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Tricyclic challenges: synthetic approaches toward dodecahydrocyclopenta[*a*]indenes

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ABSTRACT

Tetrahydrospiro[1,3-dioxolane-2,1′-pentalen]-4′-ones were stereoselectively converted to either (*cis*,-*anti*,*cis*)- or (*cis*,*syn*)-linear dodecahydrocyclopenta[*a*]indene isomers employing a 1,4- or 1,2-conjugate addition of organometallic reagents and an intramolecular aldol reaction as the key steps. The relative configuration of the products was determined by X-ray crystal structure analysis and 1D NOE spectroscopy.

1. Introduction

While the decahydro-1*H*-cyclopenta[*a*]pentalene skeleton (**1**) is quite common in natural products and derivatives thereof,[1] the corresponding six-membered homologous dodecahydrocyclopenta[*a*]indene (**5**) is very rare (Fig. 1). Typical examples for **1** are (−)-$\Delta^{9(12)}$-capnellene (**2**) from the soft coral *Capnella imbricata*[2] or the sesquiterpenes hirsutene (**3**)[3] and coriolin (**4**)[4] from a Japanese mushroom, *Coriolus consors*.[5]

Natural products with cyclopenta[*a*]indene core **5** are tetramic acid macrolactams discodermide (**6**), which was isolated from the Caribbean marine sponge *Discodermia dissoluta*[6] and maltophilin (**7**) obtained from strains of *Stenotrophomonas maltophilia* R3089.[7] While discodermide (**6**) was found to inhibit in vitro proliferation of P388 murine leukemia cells and to inhibit growth of the yeast *Candida albicans*,[6] maltophilin (**7**) is an antifungal compound, which is active against various human-pathogenic and phytopathogenic fungi.[7] In contrast to tricyclic system **1** for which a variety of synthetic methods,[8] in particular radical reactions,[8b,9] were established, synthetic access toward tricyclic system **5** has only been poorly explored.[10]

We were therefore interested to prepare stereoisomers of the dodecahydrocyclopenta[*a*]indene core and focussed on a linear approach via 1,4-addition followed by an intramolecular aldol reaction as the key step starting from the known diketone **12**[11,12] (Scheme 1). Our results in exploring the access to tricyclic components are reported below.

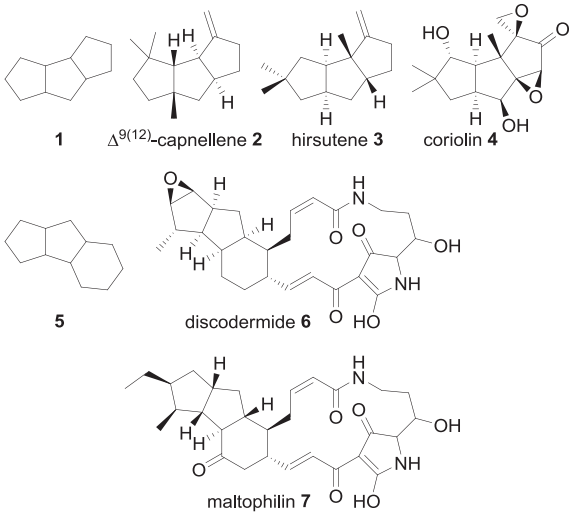

Fig. 1. Linear triquinane natural products **2**–**4** and cyclopenta[*a*]indene core containing **6**, **7**.

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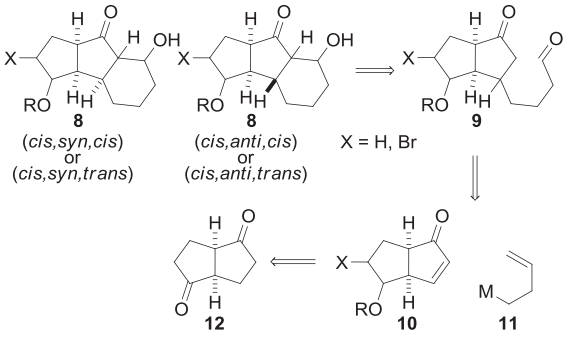
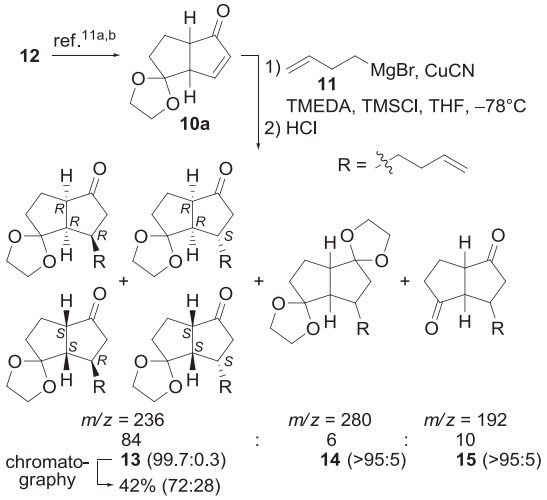


Scheme 1. Retrosynthetic route to dodecahydrocyclopenta[*a*]indene derivatives. Stereochemical nomenclature of compounds **8** was used in analogy to the literature.[1a]

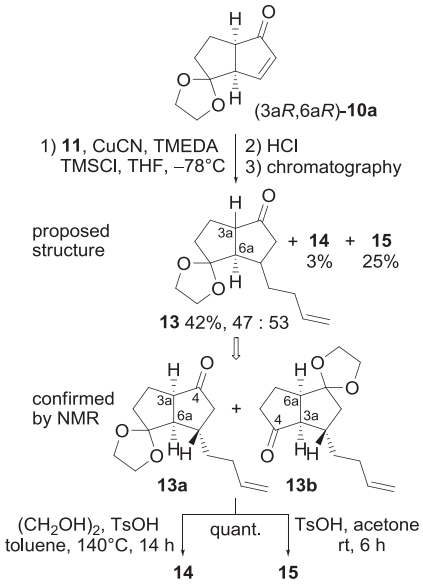
2. Results and discussion

As previously described, racemic diketone **12** was converted to bicyclo[3.3.0]octenone **10a** by TsOH mediated ketalization with ethylene glycol followed by oxidation of the intermediate ketone according to Nicolaou's methodology.[11a,b] Derivative **10a** was submitted to a Grignard reaction with 3-butenylmagnesiumbromide (**11**)/CuCN in the presence of chlorotrimethylsilane (TMSCl) and tetramethylethylenediamine (TMEDA) (Scheme 2).[13]



Scheme 2. Conjugate addition of Grignard reagent **11** to pentalenone **10a**.

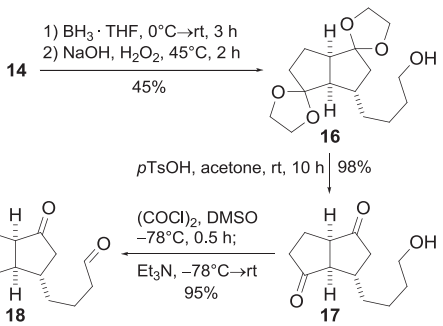
After hydrolytic workup, the GC–MS analysis of the crude product showed as the major product a mixture of two compounds (ratio 99.7:0.3) each with a molpeak at *m*/*z*=236, corresponding to the diastereomers of **13**. Additionally, a compound with *m*/*z*=280, indicative of the diketal **14** and a compound with *m*/*z*=192, i.e., hexahydropentalene-1,4-dione **15** were detected. After chromatographic purification on SiO_2, keto ketal **13** was isolated in 42%, however, in a decreased ratio of 72:28. As we surmised a diastereoselective reaction but an epimerization of the α-stereogenic center relative to the ketone moiety under the slightly acidic conditions during chromatography, the addition reaction was performed using chiral (3a*R*,6a*R*)-**10a**[11a,b] (Scheme 3). Based on our assumption, only one diastereomer should be formed. But again, the two MS peaks at *m*/*z*=236 (ratio 47:53) were detected together with those of **14** and **15**. From ^{1}H NMR spectra an epimerization could be excluded, and NOESY spectra of **13** derived from (3a*R*,6a*R*)-**10a** clearly revealed the cis-configuration of 3a-H and 6a-H for both ketals (Figs. S1 and S2, Supplementary data). Careful analysis of the NMR spectra finally indicated that ketal migration had taken place and **13a**,**b** were present in the mixture of **13**



Scheme 3. Grignard reaction of (3a*R*,6a*R*)-**10a** and characterization of product **13**.

(Scheme 3). To confirm this assignment, the 47:53 mixture of **13a**,**b** was treated with ethylene glycol giving indeed the corresponding diketal **14** quantitatively, while treatment of **13a**,**b** with TsOH in acetone led to the diketone **15** in quantitative yield. Consequently, the Cu-catalyzed Grignard reaction proceeded diastereoselectively with >99% de albeit with competing ketal migration.

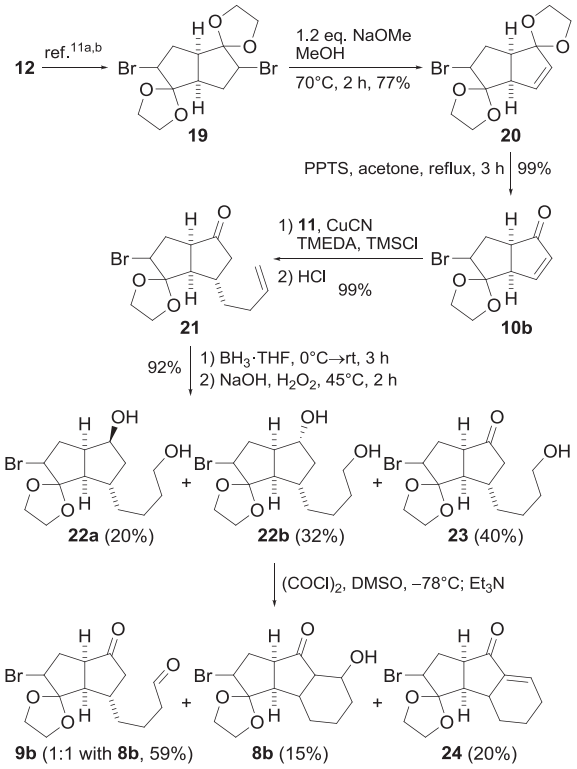
The planned synthesis was then continued using compound **14** (Scheme 4). Hydroboration of **14** yielded alcohol **16** in 45%, which was deprotected to give derivative **17**. The latter was submitted to Swern oxidation to afford aldehyde **18** in 95% yield. In the crude reaction mixture of subsequent aldol reactions in the presence of LDA two products were detected, however, after workup, only product **18** was recovered. Presumably, ring closure competed with a retro aldol reaction.



Scheme 4. First attempt to synthesize a cyclopenta[*a*]indene derivative.

To circumvent the described problems, the brominated pentalenone **10b** was prepared from dibromo derivative **19**[11a,b,14] by treatment with NaOMe and selective ketal cleavage in the mono elimination product **20** with pyridinium *p*-toluenesulfonate (PPTS) in acetone (Scheme 5).

Conjugate addition of **11**/CuCN to **10b** and hydroboration of the resulting addition product **21** provided a mixture of the diols **22a**,**b** and monoalcohol **23**, which could be separated by flash chromatography for full characterization. It should be emphasized that compound **21** did not undergo ketal migration and the sequence from **19** to **22**/**23** did not require any chromatographic separation. The mixture of **22**/**23** was oxidized under Swern conditions, resulting in three compounds, i.e., the bicyclic ketoaldehyde **9b**, the



Scheme 5. Alternative preparation of *trans*-fused cyclopenta[*a*]indene derivatives.

tricyclic aldol product **8b**, and the tricyclic enone **24**. Ketoaldehyde **9b** and tricyclic β-hydroxy ketone **8b** were found to display an odd behavior. In $CDCl_3$ solution or upon storage in the freezer aldol product **8b** underwent a retro aldol reaction. Conversely, treatment of **9b** with KO*t*-Bu, KHMDS or LDA or even silica gel afforded the ketol **8b**. During column chromatography **9b** and **8b** behaved like a 'chromatographic azeotrope', that means, first 59% of a (1:1) mixture of **9b** and **8b** was isolated [R_f 0.5 (hexanes/EtOAc=1:1)] and in a later fraction [R_f 0.2 (hexanes/EtOAc=1:1)] pure compound **8b** was obtained in 15% yield.

X-ray single-crystal structure analysis of **8b** and **24** reveals the cis,trans-configuration for both tricyclic derivatives (Fig. 2). Linear (*cis*,*anti*,*cis*)-isomer **8b** crystallized in the monoclinic, acentric space group *Cc* with two independent conformers, which have the same configuration, whereas compound **24** crystallized as pure enantiomer in an acentric space group. The absolute configuration could be determined directly by anomalous dispersion.

The access to (*cis*,*syn*,*cis*)-dodecahydrocyclopenta[*a*]indene derivatives required a modified synthetic route. Mehta[15] and Piers[16] demonstrated in the synthesis of kelsoene that both heterogenous and homogenous catalytic hydrogenation of a bicyclo[3.3.0] octenone with exocyclic double bond proceeded with good diastereoselectivity. The incoming hydrogen atoms were located on the same side as the angular hydrogen atoms thus favoring an all-cis-configuration. This literature precedence motivated us to develop a stereoselective synthetic strategy to a (*cis*,*syn*,*cis*)-cyclohexano diquinane by using a hydrogenation to generate the first stereocenter followed by aldol reaction for ring closure. The reaction sequence commenced with a 1,2-addition reaction of Grignard reagent **25** derived from benzyl 4-bromobutyl ether[17] to pentalenone **10a** to give an inseparable mixture of the 1,2-addition product **26** and 4-benzyloxy-1-butanol **27**[18] besides the 1,4-addition product, 6′-[4-(benzyloxy)butyl]hexahydro-4′*H*-spiro [1,3-dioxolane-2,1′-pentalen]-4′-one, which could be separated by flash chromatography (Scheme 6).

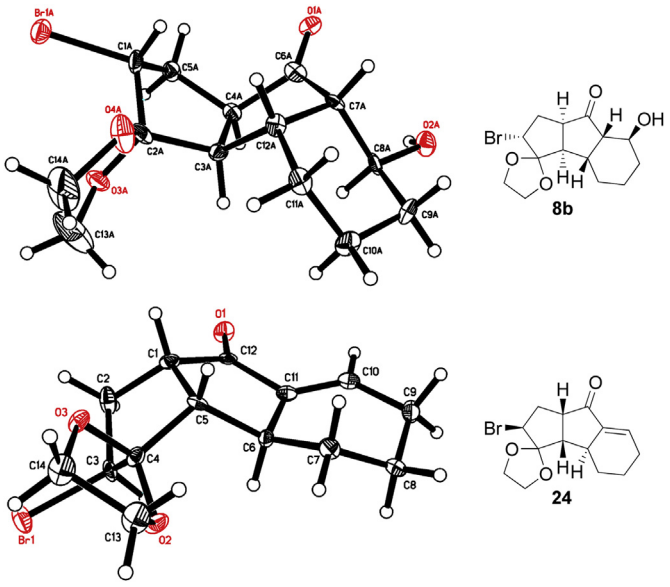
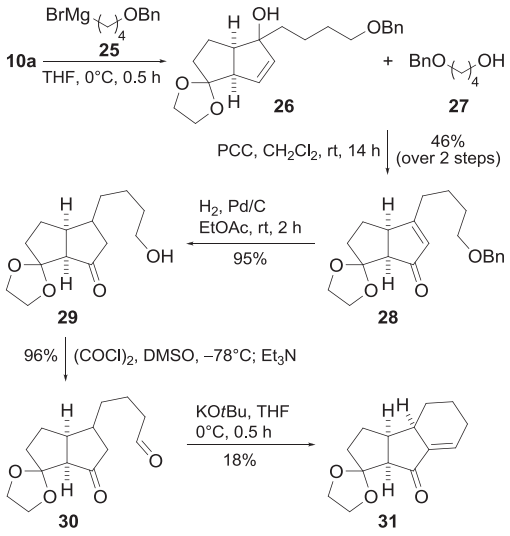


Fig. 2. Structure of tricyclic β-hydroxy ketone **8b** and tricyclic enone **24** in the solid state.



Scheme 6. Preparation of (*cis*,*syn*)-cyclopenta[*a*]indene derivative **31**.

The crude mixture of **26** and **27** was reacted with pyridinium chlorochromate (PCC) according to a literature procedure[19] to yield the rearranged enone **28** after chromatographic separation of **27** in 46% over both steps. Hydrogenolytic removal of the benzyl group in **28** and subsequent Swern oxidation of the resulting alcohol **29** provided the ketoaldehyde **30** in 91% overall yield. Upon reaction of **30** with KO*t*-Bu, an aldol condensation gave the tricyclic enone **31** as the main product. Although GC–MS of the crude product displayed only one major peak at *m*/*z*=234 resulting from **31** together with some minor impurities (Fig. S3, Supplementary data), purification by chromatography provided **31** in only 18% yield presumably due to decomposition on SiO_2. The relative configuration of **31** could be determined by 1D NOE experiments to be cis,syn (for details see Supplementary data).

3. Conclusion

Two synthetic strategies towards dodecahydrocyclopenta[*a*] indene isomers **8b**, **24**, and **31** are presented. The first route

involving a Cu-catalyzed Grignard reaction of 3-butenylmagnesiumbromide **11** and 2-bromopentalenone **10b** to give the 1,4-addition product **21** and final ring closure by aldol reaction led to the linearly fused tricyclic (*cis*,*anti*,*cis*)-isomer **8b** and (*cis*,*anti*)-isomer **24**. However, in the case of pentalenone **10a**, a ketal migration was observed during the conjugate addition of **11**.

The second synthetic route, which utilized a hydrogenation to create the first stereocenter, provided the tricyclic (*cis*,*syn*)-isomer **31**. In this case, the addition of Grignard reagent **25** derived from benzyl 4-bromobutyl ether to **10a** yielded the 1,2-addition product **26**, which was converted to derivative **31** by hydrogenolytic debenzylation, Swern oxidation, and final aldol reaction. The configurations of **8b** and **24** were unambiguously verified by X-ray single-crystal structure analysis, while the structure of **31** was determined by 1D NOE spectroscopy. Previous reports[15,16] suggested that hydrogenation of enone **31** should lead to (*cis*,*syn*,*cis*)-linear cyclohexano diquinanes, which are conceivable precursors in the synthesis of discodermide (**6**).

4. Experimental section

4.1. General methods

Melting points were measured on a Büchi SMP 20 and are uncorrected. NMR spectra were recorded on a Bruker Avance 300 or 500 spectrometer with TMS (δ=0.00) as internal standard. Nuclear Overhauser effect (NOESY), homonuclear (^{1}H/^{1}H) correlation spectroscopy (COSY), and inverse gradient heteronuclear (^{1}H/^{13}C) correlation spectroscopy (HSQC and HMBC) were obtained using the standard Bruker pulse sequence for structural assignment of NMR spectra. IR spectra were recorded on a Bruker FT-IR-spectrometer Vector 22 with MKII golden gate single reflection Diamant ATR-system. Mass spectra were recorded on a Finnigan MAT 95 spectrometer (CI) with methane as carrier gas, a Varian MAT 711 (EI, 70 eV), and a Bruker Daltonics micrOTOF_Q (ESI). Optical rotations were measured with a Perkin–Elmer 241 polarimeter at 20 °C. Flash chromatography was performed on silica gel, grain size 40–63 μm (Fluka). X-ray single-crystal structure analysis was performed on a Bruker κ APEX II Duo diffractometer (λ=0.71073 Å) at 100 K. All reactions were performed in oven-dried glassware. All reagents were used as purchased unless otherwise noted. Hexanes, EtOAc, and acetone were distilled prior to use. THF and Et_2O were distilled from sodium/benzophenone, CH_2Cl_2 from CaH_2, MeOH from magnesium. The reactions were monitored by TLC (Merck 60 F_{254} plates) and visualized with an ethanolic solution of *p*-anisaldehyde and sulfuric acid.

4.2. Grignard reaction of (3a′*R*,6a′*R*)-2′,3′,3a′,6a′-tetrahydro-4′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (3a*R*,6a*R*)-10a

To a suspension of CuCN (0.20 mg, 2.33 mmol) in freshly distilled THF was added TMEDA (0.25 mL, 0.20 g, 1.67 mmol) and the reaction mixture cooled to −78 °C. A solution of Grignard reagent **11**, freshly prepared from Mg (0.16 g, 6.67 mmol) and 4-bromo-1-butene (0.34 mL, 0.45 g, 3.37 mmol), was added dropwise and the resulting mixture stirred at −78 °C for 20 min. Then TMSCl (0.26 mL, 0.22 g, 2.00 mmol) was added followed by a cooled solution of (3a*R*,6a*R*)-**10a**[11a,b] (1 mL, 0.30 g, 1.67 mmol) in THF (5 mL). After stirring for 30 min, the reaction mixture was hydrolyzed with a mixture of a satd NH_4Cl solution/25%ic NH_3 solution (10:1, 15 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). A 1 N HCl solution (50 mL) was added to the combined organic layers, and the mixture stirred for 30 min to hydrolyze the formed silyl enol ether. The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on SiO_2 (hexanes/EtOAc=3:1) to give **14** (15 mg, 0.05 mmol, 3%), a mixture of **13** (160 mg, 0.68 mmol, 42%) and **15** (80 mg, 0.42 mmol, 25%) as colorless oils. The mixture of **13** was re-chromatographed on SiO_2 (hexanes/EtOAc=5:1) to give analytically pure **13a** and **13b**.

*4.2.1. 3′-But-3-enylhexahydrodispiro[1,3-dioxolane-2,1′-pentalene-4′,2″-[1,3]dioxolane] (**14**).* R_f 0.6 (hexanes/EtOAc=2:1); $[\alpha]_D^{20}$ +21.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27–1.43 (m, 2H, 2-H_a, 7-H_a), 1.58–1.74 (m, 4H, 5-H_a, 6-H, 7-H_b), 1.81–1.89 (m, 1H, 5-H_b), 1.91–2.08 (m, 5H, 2-H_b, 3-H, 3a-H, 8-H), 2.89 (td, *J*=10.0, 3.9 Hz, 1H, 6a-H), 3.84–3.95 (m, 8H, OCH_2CH_2O), 4.91–5.03 (m, 2H, 10-H), 5.79 (ddt, *J*=16.6, 10.2, 6.7 Hz, 1H, 9-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7 (C-6), 32.9 (C-8), 35.1 (C-5), 35.8 (C-7), 38.3 (C-3), 42.0 (C-2), 48.6 (C-6a), 54.7 (C-3a), 64.0, 64.4, 65.0, 65.2 (OCH_2CH_2O), 114.3 (C-10), 117.9, 119.1 (C-1, C-4), 139.2 (C-9); FTIR (ATR) $\tilde{\nu}$ 2934 (m), 2881 (m), 1437 (w), 1337 (w), 1264 (s), 1120 (m), 1036 (m), 947 (w), 908 (w) cm^{-1}; MS (ESI) *m*/*z* 303.2 [M+Na]$^+$, 281.2 [M+H]$^+$, 237.2, 219.1, 193.1, 175.1, 133.1. HRMS (ESI) calculated for $C_{16}H_{24}NaO_4^+$ 303.1572, found 303.1575.

*4.2.2. (3a′R,6′S,6a′R)-6′-But-3-enylhexahydro-4′H-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (**13a**).* Yield: 0.80 g, 21%; R_f 0.5 (hexanes/EtOAc=2:1); $[\alpha]_D^{20}$ +50.9 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35–1.43 (m, 1H, 7-H_a), 1.65–1.85 (m, 4H, 2-H, 3-H_a, 7-H_b), 1.91–2.19 (m, 5H, 5-H_a, 6-H, 3-H_b, 8-H), 2.38 (ddd, *J*=9.8, 5.4, 0.6 Hz, 1H, 6a-H), 2.49 (ddt, *J*=17.7, 7.9, 0.7 Hz, 1H, 5-H_b), 2.73–2.80 (m, 1H, 3a-H), 3.91–3.99 (m, 4H, OCH_2CH_2O), 4.96–5.06 (m, 2H, 10-H), 5.81 (ddt, *J*=17.1, 10.4, 6.7 Hz, 1H, 9-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.9 (C-6), 32.2 (C-8), 34.6 (C-5), 35.2 (C-3), 36.2 (C-7), 45.1 (C-2), 49.4 (C-6a), 53.1 (C-3a), 64.5, 65.3 (OCH_2CH_2O), 115.3 (C-10), 118.8 (C-4), 138.5 (C-9), 221.6 (C-1); FTIR (ATR): $\tilde{\nu}$ 2964 (m), 2930 (m), 2883 (m), 1736 (vs), 1640 (w), 1440 (w), 1338 (w), 1214 (w), 1176 (w), 1147 (m), 1117 (m), 1021 (m), 949 (m), 914 (m) cm^{-1}; MS (ESI) *m*/*z* 259.1 [M+Na]$^+$, 237.2 [M+H]$^+$, 193.1, 175.1, 147.2, 133.1; HRMS (ESI) calculated for $C_{14}H_{20}NaO_3^+$ 259.1310, found 259.1310.

*4.2.3. (3′S,3a′R,6a′R)-3′-But-3-enylhexahydro-4′H-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (**13b**).* Yield: 0.78 g, 20%; R_f 0.5 (hexanes/EtOAc=2:1); $[\alpha]_D^{20}$ +75.0 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44–1.53 (m, 2H, 5-H_a, 7-H_a), 1.66–1.75 (m, 1H, 7-H_b), 1.86–2.13 (m, 6H, 5-H_b, 3-H, 6-H, 8-H), 2.19 (dddd, *J*=18.1, 9.5, 5.2, 2.0 Hz, 1H, 2-H_a), 2.31 (ddd, *J*=10.0, 5.0, 1.6 Hz, 1H, 3a-H), 2.39 (dd, *J*=18.1, 9.1 Hz, 1H, 2-H_b), 2.83–2.90 (m, 1H, 6a-H), 3.89–3.99 (m, 4H, OCH_2CH_2O), 4.92–5.04 (m, 2H, 10-H), 5.81 (ddt, *J*=17.1, 10.4, 6.6 Hz, 1H, 9-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5 (C-6), 32.1 (C-8), 35.9 (C-7), 37.8 (C-2), 38.9 (C-3), 42.0 (C-5), 47.4 (C-6a), 55.7 (C-3a), 64.8, 64.9 (OCH_2CH_2O), 114.8 (C-10), 117.8 (C-1), 138.5 (C-9), 221.9 (C-4); FTIR (ATR) $\tilde{\nu}$ 2956 (m), 2923 (m), 2877 (m), 1734 (vs), 1639 (w), 1453 (w), 1336 (w), 1306 (w), 1264 (m), 1162 (s), 1126 (s), 1034 (s), 948 (m), 911 (m) cm^{-1}; MS (ESI) *m*/*z* 259.1 [M+Na]$^+$, 237.2 [M+H]$^+$, 193.1, 181.1 [M−C_4H_7]$^+$, 175.1, 147.2, 133.1; HRMS (ESI) calculated for $C_{14}H_{20}NaO_3^+$ 259.1310, found 259.1308.

*4.2.4. 3-But-3-enylhexahydropentalene-1,4-dione (**15**).* R_f 0.3 (hexanes/EtOAc=2:1); $[\alpha]_D^{20}$ +150.3 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41–1.50 (m, 1H, 7-H_a), 1.71–1.80 (m, 1H, 7-H_b), 2.03–2.23 (m, 6H, 2-H_a, 5-H_a, 6-H, 8-H), 2.27–2.40 (m, 3H, 2-H_b, 3-H, 5-H_b), 2.62 (dd, *J*=9.1, 4.3 Hz, 1H, 3a-H), 2.97 (td, *J*=9.1, 4.9 Hz, 1H, 6a-H), 4.94–5.03 (m, 2H, 10-H), 5.76 (ddt, *J*=16.8, 10.2, 6.6 Hz, 1H, 9-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0 (C-6), 31.9 (C-8), 35.1 (C-7), 36.8 (C-3), 37.6 (C-5), 44.5 (C-2), 49.2 (C-6a), 55.3 (C-3a), 115.5 (C-10), 137.6 (C-9), 218.9, 219.1 (C-1, C-4); FTIR (ATR) $\tilde{\nu}$ 2927 (m), 2183 (w), 1972 (w), 1728 (vs), 1640 (m), 1455 (m), 1408 (m), 1167 (m), 1132 (s), 936 (m), 913 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 192.1 (63) [M]$^+$, 181.1 (8), 164.1 (40), 149.1 (18), 137.0 (20) [M−C_4H_7]$^+$, 122.0 (18), 110.1 (55), 95.0

(20), 83.0 (100), 81.0 (25), 67.0 (18), 55.0 (17), 41.0 (16); HRMS (ESI) calculated for $C_{12}H_{16}NaO_2^+$ 215.1048, found 215.1051.

4.3. 2′-Bromo-6′-but-3-enylhexahydro-4′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (21)

As described above for **10a**, from **10b** (1.57 g, 6.09 mmol), Mg (0.87 g, 37.0 mmol), **11** (1.83 mL, 2.43 g, 18.0 mmol), TMEDA (0.92 mL, 0.71 g, 6.09 mmol), TMSCl (0.93 mL, 0.79 g, 7.30 mmol), and CuCN (0.73 g, 8.52 mmol), crude yield: 1.90 g (6.03 mmol, 99%), brown oil; R_f 0.7 (hexanes/EtOAc=2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38–1.47 (m, 1H, 7-H_a), 1.65–1.73 (m, 1H, 7-H_b), 2.00–2.17 (m, 4H, 2-H_a, 3-H, 8-H), 2.30–2.40 (m, 2H, 6-H), 2.54 (dd, J=17.8, 8.1 Hz, 1H, 2-H_b), 2.78 (dd, J=10.8, 4.5 Hz, 1H, 3a-H), 2.89 (td, J=10.2, 4.5 Hz, 1H, 6a-H), 3.92–4.12 (m, 5H, O*CH*$_2$*CH*$_2$O, 5-H), 4.95–5.05 (m, 2H, 10-H), 5.79 (ddt, J=17.0, 10.2, 6.6 Hz, 1H, 9-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.6 (C-8), 34.0 (C-3), 35.1 (C-6), 36.3 (C-7), 45.0 (C-2), 46.8 (C-6a), 49.8 (C-3a), 53.2 (C-5), 65.8, 66.0 (O*CH*$_2$*CH*$_2$O), 115.4 (C-10), 116.8 (C-4), 138.2 (C-9), 220.0 (C-1); FTIR (ATR) $\tilde{\nu}$ 2962 (w), 2853 (w), 1699 (vs), 1586 (w), 1453 (m), 1344 (w), 1298 (w), 1260 (m), 1166 (s), 1130 (m), 1038 (m), 1011 (m), 847 (w) cm^{-1}; MS (EI, 70 eV) m/z (%) 316.0 (5), 314.0 (5) $[M]^+$, 235.1 (25) $[M-Br]^+$, 178.9 (20), 176.9 (20) $[C_5H_7BrO_2]$, 165.9 (45), 163.9 (45), 125.0 (10), 99.0 (100) $[C_5H_8O_2]$, 81.0 (5), 55.0 (9); HRMS (EI) calculated for $C_{14}H_{19}BrO_3$ $[M]^+$ 314.0518, found 314.0513.

4.4. 4-Hexahydrodispiro[1,3-dioxolane-2,1′-pentalene-4′,2″-[1,3]dioxolan]-3′-ylbutan-1-ol (16)

To a solution of **14** (370 mg, 1.32 mmol) in dry THF (15 mL) at 0 °C was slowly added a 1 M solution of BH_3·THF in THF (1.3 mL, 1.32 mmol), the reaction mixture warmed to room temperature and stirred for 3 h. Then a 3 M NaOH solution (0.6 mL) and a 30%ic H_2O_2 solution (0.3 mL) were added and the reaction mixture stirred for a further 2 h at 45 °C. After addition of Et_2O (5 mL), the layers were separated and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on SiO_2 (hexanes/EtOAc=1:7) to give **16** (150 mg, 0.50 mmol, 45%) as a yellow oil; R_f 0.6 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15–1.37 (m, 4H, 2-H_a, 5-H_a, 7-H), 1.45–1.59 (m, 5H, 5-H_b, 6-H_a, 8-H_a, 9-H), 1.60–1.68 (m, 1H, 6-H_b), 1.74–1.99 (m, 4H, 3-H, 2-H_b, 3a-H, 8-H_b), 2.57 (td, J=9.6, 3.1 Hz, 1H, 6a-H), 3.56 (t, J=6.8 Hz, 2H, 10-H), 3.76–3.87 (m, 8H, O*CH*$_2$*CH*$_2$O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4 (C-6), 24.5 (C-7), 32.9 (C-9), 34.7 (C-8), 35.8 (C-5), 38.4 (C-3), 41.8 (C-2), 48.4 (C-6a), 54.4 (C-3a), 63.0 (C-10), 63.9, 64.3, 64.9, 65.1 (O*CH*$_2$*CH*$_2$O), 117.8, 119.0 (C-1, C-4); FTIR (ATR) $\tilde{\nu}$ 3454 (w), 2934 (m), 2882 (m), 1965 (m), 1436 (w), 1337 (w), 1264 (s), 1121 (m), 1033 (m), 947 (w) cm^{-1}; MS (ESI) m/z 321.2 $[M+Na]^+$, 299.2 $[M+H]^+$, 283.1, 255.2, 237.1; HRMS (ESI) calculated for $C_{16}H_{26}NaO_5^+$ 321.1678, found 321.1672.

4.5. 3-(4-Hydroxybutyl)hexahydropentalene-1,4-dione (17)

A solution of **16** (120 mg, 0.40 mmol) and *p*-TsOH (30.0 mg, 0.16 mmol) in acetone (10 mL) was stirred at room temperature for 10 h. After addition of a satd $NaHCO_3$ solution (10 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give **17** (55 mg, 0.156 mmol, 98%, >97% GC purity) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30–1.42 (m, 3H, 5-H_a, 7-H), 1.47–1.56 (m, 2H, 5-H_b, 6-H_a), 2.00–2.40 (m, 8H, 2-H, 3-H, 6-H_b, 8-H, 9-H), 2.58 (dd, J=9.2, 4.7 Hz, 1H, 3a-H), 2.90–2.97 (m, 1H, 6a-H), 3.58 (t, J=6.5 Hz, 2H, 10-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0 (C-6), 22.9 (C-7), 31.5 (C-9), 34.7 (C-8), 36.3 (C-3), 36.7 (C-5), 43.5 (C-2), 48.1 (C-6a), 54.2 (C-3a), 61.5 (C-10), 218.0, 218.4 (C-1, C-4); FTIR (ATR) $\tilde{\nu}$ 3449 (m), 2932 (s), 1732 (s), 1458 (w), 1407 (w), 1357 (w), 1263 (m), 1175 (m), 1134 (m), 1058 (m) cm^{-1}; MS (EI, 70 eV) m/z (%) 210.1 (20) $[M]^+$, 199.1 (10), 182.1 (18), 164.1 (14), 155.0 (38), 150.1 (8), 137.1 (23) $[M-C_4H_9O]^+$, 122.1 (13), 110.1 (21), 95.1 (18), 91.0 (60), 83.0 (100), 67.1 (18), 55.0 (38), 45.0 (22); HRMS (ESI) calculated for $C_{12}H_{18}NaO_3^+$ 233.1154, found 233.1155.

4.6. General procedure for the Swern oxidation

To a solution of oxalyl chloride (1.1–2.5 equiv) in dry CH_2Cl_2 at −78 °C was slowly added a solution of DMSO (2.2–5 equiv) in CH_2Cl_2 whereby the temperature did not exceed −60 °C. Then a solution of the appropriate alcohol (1 equiv) in CH_2Cl_2 (1.5 mL) was slowly added and the reaction mixture stirred at −78 °C for 20 min. After addition of NEt_3 (5–12 equiv) (temperature did not exceed −60 °C), the reaction mixture was stirred at −78 °C for a further 15 min and then allowed to warm to room temperature. The mixture was hydrolyzed with H_2O, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The product was used without further purification unless otherwise noted.

*4.6.1. 4-(3,6-Dioxooctahydropentalen-1-yl)butanal (**18**).* From $(COCl)_2$ (0.07 mL, 99.2 mg, 0.79 mmol), DMSO (0.11 mL, 0.12 g, 1.57 mmol), **17** (150 mg, 0.71 mmol) and Et_3N (0.50 mL, 0.37 g, 3.57 mmol). Yellow oil, 140 mg, yield: 95%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36–1.49 (m, 1H, 7-H_a), 1.60–1.73 (m, 3H, 7-H_b, 8-H), 2.06–2.53 (m, 9H, 2-H, 3-H, 5-H, 6-H, 9-H), 2.63 (dd, J=9.1, 4.7 Hz, 1H, 3a-H), 2.94–3.04 (m, 1H, 6a-H), 9.76 (t, J=1.3 Hz, 1H, 10-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1 (C-8), 23.0 (C-7), 35.4 (C-6), 37.1 (C-3), 37.6 (C-5), 43.5 (C-2), 44.4 (C-9), 49.1 (C-6a), 55.0 (C-3a), 201.7 (C-10), 218.5, 219.0 (C-1, C-4); MS (EI, 70 eV) m/z (%) 208.1 (20) $[M]^+$, 190.2 (40) $[M-H_2O]^+$, 180.2 (22), 162.2 (65), 155.2 (22), 137.2 (78) $[M-C_4H_7O]^+$, 123.1 (30), 109.1 (57), 98.1 (39), 83.1 (100), 79.1 (55), 77.1 (20), 67.1 (20), 55.1 (38).

*4.6.2. Products **8b**, **9b**, and **24**.* From $(COCl)_2$ (1.50 mL, 2.18 g, 17.2 mmol) in dry CH_2Cl_2 (20 mL), DMSO (2.44 mL, 2.66 g, 34.0 mmol) in CH_2Cl_2 (15 mL), **22**/**23** (2.30 g, 6.89 mmol), and Et_3N (11.5 mL, 8.40 g, 83.0 mmol); chromatographed on SiO_2 (hexanes/EtOAc=3:1). *2-Bromo-1,2,3a,3b,4,5,6,8a-octahydro-8H-spiro[cyclopenta[a]indene-3,2′-[1,3]dioxalan]-8-one (**24**).* Colorless solid, 430 mg, yield: 20%; R_f 0.7 (hexanes/EtOAc=1:1); mp 175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03–1.20 (m, 1H, 4-H_a), 1.50–1.69 (m, 1H, 5-H_a), 1.83–1.94 (m, 1H, 5-H_b), 2.15–2.51 (m, 7H, 1-H, 3a-H, 3b-H, 4-H_b, 6-H), 2.85–2.95 (m, 1H, 8a-H), 3.95–4.27 (m, 5H, O*CH*$_2$*CH*$_2$O, 2-H), 6.63 (q, J=3.5 Hz, 1H, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3 (C-5), 25.2 (C-6), 29.5 (C-4), 35.0 (C-1), 39.2 (C-3b), 47.5 (C-8a), 49.2 (C-3a), 51.7 (C-2), 66.0, 66.5 (O*CH*$_2$*CH*$_2$O), 116.9 (C-3), 134.0 (C-7), 141.7 (C-7a), 207.6 (C-8); FTIR (ATR) $\tilde{\nu}$ 2938 (w), 2253 (w), 1714 (m), 1649 (m), 1421 (w), 1264 (s), 1171 (w), 1041 (w), 951 (w), 704 (s), 650 (w) cm^{-1}; MS (ESI) m/z 315.0, 313.0 $[M+H]^+$, 271.0, 269.0, 253.0, 251.0, 233.1 $[M-Br]^+$, 189.1, 179.0, 177.0, 171.1, 161.1, 143.1; HRMS (ESI) calculated for $C_{14}H_{17}BrO_3$ $[M+H]^+$ 313.0439, found 313.0434.

*4.6.2.1. 4-(2′-Bromo-4′-oxohexahydro-2′H-spiro[1,3-dioxolane-2,1′-pentalen]-6′-yl)butanal (**9b**).* Colorless oil, 1.34 g, yield: 59% (1:1 mixture of **9b** and **8b**); R_f 0.5 (hexanes/EtOAc=1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35–1.47 (m, 1H, 7-H_a), 1.55–1.63 (m, 1H, 7-H_b), 1.63–1.71 (m, 2H, 8-H), 2.06 (ddd, J=17.5, 6.9, 1.8 Hz, 1H, 2-H_a), 2.09–2.17 (m, 1H, 3-H), 2.29–2.43 (m, 2H, 6-H), 2.47 (td, J=7.1, 1.4 Hz, 2H, 9-H), 2.56 (dd, J=17.5, 8.0 Hz, 1H, 2-H_b), 2.78 (dd, J=10.7, 4.5 Hz, 1H, 3a-H), 2.91 (td, J=10.0, 4.5 Hz 1H, 6a-H), 3.93–4.10 (m, 5H, O*CH*$_2$*CH*$_2$O, 5-H), 9.77 (t, J=1.6 Hz, 1H, 10-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3 (C-8), 34.4 (C-3), 35.2 (C-6), 36.6 (C-7), 43.9 (C-9), 45.0 (C-2), 46.8 (C-6a), 49.9 (C-3a), 53.2 (C-5), 65.8, 66.0

(OCH_2CH_2O), 116.9 (C-4), 202.1 (C-10), 219.5 (C-1); FTIR (ATR) $\tilde{\nu}$ 2935 (w), 2253 (w), 1736 (m), 1714 (m), 1414 (w), 1359 (w), 1264 (m), 1165 (w), 1034 (w), 949 (w), 649 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (%) 332.1 (1), 330.1 (1) $[M]^+$, 304.2 (5), 302.2 (5), 263.1 (10), 261.1 (10), 251.1 (20) $[M-Br]^+$, 233.2 (12), 223.2 (12), 179.0 (15), 177.0 (15), 166.0 (11), 164.0 (11), 153.0 (10), 125.1 (18), 99.1 (100) $[C_5H_7O_2]$, 55.1 (16); HRMS (EI) calculated for $C_{14}H_{19}BrO_4$ $[M]^+$ 330.0467, found 330.0468.

*4.6.2.2. 2-Bromo-7-hydroxydecahydro-8H-spiro[cyclopenta[a]indene-3,2′-[1,3]dioxolan]-8-one (**8b**).* Colorless solid, 330 mg, yield: 15%; R_f 0.2 (hexanes/EtOAc=1:1); mp 240 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.17–1.28 (m, 1H, 4-H_a), 1.43–1.57 (m, 3H, 5-H_a, 6-H), 1.61–1.75 (m, 2H, 4-H_b, 5-H_b), 2.21–2.29 (m, 1H, 1-H_a), 2.30–2.38 (m, 1H, 1-H_b), 2.38–2.44 (m, 1H, 3b-H), 2.57 (dd, *J*=6.8, 5.6 Hz, 1H, 7a-H), 2.70 (dd, *J*=10.4, 4.6 Hz, 1H, 3a-H), 2.98 (td, *J*=10.4, 5.4 Hz, 1H, 8a-H), 3.95–4.10 (m, 6H, OCH_2CH_2O, 2-H, 7-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.5 (C-5), 29.2 (C-4), 32.0 (C-6), 34.0 (C-3b), 35.9 (C-1), 46.4 (C-8a), 47.7 (C-3a), 54.1 (C-2), 56.9 (C-7a), 66.0, 66.6 (OCH_2CH_2O), 66.5 (C-7), 116.9 (C-3), 218.7 (C-8); FTIR (ATR) $\tilde{\nu}$ 3447 (w), 2933 (m), 1730 (m), 1447 (w), 1264 (s), 1173 (w), 1118 (w), 1033 (m), 1014 (w), 947 (w) cm^{-1}; MS (ESI) *m/z* 355.0, 353.0 $[M+Na]^+$, 333.1, 331.1 $[M+H]^+$, 315.0, 313.0 $[M-H_2O+H]$; HRMS (ESI) calculated for $C_{14}H_{19}BrO_4$ $[M+H]^+$ 331.0545, found 331.0539.

*4.6.3. 4-(6′-Oxohexahydro-2′H-spiro[1,3-dioxolane-2,1′-pentalen]-4′-yl)butanal (**30**).* From $(COCl)_2$ (0.014 mL, 20.7 mg, 0.16 mmol) in dry CH_2Cl_2 (2 mL), DMSO (0.024 mL, 26.4 mg, 0.34 mmol) in CH_2Cl_2 (2 mL), **29** (35 mg, 0.14 mmol), and Et_3N (0.11 mL, 80.3 mg, 0.83 mmol). Colorless oil, 34 mg, yield: 96%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41–1.87 (m, 8H, 5-H, 6-H, 7-H, 8-H), 2.03–2.15 (m, 3H, 1-H, 2-H), 2.45 (td, *J*=7.2, 1.6 Hz, 2H, 9-H), 2.64 (dd, *J*=9.6, 4.5 Hz, 1H, 3a-H), 2.78–2.95 (m, 1H, 6a-H), 3.69–4.04 (m, 4H, OCH_2CH_2O), 9.74 (t, *J*=1.6 Hz, 1H, 10-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (C-8), 24.0 (C-6), 30.7 (C-7), 36.1 (C-1), 38.9 (C-5), 42.9 (C-2), 43.4 (C-6a), 44.0 (C-9), 61.8 (C-3a), 65.3, 65.4 (OCH_2CH_2O), 117.5 (C-4), 202.7 (C-10), 214.8 (C-3); FTIR (ATR) $\tilde{\nu}$ 2944 (w), 2253 (w), 1733 (m), 1460 (w), 1077 (w), 1009 (w), 649 (s) cm^{-1}; MS (EI, 70 eV) *m/z* (%) 252.3 (3) $[M]^+$, 208.2 (18), 191.2 (16), 164.2 (5), 137.2 (12), 127.1 (12), 109.1 (10), 99.1 (100) $[C_5H_7O_2]$, 86.1 (17), 67.1 (12), 55.2 (20); HRMS (ESI) calculated for $C_{14}H_{20}O_4$ $[M]^+$ 252.1362, found 252.2363.

4.7. 2′-Bromo-2′,3′,3a′,6a′-tetrahydrodispiro[1,3-dioxolane-2,1′-pentalene-4′,2″-[1,3]dioxolane (20)

NaOMe (588 mg, 10.9 mmol), which was freshly prepared by dissolving sodium (250 mg, 10.9 mmol) in methanol (15 mL) followed by removal of excess solvent, was solved in DMSO (20 mL) and slowly added to a solution of **19**[11a,b] (2.85 g, 7.42 mmol) in DMSO (10 mL), and the reaction mixture was then heated to 70 °C for 2 h. After addition of H_2O (40 mL), the reaction mixture was extracted with Et_2O (3×40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give crude **20** (1.66 g, 5.5 mmol, 75%) as a colorless oil; R_f 0.6 (hexanes/EtOAc=2:1); ^1H NMR (500 MHz, $CDCl_3$) δ 2.01–2.14 (m, 1H, 6-H_a), 2.41 (ddd, *J*=13.0, 6.6, 2.3 Hz, 1H, 6-H_b), 2.72 (td, *J*=8.8, 2.4 Hz, 1H, 6a-H), 3.19 (dt, *J*=7.8, 2.4 Hz, 1H, 3a-H), 3.87–4.22 (m, 9H, OCH_2CH_2O, 5-H), 5.59 (dd, *J*=5.7, 1.9 Hz, 1H, 2-H), 6.07 (dd, *J*=5.7, 2.6 Hz, 1H, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.6 (C-6), 45.6 (C-6a), 52.8 (C-5), 53.8 (C-3a), 64.4, 65.5, 65.6, 66.2 (OCH_2CH_2O), 114.7, 119.2 (C-1, C-4), 133.0 (C-3), 135.6 (C-2); FTIR (ATR) $\tilde{\nu}$ 2890 (w), 2253 (w), 1362 (w), 1306 (w), 1157 (m), 1087 (w), 1042 (w), 1017 (w), 948 (w), 649 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (%) 304.0 (3), 302.0 (3) $[M]^+$, 223.1 (100) $[M-Br]^+$, 179.0 (23), 177.0 (23) $[C_5H_7BrO_2]$, 151.1 (10), 138.1 (7), 99.1 (40) $[C_5H_7O_2]$, 79.1 (3), 55.1 (7). HRMS (EI) calculated for $C_{12}H_{15}BrO_4$ $[M]^+$ 302.0154, found 302.0152.

4.8. 2′-Bromo-2′,3′,3a′,6a′-tetrahydro-4′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (10b)

A solution of **20** (1.66 g, 5.50 mmol) and PPTS (400 mg, 3.18 mmol) in acetone/3% H_2O (100 mL) was heated at reflux for 3 h. Then the solvent was removed under vacuum, the residue was taken up in Et_2O (40 mL) and washed with brine. The organic layer was dried ($MgSO_4$) and evaporated to give **10b** (1.41 g, 99%) as a colorless solid; mp 118 °C; R_f 0.2 (hexanes/EtOAc=2:1); ^1H NMR (500 MHz, $CDCl_3$) δ 2.23–2.34 (m, 2H, 6-H), 2.79–2.84 (m, 1H, 6a-H), 3.30–3.33 (m, 1H, 3a-H), 3.86–3.91 (m, 1H, 5-H), 4.01–4.25 (m, 4H, OCH_2CH_2O), 6.24 (dd, *J*=5.7, 2.0 Hz, 1H, 2-H), 7.60 (dd, *J*=5.7, 3.0 Hz, 1H, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1 (C-6), 45.4 (C-6a), 50.9 (C-5), 51.8 (C-3a), 65.9, 66.6 (OCH_2CH_2O), 113.5 (C-4), 136.2 (C-2), 163.1 (C-3), 210.5 (C-1); FTIR (ATR) $\tilde{\nu}$ 2957 (w), 2849 (w), 1704 (vs), 1585 (w), 1450 (w), 1341 (w), 1302 (w), 1266 (m), 1166 (s), 1144(m), 1037 (m), 1006 (m), 1017 (w), 948 (m) cm^{-1}; MS (EI, 70 eV) *m/z* (%) 260.0 (27), 258.0 (28) $[M]^+$, 179.0 (100) $[M-Br]^+$, 177.0 (98), 165.9 (14), 163.9 (15), 151.1 (7), 135.0 (12), 107.1 (7), 99.1 (41) $[C_5H_7O_2]$, 79.1 (15), 55.1 (15); HRMS (EI) calculated for $C_{10}H_{11}BrO_3$ $[M]^+$ 257.9892, found 257.9893.

4.9. Hydroboration of 21 to alcohols 22, 23

To a solution of **21** (150 mg, 0.48 mmol) in dry THF (10 mL) at 0 °C was slowly added a 1 M solution of $BH_3\cdot THF$ in THF (1.05 mL, 1.05 mmol), and the reaction mixture was warmed to room temperature and stirred for a further 3 h. After addition of a 3 M NaOH solution (2 mL) and H_2O_2 (30%ic, 2 mL), the reaction mixture was stirred for a further 2 h at 45 °C. Then Et_2O (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a mixture of alcohols **22a**,**b**, **23** (147 mg, 92%), which were separated by flash chromatography (hexanes/EtOAc=1:2). Further reactions were performed with a mixture of **22**/**23**.

*4.9.1. (4′S)-2′-Bromo-6′-(4-hydroxybutyl)hexahydro-2′H-spiro[1,3-dioxolane-2,1′-pentalen]-4′-ol (**22a**).* Colorless solid, 32 mg, yield: 20%; mp 128 °C; R_f 0.35 (EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 1.30–1.49 (m, 4H, 2-H_a, 7-H, 9-H_a), 1.49–1.63 (m, 3H, 8-H, 9-H_b), 2.00–2.15 (m, 3H, 2-H_b, 3-H, 6-H_a), 2.44–2.52 (m, 1H, 6-H_b), 2.55 (dd, *J*=11.3, 7.3 Hz, 1H, 3a-H), 2.75–2.85 (m, 1H, 6a-H), 3.65 (t, *J*=6.5 Hz, 2H, 10-H), 3.92–4.15 (m, 5H, OCH_2CH_2O, 1-H), 4.31 (t, *J*=5.6 Hz, 1H, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8 (C-7), 31.9 (C-6), 32.9 (C-8), 36.2 (C-9), 36.3 (C-3), 44.5 (C-2), 44.6 (C-6a), 52.1 (C-3a), 56.8 (C-5), 63.5 (C-10), 65.7, 65.9 (OCH_2CH_2O), 73.3 (C-1), 116.1 (C-4); FTIR (ATR) $\tilde{\nu}$ 3351 (w), 2932 (w), 2252 (w), 1299 (w), 1165 (w), 1114 (w), 1034 (m), 949 (w), 804 (w), 648 (w) cm^{-1}; MS (EI, 70 eV) *m/z* (%) 336.1 (17), 334.1 (16) $[M]^+$, 263.0 (29), 261.0 (30) $[M-C_4H_9O]^+$, 255.1 (28) $[M-Br]^+$, 237.0 (10), 207.0 (8), 205.0 (8), 193.1 (21), 171.1 (18), 125.0 (8) $[C_7H_9O_2]$, 99.0 (100) $[C_5H_7O_2]$, 55.0 (16); HRMS (EI) calculated for $C_{14}H_{23}BrO_4$ $[M]^+$ 334.0780, found 334.0778. Elemental Anal. Calcd for $C_{14}H_{23}BrO_4$: C, 50.16; H, 6.92; Br, 23.84. Found: C, 50.04; H, 6.91; Br, 23.87.

*4.9.2. (4′R)-2′-Bromo-6′-(4-hydroxybutyl)hexahydro-2′H-spiro[1,3-dioxolane-2,1′-pentalen]-4′-ol (**22b**).* Colorless solid, 51 mg, yield: 32%; mp 130 °C; R_f 0.45 (EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 1.30–1.43 (m, 4H, 2-H_a, 7-H, 9-H_a), 1.52–1.64 (m, 3H, 8-H, 9-H_b), 1.85–1.94 (m, 1H, 3-H), 2.02–2.09 (m, 1H, 6-H_a), 2.09–2.16 (m, 1H, 2-H_b), 2.20–2.29 (m, 1H, 6-H_b), 2.35 (dd, *J*=11.0, 7.4 Hz, 1H, 3a-H), 2.47–2.54 (m, 1H, 6a-H), 3.64 (t, *J*=6.6 Hz, 2H, 10-H), 3.86–4.17 (m, 6H, OCH_2CH_2O, 1-H, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8 (C-7), 32.6 (C-8), 36.2 (C-9), 36.6 (C-6), 38.1 (C-3), 42.2 (C-2), 48.1 (C-6a), 52.2 (C-3a), 54.2 (C-5), 63.0 (C-10), 65.4, 66.2 (OCH_2CH_2O), 79.6 (C-1), 116.5 (C-4); FTIR (ATR) $\tilde{\nu}$ 3351 (w), 2932 (w), 2252 (w), 1299 (w),

1165 (w), 1114 (w), 1034 (m), 949 (w), 804 (w), 648 (w) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 336.1 (9), 334.1 (9) $[M]^+$, 255.1 (7) $[M-Br]^+$, 237.0 (8), 207.0 (5), 205.0 (5), 193.1 (8), 175.1 (9), 133.0 (8), 99.0 (100) $[C_5H_7O_2]$, 55.0 (10); HRMS (ESI) calculated for $C_{14}H_{23}BrO_4$ $[M+Na]^+$ 357.0677, found 357.0672.

*4.9.3. 2′-Bromo-6′-(4-hydroxybutyl)hexahydro-4′H-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (**23**).* Colorless oil, 64 mg, yield: 40%; R_f 0.5 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28–1.42 (m, 3H, 7-H, 8-H_a), 1.46–1.59 (m, 3H, 8-H_b, 9-H), 1.93–2.12 (m, 2H, 2-H_a, 3-H), 2.25–2.36 (m, 2H, 6-H), 2.44–2.56 (m, 1H, 2-H_b), 2.74 (dd, *J*=10.7, 3.9 Hz, 1H, 3a-H), 2.79–2.88 (m, 1H, 6a-H), 3.64 (t, *J*=6.5 Hz, 2H, 10-H), 3.91–4.10 (m, 5H, OCH_2CH_2O, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9 (C-7), 32.6 (C-9), 34.3 (C-3), 35.0 (C-6), 35.7 (C-8), 44.9 (C-2), 46.6 (C-6a), 49.5 (C-3a), 53.0 (C-5), 62.7 (C-10), 65.7, 65.9 (OCH_2CH_2O), 116.9 (C-4), 220.2 (C-1); FTIR (ATR) $\tilde{\nu}$ 3387 (w), 2932 (m), 1735 (s), 1442 (w), 1298 (w), 1264 (m), 1168 (w), 1138 (m), 1036 (m), 949 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 334.1 (6), 332.1 (6) $[M]^+$, 253.1 (25) $[M-Br]^+$, 179.0 (7), 177.0 (7), 165.9 (6), 163.9 (6), 125.1 (5) $[C_7H_9O_2]$, 99.0 (100) $[C_5H_7O_2]$, 55.0 (7); HRMS (EI) calculated for $C_{14}H_{21}BrO_4$ $[M]^+$ 332.0623, found 332.0621.

4.10. Grignard reaction of 25 and enone 10a

A Grignard solution of **25**, freshly prepared from Mg (450 mg, 18.8 mmol), covered with dry THF (10 mL), under N_2 atmosphere by addition of a mixture of benzyl 4-bromobutyl ether[17] (1.80 mL, 2.30 g, 9.40 mmol) and THF (10 mL) and heating at reflux for 30 min, was added to a solution of **10a** (170 mg, 0.94 mmol) in THF (5 mL) at 0 °C and the reaction mixture was stirred for 30 min at 0 °C. The excess Grignard reagent was hydrolyzed by addition of H_2O (15 mL) followed by addition of Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc=2:1) to give the 1,4-addition product 6′-[4-(benzyloxy)butyl]hexahydro-4′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one (65.0 mg, 20%) and an inseparable mixture of **26** and **27** (270 mg).

4.10.1. 6′-[4-(Benzyloxy)butyl]hexahydro-4′H-spiro[1,3-dioxolane-2,1′-pentalen]-4′-one. R_f 0.6 (hexanes/EtOAc=1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17–1.28 (m, 1H, 7-H_a), 1.28–1.39 (m, 2H, 8-H), 1.50–1.65 (m, 5H, 5-H, 7-H_b, 9-H), 1.70–1.77 (m, 1H, 6-H_a), 1.83–1.90 (m, 1H, 6-H_b), 1.92 (ddd, *J*=17.6, 8.2, 1.7 Hz, 1H, 2-H_a), 2.00–2.08 (m, 1H, 3-H), 2.28 (dd, *J*=9.8, 5.4 Hz, 1H, 3a-H), 2.39 (dd, *J*=17.6, 8.1 Hz, 1H, 2-H_b), 2.64–2.70 (m, 1H, 6a-H), 3.40 (t, *J*=6.5 Hz, 2H, 10-H), 3.79–3.89 (m, 4H, OCH_2CH_2O), 4.43 (s, 2H, CH_2Ph), 7.17–7.31 (m, 5H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6 (C-8), 24.7 (C-6), 29.8 (C-9), 34.5 (C-5), 35.6 (C-3), 36.7 (C-7), 45.1 (C-2), 49.3 (C-6a), 52.9 (C-3a), 64.3, 65.1 (OCH_2CH_2O), 70.3 (C-10), 73.0 (CH_2Ph), 118.8 (C-4), 127.0, 127.6, 127.7, 128.4, 128.6, 138.6 (Ph), 221.5 (C-1); FTIR (ATR) $\tilde{\nu}$ 3053 (w), 2986 (w), 2254 (w), 1732 (m), 1421 (w), 1264 (s), 1097 (m), 1022 (w) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 344.2 (22) $[M]^+$, 253.2 (28) $[M-CH_2Ph]$, 238.2 (4), 220.1 (4), 181.1 (14) $[M-C_{11}H_{15}O]^+$, 134.1 (12), 107.0 (15), 99.0 (100) $[C_5H_8O_2]$, 91.1 (53) $[CH_2Ph]$, 86.0 (29), 79.0 (13), 77.0 (6), 55.0 (12); HRMS (ESI) calculated for $C_{21}H_{28}O_4$ $[M+Na]^+$ 367.1885, found 367.1882.

*4.10.2. 4′-[4-(Benzyloxy)butyl]-3′,3a′,4′,6a′-tetrahydro-2′H-spiro[1,3-dioxolane-2,1′-pentalen]-4′-ol (**26**).* R_f 0.5 (hexanes/EtOAc=1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38–1.48 (m, 2H, 6-H_a, 8-H_a), 1.50–1.58 (m, 1H, 7-H_a), 1.58–1.64 (m, 1H, 7-H_b), 1.65–1.76 (m, 3H, 6-H_b, 9-H), 1.82 (t, *J*=7.6 Hz, 2H, 5-H), 1.90–1.98 (m, 1H, 8-H_b), 2.21 (br, 1H, OH), 2.57 (td, *J*=8.6, 4.6 Hz, 1H, 6a-H), 3.03 (dt, *J*=8.6, 1.9 Hz, 1H, 3a-H), 3.47 (t, *J*=6.6 Hz, 2H, 10-H), 3.84–3.98 (m, 4H, OCH_2CH_2O), 4.49 (s, 2H, CH_2Ph), 5.72 (dd, *J*=5.7, 2.5 Hz, 1H, 3-H), 5.75 (dd, *J*=5.7, 1.7 Hz, 1H, 2-H), 7.24–7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (C-8), 21.0 (C-6), 30.2 (C-9), 36.4 (C-5), 41.1 (C-7), 47.8 (C-6a), 57.3 (C-3a), 64.6, 64.7 (OCH_2CH_2O), 70.3 (C-10), 72.9 (CH_2Ph), 84.6 (C-1), 117.0 (C-4), 130.2 (C-3), 139.4 (C-2), 127.5, 127.6, 128.3, 138.6 (Ph); FTIR (ATR) $\tilde{\nu}$ 3426 (w), 3054 (w), 2939 (m), 2863 (m), 2361 (w), 2252 (w), 2007 (w), 1453 (m), 1362 (m), 1264 (s), 1100 (m), 1027 (w), 906 (vs), 728 (vs) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 326.2 (65) $[M-H_2O]^+$, 258.1 (7), 253.2 (18), 220.2 (4), 191.1 (12), 180.2 (7), 173.1 (12), 163.1 (7) $[M-C_{10}H_{13}O_3]^+$, 149.1 (28), 131.1 (21), 121.1 (8), 105.1 (16), 99.1 (100) $[C_5H_8O_2]$, 91.1 (98), 71.1 (17), 55.0 (18); HRMS (ESI) calculated for $C_{21}H_{28}O_4$ $[M+Na]^+$ 367.1885, found 367.1882. The spectroscopic data of **27** were in accordance with those in the literature.[18]

4.11. 4′-[4-(Benzyloxy)butyl]-2′,3′,3a′,6a′-tetrahydro-6′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-6′-one (28)

To a solution of **26**/**27** (270 mg) in CH_2Cl_2 (10 mL) was added PCC (500 mg, 2.30 mmol) and the reaction mixture stirred at room temperature for 14 h. The residue was filtered off through Celite and washed with CH_2Cl_2 (3×20 mL). The filtrate was concentrated under reduced pressure and the crude product chromatographed on SiO_2 (hexanes/EtOAc=2:1) to give **28** (148 mg, 0.43 mmol, 46% referred to **10a**) as a yellow oil; R_f 0.5 (hexanes/EtOAc=1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59–1.76 (m, 5H, 6-H_a, 7-H, 9-H), 1.77–1.88 (m, 2H, 5-H), 1.91–2.04 (m, 1H, 6-H_b), 2.22–2.38 (m, 1H, 8-H_a), 2.39–2.54 (m, 1H, 8-H_b), 2.78 (d, *J*=6.6 Hz, 1H, 3a-H), 3.26–3.36 (m, 1H, 6a-H), 3.49 (t, *J*=5.8 Hz, 2H, 10-H), 3.83–4.18 (m, 4H, OCH_2CH_2O), 4.51 (s, 2H, CH_2Ph), 5.84–5.86 (m, 1H, 2-H), 7.27–7.39 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9 (C-9), 25.3 (C-6), 29.6 (C-7), 31.1 (C-8), 35.6 (C-5), 47.7 (C-6a), 57.7 (C-3a), 64.3, 65.4 (OCH_2CH_2O), 69.7 (C-10), 73.0 (CH_2Ph), 115.0 (C-4), 129.4 (C-2), 127.62, 127.64, 128.4, 138.5 (Ph), 183.0 (C-1), 205.8 (C-3); FTIR (ATR) $\tilde{\nu}$ 3053 (w), 2253 (w), 2183 (w), 1695 (m), 1612 (w), 1422 (w), 1264 (s), 1098 (w) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 342.2 (18) $[M]^+$, 299.2 (24), 251.2 (5) $[M-CH_2Ph]^+$, 207.1 (3), 163.1 (2), 127.1 (3), 99.1 (100) $[C_5H_8O_2]$, 91.1 (44) $[CH_2Ph]^+$, 65.0 (3), 55.0 (7); HRMS (ESI) calculated for $C_{21}H_{26}O_4$ $[M+Na]^+$ 365.1729, found 365.1725.

4.12. 4′-(4-Hydroxybutyl)hexahydro-6′*H*-spiro[1,3-dioxolane-2,1′-pentalen]-6′-one (29)

To **28** (75 mg, 0.22 mmol) and Pd/C (20 mg) under a satd H_2 atmosphere (balloon technique) was added EtOAc (2 mL), and the mixture was then stirred at room temperature for 2 h under a continuous stream of H_2. The black solid was filtered off through Celite and washed with EtOAc (3×5 mL). The filtrate was concentrated under reduced pressure to give **29** (52.9 mg, 95%) as a colorless oil; ^{1}H NMR (500 MHz, C_6D_6) δ 1.12–1.22 (m, 4H, 7-H, 8-H), 1.34–1.43 (m, 2H, 9-H), 1.48–1.55 (m, 1H, 6-H_a), 1.55–1.63 (m, 1H, 6-H_b), 1.65–1.77 (m, 1H, 1-H), 1.87–1.99 (m, 2H, 5-H), 2.09 (d, *J*=11.7 Hz, 2H, 2-H), 2.44–2.52 (m, 1H, 6a-H), 2.75 (d, *J*=10.0 Hz, 1H, 3a-H), 3.44 (t, *J*=6.4 Hz, 2H, 10-H), 3.74–4.11 (m, 4H, OCH_2CH_2O); ^{13}C NMR (125 MHz, C_6D_6) δ 24.1 (C-6), 24.4 (C-8), 31.0 (C-7), 32.9 (C-9), 36.2 (C-1), 39.4 (C-5), 43.0 (C-2), 43.6 (C-6a), 61.5 (C-3a), 62.8 (C-10), 65.0, 65.1 (OCH_2CH_2O), 117.2 (C-4), 215.3 (C-3); FTIR (ATR) $\tilde{\nu}$ 3460 (w), 2932 (m), 1734 (s), 1411 (w), 1264 (s), 1218 (m), 1075 (m), 1008 (m), 948 (w), 649 (m) cm^{-1}; MS (EI, 70 eV) *m*/*z* (%) 254.1 (18) $[M]^+$, 127.1 (7), 99.0 (100) $[C_5H_7O_2]$, 86.0 (15), 67.0 (3), 55.0 (6); HRMS (EI) calculated for $C_{14}H_{22}O_4$ $[M]^+$ 254.1518, found 254.1518.

4.13. 2,3,3a,3b,4,5,6,8a-Octahydro-8*H*-spiro[cyclopenta[*a*]indene-1,2′-[1,3]dioxolan]-8-one (31)

To a solution of **30** (30 mg, 0.12 mmol) in freshly distilled THF (3 mL) at 0 °C was added KO*t*-Bu (16 mg, 0.14 mmol) and the

reaction mixture stirred for 30 min. The reaction mixture was then hydrolyzed with a satd NH_4Cl solution (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on SiO_2 (hexanes/EtOAc=3:1) to give **31** (5 mg, 0.02 mmol, 18%) as a colorless oil; R_f 0.8 (hexanes/EtOAc=1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.33 (m, 1H, 4-H_a), 1.35–1.46 (m, 1H, 3-H_a), 1.51–1.60 (m, 1H, 5-H_a), 1.71–1.79 (m, 1H, 3-H_b), 1.83–1.96 (m, 4H, 5-H_b, 4-H_b, 2-H), 2.13–2.31 (m, 2H, 6-H), 2.63–2.73 (m, 1H, 3b-H), 2.77 (d, J=9.6 Hz, 1H, 8a-H), 2.85–2.94 (m, 1H, 3a-H), 3.78–4.12 (m, 4H, OCH_2CH_2O), 6.60–6.70 (m, 1H, 7-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3 (C-5), 24.6 (C-4), 25.5 (C-6), 26.0 (C-3), 37.8 (C-3b), 39.4 (C-2), 42.9 (C-3a), 61.2 (C-8a), 65.2, 65.8 (OCH_2CH_2O), 117.5 (C-1), 132.4 (C-7), 141.3 (C-7a), 202.0 (C-8); IR (ATR) $\tilde{\nu}$ 2984 (w), 1735 (s), 1446 (m), 1372 (m), 1235 (s), 1043 (s) cm^{-1}; MS (EI, 70 eV) m/z (%) 234.2 (5) $[M]^+$, 191.1 (55), 173.1 (3), 144.1 (5), 125.1 (7), 99.1 (100) $[C_5H_7O_2]$, 91.1 (12), 79.1 (18), 65.0 (6), 55.1 (10); HRMS (EI) calculated for $C_{14}H_{18}O_3$ $[M]^+$ 234.1256, found 234.1256.

4.14. X-ray crystallographic analysis

Crystals of **8b** suitable for X-ray diffraction were obtained by slow evaporation of the solvent $CDCl_3$. Formula $C_{14}H_{19}BrO_4$, FW 331.20, crystal dimension 0.32×0.06×0.05 mm, monoclinic, space group Cc, Z=8, a=5.9552(13) Å, b=23.968(5) Å, c=19.200(4) Å, V=2737.3(10) Å^3, D_{calcd}=1.607 g cm^{-3}, R_1=0.0418, $wR2$=0.0600 (all reflections) for 4817 reflections and 345 parameters, GOF=0.873.

Crystals of **24** were obtained by slow evaporation of the solvent $CDCl_3$. Formula $C_{14}H_{17}BrO_3$, FW 313.19, crystal dimension 0.29×0.14×0.07 mm, orthorhombic, space group $P2_{(1)}2_{(1)}2_{(1)}$, Z=4, a=6.2781(6) Å, b=10.2482(9) Å, c=19.8601(19) Å, V=1277.8(2) Å^3, D_{calcd}=1.628 g cm^{-3}, R_1=0.0369, $wR2$=0.0554 (all reflections) for 2608 reflections and 163 parameters, GOF=0.955.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-926793 (**8b**) and CCDC-926792 (**24**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.UK).

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Supplementary data

Further experimental results and determination of structures and relative configurations of isomers **13** and **31** by spectroscopic methods. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.06.070.

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