First Synthesis of the Functionalized Dioxatricyclic Core Structure of Dictyoxetane and Proposed Biogenesis in *Dictyota dichotoma*

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Dedicated to Professor Rolf Huisgen on the occasion of his 75th birthday

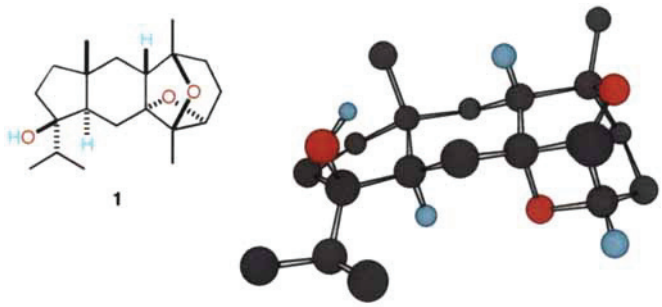
Abstract: 6,8-Dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonan-4β-ol (**9aβ**) has been prepared from readily accessible starting materials in eight steps (14% overall yield). The parent dioxatricyclic framework **11** was obtained from 1,5-dimethyl-8-oxabicyclo[3.2.1]oct-3-en-6α-ol (**7**) in six steps (28% yield with respect to **7**). Based on the experimental introduction of the oxetane moiety in vitro, a biosynthetic pathway is proposed for dictyoxetane (**1**) from a known dolabellane metabolite.

Keywords
chemotaxonomy · diterpene metabolites · dolabellanes · marine natural products · oxetanes

Introduction

The brown alga *Dictyota dichotoma* collected from the Indian and other oceans has been the source of a variety of diterpenes and their metabolites.[1-3] Of these marine natural products, the pentacyclic dictyoxetane[1] (**1**) is structurally related to the class of dolabellanes.[1-3] *Dictyota dichotoma* and dolabellanes also enter the food chain of marine invertebrates and thus are part of finely balanced marine ecosystems. The intricate dioxatricyclic network of dictyoxetane is unprecedented in Nature. This skeletal type has also never been encountered in unnatural products (Chemical Abstracts on-line search).

Scheme 1 shows a three-dimensional structure of **1**, which we derived by MM2 calculations (for the gas phase). The bond angles and lengths are in good agreement[4] with the experimental structure in the crystal state, as determined by Clardy and co-workers.[1] We here report a flexible synthesis of the dioxatricyclic framework of dictyoxetane (**1**).



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Scheme 1. Dictyoxetane (**1**), a pentacyclic diterpene of the dolabellane class.

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Results and Discussion

Considering the possible biosynthetic pathway to dictyoxetane (**1**) shown in Scheme 6 below, we attempted to construct the strained, key four-membered heterocycle late in the synthesis, by using a stereoelectronically favourable, intramolecular nucleophilic displacement reaction. Our strategy and its experimental execution is outlined in Scheme 2.

1,5-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**2**) was prepared by the triethyl borate method of Hoffmann and Iqbal[5] from readily available substances in 59% overall yield (20 g per batch). Alternatively, 2,5-dimethylfuran and 1,1,3,3-tetrabromo-2-propanone in dioxane were allowed to react with zinc/copper powder by the ultrasound procedure,[6] to give 62% of the desired product **2**. Of the two procedures, the triethyl borate method can be scaled up more conveniently. Reduction of ketoolefin **2** with diisobutylaluminium hydride (DIBAH) was stereoselective, giving unsaturated *endo* alcohol **3** in good yield. Treatment of **3** with methanesulfonyl chloride/triethylamine furnished the potentially sensitive secondary mesylate **4**. Therefore we were pleased to find that a combined hydroboration/oxidation[7] was feasible, giving ketomesylate **5**. After desymmetrization of the etheno bridge in bicyclic **4**, the next step was to deal with the regiocontrolled functionalization of the three-carbon bridge in bicyclic **5**. Presumably, because of the σ-acceptor effect of the carbonyl group in ketomesylate **5**, a conventional base mediated elimination afforded the desired ketoolefin **6a** as the major product (**6a**:**6b** = 8:1). Moreover, the isomeric bicyclics **6a** and **6b** were separable by column chromatography.

Reduction of the carbonyl group proceeded stereoselectively with DIBAH (**6a** → **7a**), as did the alkylation with methylmagnesium bromide (**6a** → **7b**). Again attack of the bicyclic skeleton proceeded from the *exo* face. Epoxidation of homoallylic alcohols **7a** and **7b** furnished tricyclic epoxides **8a** and **8b**, respectively. Simple treatment of epoxyalcohol **8a** with base afforded tricyclic oxetane **9aβ** in 82% yield at room temperature! Similarly, **9bβ** was obtained in 80% yield.

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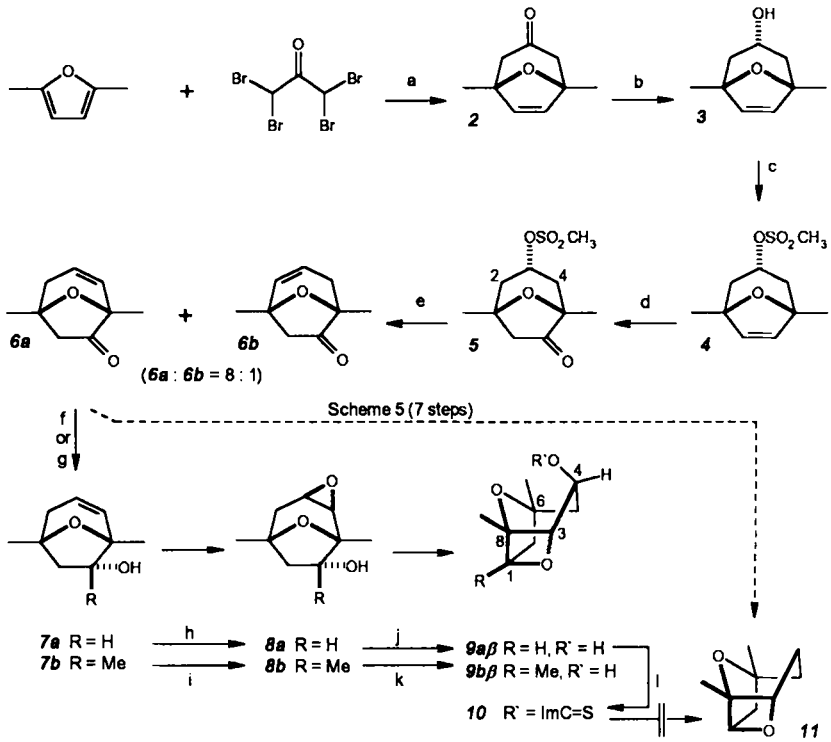
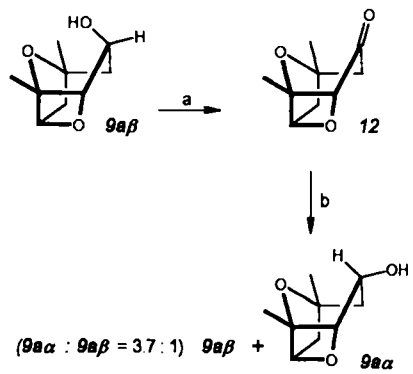


Scheme 2. Synthesis of **9aβ**: a) Zn, $B(OEt)_3$, THF, RT, then Zn, CuCl, NH_4Cl, MeOH, 15 °C → RT, 59%; b) DIBAH, THF, −78 °C → RT, 88%; c) CH_3SO_2Cl, NEt_3, 0 °C, 73%; d) BH_3, THF, 0 °C, then PCC, CH_2Cl_2, RT, 79%; e) DBU, acetonitrile, reflux, 79%; f) DIBAH, THF, −78 → −10 °C, 94%; g) CH_3MgBr, THF, −78 °C, 55%; h) *m*-CPBA, CH_2Cl_2, 0 °C → RT, 75%; i) *m*-CPBA, CH_2Cl_2, 0 °C, 58%; j) KOH, DMSO/H_2O, RT, 82%; k) KOH, DMSO/H_2O, RT, 80%; l) $(Im)_2C{=}S$, CCl_4, reflux, 93% (Im = imidazolide).

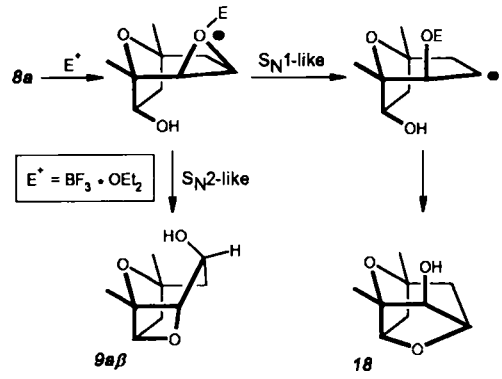
The assigned structure **9aβ** is in good agreement with spectroscopic data for oxetanes. The pronounced downfield shift of the H(1) ($\delta = 4.88$) and H(3) ($\delta = 4.44$) signals is accompanied by a downfield shift in the ^{13}C spectrum [C(1), $\delta = 90.7$; C(3), $\delta = 85$]. After H/D exchange at the hydroxyl group, the signals for H(3) and H(4) could be assigned unambiguously. Proton H(1) appears as a clean doublet, in accord with calculated torsion angles [90° with respect to *endo*-H(9)].

Hydroxyoxetane **9aβ** was readily oxidized to tricyclic ketooxetane **12**, which was treated with $BH_3 \cdot THF$ at low temperature; the epimeric alcohol **9aα** was obtained as the major product (**9aα**:**9aβ** = 3.7:1) (Scheme 3).

Hydroxyoxetane **9aβ** was prepared from epoxyalcohol **8a** not only under basic conditions, but also under Lewis acid catalysis with $BF_3 \cdot OEt_2$ (Scheme 4). In the latter reaction, the yield was lower and, in addition to tricyclic oxetane **9aβ**, isomeric bistetrahydrofuran **18** was also formed (**9aβ**:**18** = 2:1), probably in an S_N1-like cyclization.

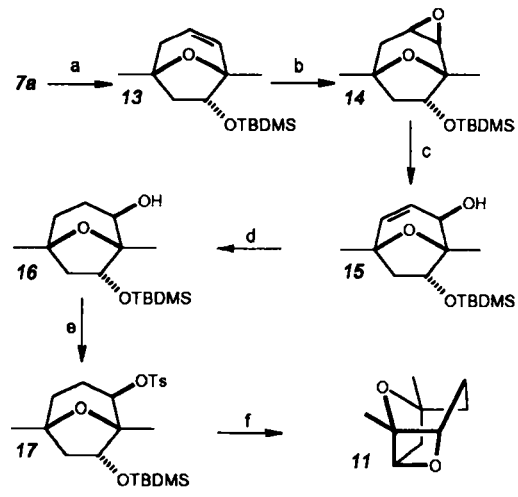


Scheme 3. Epimeric tricyclic hydroxyoxetanes **9aα** and **9aβ**, and tricyclic oxetanone **12**: a) PDC, molecular sieves 4 Å, CH_2Cl_2, RT, 82%; b) BH_3, CH_2Cl_2, −90 → −60 °C, 53%.



Scheme 4. Biomimetic cyclization of hydroxyepoxide **8a** to tricyclic oxetane **9aβ**.

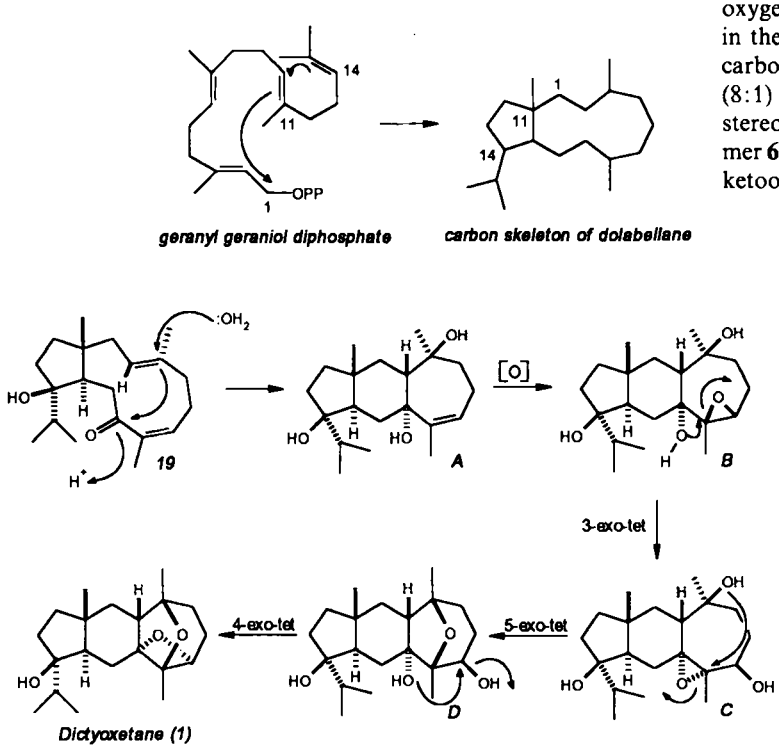
Interestingly, attempts to deoxygenate hydroxyoxetane **9aβ** by means of a radical methodology failed (**10** ↛ **11**, Scheme 2).[8] We therefore developed an alternative route to parent dioxatricycle **11**, starting from diastereomerically pure alcohol **7a**, which was again obtained from bicyclic enone **6a** (Schemes 2 and 5). Epoxidation of protected homoallylic alcohol **13** afforded *exo*-epoxide **14**, which was opened by base to give allylic alcohol **15**. The yield of this step was 94%. Hydrogenation followed by tosylation furnished protected 7-*endo*-hydroxy-2-*exo*-tosylate **17**, which was deprotected (TLC monitoring) and cyclized in a one-pot reaction, by using tetrabutylammonium fluoride (TBAF) at room temperature in the presence of molecular sieves and finally heating. Thus, the compact parent 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonane (**11**) was obtained as a volatile liquid.



Scheme 5. Synthesis of parent structure **11**: a) TBDMSOTf, NEt_3, CH_2Cl_2, 0 °C, 86%; b) *m*-CPBA, CH_2Cl_2, 0 °C, 93%; c) LDA, DMPU, Et_2O, RT, 94%; d) H_2, Pd/C, EtOH, 99%; e) BuLi, THF, TsCl, −78 °C → RT, 97%; f) TBAF, THF, RT → reflux, 39%. TBDMS = *t*$BuMe_2Si$.

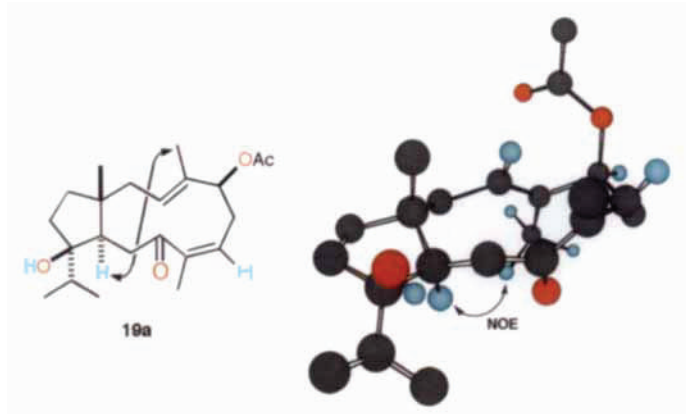
The difference in yield for the cyclization to hydroxyoxetane **9aβ** and to oxetane **11** (82% vs. 39%) may be due to the higher volatility of **11** compared to that of **9aβ**, and, more importantly, to the favourable trajectory of the intramolecular nucleophilic displacement reaction involving opening of the *epoxide* (**8a** → **9aβ**). Considering the known lability of many oxetanes, the oxetane ring in **9aβ** is remarkably robust. For example, on contact with $BF_3 \cdot OEt_2$ in CH_2Cl_2 for 24 h (0.01 M solution, 10 mol% $BF_3 \cdot OEt_2$, room temperature), the tricyclic skeleton of **9aβ** survived unchanged (GC analysis).

Proposed Biogenesis of Dictyoxetane: As yet, nothing is known about the biogenetic origin of dictyoxetane. We suggest that the known dolabellane metabolite **19**[1, 9] undergoes a transannular cyclization (**19** → **A**) (Scheme 6). In fact, König and co-workers



Scheme 6. Proposed biosynthetic pathway to dictyoxetane (**1**).

have shown by NOE that the (*E*)-configurated double bond of **19a** is proximate to the transannular carbonyl group[9] (Scheme 7) as required for the postulated cyclization (**19** → **A**)



Scheme 7. Conformation and folding of hydroxydolabelladienone **19a**, a metabolite from marine alga *Dictyota pardalis* f. *pseudohamata*.

(Scheme 6).[10] Attack of water occurs preferentially from the *exo* face, giving tricyclic tritertiary triol **A**. Stereoselective epoxidation (**A** → **B**) and epoxide rearrangement (**B** → **C**) generate a new epoxide, which is opened with formation of a tetrahydrofuran ring (**C** → **D**). Now the molecule is set up for the crucial oxetane formation (**D** → **1**), which becomes plausible in light of the synthesis of both hydroxyoxetanes **9aβ**, **9bβ** and also of the parent tricyclic oxetane **11** in vitro.

Conclusions

In probing the possible biogenesis of **1**, we have described an efficient synthesis of the key dioxatricyclic network for the first time. In fact, the required nine carbon atoms and one ether oxygen of the target are assembled with the correct connectivity in the first step. Interestingly, the deprotonation of the three-carbon bridge in **5** (Scheme 2) proceeds with good regiocontrol (8:1) and the functionality is adjusted throughout with high stereoselectivity. Unsaturated bicyclic ketone **6a**, its regioisomer **6b**, the epimeric tricyclic hydroxyoxetanes **9aα** and **9aβ** and ketooxetane **12** are all useful intermediates for further synthetic manoeuvres and with a view to the total synthesis of **1**. They also provide access to a wide variety of structurally modified derivatives of the basic dioxatricyclic framework for evaluation of biological activity and as a pharmacophore.

Our proposed mechanism for the biogenesis of dictyoxetane (**1**) is supported by the rapid formation of the tricyclic oxetane core under mild conditions and in high yield from the appropriate epoxyalcohols **8a** and **8b** in vitro. Oxetane formation from **17** via the corresponding hydroxytosylate (Scheme 5) is also feasible, but because of the somewhat less favourable trajectory and also experimental difficulties, the yield is lower. As a pentacyclic trioxygenated dolabellane, dictyoxetane (**1**) is a later metabolite than hydroxydolabelladienone **19** and its precursors. Thus, dictyoxetane also serves as a chemotaxonomic and phylogenetic marker,[11] which illustrates biodiversity and evolution within this class of marine natural products.

Experimental Procedure

Melting points: Büchi apparatus. Infrared spectra: Perkin-Elmer 1710 spectrometer. ^1H NMR spectra: Bruker WH 90, WP 200 SY or AM 300 spectrometer; chemical shifts relative to tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra: Bruker WP 200 SY or a Bruker AM 300; chemical shifts relative to TMS. APT (attached proton test): spin echo-based selection of multiplicities of ^{13}C signals; quaternary C and CH_2 carbon atoms give positive signals (+), while CH and CH_3 give negative signals (-). Low- and high-resolution electron-impact mass spectra: Finnigan MAT 312 spectrometer with an ionization potential of 70 eV at room temperature, unless stated otherwise. Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover. Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30–60 μm). Analytical TLC was carried out on aluminum-backed 0.2 mm silica gel 60 F_{254} plates (E. Merck). PE (light petroleum, b.p. 40–60 °C).

1,5-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (2): To a suspension of zinc powder (23.79 g, 364 mmol) and 2,5-dimethylfuran (21.15 g, 220 mmol) in THF (26 mL) was added a solution of tetrabromoacetone (123.4 g, 330 mmol) and triethyl borate (79 mL, 464 mmol) in THF (78 mL) within 1 h. During the addition the reaction mixture warmed up to reflux. After stirring for 16 h at RT under exclusion of light the reaction mixture was cooled to −15 °C. Water (90 mL) was added, the mixture allowed to reach 0 °C and stirring continued for 30 min. The solid components were removed by filtration and washed with Et_2O. The filtrate was diluted with water (270 mL) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The crude dibromoketone was dissolved in

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MeOH (90 mL) and added to a mixture of zinc powder (75 g, 1.15 mol), CuCl (11.4 g, 115 mmol) and NH_4Cl (81 g) in MeOH (300 mL). The reaction temperature was maintained below 15 °C during the addition. The mixture was then stirred for 16 h at RT and then filtered under suction. The filtrate was diluted with water (500 mL) and extracted with CH_2Cl_2. Precipitation was dissolved by addition of 2 N HCl. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography (silica gel, Et_2O/PE, 1:2) to give a light yellow solid (19.64 g, 59%), m.p. 61 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 2980, 1708, 1380, 1336, 1176, 1144, 1120 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.50 (s, 6H; CH_3), 2.35 (d, ^2J = 16 Hz, 2H; H-2, H-4), 2.48 (d, ^2J = 16 Hz, 2H; H-4, H-2), 5.97 (s, 2H; H-6, H-7); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.23 (−, 2 × CH_3), 50.95 (+, C-2, C-4), 83.61 (+, C-1, C-5), 136.17 (−, C-6, C-7), 206.38 (+, C-3); MS (70 eV): *m/z* (%): 152 (40) [M^+], 137 (5), 109 (100), 95 (100), 81 (17), 67 (24). HRMS calcd for $C_9H_{12}O_2$: 152.0837, found 152.0838.

1,5-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3α-ol (3): To a solution of ketone **2** (1.0 g, 6.6 mmol) in THF (15 mL) was added DIBAH (10 mL, 12 mmol, 1.2 M solution in toluene) at −78 °C. After being stirred for 2 h at the same temperature, the reaction mixture was allowed to reach RT. Stirring was continued for 16 h at RT to complete the reduction, then the reaction was quenched by addition of water. The aqueous phase was acidified (2 N HCl) and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), evaporated and chromatographed (silica gel, Et_2O/PE) to afford **3** as an oil (990 mg, 98%) (axial alcohol/equatorial alcohol, 10:1). IR ($CHCl_3$): $\tilde{\nu}$ = 3596, 3040, 2976, 1452, 1152, 860 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.37 (s, 6H; 2 × CH_3), 1.76 (dd, ^2J = 14.5, $J \approx 1$ Hz, 2H; H-2, H-4), 1.95 (dd, ^2J = 14.5, ^3J = 5.8 Hz, 2H; H-4, H-2), 2.59 (br s, 1H; OH), 4.02 (m, 1H; H-3), 6.12 (s, 2H, H-6; H-7); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.16 (−, 2 × CH_3), 41.51 (+, C-2, C-4), 65.95 (−, C-3), 83.63 (+, C-1, C-5), 138.54 (−, C-6, C-7); MS (70 eV): *m/z* (%): 154 (0) [M^+], 139 (2), 136 (1) [$M^+ - H_2O$], 121 (14), 109 (23), 96 (100), 67 (16), 55 (8).

1,5-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3α-yl methanesulfonate (4): To an ice-cold solution of alcohol **3** (4.0 g, 26 mmol) in CH_2Cl_2 (125 mL) was added NEt_3 (5.45 mL, 39.0 mmol) followed by methanesulfonyl chloride (2.22 mL, 28.7 mmol). After 2 h of stirring at 0 °C ice-water was added. The organic layer was extracted with 1 N HCl, sat. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by chromatography (silica gel, Et_2O/PE) to give **4** as a colourless solid (4.4 g, 73%), m.p. 66 °C. IR (KBr): $\tilde{\nu}$ = 3012, 3002, 2965, 2942, 2930, 2913, 1456, 1360, 1181, 1159, 909 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.38 (s, 6H; 2 × CH_3), 1.99 (m, 4H; H-2, H-4), 2.97 (s, 3H; OSO_2CH_3), 5.03 (m, 1H; H-3), 5.98 (s, 2H; H-6, H-7); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.92 (−, 2 × CH_3), 38.46 (−, OSO_2CH_3), 38.50 (+, C-2, C-4), 76.34 (−, C-3), 83.02 (+, C-1, C-5), 136.60 (−, C-6, C-7); MS (70 eV): *m/z* (%): 232 (9) [M^+], 219 (1), 204 (1), 178 (2), 165 (1), 153 (70), 137 (56), 122 (60), 109 (23), 93 (100), 83 (7), 77 (35). $C_{10}H_{16}O_4S$: calcd C 51.71, H 6.95; found C 51.71, H 6.97.

1,5-Dimethyl-8-oxabicyclo[3.2.1]octan-6-on-3α-yl methanesulfonate (5): To a solution of **4** (658 mg, 2.83 mmol) in THF (5.6 mL) was added BH_3·THF (1.56 mL, 1.56 mmol, 1 M solution in THF) slowly at 0 °C. After 5.5 h at the same temperature a further portion of BH_3·THF (0.94 mL, 0.94 mmol) was added. The mixture was stirred for 1 h, then the solvent was removed under strict exclusion of air and moisture. The residue was dissolved in CH_2Cl_2 (10 mL) and slowly added to a suspension of pyridinium chlorochromate (PCC) (3.03 g, 12 mmol) in CH_2Cl_2 (14.5 mL). The mixture was stirred for 19 h at RT and then filtered through a short column (silica gel, eluent Et_2O). The solvent was evaporated, and the residue purified by chromatography (Et_2O/PE) to give **5** as a colourless solid (554 mg, 79%), m.p. 79–80 °C. IR (KBr): $\tilde{\nu}$ = 3022, 2979, 2937, 1752, 1455, 1348, 1236, 1176, 1165, 1142, 967, 909, 861, 795, 703, 553 cm^{-1}; ^1H NMR (200 MHz, [D_6]acetone): δ = 1.17 (s, 3H; CH_3), 1.43 (s, 3H; CH_3), 1.90–2.15 (m, 4H; H-2, H-4), 2.27 (dd, ^2J = 17.5, $^4J \approx 1$ Hz, 1H; H-7), 2.89 (d, ^2J = 17.5 Hz, 1H; H-7), 3.05 (s, 3H; OSO_2CH_3), 5.12 (m, 1H; H-3); ^{13}C NMR (50 MHz, [D_6]acetone): δ = 20.78 (−, CH_3), 27.13 (−, CH_3), 38.52 (−, OSO_2CH_3), 40.11 (+, CH_2), 40.28 (+, CH_2), 48.35 (+, CH_2), 76.57 (−, C-3), 76.62 (+, C-1), 80.63 (+, C-5), 215.50 (+, C-6); MS (70 eV): *m/z* (%): 249 (1) [$M^+ + 1$], 248 (7) [M^+], 221 (1), 162 (3), 153 (18), 139 (18), 139 (4), 124 (100), 109 (39), 95 (21). HRMS calcd for $C_{10}H_{16}O_5S$: 248.0718, found 248.0712. $C_{10}H_{16}O_4S$: calcd C 48.37, H 6.50; found C 48.64, H 6.52.

1,5-Dimethyl-8-oxabicyclo[3.2.1]oct-3-en-6-one (6a) and 1,5-dimethyl-8-oxabicyclo[3.2.1]-oct-2-en-6-one (6b): To a solution of **5** (3.36 g, 13.5 mmol) in MeCN (130 mL) was added DBU (6 mL, 40 mmol) at RT. The mixture was heated to reflux for 6.5 h and then poured onto ice-water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with 1 N HCl, sat. aq. $NaHCO_3$ and brine. After it had been dried ($MgSO_4$), the solvent was removed, and the crude product purified by chromatography (Et_2O/PE) to give **6a** (1.44 g, 70%) and **6b** (185 mg, 9%) as colourless oils.

Spectroscopic data for **6a**: IR (film): $\tilde{\nu}$ = 3039, 2979, 2933, 1757, 1445, 1429, 1404, 1385, 1277, 1186, 1142, 1103, 1046, 917, 850, 680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 3H; CH_3), 1.48 (s, 3H; CH_3), 2.01 (ddd, ^2J = 18.2, ^3J = 4.3, ^4J = 1.7 Hz, 1H; H-2), 2.33 (dd, ^2J = 18, ^4J = 1 Hz, 1H; H-7), 2.46 (ddt (unresolved dddd), ^2J = 18.2, $^3J \approx {}^3J$ = 2.6, ^4J = 1 Hz, 1H; H-2), 2.53 (d, ^2J = 18 Hz, 1H; H-7), 5.65 (ddd, ^3J = 9.7, ^4J = 2.6, ^4J = 1.7 Hz, 1H; H-4), 5.96 (ddd, ^3J = 9.7, ^3J = 4.3, ^3J = 2.6 Hz, 1H; H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.41 (−, CH_3), 27.15 (−, CH_3), 37.64 (+, C-2), 47.51 (+, C-7), 75.58 (+, C-1), 80.35 (+, C-5), 129.13 (−, C=C), 129.23 (−, C=C), 209.69 (+, C-6); MS (70 eV): *m/z* (%): 153 (6) [$M^+ + 1$], 152 (24) [M^+], 136 (20), 135 (20), 121 (6), 109 (100), 95 (92). HRMS calcd for $C_9H_{12}O_2$: 152.0837, found 152.0839.

Spectroscopic data for **6b**: IR (film): $\tilde{\nu}$ = 3037, 2978, 2933, 1759, 1445, 1382, 1202, 1000, 922, 899, 861, 765 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 3H; CH_3), 1.53 (s, 3H; CH_3), 2.06 (ddd, ^2J = 18, ^3J = 4.2, ^4J = 1.9 Hz, 1H; H-4), 2.28 (dt (unresolved ddd), ^2J = 18, $^3J \approx {}^4J$ = 1.8–2.4 Hz, 1H; H-4), 2.41 (d, ^2J = 16, 1H; H-7), 4.55 (d, ^2J = 16 Hz, 1H; H-7), 5.68 (ddd, ^3J = 9.8, ^3J = 4.2, ^3J = 2.4 Hz, 1H; H-3), 5.90 (dt (unresolved ddd), ^3J = 9.8, $^4J \approx {}^4J$ = 1.9–2.3 Hz, 1H; H-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.83 (−, CH_3), 23.68 (−, CH_3), 35.51 (+, C-4), 52.66 (+, C-7), 76.64 (+, C-1), 82.05 (+, C-5), 124.85 (−, C=C), 135.33 (−, C=C), 218.31 (+, C-6); MS (70 eV): *m/z* (%): 154 (6) [$M^+ + 2$], 153 (24) [$M^+ + 1$], 136 (59), 121 (36), 117 (2), 109 (65), 105 (4), 97 (8), 93 (100). HRMS calcd for $C_9H_{12}O_2$: 152.0837, found 152.0838.

1,5-Dimethyl-8-oxabicyclo[3.2.1]oct-3-en-6α-ol (7a): To a solution of **6a** (965 mg, 6.35 mmol) in THF (24 mL) was added slowly DIBAH (6.5 mL, 7.8 mmol, 1.2 M solution in toluene) at −78 °C. The mixture was stirred for 5 h at −60 to −10 °C and then quenched by addition of water. The aqueous layer was acidified (2 N HCl), saturated with NaCl and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated. The crude product was chromatographed (Et_2O/PE) to afford **7** (916 mg, 94%) as a clear oil. IR (film): $\tilde{\nu}$ = 3432, 3036, 2971, 2930, 2895, 1449, 1374, 1276, 1250, 1153, 1068, 1020, 856, 799 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 3H; CH_3), 1.37 (s, 3H; CH_3), 1.64 (dd, ^2J = 13, ^3J = 5.9 Hz, 1H; H-7), 1.92 (ddd, ^2J = 17.4, ^3J = 4, ^4J = 1.3 Hz, 1H; H-2), 2.22 (ddd, ^2J = 13, ^3J = 9.6, ^4J = 1.5 Hz, 1H; H-7), 2.36 (m, 1H; H-2), 4.03 (m, 1H; H-6), 5.79 (dt (unresolved ddd), ^3J = 9.8, $^4J \approx {}^4J$ = 1.3–1.8 Hz, 1H; H-4), 5.90 (ddd, ^3J = 9.8, ^3J = 4, ^3J = 2.2 Hz, 1H; H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.36 (−, CH_3), 27.38 (−, CH_3), 40.57 (+, C-2), 46.18 (+, C-7), 77.68 (+, C-1), 79.79 (+, C-5), 83.25 (−, C-6), 127.03 (−, C=C), 131.99 (−, C=C); MS (70 eV): *m/z* (%): 154 (2) [M^+], 152 (1), 140 (1), 136 (26), 132 (1), 126 (12), 121 (28), 117 (1), 109 (76), 105 (2), 99 (3), 95 (100). HRMS calcd for $C_9H_{14}O_2$: 154.0994, found 154.0997.

1,5-Dimethyl-3,4-epoxy-8-oxabicyclo[3.2.1]octan-6α-ol (8a): To a mixture of **7a** (750 mg, 4.87 mmol) in CH_2Cl_2 (21 mL) was added *m*-CPBA (1.26 g, ca. 75%) in two portions at 0 °C. The mixture was stirred for 4 h at RT, and a third portion of *m*-CPBA (300 mg, ca. 75%) was added. The resulting mixture was stirred for 18 h at RT. CH_2Cl_2 was added and the organic layer was extracted with aq. $Na_2S_2O_3$ solution (10%), sat. aq. $NaHCO_3$ solution and brine. The combined aqueous layers were extracted until no more product could be detected in the aqueous phase. The combined organic layers were dried ($MgSO_4$), evaporated and chromatographed (Et_2O/PE) to give the 3α,4α-epoxide (149 mg, 18%) and the 3β,4β-epoxide (622 mg, 75%) as colourless oils.

Spectroscopic data for 3α,4α-epoxide: IR (KBr): $\tilde{\nu}$ = 3556, 2976, 2936, 1724, 1446, 1415, 1380, 1279, 1234, 1116, 1069, 952, 928, 831 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.28 (s, 3H; CH_3), 1.53 (s, 3H; CH_3), 1.64 (dd, ^2J = 12.6, ^3J = 6 Hz, 1H; H-7), 1.83 (ddd, ^2J = 15, ^3J = 3, J = 1.5 Hz, 1H; H-2), 2.04 (dd, ^2J = 15, J < 1 Hz, 1H; H-2), 2.14 (ddd, ^2J = 12.6, ^3J = 10.6, ^4J = 1.5 Hz, 1H; H-7), 3.26 (d, ^3J = 4 Hz, 1H; H-4), 3.44 (dd, ^3J = 4, ^3J = 3 Hz, 1H; H-3), 3.85 (dd, ^3J = 10.6, ^3J = 6 Hz, 1H; H-6); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.62 (−, CH_3), 28.15 (−, CH_3), 37.37 (+, C-2), 45.76 (+, C-7), 51.71 (−, C-3), 57.48 (−, C-4), 75.83 (+, C-1), 79.37 (+, C-5), 80.03 (−, C-6); MS (70 eV): *m/z* (%): 170 (0.3) [M^+], 152, (1), 142 (0.4), 134 (4), 124 (9), 109 (36), 95 (17), 87 (100).

Spectroscopic data for 3β,4β-epoxide: IR ($CHCl_3$): $\tilde{\nu}$ = 3620, 2976, 2932, 1424, 1376, 1320, 1264, 1232, 1120, 1040, 968, 952, 932, 916, 888, 832 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (s, 3H; CH_3), 1.42 (s, 3H; CH_3), 1.77 (ddd, ^2J = 13, ^3J = 6, $J \approx 1$ Hz, 1H; H-7), 1.78 (dd, ^2J = 15, ^3J = 4.5 Hz, 1H; H-2), 2.03 (br d, ^2J = 15 Hz, 1H; H-2), 2.26 (ddd, ^2J = 13, ^3J = 10, $J \approx 1$ Hz, 1H; H-7), 2.83 (br s, 1H; OH), 3.19 (dd, ^3J = 4, J < 1 Hz, 1H; H-4), 3.32 (dd, ^3J = 4.5, ^3J = 4 Hz, 1H; H-3), 4.13 (dd, ^3J = 10, ^3J = 6 Hz, 1H; H-6); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.96 (−, CH_3), 27.04 (−, CH_3), 37.22 (+, C-2), 45.65 (+, C-7), 49.86 (−, C-3), 53.23 (−, C-4), 77.15 (+, C-1), 77.52 (+, C-5), 78.39 (−, C-6); MS (70 eV): *m/z* (%): 170 (2) [M^+], 156 (5), 139 (6), 127 (28), 115 (69), 109 (62), 97 (80), 91 (4), 85 (69), 81 (100).

6,8-Dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonan-4β-ol (9aβ): *Cyclization with KOH/DMSO/H_2O*: To a solution of **8a** (77 mg, 0.45 mmol) in DMSO (2.5 mL) were added H_2O (0.625 mL) and finely powdered KOH (254 mg, 4.53 mmol). The mixture was stirred for 73 h at RT, then diluted with Et_2O and acidified by addition of 2 N HCl (pH ≈ 3). The aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography (*t*BuOEt) afforded **9aβ** (63 mg, 82%) as a colourless solid, m.p. 55–56 °C.

Cyclization with tBuOK/tBuOH: To a solution of **8a** (40.3 mg, 0.236 mmol) in *t*BuOH (2 mL) was added *t*BuOK (26.5 mg, 0.236 mmol) under N_2. After stirring for 4 h the reaction mixture was diluted with Et_2O and acidified by addition of 2 N HCl. The aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography (Et_2O) afforded **9aβ**

(31.4 mg, 78%). IR (KBr): $\tilde{\nu}$ = 3456, 2980, 2928, 1443, 1388, 1190, 1133, 1002, 972, 905 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.48 (s, 3H; CH_3), 1.60 (s, 3H; CH_3), 1.61 (m, 1H), 1.90–2.10 (m, 2H), 2.21 (d, ^3J = 11 Hz, 1H; OH), 2.36 (dd, ^2J = 15, ^3J = 6 Hz, 1H; H-5), 4.05 (m, 1H; H-4), 4.44 (d, ^3J = 4 Hz, 1H; H-3), 4.88 (d, ^3J = 4.5 Hz, 1H; H-1); ^1H NMR (200 MHz, $CDCl_3$, D_2O): δ = 1.48 (s, 3H; CH_3), 1.60 (s, 3H; CH_3), 1.61 (m, 1H), 1.90–2.10 (m, 2H), 2.36 (dd, ^2J = 15, ^3J = 6 Hz, 1H; H-5), 4.05 (brt, ^3J = 5 Hz, 1H; H-4), 4.44 (d, ^3J = 4 Hz, 1H; H-3), 4.88 (d, ^3J = 4.5 Hz, 1H; H-1); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.95 (–, CH_3), 27.58 (–, CH_3), 41.37 (+, C-5), 47.24 (+, C-9), 67.37 (–, C-4), 81.81 (+, C-6), 81.90 (+, C-8), 85.03 (–, C-3), 90.69 (–, C-1); MS (70 eV): *m/z* (%): 170 (1) [M^+], 152 (7), 142 (11), 125 (40), 109 (89), 97 (60), 84 (100), 79 (18). $C_9H_{14}O_3$: calcd C 63.49, H 8.30; found C 63.42, H 8.30.

1,5,6-Trimethyl-8-oxabicyclo[3.2.1]oct-3-en-6α-ol (7b): To a solution of **6a** (595 mg, 3.9 mmol) in THF (8 mL) was added MeMgBr (3.35 mL, 4.7 mmol, 1.4 M solution in THF) dropwise at −78 °C. After 3 h at the same temperature water was added. The precipitate was dissolved by addition of 2 N HCl, and the mixture was allowed to reach RT. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (K_2CO_3). The solvent was removed, and the crude product purified by chromatography (Et_2O/PE) to give **7b** (361 mg, 55%) as a colourless oil. IR (KBr): $\tilde{\nu}$ = 3436, 3048, 2968, 2942, 1626, 1448, 1371, 1341, 1274, 1183, 1107, 1065, 953, 864, 770, 709, 675 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (s, 3H; CH_3), 1.29 (s, 3H; CH_3), 1.31 (s, 3H; CH_3), 1.86–2.00 (m, 3H), 2.35 (d, ^2J = 17 Hz, 1H), 5.88 (brs, 2H; H-3, H-4); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.78 (–, CH_3), 24.69 (–, CH_3), 27.29 (–, CH_3), 40.29 (+, CH_2), 53.50 (+, CH_2), 76.26 (+), 81.08 (+), 84.88 (+), 126.54 (–, C=C), 134.04 (–, C=C); MS (70 eV): *m/z* (%): 168 (2) [M^+], 150 (8), 135 (6), 125 (7), 117 (1), 111 (56), 95 (100). $C_{10}H_{16}O_2$: calcd C 71.38, H 9.59; found C 70.92, H 9.50.

3β,4β-Epoxy-1,5,6-trimethyl-8-oxabicyclo[3.2.1]octan-6α-ol (8b): To a solution of **7b** (293 mg, 1.74 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (290 mg, ca. 75%) at 0 °C. After 5 h a further portion of *m*-CPBA (290 mg) was added, and the mixture was stirred for 16 h at 0 °C. $CHCl_3$ was added, and the organic layer washed with aq. $Na_2S_2O_3$ solution (10%), sat. aq. $NaHCO_3$ solution and brine. Each aqueous layer was reextracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography (Et_2O/PE) of the crude product afforded **8b** (185 mg, 58%) as a colourless oil. IR (KBr): $\tilde{\nu}$ = 3480, 3034, 2967, 2937, 1450, 1373, 1265, 1265, 1197, 1137, 1076, 961, 863, 774, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.21 (s, 3H; CH_3), 1.30 (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 1.72 (dd, ^2J = 15, ^3J = 5 Hz, 1H; H-2), 1.88 (dd, ^2J = 13, J < 1 Hz, 1H; H-7), 2.00 (dd, ^2J = 15, $J \approx 1$ Hz, 1H; H-2), 2.09 (d, ^2J = 13 Hz, 1H; H-7 + (1H; OH)), 3.26 (dd, ^3J = 4, $^4J \approx 1$ Hz, 1H; H-4) 3.35 (dd, ^3J = 5, ^3J = 4 Hz, 1H; H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.68 (–, CH_3), 26.58 (–, CH_3), 27.11 (–, CH_3), 37.18 (+, CH_2), 50.61 (–, C-3), 52.95 (+, CH_2), 54.55 (–, C-4), 76.08 (+), 79.38 (+), 80.79 (+); MS (70 eV): *m/z* (%): 185 (1) [M^+ + 1], 184 (4) [M^+], 169 (4), 151 (8), 141 (9), 123 (29), 109 (72), 99 (41), 95 (47), 85 (100). HRMS calcd for $C_{10}H_{16}O_3$: 184.1099, found 184.1091. $C_{10}H_{16}O_3$: calcd C 65.18, H 8.76; found C 65.31, H 8.70.

1,6,8-Trimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-4β-ol (9bβ): Epoxyalcohol **8b** (50 mg, 0.27 mmol), DMSO (2.15 mL), H_2O (0.54 mL) and KOH (153 mg, 2.7 mmol) were allowed to react according to the procedure described for compound **9aβ** to give after chromatography (*t*BuOEt) **9bβ** (40 mg, 80%) as a colourless solid, m.p. 61–62 °C. IR (KBr): $\tilde{\nu}$ = 3431, 2969, 2927, 1445, 1402, 1328, 1352, 1328, 1291, 1223, 1198, 1178, 1120, 1095, 1039, 990, 955, 921, 853, 828 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.40 (s, 3H; CH_3), 1.43 (s, 3H; CH_3), 1.44 (s, 3H; CH_3), 1.56 (dd, ^2J = 13, J = 2 Hz, 1H; H-9), 1.96 (brd, ^2J = 15 Hz, 1H; H-5), 2.05 (d, ^2J = 13 Hz, 1H; H-9), 2.22 (d, ^3J = 11 Hz, 1H; OH), 2.36 (dd, ^2J = 15, ^3J = 6 Hz, 1H; H-5), 4.05 (ddd, ^3J = 11, ^3J = 6, ^3J = 4 Hz, 1H; H-4), 4.33 (dd, ^3J = 4, ^4J = 1.5 Hz, 1H; H-3); ^1H NMR (200 MHz, $CDCl_3$, D_2O): δ = 1.40 (s, 3H; CH_3), 1.43 (s, 3H; CH_3), 1.44 (s, 3H; CH_3), 1.56 (dd, ^2J = 13, J = 2 Hz, 1H; H-9), 1.96 (brd, ^2J = 15 Hz, 1H; H-5), 2.05 (d, ^2J = 13 Hz, 1H; H-9), 2.36 (dd, ^2J = 15, ^3J = 6 Hz, 1H; H-5), 4.05 (brt, ^3J = 6 Hz, 1H; H-4), 4.33 (dd, ^3J = 4, ^4J = 1.5 Hz, 1H; H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.80 (–, CH_3), 20.27 (–, CH_3), 27.81 (–, CH_3), 41.34 (+, C-5), 52.47 (+, C-9), 67.82 (–, C-4), 80.00 (+, C-6), 82.12 (–, C-3), 82.59 (+, C-8), 95.23 (+, C-1); MS (70 eV): *m/z* (%): 184 (1) [M^+], 166 (13), 151 (14), 141 (3), 136 (1), 125 (69), 111 (100), 100 (18), 95 (19), 87 (81). $C_{10}H_{16}O_3$: calcd C 65.18, H 8.76; found C 64.83, H 8.72.

6,8-Dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-4-one (12): To a mixture of alcohol **9aβ** (200 mg, 1.17 mmol), pyridinium dichromate (PDC) (442 mg, 1.17 mmol) and molecular sieves (400 mg, 4 Å) was added CH_2Cl_2 (10 mL). After 27 h at RT a further portion of PDC (207 mg, 0.55 mmol) and molecular sieves (240 mg) was added and the mixture was stirred for 3 h at RT. The reaction mixture was filtered through a short column with silica gel (eluent *t*BuOEt). The solvent was removed and the residue chromatographed (Et_2O/PE) to give **12** (161 mg, 82%) as a colourless oil. IR (film): $\tilde{\nu}$ = 2975, 2933, 2873, 1739, 1725, 1450, 1430, 1381, 1258, 1142, 1080, 990, 961, 903, 848 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 3H; CH_3), 1.60 (s, 3H; CH_3), 1.83 (ddd, ^2J = 13.8, ^3J = 5, ^4J = 2.3 Hz, 1H; H-9), 2.36 (d, ^2J = 13.8 Hz, 1H; H-9), 2.51 (dd, ^2J = 18, J = 1.5 Hz, 1H; H-5), 3.01 (d, ^2J = 18 Hz, 1H; H-5), 4.29 (s, 1H; H-3), 5.06 (d, ^3J = 5 Hz, 1H; H-1); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.00 (–, CH_3), 26.93 (–, CH_3), 47.40/49.58 (+, C-5/C-9), 82.02 (+, C-6), 83.75 (+, C-8), 89.29/93.59 (–, C-1/C-3), 204.96 (+, C-4); MS (70 eV): *m/z* (%): 168 (0) [M^+], 153 (1), 152 (0.4), 151 (1), 150 (3), 139 (2), 135 (8), 125 (9), 112 (11), 96 (100), 85 (52); FAB-MS: 169 (50) [M^+ + 1].

6,8-Dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-4α-ol (9aα): To a solution of **12** (66 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) was slowly added BH_3·THF (0.68 mL, 0.68 mmol, 1 M solution in THF) dropwise at −90 °C. The mixture was allowed to reach −60 °C within 2 h and was then quenched by addition of water. Under ice-cooling 2 N HCl was added until the mixture became a clear solution. The aqueous layer was extracted with Et_2O; the combined organic layers were dried (K_2CO_3) and evaporated. The crude product (**9aβ**:**9aα**, 1:3.7) was chromatographed (*t*BuOEt/cyclohexane) to give **9aα** (35 mg, 53%) as a colourless oil, which crystallized at −18 °C, m.p. 52–53 °C. IR (KBr): $\tilde{\nu}$ = 3480, 2968, 2934, 1445, 1390, 1376, 1247, 1185, 1147, 1114, 1081, 1042, 999, 963, 927, 908, 854, 813 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.46 (s, 3H; CH_3), 1.56 (s, 3H; CH_3), 1.61 (ddd, ^2J = 13, ^3J = 4.5, $J \approx 1.5$ Hz, 1H; H-9), 1.74 (dd, ^2J = 13, ^3J = 8 Hz, 1H; H-5), 2.07 (d, ^2J = 13 Hz, 1H; H-9), 2.35 (dddd, ^2J = 13, ^3J = 8.5, ^4J = 1.5, $^4J \approx 1$ Hz, 1H; H-5), 2.48 (brs, 1H; OH), 3.81 (m, 1H; H-4), 4.57 (d, ^3J = 2 Hz, 1H; H-3), 4.88 (d, ^3J = 4.5 Hz, 1H; H-1); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.87 (–, CH_3), 27.00 (–, CH_3), 41.14 (+, C-5), 47.65 (+, C-9), 66.68 (–, C-4), 80.98 (+, C-6), 81.85 (+, C-8), 88.49 (–, C-3), 91.16 (–, C-1); MS (70 eV): *m/z* (%): 170 (1) [M^+], 152 (9), 142 (7), 137 (4), 124 (11), 109 (83), 97 (54), 87 (100). $C_9H_{14}O_3$: calcd C 63.49, H 8.30; found C 63.40, H 8.29.

6,8-Dimethyl-4β-*O*-(thiocarbonylimidazol)-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane (10): A solution of **9aβ** (262.8 mg, 1.545 mmol) and thiocarbonyldiimidazol (551 mg, 3.09 mmol) in CCl_4 (4.8 mL) was heated to reflux for 1.5 h under exclusion of light. After the reaction had cooled to RT, CH_2Cl_2 was added and the organic layer was extracted with 2 N HCl, sat. aq. $NaHCO_3$ and brine. Each aqueous layer was reextracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography (*t*BuOEt/cyclohexane) to afford **10** (403 mg, 93%) as a light yellow solid, m.p. 79 °C. IR (KBr): $\tilde{\nu}$ = 3125, 2972, 2933, 1533, 1468, 1393, 1345, 1288, 1246, 1234, 1136, 1100, 1041, 985, 950, 851, 756 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2): δ = 1.44 (s, 3H; CH_3), 1.59 (s, 3H; CH_3), 1.67 (ddd, ^2J = 13.5, ^3J = 4, ^4J = 2 Hz, 1H; H-9), 2.11 (d, ^2J = 13.5 Hz, 1H; H-9), 2.13 (d, ^2J = 15.5 Hz, 1H; H-5), 2.47 (dd, ^2J = 15.5, ^3J = 7 Hz, 1H; H-5), 4.53 (d, ^3J = 3.5 Hz (with further coupling J < 1 Hz), 1H; H-3), 4.91 (d, ^3J = 4 Hz, 1H; H-1), 5.88 (dd, ^3J = 7, ^3J = 3.5 Hz, 1H; H-4), 7.00 (dd, ^3J = 1.5, $^4J \approx 1$ Hz, 1H; H-11), 7.62 (t, J = 1.5 Hz, 1H; H-10), 8.30 (brs, 1H; H-12); ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 19.74 (–, CH_3), 27.32 (–, CH_3), 38.39 (+, C-5), 47.60 (+, C-9), 77.65 (–, C-4), 80.86 (+, C-6), 81.66 (+, C-8), 83.02 (–, C-3), 92.26 (–, C-1), 118.38 (–, arom. C), 131.14 (–, arom. C), 183.68 (+, C=S); MS (70 eV): *m/z* (%): 282 (1) [M^+ + 2], 281 (2) [M^+ + 1], 280 (5) [M^+], 247 (13), 220 (4), 195 (2), 185 (2), 169 (3), 1523 (93), 135 (6), 125 (11), 109 (69), 96 (100). $C_{13}H_{16}N_2O_3S$: calcd C 55.70, H 5.76, N 10.00: found C 55.67, H 5.76, N 9.98.

1,3-Dimethyl-2,6-dioxatricyclo[3.3.1.0^{3,7}]nonan-4β-ol (18): A solution of **8a** (154 mg, 0.90 mmol) and BF_3·Et_2O (11 μL, 10 mol%) in CH_2Cl_2 (9 mL) was stirred for 45 min at 0 °C. Sat. aq. $NaHCO_3$ solution (4 drops) was added and the mixture was stirred for 10 min. The organic layer was dried (K_2CO_3) and evaporated. The residue was chromatographed (Et_2O) to give **18** (26 mg) as a colourless solid, **9aβ** (48 mg) and an unidentified byproduct (44 mg). Spectroscopic data for **18** (m.p. 86 °C): IR (KBr): $\tilde{\nu}$ = 3430, 2973, 2934, 1442, 1395, 1321, 1237, 1108, 1094, 996, 859, 833, 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 1.56–1.79 (m, 3H), 1.96 (d, ^2J = 11 Hz, 1H), 2.72 (d, ^3J = 11 Hz, 1H; OH), 3.69 (dd, ^3J = 11, ^3J = 4.5 Hz, 1H; H-4), 4.17 (brt, ^3J = 4.5 Hz, 1H; H-5), 4.40 (d, ^3J = 3 Hz, 1H; H-7); ^1H NMR (200 MHz, $CDCl_3$, D_2O): δ = 1.30 (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 1.56–1.79 (m, 3H; H-8, H-9), 1.96 (d, ^2J = 11 Hz, 1H; H-8), 3.69 (d, ^3J = 4.5 Hz, 1H; H-4), 4.17 (t, ^3J = 4.5 Hz, 1H; H-5), 4.40 (d, ^3J = 3 Hz, 1H; H-7); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.32 (–, CH_3), 23.94 (–, CH_3), 34.41 (+, C-9), 44.95 (+, C-8), 74.92 (–, C-4), 75.64 (–, C-5), 81.36 (+, C-1), 85.04 (–, C-7), 85.35 (+, C-3); MS (70 eV): *m/z* (%): 171 (5) [M^+ + 1], 170 (42) [M^+], 152 (9), 142 (7), 126 (16), 109 (68), 97 (100).

1,5-Dimethyl-8-oxabicyclo[3.2.1]oct-3-en-6α-yl *tert*-butyldimethylsilylether (13): To a solution of alcohol **7a** (974 mg, 6.32 mmol) in CH_2Cl_2 (19 mL) were added NEt_3 (1.75 mL, 12.6 mmol) and TBDMS triflate (1.75 mL, 7.61 mmol) at 0 °C. After 15 min at 0 °C CH_2Cl_2 was added. The organic layer was washed with sat. aq. $NaHCO_3$ solution (2×) and brine and dried ($MgSO_4$). Removal of the solvent and chromatography (Et_2O/PE) afforded **13** (1.46 g, 86%) as a colourless oil. IR (film): $\tilde{\nu}$ = 3038, 2958, 2930, 1642, 1473, 1447, 1361, 1252, 1189, 1159, 1085, 979, 907, 865, 838, 776 cm^{-1}; ^1H NMR (200 MHz, C_6D_6): δ = 0.09 (s, 3H; $SiCH_3$), 0.11 (s, 3H; $SiCH_3$), 1.04 (s, 9H; $SiC(CH_3)_3$), 1.33 (s, 3H; CH_3), 1.47 (s, 3H; CH_3), 1.69 (ddd, ^2J = 16, ^3J = 4, ^4J = 2 Hz, 1H; H-2), 1.75 (ddd, ^2J = 12, ^3J = 6, ^4J < 1 Hz, 1H; H-7), 2.00 (ddd, ^2J = 12, ^3J = 9, ^4J = 1.5 Hz, 1H; H-7), 2.34 (brd, ^2J = 16 Hz, 1H; H-2), 4.09 (dd, ^3J = 9, ^3J = 6 Hz, 1H; H-6), 5.74 (ddd, ^3J = 10, ^3J = 4, ^3J = 2 Hz, 1H; H-3), 5.94 (ddd, ^3J = 10, ^4J = 2, ^4J = 1.8 Hz, 1H; H-4); ^{13}C NMR (50 MHz, C_6D_6): δ = −4.88 (–, $SiCH_3$), −4.47 (–, $SiCH_3$), 18.14 (+, $SiC(CH_3)_3$), 21.81 (–, CH_3), 25.96 (–, $SiC(CH_3)_3$), 27.82 (–, CH_3), 40.73 (+, CH_2), 46.26 (+, CH_2), 77.51 (+, C-1), 80.03 (+, C-5), 84.17 (–, C-6), 124.33 (–, C=C), 133.96 (–, C=C); MS (70 eV): *m/z* (%): 268 (1) [M^+], 266 (1), 253 (4), 225 (2),

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211 (96), 185 (17), 165 (10), 137 (22), 119 (31), 109 (49), 95 (85), 75 (100). HRMS calcd for $C_{15}H_{28}O_2Si$: 268.1858, found 268.1856.

1,5-Dimethyl-3β,4β-epoxy-8-oxabicyclo[3.2.1]octan-6α-yl *tert*-butyldimethylsilylether (14): To a solution of **13** (955 mg, 3.56 mmol) in CH_2Cl_2 (16 mL) was added *m*-CPBA (930 mg, ca. 75%) in 4 portions at 0 °C under N_2. After 1 h of stirring at RT, a further portion of *m*-CPBA (260 mg) was added. The mixture was stirred for 17 h at 0 °C and then worked up as described for compound **8a**. Chromatography (Et_2O/PE) gave **14** (938 mg, 93%) as a colourless oil. IR ($CHCl_3$): $\tilde{\nu}$ = 2999, 2956, 2923, 2854, 1471, 1376, 1256, 1168, 1137, 1094, 1078, 1041, 912, 826 cm^{-1}; ^1H NMR (200 MHz, C_6D_6): δ = 0.05 (s, 3H; $SiCH_3$), 0.06 (s, 3H; $SiCH_3$), 1.02 (s, 9H; $SiC(CH_3)_3$), 1.16 (s, 3H; CH_3), 1.32 (dd, ^2J = 14, ^3J = 5.5 Hz, 1H; H-2), 1.53 (s, 3H; CH_3), 1.57 (ddd, 1H; ^2J = 12.5, ^3J = 6, $^4J \approx 1$ Hz, 1H; H-7), 1.96 (ddd, ^2J = 12.5, ^3J = 9.5, ^4J = 1.5 Hz, 1H; H-7), 2.01 (dd, ^2J = 14, J = 1.5 Hz, 1H; H-2), 3.07 (dd, ^3J = 5.5, ^3J = 4 Hz, 1H; H-3), 3.23 (dd, ^3J = 4, $^4J \approx 1$ Hz, 1H; H-4), 3.97 (dd, ^3J = 9.5, ^3J = 6 Hz, 1H; H-6); ^{13}C NMR (50 MHz, CD_2Cl_2): δ = −4.92 (−, $SiCH_3$), −4.51 (−, $SiCH_3$), 18.23 (+, $SiC(CH_3)_3$), 20.34 (−, CH_3), 25.95 (−, $SiC(CH_3)_3$), 27.52 (−, CH_3), 37.94 (+, C-2), 46.77 (+, C-7), 49.82 (−, C-3), 53.46 (−, C-4), 77.54 (+, C-1), 78.09 (+, C-5), 79.77 (−, C-6); MS (70 eV): *m/z* (%): 284 (0.5) [M^+], 269 (2), 239 (5), 227 (14), 209 (7), 182 (12), 157 (15), 142 (39), 130 (12), 124 (12), 108 (58), 93 (21), 75 (100).

1,5-Dimethyl-2β-hydroxy-8-oxabicyclo[3.2.1]oct-3-en-7α-yl *tert*-butyldimethylsilylether (15): To a solution of diisopropylamine (1.43 mL, 11 mmol) in Et_2O (6.7 mL) was added BuLi (6.2 mL, 9.9 mmol, 1.6 M solution in hexane) dropwise at −14 °C. After the solution had been stirred for 25 min at RT, DMPU (2.45 mL) was added followed by a solution of **14** (1.40 g, 4.93 mmol) in Et_2O (6.7 mL). The mixture was stirred for 20 h at RT, and a further portion of lithium diisopropylamide (7 mL, 4.8 mmol, 0.69 M solution in Et_2O) was added. After 3 h the reaction was quenched by addition of sat. aq. NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic layers were dried (K_2CO_3) and evaporated. Chromatography (Et_2O/PE) gave **15** (1.31 g, 94%) as a colourless solid, m.p. 74–75 °C. IR (KBr): $\tilde{\nu}$ = 3462, 3434, 3026, 2952, 2929, 2856, 1463, 1374, 1253, 1165, 1098, 1068, 1010, 957, 898, 861, 838, 776 cm^{-1}; ^1H NMR (200 MHz, [D$_6$]DMSO): δ = 0.01 (s, 3H; $SiCH_3$), 0.03 (s, 3H; $SiCH_3$), 0.84 (s, 9H; $SiC(CH_3)_3$), 1.22 (s, 3H; CH_3), 1.24 (s, 3H; CH_3), 1.51 (dd, ^2J = 12, ^3J = 2 Hz, 1H; H-6), 1.95 (dd, ^2J = 12, ^3J = 9 Hz, 1H; H-6), 3.73 (ddd, ^3J = 8.5, ^3J = 4, $^4J \approx 1$ Hz, 1H; H-2), 4.17 (dd, ^3J = 9, ^3J = 2 Hz, 1H; H-7), 4.58 (d, ^3J = 8.5 Hz, 1H; OH), 5.66 (dd, ^3J = 9.5, ^3J = 4 Hz, 1H; H-3), 5.92 (dd, ^3J = 9.5, $^4J \approx 1$ Hz, 1H; H-4); ^{13}C NMR (50 MHz, CD_2Cl_2): δ = −4.94 (−, $SiCH_3$), −4.68 (−, $SiCH_3$), 18.16 (+, $SiC(CH_3)_3$), 22.06 (−, CH_3), 23.94 (−, CH_3), 25.92 (−, $SiC(CH_3)_3$), 49.20 (+, C-6), 65.57 (−, C-2), 78.89 (+, C-1), 79.98 (−, C-7), 85.00 (+, C-5), 127.99 (−, C=C), 137.71 (−, C=C); MS (70 eV, 50 °C): *m/z* (%): 284 (2) [M^+], 269 (1), 251 (1), 241 (2), 227 (45), 201 (10), 188 (37), 165 (9), 152 (8), 131 (98), 109 (51), 97 (41), 75 (100). $C_{15}H_{28}O_3Si$: calcd C 63.34, H 9.93; found C 63.50, H 9.91.

1,5-Dimethyl-2β-hydroxy-8-oxabicyclo[3.2.1]octan-7α-yl *tert*-butyldimethylsilylether (16): A suspension of **15** (319 mg, 1.12 mmol) and Pd/C (5%) (30 mg) in EtOH (7 mL) was hydrogenated for 63 h at RT under normal pressure. The mixture was filtered through silica gel (eluent Et_2O) and evaporated to give **16** (319 mg, 99%) as a colourless waxy solid, m.p. 54 °C. IR (KBr): $\tilde{\nu}$ = 3505, 2958, 2927, 2856, 1471, 1373, 1255, 1215, 1155, 1101, 1078, 1033, 1008, 933, 908, 858, 836, 797, 777 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2): δ = 0.06 (s, 6H; $Si(CH_3)_2$), 0.90 (s, 9H; $SiC(CH_3)_3$), 1.20 (s, 3H; CH_3), 1.21 (s, 3H; CH_3), 1.32 (m, 1H; CH_2), 1.58–1.80 (m, 3H; CH_2), 2.05 (dd, 1H; ^2J = 12, ^3J = 10.2 Hz, 1H; H-6), 2.17 (brd, ^3J = 10 Hz, 1H; OH), 2.28 (m, 1H; CH_2), 3.46 (brd, J = 9.5 Hz, 1H; H-2), 4.09 (dd, ^3J = 10.2, ^3J = 3.9 Hz, 1H; H-7); ^{13}C NMR (50 MHz, CD_2Cl_2): δ = −4.98 (−, $SiCH_3$), −4.61 (−, $SiCH_3$), 18.17 (+, $SiC(CH_3)_3$), 21.63 (−, CH_3), 25.95 (−, $SiC(CH_3)_3$), 26.88 (+, CH_2), 27.25 (−, CH_3), 32.58 (+, CH_2), 45.30 (+, CH_2), 67.64 (−, C-2), 79.33 (−, C-7), 80.43/83.87 (+, C-1/C-5); MS (70 eV): *m/z* (%): 287 (1) [$M^+ + 1$], 286 (6) [M^+], 243 (2), 227 (11), 211 (17), 199 (18), 185 (24), 167 (3), 154 (21), 137 (20), 126 (85), 111 (31), 93 (36), 75 (100). HRMS calcd for $C_{15}H_{30}O_3Si$: 286.1964, found 286.1960. $C_{15}H_{30}O_3Si$: calcd C 62.89, H 10.56; found C 62.99, H 10.51.

1,5-Dimethyl-7α-(*tert*-butyldimethylsilyloxy)-8-oxabicyclo[3.2.1]octan-2β-yl *p*-toluenesulphonate (17): To a solution of **16** (704 mg, 2.46 mmol) in THF (9.8 mL) was added slowly *n*BuLi (1.82 mL, 2.91 mmol, 1.6 M solution in hexane) dropwise at −78 °C under N_2. After 15 min at the same temperature was added tosyl chloride (559 mg, 2.93 mmol) in one portion. The mixture was stirred for 30 min at −78 °C, for 2 h at 0 °C and for 5.5 h at RT. After addition of Et_2O the organic layer was extracted with ice-cold 1 N HCl, sat. aq. $NaHCO_3$ and brine. Each aqueous layer was reextracted with Et_2O, and the combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography (Et_2O/PE) to afford **17** (1.05 g, 97%) as a highly viscous oil, which crystallized at −18 °C, m.p. 69–70 °C. IR (film): $\tilde{\nu}$ = 2954, 2931, 2858, 1599, 1496, 1368, 1258, 1176, 1015, 937, 906, 857, 840, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = −0.01 (s, 3H; $SiCH_3$), 0.01 (s, 3H; $SiCH_3$), 0.87 (s, 9H; $SiC(CH_3)_3$), 0.99 (s, 3H; CH_3), 1.23 (s, 3H; CH_3), 1.30 (brdd, ^2J = 13.5, ^3J = 5.4 Hz, 1H; H-4), 1.59 (dd, ^2J = 12.6, ^3J = 3.6 Hz, 1H; H-6), 1.75 (m, 1H), 1.90 (m, 1H), 2.04 (dd, ^2J = 12.6, ^3J = 10.8 Hz, 1H; H-6), 2.23 (m, 1H), 2.43 (s, 3H; CH_3), 3.98 (dd, ^3J = 10.8, ^3J = 3.6 Hz, 1H; H-7), 4.45 (m, 1H; H-2), 7.30 (d, ^3J = 8.5 Hz, 2H; arom. H), 7.78 (d, ^3J = 8.5 Hz, 2H; arom. H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.24 (−, $SiCH_3$), −4.84 (−, $SiCH_3$), 17.79 (+, $SiC(CH_3)_3$), 21.26 (−, CH_3), 21.57 (−, CH_3), 24.62 (+, CH_2), 25.67 (−, $SiC(CH_3)_3$), 26.75 (−, CH_3), 31.95 (+, CH_2), 44.59 (+, CH_2), 78.54/79.11 (−, C-2/C-7), 79.54 (+, C-5), 82.16 (+, C-1), 127.96 (−, arom. C), 129.62 (−, arom. C), 134.29 (+, arom. C), 144.43 (+, arom. C); MS (70 eV, 100 °C): *m/z* (%): 440 (2) [M^+], 413 (2), 384 (4), 367 (2), 339 (2), 208 (2), 285 (4), 267 (4), 254 (3), 229 (31), 211 (35), 185 (5), 173 (52), 155 (52), 137 (28), 107 (16), 91 (100). $C_{22}H_{36}O_5SSi$: calcd C 59.97, H 8.24; found C 59.59, H 8.18.

6,8-Dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane (11): To a solution of **17** (522 mg, 1.18 mmol) in THF (94 mL) were added molecular sieves (4 Å) (485 mg) and TBAF (1.3 mL, 1.3 mmol, 1 M solution in THF). The mixture was stirred for 3 h at RT, heated at reflux for 6 h and allowed to cool to RT. Sat. aq. NH_4Cl solution was added, and the aqueous layer washed with Et_2O. The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure after addition of a small amount of silica gel. The residue was purified by chromatography (Et_2O/pentane, 1:3) to give **11** (70 mg, 39%) as a colourless, relatively volatile liquid. IR (film): $\tilde{\nu}$ = 3420, 2968, 2928, 1452, 1428, 1284, 1252, 1208, 1144, 1008, 960, 908, 880, 848 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2): δ = 1.37 (s, 3H; CH_3), 1.46 (s, 3H; CH_3), 1.55 (dd, ^2J = 13.5, ^3J = 4.5 (with further coupling J < 1 Hz), 1H; H-9), 1.60–1.89 (m, 4H; H-4, H-5), 1.93 (d, ^2J = 13.5 Hz, 1H; H-9), 4.50 (m, 1H; H-3), 4.76 (d, ^3J = 4.5 Hz, 1H; H-1); ^{13}C NMR (50 MHz, CD_2Cl_2): δ = 19.29 (−, CH_3), 24.00 (+, C-4 or C-5), 27.69 (−, CH_3), 31.05 (+, C-5 or C-4), 48.17 (+, C-9), 81.55 (+, C-6), 82.30 (+, C-8), 86.54 (−, C-3), 90.87 (−, C-1); GC-MS (R_t = 2.36 = 100%): *m/z* (%): 155 (0.1) [$M^+ + 1$], 154 (0.3) [M^+], 153 (0.02), 138 (0.06), 136 (2.3), 126 (90), 111 (75), 97 (63), 79 (24), 71 (88), 55 (100). HRMS calcd for $C_9H_{14}O_2$: 154.0993, found 154.0987.

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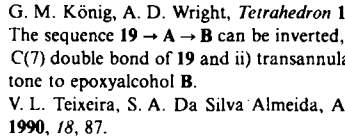

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