Synthetic studies toward the kempane diterpenes. Approaches to the assembly of the ring system

Guanglin Bao, Chunjian Liu and D. Jean Burnell*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7. E-mail: jburnell@mun.ca; Fax: 709-737-3702; Tel: 709-737-8535

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The ring system of the kempane diterpenes has been assembled from the Diels–Alder adduct **7** by a highly chemo- and stereoselective attack of lithium ethoxyacetylide on its apparently more encumbered carbonyl (to give **11**), removal of the silyl protecting group (**12** and **13**), concomitant deoxygenation and ethoxyethyne solvolysis (**18** and **19**), reconjugation and epimerization (**21**), and then a series of reductive and protection steps before cyclization of the final seven-membered ring (**31**). An alternative approach is outlined which was thwarted by an unusual cyclization of a dimethyl ether moiety (**48**) to a tetrahydrofuran (**49**).

Introduction

The kempane diterpenes (**1**–**3** in Fig. 1) are challenging synthetic targets due to their compact structures with numerous contiguous stereogenic centres.[1]

Previous synthetic approaches, to **1** by Dauben[2] and to **2** (unsuccessfully) by Paquette,[3] began with the construction of the decalin ring system, and upon this were built successively the five- and the seven-membered rings. Our approach has been different. We sought a route to the kempane system that could be modified to produce any of the kempanes. We envisaged the use of a diene that incorporates the five-membered ring, and to this would be added a quinone to establish the decalin system. In detail, the enone-lactone **4** was converted into the diene **5**, which bore oxygen functions at synthetically useful positions, and the Diels–Alder addition of **5** to 2,6-dimethyl-*p*-benzoquinone (**6**) provided the tetracyclic adduct **7** selectively.[4] Monoreduction of a 10-methyl analogue of **7** took place with very good selectivity to give only **8** (Scheme 1). Although the reduction took place on the apparently more congested ketone, this result was predicted after an evaluation of the steric interactions during axial addition.[5] Using a model compound, some success was also achieved with addition of a carbon at C-2a.[4] Herein is described the assembly of the ring system of the kempanes. Some aspects of this work have been communicated.[6]

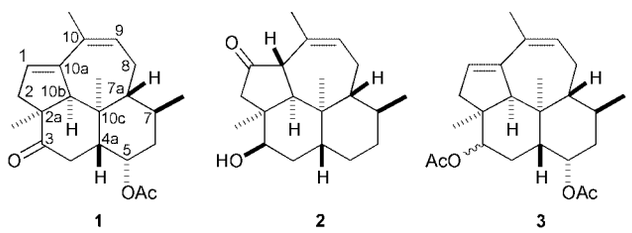
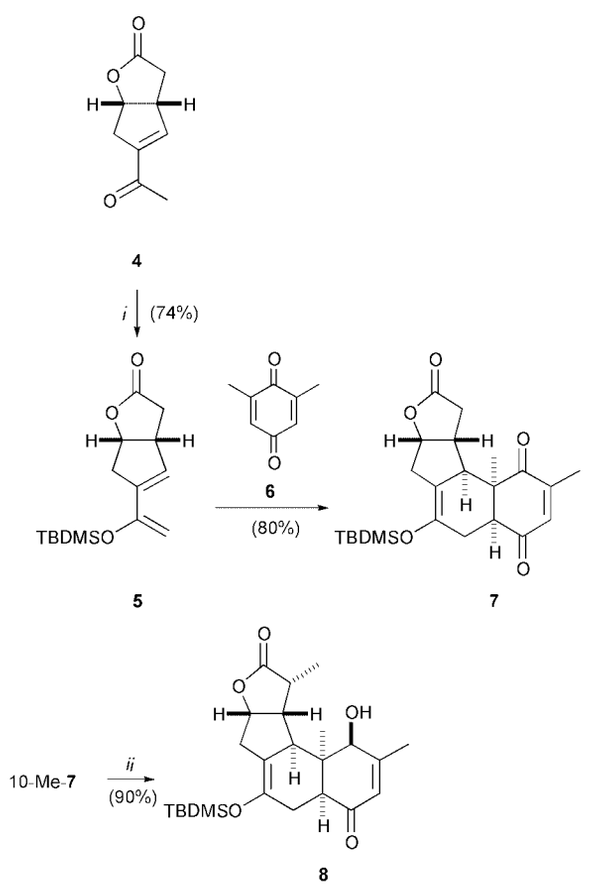


Fig. 1 Kempane diterpenes.

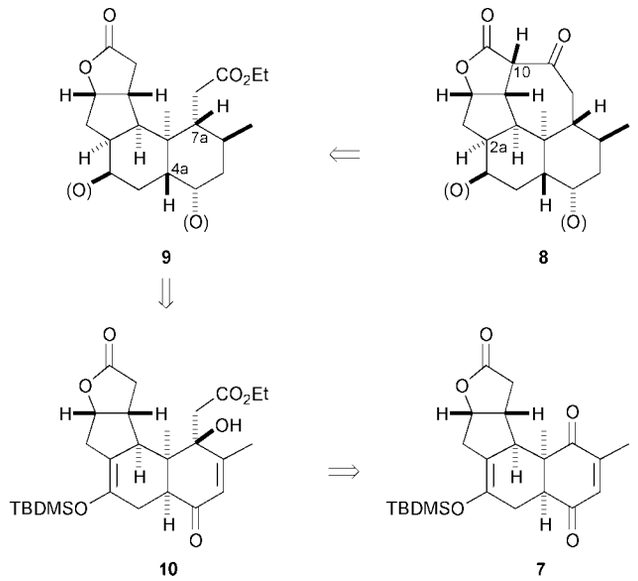
Results and discussion

Our initial approach had demonstrated the viability of the Diels–Alder reaction to establish key stereochemistry in potential precursors to the kempane diterpenes. The work also revealed potential difficulties with the development of stereochemistry about the decalin system. These were: alkylation of **7** at C-2a, the cyclization of a chain onto C-7a to form the seven-membered ring, and the establishment of the correct stereochemistry at C-7 and C-4a by equilibration. This led to the modified approach to the kempane ring system that is outlined as a retrosynthetic sequence in Scheme 2.

In terms of the carbon framework of the kempanes, the target compound **8** requires only the methyl C-2a, if the lactone carbonyl can be reduced to provide the methyl group at C-10. In contrast with the earlier route,[4] cyclization of the seven-membered ring was to take place with **9** by a Dieckmann process. A number of stereoselective reductions were to be used to link **10** to **9**. Although cyclization onto C-7a was problematic, the chemoselective addition of a two-carbon synthon onto



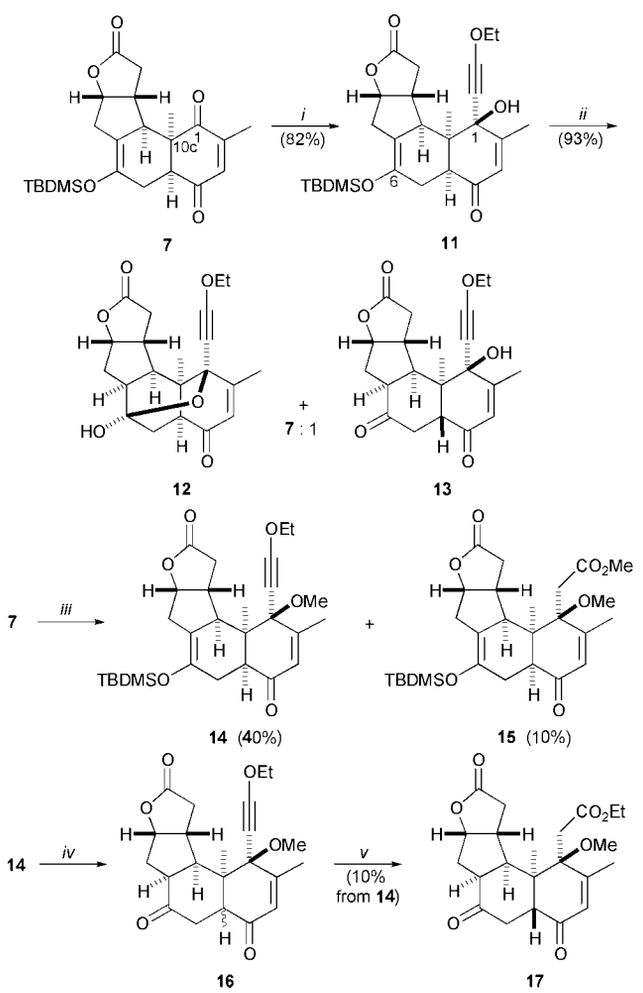
Scheme 1 Access to a kempane precursor *via* a Diels–Alder addition and selective reduction of an enedione adduct. *Reagents and conditions*: *i*, TBDMSOTf, Et_3N; *ii*, $LiAl(OBu^t)_3H$.



Scheme 2 Retrosynthetic analysis. (Compound numbering in this Scheme follows that of the kempanes.)

the Diels–Alder adduct **7** was predicted based on the result of the reduction that had produced **8** exclusively[4,6] and other alkylations with cyclohexenediones.[7–9]

As shown in Scheme 3, when lithium ethoxyacetylide was added to **7**, a single product **11** was obtained in good yield. Although the change in the chemical shift of the olefinic



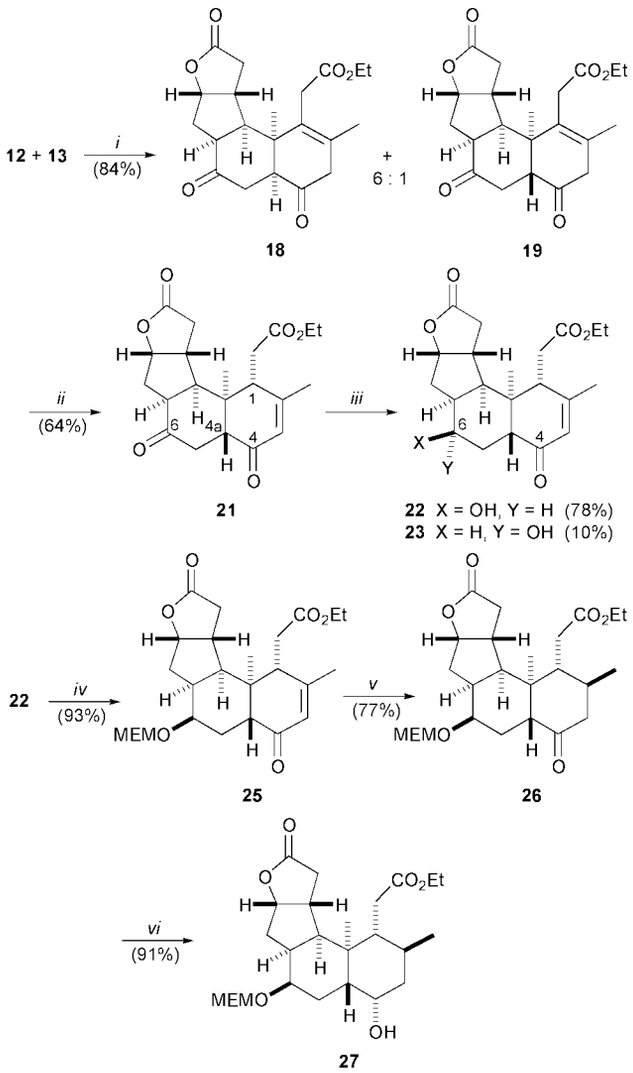
Scheme 3 Acetylide additions. *Reagents and conditions*: *i*, EtOC≡CLi, THF, −78 °C; *ii*, KF, MeOH; *iii*, EtOC≡CLi, THF, −78 °C, then CH_3I, HMPA; *iv*, Bu_4NF; *v*, H_2SO_4, THF, RT, 3 days. (Compound numbering in this and subsequent schemes is that of the IUPAC name.)

hydrogen made it obvious that addition had taken place at C-7a, the stereochemistry at the carbinol centre was not obvious from the NMR spectra. This was revealed in an unexpected manner in the subsequent step. It was the intention simply to release the silyl enol ether to leave the ketone at C-6. This was accomplished with tetrabutylammonium fluoride (TBAF), but the yield was much higher when potassium fluoride in methanol was employed. Two products were obtained, regardless of the procedure. The major product showed only one carbonyl resonance in its ^{13}C NMR spectrum, and this compound proved to be the hemi-acetal **12**. The formation of this pentacyclic compound would only be possible if the acetylide had added to the face of **7** *syn* to its 10c-methyl. The minor product **13** could not cyclize in the same way since NOE measurements showed that its decalin ring-junction had equilibrated from *cis* to *trans*.

An effort was made to trap the alkoxide that must have been the immediate product of the acetylide addition in order to avoid the production of two products. Introduction of iodomethane in HMPA prior to aqueous work-up gave the ether **14**, but, although this was the most abundant product, the 40% yield of **14** was disappointing. An unexpected by-product of this reaction was **15**. Although this was obtained in only 10% yield, it was curious that none of the corresponding ethyl ester was detected. Therefore, this could not have been simply the result of solvolysis during work-up. It seems likely that the loss of the ethyl group was provoked by iodide in the medium because the addition of solid sodium iodide to the reaction medium increased the yield of **15** to 18%, and the yield of **14** was decreased to 27%. This observation is consistent with removal of the ethyl group by iodide to generate an ynolate. This could eliminate methoxide (producing an intermediate with cumulated double bonds). The same ynolate might be reprotonated by the medium to give an intermediate ketene. Shindo has observed a similar phenomenon.[10] The ketene would react with the methoxide to give an enolate that would become only the methyl ester during aqueous work-up. Treatment of **14** with TBAF gave the diketone **16**, which was immediately introduced into a strongly acidic medium in an attempt to solvolyse the ethoxyethynyl group.[11] The desired diketo-ester **17** was isolated in a yield of only 10%. At this point, it became clear that trapping the alkoxide as an ether was not a synthetically viable option.

Deoxygenation at the carbinol centre could be carried out in good yield with the mixture of enones **12** and **13** using zinc in acetic acid,[12] and, in addition, concomitant solvolysis of the ethoxyethynyl group was achieved to give the epimeric mixture of the β,γ-unsaturated ketones **18** and **19** in a single operation. However, reconjugation of the double bond in **18** and **19** and complete epimerisation at C-4a did not proceed well in acetic acid. Indeed, heating a mixture of **18** and **19** in acetic acid gave a complex mixture in which the most abundant component (20%) was the reconjugated, but oxidized, compound **20**. Facile oxidation of similar molecules had been observed previously.[4] Nevertheless, treatment of the mixture of **18** and **19** with methanolic HCl gave the desired, epimerized enone **21** in 64% yield (Scheme 4). It should be noted that the substituent at C-1 in **21** was found in the predicted, equatorial position.

Reduction of the carbonyl of **21** at C-6 to give **22**, with the axial-hydroxy required for kempane **2**, could be carried out with high chemoselectivity with $LiAl(OBu^t)_3H$. $NaBH_4$ in CH_2Cl_2[13] was also extremely chemoselective, but this gave a larger proportion of the epimeric by-product **23**. Dissolving-metal reduction of **22** rapidly led to the production of a mixture of over-reduced compounds. Major components of this mixture appeared to be the epimeric hemi-acetals **24** (in a ratio of 4 : 1). This was based on signals in the complex ^1H NMR spectrum at δ (CD_3OD) 5.50 (d, *J* 4.6 Hz) and 5.36 (dd, *J* 7.9 and 3.3 Hz), and in the ^{13}C NMR spectrum there were signals at δ (CD_3OD) 102.9 and 102.5 for lactol carbons instead of the signal for



Scheme 4 Deoxygenation and reduction sequence to **27**. *Reagents and conditions*: *i*, Zn dust, AcOH, Δ; *ii*, 6 M HCl, MeOH; *iii*, $LiAl(OBu^t)_3$; *iv*, MEMCl, $EtNPr^i_2$; *v*, Li, NH_3, then PCC; *vi*, L-Selectride, THF.

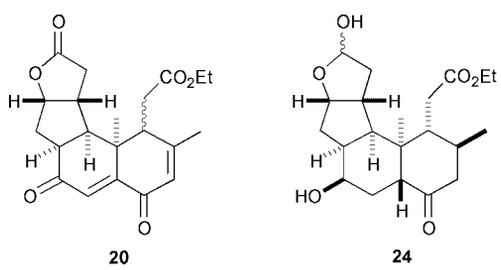
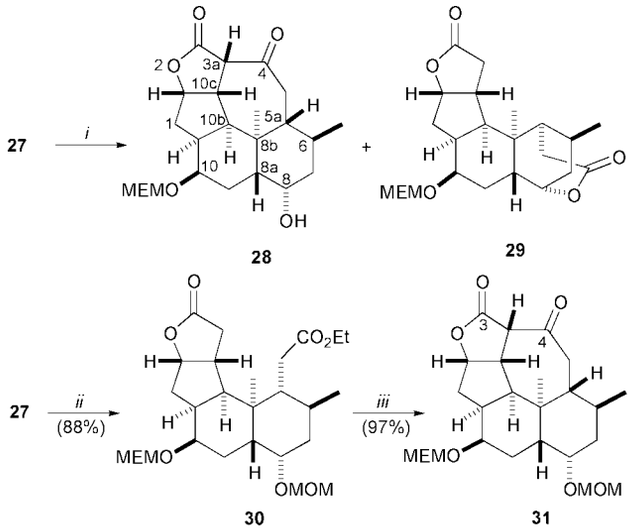


Fig. 2 Side-products.

the carbonyl of the lactone. It was not feasible to oxidize these epimers back to the lactone without re-oxidizing the C-6 alcohol. Therefore, the alcohol function of **22** was protected first as the MEM-ether[14] **25**, and then dissolving-metal reduction led to **26** in a reasonable yield. Next, reduction from the equatorial direction[2,15] of the ketone at C-4 with L-Selectride was effected to give compound **27**, which has the correct relative stereochemistry at all eight stereogenic centres on the decalin system.

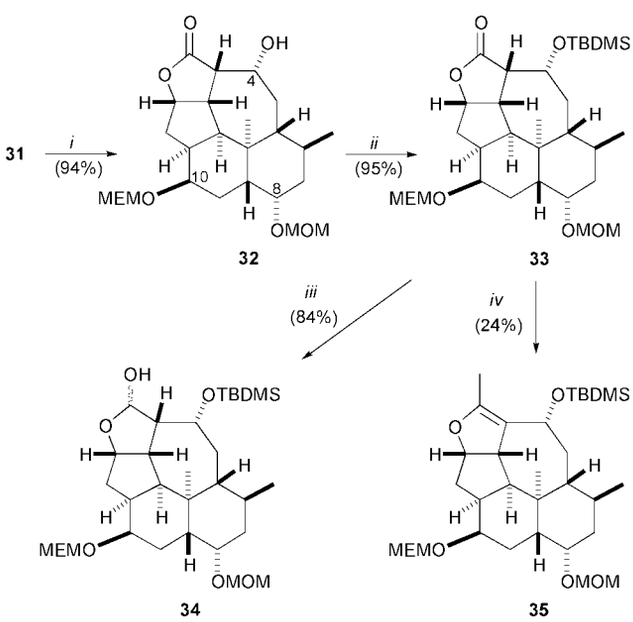
Dieckmann closure (Scheme 5) of the seven-membered ring by addition of potassium *tert*-butoxide[16] to **27** in boiling benzene provided the pentacyclic compound **28** in 61% yield. Lactone **29** was a sparingly soluble by-product, and, even with extended reaction times, some of the starting material **27** was always recovered. However, after the hydroxy at C-4 of **27** was blocked as the MOM-ether **30**, Dieckmann cyclization with



Scheme 5 Cyclization to the kempane ring system. *Reagents and conditions*: *i*, $KOBu^t$, benzene, reflux; *ii*, MOMCl, $EtNPr^i$, reflux; *iii*, NaH, benzene, reflux.

sodium hydride in benzene took place to give **31** in excellent yield.

Both **28** and **31** possess the complete ring-system of the kempanes, with all the stereochemistry for the kempanes **1**–**3**. What was still to be accomplished were the addition of a methyl group at C-10a and the reduction of the lactone carbonyl to provide the methyl at C-3a. The former was to be added by 1,4-addition directed by a carbonyl at C-1 (kempane numbering) at the very end of the synthesis. Considerable effort was made to accomplish the latter (Scheme 6). Firstly, the C-4 ketone of **31**

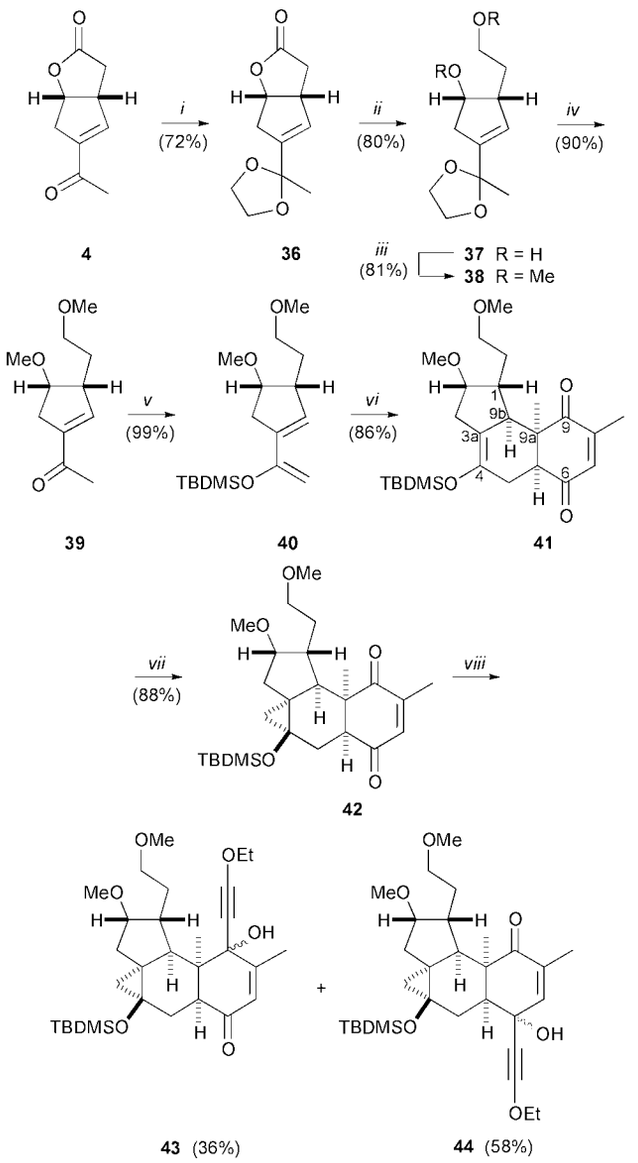


Scheme 6 Manipulation of the pentacyclic lactone. *Reagents and conditions*: *i*, $NaBH_4$, CH_3OH; *ii*, TBDMSOTf, 2,4-lutidine; *iii*, DIBAL, THF, RT; *iv*, MeLi.

was reduced stereoselectively to give **32**, and this alcohol was stabilized by transformation into the silyl ether **33**. Reduction of the lactone under a multitude of conditions never proceeded beyond the epimeric mixture of lactols **34**. The best yield of **34** was with DIBAL. Attempts to reduce **34** further using very vigorous conditions, or to trap intermediate, ring-opened aldehyde forms led either to complete destruction of the substrate or to quantitative recovery of **34**. Alternative approaches that were explored were to methylate at C-3a and then to decarbonylate the lactone carbonyl, and to remove

the lactone carbon completely by ozonolysis of a double bond. Alkylation was possible, but decarbonylation was not. Attempts to dehydrate the lactol **34** to give an oxidatively cleavable dihydrofuran, including *via* the formation of the mesylate, once again returned the lactol (or its mesylate) or led to destruction of the substrate. The reaction of **33** with methyllithium did give dehydrated derivative **35**, but the yield of **35** was very poor. It became clear that the rigidly held lactone was not amenable to the processes that had been envisaged for the reduction to, or the introduction of, the C-3a methyl group.

The problem with the lactone/lactol might be avoided by simply reducing the lactone very much earlier in the reaction sequence. This idea was explored in the sequence that begins in Scheme 7.

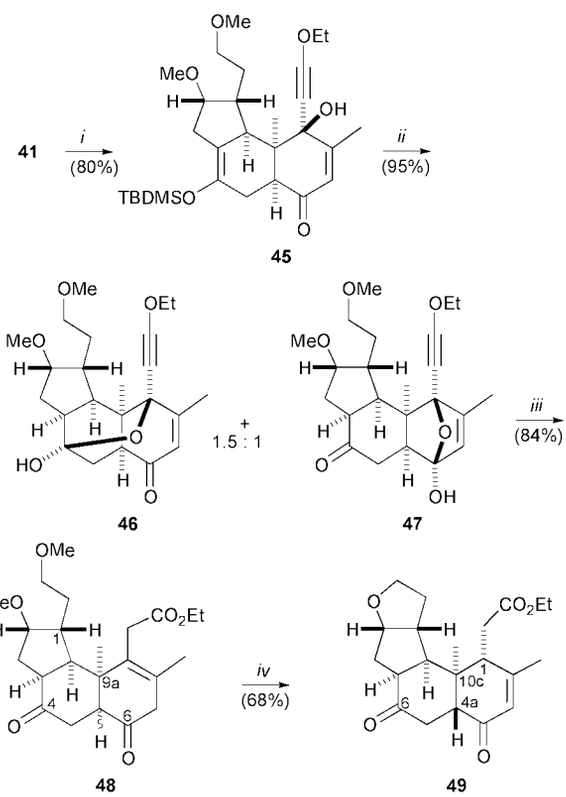


Scheme 7 Alternative strategy and cyclopropanation of the silyl enol ether. *Reagents and conditions*: *i*, $(CH_2OH)_2$, $(CO_2H)_2$, benzene, reflux; *ii*, $LiAlH_4$, Et_2O; *iii*, NaH, CH_3I; *iv*, acetone–H_2O, PPTS; *v*, TBDMSOTf, Et_3N; *vi*, **6**, toluene, reflux, 3 days; *vii*, CH_2I_2, Et_2Zn; *viii*, EtOC≡CLi, THF, −78 °C.

The ketone function of **4** was first protected as the acetal **36** before reduction with $LiAlH_4$ to give the diol **37**. By protection of these as methyl ethers **38**, it was hoped that these oxygens would be unreactive until the very last stages of the synthesis. Hydrolysis of the acetal to enone **39**, formation of the silyloxydiene **40**, and then Diels–Alder addition of the quinone **6**[4] with complete regio- and stereochemical control provided the tricyclic adduct **41** in excellent yield.

Model studies[4] had suggested that the methyl group at C-2a (kempane numbering) might be added indirectly *via* cyclopropanation of the electron-rich double bond of the Diels–Alder adduct. This process had failed with a methyl-analogue of adduct **7**, but treatment of adduct **41** with large excesses of diiodomethane and diethylzinc gave **42**. Cyclopropanation had taken place exclusively *syn* to the methyl at C-9a. However, in contrast with the reaction of **7**, addition of ethoxyacetylide was not regioselective. The alkyne with the desired gross structure **43** was the minor product; **44** was the major product. †

Addition of ethoxyacetylide to the Diels–Alder adduct **41** proceeded as expected. Compound **45** was the only product, so, once again, the strategy returned to addition of the C-2a methyl group at the end of the synthesis. Following the process that had given the pentacyclic lactones, desilylation of **45** was carried out with potassium fluoride. The major product was the analogous hemi-acetal **46**, but the minor product was a second hemi-acetal **47** (Scheme 8). The mixture of hemi-acetals was



Scheme 8 Diether approach to kempanes. *Reagents and conditions*: EtOC≡CLi, THF, −78 °C; *ii*, KF, MeOH; *iii*, Zn dust, AcOH, reflux; *iv*, *p*-TsOH, toluene, reflux.

treated with zinc in hot acetic acid. As before, deoxygenation at C-1 with concomitant solvolysis of the ethoxyethyne unit gave the β,γ-unsaturated ketone, as a 1 : 1 mixture of epimers at C-5a **48**. What appeared to be a trivial and analogous process to **18** and **19** ⟶ **21** was not. Reconjugation and complete epimerization would not take place with methanolic HCl, nor with H_2SO_4, nor a variety of other acidic media. In most instances, the 1 : 1 epimeric mixture **48** was returned unchanged. It seemed clear that the reconjugated and epimerized isomer of **48** could not be energetically preferred, whereas in the lactone series it was. It is remarkable that a structural difference so distant from the location of the double bond could be so important to the relative stability of the α,β-unsaturated ketone *versus* the β,γ-unsaturated ketone. The structural feature in **21** that leads to its stability relative to **18** or **19** is the oxygen-containing ring,

† Both **43** and **44** were obtained as single diastereomers, but the relative stereochemistry at the carbinol centre was not determined with either molecule.

not the presence of the lactone carbonyl. This became apparent from the following unexpected result. Heating a toluene solution of **48** and toluene-*p*-sulfonic acid slowly produced a reconjugated and epimerized product. However, the product was not the dimethoxy compound, but the tetrahydrofuran **49**. The implications of this result are that until the cyclic ether is produced, the thermodynamic preference remains with the β,γ-unsaturated ketone, and that until the double bond is reconjugated there is no thermodynamic bias in favour of the *trans*-ring junction for the decalin system.

In conclusion, this synthetic approach had provided the ring system of the kempanes efficiently. The overall yield of **31** over the ten steps from the Diels–Alder adduct **7** was 17%. Furthermore, the stereochemical control in the assembly of **31** was very good. The very considerable stability of the oxygen-containing ring of **31** resisted all attempts to generate the C-10 methyl of the kempanes. Even when the lactone was reduced at a very early stage in the synthesis, the tetrahydrofuran ring (of **49**) was formed from normally unreactive methyl ethers under prolonged treatment with acid. This indicates that the oxygen-containing ring contributes very significantly to the stabilization of these compounds even before the seven-membered ring has cyclized. Further approaches should avoid at all costs any opportunity to cyclize this "extra" ring. Such a route is currently under investigation in our laboratories.

Experimental ‡

(1α,4aβ,7aα,10aα,10bβ,10cβ)-6-[(1,1-Dimethylethyl)dimethylsilyloxy]-1-(ethoxyethynyl)-4a,5,7,7a,10,10a,10b,10c-octahydro-1-hydroxy-2,10c-dimethyl-1*H*-benz[6,7]indeno[2,1-*b*]furan-4,9-dione 11

n-Butyllithium (0.58 ml of a 2.5 M solution in hexane, 1.4 mmol) was added over 5 min to a solution of ethoxyethyne (0.38 ml of a 50% w/w solution in hexane, 1.9 mmol) in dry THF (35 ml) under −78 °C. The mixture was stirred for 30 min before it was transferred by cannula over 30 min to a solution of **7** (506 mg, 1.21 mmol) in dry THF (35 ml) at −78 °C. This mixture was stirred for 2 h before it was warmed to 0 °C then quenched with H_2O (20 ml). Diethyl ether (200 ml) was added, and the solution was washed with water (3 × 40 ml) and brine (50 ml), dried and concentrated under vacuum. Chromatography of the residue afforded **11** (481 mg, 82%) as a very pale yellow solid: mp 156.5–158 °C; $\nu_{max}(CCl_4)/cm^{-1}$ 3418 (broad), 2258, 1770 and 1672; δ_H (CD_2Cl_2, −85 °C since signals were broad at RT, *major conformer*) 5.70 (1 H, s, 3-H), 4.69 (1 H, m, 7a-H), 4.06 (2 H, q, *J* 7.3, OCH_2CH_3), 3.49 (1 H, broad d, *J* 18.6), 2.96–2.81 (2 H, m), 2.62 (1 H, broad d, *J* 16.6), 2.48–2.28 (2 H, m), 2.15–1.92 (3 H, m), 2.00 (3 H, s, 2-methyl), 1.34 (3 H, s, 10c-methyl), 1.26 (3 H, t, *J* 7.3, OCH_2CH_3), 0.86 (9 H, s, $SiC(CH_3)_3$), 0.050 (3 H, s, $SiCH_3$) and 0.043 (3H, s, $SiCH_3$); δ_C (CD_2Cl_2, −85 °C, *major conformer*) 197.9 (C-4), 180.4 (C-9), 163.0 (C-2), 140.4 (C-6), 125.0, 117.5, 94.0, 83.9, 75.0, 73.6, 49.5, 47.6, 46.3, 42.3, 41.1, 37.2, 32.7, 30.9, 25.0 ($SiC(CH_3)_3$), 19.1, 17.6, 14.1, −4.8 ($SiCH_3$) and −5.0 ($SiCH_3$); *m*/*z* 486.2412 (M^+, <1%, $C_{27}H_{38}O_6Si$ requires 486.2438), 359 (14), 224 (21), 223 (33), 195 (12), 181 (19), 117 (18), 103 (13), 75 (97) and 73 (100).

(1*R,2*S**,3*S**,4*S**,8*R**,10*R**,11*S**,13*R**)-1-(Ethoxyethynyl)-11-hydroxy-2,16-dimethyl-7,17-dioxapentacyclo[9.5.1.$0^{2,13}$.$0^{3,10}$.$0^{4,8}$]heptadec-15-ene-6,14-dione 12 and (1α,4aα,6aβ,7aα,10aα,10bβ, 10cβ)-1-(ethoxyethynyl)-4a,6a, 7,7a,10,10a,10b,10c-octahydro-1-hydroxy-2,10c-dimethyl-1*H*-benz[6,7]indeno-[2,1-*b*]furan-4,6,9(5*H*)-trione 13**

A solution of **11** (1.31 g, 2.67 mmol) in methanol (50 ml) was combined with a solution of $KF{\cdot}2H_2O$ (1.26 g, 13.4 mmol) in methanol (40 ml), and this was stirred at RT for 7 h. About 70% of the solvent was removed under vacuum. Water (60 ml) was added, and the aqueous layer was extracted with ethyl acetate (4 × 40 ml). The combined organic solutions were washed with water (40 ml) and brine (2 × 40 ml), dried and concentrated under vacuum. Chromatography of the residue afforded 0.924 g (93%) of a mixture of **12** and **13** in a 7 : 1 ratio. Homogeneous samples of each were obtained by repeated chromatography.

For **12**: white foam, ν_{max}(Nujol)/cm^{-1} 3404 (broad), 2260, 1772 and 1674; δ_H 5.77 (1 H, d, *J* 1.3, 15-H), 5.04 (1 H, apparent t, *J* 4.5, 8-H), 4.19 (2 H, q, *J* 7.1, OCH_2CH_3), 3.93 (1 H, dd, *J* 5.8 and 2.5, 4-H), 2.96 (1 H, s, OH), 2.89 (1 H, dd, *J* 17.6 and 8.2, 5-H *syn* to 4-H), 2.68 (1 H, m, 10-H), 2.51 (1 H, m, 9-H *syn* to 8-H), 2.41–2.33 (2 H, m, 13-H and 5-H *anti* to 4-H), 2.18 (1 H, dd, *J* 13.9 and 1.8, 12-H), 2.13 (3 H, d, *J* 1.3, 16-methyl), 1.95 (1 H, dd, *J* 11.9 and 5.8, 3-H), 1.67 (1 H, dd, *J* 13.9 and 4.2, 12-H), 1.42 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.08 (3 H, s, 2-methyl); NOE data 5.04 (3.93, 6%; 2.51, 4%), 3.93 (5.04, 7%; 2.89, 3%), 2.68 (1.95, 5%) and 1.08 (3.93, 7%, 2.41–2.33, 4%; 1.95, 3%); δ_C 199.8 (C-14), 176.7 (C-6), 158.8 (C-16), 121.6 (C-15), 98.2 (0), 97.1 (2 C, 0), 87.7 (C-8), 75.0 (OCH_2CH_3), 56.9 (C-3), 51.9 (C-13), 45.7 (C-10), 41.8 (C-4), 38.6 (C-5), 37.9 (0), 37.2 (0), 34.8 (C-12), 32.6 (C-9), 20.7 (16-methyl), 18.9 (2-methyl) and 14.7 (OCH_2CH_3); *m*/*z* 343.1182 (M^+ − 29, 13%, $C_{19}H_{19}O_6$ requires 343.1182), 302 (16), 203 (18), 178 (19), 175 (42), 161 (27), 151 (34), 150 (39), 148 (23), 147 (24), 138 (34), 137 (72), 135 (20), 122 (20), 121 (19), 119 (18), 117 (19), 110 (44), 91 (71), 79 (64), 77 (72), 69 (64), 68 (46), 55 (95) and 41 (100).

For **13**: white solid, mp 180 °C (dec.); ν_{max}(Nujol)/cm^{-1} 3381, 2266, 1759, 1702 and 1660; δ_H (CD_2Cl_2) 5.83 (1 H, d, *J* 1.4, 3-H), 4.89 (1 H, dd, *J* 14.3 and 8.6, 7a-H), 4.20 (2 H, q, *J* 7.1, OCH_2CH_3), 3.34 (1 H, dd, *J* 13.0 and 4.8, 4a-H), 3.15–3.05 (2 H, m, 6a-H and 10α-H), 2.94 (1 H, dd, *J* 13.5 and 8.0, 7α-H), 2.92–2.77 (2 H, m, 10a-H and 10β-H), 2.71 (1 H, dd, *J* 14.9 and 5.1, 5α-H), 2.63 (1 H, dd, *J* 10.1 and 6.2, 10b-H), 2.42 (1 H, dd, *J* 14.9 and 3.1, 5β-H), 2.15 (3 H, d, *J* 1.4, 2-methyl), 1.47 (1 H, m, 7β-H), 1.42 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.37 (3 H, s, 10c-methyl); NOE data 4.89 (2.94, 4%), 3.34 (2.92–2.77, 15%; 2.71, 5%) and 1.37 (2.63, 8%; 2.42, 5%); δ_C (CD_2Cl_2) 210.0 (C-6), 198.0 (C-4), 178.3 (C-9), 159.2 (C-2), 124.7 (C-3), 98.4 (0), 84.6 (C-7a), 76.1 (OCH_2CH_3), 75.0 (0), 58.2 (C-10b), 52.4 (C-6a), 46.8 (C-10c), 45.0 (C-4a), 39.6 (C-10a), 37.5 (C-5), 37.4 (C-10), 31.6 (C-7), 22.1 (10c-methyl), 21.3 (2-methyl) and 15.0 (OCH_2CH_3); *m*/*z* 344 (M^+ − 28), 203 (14), 175 (22), 166 (32), 137 (100), 110 (35), 91 (24), 79 (21) and 77 (21). Found: C, 67.6; H, 6.9. $C_{21}H_{24}O_6$ requires C, 67.7; H, 6.5%.

(1α,4aβ,7aα,10aα,10bβ,10cβ)-6-[(1,1-Dimethylethyl)dimethylsilyloxy])-1-(ethoxyethynyl)-4a,5,7,7a,10,10a,10b,10c-octahydro-1-methoxy-2,10c-dimethyl-1*H*-benz[6,7]indeno-[2,1-*b*]furan-4,9-dione 14 and (1α,4aβ,7aα,10aα,10bβ,10cβ)-6-[(1,1-dimethylethyl)dimethylsilyloxy]-4a,5,7,7a,10,10a,10b,10c-octahydro-1-methoxy-2,10c-dimethyl-4,9-dioxo-1*H*-benz[6,7]-indeno[2,1-*b*]furan-1-acetic acid methyl ester 15

n-Butyllithium (0.30 ml of a 2.5 M solution in hexane, 0.75 mmol) was added to a solution of ethoxyethyne (0.20 ml of a 50% w/w solution in hexane, 1.02 mmol) in dry THF (18 ml) at −78 °C. This solution was stirred for 30 min before it was transferred (using a double-tipped needle) over 20 min into a solution of **7** (258 mg, 0.619 mmol) in dry THF (18 ml) at −78 °C. This solution was stirred for 2 h before a solution of iodomethane (0.19 ml, 3.05 mmol) in HMPA (7.0 ml) was added. This mixture was warmed to RT and stirred for 12 h. Water (60 ml) was added and this was extracted with ethyl acetate (4 × 25 ml). The combined extracts were washed with

‡ For general information regarding the equipment, the spectra, and chromatography see the preceding paper.[4]

brine (3 × 40 ml), dried and concentrated under vacuum. Chromatography of the residue gave **14** (130 mg, 40%) and **15** (30 mg, 10%).

For **14**: foam, $\nu_{max}(CCl_4)/cm^{-1}$ 2257, 1772 and 1672; δ_H (CD_2Cl_2, −80 °C since signals were broad at RT) 5.60 (1 H, s, 3-H), 4.59 (1 H, m, 7a-H), 4.12 (2 H, q, *J* 7.2, OCH_2CH_3), 3.54 (3 H, s, OCH_3), 3.25 (1 H, m), 2.13–1.86 (3 H, m), 1.98 (3 H, s, 2-methyl), 1.31 (3 H, t, *J* 7.2, OCH_2CH_3), 1.23 (3 H, s, 10c-methyl), 0.86 (9 H, s, $SiC(CH_3)_3$), 0.04 (3 H, s, $SiCH_3$) and 0.03 (3 H, s, $SiCH_3$); δ_C (CD_2Cl_2, −80 °C) 197.6, 178.7, 163.2, 140.2, 125.0, 117.6, 97.4, 82.8, 80.6, 75.2, 56.7, 49.7, 48.3, 47.7, 42.2, 32.94, 32.89, 31.2, 25.3, 25.1, 24.9, 18.8, 17.7, 14.3, −4.8 and −4.9; *m*/*z* 472.2297 ($M^+ - C_2H_4$, 4%, $C_{28}H_{40}O_6$ requires 472.2281), 415 (10), 224 (21), 223 (31), 181 (16), 151 (13), 117 (18), 103 (12), 75 (79) and 73 (100).

For **15**: pale yellow solid, mp 145–147 °C; ν_{max}(Nujol)/cm^{-1} 1777, 1727 and 1660; δ_H 5.88 (1 H, d, *J* 1,2, 3-H), 4.62 (1 H, m, 7a-H), 3.70 (3 H, s, CO_2CH_3), 3.65 (1 H, s, OCH_3), 3.09–2.86 (2 H, m, 7α-H and 10α-H), 3.08 (1 H, d, *J* 13.3, $CH_2CO_2CH_3$), 3.02 (1 H, d, *J* 13.3, $CH_2CO_2CH_3$), 2.83 (1 H, d, *J* 17.6, 5-H), 2.61–2.53 (3 H, m, 4a-H, 10β-H and 10a-H), 2.20–2.10 (2 H, m, 5-H and 10b-H), 2.00 (3 H, d, *J* 1.2, 2-methyl), 1.94 (1 H, m, 7β-H), 1.38 (3 H, s, 10c-methyl), 0.95 (9 H, s, $SiC(CH_3)_3$), 0.18 (3 H, s, $SiCH_3$) and 0.13 (3 H, s, $SiCH_3$); NOE data 4.62 (3.09–2.86, 3%; 2.61–2.53, 5%), 2.20–2.10 (2.61–2.53, 10%) and 1.38 (3.70, 2%; 2.61–2.53, 13%; 2.20–2.10, 18%); δ_C 196.0 (C-4), 178.2 (C-9), 170.7 (CO_2CH_3), 162.6 (C-2), 141.4 (C-6), 128.3 (C-3), 115.6 (C-6a), 82.5 (C-7a), 82.3 (C-1), 54.6 (CO_2CH_3), 52.6 (C-10b), 52.3 (OCH_3), 49.1 (C-10a), 48.8 (C-10c), 42.0 (C-4a), 37.0 ($CH_2CO_2CH_3$), 35.4 (C-10), 32.2 (C-7), 25.7 ($SiC(CH_3)_3$), 25.6 (C-5), 24.9 (10c-methyl), 20.4 (2-methyl), 18.1 ($SiC(CH_3)_3$), −3.8 ($SiCH_3$) and −4.3 ($SiCH_3$); *m*/*z* 504.2536 (M^+, 3%, $C_{27}H_{40}O_7Si$ requires 504.2543), 447 (10), 281 (8), 224 (26), 224 (39), 181 (19), 117 (26), 103 (13), 75 (80), 73 (100) and 59 (15).

(1α,4aα,6aβ,7aα,10aα,10bβ,10cβ)-4,4a,5,6,6a,7,7a,9,10,10a,-10b,10c-Dodecahydro-1-methoxy-2,10c-dimethyl-4,6,9-trioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-acetic acid ethyl ester 17

To a solution of **14** (155 mg, 0.130 mmol) in THF (8.0 ml) at 0 °C was added tetrabutylammonium fluoride (0.50 ml of a 1.0 M solution in THF, 0.50 mmol). The mixture was stirred at 0 °C for 10 min before ethyl acetate (60 ml) was added. This solution was washed with water (2 × 30 ml) and brine (30 ml), dried and concentrated under vacuum to give crude triketone **16**, which was redissolved in THF (10 ml) and 5% aqueous H_2SO_4 (4 ml) was added. This solution was stirred for 3 days at RT. Ethyl acetate (60 ml) was added and the solution was washed with water (3 × 20 ml), dried and concentrated under vacuum. Chromatography provided **17** (13 mg, 10% yield from **14**) as a pale yellow solid: mp 181–183 °C; ν_{max}(Nujol)/cm^{-1} 1758, 1738, 1709 and 1662; δ_H 6.18 (1 H, d, *J* 1.6, 3-H), 4.88 (1 H, m, 7a-H), 4.19 (2 H, m, OCH_2CH_3), 3.37 (1 H, dd, *J* 12.4 and 5.1, 4a-H), 3.32 (3 H, s, OCH_3), 3.12 (1 H, d, *J* 15.7, CH_2CO_2Et), 3.02–2.95 (2 H, m, 6a-H and 7α-H), 2.82–2.75 (5 H, m, 5α-H, 10α-H, 10β-H, 10a-H and OCH_2CH_3), 2.57 (1 H, m, 10b-H), 2.48 (1 H, dd, *J* 16.2 and 12.4, 5β-H), 2.31 (3 H, t, *J* 7.2, OCH_2CH_3) and 1.24 (3 H, s, 10c-methyl); NOE data 4.88 (3.02–2.95, 4%; 2.82–2.75, 4%), 3.37 (2.82–2.75, 8%) and 1.24 (3.02–2.95, 10%; 2.57, 6%; 2.48, 9%); δ_C 209.0 (C-6), 197.4 (C-4), 177.2 (C-9), 169.7 (CO_2Et), 156.0 (C-2), 130.0 (C-3), 83.3 (C-7a), 81.8 (C-1), 61.3 (OCH_2CH_3), 57.1 (C-10b), 53.4 (OCH_3), 51.5 (C-6a), 49.9 (C-10c), 45.2 (C-4a), 39.0 (C-10a), 37.1 (CH_2CO_2Et), 36.5 (C-10), 36.2 (C-5), 31.6 (C-7), 23.7 (2-methyl), 20.1 (10c-methyl) and 19.0 (OCH_2CH_3); *m*/*z* 372.1551 (M^+-CH_4O, 29%, $C_{21}H_{24}O_6$ requires 372.1573), 317 (11), 299 (19), 198 (100), 175 (12), 141 (25), 125 (59), 111 (35), 105 (12), 91 (14), 79 (13) and 77 (10).

(4aα,6aα,7aβ,10aβ,10bα,10cα)-4,4a,5,6,6a,7,7a,9,10,10a,10b,10c-Dodecahydro-2,10c-dimethyl-4,6,9-trioxo-3*H*-benz[6,7]-indeno[2,1-*b*]furan-1-acetic acid ethyl ester 18 and (4aα,6aβ,7aα,10aα,10bβ,10cβ)-4,4a,5,6,6a,7,7a,9,10,10a,10b,10c-dodecahydro-2,10c-dimethyl-4,6,9-trioxo-3*H*-benz[6,7]indeno[2,1-*b*]-furan-1-acetic acid ethyl ester 19

A 7 : 1 mixture of **12** and **13** (920 mg, 2.47 mmol) was dissolved in glacial acetic acid (35 ml) and heated under reflux. Analytical grade zinc dust (total 6.4 g) was added in small portions until TLC revealed complete consumption of the starting materials (approximately 45 min). After filtration, the solution was cooled to RT. Ethyl acetate (100 ml) and water (100 ml) were added to the filtrate, which was neutralized by addition of solid Na_2CO_3. The aqueous layer was re-extracted with ethyl acetate (3 × 30 ml). The combined organic layers were washed with water (50 ml) and brine (50 ml), dried and concentrated under vacuum. Chromatography provided **18** and **19** (779 mg, 84%) as a 6 : 1 *cis–trans* mixture, epimeric at C-4a. These epimers were separable by repeated chromatography.

For **18**: white solid, mp 188–190 °C; ν_{max}(Nujol)/cm^{-1} 1775, 1740 and 1715; δ_H (CD_2Cl_2) 4.66 (1 H, m, 7a-H), 4.17 (2 H, m, OCH_2CH_3), 3.31 (1 H, d, *J* 16.9, 3β-H), 3.20 (1 H, d, *J* 22.0, CH_2CO_2Et), 3.10 (1 H, d, *J* 6.8, 4a-H), 3.04–2.90 (4 H, m), 2.81 (1 H, d, *J* 22.0, CH_2CO_2Et), 2.55 (1 H, dd, *J* 14.9 and 6.7, 5α-H), 2.45 (1 H, dd, *J* 17.8 and 9.6, 10β-H), 2.30 (1 H, dd, *J* 11.1 and 6.8, 10b-H), 2.05–1.91 (2 H, m, 10α-H and 10a-H), 1.75 (3 H, s, 2-methyl), 1.60 (3 H, s, 10c-methyl), 1.53 (1 H, m, 7a-H) and 1.27 (3 H, t, *J* 7.1, OCH_2CH_3); NOE data 2.55 (3.10, 3%), 2.05–1.91 (4.66, 6%; 3.31, 2%) and 1.60 (3.10, 12%; 2.55, 2%; 2.30, 8%); δ_C 208.8 (0), 207.3 (0), 176.5 (C-9), 171.3 (CO_2Et), 131.6 (0), 128.7 (0), 83.7 (C-7a), 61.6 (OCH_2CH_3), 56.9 (C-10b), 55.1 (C-4a), 50.4 (C-6a), 46.2 (CH_2CO_2Et), 44.8 (C-10c), 40.4 (C-10a), 35.8 (C-5), 35.2 (C-3), 34.9 (C-10), 32.2 (C-7), 27.1 (10c-methyl), 20.1 (2-methyl) and 14.5 (OCH_2CH_3); *m*/*z* 374.1705 (M^+, 25%, $C_{21}H_{26}O_6$ requires 374.1729), 301 (14), 249 (17), 222 (24), 221 (90), 208 (54), 180 (19), 175 (59), 148 (35), 135 (93), 107 (47), 106 (42), 105 (40), 91 (56), 79 (40), 55 (47), 41 (49) and 29 (100).

For **19**: pale yellow solid, mp 184.5–187 °C; ν_{max}(Nujol)/cm^{-1} 1768, 1736 and 1708; δ_H (CD_2Cl_2) 4.76 (1 H, dd, *J* 14.3 and 7.0, 7a-H), 4.13 (2 H, m, OCH_2CH_3), 3.29 (1 H, d, *J* 17.0), 3.15 (1 H, d, *J* 20.4), 3.04–2.92 (3 H, m), 2.85–2.59 (6 H, m), 2.44 (1 H, dd, *J* 4.4 and 1.2), 2.39 (1 H, d, *J* 4.8), 1.72 (1 H, m, 7β-H), 1.67 (3 H, s, 2-methyl), 1.24 (3 H, t, *J* 7.1, OCH_2CH_3), 1.11 (3 H, s, 10c-methyl); δ_C (CD_2Cl_2) 209.9 (0), 206.7 (0), 176.5 (C-9), 171.0 (CO_2Et), 133.0 (0), 129.8 (0), 84.2 (C-7a), 61.6 (OCH_2CH_3), 57.8 (1), 50.4 (1), 49.7 (1), 47.5 (C-10c), 46.8 (2), 39.8 (1), 36.5 (2), 36.0 (2), 35.3 (2), 34.4 (2), 21.5 (10c-methyl), 20.4 (2-methyl) and 14.5 (OCH_2CH_3); *m*/*z* 374.1717 (M^+, 38%, $C_{21}H_{26}O_6$ requires 374.1729), 328 (14), 301 (17), 222 (23), 221 (74), 175 (58), 135 (59), 119 (30), 107 (36), 106 (32), 105 (44), 91 (52), 79 (40), 55 (44), 41 (45) and 29 (100).

(6aα,7aβ,10aβ,10bα,10cα)-4,6,6a,7,7a,9,10,10a,10b,10c-Decahydro-2,10c-dimethyl-4,6,9-trioxo-1*H*-benz[6,7]indeno-[2,1*b*]furan-1-acetic acid ethyl ester 20

A solution of **18** and **19** (6 : 1, 30 mg, 0.080 mmol) in glacial acetic acid was heated under reflux for 5 h. After cooling to RT, the solution was poured into ethyl acetate (30 ml) and water (30 ml). Solid Na_2CO_3 was added until CO_2-evolution ceased. The aqueous layer was re-extracted with ethyl acetate (2 × 15 ml), and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ (20 ml) and brine (20 ml), dried and concentrated under vacuum. Chromatography gave only 6 mg (20%) of **20** as yellow crystals: mp 142–142.5 °C; δ_H (CD_2Cl_2) 6.65 (1 H, s, 5-H), 6.21 (1 H, s, 3-H), 4.77 (1 H, m, 7a-H), 4.25 (2 H, m, OCH_2CH_3), 3.34 (1 H, d, *J* 9.4), 3.12–3.03 (2 H, m), 2.95–2.77 (2 H, m), 2.61–2.52 (3 H, m), 2.38 (1 H, dd, *J* 18.1 and 4.1), 2.00 (3 H, s, 2-methyl), 1.82 (1 H, m), 1.34 (3 H, s,

10c-methyl) and 1.31 (3 H, t, *J* 7.1, OCH_2CH_3); δ_C (CD_2Cl_2) 199.3, 184.4, 176.7, 172.8, 163.3, 154.0,128.0, 126.8, 83.3, 62.2, 55.8, 48.3, 43.2, 41.5, 39.4, 36.9, 35.4, 32.7, 25.2, 23.2 and 14.4.

(1α,4aβ,6aα,7aβ,10aβ,10bα,10cα)-4,4a,5,6,6a,7,7a,9,10,10a,10b,10c-Dodecahydro-2,10c-dimethyl-4,6,9-trioxo-1*H*-benz[6,7]-indeno[2,1-*b*]furan-1-acetic acid ethyl ester 21

To a solution of **18** and **19** (6 : 1, 245 mg, 0.654 mmol) in methanol (30 ml) was added 10 ml of aqueous 6 M HCl, and the mixture was heated under reflux for 3.5 h. The mixture was cooled to RT, and ethyl acetate (150 ml) was added. The organic solution was washed with water (2 × 40 ml) and brine (40 ml), dried and concentrated under vacuum. Chromatography provided **21** (156 mg, 64%) as a pale yellow solid, mp 209–210 °C; ν_{max}(Nujol)/cm^{-1} 1764, 1720, 1702 and 1669; δ_H (CD_3COCD_3) 5.90 (1 H, s, 3-H), 4.79 (1 H, dd, *J* 15.8 and 7.7, 7a-H), 4.23 (2 H, m, OCH_2CH_3), 3.29 (1 H, d, *J* 10.8, 1-H), 3.17–3.10 (2 H, m, 4a-H and 6a-H), 2.96–2.81 (5 H, m), 2.63–2.43 (4 H, m), 1.91 (3 H, s, 2-methyl), 1.48 (1 H, m, 7α-H), 1.28 (3 H, t, *J* 7.0, OCH_2CH_3) and 1.20 (3 H, s, 10c-methyl); NOE data 3.92 (3.17–3.10, 2%), 3.17–3.10 (3.29, 3%), 1.48 (3.17–3.10, 3%) and 1.20 (3.17–3.10, 9%); δ_C (CD_3COCD_3) 210.3 (C-6), 197.9 (C-4), 177.3 (C-9), 173.9 (CO_2Et), 160.3 (C-2), 126.9 (C-3), 83.4 (C-7a), 61.7 (OCH_2CH_3), 58.1 (1), 50.8 (1), 49.9 (1), 44.8 (1), 43.0 (C-10c), 37.9 (1), 37.2 (2), 35.2 (2), 33.4 (2), 33.2 (2), 22.2 (2 methyl), 16.2 (10c-methyl) and 14.5 (OCH_2CH_3); *m*/*z* 374.1717 (M$^+$, 39%, $C_{21}H_{26}O_6$ requires 374.1729), 329 (11), 277 (10), 241 (10), 221 (24), 203 (14), 175 (100), 149 (13), 135 (28), 123 (14), 119 (14), 105 (19), 95 (51), 91 (30), 79 (26) and 77 (17).

(1α,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-4,4a,5,6,6a,7,7a,9,10,10a,10b,10c-Dodecahydro-6-hydroxy-2,10c-dimethyl–4,9-dioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-acetic acid ethyl ester 22 and (1α,4aβ,6α,6aα,7aβ,10aβ,10bα,10cα)-4,4a,5,6,6a,7,7a,9,10,10a,10b,10c-dodecahydro-6-hydroxy-2,10c-dimethyl–4,9-dioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-acetic acid ethyl ester 23

$LiAl(OBu^t)_3H$ (2.10 ml of a 1.0 M solution in THF, 2.10 mmol) was added over 5 min to a solution of **21** (520 mg, 1.39 mmol) in dry THF (55 ml) at −20 °C. The solution was allowed to warm to 0 °C over 1 h, and then it was stirred at 0 °C for 1 h. A dilute aqueous NH_4Cl solution (100 ml) was added, and this was extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed with brine (2 × 50 ml), dried and concentrated under vacuum. Chromatography provided **22** (410 mg, 78%) and **23** (51 mg, 10%).

For **22**: white solid, mp 221.5–223 °C; ν_{max}(Nujol)/cm^{-1} 3512, 1758, 1732 and 1666 (s); δ_H (CD_2Cl_2) 5.87 (1 H, narrow m, 3-H), 5.19 (1 H, m, 7a-H), 4.23 (2 H, m, OCH_2CH_3), 3.95 (1 H, m, 6-H), 3.17 (1 H, d, *J* 9.7, 1-H), 3.06 (1 H, m, 10a-H), 2.86 (1 H, dd, *J* 18.6 and 10.3, 10β-H), 2.80 (1 H, dd, *J* 12.2 and 3.6, 4a-H), 2.56–2.33 (3 H, m, 7β-H and CH_2CO_2Et), 2.30 (1 H, m, 6a-H), 2.25 (1 H, dd, *J* 18.9 and 3.8, 10α-H), 2.07 (1 H, m, 5β-H), 1.91 (1 H, dd, *J* 10.8 and 5.8, 10b-H), 1.86 (3 H, apparent t, *J* 1.1, 2-methyl), 1.83–1.74 (2 H, m, 7α-H and OH), 1.65 (1 H, m, 5α-H), 1.30 (3 H, t, *J* 7.1, OCH_2CH_3) and 0.86 (3 H, s, 10c-methyl); NOE data 3.95 (2.30, 6%), 3.17 (2.80, 2%), 3.06 (5.19, 7%; 2.80, 5%) and 0.86 (2.30, 4%; 1.91, 4%; 1.65, 6%); δ_C (CD_2Cl_2) 200.4 (C-4), 178.1 (C-9), 173.4 (CO_2Et), 159.5 (C-2), 127.2 (C-3), 86.7 (C-7a), 68.3 (C-6), 61.8 (OCH_2CH_3), 54.1 (C-10b), 44.0 (C-1), 42.4 (C-10c), 42.2 (C-4), 42.0 (C-6a), 39.8 (C-10a), 37.9 (C-7), 36.0 (C-10), 33.6 (CH_2CO_2Et), 29.4 (C-5), 22.6 (2-methyl), 16.4 (10c-methyl) and 14.4 (OCH_2CH_3); *m*/*z* 376.1878 (M$^+$, 6%, $C_{21}H_{28}O_6$ requires 376.1886), 358 (32), 340 (17), 271 (21), 270 (13), 269 (18), 234 (39), 221 (67), 211 (17), 196 (18), 177 (25), 161 (26), 149 (22), 147 (17), 135 (54), 123 (41), 122 (43), 121 (17), 119 (21), 107 (16), 105 (29), 95 (100), 91 (40) and 79 (32).

For **23**: white solid, mp 195–196 °C; ν_{max}(Nujol)/cm^{-1} 3418, 1765, 1730 and 1665; δ_H (CD_3COCD_3) 5.88 (1 H, narrow m, 3-H), 5.06 (1 H, m, 7a-H), 4.22 (2 H, m, OCH_2CH_3), 3.28 (1 H, m), 3.20–3.08 (2 H, m), 2.92–2.79 (2 H, m), 2.72–2.65 (2 H, m), 2.49 (1 H, dd, *J* 17.8 and 10.9), 2.42–2.33 (2 H, m), 2.17 (1 H, ddd, *J* 14.1, 5.2 and 3.7), 2.06 (1 H, m), 1.86 (3 H, broadened s, 2-methyl), 1.55 (1 H, m), 1.33 (1 H, m), 1.28 (3 H, t, OCH_2CH_3) and 0.93 (3 H, s, 10c-methyl); δ_C (CD_3COCD_3) 198.8, 177.7, 174.1, 159.8, 127.2, 121.3, 84.4, 69.5, 61.6, 56.4, 48.2, 46.4, 44.7, 42.9, 37.7, 36.4, 35.8, 33.5, 30.1, 22.2, 16.5 and 14.5; *m*/*z* 376.1889 (M$^+$, 9%, $C_{21}H_{28}O_6$ requires 376.1886), 358 (4), 317 (7), 268 (18), 251 (12), 223 (35), 195 (100), 177 (72), 135 (23), 123 (20), 122 (18), 95 (39), 43 (20) and 41 (21).

(1α,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-4,4a,5,6,6a,7,7a,9,10,10a,10b,10c-Dodecahydro-6-[(2-methoxyethoxy)methoxy]-2,10c-dimethyl–4,9-dioxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-acetic acid ethyl ester 25

To a solution of **22** (160 mg, 0.425 mmol) in dry dichloromethane (10 ml) were added successively chloro(2-methoxyethoxy)-methane (0.48 ml, 4.2 mmol) and ethyldiisopropylamine (0.95 ml, 5.4 mmol). The solution was heated at reflux for 12 h. After cooling to RT, dichloromethane (80 ml) was added, and this solution was washed with aqueous 1% HCl (2 × 30 ml) and brine (30 ml), dried and concentrated under vacuum. Chromatography afforded **25** (182 mg, 93%) as a white solid, mp 155–157 °C; ν_{max}(Nujol)/cm^{-1} 1769, 1738 and 1661; δ_H (CD_2Cl_2) 5.86 (1 H, s, 3-H), 5.12 (1 H, m, 7a-H), 4.72 (1 H, d, *J* 6.9, OCH_2O), 4.60 (1 H, d, *J* 6.9, OCH_2O), 4.22 (2 H, m, OCH_2CH_3), 3.76 (1 H, m, 6-H), 3.72–3.56 (2 H, m, $OCH_2CH_2OCH_3$), 3.49 (2 H, t, *J* 4.5, $OCH_2CH_2OCH_3$), 3.32 (3 H, s, OCH_3), 3.15 (1 H, d, *J* 10.4, 1-H), 2.98 (1 H, m, 10a-H), 2.84 (1 H, dd, *J* 18.6 and 10.9, 10β-H), 2.67 (1 H, dd, *J* 12.3 and 3.1, 4a-H), 2.51 (1 H, dd, *J* 17.7 and 1.8, CH_2CO_2Et), 2.44–2.23 (5 H, m), 1.91 (1 H, dd, *J* 11.0 and 5.8, 10b-H), 1.85 (3 H, s, 2-methyl), 1.76 (1 H, m, 7α-H), 1.44 (1 H, m, 5α-H), 1.29 (3 H, t, *J* 7.2, OCH_2CH_3) and 0.86 (3 H, s, 10c-methyl); δ_C (CD_2Cl_2) 200.0 (C-4), 177.8 (C-9), 173.4 (CO_2Et), 159.2 (C-2), 127.2 (C-3), 94.6 (OCH_2O), 86.5 (C-7a), 74.1 (C-6), 72.3 ($OCH_2CH_2OCH_3$), 68.3 ($OCH_2CH_2OCH_3$), 61.8 (OCH_2CH_3), 59.2 (OCH_3), 54.1 (C-10b), 44.0 (C-1), 42.7 (C-4), 42.3 (C-10c), 42.1 (C-6a), 39.8 (C-10b), 37.7 (C-7), 35.8 (C-10), 33.7 (CH_2CO_2Et), 24.7 (C-5), 22.5 (2-methyl), 16.6 (10c-methyl) and 14.4 (OCH_2CH_3); *m*/*z* 464.2419 (M$^+$, 2%, $C_{25}H_{36}O_8$ requires 464.2408), 388 (3), 359 (7), 358 (5), 285 (4), 221 (7), 159 (3), 95 (6), 89 (100) and 59 (86).

(1α,2β,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-Tetradecahydro-6-[(2-methoxyethoxy)methoxy]-2,10c-dimethyl–4,9-dioxo-1*H*-benz-[6,7]indeno[2,1-*b*]furan-1-acetic acid ethyl ester 26

To sodium-dried liquid ammonia (approximately 270 ml) was added lithium metal shavings (82.7 mg, 11.9 mmol) in one portion. The blue solution was allowed to warm to −50 °C before a solution of **25** (738 mg, 1.59 mmol) in 1 : 1 dry 1,4-dioxane–diethyl ether (60 ml) was introduced over 1.5 min. The mixture was stirred for 5 min before solid NH_4Cl (just sufficient to discharge the blue colour) was added. The ammonia was allowed to evaporate as the mixture warmed to RT. Water (300 ml) was added, and this was extracted with ethyl acetate (4 × 150 ml). The combined organic extracts were washed with brine (2 × 100 ml) and dried. The residue was redissolved in dichloromethane (20 ml), and this solution was added dropwise to a suspension of pyridinium chlorochromate (874 mg, 3.97 mmol) in dichloromethane (30 ml). The resulting mixture was stirred for 1.5 h before filtration through Celite. The filtrate was concentrated, and chromatography afforded **26** (572 mg, 77%) as a white solid, mp 154–155 °C; ν_{max}(Nujol)/cm^{-1} 1762, 1720 and 1699; δ_H (CD_2Cl_2) 5.14 (1 H, dd, *J* 14.7 and 7.7, 7a-H), 4.67 (1 H, d, *J* 7.2, OCH_2O), 4.57 (1 H, d, *J* 7.2, OCH_2O), 4.16 (2 H, m, OCH_2CH_3), 3.72 (1 H, m, 6-H), 3.69–3.56 (2 H, m, $OCH_2CH_2OCH_3$), 3.48 (2 H, t, *J* 4.7, $OCH_2CH_2OCH_3$), 3.31 (3 H, s,

OCH_3), 3.00–2.81 (2 H, m, 10β-H and 10a-H), 2.68 (1 H, dd, *J* 12.6 and 2.5, 4a-H), 2.51 (1 H, d, *J* 16.4, CH_2CO_2Et), 2.38 (1 H, m, 6a-H), 2.33–2.05 (6 H, m), 1.96–1.88 (2 H, m, 5β-H and 10b-H), 1.85 (1 H, m, 2-H), 1.72 (1 H, m, 7α-H), 1.56 (1 H, m, 5α-H), 1.27 (3 H, t, *J* 7.2, OCH_2CH_3), 0.94 (3 H, d, *J* 6.4, 2-methyl) and 0.79 (3 H, s, 10c-methyl); NOE data 3.72 (2.38, 6%; 1.56, 2%), 2.68 (3.00–2.81, 7%) and 0.79 (2.38, 6%; 1.85, 6%; 1.56, 8%); δ_C (CD_2Cl_2) 211.7 (C-4), 178.1 (C-9), 173.6 (CO_2Et), 94.6 (OCH_2O), 86.8 (C-7a), 74.2 (C-6), 72.3 ($OCH_2CH_2OCH_3$), 68.3 ($OCH_2CH_2OCH_3$), 61.4 (OCH_2CH_3), 59.2 (OCH_3), 54.5 (C-10b), 50.1 (C-3), 45.5 (C-4a), 45.1 (C-1), 44.6 (C-10c), 42.3 (C-6a), 39.0 (C-10a), 38.0 (C-2), 37.5 (C-7), 36.0 (C-10), 35.4 (CH_2CO_2Et), 24.8 (C-5), 20.8 (2-methyl), 16.8 (10c-methyl) and 14.5 (OCH_2CH_3); *m*/*z* 466 (M^+, 0.5%), 390 (5), 377 (15), 359 (11), 331 (5), 313 (5), 273 (5), 89 (100) and 59 (81).

(1α,2β,4α,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-Tetradecahydro-4-hydroxy-6-[(2-methoxyethoxy)methoxy]-2,10c-dimethyl-9-oxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-acetic acid ethyl ester 27

L-Selectride (Aldrich, 0.28 ml, 0.28 mmol) was added to a solution of **26** (108 mg, 0.231 mmol) in dry THF (20 ml) at −78 °C. The solution was stirred for 1 h before the reaction was quenched with aqueous 5% NaOH (1.0 ml) followed by 30% H_2O_2 (1.0 ml). When the mixture attained RT, it was diluted with ethyl acetate (100 ml). The organic solution was washed with aqueous 5% HCl (25 ml) and brine (2 × 25 ml), dried and concentrated under vacuum. Chromatography provided **27** (98.5 mg, 91%) as a white solid, mp 112.5–113.5 °C; ν_{max}(Nujol)/cm^{-1} 3515, 1761 and 1731; δ_H (CD_2Cl_2) 5.08 (1 H, dd, *J* 14.3 and 7.6, 7a-H), 4.71 (1 H, d, *J* 7.1, OCH_2O), 4.61 (1 H, d, *J* 7.1, OCH_2O), 4.12 (2 H, m, OCH_2CH_3), 3.80 (1 H, apparent s, 4-H), 3.71 (1 H, m, 6-H), 3.65 (2 H, m, $OCH_2CH_2OCH_3$), 3.50 (2 H, t, *J* 4.4, $OCH_2CH_2OCH_3$), 3.33 (3 H, s, OCH_3), 2.83–2.71 (2 H, m, 10β-H and 10a-H), 2.45–2.36 (2 H, m, 6a-H and CH_2CO_2Et), 2.30 (1 H, d, *J* 15.7, 10α-H), 2.23 (1 H, dd, *J* 13.3 and 7.4, 7β-H), 2.09 (1 H, dd, *J* 16.9 and 9.8, CH_2CO_2Et), 1.93–1.82 (2 H, m, 2-H and 5α-H), 1.77–1.61 (5 H, m), 1.58 (1 H, m, 5β-H) and 1.46–1.36 (2 H, m, 3β-H and OH); NOE data 3.80 (1.58, 3%; 1.46–1.36, 8%), 2.83–2.71 (5.08, 9%), 2.45–2.36 (3.71, 7%), 1.93–1.82 (3.71, 3%) and 1.46–1.36 (3.80, 11%); δ_C (CD_2Cl_2) 178.5 (C-9), 174.3 (CO_2Et), 94.9 (OCH_2O), 87.0 (C-7a), 75.9 (C-6), 72.4 ($OCH_2CH_2OCH_3$), 72.3 (C-4), 68.1 ($OCH_2CH_2OCH_3$), 61.0 (OCH_2CH_3), 59.2 (OCH_3), 55.8 (1), 45.8 (1), 43.5 (C-3), 42.7 (C-6a), 39.3 (C-10c), 38.9 (C-10a), 37.6 (C-7), 36.0 (C-10), 35.4 (CH_2CO_2Et), 35.3 (1), 30.3 (C-5), 29.9 (C-2), 20.4 (2-methyl), 18.8 (10c-methyl) and 14.5 (OCH_2CH_3); *m*/*z* no M^+, 392 (1%), 361 (8), 255 (6), 195 (5), 167 (6), 119 (6), 105 (6), 93 (6), 89 (77) and 59 (100).

(1aα,3aα,5aα,6α,8β,8aα,8bβ,10α,10aβ,10bβ,10cα)-Dodecahydro-8-hydroxy-10-[(2-methoxyethoxy)methoxy]-6,8b-dimethyl-1*H*-naphth[2′,1′,8′:3,4,5]azuleno[1,8-*bc*]furan-3,4(1a*H*,5*H*)-dione 28 and (1*R**,2*S**,3*S**,4*R**,8*S**,10*S**,11*R**,13*R**,14*S**,18*S**)-11-[(2-methoxyethoxy)methoxy]-2,18-dimethyl-7,15-dioxapentacyclo[12.3.2.$0^{2,13}$.$0^{3,10}$.$0^{4,8}$]nonadecane-6,16-dione 29

Potassium *tert*-butoxide (29 mg, 0.24 mmol) was added to a solution of **27** (31 mg, 0.066 mmol) in dry benzene (15 ml). The mixture was heated under reflux for 4 h. After it had cooled to RT, the mixture was washed with cooled aqueous 1% HCl (30 ml), and the aqueous layer was re-extracted with ethyl acetate (4 × 20 ml). The combined organic extracts were washed with brine (30 ml), dried and concentrated under vacuum. ^{1}H NMR analysis revealed signals for **27**, **28** and **29** in a ratio of 1 : 5 : 1, respectively. Chromatography provided homogeneous **28** (17 mg, 61%). A small sample (approximately 8% isolated yield) of the by-product **29** was obtained by pooling and repurifying column fractions from different reaction runs.

For **28**: white solid, mp 165–167 °C; ν_{max}(Nujol)/cm^{-1} 3534, 1782 and 1693; δ_H (CD_2Cl_2) 4.86 (1 H, m, 1a-H), 4.69 (1 H, d, *J* 7.0, OCH_2O), 4.61 (1 H, d, *J* 7.0, OCH_2O), 3.91 (1 H, narrow m, 8-H), 3.76 (1 H, narrow m, 10-H), 3.70 (1 H, d, *J* 10.6, 3a-H), 3.64 (2 H, m, $OCH_2CH_2OCH_3$), 3.50 (2 H, t, *J* 4.6, $OCH_2CH_2OCH_3$), 3.33 (3 H, s, OCH_3), 3.24 (1 H, m, 10c-H), 2.58 (1 H, dd, *J* 16.9 and 3.9, 5α-H), 2.43–2.33 (2 H, m, 5β-H and 10a-H), 2.27 (1 H, dd, *J* 14.4 and 7.8, 1α-H), 1.91–1.66 (5 H, m), 1.64–1.53 (3 H, m), 1.49–1.38 (2 H, m, 7α-H and OH), 1.14 (3 H, s, 8b-methyl) and 0.90 (3 H, d, *J* 6.2, 6-methyl); NOE data 3.76 (2.43–2.33, 6%), 3.24 (4.86, 5%; 3.70, 4%), 1.49–1.38 (3.91, 13%), 1.14 (2.43–2.33, 8%) and 0.90 (2.58, 6%); δ_C (CD_2Cl_2) 204.0 (C-4), 172.9 (C-3), 95.0 (OCH_2O), 83.9 (C-1a), 75.9 (C-10), 72.4 ($OCH_2CH_2OCH_3$), 72.2 (1), 68.1 ($OCH_2CH_2OCH_3$), 59.3 (OCH_3), 55.8 (C-3a), 54.7 (1), 50.2 (1), 44.7 (C-7), 43.5 (C-5), 42.4 (C-10a), 40.6 (C-10c), 37.5 (C-1), 37.1 (1), 29.0 (C-9), 27.0 (1), 20.2 (6-methyl) and 18.2 (8b-methyl); *m*/*z* 422.2270 (M^+, 1%, $C_{23}H_{34}O_7$ requires 422.2302), 346 (4), 331 (13), 315 (6), 299 (8), 105 (4), 89 (65) and 59 (100).

For **29**: white solid, mp 191–192 °C; ν_{max}(Nujol)/cm^{-1} 1759 and 1718; δ_H (CD_3OD) 5.16 (1 H, dd, *J* 14.3 and 7.2, 8-H), 4.76 (1 H, d, *J* 7.0, OCH_2O), 4.66 (1 H, d, *J* 7.0, OCH_2O), 3.76 (1 H, d, *J* 2.7), 3.72 (1 H, m), 3.71–3.68 (2 H, m, $OCH_2CH_2OCH_3$), 3.57–3.54 (2 H, m, $OCH_2CH_2OCH_3$), 3.36 (3 H, s, OCH_3), 2.87–2.77 (2 H, m), 2.55 (1 H, d, *J* 17.7), 2.48–2.35 (2 H, m), 2.25 (1 H, dd, *J* 13.3 and 7.7), 2.06 (1 H, dd, *J* 17.7 and 9.9), 1.99–1.85 (3 H, m), 1.75–1.57 (5 H, m), 1.39 (1 H, m), 1.08 (3 H, s, 2-methyl) and 0.88 (3 H, d, *J* 7.0, 18-methyl); δ_C (CD_3OD) 181.4, 178.0, 95.8, 88.9, 77.4, 73.1, 72.8, 68.8, 59.4, 56.5, 46.6, 44.1, 43.7, 40.2, 39.9, 38.2, 36.9, 36.5, 35.8, 31.2, 31.1, 20.8 and 19.0; *m*/*z* no M^+, 333 (11%), 257 (6), 183 (5), 167 (7), 149 (13), 119 (10), 105 (12), 93 (10), 91 (12), 89 (68) and 59 (100).

(1α,2β,4α,4aβ,6β,6aα,7aβ,10aβ,10bα,10cα)-Tetradecahydro-6-[(2-methoxyethoxy)methoxy]-4-(methoxymethoxy)-2,10c-dimethyl-9-oxo-1*H*-benz[6,7]indeno[2,1-*b*]furan-1-acetic acid ethyl ester 30

To a solution of **27** (751 mg, 1.60 mmol) in dry dichloromethane (100 ml) were added successively chloromethyl methyl ether (1.22 ml, 16.0 mmol) and ethyldiisopropylamine (3.63 ml, 20.8 mmol). This solution was heated under reflux for 15 h. After dilution with dichloromethane (100 ml), the solution was washed with 0.5% aqueous HCl (2 × 50 ml) and brine (50 ml). The solution was dried and then concentrated under vacuum. Chromatography of the residue provided **30** (720 mg, 88%) as a white solid: mp 71–73 °C; ν_{max}(Nujol)/cm^{-1} 1721; δ_H 5.11 (1 H, dd, *J* 14.2 and 7.7, 7a-H), 4.75 (1 H, d, *J* 6.8, OCH_2O), 4.64 (1 H, d, *J* 6.8, OCH_2O), 4.62 (1 H, d, *J* 6.9, OCH_2O), 4.51 (1 H, d, *J* 6.9, OCH_2O), 4.14 (2 H, m, OCH_2CH_3), 3.73 (1 H, m, 4-H), 3.69 (2 H, m, $OCH_2CH_2OCH_3$), 3.61 (1 H, m, 6-H), 3.55 (2 H, t, *J* 4.0, $OCH_2CH_2OCH_3$), 3.39 (3 H, s, OCH_3), 3.34 (3 H, s, OCH_3), 2.89–2.76 (2 H, m, 10β-H and 10a-H), 2.44–2.34 (2 H, m, 6a-H and CH_2CO_2Et), 2.28 (1 H, d, *J* 5.3, 10α-H), 2.24 (1 H, dd, *J* 13.5 and 7.8, 7β-H), 2.10 (1 H, dd, *J* 16.9 and 9.5, CH_2CO_2Et), 1.97–1.85 (2 H, m, 2-H and 5α-H), 1.82–1.74 (4 H, m), 1.68 (1 H, dd, *J* 15.4 and 7.7), 1.58 (1 H, m), 1.27 (3 H, t, *J* 7.2, OCH_2CH_3), 1.24 (1 H, m), 1.02 (3 H, s, 10c-methyl) and 0.82 (3 H, d, *J* 6.1, 2-methyl); NOE data 5.11 (2.89–2.76, 8%) and 0.82 (1.82–1.74, 7%; 1.68, 4%); δ_C 178.2 (C-9), 173.6 (CO_2Et), 95.6 (OCH_2O), 94.2 (OCH_2O), 86.5 (C-7a), 77.7 (C-6), 75.2 (C-4), 71.7 ($OCH_2CH_2OCH_3$), 67.5 ($OCH_2CH_2OCH_3$), 60.6 (OCH_2CH_3), 59.1 (OCH_3), 55.4 (OCH_3), 55.3 (1), 45.2 (1), 42.0 (C-6a), 39.4 (2), 39.0 (C-10c), 38.4 (C-10a), 37.2 (C-7), 35.5 (C-10), 34.9 (1), 34.7 (2), 29.8 (C-2), 29.7 (2), 20.0 (2-methyl), 18.3 (10c-methyl) and 14.1 (OCH_2CH_3); *m*/*z* 512.2977 (M^+, <1%, $C_{27}H_{44}4O_9$ requires 512.2983), 423 (1), 391 (2), 373 (3), 363 (3), 361 (8), 89 (81), 59 (84) and 45 (100).

(1aα,3aα,5aα,6α,8β,8aα,8bβ,10α,10aβ,10bβ,10cα)-Dodecahydro-10-[(2-methoxyethoxy)methoxy]-8-(methoxymethoxy)-6,8b-dimethyl-1*H*-naphth[2′,1′,8′:3,4,5]azuleno[1,8-*bc*]furan-3,4(1a*H*,5*H*)-dione 31

Sodium hydride (40 mg, 1.6 mmol) was added to a solution of **30** (81.5 mg, 0.159 mmol) in dry benzene (50 ml). This was heated under reflux for 60 h. The solution was washed with ice-cold 0.5% aqueous HCl (2 × 30 ml). The aqueous layer was re-extracted with ethyl acetate (4 × 40 ml). The organic solutions were combined, washed with brine (40 ml), dried and concentrated under vacuum. Chromatography provided **31** (71.5 mg, 97%) as a white solid: mp 88–89 °C; ν_{max}(film)/cm^{-1} 1776 and 1710; δ_H 4.89 (1 H, m, 1a-H), 4.73 (1 H, d, *J* 6.9, OCH_2O), 4.65 (2 H, apparent d, *J* 6.9), 4.52 (1 H, d, *J* 6.9, OCH_2O), 3.79 (1 H, broad s), 3.73–3.66 (4 H, m), 3.56 (2 H, t, *J* 4.5, $CH_3OCH_2CH_2$), 3.40 (3 H, s, OCH_3), 3.35 (3 H, s, OCH_3), 3.23 (1 H, m, 10c-H), 2.59 (1 H, dd, *J* 16.8, 3.8, 4α-H), 2.49–2.36 (2 H, m), 2.28 (1 H, dd, *J* 14.3 and 7.9), 2.03 (1 H, m), 1.91–1.52 (7 H, m), 1.27 (1 H, m), 1.12 (3 H, s, 8b-methyl) and 0.91 (3 H, d, *J* 6.8, 6-methyl); NOE data 4.89 (3.23, 5%; 2.28, 4%), 3.23 (4.89, 6%; 3.73–3.66, 3%; 1.67–1.53, 6%) and 0.91 (1.89–1.71, 7%; 2.59, 5%); δ_C 203.1 (C-4), 172.4 (C-3), 95.6 (OCH_2O), 94.4 (OCH_2O), 83.3 (C-1a), 77.3 (C-10), 75.2 (C-8), 71.7 ($CH_3OCH_2CH_2$), 67.6 ($CH_3OCH_2CH_2O$), 59.1 (OCH_3), 55.4 (OCH_3), 55.1 (C-3a), 53.3 (1), 49.8 (1), 42.8 (2), 41.7 (1), 40.7 (2), 40.1 (1), 37.1 (C-8b), 36.9 (2), 36.6 (1), 28.6 (2), 26.7 (1), 20.0 (6-methyl) and 17.7 (8b-methyl); *m*/*z* 466.2542 (M^+, <1%, $C_{25}H_{38}O_8$ requires 466.2564), 390 (9), 315 (13), 89 (87), 59 (100).

(1aα,3aα,4β,5aα,6α,8β,8aα,8bβ,10α,10aβ,10bβ,10cα)-Tetradecahydro-4-hydroxy-10-[(2-methoxyethoxy)methoxy]-8-(methoxymethoxy)-6,8b-dimethyl-1*H*-naphth[2′,1′,8′:3,4,5]azuleno[1,8-*bc*]furan-3(1a*H*)-one 32

To a solution of **31** (840 mg, 1.80 mmol) in methanol (100 ml) was added $NaBH_4$ (0.35 g, 9.0 mmol) at RT. The mixture was stirred at RT for 10 h. Water (50 ml) was added, and this was extracted with ethyl acetate (4 × 80 ml), and the combined extracts were washed with brine (50 ml), dried, and concentrated under vacuum. Chromatography was carried out affording **32** (789 mg, 94%) as a viscous oil: ν_{max}(film)/cm^{-1} 3434 (broad) and 1710; δ_H 4.83 (1 H, m, 1a-H), 4.72 (1 H, d, *J* 7.3, OCH_2O), 4.65 (1 H, d, *J* 7.3, OCH_2O), 4.63 (1 H, d, *J* 6.8, OCH_2O), 4.51 (1 H, d, *J* 6.8, OCH_2O), 3.90 (1 H, broad s, 3-H), 3.70–3.64 (4 H, m, 8-H, 10-H and $CH_3OCH_2CH_2O$), 3.55 (2 H, broad t, *J* 4.3, $CH_3OCH_2CH_2O$), 3.39 (3 H, s, OCH_3), 3.35 (3 H, s, OCH_3), 3.20 (1 H, t, *J* 7.0, 3a-H), 2.88 (1 H, m, 10c-H), 2.44 (1 H, broad m), 2.17–2.08 (2 H, m), 2.04 (1 H, m), 1.99 (1 H, dd, *J* 3.8 and 2.2), 1.90 (1 H, d, *J* 3.0), 1.85 (1 H, d, *J* 3.6), 1.80 (2 H, broad t, *J* 6.4), 1.75–1.72 (2 H, m), 1.69–1.53 (3 H, m), 1.17 (1 H, dd, *J* 14.5 and 3.7), 1.09 (3 H, s, 8b-methyl), 0.95 (3 H, d, *J* 6.6, 6-methyl) and 0.65 (1 H, dd, *J* 10.7 and 7.0); NOE data 3.90 (3.20, 11%; 0.65, 10%), 2.88 (4.83, 6%), 2.44 (3.70–3.64, 5%) and 1.09 (1.75–1.72, 12%); δ_C 178.7 (C-3), 95.6 (OCH_2O), 94.7 (OCH_2O), 85.9 (C-1a), 77.7 (C-8), 76.2 (C-10), 73.5 (C-4), 71.7 ($CH_3OCH_2CH_2O$), 67.5 ($CH_3OCH_2CH_2O$), 59.1 (OCH_3), 55.4 (OCH_3), 52.0 (1), 49.6 (1), 46.3 (C-3a), 43.8 (1), 41.3 (1), 41.2 (2), 38.0 (1), 36.2 (C-8b), 33.4 (2), 30.5 (2), 29.2 (2), 27.3 (1), 20.0 (6-methyl) and 18.6 (8b-methyl).

(1aα,3aα,4β,5aα,6α,8β,8aα,8bβ,10α,10aβ,10bβ,10cα)-4-[(1,1-Dimethylethyl)dimethylsilyloxy]tetradecahydro-10-[(2-methoxyethoxy)methoxy]-8-(methoxymethoxy)-6,8b-dimethyl-1*H*-naphth[2′,1′,8′:3,4,5]azuleno[1,8-*bc*]furan-3(1a*H*)-one 33

To a solution of **32** (17 mg, 0.036 mmol) in dry dichloromethane (10 ml) was added 2,6-lutidine (0.064 ml, 0.54 mmol) and *tert*-butyldimethylsilyl triflate§ (0.085 ml, 0.36 mmol) at RT. The mixture was stirred at RT for 6 h before it was diluted with dichloromethane (100 ml). This mixture was washed with 0.5% aqueous HCl (20 ml), brine (20 ml), dried, and concentrated under vacuum. Chromatography gave **33** (20 mg, 95%) as a white solid: mp 145–146 °C; ν_{max}(CH_2Cl_2)/cm^{-1} 1775; δ_H 4.82 (1 H, m, 1a-H), 4.71 (1 H, d, *J* 7.0, OCH_2O), 4.65 (1 H, d, *J* 6.9, OCH_2O), 4.63 (1 H, d, *J* 7.0, OCH_2O), 4.58 (1 H, dd, *J* 7.9 and 4.2, 4-H), 4.52 (1 H, d, *J* 6.9, OCH_2O), 3.75 (1 H, m), 3.72–3.65 (2 H, m), 3.65 (1 H, d, *J* 3.3), 3.55 (2 H, t, *J* 4.5), 3.39 (3 H, s, OCH_3), 3.35 (3 H, s, OCH_3), 3.34 (1 H, dd, *J* 12.5 and 6.8), 2.93 (1 H, dd, *J* 12.3 and 9.0), 2.74 (1 H, dd, *J* 10.8 and 3.9), 2.33 (1 H, m), 2.23 (1 H, dd, *J* 13.9 and 7.8), 2.19 (1 H, dd, *J* 12.0 and 3.9), 1.96 (2 H, broad dd, *J* 12.0 and 1.8), 1.87–1.73 (5 H, m), 1.54 (1 H, m), 1.13 (3 H, s, 8b-methyl), 1.04 (1 H, m), 0.86 (3 H, d, *J* 3.2, 6-methyl), 0.85 (9H, s, $SiC(CH_3)_3$), 0.10 (3 H, s, $SiCH_3$) and 0.09 (3 H, s, $SiCH_3$); δ_C 178.3 (C-3), 95.6 (OCH_2O), 94.3 (OCH_2O), 83.4 (C-1a), 78.1 (1), 75.6 (1), 71.7 ($CH_3OCH_2CH_2O$), 70.4 (C-4), 67.3 ($CH_3OCH_2CH_2O$), 59.1 (1), 55.3 (OCH_3), 52.1 (OCH_3), 47.2 (1), 46.2 (1), 41.7 (1), 41.4 (2), 41.0 (1), 37.3 (2), 37.1 (1), 36.2 (C-8b), 34.3 (2), 29.1 (2), 27.4 (1), 25.8 ($SiC(CH_3)_3$), 20.5 (6-methyl), 17.8 ($SiC(CH_3)_3$), 17.5 (8b-methyl), −3.6 ($SiCH_3$) and −5.9 ($SiCH_3$); *m*/*z* no M^+, 378 (1), 377 (2), 376 (2), 363 (2), 333 (8), 257 (5), 89 (89), 59 (93), 45 (100).

(1aα,3aα,4β,5aα,6α,8β,8aα,8bβ,10α,10aβ,10bβ,10cα)-4-[(1,1-Dimethylethyl)dimethylsilyloxy]hexadecahydro-10-[(2-methoxyethoxy)methoxy]-8-(methoxymethoxy)-6,8b-dimethyl-1*H*-naphth[2′,1′,8′:3,4,5]azuleno[1,8-*bc*]furan-3-ol 34

To a solution of **33** (62 mg, 0.11 mmol) in THF (10 ml) was added diisobutylaluminium hydride (0.35 ml of a 1.5 M solution in toluene, 0.53 mmol) at −78 °C. The mixture was allowed to warm to RT and was maintained at RT with stirring for 4 h. The reaction was quenched with methanol (1 ml), and the solution was diluted with ethyl acetate (100 ml). The solution was washed with 0.5% aqueous HCl solution (20 ml) and brine (20 ml), dried and concentrated under vacuum. Chromatography provided the mixture of epimers **34** (52 mg, 84%): δ_H 5.51 (1 H, d, *J* 5.1, 3-H), 5.48 (1 H, d, *J* 4.8, 3-H), 4.74 (1 H, m, 1a-H), 4.70 (1 H, d, *J* 6.9, OCH_2O), 4.65 (1 H, d, *J* 6.9, OCH_2O), 4.61 (1 H, d, *J* 6.8, OCH_2O) 4.51 (1 H, d, *J* 6.8, OCH_2O), 4.08–4.39 (2H, m), 3.70–3.62 (m), 3.56–3.53 (m), 3.39 (3 H, s, OCH_3), 3.34 (3 H, s, OCH_3), 3.10 (1 H, s, OH), 2.77–2.50 (m), 2.41–2.35 (m), 2.13 (1 H, dd, *J* 12.9 and 7.0), 2.50–1.50 (m), 1.16 (1 H, m), 1.07 (3 H, s, 8b-methyl), 0.91 (3 H, dd, *J* 7.3, 6-methyl), 0.90 (9H, s, $SiC(CH_3)_3$), 0.74 (1 H, m), 0.10 (6 H, s, $Si(CH_3)_2$), 0.09 (3 H, s, $SiCH_3$) and 0.08 (3 H, s, $SiCH_3$); δ_C 102.1 (C-3), 100.0 (C-3), 95.6 (OCH_2O), 94.7 (OCH_2O), 94.5 (OCH_2O), 88.9 (C-1a), 85.3 (C-4), 78.0 (1), 76.8 (1), 74.5 (1), 73.8 (1), 71.7 ($CH_3OCH_2CH_2O$), 67.2 ($CH_3OCH_2CH_2O$), 67.1 ($CH_3OCH_2CH_2O$), 59.1 (OCH_3), 55.3 (OCH_3), 52.6 (1), 51.5 (1), 50.6 (1), 49.2 (1), 49.0 (1), 48.5 (1), 46.4 (1), 44.3 (1), 42.6 (1), 42.1 (1), 41.4 (2), 37.7 (1), 37.6 (2), 37.2 (1), 36.2 (2), 34.9 (2), 31.7 (2), 30.8 (2), 29.5 (2), 29.1 (2), 27.3 (1), 27.0 (1), 25.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 20.6 (6-methyl), 20.2 (6-methyl), 18.5 (8b-methyl), 18.4 (8b-methyl), 18.0 ($SiC(CH_3)_3$), −4.4 ($SiCH_3$), −4.8 ($SiCH_3$), −4.9 ($SiCH_3$), and −5.2 ($SiCH_3$).

(1aα,3aα,4β,5aα,6β,8β,8aα,8bβ,10α,10aα,10bβ,10cα)-4-[(1,1-Dimethylethyl)dimethylsilyloxy]-1a,4,5,5a,6,7,8,8a,8b,9,10,10a,10b,10c-tetradecahydro-10-[(2-methoxyethoxy)methoxy]-8-(methoxymethoxy)-3,6,8b-trimethyl-1*H*-naphth[2′,1′,8′:3,4,5]azuleno[1,8-*bc*]furan 35

To a solution of **33** (25 mg, 0.043 mmol) in dry THF (5 ml) at RT was added methyllithium (61 μl of a 1.4 M solution in diethyl ether, 0.086 mmol). The mixture was stirred for 30 min before 0.5% aqueous HCl (2 ml) was added, and this was extracted with ethyl acetate (50 ml). The organic solution was

§ The IUPAC name for triflate is trifluoromethanesulfonate.

washed with brine (20 ml), dried and concentrated under vacuum. Chromatography provided **35** (6 mg, 24%) and 9 mg of **33** was recovered. For **35**: δ_H 4.90–4.26 (6 H, m), 3.77–3.51 (6 H, m), 3.39 (3 H, s), 3.34 (3 H, s), 2.94 (1 H, broadened t, *J* 10.3), 2.24 (2 H, m), 2.01 (1 H, m), 1.90 (3 H, s), 1.06 (3 H, s), 0.94 (12 H, broadened s, likely 6-methyl under $SiC(CH_3)_3$), 0.12 (3 H, s) and 0.09 (3 H, s) with many remaining, poorly resolved signals 2.0–1.2; δ_C 144.2, 113.4, 95.6, 94.2, 84.4, 78.1, 75.8, 74.2, 71.8, 67.2, 59.1, 58.5, 55.3, 51.2, 50.3, 41.7, 41.2, 39.6, 37.8, 36.4, 34.1, 29.2, 27.4, 26.2 (3 C), 21.1, 18.5, 18.2, 13.4, −4.4 and −4.7.

cis-3,3a,6,6a-Tetrahydro-5-(2-methyl-1,3-dioxolan-2-yl)-2*H*-cyclopenta[*b*]furan-2-one 36

A solution of **4** (2.28 g, 13.7 mmol), ethane-1,2-diol (7.75 ml, 137 mmol) and oxalic acid (630 mg, 6.87 mmol) in benzene (150 ml) was heated under reflux with a Dean–Stark apparatus for 15 h. The solvent was removed under reduced pressure. The residue was redissolved in ethyl acetate (300 ml), and this solution was washed with a saturated aqueous $NaHCO_3$ solution (2 × 50 ml) and a brine solution (50 ml). The solution was dried, and the solvent was evaporated under reduced pressure. Chromatography provided **36** (2.08 g, 72%) as a pale yellow oil: ν_{max}(film)/cm^{-1} 1714, 1660 and 1616; δ_H 5.57 (1 H, d, *J* 1.7, 4-H), 5.14 (1 H, m, 6a-H), 4.00–3.95 (2 H, m, OCH_2CH_2O), 3.87–3.83 (2 H, m, OCH_2CH_2O), 3.55 (1 H, m, 3a-H), 2.83 (1 H, dd, *J* 18.0 and 9.7, 3-H *syn* to 3a-H), 2.76–2.72 (2 H, m, 6-H), 2.45 (2 H, dd, *J* 18.0 and 1.7, 3-H *anti* to 3a-H) and 1.49 (3 H, s, CH_3); δ_C 109.8 (C-2 of dioxolane), 102.4 ($CH(OCH_3)_2$), 64.5 (C-4 and C-5 of dioxolane), 53.1 (OCH_3), 50.8 (C-2 of dithiane), 41.5 ($CH_2CH(OCH_3)_2$), 33.2 (2), 33.1 (2), 26.0 (C-4 and C-6 of dithiane), 25.1 (C-5 of dithiane) and 23.9 (2-methyl); *m*/*z* 322.1277 (M$^+$, 2%, $C_{14}H_{26}O_4S_2$ requires 322.1272), 233 (3), 87 (21) and 75 (100).

cis-2-(2-Hydroxyethyl)-4-(2-methyl-1,3-dioxolan-2-yl)cyclopent-3-en-1-ol 37

To a solution of **36** (125 mg, 0.590 mmol) in anhydrous ether (10 ml), at RT was added $LiAlH_4$ (45.0 mg, 1.18 mmol). The mixture was stirred at RT for 3 h. An aqueous $NaHSO_4$ solution (0.24 M, 2 ml) was added, and the aqueous layer was extracted with ethyl acetate (3 × 40 ml). The combined extracts were washed with a brine solution (40 ml), dried and concentrated under reduced pressure. Chromatography of the residue provided **37** (100 mg, 80%) as an oil: ν_{max}(film)/cm^{-1} 3408 and 1670; δ_H 5.56 (1 H, m, 3-H), 4.48 (1 H, ddd, *J* 9.3, 6.3 and 3.1, 1-H), 3.98–3.95 (2 H, m, OCH_2CH_2O), 3.93–3.88 (2 H, m, OCH_2CH_2O), 3.80 (1 H, m,CH_2OH), 3.67 (1 H, m, CH_2OH), 2.80 (1 H, m, 2-H), 2.67 (1 H, ddt, *J* 16.6, 7.0 and 2.2, 5-H), 2.36 (1 H, dm, *J* 16.6, 5-H), 1.94–1.70 (2 H, m, CH_2) and 1.49 (3 H, s, CH_3); δ_C 142.2 (C-4), 128.5 (C-3), 107.0 (OCO), 72.6 (C-1), 64.6 (OCH_2CH_2O), 61.6 (CH_2OH), 49.0 (C-2), 40.4 (C-5), 30.3 (CH_2) and 23.7 (CH_3); *m*/*z* 214.1223 (M$^+$, <1%, $C_{11}H_{18}O_4$ requires 214.1205), 199 (1), 139 (4), 109 (4), 87 (23), 73 (11) and 43 (100).

cis-4-Methoxy-3-(2-methoxyethyl)-1-(2-methyl-1,3-dioxolan-2-yl)cyclopent-1-ene 38

Sodium hydride (120 mg, 5.00 mmol) and iodomethane (0.62 ml, 10 mmol) were added to a solution of **37** (215 mg, 1.00 mmol) in THF (40 ml). This was stirred at RT for 24 h before it was cooled to 0 °C and water was added. The aqueous solution was extracted with ethyl acetate (3 × 40 ml). The combined extracts were washed with brine (40 ml), dried and concentrated under reduced pressure. Chromatography provided **38** (196 mg, 81%) as an oil: ν_{max}(film)/cm^{-1} 1672; δ_H 5.71 (1 H, dd, *J* 2.7 and 1.8, 2-H), 3.97 (1 H, m, 4-H), 4.00–3.85 (4 H, m, OCH_2CH_2O), 3.44 (2 H, t, *J* 5.9, CH_2O), 3.34 (3 H, s, OCH_3), 3.31 (3 H, s, OCH_3), 2.83 (1 H, m, 3-H), 2.49 (1 H, ddm, *J* 15.8 and 6.5, 5-H), 2.36 (1 H, ddt, *J* 15.8, 5.2 and 1.7, 5-H), 1.89 (1 H, m, CH_2), 1.57 (1 H, m, CH_2) and 1.48 (3 H, s, CH_3); δ_C 141.8 (C-1), 128.8 (C-2), 107.1 (OCO), 82.3 (C-4), 71.5 (CH_2O), 64.6 (OCH_2CH_2O), 58.5 (OCH_3), 57.1 (OCH_3), 44.3 (C-3), 35.7 (C-5), 27.9 (CH_2) and 23.6 (CH_3); *m*/*z* 197 (M$^+$−45, 1%), 138 (6), 125 (10), 87 (23), 73 (17) and 45 (100).

cis-1-Acetyl-4-methoxy-3-(2-methoxyethyl)cyclopent-1-ene 39

To a solution of **38** (605 mg, 2.50 mmol) in 50 ml of acetone–water (50 : 1) was added pyridinium toluene-*p*-sulfonate[17] (12.5 mg, 0.500 mmol). The mixture was heated under reflux for 3 h. The solvent was removed under vacuum, and the residue was redissolved in ethyl acetate (100 ml), washed with saturated $NaHCO_3$ solution (30 ml) and brine (30 ml) and then dried. After the solvent was evaporated under vacuum, the residue was subjected to chromatography to afford **39** (445 mg, 90%) as a yellow oil: ν_{max}(film)/cm^{-1} 1713, 1673 and 1622; δ_H 6.67 (1 H, m, 2-H), 3.95 (1 H, ddd, *J* 11.3, 5.7 and 2.8, 4-H), 3.50 (2 H, ddd, *J* 12.1, 6.1 and 2.0, CH_2O), 3.36 (3 H, s, OCH_3), 3.30 (3 H, s, OCH_3), 3.05 (1 H, m, 3-H), 2.70 (1 H, dm, *J* 16.7, 5-H), 2.59 (1 H, ddt, *J* 16.7, 5.7 and 1.5, 5-H), 2.32 (3 H, s, CH_3), 1.98 (1 H, ddd, *J* 27.9, 14.0 and 6.7, CH_2), 1.76 (1 H, ddd, *J* 27.9, 14.1 and 6.7, CH_2); δ_C 196.7 (C=O), 146.0 (C-2), 142.5 (C-1), 81.4 (C-4), 71.3 (CH_2O), 58.5 (OCH_3), 56.9 (OCH_3), 47.4 (C-3), 35.2 (C-5), 27.1 (CH_2), 26.2 (CH_3); *m*/*z* 198.1236 (M$^+$, 2%, $C_{11}H_{18}O_3$ requires 198.1255), 182 (3), 170 (2), 166 (3), 153 (6), 138 (6), 127 (7), 125 (8), 111 (5), 97 (5), 85 (5), 83 (5), 79 (6), 58 (10) and 45 (100).

(1α,2α,5aα,9aα,9bα)-4-[(1,1-Dimethylethyl)dimethylsilyloxy]-2,3,5,5a,9a,9b-hexahydro-2-methoxy-1-(2-methoxyethyl)-8,9a-dimethyl-1*H*-benz[*e*]indene-6,9-dione 41

To a mixture of enone **39** (1.72 g, 8.66 mmol) and *tert*-butyldimethylsilyl triflate (2.23 ml, 9.52 mmol) in dry CH_2Cl_2 (100 ml) was added dry triethylamine (1.57 ml, 11.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min. The solvent was removed under vacuum. The residue was passed rapidly through a silica gel column (30% dry ethyl acetate–hexane) to afford crude diene **40** (2.66 g, *ca.* 98%) as an orange oil. A solution of the moisture-sensitive diene **40** (2.66 g, 8.51 mmol) and 2,6-dimethyl-*p*-benzoquinone (**6**) (2.34 g, 17.0 mmol) in dry toluene (180 ml) was heated under reflux for 3 days. The solvent was removed under vacuum, and the residue was purified by chromatography (55% anhydrous ether–hexane) to afford **41** (3.28 g, 86%) as yellow solid: mp 67–69 °C; ν_{max}(Nujol)/cm^{-1} 1739, 1712 and 1624; δ_H 6.40 (1 H, t, *J* 1.5, 7-H), 3.86 (1 H, q, *J* 4.8, 2-H), 3.44 (2 H, ddd, *J* 13.4, 6.9 and 2.3, CH_2O), 3.33 (3 H, s, OCH_3), 3.31 (3 H, s, OCH_3), 2.99–2.87 (2 H, m, 1-H and 5a-H), 2.40 (2 H, m, 3-H), 2.27 (1 H, d, *J* 8.8, 9b-H), 2.16–2.02 (2 H, m, 5-H), 1.95 (3 H, d, *J* 1.4, 8-methyl), 1.90 (1 H, ddd, *J* 13.3, 7.0 and 2.3, 1-CH_2), 1.69 (1 H, m, 1-CH_2), 1.40 (3 H, s, 9a-methyl), 0.89 (9 H, s, $SiC(CH_3)_3$) and 0.04 (6 H, s, $SiCH_3$); NOE data 3.86 (2.99–2.87, 10%, 2.40, 6%) and 1.40 (2.99–2.87, 12%; 2.27, 8%); δ_C 202.4 (0), 200.8 (0), 148.2 (C-8), 138.7 (C-4), 133.4 (C-7), 118.4 (C-3a), 81.1 (C-2), 71.4 (CH_2O), 58.5 (OCH_3), 57.6 (C-5a), 56.6 (OCH_3), 51.6 (C-9b), 50.9 (C-9a), 41.5 (C-1), 32.0 (C-3), 31.9 (C-5), 29.5 (1-CH_2), 25.6 ($SiC(CH_3)_3$), 25.6 (9a-methyl), 18.0 ($SiC(CH_3)_3$), 16.6 (8-methyl) and −4.0 ($SiCH_3$); *m*/*z* 448.2638 (M$^+$, 2%, $C_{25}H_{40}O_5Si$ requires 448.2645), 415 (13), 414 (11), 370 (12), 369 (11), 224 (9), 223 (12), 178 (12), 89 (34), 75 (26) and 73 (100).

(1α,2α,3aα,4β,5aα,9aα,9bα)-4-[(1,1-Dimethylethyl)dimethylsilyloxy]-2,3,3a,4,5,5a,9a,9b-octahydro-3a,4-methano-2-methoxy-1-(2-methoxyethyl)-8,9a-dimethyl-1*H*-benz[*e*]indene-6,9-dione 42

To a solution of **41** (238 mg, 0.530 mmol) in dry toluene (15 ml) was added diethylzinc (5.30 ml of a 1.0 M solution in hexane,

5.30 mmol) and diiodomethane (0.86 ml, 10.6 mmol) at RT. The mixture was stirred at RT for 2 h before it was poured into a saturated NH_4Cl solution (40 ml). The resulting mixture was extracted with diethyl ether (4 × 40 ml). The combined extracts were washed with water (40 ml) and brine (40 ml), dried and concentrated under vacuum. Chromatography provided **42** (216 mg, 88%) as a yellow oil: ν_{max}(film)/cm^{-1} 1703 and 1622; δ_H 6.32 (1 H, t, *J* 1.2, 7-H), 4.05 (1 H, q, *J* 4.5, 2-H), 3.41 (2 H, dt, *J* 6.6 and 3.6, C*H*$_2$OCH$_3$), 3.33 (3 H, s, OCH$_3$), 3.31 (3 H, s, OCH$_3$), 3.05 (1 H, m, 1-H), 2.31–2.17 (3 H, m, 5a-H and 5-H or 3-H), 1.98 (3 H, d, *J* 1.8, 8-methyl), 1.95 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.79 (2 H, dt, *J* 12.8 and 1.3, 3-H or 5-H), 1.62 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.29 (3 H, s, 9a-methyl), 1.27 (1 H, m, 9b-H), 0.80 (9 H, s, SiC(CH$_3$)$_3$), 0.75 (1 H, d, *J* 5.7, cyclopropyl), 0.46 (1 H, d, *J* 5.7, cyclopropyl) and 0.01 (6 H, s, Si(CH$_3$)$_2$); NOE data 4.05 (3.05, 5%) and 0.46 (2.31–2.17, 2%; 1.29, 3%); δ_C 202.5 (0), 201.1 (0), 150.1 (C-8), 132.4 (C-7), 82.0 (C-2), 71.5 (*C*H$_2$OCH$_3$), 58.5 (OCH$_3$), 57.4 (C-5a), 57.0 (C-4), 56.9 (OCH$_3$), 56.5 (C-9b), 50.2 (0), 41.4 (C-1), 34.9 (C-3 and C-5), 30.3 (*C*H$_2$CH$_2$OCH$_3$), 28.5 (0), 27.3 (cyclopropyl CH$_2$), 25.9 (9a-methyl), 25.6 (SiC(*C*H$_3$)$_3$), 17.7 (Si*C*(CH$_3$)$_3$), 16.6 (8-methyl), −3.3 (SiCH$_3$) and −3.9 (SiCH$_3$); *m*/*z* 462.2804 (M$^+$, 1%, $C_{26}H_{42}O_5Si$ requires 462.2801), 447 (1), 373 (3), 294 (9), 293 (34), 265 (13), 237 (5), 235 (4), 105 (8), 89 (19), 75 (23), 73 (100) and 45 (40).

(1α,2α,3aα,4β,5aα,9aα,9bα)-4-[(1,1-Dimethylethyl)dimethylsilyloxy]-9-(ethoxyethynyl)-2,3,3a,4,5,5a,9a,9b-octahydro-9-hydroxy-3a,4-methano-2-methoxy-1-(2-methoxyethyl)-8,9a-dimethyl-1*H*-benz[*e*]inden-6(9*H*)-one 43 and (1α,2α,3aα,4β,5aα,9aα,9bα)-4-[(1,1-dimethylethyl)dimethylsilyloxy]-6-(ethoxyethynyl)-2,3,3a,4,5,5a,9a,9b-octahydro-6-hydroxy-3a,4-methano-2-methoxy-1-(2-methoxyethyl)-8,9a-dimethyl-1*H*-benz[*e*]inden-9(6*H*)-one 44

To a solution of ethoxyethyne (0.55 ml of a 50% w/w solution in hexane, 2.8 mmol) in dry THF (15 ml) at −78 °C was introduced *n*-butyllithium (0.56 ml of a 2.5 M solution in hexane, 1.4 mmol) over 5 min. The solution was stirred for 30 min and then transferred with a double-headed needle to a solution of enedione **42** (324 mg, 0.700 mmol) in dry THF (15 ml) at −78 °C. This mixture was stirred at −78 °C for 2 h and then at 0 °C for 1 h. Water (10 ml) and then diethyl ether (200 ml) were added. The organic solution was washed with water (3 × 20 ml) and brine (20 ml). The resulting solution was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Chromatography gave **43** (135 mg, 36%) and **44** (215 mg, 58%).

For **43**: yellow oil, ν_{max}(CH_2Cl_2)/cm^{-1} 3424 (broad), 2259, 1712 and 1678; δ_H 5.72 (1 H, m, 7-H), 4.22–4.09 (2 H, m, OC*H*$_2$CH$_3$), 3.82 (1 H, m, 2-H), 3.46 (1 H, m, C*H*$_2$OCH$_3$), 3.34 (3 H, s, OCH$_3$), 3.33 (3 H, s, OCH$_3$), 3.12 (1 H, m), 2.43 (1 H, s, OH), 2.21 (1 H, ddd, *J* 13.7, 12.5 and 1.1), 2.16 (3 H, t, *J* 1.1, 8-methyl), 2.11–1.96 (m), 1.87 (1 H, dd, *J* 13.5 and 5.6), 1.56 (1 H, m), 1.38 (3 H, t, *J* 7.0, OCH$_2$C*H*$_3$), 1.25 (1 H, m), 1.13 (3 H, s, 9a-methyl), 0.81 (9 H, SiC(CH$_3$)$_3$), 0.78 (1 H, d, *J* 5.2, cyclopropyl), 0.54 (1 H, d, *J* 5.2, cyclopropyl), 0.05 (3 H, s, SiCH$_3$) and 0.03 (3 H, s, SiCH$_3$); δ_C 201.9 (C-6), 156.9 (C-8), 121.9 (C-7), 97.1 (0), 82.0 (C-2), 74.6 (O*C*H$_2$CH$_3$), 73.9 (0), 71.9 (*C*H$_2$OCH$_3$), 58.5 (OCH$_3$), 58.4 (0), 56.7 (1), 56.3 (OCH$_3$), 54.3 (1), 44.2 (1), 41.7 (0), 39.2 (0), 35.5 (2), 35.2 (2), 30.2 (2), 29.6 (0), 28.0 (9a-methyl), 27.9 (cyclopropyl), 25.6 (SiC(*C*H$_3$)$_3$), 19.7 (8-methyl), 17.8 (Si*C*(CH$_3$)$_3$), 14.7 (OCH$_2$*C*H$_3$), −3.2 (SiCH$_3$) and −4.0 (SiCH$_3$); *m*/*z* 532.3224 (M$^+$, <1%, $C_{30}H_{48}O_6Si$ requires 532.3220), 503 (1), 485 (1), 293 (5), 231 (4), 203 (8), 175 (4), 105 (7), 91 (7), 89 (12), 75 (24), 73 (100) and 45 (33).

For **44**: yellow oil. ν_{max}(film)/cm^{-1} 3402 (broad), 2259 and 1712; δ_H 6.13 (1 H, s, 7-H), 4.18 (1 H, m, 2-H), 4.15–4.08 (2 H, m, OC*H*$_2$CH$_3$), 3.43 (2 H, t, *J* 6.6, C*H*$_2$OCH$_3$), 3.35 (3 H, s, OCH$_3$), 3.31 (3 H, s, OCH$_3$), 2.90 (1 H, q, *J* 6.0), 2.67 (1 H, dd, *J* 13.7 and 3.8), 2.42 (1 H, m), 2.25 (1 H, dd, *J* 13.5 and 5.3), 2.03 (1 H, m), 1.78 (3 H, t, *J* 1.6, 8-methyl), 1.64 (1 H, dd, *J* 13.5 and 6.1), 1.58 (2 H, dd, *J* 13.5 and 5.8), 1.49 (1 H, dd, *J* 24.4 and 12.9), 1.40 (3 H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.38 (3 H, s, 9a-methyl), 1.26 (2 H, t, *J* 7.2), 0.82 (9 H, s, SiC(CH$_3$)$_3$), 0.64 (1 H, d, *J* 5.2, cyclopropyl), 0.44 (1 H, d, *J* 5.2, cyclopropyl), 0.05 (3 H, s, SiCH$_3$) and 0.04 (3 H, s, SiCH$_3$); δ_C 203.3 (C-9), 137.8 (C-7), 132.8 (C-8), 96.1 (0), 82.1 (C-2), 74.8 (O*C*H$_2$CH$_3$), 71.6 (*C*H$_2$OCH$_3$), 69.7 (0), 60.3 (0), 58.4 (OCH$_3$), 57.9 (2), 56.6 (OCH$_3$), 50.4 (1), 48.3 (0), 41.5 (1), 41.4 (0), 36.1 (2), 34.6 (2), 30.5 (2), 28.0 (0), 26.7 (cyclopropyl), 26.5 (9a-methyl), 25.6 (SiC(*C*H$_3$)$_3$), 17.8 (Si*C*(CH$_3$)$_3$), 16.0 (8-methyl), 14.5 (OCH$_2$*C*H$_3$), −3.2 (SiCH$_3$) and −3.8 (SiCH$_3$); *m*/*z* 532.3224 (M$^+$, <1%, $C_{30}H_{48}O_6Si$ requires 532.3220), 487 (4), 357 (5), 293 (6), 165 (4), 161 (4), 135 (7), 105 (7), 89 (12), 75 (22), 73 (100) and 45 (25).

(1α,2α,5aα,9β,9aα,9bα)-4-[(1,1-Dimethylethyl)dimethylsilyloxy]-9-(ethoxyethynyl)-2,3,5,5a,9a,9b-octahydro-9-hydroxy-2-methoxy-1-(2-methoxyethyl)-8,9a-dimethyl-1*H*-benz[*e*]inden-6(9*H*)-one 45

To a solution of ethoxyethyne (0.88 ml of a 50% w/w solution in hexane, 4.50 mmol) in dry THF (30 ml) −78 °C was introduced *n*-butyllithium (1.20 ml of a 2.5 M solution in hexane, 3.00 mmol) over 5 min. The solution was stirred for 30 min, and then it was transferred with a double-headed needle over 30 min to a solution of **41** (673 mg, 1.50 mmol) in dry THF (30 ml) at −78 °C. This mixture was stirred at −78 °C for 2 h and then at 0 °C for 1 h. The reaction was quenched with water (20 ml), diluted with diethyl ether (200 ml), and washed with water (3 × 40 ml) and brine (40 ml). The solution was dried and concentrated under vacuum. Chromatography provided **45** (622 mg, 80%) as a pale yellow solid: mp 54–56 °C. ν_{max}(Nujol)/cm^{-1} 3368 (broad), 2262 and 1712; δ_H 5.74 (1 H, d, *J* 0.8, 7-H), 4.19 (2 H, q, *J* 7.7, OC*H*$_2$CH$_3$), 3.67 (1 H, t, *J* 3.9, 2-H), 3.65 (1 H, s, OH), 3.54–3.38 (2 H, m, CH$_2$O), 3.34 (3 H, s, OCH$_3$), 3.28 (3 H, s, OCH$_3$), 2.65 (1 H, broad m, 1-H), 2.61 (1 H, dd, *J* 10.6 and 2.8, 5a-H), 2.50 (1 H, broad m, 9b-H), 2.36 (2 H, m), 2.30 (1 H, m), 2.25 (2 H, dm, *J* 1.7), 2.14 (3 H, d, *J* 1.2, 8-methyl), 1.95 (1 H, m), 1.38 (3 H, t, *J* 6.8, OCH$_2$C*H*$_3$), 1.29 (3 H, s, 9a-methyl), 0.90 (9H, s, SiC(CH$_3$)$_3$), 0.10 (3 H, s, SiCH$_3$) and 0.07 (3 H, s, SiCH$_3$); δ_C 201.0 (C-6), 156.5 (0), 141.2 (C-7), 121.4 (0), 119.0 (0), 96.5 (0), 80.5 (C-2), 74.4 (O*C*H$_2$CH$_3$), 74.3 (0), 71.8 (CH$_2$O), 58.5 (OCH$_3$), 56.2 (OCH$_3$), 54.5 (C-5a), 52.0 (1), 44.5 (1), 42.4 (C-1), 39.5 (C-9a), 32.5 (2), 30.7 (2), 29.3 (2), 27.6 (9a-methyl), 25.6 (SiC(*C*H$_3$)$_3$), 20.0 (8-methyl), 18.0 (Si*C*(CH$_3$)$_3$), 14.7 (OCH$_2$*C*H$_3$), −3.6 (SiCH$_3$) and −3.7 (SiCH$_3$); *m*/*z* 518.3066 (M$^+$, 3%, $C_{29}H_{46}O_6Si$ requires 518.3063), 505 (2), 489 (4), 461 (3), 428 (2), 427 (4), 280 (5), 261 (3), 147 (2), 119 (2), 91 (3), 77 (12), 76 (7) and 75 (100).

(1*R**,2*S**,3*S**,4*S**,5*R**,7*S**,8*S**,10*R**)-1-(Ethoxyethynyl)-8-hydroxy-5-methoxy-4-(2-methoxyethyl)-2,13-dimethyl-14-oxatetracyclo[6.5.1.0^{2,10}.0^{3,7}]tridec-12-en-11-one 46 and (1*R**,2*R**,5*S**,7*S**,8*R**,9*R**,10*R**,11*S**)-11-(ethoxyethynyl)-1-hydroxy-7-methoxy-8-(2-methoxyethyl)-10,12-dimethyl-14-oxatetracyclo[9.2.1.0^{2,10}.0^{3,7}]tridec-12-en-4-one 47

A solution of **45** (2.44 g, 4.70 mmol) in methanol (80 ml) and a solution of KF·2H$_2$O (2.21 g, 23.5 mmol) in methanol (80 ml) were combined and stirred at RT for 7 h. Most of the solvent was removed under vacuum, the residue was diluted with water (100 ml) and extracted with ethyl acetate (4 × 50 ml). The combined extracts were washed with water (50 ml) and brine (50 ml), dried and concentrated under vacuum. Chromatography of the residue provided **46** and **47** (1.80 g, 95%) in a ratio of 1.5 : 1 favouring **46**. Small analytical samples of **46** and **47** were separated by repeated chromatography.

For **46**: pale yellow solid, mp 125–127 °C; ν_{max}(Nujol)/cm^{-1} 3421 (broad), 2260, 1712 and 1666; δ_H 5.72 (1 H, t, *J* 1.1, 12-H), 4.18 (2 H, q, *J* 7.1, OC*H*$_2$CH$_3$), 3.81 (1 H, t, *J* 3.4, 5-H), 3.47–

3.37 (2 H, m), 3.32 (3 H, s, OCH_3), 3.30 (1 H, m), 3.29 (3 H, s, OCH_3), 2.48 (1 H, ddd, *J* 23.0, 11.5 and 7.0), 2.36 (1 H, dd, *J* 11.8 and 4.3), 2.13 (1 H, dd, *J* 23.1 and 1.9), 2.12 (3 H, d, *J* 1.5, 13-methyl), 2.03 (1 H, dd, *J* 8.1 and 3.0), 1.97 (1 H, t, *J* 2.7), 1.93 (1 H, d, *J* 3.0), 1.89–1.78 (4 H, m), 1.67 (1 H, dd, *J* 13.5 and 4.5), 1.39 (3 H, t, *J* 7.2, OCH_2CH_3), 1.11 (3 H, s, 2-methyl); δ_C 200.9 (C-11), 159.3 (0), 121.1 (C-12), 98.4 (0), 97.7 (0), 82.0 (C-5), 76.8 (0), 74.6 (OCH_2CH_3), 71.6 (CH_2OCH_3), 58.3 (OCH_3), 56.1 (OCH_3), 53.1 (1), 52.5 (1), 44.7 (1), 41.9 (1), 38.6 (0), 37.6 (0), 34.9 (2), 30.2 (2), 28.9 (2), 20.6 (13-methyl), 19.6 (2-methyl) and 14.7 (3, OCH_2CH_3); *m*/*z* 404.2197 (M^+, <1%, $C_{23}H_{32}O_6$ requires 404.2199), 375 (1), 345 (1), 343 (3), 325 (3), 203 (10), 175 (18), 147 (11), 137 (17), 123 (11), 109 (17), 93 (10), 91 (22), 81 (10), 77 (15), 71 (10), 69 (14), 55 (19) and 45 (100).

For **47**: white solid, mp 142–143 °C; ν_{max}(Nujol)/cm^{-1} 3373 (broad), 2263 and 1712; δ_H 5.38 (1 H, d, *J* 1.3, 13-H), 4.10 (2 H, q, *J* 7.1, OCH_2CH_3), 3.70 (1 H, t, *J* 4.1, 7-H), 3.35 (1 H, m), 3.32 (3 H, s, OCH_3), 3.29 (3 H, s, OCH_3), 3.25 (1 H, dd, *J* 9.6 and 5.3), 3.08 (1 H, s, OH), 2.82 (1 H, d, *J* 5.2), 2.57 (1 H, dd, *J* 18.5 and 5.1), 2.43 (1 H, d, *J* 18.1), 2.30–2.22 (2 H, m), 2.17 (1 H, d, *J* 14.8), 1.90 (3 H, d, *J* 1.0, 12-methyl), 1.86 (2 H, d, *J* 12.2, 3-H), 1.80 (1 H, m), 1.37 (3 H, t, *J* 7.2, OCH_2CH_3), 1.33 (3 H, s, 10-methyl), 1.30 (1 H, d, *J* 4.3); δ_C 211.7 (C-4), 140.3 (C-12), 126.3 (C-13), 94.8 (0), 85.3 (C-7), 82.6 (0), 74.6 (OCH_2CH_3), 72.9 (0), 71.3 (2), 58.4 (OCH_3), 57.3 (1), 56.2 (OCH_3), 54.3 (1), 50.3 (0), 42.1 (1), 40.6 (0), 35.8 (2), 26.3 (2), 22.6 (2), 20.8 (10-methyl), 16.8 (12-methyl) and 14.4 (OCH_2CH_3); *m*/*z* 404.2191 (M^+, <1%, $C_{23}H_{32}O_6$ requires 404.2199), 390 (1), 362 (2), 302 (6), 270 (5), 257 (8), 247 (4), 239 (5), 206 (5), 196 (21), 175 (12), 161 (9), 152 (7), 147 (16), 137 (14), 135 (19), 123 (12), 119 (34), 109 (11), 107 (12), 91 (28), 79 (15), 77 (18), 55 (15) and 45 (100).

(1α,2α,3aα,9aα,9bα)-2,3,3a,4,5,5a,6,7,9a,9b-Decahydro-2-methoxy-1-(2-methoxyethyl)-8,9a-dimethyl-4,6-dioxo-1*H*-benz[*e*]inden-9-acetic acid ethyl ester 48

A 1.5 : 1 mixture of **46** and **47** (1.42 g, 3.51 mmol) was dissolved in glacial acetic acid (120 ml). The solution was heated under reflux as Zn dust (17 g, 0.26 mol) was added in portions until **46** and **47** was converted into **48**, as monitored by TLC. The solid was removed by filtration after the reaction mixture had cooled to RT. The filtrate was poured into a mixture of ethyl acetate (300 ml) and water (300 ml), and it was then neutralized by addition of solid Na_2CO_3 until CO_2-evolution ceased. The aqueous layer was re-extracted with ethyl acetate (3 × 40 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried and concentrated under vacuum. Chromatography afforded **48** (1.19 g, 84%) as a 1 : 1 epimeric mixture. These two compounds could not be separated by column chromatography. For the epimeric mixture: yellow viscous oil, ν_{max}(Nujol)/cm^{-1} 1712; δ_H 4.17 (2 H, q, *J* 7.1, OCH_2CH_3), 3.52 (1 H, m, 2-H), 3.47 (1 H, d, *J* 1.5), 3.27 (1 H, m), 3.25 (3 H, s, OCH_3), 3.20 (3 H, s, OCH_3), 3.17–3.13 (2 H, m, CH_2O), 3.03–3.00 (2 H, m), 2.97 (1 H, d, *J* 4.5, 5a-H), 2.96 (1 H, m), 2.90 (1 H, t, *J* 8.9, 3a-H), 2.33 (1 H, dd, *J* 17.9 and 9.3), 2.16 (1 H, t, *J* 9.4, 9b-H), 1.97 (1 H, dd, *J* 13.6 and 7.9, 3-H), 1.76 (1 H, dd, *J* 23.4 and 4.0, 3-H), 1.75 (3 H, s, 8-methyl), 1.65–1.56 (2 H, m), 1.51 (1 H, m, 1-H), 1.30 (3 H, s, 9a-methyl) and 1.27 (3 H, t, *J* 7.0, OCH_2CH_3); δ_C 213.0 (0), 208.5 (0), 171.3 (CO_2Et), 130.7 (0), 129.0 (0), 81.5 (C-2), 71.2 (CH_2O), 60.9 (OCH_2CH_3), 58.6 (OCH_3), 56.2 (OCH_3), 53.6 (C-5a), 52.1 (C-9b), 48.1 (C-3a), 45.8 (2), 44.9 (C9a), 44.1 (C-1), 35.1 (2), 32.5 (2), 31.6 (2), 28.6 (2), 27.4 (9a-methyl), 19.6 (8-methyl) and 14.2 (OCH_2CH_3); *m*/*z* 406.2360 (M^+, 3%, $C_{23}H_{34}O_6$ requires 406.2355), 374 (10), 248 (11), 222 (12), 221 (21), 208 (16), 185 (12), 175 (26), 153 (27), 135 (44), 125 (22), 121 (17), 119 (14), 107 (17), 105 (18), 93 (43), 91 (30), 79 (21), 77 (17), 58 (25) and 45 (100).

(1α,4aβ,6aα,7aβ,10aβ,10bα,10cα)-4,4a,5,6,6a,7,7a,9,10,10a,10b,10c-Dodecahydro-2,10c-dimethyl-4,6-dioxo-1*H*-benz[6,7]-indeno[2,1-*b*]furan-1-acetic acid ethyl ester 49

A solution of **48** (1 : 1 mixture of epimers, 623 mg, 1.53 mmol) and toluene-*p*-sulfonic acid (294 mg, 1.53 mmol) in toluene (40 ml) was heated under reflux for 4 h. After cooling to RT, the mixture was diluted with ethyl acetate (150 ml). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 40 ml) and brine (40 ml), dried and concentrated under vacuum. Chromatography provided **49** (374 mg, 68%) as a yellow solid: mp 219–221 °C; ν_{max}(Nujol)/cm^{-1} 1723, 1703, 1673 and 1623; δ_H 5.96 (1 H, s, 3-H), 4.45 (1 H, dd, *J* 15.2 and 7.5, 7a-H), 4.23 (2 H, m, OCH_2CH_3), 3.93 (1 H, m, 9-H), 3.75 (1 H, m, 9-H), 3.33 (1 H, d, *J* 9.6, 1-H), 2.95 (2 H, dd, *J* 12.7 and 4.7, 4a-H and 6a-H), 2.80 (1 H, dd, *J* 12.8 and 7.7, 7-H), 2.68 (2 H, dd, *J* 15.8 and 4.7), 2.55 (2 H, d, *J* 26.0), 2.39 (1 H, m, 10a-H), 2.34 (1 H, dd, *J* 9.9 and 6.0, 10b-H), 2.16 (1 H, m, 10-H), 1.90 (3 H, s, 2-methyl), 1.52 (1 H, m, 10-H), 1.37 (1 H, dd, *J* 13.1 and 6.4, 7-H), 1.31 (3 H, t, *J* 6.7, OCH_2CH_3) and 1.11 (3 H, s, 10c-methyl); NOE data 4.45 (2.39, 5%), 3.33 (2.95, 6%) and 1.11 (2.95, 11%); δ_C 210.2 (C-6), 197.6 (C-4), 172.6 (CO_2Et), 159.3 (C-2), 126.5 (C-3), 83.2 (C-7a), 69.6 (C-9), 61.2 (OCH_2CH_3), 57.7 (C-10b), 52.5 (C-4a), 49.3 (C-6a), 43.7 (C-1), 42.9 (C-10a), 42.2 (C-10c), 36.4 (2), 33.3 (2), 32.6 (2), 31.5 (2), 22.1 (2-methyl), 16.2 (10c-methyl) and 14.1 (OCH_2CH_3); *m*/*z* 360.1951 (M^+, 4%, $C_{21}H_{28}O_5$ requires 360.1937), 276 (8), 273 (16), 203 (20), 189 (20), 185 (28), 175 (28), 161 (9), 135 (34), 123 (12), 121 (12), 119 (13), 109 (19), 105 (18), 95 (35), 93 (17), 91 (34), 85 (33) and 84 (100).

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