, $CDCl_3$): 4.62 (s, 2H), 4.51 (brd, *J* = 7.7 Hz, 1H), 3.36 − 3.44 (m, 1 H), 1.91 − 1.96 (m, 2 H), 1.26 − 1.53 (m, 6 H), 0.92 (s, 6 H)

HRMS (ESI): calcd. for $C_{10}H_{18}Cl_3NO_3S$ $[M+Na]^+$: 359.9971; found: 359.9960.

C−H oxidation of (+)-Sclareolide via nitrene insertion:



A microwave vial was charged with (+)-sclareolide (250.4 mg, 1.0 mmol, 5.0 equiv.), $Rh_2(esp)_2$ (7.6 mg, 10.0 μmol, 0.05 equiv.), $CCl_3CH_2OSO_2NH_2$ (45.0 mg, 0.2 mmol, 1.0 equiv.) and benzene (0.5 mL, 0.4 M of the sulfamate). To this green mixture was added 0.50 mL of a 0.8 M benzene solution of iodobenzene diacetate (162.5 mg, 0.40 mmol, 2.0 equiv.) via syringe pump over 3 hours. After addition, the resulting dark-red solution was stirred for an additional 30 minutes before subjected to chromatography (silica gel) directly. Extra benzene (*ca*. 1 mL) was used for rinsing the vial and transferring the reaction to the column in crude form. Gradient eluding (from 4:1 to 1:1 hexanes:EtOAc) provide two fractions. The less polar fraction afforded recovered (+)-sclareolide (196.3 mg, 78% based on sclareolide), while the more polar fraction afforded sulfamate **16** (93.1 mg, 98 % based on sulfamate).

Physical State: white solid (mp 108-110°C)

R_f: 0.55 (silica gel, 1:1 hexanes: EtOAc)

IR (film) ν_{max}: 2929, 1701, 1523, 1389, 1286, 1246, 1156 cm^{-1}

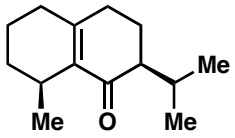
^{1}H NMR (600 MHz, $CDCl_3$): 5.24 (d, *J* = 8.2 Hz, 1 H), 4.60 (s, 2 H), 3.71 − 3.78 (m, 1 H), 2.44 (dd, *J* = 16.0, 15.0 Hz, 1 H), 2.22 (dd, *J* = 6.4, 16.1 Hz, 1 H), 2.09 (dt, *J* = 12.0, 3.2

Hz, 1 H), 1.88 − 1.99 (m, 4 H), 1.67 (dt, *J* = 3.8, 12.5 Hz, 1 H), 1.32 (s, 3H), 1.31 − 1.40 (m, 1 H), 1.19 (t, *J* = 12.5 Hz, 1 H), 1.00 − 1.07 (m, 2 H), 0.96 (s, 3 H), 0.94 (s, 3 H), 0.89 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): 176.7, 93.6, 86.3, 78.0, 58.7, 55.9, 48.9, 48.3, 46.4, 38.4, 37.2, 34.6, 33.0, 28.8, 21.7, 21.4, 20.3, 15.8

References:

1. K. Chen, P. S. Baran, *Nature* **2009**, *459*, 824 – 828.
2. A. Srikrishna, B. Beeraiah, *Synth. Commun.* **2005**, *37*, 2855 – 2860.
3. C. M. Shiner, T. D. Lash, *Tetrahedron* **2005**, *61*, 11628 – 11640.



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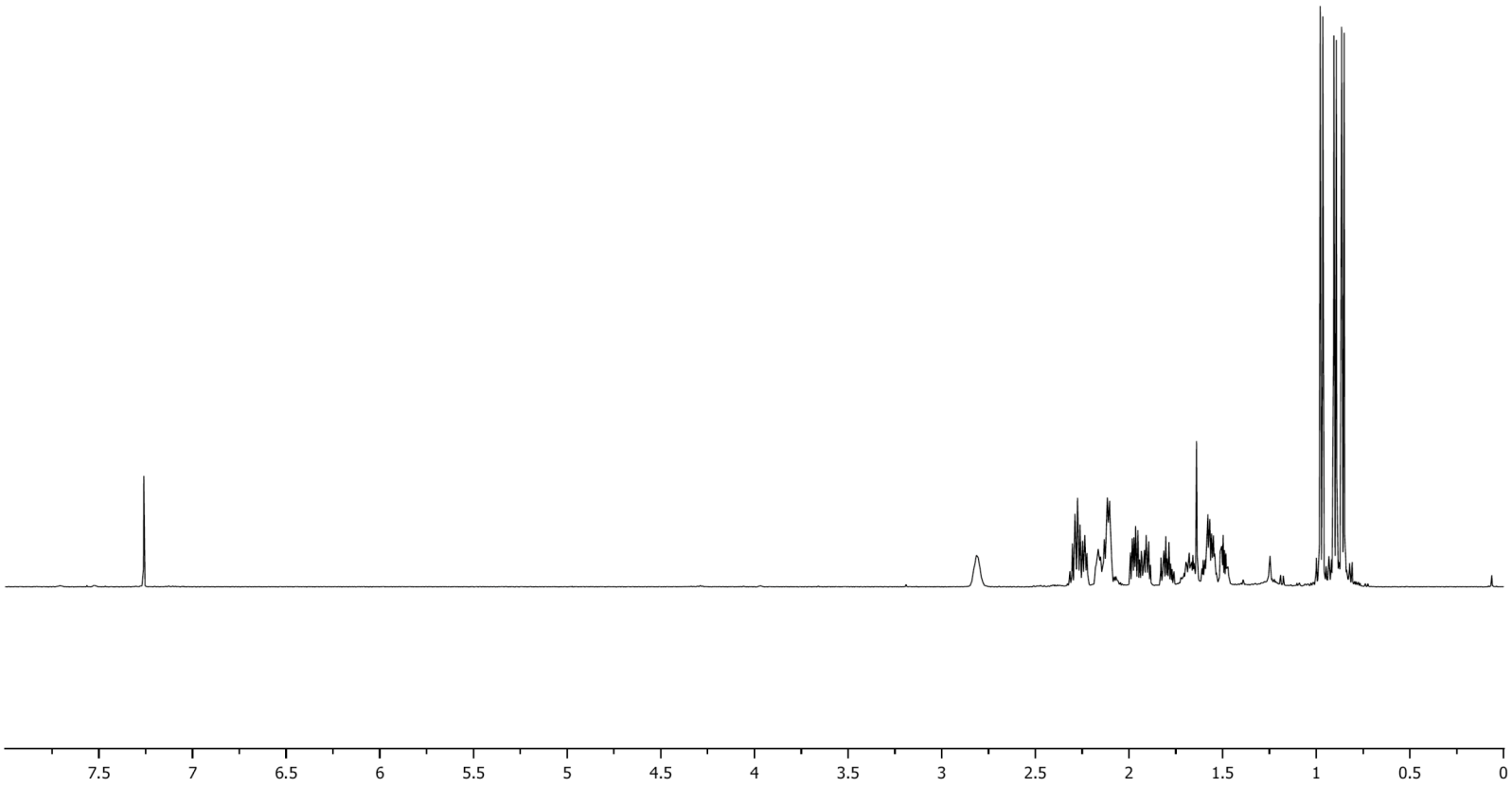

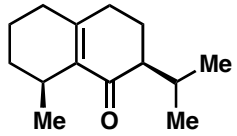
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O
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5

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10
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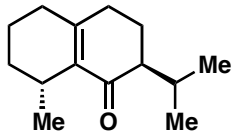
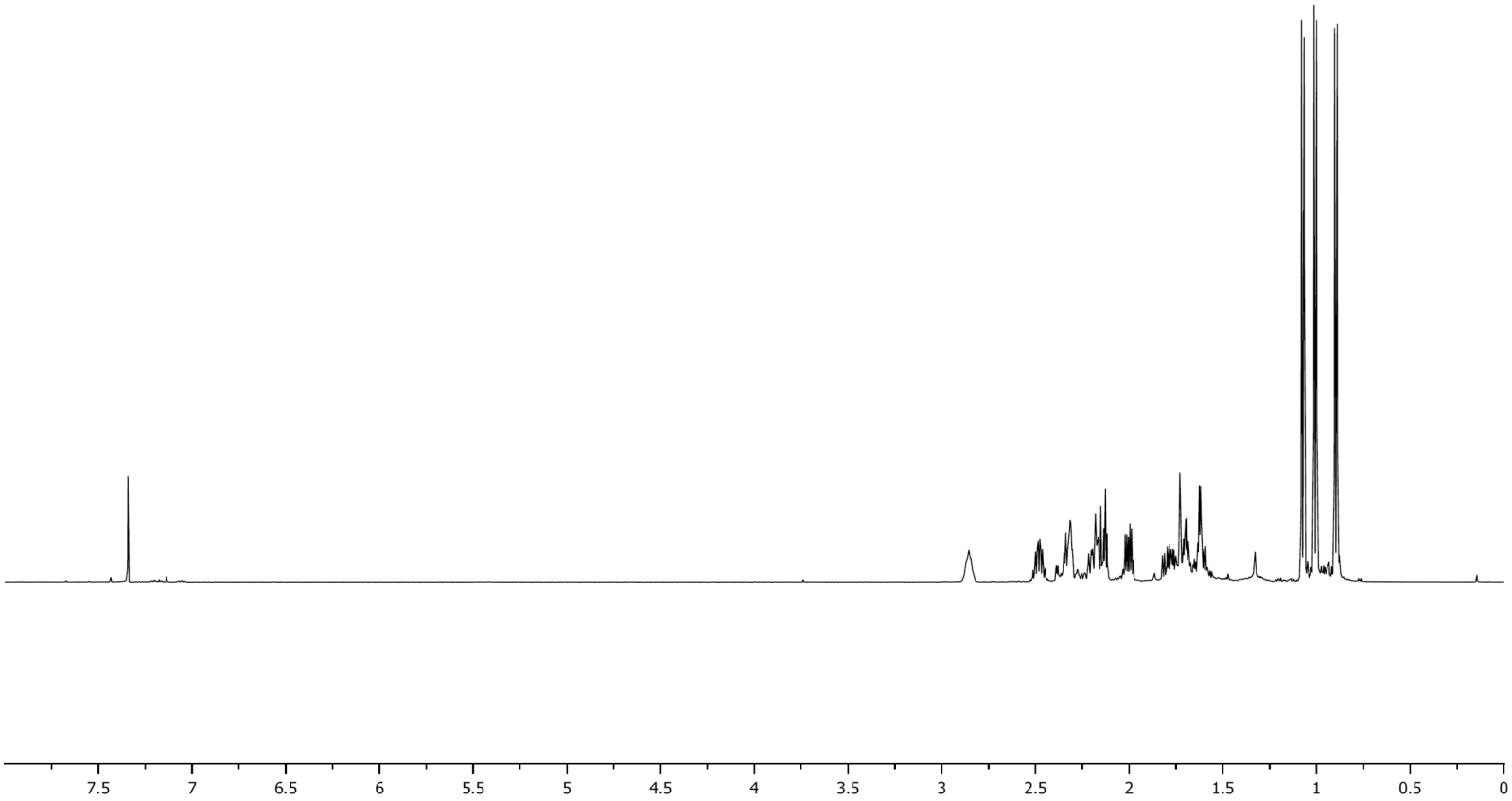
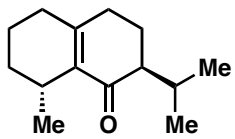


S1

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Me
O
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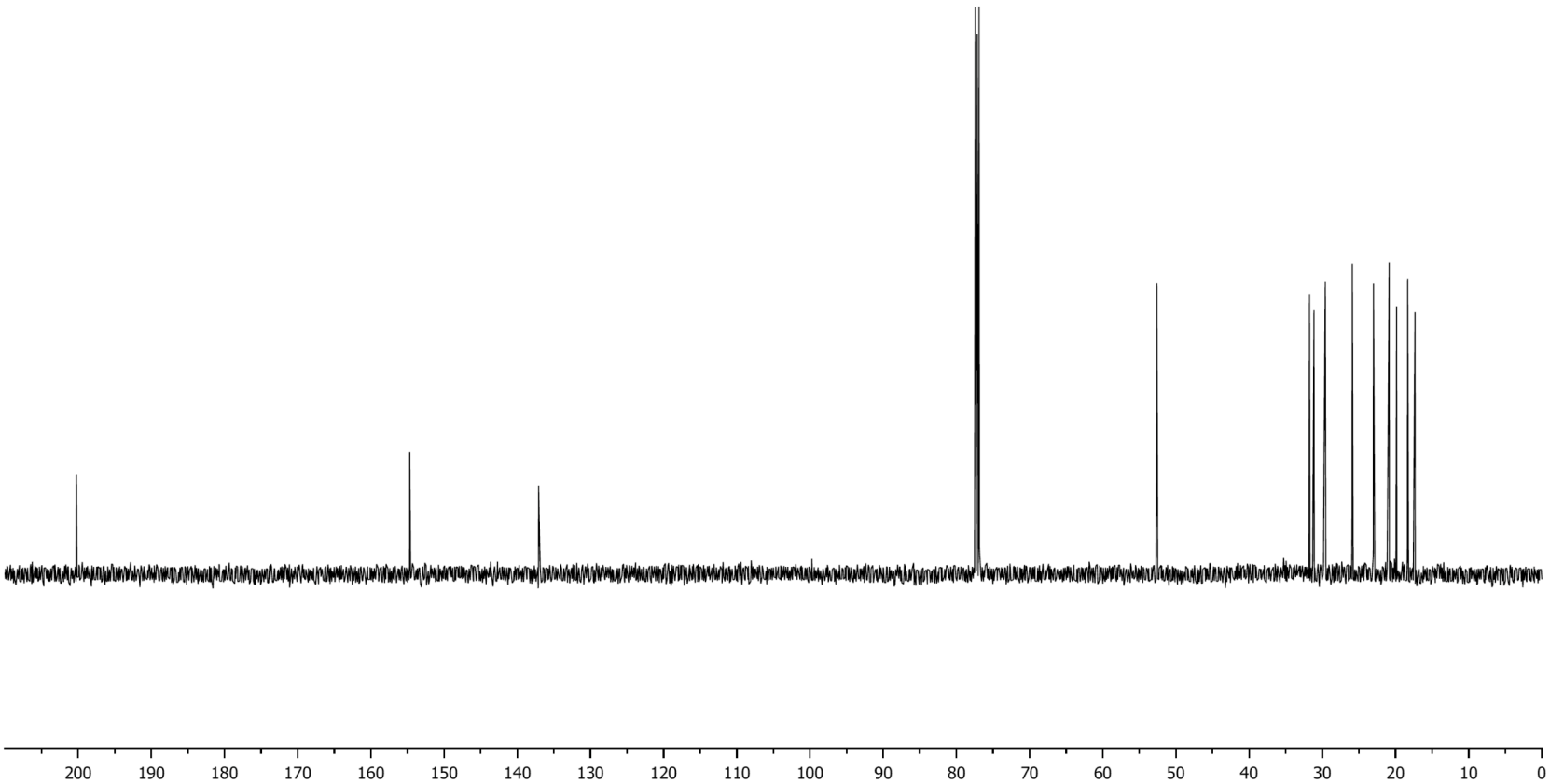
S1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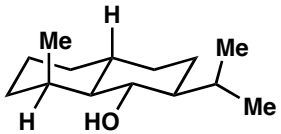

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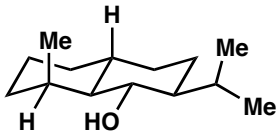
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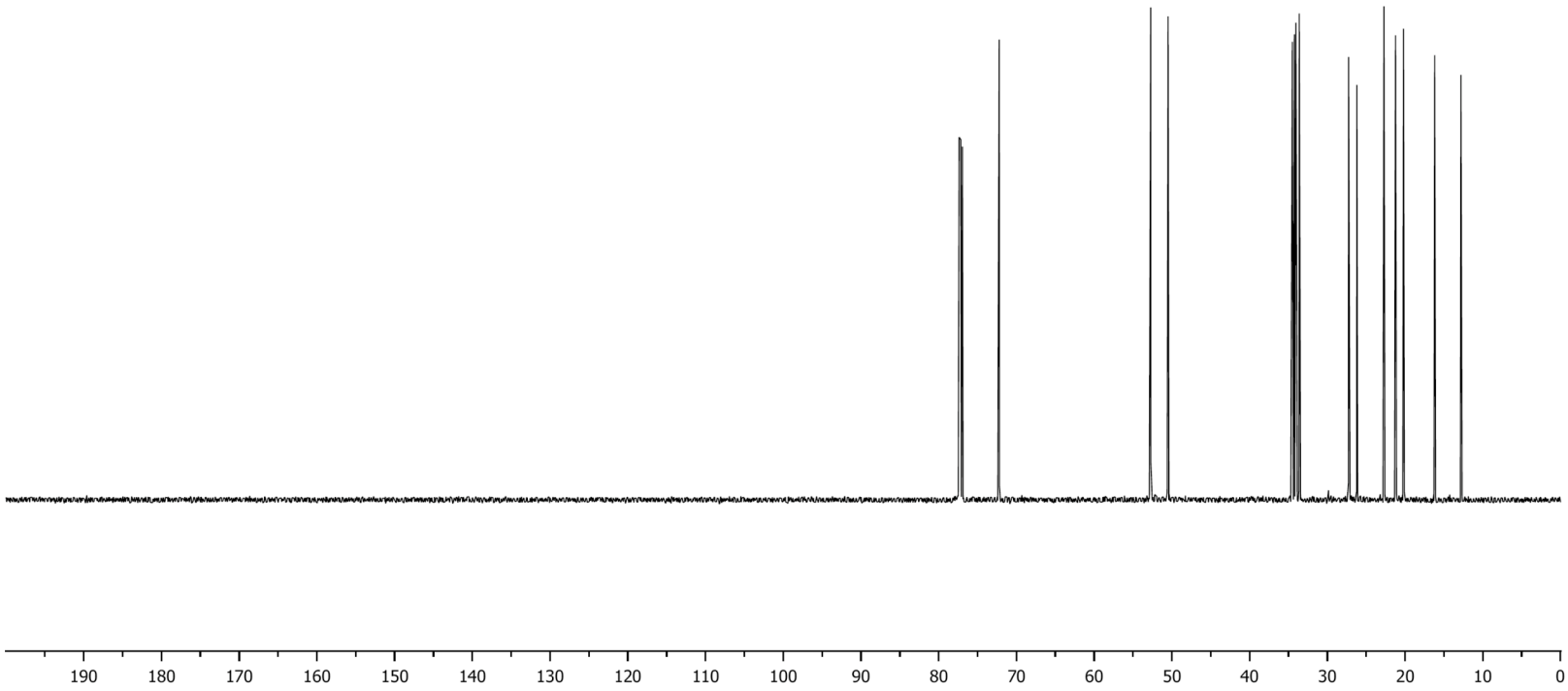
H
HO

6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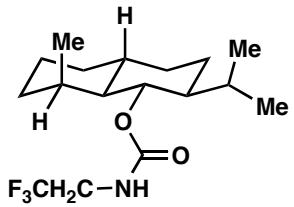

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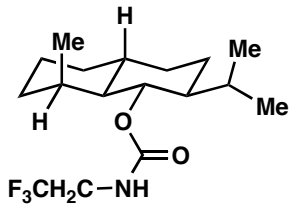
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F3CH2C–NH

3

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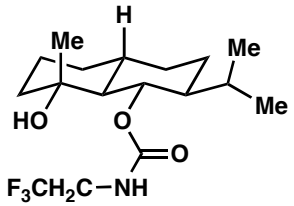

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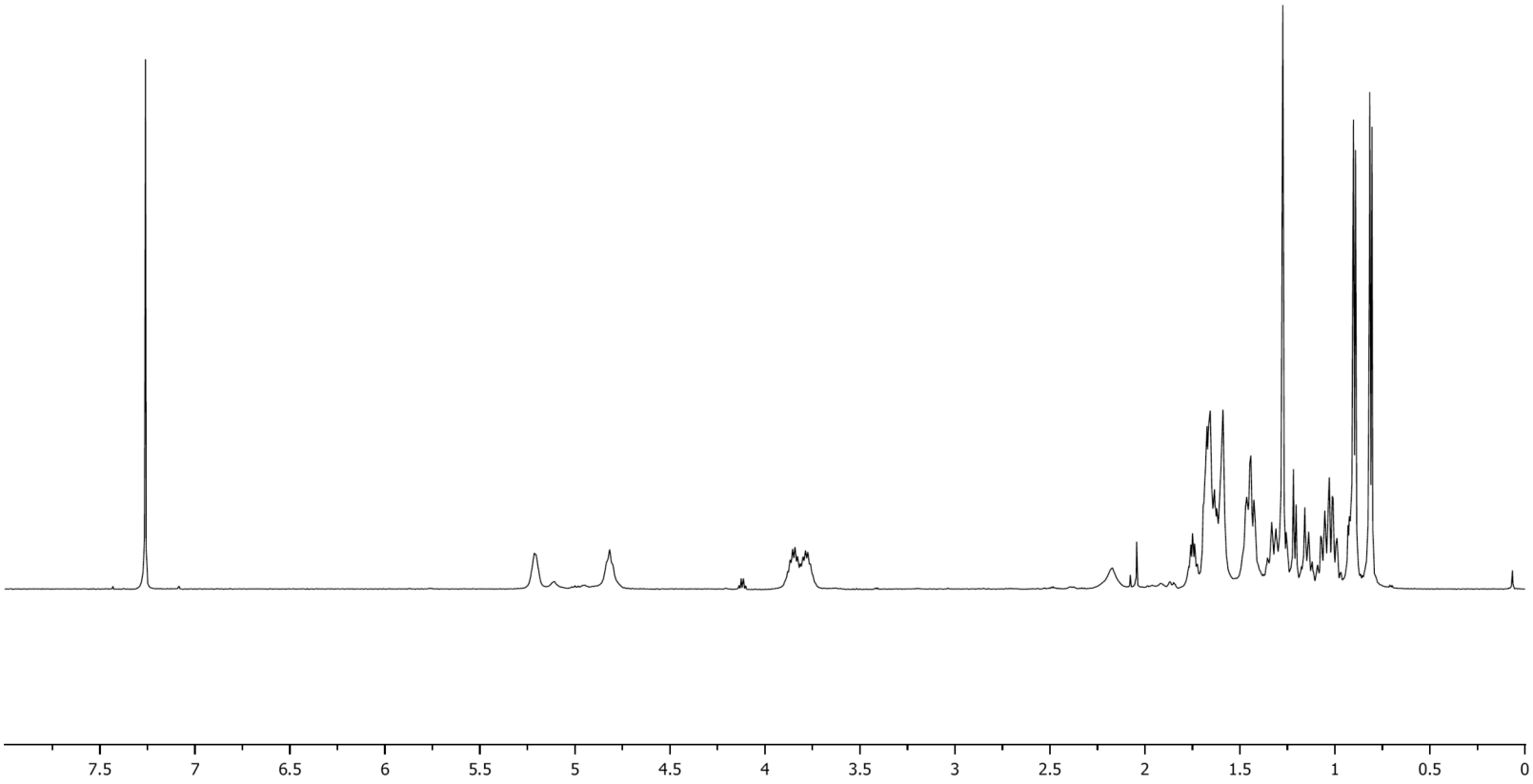

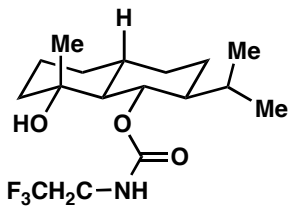
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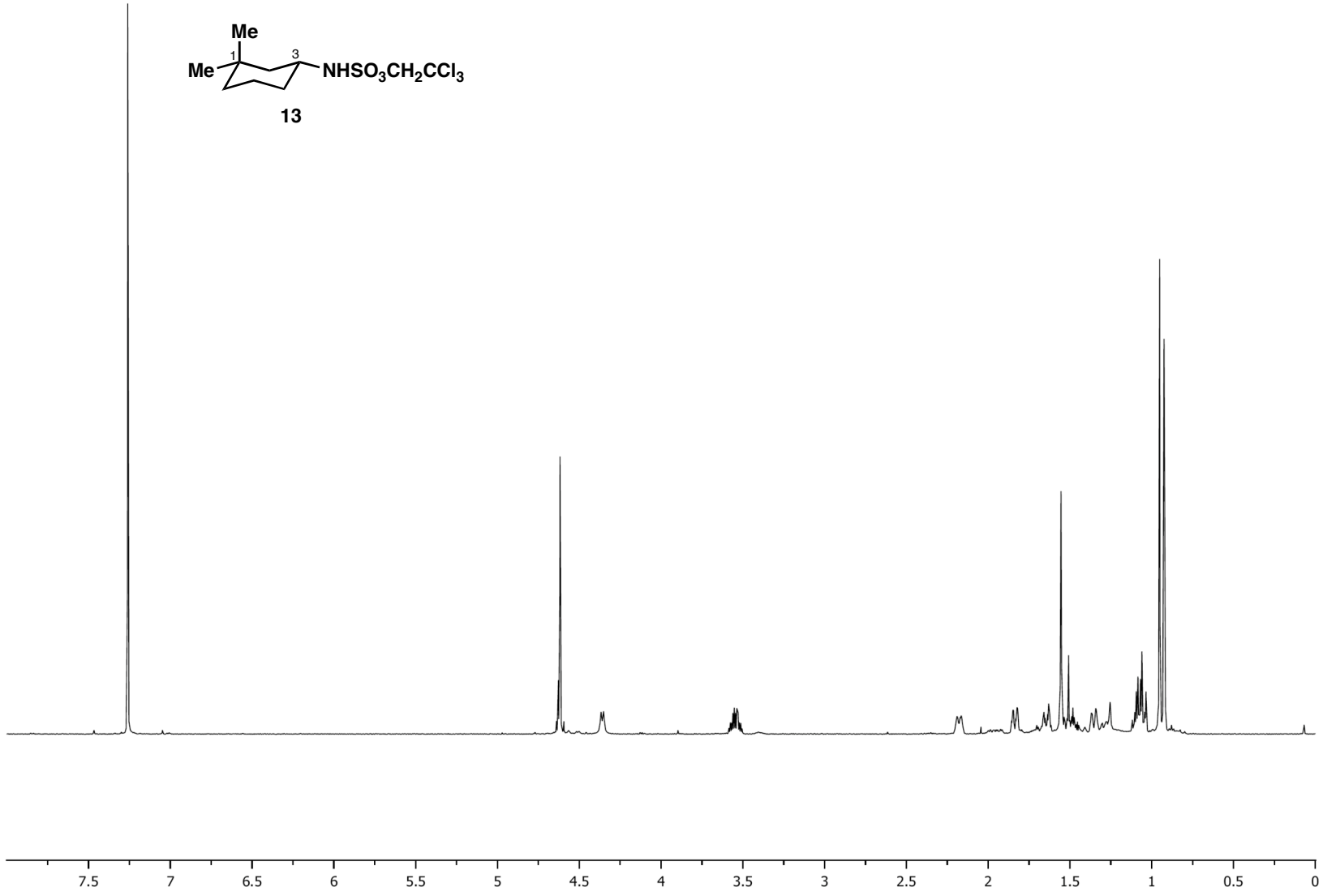
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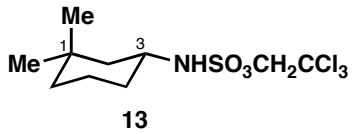
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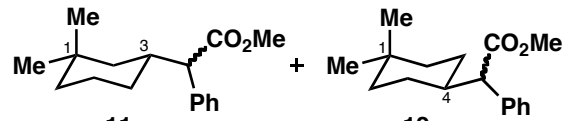
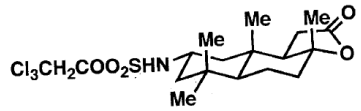


11

12

obtained as a 1:1 mixture
of α and β isomers at C_3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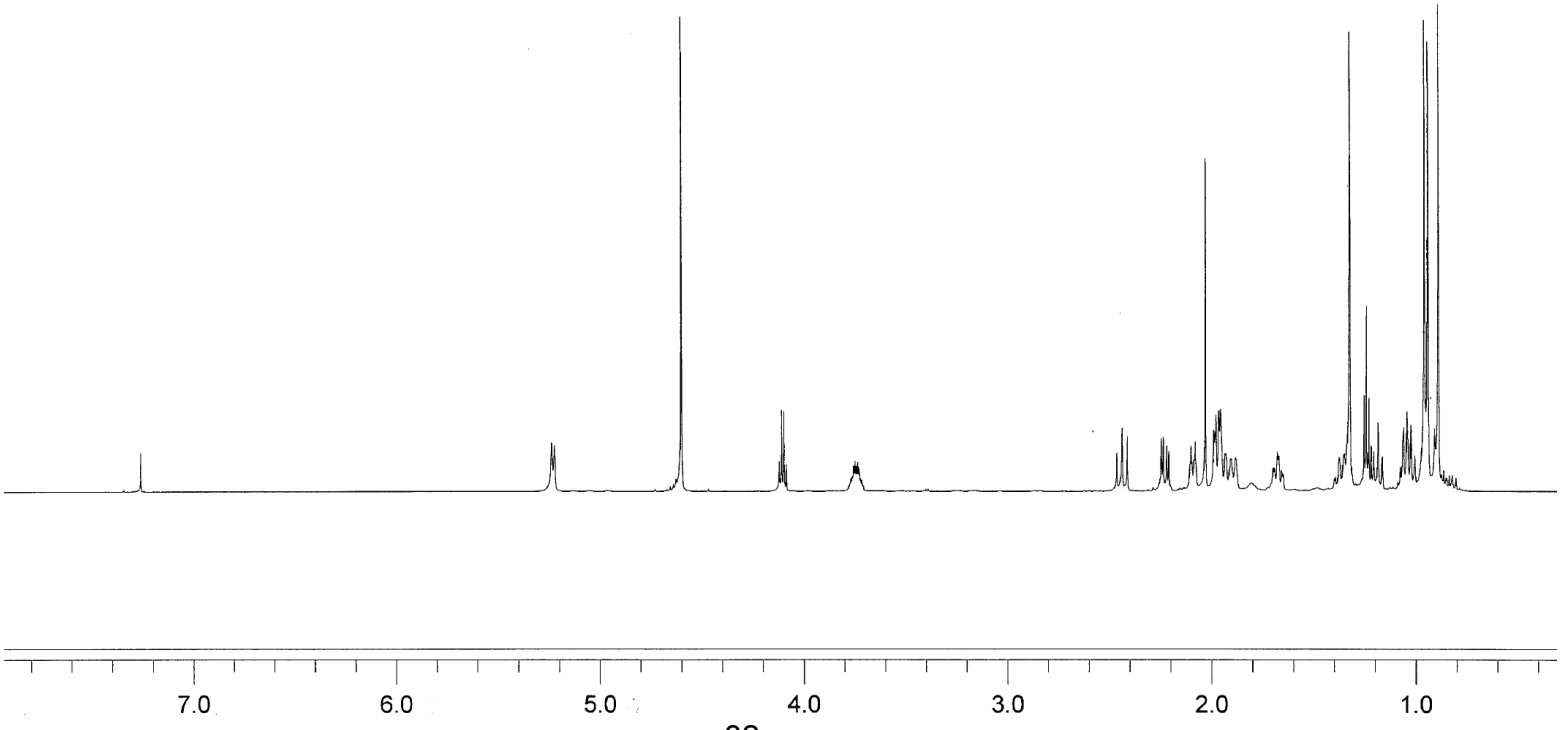
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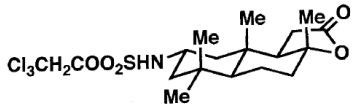
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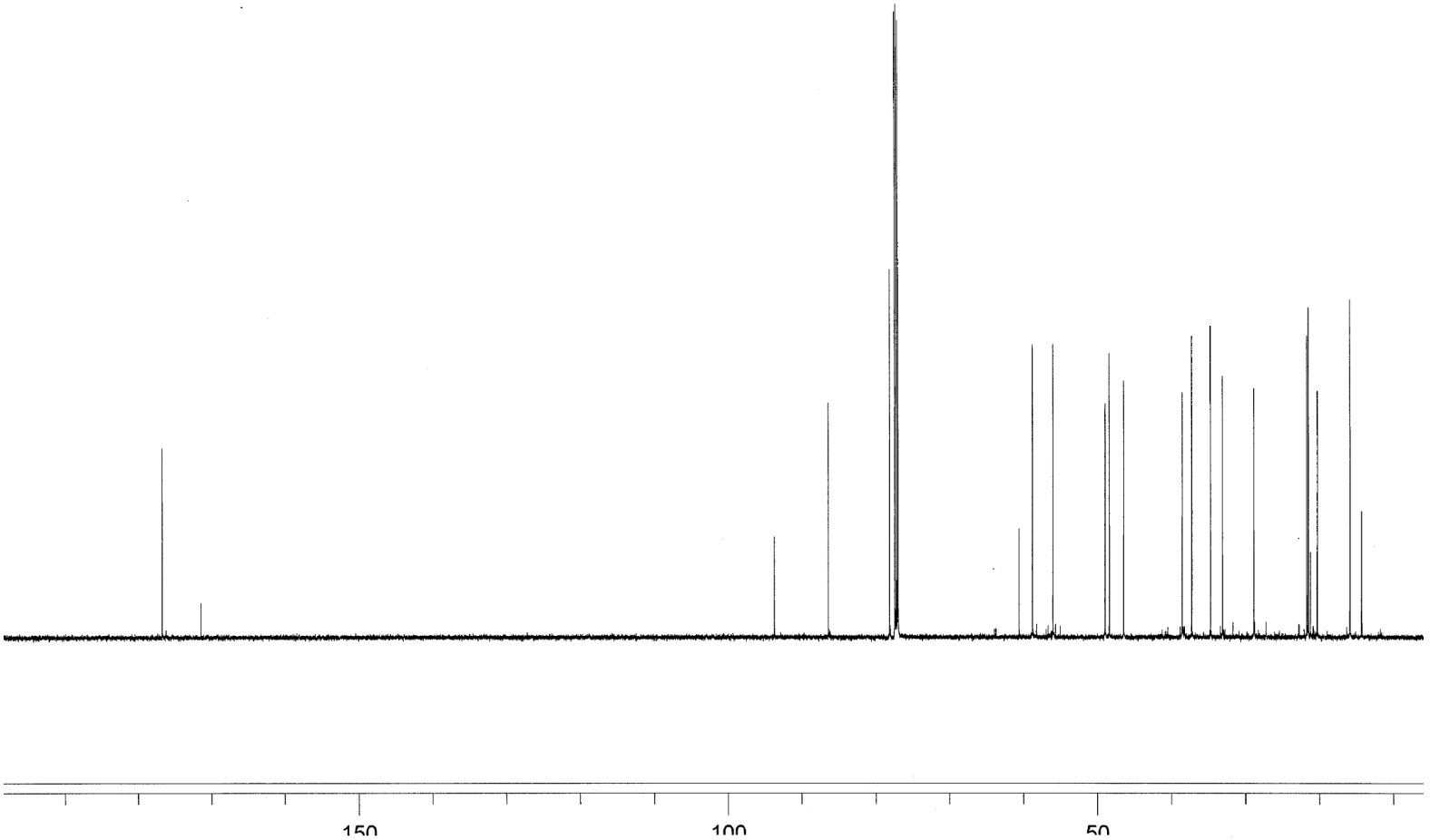
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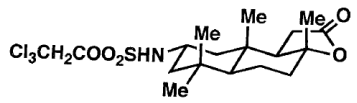
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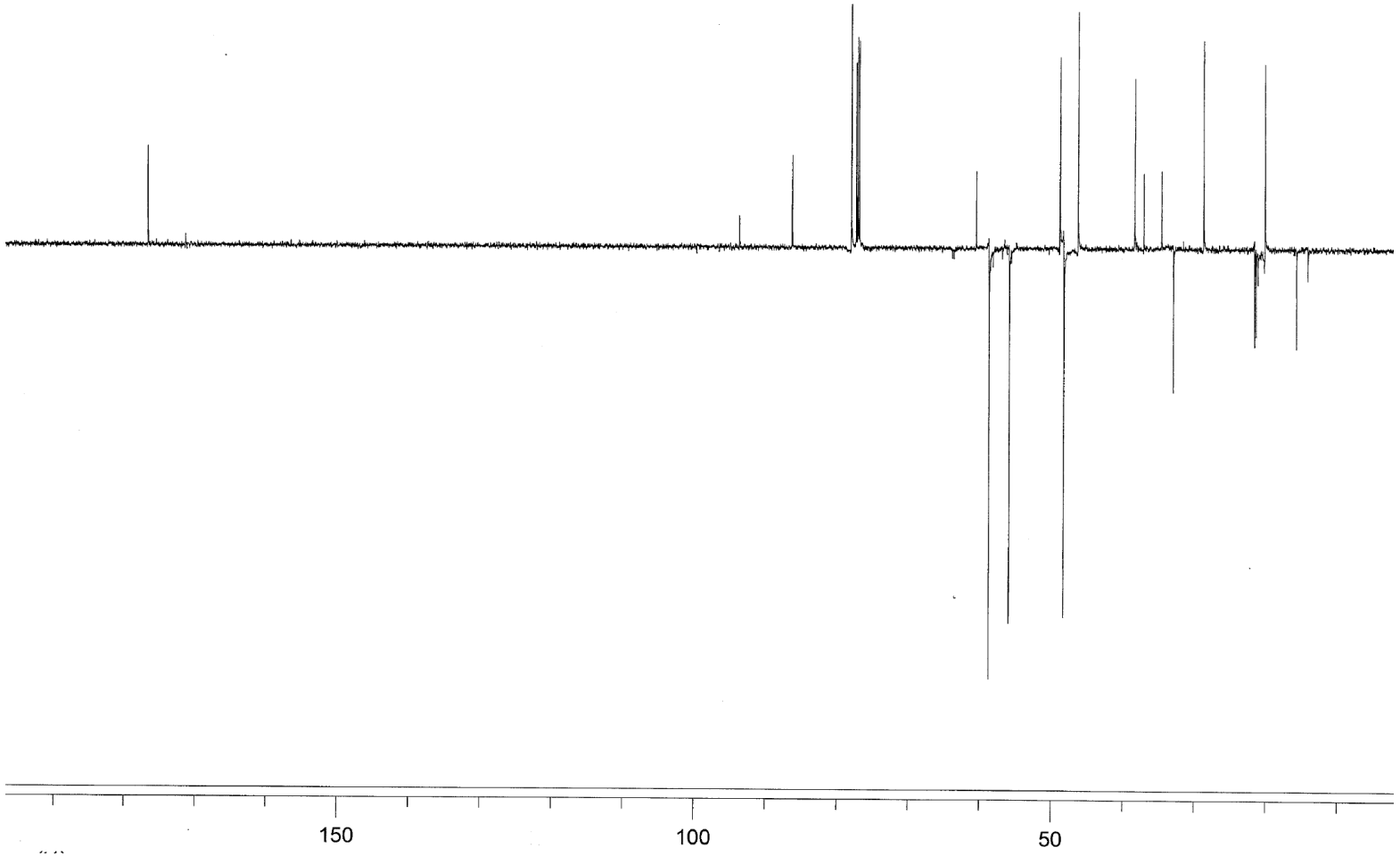
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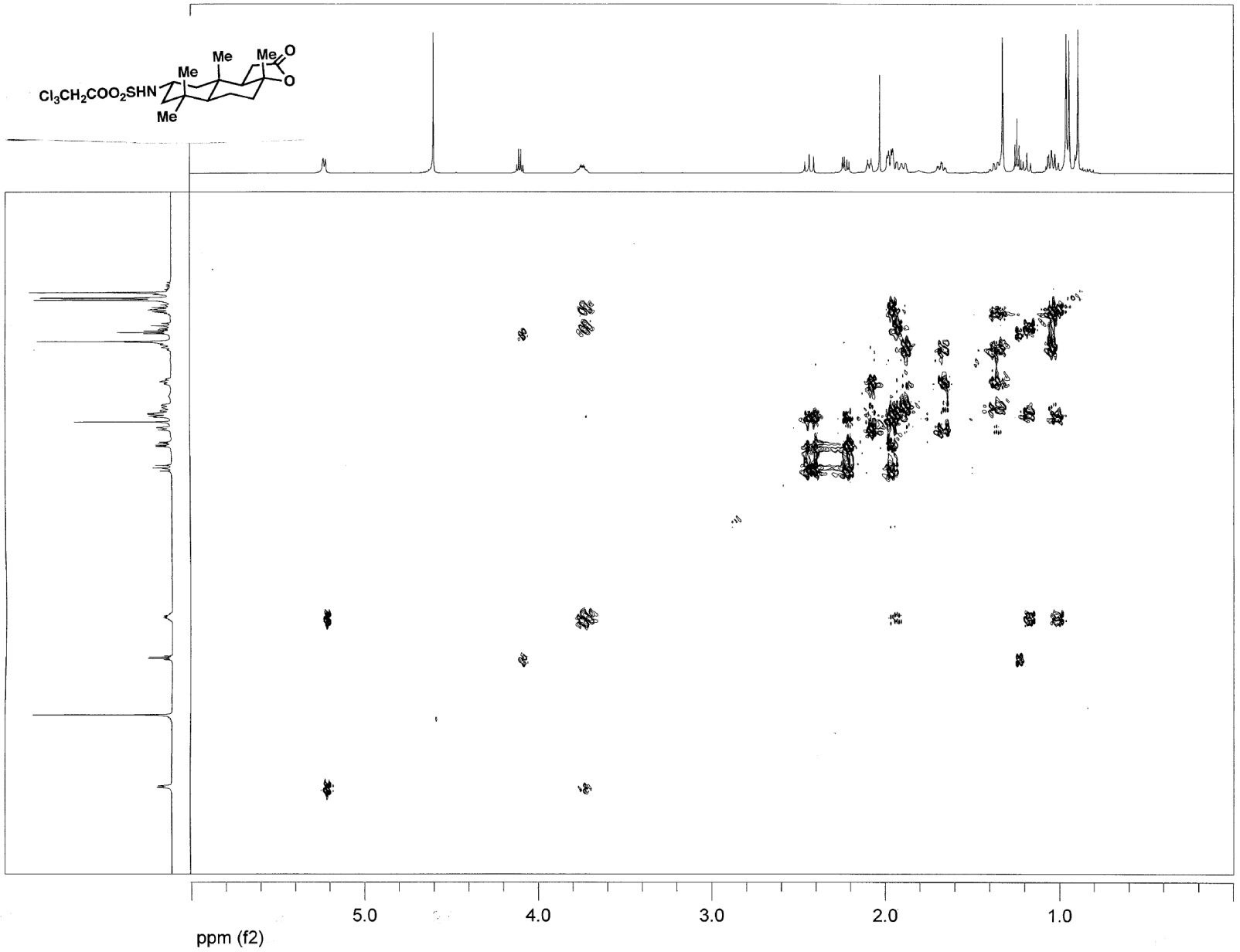
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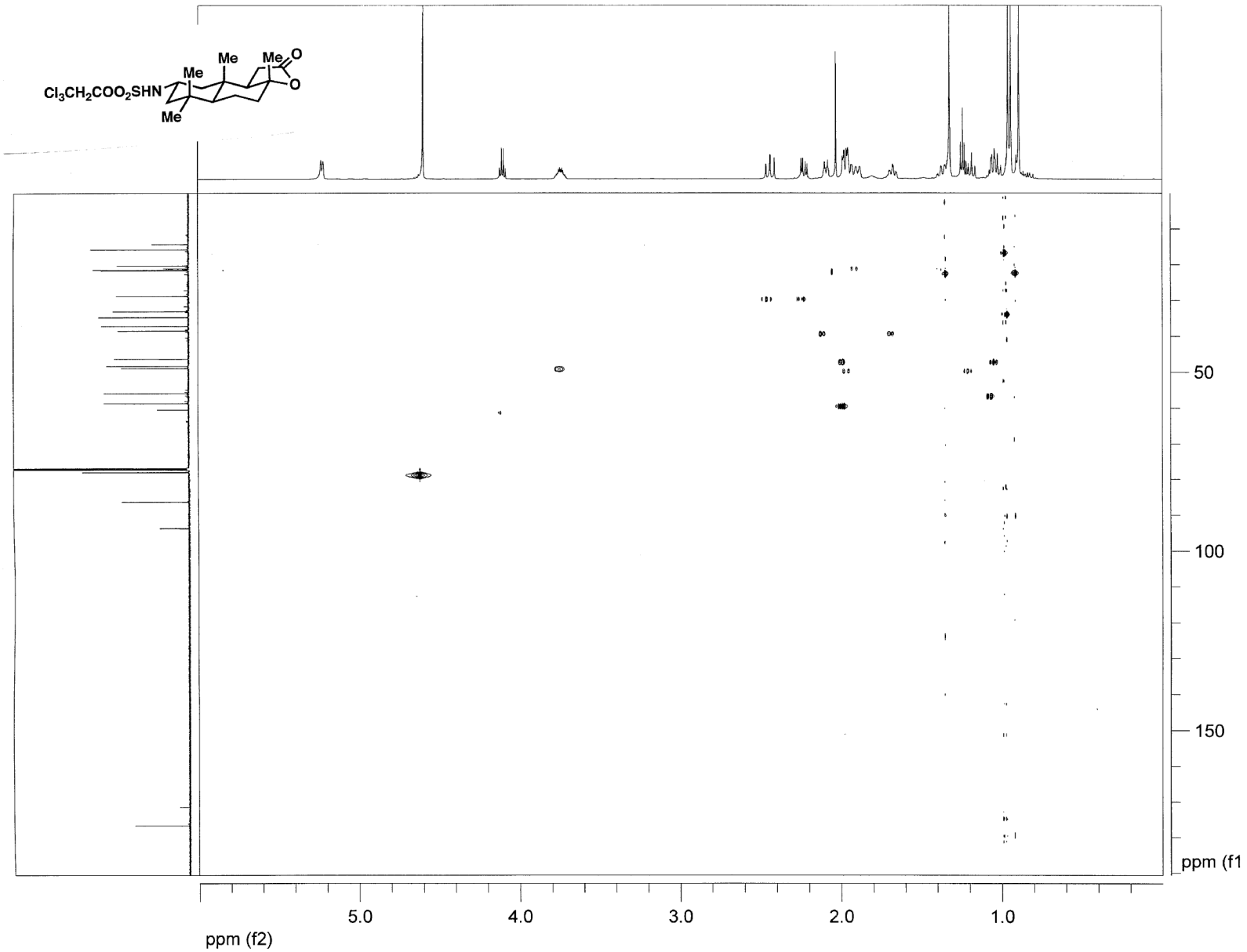
ppm (f2)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ppm (f2)