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Synthesis of optically active bridged cyclopropane derivatives

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Abstract—Treatment of the cyclobutene **3** with sodium methoxide leads to the cyclopropane esters **4** and **5**. Experiments with deuterated compounds supply information about the course of this reaction. The optically active epoxyoxepine (+)-**2a** is the starting material for the synthesis of (+)-**3**, (−)-**4** and (+)-**5**. The syntheses of the functionalized cyclopropanes (+)-**10a**, (−)-**10b** and (+)-**12** are also described.

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1. Introduction

New approaches to highly functionalized cyclopropanes are of great interest for various reasons.[1] Here we report on a new and not planned possibility to obtain the title compounds.

In the last 20 years we have shown that dimethyl 3,6-hexano-oxepine 4,5-dicarboxylate (**1a**) is a useful starting material for the synthesis of [6]paracyclophanes, hydroazulenes and bridged carbohydrate derivatives.[2] In the course of these studies, we also synthesized the epoxide (±)-**2a** and the cyclobutene (±)-**3**.[3]

Moreover, (+)-**2a** and (+)-**3** are readily available by the highly diastereoselective epoxidation of the diisopropylidene glucose ester derivative (−)-**1b**, transesterification with methanol/sodium methoxide and subsequent irradiation (Scheme 1).[4]

In the course of our synthesis of bridged furanosides from **1a**[5] we wanted to open the oxirane ring of (±)-**3** with sodium methoxide in methanol. To our surprise we isolated the cyclopropanes (±)-**4** and (±)-**5** in 31 and 35% yield. **4** and **5** could be easily separated by column chromatography. The structures of these new cyclopropanes were established by X-ray analysis (Fig. 1, Scheme 2).

It is noteworthy that the ester groups of **4** are in *trans* position, whereas those of **5** occupy a *cis* position on the cyclopropane ring.

2. Mechanistic considerations

In order to get insight into this unexpected cyclopropane formation two different experiments with deuterated reagents were carried out. In the first one deuterated methoxide was prepared from [D_4]methanol and the run was quenched with water, in the second one normal methoxide was used and quenching was carried out with deuterium oxide (Scheme 3).

In the first experiment the partially deuterated compounds [D_m]**4** and [D_m]**5** were obtained. The signals of the ether methoxy group have disappeared in the ^{1}H NMR spectra of both cyclopropanes, in addition the ester methoxy groups were also exchanged to a large extent (for details see Section 6). Most important is the result that deuterium was introduced into the bridge on C-3 of **4** and on C-2 of **5**. This points to an intermediate in which these positions show some C–H acidity.

Different results were obtained concerning the cyclopropane proton.

The signal of 11-H in **4** at δ=2.84 had completely disappeared in [D_m]**4**, whereas the corresponding one of 13-H in [D_m]**5** at δ=2.34 was only diminished by about 70%. When the reaction with methoxide was quenched with deuterium oxide (see Scheme 3) **4** contained no deuterium as expected, however [D_n]**5** was highly deuterated on C-13 of the cyclopropane ring.

The X-ray analyses of **4** and **5** and the deuteration experiments allow a tentative proposal for the formation of these cyclopropanes.

An attack of the methoxide on the more hindered position of the oxirane **3** is unlikely for several reasons. The introduced

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Keywords: oxepines; cyclopropanes; X-ray structural analysis; ring transformation reactions.

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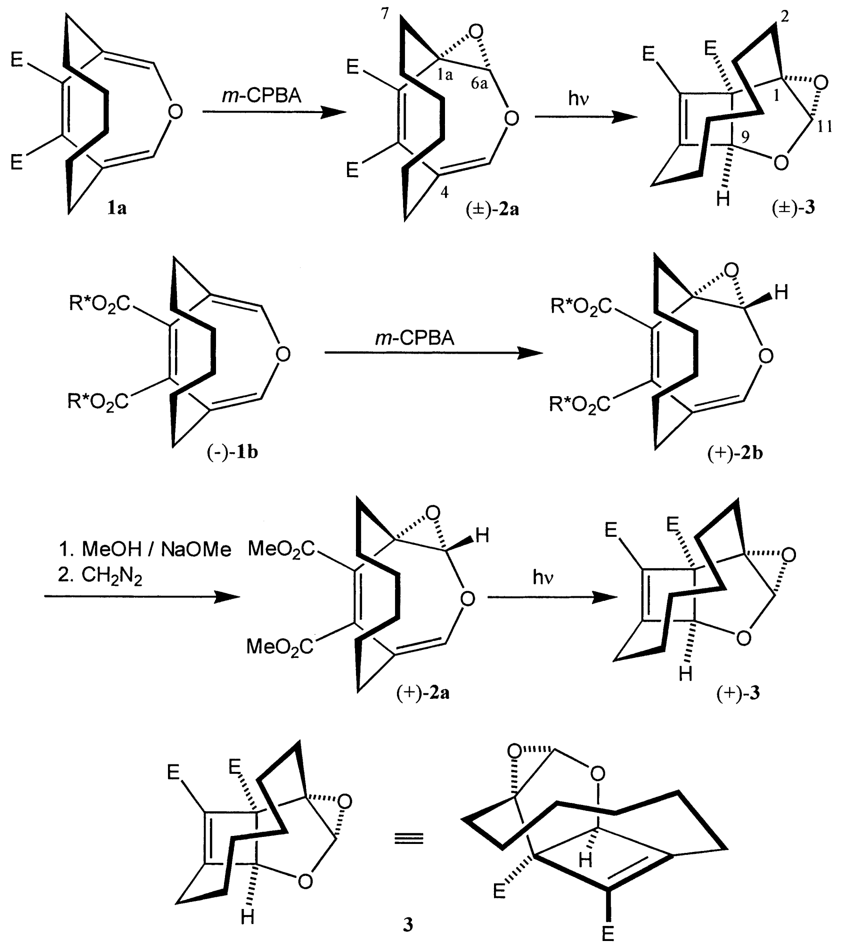


$E = COOCH_3$

Scheme 1. Synthesis of racemic and optically active starting materials R*OH: 1,2;5,6-diisopropylidene-α-D-glucofuranose.

methoxy group on the bridgehead lies on the same side of the former oxirane ring. Moreover the deuteration of the hexano bridge in both products (80% for one 3-H in [D_m]**4,** 70% for one 2-H in [D_m]**5**) could not be explained by such a pathway. Therefore we assume an attack of methoxide on C-9 of the cyclobutene ring to give an intermediate **6** as first step. **3** is a donor–acceptor substituted cyclobutene. Reissig[6] has reported many examples in which the weakened bond between these substituents in cyclopropanes is easily cleaved by nucleophiles to give ring opened products. Although the strain of cyclobutene is less than that one of cyclopropane[7] bond cleavage of **3** can be facilitated by a concerted ring opening of the oxirane ring to afford **6**. The proposal of **6** and/or of its protonated form explains also the observed H/D-exchange in the α-position of the hexano bridge. Attack of the second methoxide on the

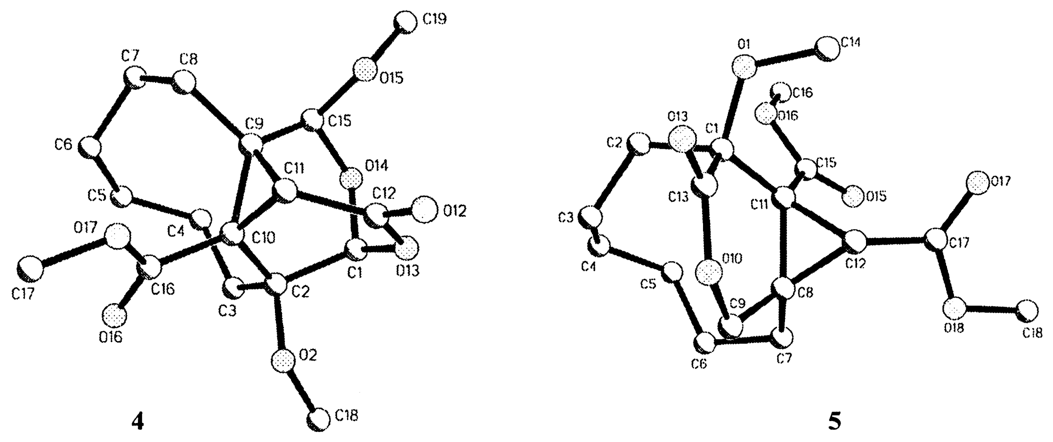
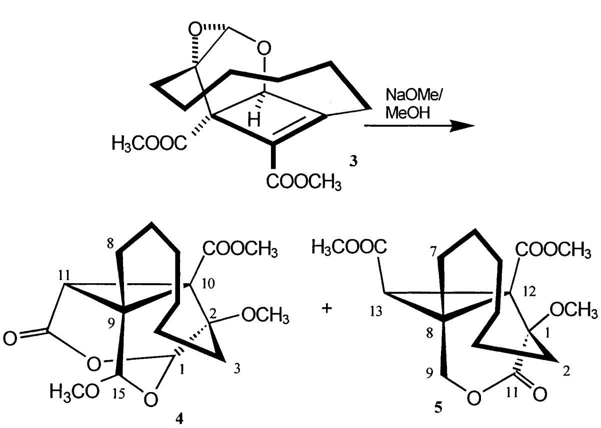


Figure 1. Molecules of **4** and **5** in the crystal, arbitrary numbering.



Scheme 2. Formation of the cyclopropanes **4** and **5** from **3**.

unsaturated ester part and ring closure lead to the cyclopropane ester enolate **7**. Protonation from the 'upper side' gives **8** that can cyclize under formation of the additional lactone bridge of **4**.

The intermediate **7** can also be the precursor of the second product **5**. Hydride shift in a Claisen–Tischtschenko reaction gives a γ-lactone, and protonation from the 'down side' finally the diester **5**.

Another point is worth of discussion. On the one hand the deuterium of $[D_m]$**4** comes completely from $[D_4]$methanol and not from deuterium oxide, on the other hand the ^1H NMR spectra of $[D_m]$**5** and $[D_n]$**5** indicate that the cyclopropane ring is protonated partially or deuterated (to 95%) after the addition of water or deuterium oxide, respectively (see Scheme 3). Therefore an enolate or an equivalent seems to be present here to a considerable extent before quenching the reaction. This is not the case in the sequence leading finally to **4** and also not for simple cyclopropane esters under our conditions (Scheme 4).[8] At present we can only speculate that the additional oxygen functions of an intermediate on the way to **5** stabilize an anion which is finally protonated.

3. Synthesis of other cyclopropane derivatives

The easy access to **4** and **5** in gramme amounts offers the possibility to synthesize other cyclopropanes. The reduction of **5** with lithium aluminium hydride leads to the γ-lactones **10a** (45%) and **10b** (24%) and the tetrahydroxy derivative **11** (17%) (Scheme 5).

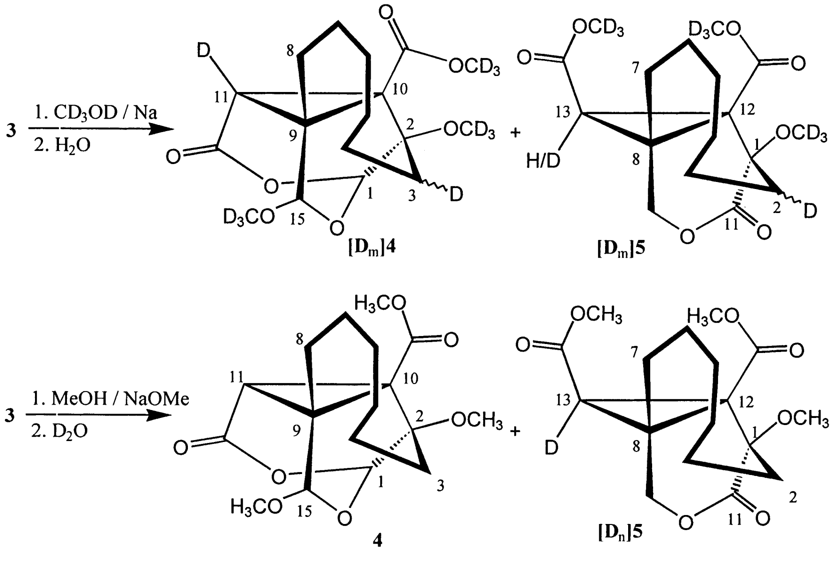
The diacetate **10b** was isolated after treatment of the hydroxide precipitate obtained on hydrolysis with acetic anhydride (for details see Section 6). The position of the γ-lactone ring follows from the observed ^3J coupling constants of 5.7 and 0.7 Hz of the cyclopropane proton 10-H at δ=3.28 with the methylene protons on C-11.

Obviously, the reduction of the ester group on the quarternary carbon C-12 of **5** is sterically hindered and a γ-lactone ring is formed under the conditions used here.

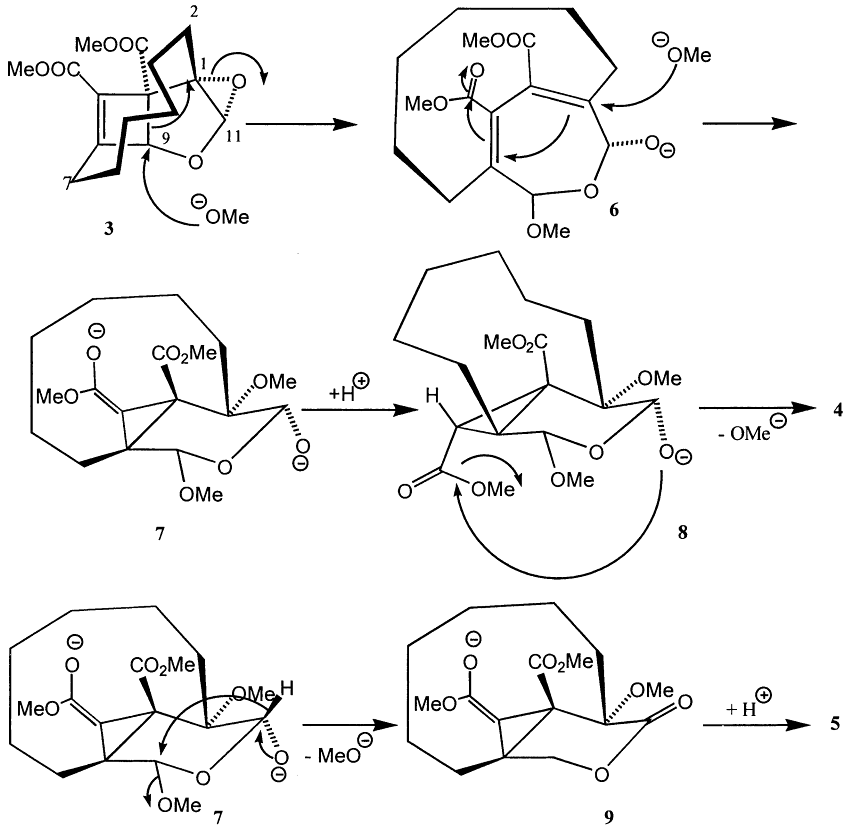
A remarkable reaction took place when **4** was treated with boron trifluoride etherate. The structure of the product **12** with an unsaturated bridge was established by X-ray analysis (Fig. 2). The Lewis acid eliminates the methoxide group on C-15 under formation of an oxonium/carbenium ion. A transannular hydride shift[9] from C-4 being in the neighbourhood of the positive charge on C-15 and the loss of a proton on C-5 yields **12**, that was isolated in 69% yield (Scheme 6).

The tetraacetate **13** was obtained in 64% yield by reduction of **12** with lithium aluminium hydride and subsequent acetylation.

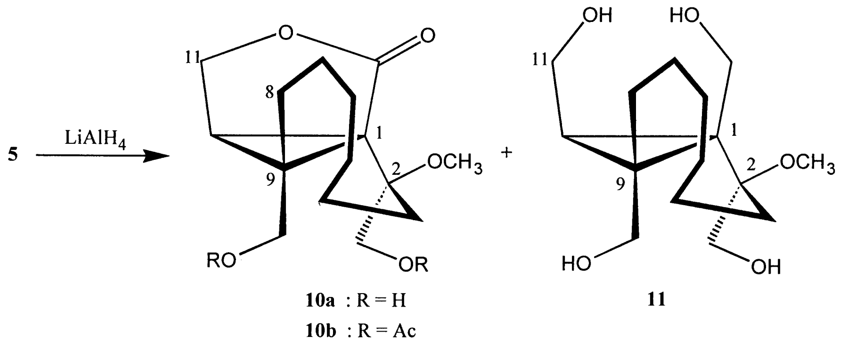
The *trans* position of the two ester groups in **12** excludes a γ-lactone formation here.



Scheme 3. Experiments with deuterated compounds.



Scheme 4. Tentative proposals for the formation of **4** and **5**. The protonated forms of the intermediates are not shown.



Scheme 5. Reduction of **5**.

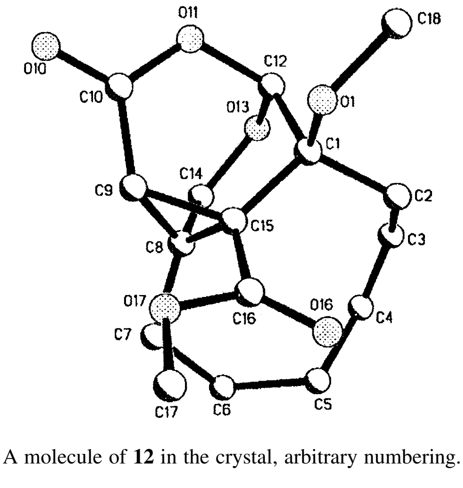


Figure 2. A molecule of **12** in the crystal, arbitrary numbering.

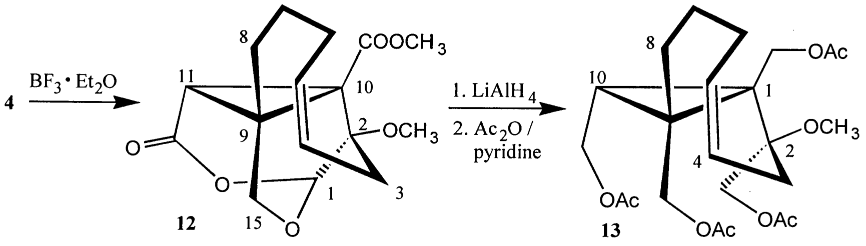
4. Synthesis of optically active compounds

The highly diastereoselective epoxidation of (−)-**1b** to (+)-**2b** opened the possibility to prepare the enantiomerically pure cyclopropanes (−)-**4**, (+)-**5**, (+)-**10a**, (−)-**10b** and (+)-**12** using (+)-**3** as starting material (Scheme 7). All details are described in Section 6.

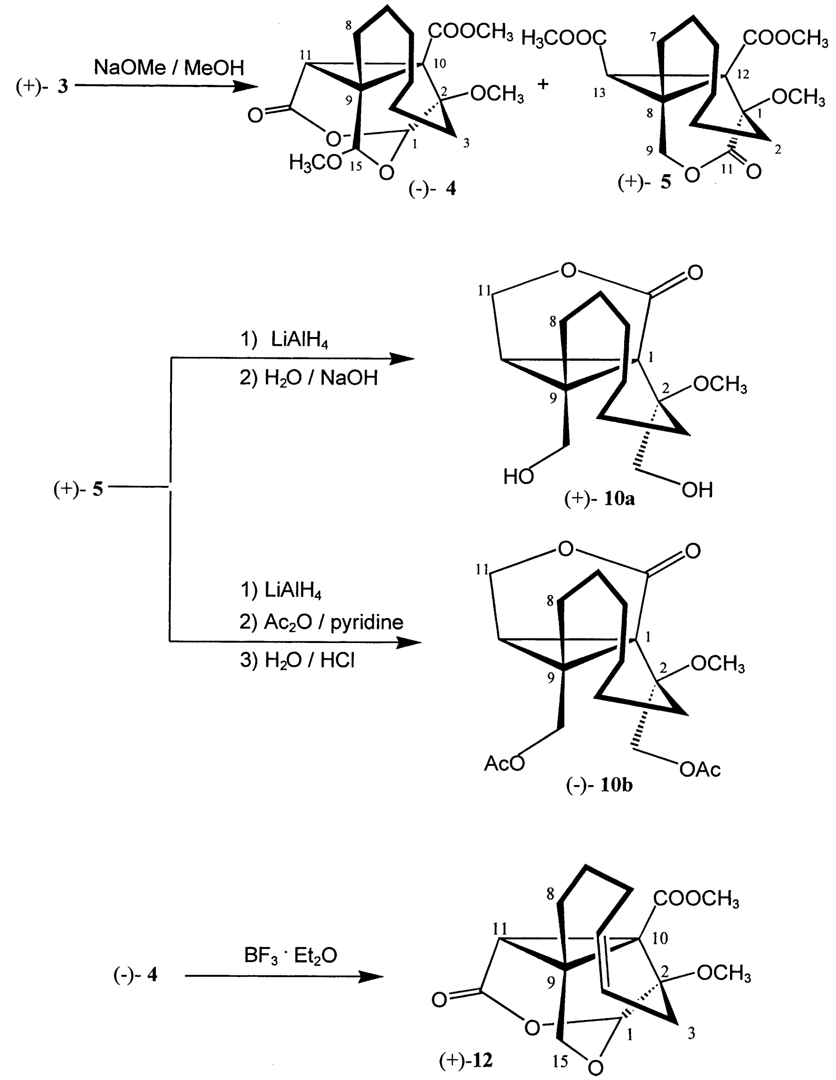
The enantiomers would also be accessible by using 1,2;5,6-diisopropylidene-L-glucofuranose as the chiral auxiliary.[4]

5. Conclusions

In summary, various highly functionalized racemic and



Scheme 6. Regioselective introduction of a double bond into the hexano bridge.



Scheme 7. Synthesis of optically active cyclopropanes.

optically active cyclopropanes are available via the unexpected course of the reaction of the cyclobutene **3** with sodium methoxide.

6. Experimental

IR spectra were recorded on a Perkin–Elmer Paragon 1600 FTIR spectrometer. $^1H/^{13}C$ NMR spectra (reference: TMS int) were taken in $CDCl_3$ on Bruker AC 200 P, Bruker AM 300 or Bruker DRX 500 spectrometers, respectively. The assignment of data marked with * and ** may be exchanged. EI (70 eV)and CI (*i*BuH) mass spectra were obtained on a Finnigan-MAT 8230 spectrometer. Column chromatography was performed on Baker Silicagel 30–60 μm and analytical TLC on Macherey–Nagel SIL G/ UV_{254} plates. Photochemical reactions were performed in a Duran glass reactor using a mercury-vapour lamp (Hanau TQ 150, Original Hanau Quarzlampen GmbH). Reactions with hydrides, alkoxides and boron trifluoride etherate were performed under nitrogen. Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium Ilse Beetz, D-96301 Kronach.

6.1. Synthesis of starting materials (±)-2a and (±)-3

Procedure. 70% *m*-chloroperbenzoic acid (4.00 g, 16.30 mmol) was added to a solution of **1a** (5.00 g; 17.10 mmol)[3] in 50 mL dichloromethane. The solution was stirred at room temperature for 1 h. A precipitate was formed. The mixture was purified by filtration over aluminium oxide (neutral, act. II–III) with dichloromethane to provide 4.71 g (89%) (±)-**2a** as colourless crystals, mp 106°C (diethyl ether/*n*-pentane).

6.1.1. (±)-Dimethyl (1a*R, 6a*R**)-1a,6a-dihydro-4,6a-hexano-oxireno[b]oxepine-5,6-dicarboxylate ((±)-2a).** IR (KBr, cm^{-1}) $\tilde{\nu}$ 1725, 1720 (C=O), 1630, 1605 (C=C); ^{1}H NMR ($CDCl_3$, ppm) δ 1.20–2.63 (m, 12H. 6 CH_2), 3.80 (s, $COOCH_3$), 3.82 (s, $COOCH_3$), 5.06 (s, 1H, 1a-H), 6.77 (d, ^{4}J=1.8 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.67 (t, CH_2), 22.79 (t, CH_2), 25.32 (t, CH_2), 27.96 (t, CH_2), 29.81 (t, C-12), 31.24 (t, C-7), 52.49 (q, OCH_3), 52.64 (q, OCH_3), 62.76 (s, C-6a), 93.37 (d, C-1a), 129.54 (s, C-4), 130.37 (s, C-6), 139.73 (s, C-5), 144.63 (d, C-3), 165.01 (s, $COOCH_3$), 166.64 (s, $COOCH_3$); MS (CI, %) *m*/*z* 309 (50) [M^{+}+H], 291 (28) [M^{+}+H–H_2O], 277 (100) [M^{+}+H–CH_3OH], 249 (20) [M^{+}+H–$COOCH_3$].

Procedure. A solution of (±)-**2a** (4.71 g, 15.28 mmol) in 1 L diethyl ether was irradiated under nitrogen at room temperature for 4 h. Purification by silica gel chromatography (diethyl ether/*n*-pentane, 1:1) provided 3.63 g (77%) of (±)-**3** (R_f=0.27) as colourless crystals, mp 140°C.

6.1.2. (±)-Dimethyl (1*R, 9*R**, 11*R**, 13*R**)-10,12-dioxa-tetracyclo[6.4.2.0^{1,11}.0^{9,13}]tetradec-8(14)-ene-13,14-dicarboxylate ((±)-3).**[3] IR (KBr, cm^{-1}) $\tilde{\nu}$ 1725, 1710 (C=O), 1625 (C=C); ^{1}H NMR ($CDCl_3$, ppm) δ 1.20–1.93 (m, 9H), 2.33 (ddd, ^{2}J=14.4 Hz, ^{3}J=10.0, 5.8 Hz, 1H, 7-H_a), 2.49 (ddd, ^{2}J=14.4 Hz, ^{3}J=6.5, 4.3 Hz, 1H, 2-H_a), 2.78 (dt, ^{2}J=14.8 Hz, ^{3}J=4.5 Hz, 1H, 7-H_b), 3.81 (s, 6H, 2 $COOCH_3$), 4.84–4.85 (m, 1H, 9-H), 5.05 (d, ^{4}J=1.3 Hz, 1H, 11-H); ^{13}C NMR ($CDCl_3$, ppm) δ 24.34 (t, C-5), 26.32 (t, C-6), 26.37 (t, C-3), 27.67 (t, C-4), 29.08 (t, C-2), 30.91 (t, C-7), 51.91 (q, OCH_3), 52.25 (q, OCH_3), 61.60 (s, C-13), 67.74 (s, C-1), 85.18 (d, C-9), 89.97 (d, C-11), 131.39 (s, C-14), 162.13 (s, 14-$COOCH_3$), 168.78 (s, C-8), 168.85 (s, 13-$COOCH_3$); MS (CI, %) *m*/*z* 309 (100) [M^{+}+H], 277 (78) [M^{+}+H–CH_3OH]; Anal calcd for $C_{16}H_{20}O_6$ (308.33), C 62.33, H 6.54; found, C 62.17 H 6.54.

6.2. Synthesis of the bridged cyclopropanes (±)-4 and (±)-5

Procedure. To a solution of (±)-**3** (5.04 g, 16.40 mmol) in 250 mL dry methanol was added sodium methoxide (2.62 g, 48.50 mmol). After heating at reflux for 1 h, the cooled solution was mixed with 300 mL water and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried with sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (acetone/dichloromethane/*n*-pentane, 1:2:9), providing 1.73 g (31%) of crystalline (±)-**4** (R_f=0.25, mp 218°C) and 1.95 g (35%) of crystalline (±)-**5** (R_f=0.15, mp 168°C).

6.2.1. (±)-Methyl (1*R, 2*R**, 9*S**, 10*S**, 11*R**, 15*R**)-2,15-dimethoxy-13,14-dioxa-12-oxo-tetracyclo[7.4.2.0^{2,10}.0^{9,11}]-pentadecane-10-carboxylate ((±)-4).** IR (KBr, cm^{-1}) $\tilde{\nu}$ 1737 (s, lactone C=O), 1715 (s, ester C=O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.39 (m, 1H, 6-CH_2), 1.43 (m, 1H, 7-CH_2), 1.48 (m, 1H, 5-CH_2), 1.50 (m, 1H, 6-CH_2), 1.60 (m, 1H, 4-CH_2), 1.64 (m, 1H, 7-CH_2), 1.82 (ddd, ^{2}J=15.0 Hz, *J*=7.7, 4.9 Hz, 1H, 8-H_a), 1.90 (m, 1H, 5-CH_2), 2.00 (m, 1H, 4-CH_2), 2.07 (ddd, ^{2}J=15.0 Hz, *J*=7.8, 4.8 Hz, 1H, 8-H_b), 2.09 (ddd, ^{2}J=14.3 Hz, *J*=7.2, 1.6 Hz, 1H, 3-H_a), 2.67 (ddd, ^{2}J=14.3, 11.7, 1.7 Hz, 1H, 3-H_b), 2.84 (d, *J*=0.6 Hz, 1H, 11-H), 3.28 (s, 3H, OCH_3 at C-2), 3.48 (s, 3H, OCH_3 at C-15), 3.78 (s, 3H, $COOCH_3$), 5.10 (d, *J*=0.8 Hz, 1H, 15-H), 5.34 (s, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.98 (t, C-4), 24.99 (t, C-7), 26.04 (t, C-6), 28.14, (t, C-5), 29.22 (t, C-8), 33.48 (t, C-3), 33.48 (d, C-11), 37.26 (s, C-10), 41.40 (s, C-9), 50.12 (q, 2-OCH_3), 52.55 (q, 10-$COOCH_3$), 56.13 (q, 15-OCH_3), 68.53 (s, C-2), 98.08 (d, C-1), 100.73 (d, C-15), 167.26 (s, C-12), 168.79 (s, $COOCH_3$); MS (CI, %) *m*/*z* 341 (89) [M^{+}+1], 309 (11) [M^{+}−OCH_3]; Anal calcd for $C_{17}H_{24}O_7$ (340.37), C 59.99, H 7.11; found C 59.97, H 7.05.

6.2.2. (±)-Dimethyl (1*R, 8*S**, 12*S**, 13*S**)-1-methoxy-10-oxa-11-oxo-tricyclo[6.3.2.0^{8,12}]tridecane-12,13-dicarboxylate ((±)-5).** IR (KBr, cm^{-1}) $\tilde{\nu}$ 1742 (lactone C=O), 1715 (ester C=O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.22–1.36 (m, 2H, CH_2), 1.43–1.59 (m, 2H, CH_2), 1.62–1.73 (m, 2H, CH_2)1.78–1.89 (m, 3H, CH_2), 2.17 (ddd, ^{2}J=15.1 Hz, *J*=10.8, 1.2 Hz, 1H, 2-H_a), 2.34 (s, 1H, 13-H), 2.42 (m, 1H, 7-CH_2), 2.72 (ddd, ^{2}J=15.1 Hz, *J*=10.3, 1.3 Hz, 1H, 2-H_b), 3.40 (s, 3H, OCH_3), 3.73 (s, 3H, $COOCH_3$ at C-12), 3.79 (s, 3H, $COOCH_3$ at C-13), 4.29 (d, *J*=12.2 Hz, 1H, 9-H_a), 4.84 (d, *J*=12.2 Hz, 1H, 9-H_b); ^{13}C NMR ($CDCl_3$, ppm) δ 19.91 (t, CH_2), 22.69 (t, CH_2), 22.87 (t, CH_2), 23.90 (t, CH_2), 29.56 (s, C-8), 30.64 (t, CH_2), 33.04 (d, C13), 36.64 (s, C-12), 38.92 (t, CH_2), 52.08 (q, OCH_3), 52.48 (q, $COOCH_3$), 52.98 (q, $COOCH_3$), 68.99 (t, C-9), 80.52 (s, C-1), 167.24 (s, C-11), 168.29 (s, $COOCH_3$), 170.20 (s, $COOCH_3$); MS (CI, %) *m*/*z* 341 (2) [M^{+}+1], 309 (11) [M^{+}−OCH_3]; Anal calcd for $C_{17}H_{24}O_7$ (340.37), C 59.99, H 7.11; found C 59.82 H 7.10.

6.3. Reduction of (±)-5 with lithium aluminium hydride

Procedure. To **5** (1.00 g, 2.94 mmol) in 20 mL dry tetrahydrofuran (THF) was added a suspension of lithium aluminium hydride (570 mg, 14.8 mmol) in 50 mL THF. After heating under reflux for 6 h, the solution was cooled, diluted with diethyl ether and gradually mixed with 0.6 mL water, 0.6 mL 15% sodium hydroxide solution and finally with 1.8 mL water. The solution was stirred overnight and the insoluble material was filtered and washed with THF. The organic filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (diethyl ether/methanol) providing 375 mg (45%) of crystalline **10a** (mp 140°C) of the first fraction (R_f=0.35) and 140 mg (17%) of crystalline **11** (mp 173°C) of the second one (R_f=0.19).

The insoluble material was dried under reduced pressure and mixed under nitrogen with 2 mL dry pyridine and 2 mL dry acetic anhydride. After stirring overnight at room temp., the solution was diluted in 20 mL ice water, mixed with 2N hydrochloric acid and extracted four times with dichloromethane. The combined organic layers were washed with 2N hydrochloric acid and saturated sodium hydrogen carbonate solution and dried with sodium sulfate. The solvent was removed under reduced pressure and the residue was purified with diethyl ether by silica gel column chromatography providing 256 mg (24%) crystalline **10b** (mp 126–127°C, R_f=0.31).

6.3.1. (±)-(1*R, 2*S**, 9*R**, 10*R**)-2,9-Di-(hydroxymethyl)-2-methoxy-12-oxa-13-oxo-tricyclo[8.3.0^{1,9}.0^{1,10}]tridecane (10a).** IR (KBr, cm^{-1}) $\tilde{\nu}$ 3416 (OH), 1751 (C═O, lactone); ^{1}H NMR (pyridine-D$_5$, ppm): δ 1.10 (m,1H, 8-H$_a$), 1.15 (m, 1H, 4-CH$_2$), 1.53 (m, 2H, CH$_2$), 1.81 (m, 1H, CH$_2$), 1.99 (ddd, ^{2}J=14.1 Hz, J=11.9, 3.5 Hz, 1H, 3-H$_a$), 2.14 (m, 1H, CH$_2$), 2.63 (ddd, J=14.3, 4.5, 2.5 Hz, 1H, 8-H$_b$), 3.22 (ddd, ^{2}J=14.1 Hz, J=4.4, 3.6 Hz, 1H, 3H$_b$), 3.28 (dd, ^{3}J=5.1, 0.7 Hz, 1H, 10-H), 3.43 (s, 3H, OCH$_3$), 3.77 (d, ^{2}J=12.6 Hz, 1H, 2-CH$_2$OH), 3.90 (d, ^{3}J=12.6 Hz, 1H, 2-CH$_2$OH), 4.04 (dd, ^{2}J=10.3 Hz, J=1.5 Hz, 9-CH$_2$OH), 4.14 (dd, ^{2}J=9.7 Hz, ^{3}J=0.7 Hz, 1H, 11-H$_a$), 4.30 (dd, ^{2}J=9.7 Hz, ^{3}J=5.1 Hz, 1H, 11-H$_b$), 4.59 (d, ^{2}J=10.3 Hz, 1H, 9-CH$_2$OH), 6.39 (s, exchangeable, OH), 6.66 (s, exchangeable, OH); ^{13}C NMR (pyridine-D$_5$, ppm) δ 19.74 (t, C-3), 22.46 (t, CH$_2$), 23.12 (t, CH$_2$), 25.61 (t, C-8), 28.39 (t, C-2), 31.85 (t, CH$_2$), 32.94 (d, C-10), 33.47 (s, C-9), 42.25 (s, C-1), 50.13 (q, OCH$_3$), 63.08 (t, 2CH$_2$OH), 63.84 (t, C-11), 63.86 (t, 9-CH$_2$OH), 80.85 (s, C-2), 175.93 (s, C-13). MS (CI, %) *m*/*z* 253 (100) [M$^+$−OCH$_3$], 235 (8) [M$^+$−HOCH$_3$, –OH], 221 (68) [M$^+$−HOCH$_3$, –OCH$_3$].

6.3.2. (±)-(1*R, 2*S**, 9*R**, 10*R**)-2,9-Di-(acetoxymethyl)-2-methoxy-12-oxa-13-oxo-tricyclo[8.3.0^{1,9}.0^{1,10}]tridecane (10b).** IR (KBr, cm^{-1}) $\tilde{\nu}$ 1748 (C═O, lactone), 1740 (C═O, ester); ^{1}H NMR (CDCl$_3$, ppm) δ 0.80 (m, 1H, 4-CH$_2$), 0.98 (dddd, ^{2}J=14.6 Hz, J=13.0, 3.2 Hz, ^{4}J=1.9 Hz, 1H, 8-H$_a$), 1.37 (m, 1H, 7-CH$_2$), 1.44 (m, 1H, 5-CH$_2$), 1.57 (m, 1H, 5-CH$_2$), 1.68 (m, 2H 6-CH$_2$), 1.72 (m, 1H, 4-CH$_2$), 1.82 (ddd, ^{2}J=14.3 Hz, J=12.0, 3.4 Hz, 3-H$_a$), 1.90 (m, 1H, 7-CH$_2$), 2.00 (ddd, ^{2}J=14.6 Hz, J=4.5, 2.5 Hz, 8-H$_b$), 2.10 (s, 3H, 9-CH$_2$OOCC*H*$_3$), 2.14 (s, 3H, 2-CH$_2$OOCC*H*$_3$), 2.69 (d, ^{3}J=5.2 Hz, 1H, 10-H), 2.94 (ddd, ^{2}J=14.3 Hz, J=4.0, 4.0 Hz, 1H, 3-H$_b$), 3.25 (s, 3H, OCH$_3$), 3.83 (d, ^{2}J=12.9 Hz, 1H, 2-CH$_2$OAc), 3.95 (dd, ^{2}J=10.6 Hz, ^{4}J=1.9 Hz, 1H, 9-CH$_2$OAc), 4.12 (dd, ^{2}J=9.9 Hz, J=0.8 Hz, 1H, 11-H$_a$), 4.27 (d, ^{2}J=12,9 Hz, 1H, 2-CH$_2$OAc), 4.39 (dd, ^{2}J=9.9 Hz, ^{3}J=5.2 Hz, 1H, 11-H$_b$), 4.64 (d, ^{2}J=10.6 Hz, 1H, 9-CH$_2$OAc); ^{13}C NMR (CDCl$_3$, ppm) δ 19.66 (t, C-4), 20,93 (q, 9-OOC*C*H$_3$), 20.98 (q, 2-OOC*C*H$_3$), 21.90 (t, C6), 22.75 (t, C-7), 25.67 (t, C-8), 27.54 (t, C-3), 29.93 (s, C-9), 31.11 (t, C-5), 32.18 (d, C-10), 42.32 (s, C-1), 50.44 (q, OCH$_3$), 63.36 (t, C-11), 64.00 (t, 2-CH$_2$OAc), 65.13 (t, 9-CH$_2$OAc), 78.62 (s, C-1), 170.52 (s, 2-OO*C*CH$_3$), 170.73 (s, 9-OO*C*CH$_3$), 174.11 (s, C-13); MS (CI, %) *m*/*z* 337 (100) [M$^+$−OCH$_3$], 295 (16) [M$^+$−CH$_2$OOCCH$_3$], 277 (31) [M$^+$−CH$_3$COOH, –OCH$_3$]. Anal calcd for $C_{19}H_{28}O_7$ (368.43), C 61.94, H 7.66; found C 61.98, H 7.58.

6.3.3. (±)-(1*R, 2*R**, 9*S**, 10*S**)-1,2,9,10-Tetra-(hydroxymethyl)-2-methoxy-bicyclo[7.1.0]decane (11).** IR (KBr, cm^{-1}) $\tilde{\nu}$ 3424 (OH); ^{1}H NMR (pyridine-D$_5$, ppm) δ 1.02 ppm (m, 1H, CH$_2$), 1.19 (m, 1H, 5-H$_a$), 1.37 (ddd, ^{2}J=15.5 Hz, J=9.6, 1.8 Hz, 1H, 3-H$_a$), 1.53 (m, 1H, 8-H$_a$), 1.62–1.80 (m, 4H, CH$_2$), 1.86 (m, 1H, 5-H$_b$), 1.91 (ddd, ^{2}J=15.5 Hz, J=8.9, 1.9 Hz, 1H, 3-H$_b$), 2.39 (ddd, ^{3}J=8.8, 7.2 Hz, J=1.4 Hz, 1H, H-10), 2.58 (ddd, J=14.3, 3.6, 3.6 Hz, 1H, 8-H$_b$), 3.39 (s, 3H, OCH$_3$), 3.75 (dd, ^{2}J=11.8 Hz, J=3.7 Hz, 1H, 2-CH$_2$OH), 3.77 (dd, ^{2}J=10.4, 1.3 Hz, 1H, 9-CH$_2$OH), 3.84 (d, ^{2}J=11.8 Hz, 1H, 2-CH$_2$OH), 3.87 (dd, ^{2}J=11.9 Hz, ^{3}J=10.3 Hz, 1H, 1-CH$_2$OH), 4.22 (dd, ^{2}J=12.0 Hz, ^{3}J=8.8 Hz, 1H, 10-CH$_2$OH), 4.24 (dd, ^{2}J=12.0 Hz, ^{3}J=7.2 Hz, 1H, 10-CH$_2$OH), 4.36 (d, ^{2}J=10.4 Hz, 1H, 9-CH$_2$OH), 4.77 (d, ^{2}J=11.9 Hz, 1H, 1-CH$_2$OH), 4.87 (dd, exchangeable, ^{3}J=10.3 Hz, J=2.6 Hz, 1H, 1-CH$_2$OH), 5.06 (s, exchangeable, 1H, 10-CH$_2$OH), 5.58 (s, exchangeable, 1H, 2-CH$_2$OH), 5.89 (s, exchangeable, 1H, 9-CH$_2$OH); ^{13}C NMR (pyridine-D$_5$, ppm) δ 21.24 (t, C-4), 24.57 (t,C-8), 24.89 (t, C-6*), 25.47 (t, C-7*), 31.93 (t, C-5*), 32.27 (t, C-3), 33.30 (s, C-9), 34.69 (d, C-10), 39.48 (s, C-1), 49.15 (q, OCH$_3$), 60.12 (t, 10-CH$_2$OH), 62.95 (t, 2-CH$_2$OH), 64.43 (t, 1-CH$_2$OH), 65.24 (t, 9-CH$_2$OH), 83.13 (s, C-2); MS (CI, %) *m*/*z* 257 (7) [M$^+$−OCH$_3$], 239 (51) [M$^+$−HOCH$_3$, –OH], 221 (100) [M$^+$−HOCH$_3$, –H$_2$O, –OH]. $C_{15}H_{28}O_5$ (288.38).

6.4. Treatment of 4 with boron trifluoride etherate

Procedure. Lactone **4** (400 mg, 1.18 mmol) was dissolved in dichloromethane in a dry apparatus. Dry powdered potassium carbonate and boron trifluoride etherate 6.0 mL (48 mmol) were added to the solution. After heating under reflux for 16 h (GC control), the solution was cooled to room temperature and the reaction was quenched by addition of saturated sodium hydrogen carbonate solution. The layers were separated and the water layer was extracted three times with 20 mL dichloromethane. The combined organic layers were dried with sodium sulfate and the solvent was removed under reduced pressure. The residue was purified with acetone/dichloromethane/*n*-pentane (1:2:9) by silica gel column chromatography providing 248 mg (69%) crystalline **12** (mp 140°C, R_f=0.28).

6.4.1. (±)-Methyl (1*R, 2*R**, 9*S**, 10*S**, 11*R**)-2-methoxy-13,14-dioxa-12-oxo-tetracyclo[7.4.2.0^{2,10}.0^{9,11}]pentadec-4-ene-10-carboxylate (12).** IR (KBr, cm^{-1}) $\tilde{\nu}$ 1735 (lactone C═O), 1708 (ester C═O); ^{1}H NMR (CDCl$_3$, ppm) δ 1.60–1.90 (m, 4H, CH$_2$), 2.04 (m, 2H, CH$_2$), 2.45 (m,1H, allylic-H), 2.79 (s, 1H, 11-H), 3.33 (s, 3H, 2-OCH$_3$), 3.85 (s, 3H, 10-COOCH$_3$), 3.85 (m, 1H, allylic-H), 3.95 (d, ^{2}J=11.0 Hz, 1H at C-15), 4.04 (dd, ^{2}J=11.0 Hz, ^{4}J=0.4 Hz, 1H at C15), 5.40 (s, 1H, 1-H), 5.51–5.61 (m, 2H, 4-H and 5-H); ^{13}C NMR (CDCl$_3$, ppm) δ 23.83 (t, CH$_2$), 24.22 (t, CH$_2$), 25.84 (t, CH$_2$), 28.27 (t, CH$_2$), 32.68 (d, C-11), 36.81 (s, C-9), 38.85 (s, C-10), 50.52 (q, 10-COOC*H*$_3$), 52.76 (q, 2-OCH$_3$), 63.82 (t, C-15), 70.16 (s, C-2), 98.09 (d, C-1), 122.90 (d, C-5), 133.16 (d, C-4), 167.96 (s, C-12), 168.47 (s, 10-*C*OOCH$_3$); MS (CI, %) *m*/*z* 309 (100) [M+H]$^+$, 279 (41) [M−CH$_3$O]$^+$.

6.5. Reduction of 12

Procedure. To a suspension of lithium aluminium hydride

(250 mg, 6.58 mmol) in 20 mL dry THF was added **12** (258 mg, 0.84 mmol) in THF. The mixture was heated under reflux for 40 h and then cooled with ice. The solution was gradually mixed with 0.3 mL water, 0.3 mL 15% sodium hydroxide solution and 0.9 mL water and stirred for 3 h under warming up to room temperature. The solvents were completely removed under reduced pressure and the dry residue was mixed with 2 mL dry pyridine and acetic anhydride. The solution was stirred overnight at room temperature, mixed with ice water and 2N hydrochloric acid and was four times extracted with 20 mL dichloromethane. The combined organic layers were washed with 2N hydrochloric acid, saturated sodium hydrogen carbonate solution and dried with sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (acetone/dichloromethane/*n*-pentane, 1:2:9) providing 245 mg (64%, R_f=0.17) **13** as a colourless oil.

6.5.1. (±)-(1*R,2*R**,9*S**,10*R**)-1,2,9,10-Tetra(acetoxymethyl)-2-methoxy-bicyclo[7.1.0]dec-4-ene ((±)-13).** IR (KBr, cm^{-1}) $\tilde{\nu}$ 1741 (C=O); ^{1}H NMR ($CDCl_3$, ppm): δ 1.28–1.44 (m, 3H, CH_2, therein at δ 1.38 (dd, ^3J=8.2, 7.7 Hz, 1H at C-10)), 1.58–1.82 (m, 3H, CH_2), 2.05 (s, 3H, CH_3COO), 2.06 (s, 3H, CH_3COO), 2.14 (s, 3H, CH_3COO), 2.18 (s, 3H, CH_3COO), 2.16 (m, 1H, 8-H), 2.24 (dd, *J*=14.1, 7.5 Hz, 1H, 3-H_a), 2.65 (m, 1H, 3-H_b), 3.36 (s, 3H, OCH_3), 3.57 (dd, ^2J=12.2 Hz, *J*=2.2 Hz, 1H, 9-CH_2OAc), 4.02 (dd, ^2J=12.2 Hz, ^3J=8.2 Hz, 1H, 10-CH_2OAc), 4.08 (d, ^2J=11.5 Hz, 1H, 2-CH_2OAc), 4.25 (dd, ^2J=11.5 Hz, *J*=1.9 Hz, 1H, 2-CH_2OAc), 4.37 (d, ^2J=12.2 Hz, 1H, 1-CH_2OAc), 4.56 (dd, ^2J=12.2 Hz, ^3J=7.7 Hz, 1H, 10-CH_2OAc), 4.66 (d, ^2J=12.2 Hz, 1H, 9-CH_2OAc), 4.84 (d, ^2J=12.2 Hz, 1H, 1-CH_2OAc), 5.33 (ddd, *J*=10.0, 10.0, 7.5 Hz, 1H, 5-H), 5.68 (dtd, *J*=11.1, 11.1, 5.5 Hz, 1H, 4-H); ^{13}C NMR ($CDCl_3$, ppm): δ 20.89 (q, OOC*C*H_3), 20.92 (q, OOC*C*H_3), 20.92 (q, OOC*C*H_3), 20.98 (q, OOC*C*H_3), 24.61 (t, CH_2), 28.33 (t, C-8), 29.61 (s,C-9), 29.65 (d, C-10), 33.22 (t, C-3), 35.69 (s, C-1), 51.36 (q, OCH_3), 60.81 (t, 2-CH_2OAc), 62.70 (t, 10-CH_2OAc), 63.84 (t, 9-CH_2OAc), 66.42 (t, 1-CH_2OAc), 81.22 (s, C-2), 121.99 (d, C-5), 137.72 (d, C-4), 170.52 (s, 10-OO*C*CH_3), 170.52 (s, 2-OO*C*CH_3), 170.65 (s, 9-OO*C*CH_3), 170.84 (s, 1-OO*C*CH_3); MS (CI, %): *m*/*z* 423 (31) [M^+−OCH_3], 395 (5) [M^+−CH_3COO], 363 (17) [M^+−CH_3COO, −OCH_3], 335 (8) [M^+−CH_3COOH, −CH_3COO]; $C_{23}H_{34}O_9$ (454.52).

6.6. Experiments with deuterated compounds: (a) treatment of (±)-3 with deuterated sodium methoxide followed by hydrolysis

Procedure. Sodium (60 mg, 2.6 mmol) was dissolved in [D_4]methanol. Then (±)-**3** (230 mg, 0.75 mmol) was added and the solution was refluxed under stirring for 1 h. After cooling 5 mL water were added and the mixture was extracted four times with 20 mL dichloromethane. The combined organic layers were washed with brine and dried with sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with acetone/dichloromethane/*n*-pentane (1:2:9), providing 72 mg (28%) of crystalline [D_m]**4** (R_f=0.25) and 83 mg (33%) of crystalline [D_m]**5**.

6.6.1. (±)-Methyl (1*R,2*R**,9*S**,10*S**,11*S**,15*R**)-2,15-di(trisdeuteromethoxy)-2,11-dideutero-13,14-dioxa-12-oxo-tetracyclo[7.4.2.0^{2,10}.0^{9,11}]pentadecane-10-carboxylate ([D_m]4).** ^{1}H NMR ($CDCl_3$, ppm) δ 1.40–2.10 (m, 11H, CH_2), 2.67 (m, 0.2H*, 3-H_a), 3.78 (s, 0.9H*, $COOCH_3$), 5.10 (d, *J*=0.8 Hz, 1H, 15-H), 5.34 (s, 1H, 1-H) (* The signals of 3-H_a and of the ester methoxy group were decreased by 80 and 70%. The signals of11-H and of both ether methoxy groups were not detected.)

6.6.2. (1*S,8*R**,12*R**,13*R**)-[D_3]Dimethyl 1-trideuteromethoxy-2-deutero-11-oxo-10-oxatricyclo[6.3.2.0^{8,12}]tridecane-12,13-dicarboxylate ([D_m]5).** ^{1}H NMR ($CDCl_3$, ppm) δ 1.22–1.36 (m, 2H, CH_2), 1.43–1.59 (m, 2H, CH_2), 1.62–1.73 (m, 2H, CH_2), 1.78–1.89 (m, 3H, CH_2), 2.17 (m, 1H, 2-H_a), 2.34 (s, 0.3H*, 13-H), 2.42 (m, 1H, 7-CH_2), 2.72 (m, 0.3H*, 2-H_b), 3.79 (s, 0.9H*, $COOCH_3$ at C-13), 4.29 (d, *J*=12.2 Hz, 1H, 9-H_a), 4.84 (d, *J*=12.2 Hz, 1H, 9-H_b). (* The signals of 13-H, 2-H_b and one of the two ester methoxy groups were decreased by 70% each. The signals of the second ester methoxy group and of the ether methoxy group were not detected.)

6.7. (b) Treatment of (±)-3 with sodium methoxide/methanol followed by deuterolysis

Procedure. To a solution of (±)-**3** (230 mg, 0.75 mmol) in 5 mL dry methanol was added sodium methoxide (135 mg, 2.50 mmol). After heating at reflux for 1 h, the cooled solution was mixed with 5 mL deuterium oxide and extracted four times with 20 mL dichloromethane. The combined organic layers were washed with brine and dried with sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with acetone/dichloromethane/*n*-pentane (1:2:9), providing 68 mg (27%) of (±)-**4** and 75 mg (29%) of [D_n]**5**.

6.7.1. (±)-Methyl (1*R,2*R**,9*S**,10*S**,11*R**,15*R**)-2,15-dimethoxy-13,14-dioxa-12-oxo-tetracyclo[7.4.2.0^{2,10}.0^{9,11}]-pentadecane-10-carboxylate (±)-(4).** ^{1}H NMR ($CDCl_3$, ppm) δ 1.40–2.10 (m, 11H, CH_2), 2.67 (m, 1H, 3-H_b), 2.84 (d, *J*=0.8 Hz, 1H, 11-H), 3.28 (s, 3H, OCH_3 at C-2), 3.48 (s, 3H, OCH_3 at C-15), 3.78 (s, 3H, $COOCH_3$), 5.10 (d, *J*=0.8 Hz, 1H, 15-H), 5.34 (s, 1H, 1-H).

6.7.2. (±)-Dimethyl (1*R,8*S**,12*S**,13*S**)-13-deutero-1-methoxy-10-oxa-11-oxo-tricyclo[6.3.2.0^{8,12}]tridecane-12,13-dicarboxylate ((±)-[D_n]5).** ^{1}H NMR ($CDCl_3$, ppm) δ 1.22–1.36 (m, 2H, CH_2), 1.43–1.59 (m, 2H, CH_2), 1.62–1.73 (m, 2H, CH_2), 1.78–1.89 (m, 3H, CH_2), 2.17 (m, 1H, 2-H_a),(*), 2.42 (m, 1H, 7-CH_2), 2.72 (m, 1H, 2-H_b), 3.40 (s, 3H, OCH_3), 3.73 (s, 3H, $COOCH_3$ at C-12), 3.79 (s, 3H, $COOCH_3$ at C-13), 4.29 (d, *J*=12.2 Hz, 1H, 9-H_a), 4.84 (d, *J*=12.2 Hz, 1H, 9-H_b). (* The signal of 13-H was not detected.)

6.8. Optically active compounds

Procedure. To a solution of (+)-**2b**[4] (2.01 g, 2.63 mmol) in 40 mL methanol was added a solution of 450 mg sodium hydroxide in 40 mL water. After heating under reflux, the cooled solution was diluted in water and extracted four times with 20 mL diethyl ether. The combined organic layers were washed with water and dried with sodium sulfate. 1.28 g (94%) of 1,2;5,6-diisopropylidene-α-D-glucofuranose could be recycled.

The alkaline layer was mixed with 2N hydrochloric acid (pH=2) and extracted three times with 20 mL diethyl ether. The combined organic layers were washed with water until no acid could be detected anymore (pH control). After drying with sodium sulfate the solvent was removed under reduced pressure until 10 mL solvent were left. This residue was treated with a solution of diazomethane in diethyl ether and was stirred for 30 min. at room temp. An excess of diazomethane was destroyed by silica gel. The solution was filtered and the solvent was completely removed under reduced pressure. 558 mg (69%) of (+)-**2a** were obtained as colourless crystals from diethyl ether/*n*-pentane (mp 136–137°C).

The enantiomeric excess was determined by ^{1}H NMR shift experiments using (+)-Pr(hfc)$_3$ and was found to be ≥95% ee.

6.8.1. (+)-Dimethyl (1a*S*,6a*S*)-1a,6a-dihydro-4,6a-hexano-oxireno[b]oxepine-5,6-dicarboxylate ((+)-2a). IR (KBr, cm^{-1}) $\tilde{\nu}$ 1731, 1716 (C=O, ester); UV (acetonitrile) $\lambda_{\max}$ (log ϵ) 203 nm (4.02), 278 (3.60); CD (acetonitrile) $\lambda_{\max}$ ($\Delta\epsilon$) 206 nm (+0.51), 239 (−0.20), 284 (+1.14); ^{1}H NMR (CDCl$_3$, ppm) δ 0.95–1.10 (m, 1H), 1.30–1.96 (m, 8H), 2.09 (ddd, 1H, 12-H$_\beta$, ^2J=13.8 Hz, ^3J=11.8, 2.3 Hz), 2.38 (ddd, 1H, 7-H$_\alpha$, ^2J=14.2 Hz, ^3J=6.0, 2.2 Hz), 2.50 (ddd, 1H, 12-H$_\alpha$, ^2J=13.8 Hz, ^3J=4.4, 2.2 Hz), 3.83 (s, 3H, COOCH$_3$), 3.85 (s, 3H, COOCH$_3$), 5.09 (s, 1H, 1a-H), 6.79 (d, 1H, 3-H, ^4J=1.9 Hz); shift experiment using Pr(hfc)$_3$: ^{1}H NMR (CDCl$_3$, ppm, selected signals) (±)-**2a**: δ 6.35 and 6.55 (d, 1H each, 3-H), 4.55 and 4.65 (s, 1H each, 1a-H), (+)-**2a**: δ 6.40 (d, 1H, 3-H), 4.45 (s, 1H, 1a-H); ^{13}C NMR (CDCl$_3$, ppm) δ 21.57 (t, C-8)**, 22.68 (t, C-11)**. 25.22 (t, C-10)*, 27.92 (t, C-9)*, 29.76 (t, C-12), 31.14 (t, C-7), 52.52 and 52.65 (2q, 2 COOCH$_3$), 62.70 (s, C-6a), 93.30 (d, C-1a), 129.50 (s, C-4), 130.17 (s, C-6), 139.77 (s, C-5), 144.53 (d, C-3), 164.61 and 164.93 (2s, 2 *C*OOCH$_3$); MS (CI, %) *m/z* 309 (M$^+$+1, 100), 291 (M$^+$+1−H$_2$O, 60), 277 (M$^+$+1−CH$_4$O, 62); $[\alpha]_D^{20}=+246$, $[\alpha]_{578}^{20}=+260$, $[\alpha]_{546}^{20}=+308$, $[\alpha]_{436}^{20}=+674$, $[\alpha]_{365}^{20}=+1618$ (*c*=1.0, CH$_2$Cl$_2$). Anal calcd for C$_{16}$H$_{20}$O$_6$ (308.31), C 62.33, H 6.54; found, C 62.29, H 6.42.

6.9. Irradiation of (+)-2a

Procedure. (+)-**2a** (2.14 g, 6.95 mmol) was dissolved in 1 L diethyl ether and irradiated under nitrogen for 3 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (diethyl ether/*n*-pentane, 2:1), providing 1.58 g (74%) of crystalline (+)-**3** of mp 85°C.

The enantiomeric excess was determined by ^{1}H NMR shift experiments using (+)-Eu(hfc)$_3$ and was found to be ≥95% ee.

6.9.1. (+)-Dimethyl (1*S*,9*S*,11*S*,13*S*)-10,12-dioxa-tetracyclo[6.4.2.0^{1,11}.0^{9,13}]tetradec-8(14)-ene-dicarboxylate ((+)-3). IR (KBr, cm^{-1}) $\tilde{\nu}$ 1730, 1709 (C=O), 1630 (C=C); UV (acetonitrile) λmax (log ϵ) 229 nm (3.40); ^{1}H NMR (CDCl$_3$, ppm) δ 1.18–1.93 (m, 9H), 2.33 (ddd, 1H, 7-H$_\beta$, ^2J=14.2 Hz, ^3J=10.2, 5.8 Hz), 2.49 (ddd, 1H, 2-H$_\alpha$, ^2J=14.4 Hz, ^3J=6.5, 4.2 Hz), 2.78 (dddd, 1H, 7-H$_\alpha$, ^2J=14.3 Hz, ^3J=5.3, 4.4 Hz, ^4J=0.8 Hz), 3.81 (s, 6H, COOCH$_3$), 4.84 (dd, 1H, 9-H, ^4J=1.2, 0.7 Hz), 5.05 (d, 1H, 11-H, ^4J=1.3 Hz); shift experiment using Eu(hfc)$_3$: ^{1}H NMR (CDCl$_3$, ppm, selected signals) (±)-**3**: δ 6.20 and 6.35 (s, 1H each, 9-H), 6.60 and 6.80 (s, 1H each, 11-H), (+)-**3**: δ 5.30 (s, 1H, 9-H), 5.55 (s, 1H, 11-H); ^{13}C NMR (CDCl$_3$, ppm) δ 24.33 (t, CH$_2$), 26.31 (t, CH$_2$), 26.38 (t, CH$_2$), 27.65 (t, CH$_2$), 29.04 (t, C-2), 30.89 (t, C-7), 51.87 (q, COO*C*H$_3$), 52.22 (q, COO*C*H$_3$), 61.59 (s, C-13), 67.70 (s, C-1), 85.16 (d, C-9), 89.94 (d, C-11), 131.33 (s, C-14), 162.05 (s, *C*OOCH$_3$), 168.70 (s, C-8), 168.76 (s, *C*OOCH$_3$); MS (CI, %) *m/z* 309 (M$^+$+1, 100), 277 (M$^+$−CH$_3$O, 45); $[\alpha]_D^{20}=+109$, $[\alpha]_{578}^{20}=+115$, $[\alpha]_{546}^{20}=+135$, $[\alpha]_{436}^{20}=+268$, $[\alpha]_{365}^{20}=+532$ (*c*=0.5, CH$_2$Cl$_2$). Anal calcd for C$_{16}$H$_{20}$O$_6$ (308.31), C 62.33, H 6.54; found, C 62.37, H 6.53.

6.10. Synthesis of (−)-4 and (+)-5

Procedure. See the synthesis of (±)-**4** and (±)-**5**. Scale (+)-**3** (1.58 g, 5.13 mmol), sodium methoxide (790 mg, 14.60 mmol), 75 mL dry methanol. Yields: 681 mg (39%) of crystalline (−)-**4** with mp 238°C (R_f=0.25) and 700 mg (40%) (+)-**5** with mp 142°C (R_f=0.15).

6.10.1. (−)-Methyl (1*S*,2*S*,9*R*,10*R*,11*S*,15*S*)-2,15-dimethoxy-13,14-dioxa-12-oxo-tetracyclo[7.4.2.0^{2,10}.0^{9,11}]pentadecane-10-carboxylate ((−)-4). The spectroscopic data are identical with those of (±)-**4**. $[\alpha]_D^{20}=-44$, $[\alpha]_{578}^{20}=-46$, $[\alpha]_{546}^{20}=-52$, $[\alpha]_{436}^{20}=-82$, $[\alpha]_{365}^{20}=-112$ (*c*=1.0, CH$_2$Cl$_2$). Anal calcd for C$_{17}$H$_{24}$O$_7$ (340.37) C 59.99, H 7.11; found, C 60.04, H 7.09.

6.10.2. (+)-Dimethyl (1*S*,8*R*,12*R*,13*R*)-1-methoxy-10-oxa-11-oxotricyclo[6.3.2.0^{8,12}]tridecane-12,13-dicarboxylate ((+)-5). The spectroscopic data are identical with those of (±)-**5**. $[\alpha]_D^{20}=+18$, $[\alpha]_{578}^{20}=+19$, $[\alpha]_{546}^{20}=+21$, $[\alpha]_{436}^{20}=+40$, $[\alpha]_{365}^{20}=+72$ (*c*=1.0, CH$_2$Cl$_2$). Anal calcd for C$_{17}$H$_{24}$O$_7$ (340.37) C 59.99, H 7.11; found, C 60.00, H 7.07.

6.11. Reduction of (+)-5

Procedure. See the synthesis of (±)-**10a**. Scale (+)-**5** (200 mg, 0.59 mmol), lithium aluminium hydride (120 mg, 3.12 mmol), 5 mL dry THF. Yield: 95 mg (57%) of crystalline (+)-**10a** with mp 78°C (R_f=0.25).

6.11.1. (+)-(1*R*,2*S*,9*R*,10*R*)-2,9-Di-(hydroxymethyl)-2-methoxy-12-oxa-13-oxo-tricyclo[8.3.0^{1,9}.0^{1,10}]tridecane (+)-10a. The spectroscopic data are identical with those of (±)-**10a**. $[\alpha]_D^{20}=+34$, $[\alpha]_{578}^{20}=+36$, $[\alpha]_{546}^{20}=+41$, $[\alpha]_{436}^{20}=+70$, $[\alpha]_{365}^{20}=+106$ (*c*=1.0, CH$_3$OH).

6.12. Synthesis of (−)-10b

Procedure. (+)-**5** (245 mg, 0.72 mmol) was dissolved in 5 mL dry THF and added to a suspension of lithium aluminium hydride (160 mg, 4.17 mmol) in 15 mL THF. After heating under reflux for 3 h, the solution was cooled, diluted with diethyl ether and was gradually mixed with 0.2 mL water, 0.2 mL 15% sodium hydroxide solution and finally with 0.6 mL water. The solution was stirred overnight and the solvent was removed under reduced pressure. The solid residue was mixed with 4 mL dry pyridine and 4 mL acetic anhydride and stirred overnight at room temp.

The solution was mixed with 40 mL ice water, acidified with 2N hydrochloric acid and four times extracted with 40 mL dichloromethane each. The combined organic layers were washed with saturated sodium hydrogen carbonate solution and dried with sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography providing 120 mg (45%) crystalline (−)-**10b** (mp 211°C, R_f=0.25).

6.12.1. (1*R*,2*S*,9*R*,10*R*)-2,9-Di-(acetoxymethyl)-2-methoxy-12-oxa-13-oxo-tricyclo[8.3.0^{1,9}.0^{1,10}] tridecane (−)-10b. The spectroscopic data are identical with those of (±)-**10b**. $[\alpha]_D^{20}=-39$, $[\alpha]_{578}^{20}=-40$, $[\alpha]_{546}^{20}=-46$, $[\alpha]_{436}^{20}=-70$, $[\alpha]_{365}^{20}=-91$ (c=1.0, CH_2Cl_2); Anal calcd for $C_{19}H_{28}O_7$ (368.43) C 61.94, H 7.66; found C 61.98, H 7.63.

6.13. Synthesis of (+)-12

Procedure. See the synthesis of (±)-**12**. Scale (−)-**4** (109 mg, 0.35 mmol), 20 mL dry dichloromethane, boron trifluoride etherate (5.0 mL, 40 mmol). Yield: 66 mg (67%) crystalline (+)-**12** (mp 168°C, R_f=0.28).

6.13.1. (+)-Methyl (1*S*,2*S*,9*R*,10*R*,11*S*)-2-methoxy-13,14-dioxa-12-oxo-tetracyclo[7.4.2.0^{2,10}.0^{9,11}] pentadec-4-ene-10-carboxylate ((+)-12). IR (KBr, cm^{-1}) $\tilde{\nu}$ 1739 (lactone C=O), 1720 (ester C=O); ^1H NMR ($CDCl_3$, ppm) δ 1.6–1.9 ppm (m, 4H, CH_2), 2.04 (m, 2H, CH_2), 2.46 (m, 1H, allylic-H), 2.79 (s, 1H, 11-H), 3.33 (s, 1H, OCH_3), 3.85 (s, 3H, $COOCH_3$), 3.85 (m, 1H, allylic-H), 3.95 (d, ^2J=11.0 Hz, 1H, 15-H_a), 4.04 (dd, ^2J=11.0 Hz, J=0.8 Hz, 1H, 15-H_b), 5.40 (s, 1H, 1-H), 5.45–5.53 (m, 2H, 4-H and 5-H); ^{13}C NMR ($CDCl_3$, ppm): δ 23,74 (t, CH_2), 24.16 (t, CH_2), 25.70 (t, CH_2), 28.00 (t, CH_2), 32.53 (d, C-11), 36.82 (s, C-9), 38.78 (s, C-10), 50.50 (q, $COOCH_3$), 52.89 (q, OCH_3), 63.76 (t, C-15), 70.06 (s, C-2), 97.90 (d, C-1), 122.78 (d, C-5), 133.21 (d, C-4), 168.19 (s, C-12), 168.76 (s, $COOCH_3$); MS (CI, %) m/z 309 (100) $[M^++1]$, 277 (29) $[M^+OCH_3]$, 249 (11) $[M^+COOCH_3]$; $[\alpha]_D^{20}=+60$, $[\alpha]_{578}^{20}=+63$, $[\alpha]_{546}^{20}=+72$, $[\alpha]_{436}^{20}=+129$, $[\alpha]_{365}^{20}=+219$ (c=1.0, CH_2Cl_2). Anal calcd for $C_{16}H_{20}O_6$ (308.33) C 62.33, H 6.54; found C 62.35, H 6.47.

6.14. X-Ray structural analyses of 4, 5 and 12[10]

The data of all crystals were obtained with a Bruker AXS P4 diffractometer (Mo K_α radiation, graphite monochromator). The reflections were observed $[F_0>3\sigma(F)]$ in the θ range 1.75–27.5°, measured with ω-scan technique. The structures were solved by using direct-phase determination and refined on F by using SHELXTL-PLUS. Positional parameters, anisotropic displacement parameters for all atoms except for hydrogen atoms, groupwise isotropic displacement parameters for all hydrogen atoms, treated as rigid groups. For R_w the weighting scheme $w=1/\sigma^2(F)$ was established.

6.14.1. 4 (Dichloromethane). Crystal dimension: 0.45×0.55×0.20 mm^3; cell dimension: a=748.57 (7), b=822.67 (5), c=1325.67 (7) pm, β=93.983 (7)°; monoclinic, space group $P2_1$; Z=2, ρ_{calcd}=1.388 g cm^{-3}, 3624 observed reflections, R=0.042, R_w=0.043.

6.14.2. 5 (Dichloromethane). Crystal dimension: 0.40×0.45×0.65 mm^3; cell dimension: a=821.8 (1), b=837.1 (2), c=1291.1 (2) pm, α=88.46 (1)°, β=76.377 (5)°, γ=77.17 (1)°; triclinic, space group $P\bar{1}$; Z=2, ρ_{calcd}=1.343 g cm^{-3}, 3410 observed reflections, R=0.052, R_w=0.056.

6.14.3. 12 (Dichloromethane). Crystal dimension: 0.45×0.65×0.20 mm^3, cell dimension: a=753.2 (1), b=1353.1 (2), c=1430.2 (2) pm, β=92.65 (1)°, monoclinic, space group $P2_1/c$; Z=4, ρ_{calcd}=1.407 g cm^{-3}, 2416 observed reflections, R=0.057, R_w=0.053.

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10. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 151645 for **4**, no. CCDC 151644 for **5** and no. CCDC 151643 for **12**. Copies of the data can be obtained free of charge, on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom.