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Rearrangement pathways in the bicyclo[4.4.1]undecane ring system

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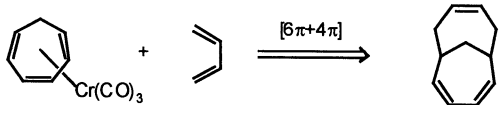
Abstract—The readily available bicyclo[4.4.1]undecane ring system can be transformed into the isomeric bicyclo[5.3.1]undecane and bicyclo[5.4.0]undecane systems via related rearrangement pathways. The resultant products constitute the AB ring substructure of the taxane diterpenes and the BC ring substructure of the tigliane diterpenes, respectively.

1. Introduction

With the advent of the highly efficient Cr(0)-promoted [6π+4π] cycloaddition process, preparation of the interesting and important bicyclo[4.4.1]undecane ring system has become quite routine (Scheme 1).[1]



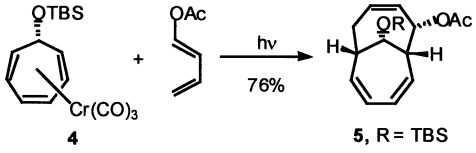
Scheme 1.

While several families of pharmacologically important natural products exhibit this structural feature,[2] it also could be viewed as an intriguing point of departure for accessing a variety of related and otherwise difficult to prepare bicyclic ring systems that are found in the structures of biologically active natural products. For example, simple one-bond reorganizations from the bicyclo[4.4.1]undecane system (**1**) could afford the isomeric bicycles **2** and **3** that constitute substructural features of the tigliane (phorbol) and taxane diterpenes, respectively (Scheme 2).

Previous work from this laboratory has established the viability of this notion for constructing the tigliane and taxane systems.[3,4] We now wish to disclose some detailed studies on the rearrangement pathways themselves.

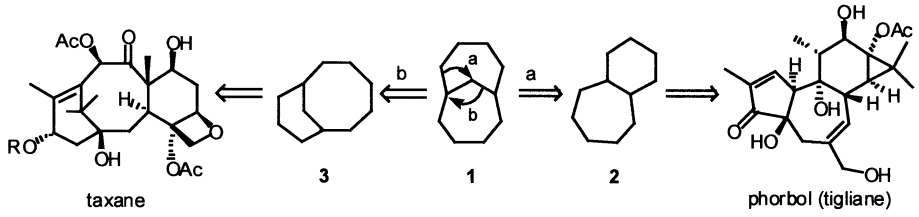
2. Results and discussion

The key bicyclo[4.4.1]undecane substrate **5**, upon which all of the subsequent studies will be based, can be prepared in good yield via the Cr(0)-mediated photocycloaddition of the stereochemically homogeneous complex **4** (Eq. (1)).[5]



(1)

It is noteworthy that the higher-order cycloaddition proceeds with complete *endo* selectivity on the triene face bearing the metal center to provide **5** as a single functional diastereomer. Two strategically positioned oxygen functions emerge from this process that will serve as the group handles for effecting the projected rearrangements. Scheme 3 depicts the routine processing of **5** into **7**, a compound



Scheme 2.

Keywords: cycloadditions; ketols; rearrangements.

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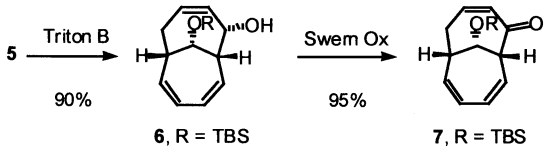


Scheme 3.

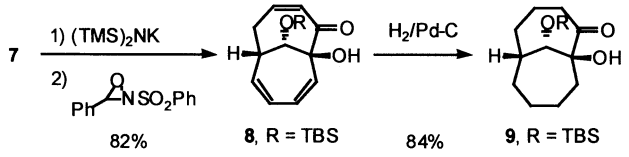
which sets the stage for the anticipated bond reorganization studies.

Key to our ability to effect, in a controlled fashion, the desired rearrangements of **7** into the isomeric bicycles is the installation of a hydroxyl group at the bridgehead position adjacent to the carbonyl group. We had previously demonstrated that bridgehead enolates are easily accessible in the bicyclo[4.4.1]undecane system,[6] and Schleyer and co-workers have shown that bridgehead double bonds are, indeed, quite stable in this ring system.[7] Thus, treatment of **7** with base, followed by oxidation with the Davis oxaziridine,[8] afforded the crucial α-ketol in good yield.

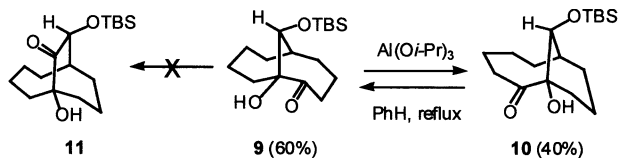
To simplify the rearrangement studies, the 'excess' unsaturation in **8** was removed via catalytic hydrogenation to provide **9** as the first substrate for evaluation (Scheme 4). An α-ketol rearrangement process was envisioned to be a useful and experimentally convenient approach to affecting the desired bond reorganizations.[9,10] It would, of course, be dependent on the relative energies of the various isomeric species that are interconverting via this reversible process (Scheme 5).

In the event, treatment of **9** under conditions of thermodynamic control in the presence of excess $Al(O\textit{i}\text{-}Pr)_3$ in refluxing benzene afforded a mixture of products comprised of 60% of **9** and 40% of the expected bicyclo[5.3.1]undecane **10**. Interestingly, none of the isomeric **11** was detected. The absence of the latter material can be rationalized by invoking chelated reaction intermediates in which only the one-carbon bridging atom is properly aligned for facile migration (Fig. 1).

A slight structural modification of compound **9** should allow production of the corresponding bicyclo[5.4.0]undecane system via an alternative α-ketol rearrangement. The



Scheme 4.



Scheme 5.

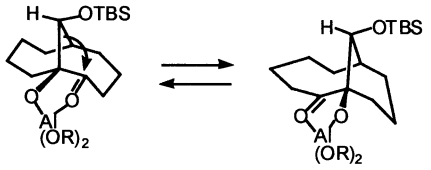
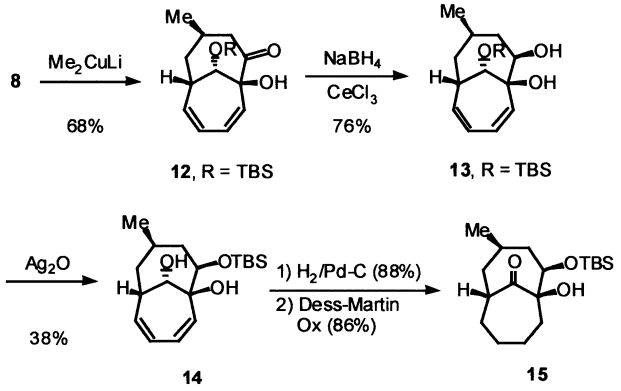


Figure 1. Facile migration of the one-carbon bridging atom.

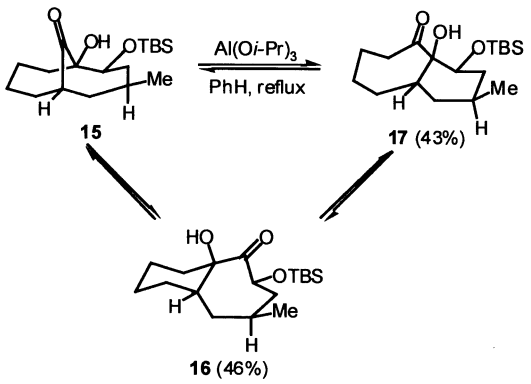


Scheme 6.

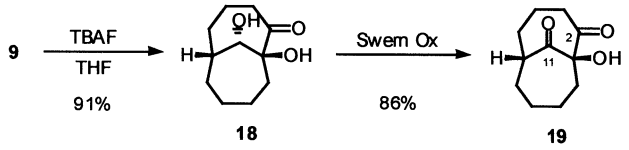
sequence of transformations necessary for effecting these changes is illustrated in Scheme 6. Routine conjugate addition of a methyl group to **8** gave **12**, which was followed by a stereoselective reduction of the resultant ketone to provide the corresponding *cis*-diol **13**.[11] Efforts to cleanly protect the secondary alcohol in **13** failed, but a serviceable solution to this problem surfaced when exposure of this compound to Ag_2O was found to provide an easily separable mixture of recovered **13** and compound **14**, in which the silyl protection had been transferred to the proximate hydroxyl group. Finally, catalytic hydrogenation of **14** and Dess–Martin oxidation gave substrate **15** in good overall yield.

With **15** in hand, our attention turned to effecting rearrangement to the requisite bicyclo[5.4.0]undecane system. In this instance, migration of either bond that flanks the α-ketol would lead to the desired ring system. However, each product would exhibit a slightly different substitution pattern, and it was unclear as to how one could manipulate the process to favor one or the other isomer. In the event, treating **15** with excess $Al(O\textit{i}\text{-}Pr)_3$ as before afforded an 89% yield of a nearly 1:1 mixture of the two possible isomeric products **16** and **17**. It is noteworthy that none of the starting material remained, indicating a strong thermodynamic preference for the bicyclo[5.4.0]undecane system (Scheme 7). Control experiments revealed that the ratio of **16** and **17** is the equilibrium ratio.

Finally, in an effort to gain some critical insight into the relative stabilities of the various bicyclo[*m.n.o*]undecane systems involved in these studies, a modified substrate was prepared in which two of the three possible migrating centers would involve a carbonyl group, the third being a simple methylene carbon. The design of this substrate was predicated on the notion that products derived only from migration of a carbonyl carbon would be obtained based



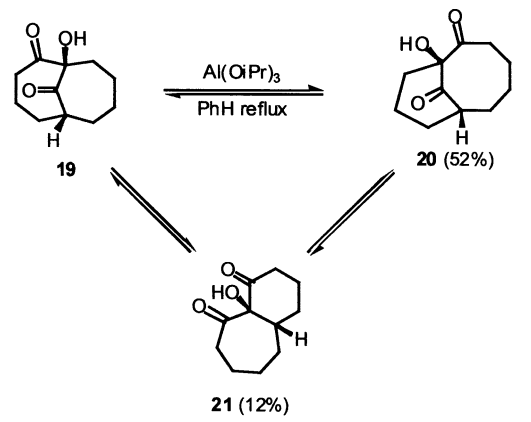
Scheme 7.



Scheme 8.

on the well-known migratory aptitude of this function.[12] A potential complication in this scheme would be competitive fragmentation of the various 1,3-dicarbonyl species in the presence of adventitious base. Once again compound **9** provided the starting point for the study. Scheme 8 details the conversion of this species into the requisite substrate.

With compound **19** in hand, the rearrangement chemistry could be examined. In this case, migration of C-2 would give the corresponding bicyclo[5.4.0] system and the shift of C-11 would afford the alternative bicyclo[5.3.1]undecane system. Thus, **19** was heated at reflux in the presence of excess Al(O*i*-Pr)$_3$ for an extended period of time (23 h) to presumably establish an equilibrium mixture. Interestingly, this transformation afforded a mixture consisting of **20** (52%) and **21** (12%). None of the starting material was isolated (Scheme 9). This result was somewhat surprising in light of prior observations (Schemes 5 and 7), in which a clear preference for the bicyclo[5.4.0]undecane system over the bicyclo[4.4.1]undecane system was evident. A similar preference for the bicyclo[5.3.1]undecane system was not established.



Scheme 9.

To shed additional light on this situation, computational studies[13] were carried out, which suggested the relative stabilities of these three isomers were in the order: bicyclo[5.4.0]undecane (−127.3 kJ/mol)>bicyclo[5.3.1]-undecane (−114.5 kJ/mol)>bicyclo[4.4.1]undecane (−105.6 kJ/mol). This trend was only partially supported by our experimental observations. However, the fact that more of compound **20** than of the presumably more stable **21** was isolated from the above reaction may, in fact, reflect the presence of decomposition pathways available to these 1,3-dicarbonyl compounds rather than the true thermodynamic stabilities of the various interconverting species. Indeed over longer reaction times (80 h) the amount of **21** decreased at a faster rate than that of **20** until little identifiable product remained, supporting the contention that decomposition pathways are competitive with rearrangement under these particular conditions. In any case, the basic premise of the study has been confirmed. The least stable bicyclo[4.4.1]undecane ring system can, indeed, serve as a precursor to other less available and more stable ring systems.

3. Experimental[14]

3.1. General

3.1.1. η^6-(7-*endo*-[*tert*-Butyldimethylsilyl)oxy]-1,3,5-cycloheptatriene)tricarbonyl chromium(0) (4). To a solution of tris-(acetonitrile)(tricarbonyl)chromium(0) in THF (50 mL), prepared in situ from $Cr(CO)_6$ (7.00 g, 31.8 mmol) and acetonitrile (100 mL), was added a solution of 7-*tert*-butyldimethylsilyloxycycloheptatriene (3.50 g, 10.40 mmol)[5a] and the resulting mixture was stirred at 35–40°C for 18 h. The reaction mixture was filtered, concentrated in vacuo to give a residue, which was purified by flash column chromatography (silica gel, hexanes) to afford 2.30 g (57%) of the chromium complex **4** as red needles: R_f 0.28 (hexanes–EtOAc, 20:1); mp 112–113°C (pentane); IR (CH_2Cl_2) ν 3048, 3021, 2955, 1964, 1924, 1871, 1558, 1465, 1405, 1252, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92–6.02 (m, 2H), 4.61–4.66 (m, 2H), 3.79 (bs, 1H), 3.26 (d, J=9.3 Hz, 2H), 0.94 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 97.1, 94.4, 66.1, 65.5, 25.6, 18.2, −5.0,; MS *m/e* (rel. int.) 358 (11), 274 (63), 217 (99), 126 (44), 91 (86); HRMS calcd for $C_{16}H_{22}O_4SiCr$ (M^+) 358.0692; found 358.0697.

3.1.2. *rac*-[1*R*,6*R*,7*R*,11*R*]-7-Acetoxy-11-[(*tert*-butyldimethylsilyl)oxy]bicyclo[4.4.1]undeca-2,4,8-triene (5). A solution of **4** (2.10 g, 5.90 mmol) and 1-acetoxybutadiene (1.32 g, 11.80 mmol) in hexanes (100 mL) was irradiated (pyrex filter) for 1 h. The reaction mixture was then stirred under a blanket of CO for 12 h and then concentrated in vacuo to ca. 5 mL. The residue was then treated with trimethylphosphite (5 mL) for 48 h at room temperature. The reaction mixture was carefully concentrated in vacuo (using a rotoevaporator equipped with a bleach trap) to give a residue which was purified by flash column chromatography (silica gel, hexanes–EtOAc, 20:1) to afford 1.48 g (76%) of the cycloadduct **5** as colorless needles: mp 59–60°C (Et_2O–pentane); IR (CH_2Cl_2) ν 3017, 2929, 1740, 1471, 1370, 1242, 1081, 839 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 6.23 (bs, 1H), 5.46–5.82 (m, 6H), 4.43 (dd, J=3.6, 3.5 Hz, 1H), 2.98–3.06 (m, 1H), 2.84–2.88 (m, 1H), 2.60–2.63 (m, 1H), 2.05–2.15 (m, 1H), 2.09 (s, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 135.8, 132.2, 128.4, 127.6, 126.8, 124.9, 71.8, 71.6, 50.5, 45.4, 25.7, 24.6, 21.3, 18.0, −5.0, −5.1; MS *m/e* (rel. int.) 277 (30), 219 (27), 143 (33), 117 (63), 91 (100); HRMS calcd for $C_{15}H_{21}O_3Si$ (M^+−*t*-Bu) 277.1259, found 277.1263; Anal. calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04. Found: C, 68.29; H, 8.79.

3.1.3. *rac*-[1*R*,6*R*,7*R*,11*R*]-11-[(*tert*-Butyldimethylsilyl)-oxy]-7-hydroxy bicyclo[4.4.1]undeca-2,4,8-triene (6). To a solution of **5** (2.00 g, 5.99 mmol) in methanol (4 mL) was added benzyltrimethylammonium hydroxide (7.40 mL, 40 wt% in methanol, 18.00 mmol) and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water (10 mL) and ethyl acetate (25 mL), the organic phase was separated and the aqueous phase was extracted with ethyl acetate (2×25 mL). The combined organic extracts were rinsed with brine (2×15 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 15:1) to afford 1.63 g (93%) of the allylic alcohol **6**: R_f 0.21 (hexanes–EtOAc, 15:1); mp 102–104°C (colorless needles, Et_2O–hexanes); IR (CH_2Cl_2) ν 3304, 3017, 2950, 1472, 1459, 1386 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 6H), 5.24 (bs, 1H), 4.41 (dd, J=3.3, 3.5 Hz, 1H), 2.84–2.94 (m, 2H), 2.55–2.60 (m, 1H), 2.21 (bs, D_2O exchangeable, 1H), 1.99–2.09 (m, 1H), 0.93 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 131.8, 128.0, 127.6, 126.5, 125.0, 71.8, 68.6, 53.6, 45.2, 25.7, 24.5, 17.9, −4.9, −5.0; MS *m/e* (rel. int.) 292 (0.4), 235 (26), 91 (100); HRMS calcd for $C_{13}H_{19}O_2Si$ (M^+−*t*-Bu) 235.1154, found 235.1150; Anal. calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65. Found: C, 69.59; H, 9.85.

3.1.4. *rac*-[1*R*,6*S*,11*S*]-11-[(*tert*-Butyldimethylsilyl)oxy]-bicyclo[4.4.1]undeca-3,7,9-triene-2-one (7). To a cold (−78°C) solution of oxalyl chloride (0.359 mL, 4.1 mmol) in CH_2Cl_2 (25 mL) was added a solution of dimethylsulfoxide (0.693 mL, 9.7 mmol) in CH_2Cl_2 (8 mL) and the resulting mixture was stirred for 20 min. At this time, a solution of the allylic alcohol **6** (1.20 g, 4.1 mmol) in CH_2Cl_2 (25 mL) was added to the reaction mixture and stirred at −78°C for an additional 1 h. Triethylamine (2.86 mL, 20.5 mmol) was then added to the reaction mixture and the mixture was stirred for an additional 1 h while slowly warming to room temperature. The reaction mixture was diluted with water (20 mL) and CH_2Cl_2 (100 mL), the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The organic extracts were combined, rinsed successively with 2% aqueous hydrochloric acid solution (20 mL), saturated aqueous sodium bicarbonate solution (20 mL), and brine (2×20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 15:1) to afford 1.130 g (95%) of the ketone **7**: R_f 0.58 (hexanes–EtOAc, 10:1); mp 66–67°C (colorless needles, hexane–ether); IR (CH_2Cl_2) ν 3019, 2927, 2855, 1658, 1251, 1067, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (ddd, J=12.3, 7.2, 4.5 Hz, 1H), 6.05 (d, J=12.3 Hz, 1H), 5.71–5.91 (m, 3H), 5.51 (dd, J=10.5, 7.8 Hz, 1H), 4.37 (dd, J=3.9, 3.8 Hz, 1H), 3.76–3.82 (m, 1H), 2.91–3.00 (m, 1H), 2.91 (ddd, J=15.9, 4.8, 4.7, 1.8 Hz, 1H), 2.38 (ddd, J=15.9, 7.2, 5.4 Hz, 1H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 142.2, 134.9, 133.5, 127.2, 124.8, 124.7, 71.2, 64.5, 46.5, 28.5, 25.6, 17.9, −5.0, −5.1; MS *m/e* (rel. int.) 290 (2), 233 (66), 215 (6), 165 (11), 91 (100); HRMS calcd for $C_{17}H_{26}O_2Si$ (M^+) 290.1701, found 290.1697.

3.1.5. *rac*-[1*R*,6*R*,11*R*]-11-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxybicyclo[4.4.1]undeca-3,7,9-triene-2-one (8). To a cold (−78°C) solution of potassium hexamethyldisilazide (7.58 mL, 0.5 M in toluene, 3.79 mmol) in dry THF (10 mL) was added a solution of the ketone **7** (1.00 g, 3.45 mmol) in THF (7 mL) and the resulting deep red enolate solution was stirred at −78°C for 0.5 h. At this time, a pre-cooled (−78°C) solution of 3-phenyl-2-phenylsulfonyl oxaziridine[8] (1.35 g, 5.17 mmol) in THF (5 mL) was added to the reaction, and the resultant mixture was stirred at −78°C for an additional 3 h. The mixture was quenched with water (3 mL). The reaction mixture was then warmed to 0°C, triethylamine (3 mL) was added, the mixture stirred for 0.5 h at room temperature and diluted with Et_2O (30 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2×20 mL). The organic phases were combined, rinsed with brine (2×10 mL) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 5:1) to afford 0.866 g (82%) of the α-ketol **8**: R_f 0.56 (hexanes–EtOAc, 5:1); mp 74–74.5°C (needles, pentane); IR (CH_2Cl_2) ν 3451, 3026, 2953, 1672, 1247, 1061, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.56 (ddd, J=12.6, 7.8, 3.9 Hz, 1H), 5.07–5.12 (m, 5H) 4.66 (s, D_2O exchangeable, 1H), 4.33 (d, J=4.2 Hz, 1H), 2.94 (dddd, J=15.9, 5.1, 3.9, 1.5 Hz, 1H), 2.87 (dd, J=11, 4.2 Hz, 1H), 2.30 (ddd, J=15.9, 7.8, 4.2 Hz, 1H), 0.85 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 142.5, 134.2, 130.7, 128.4, 125.8, 123.6, 85.5, 74.5, 45.4, 27.4, 25.7, 18.1, −5.2, −4.5; MS *m/e* (rel. int.) 306 (2), 249 (50), 231 (11), 181 (53); HRMS calcd for $C_{17}H_{26}O_3Si$ (M^+) 306.1651, found 306.1645.

3.1.6. *rac*-[1*R*,6*S*,11*R*]-11-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxybicyclo[4.4.1]undeca-2-one (9). To a solution of the ketol **8** (0.200 g, 0.660 mmol) in CH_3OH (10 mL) was added Pd/C (10%, 0.015 g) and the mixture was flushed three times with H_2 and then stirred under a blanket of H_2 (balloon) for 2 h. At this time, the reaction mixture was filtered through a bed of Celite (Et_2O, 20 mL) and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 20:1) to afford 0.174 g (84%) of the saturated ketol **9**: mp 66–67°C (Et_2O–hexanes); R_f 0.19 (hexanes–EtOAc, 20:1); IR (CH_2Cl_2) ν 3456, 2928, 1700, 1250, 1073, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (s, 1H, D_2O exchangeable), 4.03 (d, J=2.0 Hz, 1H), 2.72–2.60 (m, 2H), 2.20–2.09 (m, 2H), 2.02–1.59 (m, 11H), 0.83 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 85.2, 81.6, 42.5, 41.1, 37.6, 32.4, 28.2, 25.7, 25.5, 23.3, 20.6, 17.9, −4.8, −4.9; MS *m/e* (rel. int.) 312 (M^+, 0.3), 255 (12), 237 (33); HRMS calcd for $C_{17}H_{32}O_3Si$ (M^+−*t*-Bu) 255.1416, found

255.1420; Anal. calcd for $C_{17}H_{32}O_3Si$: C, 65.34; H, 10.32. Found: C, 65.32; H, 10.35.

3.1.7. *rac*-[1*R*,7*R*,11*S*]-11-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxybicyclo[5.3.1]undeca-2-one (10). Ketol **9** (0.025 g, 0.08 mmol) in dry benzene (10 mL) was treated with Al(O*i*-Pr)$_3$ (0.049 g, 0.24 mmol) under reflux for 68 h. This reaction mixture was cooled to room temperature and a saturated aqueous solution of Rochelle's salt (10 mL) was added and the resultant mixture was stirred for 20 min. This was diluted with diethyl ether (25 mL) and the organic phase was separated. The organic phase was washed with saturated aqueous sodium bicarbonate solution (10 mL), brine (2×10 mL) and dried over anhydrous magnesium sulfate. Solvent was removed in vacuo to give a residue which was purified by flash column chromatography (silica gel, hexanes–EtOAc, 10:1) to afford 0.015 g (60%) of the starting ketol **9** and 0.010 g (40%) of **10**: mp 74–75°C (colorless needles, ether–hexanes); R_f 0.29 (hexanes–EtOAc, 10:1); IR (CH_2Cl_2) ν 3530, 3479, 2928, 2857, 1710, 1255, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (d, J=3.0 Hz, 1H), 2.93 (ddd, J=15.0, 12.0, 3.9 Hz, 1H), 2.37 (s, 1H, D_2O exchangeable), 2.59 (dt, J=12.0, 4.5 Hz, 1H), 2.07 (m, 1H), 2.00–1.20 (m, 12H), 0.95 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 76.2, 71.9, 40.1, 37.0, 30.9, 29.7, 28.4, 27.9, 25.8, 24.2, 23.5, 18.1, −4.3, −4.7; MS *m/e* (rel. int.) 255 (33), 237 (41), 163 (17), 135 (71); HRMS calcd for $C_{11}H_{13}O_3Si$ (M^+−*t*-Bu) 255.1416, found 255.1421.

3.1.8. *rac*-[1*R*,4*R*,6*S*,11*S*]-11-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-4-methyl-bicyclo[4.4.1]undeca-7,9-diene-2-one (12). To a cold (−78°C) suspension of copper iodide (1.21 g, 6.4 mmol) in dry Et_2O (30 mL) was added dropwise a solution of methyllithium (9.08 mL, 1.4 M in Et_2O, 12.7 mmol) and the resulting mixture was stirred at −78°C for 0.5 h. At this time, a solution of the enone **8** (0.65 g, 2.12 mmol) in dry Et_2O (10 mL) was added dropwise via a cannula and the mixture was stirred for an additional 2 h, while slowly warming to 0°C. The reaction mixture was then quenched with saturated ammonium chloride solution (10 mL) and diluted with Et_2O (50 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were rinsed with brine (20 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 20:1) to afford 0.465 g (68%) of the ketone **12**: R_f 0.56 (hexanes–EtOAc, 5:1); mp 48–50°C (Et_2O–hexanes); IR (CH_2Cl_2) ν 3430, 3020, 2953, 1699, 1457, 1250, 1083, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (dd, J=11.5, 8.5 Hz, 1H), 5.95 (dd, J=12.0, 6.5 Hz, 1H), 5.87 (dd, J=11.0, 7.0 Hz, 1H), 5.32 (d, J=12.0 Hz, 1H), 4.64 (s, D_2O exchangeable, 1H), 4.11 (d, J=2.5 Hz, 1H), 2.45 (dddd, J=16.0, 11.0, 8.0, 3.5 Hz, 1H), 2.57 (ddd, J=14.0, 3.0, 1.5 Hz, 1H), 2.44 (dd, J=14.0, 12.0 Hz, 1H), 2.20 (m, 1H), 2.09 (dddd, J=14.5, 7.5, 3.0, 1.5 Hz, 1H), 1.58 (dt, J=14.5, 9.5 Hz, 1H), 0.98 (d, J=6.5 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 136.4, 129.7, 126.4, 124.5, 85.3, 76.6, 48.5, 42.1, 36.0, 25.7, 25.0, 24.7, 17.9, −4.7, −5.0; MS *m/e* (rel. int.) 323 (3), 289 (4), 265 (1), 247 (24), 145 (33), 75 (100); HRMS calcd for $C_{18}H_{30}O_3Si$ (M^+) 322.1964, found 322.1960.

3.1.9. *rac*-[1*R*,4*R*,6*S*,11*S*]-11-[(*tert*-Butyldimethylsilyl)oxy]-1,2-dihydroxy-4-methyl-bicyclo[4.4.1]undeca-7,9-diene (13). To a solution of **12** (0.428 g, 1.33 mmol) in methanol (13 mL) was added $CeCl_3 \cdot 7H_2O$ (0.495 g, 1.33 mmol) and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was then cooled to 0°C, sodium borohydride (0.101 g, 2.66 mmol) was added in one portion, and the mixture was stirred for an additional hour while slowly warming to room temperature. TMEDA (0.200 mL, 1.33 mmol) was then added to the reaction mixture, which was stirred for 15 min and treated with a saturated aqueous $NaHCO_3$ solution (15 mL). After stirring for an additional 15 min, the reaction mixture was diluted with Et_2O (100 mL), the organic phase was separated and the aqueous phase was extracted with Et_2O (2×50 mL). The combined organic phases were rinsed with water (15 mL) and brine (2×10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 6:1) to give 0.310 g (72%) of the diol **13**: R_f 0.34 (hexanes–EtOAc, 6:1); mp 65–65.5°C (colorless needles, pentane); IR (CH_2Cl_2) ν 3528, 3473, 3027, 3016, 2953, 1463, 1254, 1043, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (dd, J=11.5, 8.0 Hz, 1H), 5.88 (dd, J=12.5, 7.0 Hz, 1H), 5.75 (dd, J=11.0, 7.0 Hz, 1H), 5.47 (d, J=12.5, 1H), 4.31 (dd, J=3.0, 2.0 Hz, 1H), 4.01 (d, J=10.5 Hz, 1H), 3.82 (bs, D_2O exchangeable, 2H) 3.75 (dddd, J=10.0, 4.5, 3.0, 1.2 Hz, 1H), 2.71 (dq, J=8.0, 3.0 Hz, 1H), 2.11 (m, 2H), 1.97 (m, 1H), 1.26 (dt, J=14.5, 8.0 Hz, 1H), 0.93 (d, J=6.5 Hz, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 132.3, 125.4, 123.6, 82.2, 78.2, 77.7, 42.7, 40.9, 37.4, 25.8, 24.9, 23.3, 17.8, −4.9, −5.1; MS *m/e* (rel. int.) 324 (4), 307 (10), 289 (2), 249 (25), 192 (30), 107 (100), 75 (96); HRMS calcd for $C_{18}H_{32}O_3Si$ (M^+) 324.2121, found 324.2112; Anal. calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.55; H, 9.90.

3.1.10. *rac*-[1*R*,6*R*,7*S*,9*S*,11*R*]-9-[(*tert*-Butyldimethylsilyl)oxy]-7-methyl-1,11-dihydroxy-bicyclo[4.4.1]undeca-2,4-diene (14). To a solution of **13** (0.270 g, 0.83 mmol) in acetonitrile (8 mL) was added silver oxide (0.482 g, 2.08 mmol) and the mixture was refluxed under N_2 for 1 h. The reaction mixture was cooled to room temperature, filtered through a bed of Celite and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 20:1) to afford 0.127 g (47%) of the starting diol **13** and 0.120 g (44%) of the isomeric diol **14**: R_f 0.30 (hexanes–EtOAc, 10:1); mp 81–82°C (colorless needles, hexanes–Et_2O); IR (CH_2Cl_2) ν 3507, 3367, 3027, 2926, 1455, 1249, 1096, 829 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dd, J=12.5, 7.0 Hz, 1H), 5.80 (dd, J=12.5, 6.5 Hz, 1H), 5.30 (ddd, J=12.0, 7.0, 0.5 Hz, 1H), 5.61 (d, J=12.0 Hz, 1H), 3.97 (m, 2H), 3.73 (bs, D_2O exchangeable, 2H), 3.01 (m, 1H), 2.32 (ddd, J=12.0, 7.5, 4.0 Hz, 1H), 2.06 (m, 1H), 1.77 (ddd, J=14.5, 8.5, 6.0 Hz, 1H), 1.44 (ddd, J=15.5, 5.5, 2.5 Hz, 1H), 1.41 (dd, J=14.5, 10.5 Hz, 1H), 0.93 (s, 9H), 0.92 (d, J=8.0 Hz, 3H), 0.16 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 133.1, 124.8, 122.3, 78.7,

78.5, 77.5, 43.4, 35.7, 31.1, 25.8, 25.1, 24.6, 17.9, −4.9, −5.0; MS *m/e* (rel. int.) 324 (2), 306 (1), 268 (5), 249 (37), 157 (36), 91 (92), 75 (100); HRMS calcd for $C_{18}H_{32}O_3Si$ (M^+) 324.2120, found 324.2106.

3.1.11. *rac*-[1*R*,2*R*,4*R*]-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-4-methyl-bicyclo-[4.4.1]undeca-11-one (15). To a solution of **14** (0.056 g, 0.17 mmol) in methanol (3.0 mL) was added PtO_2 (0.010 g), the resulting mixture was purged with H_2 and stirred under a blanket (balloon) of the same gas for 3 h. At this time, the reaction mixture was then filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 20:1) to afford 0.050 g (88%) of the saturated alcohol: R_f 0.21 (hexanes–EtOAc, 10:1); mp 80–81°C (pentane); IR (CH_2Cl_2) ν 3440, 3404, 2896, 1465, 1251, 1076, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.40 (d, J=7.0 Hz, D_2O exchangeable, 1H), 4.05 (d, J=7.5 Hz, 1H), 3.87 (d, J=1.5 Hz, 1H), 3.19 (s, D_2O exchangeable, 1H), 2.37 (m, 1H), 2.30 (m, 1H), 1.77 (m, 1H), 1.77–1.44 (m, 10H), 1.36 (m, 1H), 0.91 (d, J=6.0 Hz, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.0, 80.9, 76.6, 43.7, 42.1, 39.5, 35.7, 33.5, 25.8, 25.7, 25.4, 22.1, 17.9, −4.9, −5.0; MS *m/e* (rel. int.) 328 (5), 253 (62), 196 (30), 179 (39), (65), 75 (100); HRMS calcd for $C_{18}H_{36}O_3Si$ (M^+) 328.2433, found 328.2426. To a solution of the resultant alcohol (0.040 g, 0.13 mmol) in CH_2Cl_2 (3 mL) was added under nitrogen Dess–Martin reagent (0.062 g, 0.15 mmol) and the resulting mixture was stirred at ambient temperature for 3.5 h. At this time, an aqueous sodium hydroxide solution (1.3 M, 10 mL) was added to the reaction mixture, which was stirred for 10 min and then diluted with Et_2O (40 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2×10 mL). The combined organic phases were rinsed with an aqueous sodium hydroxide solution (1.3 M, 2×10 mL), brine (2×10 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 40:1) to afford 0.036 g (86%) of the α-ketol **15**: R_f 0.55 (hexanes–EtOAc, 10:1); mp 98–99°C (colorless needles, pentane); IR (CH_2Cl_2) ν 3487, 2954, 1695, 1469, 1096, 830 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) δ 4.33 (s, D_2O exchangeable, 1H), 3.75 (t, J=3.0 Hz, 1H), 2.95 (m, 1H), 1.96 (ddd, J=13.5, 11.5, 2.0 Hz, 1H), 1.83–1.55 (m, 10H), 1.49 (m, 1H), 1.17 (m, 1H), 0.97 (d, J=6.0 Hz, 3H), 0.85 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.9, 85.2, 76.4, 50.8, 43.5, 34.7, 33.1, 31.2, 26.3, 25.7, 25.3, 24.7, 23.4, 18.0, −4.8, −4.9; MS *m/e* (rel. int.) 311 (1), 265 (68), 251 (65), 149 (75), 75 (100); HRMS calcd. for $C_{14}H_{25}O_3Si$ (M^+-t-Bu) 269.1573, found 269.1574; Anal. calcd for $C_{18}H_{34}O_3Si$: C, 66.20; H, 10.49. Found: C, 66.30; H, 10.40.

3.1.12. *rac*-[1*R*,7*R*,9*R*,11*R*]-11-[(*tert*-Butyldimethylsilyl)-oxy]-1-hydroxy-9-methylbicyclo[5.4.0]undeca-2-one (17) and *rac*-[1*R*,3*R*,5*R*,7*R*]-3-[(*tert*-butyldimethylsilyl)oxy]-1-hydroxy-5-methyl-bicyclo[5.4.0]undeca-2-one (16). A solution of **15** (0.028 g, 0.086 mmol) in dry benzene (2 mL) was treated with aluminum isopropoxide (0.052 g, 0.09 mmol) for 4 h under standard α-ketol rearrangement conditions. The reaction mixture was then cooled to room temperature, a saturated aqueous solution of Rochelle's salt (5 mL) was added, and the resulting mixture was stirred for 20 min and then diluted with Et_2O (25 mL). Standard extractive work-up procedure as described above afforded an oily residue, which was purified by flash column chromatography (silica gel, hexanes–EtOAc, 10:1) to afford 0.012 g (43%) of **17** and 0.013 g (46%) of **16**.

Compound **17**. Colorless oil: R_f 0.49 (hexanes–EtOAc, 10:1) IR (neat) ν 3545, 2952, 1704, 1454, 1254, 1076, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.93 (t, J=3.5 Hz, 1H), 3.12 (dt, J=13.0, 7.0 Hz, 1H), 2.90 (s, D_2O exchangeable, 1H), 2.50 (ddd, J=13.0, 6.5, 6.0 Hz, 1H), 2.05 (m, 1H), 1.92 (m, 1H), 1.60–1.86 (m, 9H), 1.00 (m, 1H), 0.98 (d, J=6.0 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 82.0, 72.0, 39.7, 39.6, 39.2, 36.3, 31.0, 26.4, 25.8, 23.4, 22.3, 21.9, 18.0, −4.3, −5.1; MS *m/e* (rel. int.) 293 (1.5), 269 (38), 251 (45), 177 (20), 149 (65), 75 (100); HRMS calcd for $C_{14}H_{25}O_3Si$ (M^+-t-Bu) 269.1573, found 269.1570. Compound **16**. Colorless oil; R_f 0.36 (hexanes–EtOAc, 10:1); IR (neat) ν 3480, 2954, 1715, 1457, 1257 1112, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.58 (dd, J=6.5, 4.0 Hz, 1H), 3.41 (s, D_2O exchangeable, 1H), 2.03 (m, 2H), 1.94 (ddd, J=6.5, 5.0, 1.5 Hz, 1H), 1.91 (ddd, J=6.0, 4.5, 1.5 Hz, 1H), 1.22–1.82 (m, 10H), 0.95 (d, J=6.5 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 78.2, 76.4, 42.8, 41.9, 40.0, 30.8, 29.4, 29.2, 25.8, 23.7, 21.1, 20.4, 18.5, −4.9, −5.1; MS *m/e* (rel. int.) 293 (3), 269 (48), 251 (77), 177 (21), 149 (85), 75 (100); HRMS calcd for $C_{14}H_{25}O_3Si$ (M^+-t-Bu) 269.1573, found 269.1567.

3.1.13. *rac*-[1*R*,6*S*,11*R*]-1,11-Dihydroxybicyclo[4.4.1]undecane-2-one (18). To a solution of **9** (0.170 g, 0.54 mmol) in THF (6 mL) was added a 1.0 M THF solution of tetrabutylammonium fluoride (0.600 mL, 0.6 mmol) and the resulting mixture was stirred at 0°C for 1 h. The reaction mixture was diluted with water (10 mL) and Et_2O (30 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2×10 mL). The combined organic phases were rinsed with brine (15 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 2:1) to afford 0.098 g (91%) of the alcohol **18** as colorless needles: mp 70–71°C (hexanes); R_f 0.21 (hexanes–EtOAc, 2:1); IR (CH_2Cl_2) ν 3450, 2925, 2864, 1696, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57 (s, D_2O exchangeable, 2H), 4.08 (d, J=1.2 Hz, 1H), 2.70–2.80 (m, 2H), 2.30–2.60 (m, 2H), 1.5–2.1 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.7, 85.6, 79.5, 41.4, 40.1, 37.8, 32.6, 28.4, 25.5, 22.9, 20.3; MS (EI) *m/e* (rel. int.) 198 (M^+, 11), 170 (21), 127 (100), 111 (82); HRMS calcd for $C_{11}H_{18}O_3$ (M^+) 198.1252; Anal. calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.67; H, 9.17.

3.1.14. [1*R*,6*R*]-1β-Hydroxybicyclo[4.4.1]undecane-2,11-dione (19). To a solution of oxalyl chloride (0.052 mL, 0.591 mmol) in CH_2Cl_2 (1 mL) was added dimethyl sulfoxide (0.098 mL, 1.38 mmol) in CH_2Cl_2 (1 mL) and the resulting mixture was stirred at −78°C for 20 min. At this time, a solution of **18** (0.078 g, 0.394 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture and stirred for

an additional 0.5 h. Triethylamine (0.274 mL, 1.97 mmol) was then added and the mixture was stirred at −78°C for another 0.5 h. Extractive work-up procedure as described above for **7** afforded an oily residue which was purified by flash column chromatography (silica gel, hexanes–EtOAc, 2:1) to afford 0.066 g (86%) of **19** as a colorless oil: R_f 0.42 (hexanes–EtOAc, 10:1); IR (CH_2Cl_2) ν 3436, 2935, 1729, 1692, 1444, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.50 (s, D_2O exchangeable, 1H), 3.00 (m, 1H), 2.90.(m, 3H), 2.10–1.00 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8, 203.0, 82.8, 50.4, 37.6, 36.4, 32.9, 29.6, 28.6, 24.5, 18.1; MS (EI) *m/e* (rel. int.) 196 (43), 178 (15), 168 (33), 139 (52), 126 (100); HRMS calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099, found 196.1103.

3.1.15. [1*R*,7*S*]-1-Hydroxybicyclo[5.4.0]undecane-2,11-dione (21) and [1*R*,7*S*]-1-hydroxy-bicyclo[5.3.1]undecane-2, 11-dione (20) from the α-ketol rearrangement of [1*R*,6*S*]-1-hydroxybicyclo[4.4.1]unde-cane-2,11-dione (19). To a solution of **19** (0.020 g, 0.102 mmol) in dry benzene (13 mL) was added aluminum isopropoxide (0.063 g, 0.306 mmol) and the resulting mixture was heated under reflux for 23 h. Standard work-up procedure afforded an oily residue, which was purified by flash column chromatography (silica gel, hexanes–EtOAc, 20:1) to afford 0.0025 g (12%) of **21** and 0.010 g (52%) of **20**. Compound **20**. Colorless oil, R_f 0.50 (hexanes–EtOAc, 6:1); IR (neat) ν 3437, 2956, 2864, 1713, 1701, 1448 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.69 (s, 1H, D_2O exchangeable), 2.84 (m, 1H), 2.79.(m, 1H), 2.39 (dt, J=13.0, 3.5 Hz, 1H), 2.26 (ddd, J=13.0, 7.0, 3.5 Hz, 1H), 1.98–1.80 (m, 6H), 1.69–1.59 (m, 2H), 1.43 (dt, J=13.5, 5.0 Hz, 1H), 1.21–1.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 200.1, 80.4, 50.4, 37.6, 36.4, 33.0, 29.7, 28.6, 24.5, 18.1; MS (EI) *m/e* (rel. int.) 196 (48), 178 (12), 168 (39), 126 (100); HRMS calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099, found 196.1102. Compound **21**. Colorless oil, R_f 0.38 (hexanes–EtOAc, 6:1); IR (neat) ν 3432, 2936, 1732, 1703, 1461, 1033 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.60 (s, 1H, D_2O exchangeable), 3.16 (ddd, J=13.5, 7.0, 6.5 Hz, 1H), 3.01 (ddd, J=14.5, 12.0, 7.0 Hz, 1H), 2.66 (m, 1H), 2.32 (ddd, J=14.5, 7.5, 7.0 Hz, 1H), 2.09 (m, 2H), 1.80–1.55 (m, 8H), 1.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.3, 206.2, 84.4, 38.5, 37.6, 36.2, 32.9, 29.4, 28.6, 24.3, 18.0; MS (EI) *m/e* (rel. int.) 196 (33), 178 (13), 126 (100); HRMS calcd for $C_{11}H_{16}O_3$ (M^+) 196.1099, found 196.1101.

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