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Total Synthesis of C_{19}-Diterpene Alkaloids: Construction of a Functionalized ABCD-Ring System

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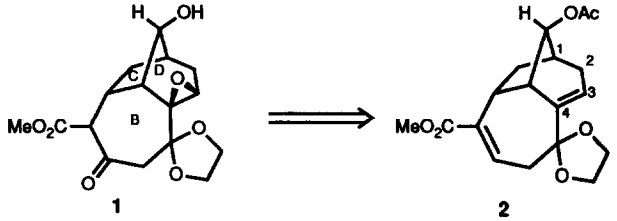
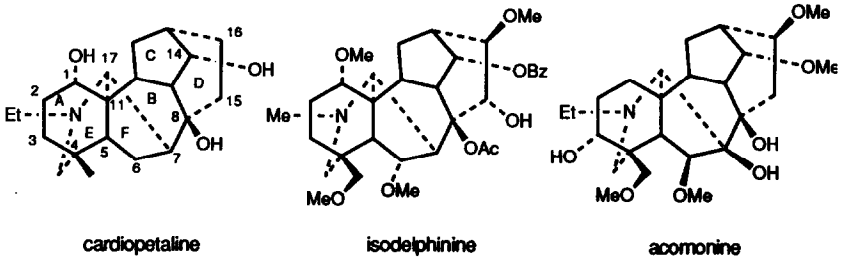
Abstract: *Starting from tricyclic intermediate* **2** *representing the BCD-skeleton of diterpene alkaloids, the functionalization of ring D and the stereospecific construction of ring A resulting in the formation of an ABCD ring system* (**14**) *of acomonine type diterpene alkaloids is described.*

Recently, we reported the synthesis of β-ketoester **1** as a general synthetic intermediate for the BCD-ring system of relatively simple C_{19}-diterpene alkaloids such as cardiopetaline (Scheme 1).[1]



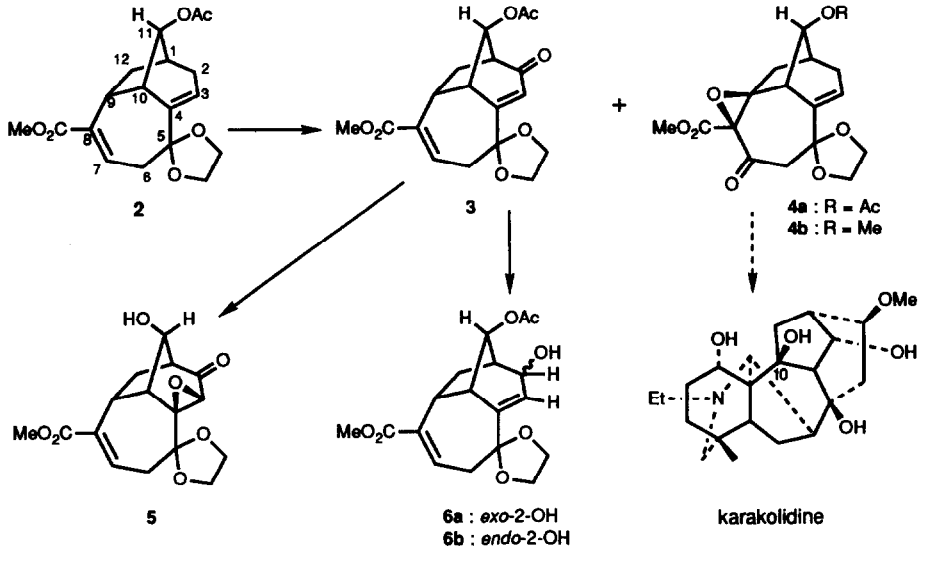


Scheme 1

1 has a full potential of functional groups for further elaboration into (suitably substituted) A-, E-, and F-rings, but lacks the possibility of easy introduction of a hydroxy or methoxy group which is present at C-16 in the majority of C_{19}-diterpene alkaloids.[2] However, in intermediate **2**, the tricyclic precursor of **1**, C-2 (corresponding to C-16 in diterpenoid alkaloids) is an allylic carbon and can, therefore, in principle be oxidized and subsequently (stereospecifically) reduced to a hydroxyl group in order to provide, *via* epoxidation of the double bond, the fully functionalized CD-ring system such as present in isodelphinine or acomonine (Scheme 1). Furthermore, transformation of the α,β-unsaturated ester group of ring B in **2** to a β-ketoester function[1] would give ample opportunity to attach ring A [with an oxygen substituent at either C-1 or C-3 (diterpene alkaloid numbering)] so that the ester carbonyl group could function as a future juncture of the E- and F-ring.
In this paper we report the further functionalization of ring D of **2** and the stereospecific construction of ring A with an oxygen function at C-3 resulting in the formation of tetracyclic intermediate **14** for the total synthesis of diterpene alkaloids of the acomonine type.

RESULTS AND DISCUSSION

The allylic oxidation of alkenes to α,β-unsaturated ketones can, in principle, be effected by a range of different reagents such as selenium dioxide/*tert*-butyl hydroperoxide,[3] *N*-bromosuccinimide/dioxane-water/hν,[4] chromium trioxide/pyridine,[5] chromium trioxide/dimethylpyrazole[6] and, more recently, *tert*-butyl hydroperoxide/chromium hexacarbonyl.[7] However, in the case of **2**, only oxidation with chromium trioxide complexes gave reasonable yields (50-60%) of ketone **3** (Scheme 2).



Scheme 2

Besides, a small amount of a byproduct was found (2% if dimethylpyrazole was used as a ligand, 15% with pyridine) which, on the basis of ^{1}H- and ^{13}C-spectroscopy, was tentatively identified as compound **4a**. This structure was confirmed by X-ray crystal structure determination[8] of the analogue **4b**, obtained in a similar fashion from the C-11–methoxy analogue of **2** (PLUTON drawing portrayed in Fig. 1).

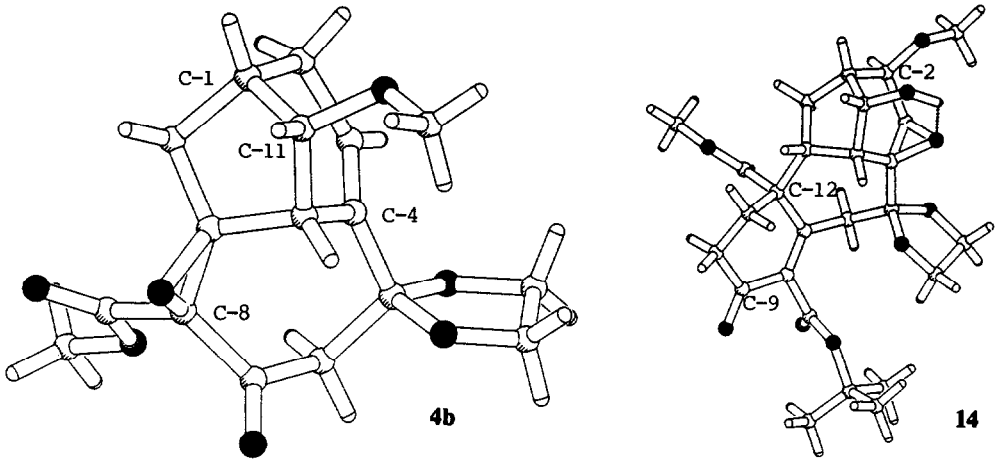


Figure 1. X-ray structures of **4b** and **14**

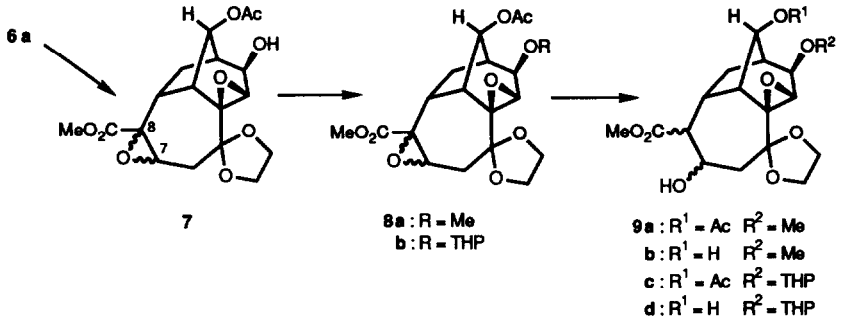
Although the formation of epoxides during the oxidation of alkenes with Cr(VI) is not uncommon,[9] the pathway of the peculiar reaction leading to β-ketoester epoxide **4** is not obvious. However, if the yield of **4** can be increased, this oxidation reaction can in principle be exploited to give synthetic access to diterpene alkaloids with an oxygen function at C-10, *e.g.* karakolidine (Scheme 2).

Introduction of an epoxy-group at C-3–C-4 of **3** was accomplished by basic epoxidation (hydrogen peroxide/potassium carbonate/60 °C). This reaction proceeded, however, with concomitant hydrolysis of the acetoxy group at C-11 and epimerization of the resulting hydroxyl group [probably by (retro)aldol reaction], to give the unwanted *exo*-isomer **5** (Scheme 2). Molecular models of **5** show that the dihedral angle between H-11 and H-1 as well as between H-11 and H-10 is *ca.* 90° so that only very small coupling constants are expected for these protons. This is in agreement with the presence of a broadened singlet at δ = 4.56 ppm which is assigned to H-11-*endo*. In all other compounds described in this paper, H-11 is *exo* and, as a consequence of dihedral angles of 30–40° relative to H-1 and H-10 , appears as a double doublet with proton coupling constants of *ca.* 4 Hz. When the reaction was performed at room temperature the acetoxy group of **3** was cleanly hydrolyzed without isomerization, but then the epoxidation reaction did not occur.

To circumvent this complication, ketone **3** was reduced with sodium borohydride/methanol at 0 °C (the reduction fails in isopropanol) to give a 3:1 mixture of the desired *exo*-alcohol **6a** and its *endo*-isomer **6b**, separable by column chromatography. The *endo*-isomer was recycled to ketone **3** by oxidation with $Py_4Ag_2Cr_2O_7$.[10] The *exo*-position of the OH-group of the major isomer **6a** was indicated by comparison of the ^{1}H-NMR spectra of the individual isomers in conjunction with molecular models which predict a larger dihedral angle between H-3 and H-2 (*exo*) in the *endo*-alcohol **6b** than between H-3 and H-2 (*endo*) in the *exo*-alcohol **6a**. The coupling constant ^3J(H-2,H-3) in the minor isomer is indeed smaller (1.9 Hz) than in the major isomer (4.5 Hz). The latter, therefore, has a smaller dihedral angle and thus is the *exo*-alcohol **6a**. This conclusion was confirmed by the crystal structure determination of the final product **14** derived from **6a** (*vide infra*).

Epoxidation of **6a** was effected with trifluoroperacetic acid and dipotassium hydrogen phosphate as a solid buffer[11] (Scheme 3). Diepoxide **7** was obtained quantitatively as a colourless amorphous solid which could not be crystallized. On the basis of ^{1}H-NMR (single peaks of the methyl groups of the methyl ester and of the acetoxy group) and of TLC (single spot) it was concluded, initially, that **7** was a single isomer. However,

methylation of **7** to **8a** (methyl iodide/silver oxide/calcium sulfate),[12] gave a mixture of two isomeric compounds (ratio 2:1) of which the major one was obtained in pure crystalline form and identified as the expected diepoxide with unknown but specific geometry (α or β) of the glycidic ester epoxide group at C-7–C-8; the minor compound was its epimer at these centers. The reason for the non-stereoselective epoxidation of C-7–C-8 in **6a** is not clear. Possibly, subtle conformational changes in the B-ring (as compared to **2** which does give a single diepoxide[1]) due to through-space interaction of the OH group of **6a** with the acetoxy group, play a role in determining the trajectory of attack of the epoxidation reagent. However, as the projected transformation of the glycidic ester into a β-ketoester will destroy the stereo-center at C-7, the formation of epimers is not detrimental for the final goal of our synthesis, although a complicating factor for purification and identification.

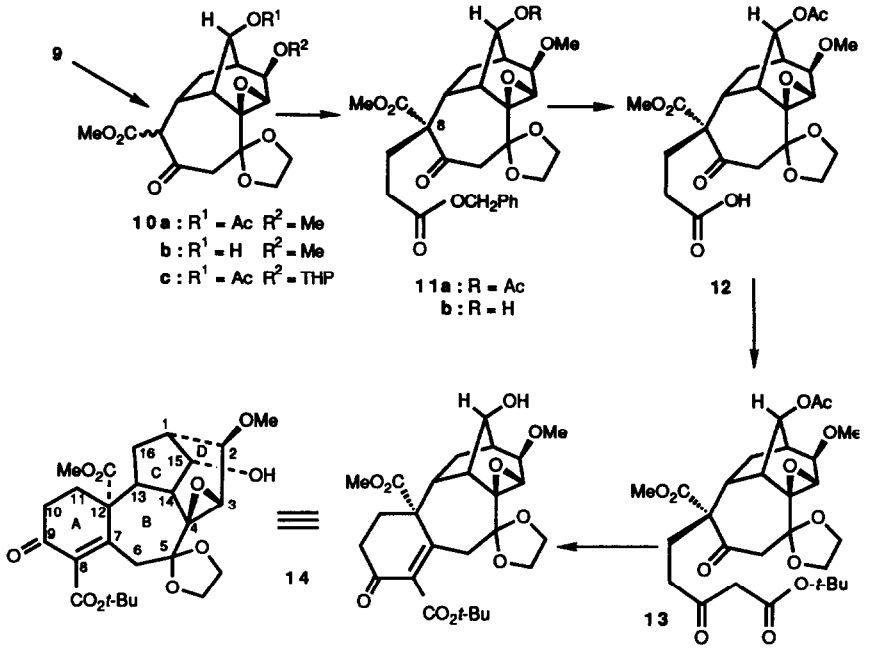


Scheme 3

Conversion of epoxyester **8a** to the corresponding β-hydroxyester **9** was accomplished with lithium and *tert*-butanol in liquid ammonia[13] at –78 °C giving a mixture of the C-11–acetoxy (**9a**) and –hydroxy derivatives (**9b**) in almost equal amounts. As expected, when the diastereomeric mixture of **8a** was used in this reaction, mixtures of diastereomers of both **9a** and **9b** were obtained. Li/NH_3 reduction of the crystalline diastereomer of diepoxide **8a**, however, gave a mixture of **9a** and **9b** (*ca.* 70 % yield), in which (according to the ^1H- and ^{13}C-NMR spectra of the separated products) both compounds were present as single diastereomers (with unknown but specific stereochemistry of the β-hydroxyester moiety). Obviously, as we have noted earlier,[1] Li/NH_3 ring opening of glycidic esters in these polycyclic systems is a regio- and stereospecific reaction. Simplification of the stereochemical situation was effected by oxidation of **9** to the desired β-ketoesters **10**. Monohydroxy compound **9a** was oxidized in high yield by the Pfitzner-Moffatt method (dimethyl sulfoxide/dicyclohexyl carbodiimide)[14] to yield **10a**. Regioselective mono-oxidation of dihydroxy compound **9b** was best realized by using the oxidation procedure of Swern (dimethyl sulfoxide/oxalyl chloride)[15] because the reagents can be applied in stoichiometric amounts at low temperature to effect discrimination of the (more hindered) OH-group in the CD-ring system; this is not possible in the Pfitzner-Moffatt method.
Application of the same synthetic procedures to **8b**, the C-2–tetrahydropyranyloxy analogue of **8a** (to enable modifications at C-2 in a later stage), furnished eventually β-ketoester **10c** via mixtures of diastereomers of β-hydroxyesters **9c** and **9d** which were even more complex than **9a** and **9b** due to the additional stereo-center of the tetrahydropyranyl group. Irrespective of the diastereomeric composition of the starting material **9**, in all cases a single product **10** was obtained which, however, during chromatographic purification over silica, was converted spontaneously to a *ca.* 3:2 mixture of epimeric β-ketoesters *via* the keto-enol equilibrium.

Having introduced the proper substituents at the CD-skeleton, the stage was set for construction of the ABCD-ring system by exploiting the versatile reactivity of the β-ketoester system in the B-ring (Scheme 4).

Michael addition of **10a** and **10b** to benzyl acrylate gave the adducts **11a** and **10b**, respectively, in *ca.* 75 % yield as single products (according to ^{1}H- and ^{13}C-NMR, and TLC). Acetylation (acetic anhydride/ dimethyl-aminopyridine/ pyridine)[16] quantitatively converted **11b** into **11a**, identical in all respects to the product obtained from direct addition of **10a** to benzyl acrylate. Models of the β-ketoester anion clearly showed that the *endo*-side of the molecule is effectively protected against attack by electrophiles. Therefore, it was assumed that both **11a** and **11b** carry the propionic ester substituent in the *exo*-position. This was corroborated by the crystal structure analysis of the final product **14** (Fig.1).



Scheme 4

In **11a**, the methoxycarbonyl group at C-8 (for numbering see Scheme 2) serves as a future junction (C-17 of diterpene alkaloids, see Scheme 1) in the construction of the E- and F-ring. The propionic ester side chain can easily be extended to furnish the constitutive elements of the A-ring using a general procedure which we developed for the synthesis of β-ketoesters.[17] Thus, the protecting benzyl group was quantitatively removed by hydrogenolysis (H_2, Pd/C) to give carboxylic acid **12** which was then activated towards nucleophilic attack by mixed anhydride formation (methyl chloroformate/triethyl amine). Reaction with the lithium salt of *tert*-butyl trimethylsilyl malonate gave a triacyl product which, without isolation, was hydrolyzed with simultaneous decarboxylation to yield β-ketoester **13**. Finally, cyclization to the A-ring with concomitant removal of the protecting acetyl group was effected in 72 % yield by treatment with 25 mol% sodium methoxide in methanol at 50 °C. Recrystallization of the obtained tetracyclic compound **14** from methanol furnished crystals suitable for X-ray crystal structure determination.

The PLUTON drawing of **14**, portrayed in Figure 1, clearly shows the correct *exo*-configuration of the introduced MeO-group at C-2 (C-16 of diterpene alkaloids) in the D-ring and the desired *endo*-configuration of the methoxycarbonyl group at C-12 (C-11 of diterpene alkaloids).

The carbonyl group introduced at C-9 in the A-ring (C-3 of diterpene alkaloids) gives synthetic access to the substitution pattern of diterpene alkaloids of the acomonine-type (Scheme 1) whereas the C-7–C-8 double bond activates C-6 towards introduction of the required oxygen containing substituent at this position.
If, instead of the Michael addition described in this paper, one applies aldol type additions to the β-ketoester function of **1** or **10**, combined with synthetic strategy similar to the procedure described above, one should in principle obtain tetracyclic intermediates with an oxygen substituent at C-11 (C-1 of diterpene alkaloids) and hence diterpene alkaloids of the cardiopetaline and isodelphinine type.
Application of this methodology will be the subject of future publications.

ACKNOWLEDGEMENT

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EXPERIMENTAL

General information

^{1}H-NMR spectra of $CDCl_3$-solutions were measured with a Bruker WH-90 (90 MHz) or a Bruker WM-250 (250 MHz) spectrometer with $CHCl_3$ (δ = 7.27 ppm) as an internal reference. ^{13}C-NMR spectra of $CDCl_3$-solutions were measured with the same spectrometers (22.63 resp. 62.8 MHz) with $CDCl_3$ (δ = 77.0 ppm) as internal standard. Chemical shifts are recorded in ppm and coupling constants J in Hz. Mass spectra were obtained with a Finnigan 4000 (70 eV) and a Varian Mat CH-5 DF (70 eV) mass spectrometer. IR spectra of *ca.* 4% solutions in $CHCl_3$ were recorded with a Perkin-Elmer 580B spectrophotometer; relevant absorptions are given in cm^{-1}. Melting points were determined on a Kofler hot stage apparatus under a Reichert microscope and are uncorrected. All reactions were performed with purified reagents under a N_2 atmosphere.

Methyl *endo*-11-acetoxy-5,5-ethylenedioxy-2-oxotricyclo[7.2.1.0^{4,10}]dodeca-3,7-diene-8-carboxylate (3) and methyl *endo*-11-acetoxy-*exo*-8,9-epoxy-5,5-ethylenedioxy-7-oxotricyclo[7.2.1.0^{4,10}]dodeca-3-ene-8-carboxylate (4a)

A solution of **2**[1] (334 mg, 1 mmole) in dry CH_2Cl_2 (2.5 ml) was added dropwise to a solution of CrO_3–3.5 dimethylpyrazole complex [prepared *in situ* from CrO_3 (2.0 g, 20 mmole) and 3,5-dimethylpyrazole (1.92 g)] in dry CH_2Cl_2 (17.5 ml) at –20 °C. After stirring for another 4 h at –20 °C, an aqueous solution of NaOH (5N, 8.5 ml) was added at -5 °– -10 °C and stirring was continued at this temperature for 1 h. Then the organic and aqueous phase were separated by centrifugation and the organic layer was washed with 1N HCl, H_2O and brine, respectively. Drying over $MgSO_4$ and evaporation gave a black product which was purified by column chromatography over SiO_2 to give **2** (53 mg, 16%), **3** (167 mg, 48%) and **4a** (7.5 mg, 2%); calculated on converted **2**, the yield of **3** is 57%. Recrystallization from methanol gave **3** and **4a** as colourless crystalline products with mp. 163-168°C and 137-139°C, respectively.

(3) ^{1}H-NMR: 6.84 (ddd, ^3J = 9, ^3J = 5, ^4J = 2, 1H, H-7), 6.17 (d, ^4J = 1.5, 1H, H-3), 5.17 (dd, ^3J = 5, ^3J = 4, 1H, H-11), 4.22-3.81 (m, 4H, OCH_2CH_2O), 3.71 (s, 3H, OCH_3), 3.62-3.41 (bm, 2H, H-1, H-9), 3.22-2.65 (bm, 3H, H-6-*exo*, H-10, H-12-*exo*), 2.56 (dd, ^2J = 15.5, ^3J = 9, 1H, H-6-*endo*), 2.00 (s, 3H, O=CCH_3), 1.60-1.20 (m, 1H, H-12-*endo*).
^{13}C-NMR (proton decoupled): 200.0, 170.1, 167.0, 156.5, 135.9, 133.7, 123.6, 110.3, 78.3, 66.0, 63.5, 51.7, 49.7, 41.3, 40.1, 35.5, 30.8, 20.6. Mass-spectrum: Calculated for $C_{18}H_{20}O_7$: 348.1208; found: 348.1224; 348 (11.9%), 261 (100%). Calculated for $C_{18}H_{20}O_7$ (348.31): C, 62.06; H 5.79; found: C, 61.83; H 5.64 %.

(4a) ^{1}H-NMR: 6.03 (bm, 1H, H-3), 5.25 (dd, ^3J = 4.5, ^3J = 4.5, 1H, H-11), 4.25-3.82 (m, 4H, OCH_2CH_2O), 3.81 (s, 3H, OCH_3), 3.76-3.44 (m, 1H, H-10), 3.20 (AB, δ_A = 3.51, δ_B = 2.89, J_{AB} = 11.5, 2H, H-6), 2.82-2.20 (m, 4H, H-1, H-2, H-12-*exo*), 2.02 (s, 3H, O=CCH_3), 1.75-1.21 (m, 1H, H-12-*endo*).
Mass-spectrum: Calculated for $C_{18}H_{20}O_8$: 364.1157; found: 364.1166; 364 (100%), 305 (12.4%).

Methyl *exo*-3,4-epoxy-5,5-ethylenedioxy-*exo*-11-hydroxy-2-oxotricyclo[7.2.1.$0^{4,10}$]dode-7-ene-8-carboxylate (5)

H_2O_2 (30.6 µl, 70%) was added dropwise in 1 h to a stirred mixture of **3** (66.3 mg, 0.19 mmole) and K_2CO_3 (53.2 mg, 0.38 mmole) in MeOH:H_2O 4:1 (300 µl) at 60 °C. After another 1.5 h at 60 °C the reaction mixture was cooled, poured into brine and extracted with EtOAc (3x). Drying over $MgSO_4$ and concentration *in vacuo* gave a yellow liquid residue which was purified by chromatography over SiO_2 to give **5** as a colourless oil (19.2 mg, 31 %). ^{1}H-NMR: 6.80 (ddd, ^3J = 7, ^3J = 6, ^4J = 1.5, 1H, H-7), 4.56 (bs, 1H, H-11), 3.96 (m, 4H, OCH_2CH_2O), 3.72 (s, 3H, OCH_3), 3.35 (d, ^4J = 0.5, 1H, H-3), 3.19 (bd, ^3J = *ca.* 5, 1H, H-10), 3.08-2.63 (m, 3H, H-1, H-6-*exo*, H-9), 2.47 (dd, ^2J = 16, ^3J = 7, 1H, H-6-*endo*), 2.14 (broad signal, 1H, OH), 1.32-1.04 (m, 2H, H-12). ^{13}C-NMR: 201.9 (s, C-2), 168.0 (s, $\underline{C}O_2CH_3$), 136.4 (s, C-8), 132.3 (d, ^1J = 203, C-7), 108.3 (s, C-5), 71.6 (d, ^1J = 153, C-11), 66.2 and 65.8 (2xt, ^1J = 151 and 150, OCH_2CH_2O), 65.5 (s, C-4), 56.2 (d, ^1J = 187, C-3), 54.2 (d, ^1J = 146, C-1), 51.9 (q, ^1J = 148, $CO_2\underline{C}H_3$), 43.2 (d, ^1J = 143, C-10), 37.9 (d, ^1J = 132, C-9), 35.9 (t, ^1J = 131, C-6), 33.6 (t, ^1J = 133, C-12). IR : 3615, 3500 (broad, OH), 1712 (C=O, ester and ketone), 1650 (C=C).

Methyl *endo*-11-acetoxy-5,5-ethylenedioxy-*exo*-2-hydroxytricyclo[7.2.1.$0^{4,10}$]dodeca-3,7-diene-8-carboxylate (6a) and methyl *endo*-11-acetoxy-5,5-ethylenedioxy-*endo*-2-hydroxytricyclo[7.2.1.$0^{4,10}$]-dodeca-3,7-diene-8-carboxylate (6b)

$NaBH_4$ (324 mg, 8.53 mmole) was added to a stirred ice-cold solution of **3** (297 mg, 0.85 mmole) in anhydrous MeOH (21 ml). After 0.5 h at 0 °C, the excess of $NaBH_4$ was destroyed by careful addition of 4N HOAc. Extraction with Et_2O (3x), washing with saturated aqueous $NaHCO_3$ and brine, respectively, drying over $MgSO_4$ and evaporation of the solvent gave a semi-solid residue which was subjected to column chromatography. **6a** (167 mg, 56%) and **6b** (54 mg, 18 %) were obtained as colourless crystalline products with m.p. 134–137 °C and 126–128 °C, respectively.

(**6a**) ^{1}H-NMR (250 MHz): 6.76 (ddd, ^3J = 9.0, ^4J = 4.7, ^4J = 1.9, 1H, H-7), 6.04 (dd, ^3J(H-3, H-2) = 4.5, ^5J(H-3,H-6-*endo*) = 1.2, 1H, H-3), 5.10 (dd, ^3J = 4.8, ^3J = 3.8, 1H, H-11), 4.13-3.91 (m, 3H, $OC\underline{H}_2C\underline{H}HO$), 3.81-3.67 (m, 2H, $OCH_2CH\underline{H}O$, H-2), 3.69 (s, 3H, OCH_3), 3.25-3.14 (m, 2H, H-9, H-10), 3.00 (ddd, ^2J = 15.6, ^3J = 4.7, ^5J(H-6-*exo*, H-9)? = 2.7, 1H, H-6-*exo*), 2.64-2.51 (m, 3H, H-1, OH, H-12-*exo*), 2.46 (dd, ^2J = 15.6, ^3J = 9.0, 1H, H-6-*endo*), 2.07 (s, 3H, O=CCH_3), 0.97-0.86 (m, 1H, H-12-*endo*). IR: 3590 (OH), 1740 (C=O, acetoxy), 1708 (C=O, methyl ester), 1635 (C=C). Mass-spectrum: Calculated for $C_{18}H_{22}O_7$: 350.1365; found: 350.1380 (87.55 %), 291 (9.7%), 43 (100%).

(**6b**) ^{1}H-NMR(250 MHz): 6.79 (ddd, ^3J = 9.0, ^3J = 4.9, ^4J = 2.1, 1H, H-7), 5.74 (dd, ^3J(H-3, H-2) = 1.9, ^5J(H-3, H-6-*endo*) = 1.9, 1H, H-3), 5.12 (dd, ^3J = 5.9, ^3J = 4.2, 1H, H-11), 4.68 (broad signal, 1H, H-2), 4.09-3.89 (m, 3H, $OC\underline{H}_2C\underline{H}HO$), 3.77-3.68 (m, 1H, $OCH_2CH\underline{H}O$), 3.70 (s, 3H, OCH_3), 3.23 (m, 1H, H-9), 3.04 (dd, ^3J = 4.5, ^3J = 4.5, 1H, H-10), 2.95 (ddd, ^2J = 15.6, ^3J = 4.9, ^5J (H-6-*exo*, H-9)? = 2.8, 1H, H-6-*exo*), 2.47 (dd, ^2J = 15.6, ^3J = 9.0, 1H, H-6-*endo*), 2.52-2.28 (m, 2H, H-1, H-12-*exo*), 2.06 (s, 3H, O=CCH_3), 1.66 (dd, ^2J = 14.3, ^3J = 7.6, 1H, H-12-*endo*), 1.56 (d, ^3J = 6.8, 1H, OH).

Methyl *endo*-11-acetoxy-*exo*-3,4-epoxy-7,8-epoxy-5,5-ethylenedioxy-*exo*-2-hydroxytricyclo-[7.2.1.$0^{4,10}$]dodecane-8-carboxylate (7)

A solution of CF_3CO_3H [prepared from H_2O_2 (130 µl 90%), $(CF_3CO)_2O$ (740 µl) in CH_2Cl_2 (1 ml) at 0 °C] was added dropwise in 15 min to a stirred suspension of **6a** (161.5 mg, 0.46 mmole) and anhydrous K_2HPO_4 (2.6 g) in CH_2Cl_2 (3.7 ml) at 40 °C. After 1 h at reflux the mixture was cooled and H_2O was added to dissolve all salts present. The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic extracts were washed, successively, with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* to yield **7** (176 mg, 100%) as a colourless foam, pure according to TLC (SiO_2, EtOAc/p.e. 3:1).^{1}H-NMR: 4.86 (bdd, ^3J = *ca.* 4, ^3J = *ca.* 4, 1H, H-11), 4.15-3.67 (m, 5H, OCH_2CH_2O, H-2), 3.73 (s, 3H, OCH_3), 3.65-3.50 (m, 1H, H-7), 3.39-2.70 (m, 4H, H-6-*exo*, H-3, H-9, H-10), 2.62-2.24 (m, 3H, H-1, H-6-*endo*, OH), 2.08 (s, 3H, O=CCH_3), 1.69-1.01 (bm, 2H, H-12).

Methyl *endo*-11-acetoxy-*exo*-3,4-epoxy-7,8-epoxy-5,5-ethylenedioxy-*exo*-2-methoxytricyclo-[7.2.1.0^{4,10}]dodecane-8-carboxylate (8a)

A mixture of **7** (1146 mg, 3 mmole), MeI (20.6 g), Ag_2O (694 mg), and dry $CaSO_4$ (956 mg) was stirred and heated under reflux during 24 h. After cooling, the resulting mixture was filtered and the solid residue was extracted thoroughly with CH_2Cl_2 and acetone, successively. Concentration *in vacuo* gave a solid product (1131 mg, 95 %) which, according to TLC and ^{1}H-NMR contained two (isomeric) compounds in a ratio of *ca.* 2:1. Crystallization from acetone gave one diastereomer of **8a** as a crystalline product (275 mg), m.p. 195-200 °C, after recrystallization 197-205 °C. Evaporation of the mother liquors gave a solid product (856 mg), m.p. 160-180 °C, which according to ^{1}H-NMR was a mixture of both diastereomers.

8a (m.p. 197-205 °C): ^{1}H-NMR: 4.71 (bdd, ^3J = *ca.*4, ^3J = *ca.* 4, 1H, H-11), 4.19-3.80 (m, 4H, OCH_2CH_2O), 3,73 (s, 3H, CO_2CH_3), 3.57-3.44 (m, 1H, H-2), 3.42 (s, 3H, OCH_3), 3.44-3.18 (m, 2H, H-3, H-7), 3.07-2.86 (m, 2H, H-6), 2.80-2.20 (m, 4H, H-1, H-9, H-10, H-12-*exo*), 2.06 (s, 3H, O=CCH_3), 1.36-0.91 (m, 1H, H-12-*endo*). ^{13}C-NMR: 171.3 (s, O=$\underline{C}CH_3$), 170.3 (s, $\underline{C}O_2CH_3$), 105.9 (s, C-5), 80.7 (d, ^1J = 135, C-2), 75.6 (d, ^1J = 161, C-11), 66.0 and 65.1 (2xt, ^1J = 150, ^1J = 151, $O\underline{C}H_2\underline{C}H_2O$), 62.2 (s, C-4), 61.6 (s, C-8), 57.7 (d, ^1J = 174, C-7), 57.1 (q, ^1J = 142, $O\underline{C}H_3$), 52.7 (q, ^1J = 148, $CO_2\underline{C}H_3$), 50.0 (d, ^1J = 180, C-3), 35.7 (2xd, ^1J = 131, C-1, C-9), 35.6 (t, ^1J = 128, C-6), 33.5 (d, ^1J = 128, C-10), 28.8 (t, ^1J = 134, C-12), 21.2 (q, ^1J = 129, O=C$\underline{C}H_3$). IR (KBr): 1738 and 1722 (ester carbonyl), 1114 (ether). Mass-spectrum: Calculated for $C_{19}H_{24}O_9$: 396.1420; found: 396.1505 (3.62 %). 125 (100 %). Calculated for $C_{19}H_{24}O_9$ (396.38): C 57.57; H 6.10; found: C 57.56; H 6.12 %.

Methyl *endo*-11-acetoxy-*exo*-3,4-epoxy-7,8-epoxy-5.5-ethylenedioxy-*exo*-2-(2-tetrahydropyranyloxy)-tricyclo[7.2.1.0^{4,10}]dodecane-8-carboxylate (8b)

p-Toluenesulfonic acid (2.3 mg) was added with stirring to a solution of **7** (170.7 mg, 0.45 mmole) in dihydropyran (1160 µl). After 0.5 h at room temperature, the mixture was diluted with dry Et_2O and washed, successively, with saturated aqueous $NaHSO_3$, saturated aqueous $NaHCO_3$ and brine. The collected washings were extracted with $CHCl_3$ (2x) and the combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed over SiO_2 and gave two fractions of **8b**: I [119 mg, 57 %, m.p.(after crystallization from methanol) 177-187 °C] and II [37 mg, 18 %, m.p.(after crystallization from methanol) 146-150 °C].

(8b)(I) ^{1}H-NMR: 4.93 (bm, 0.4H, OCHO), 4.70 (bm, 1.6H, OCHO, H-11), 4.17-3.69 (m, 5H, OCH_2CH_2O, H-2), 3.74 (s,3H, OCH_3), 3.65-3.39 (bm, 2H, H-6-*THP*), 3.24 (bm, 1H, H-7), 3.04-2.39 (bm, 6H, H-1, H-3, H-6, H-9, H-10), 2.05 (s, 3H, O=CCH_3), 1.56 (bm, 7H, H-12-*exo*, H-3-*THP*, H-4-*THP*, H-5-*THP*), 1.13-0.73 (bm, 1H, H-12-*endo*). IR: 1733 (carbonyl of methyl ester and acetoxy group). Mass-spectrum: Calculated for $C_{23}H_{30}O_{10}$: 466.1838; found: 466,1805 (3.07 %), 407 (9.2 %), 381 (39.6 %), 85 (100 %). Calculated for $C_{23}H_{30}O_{10}$(466.47): C 59.22; H 6.48; found: C 59.27; H6.48.

(8b)(II) ^{1}H-NMR: 4.88 (bm, .25 H, OCHO), 4.67 (bm, 1.75H, OCHO, H-11), 4.13-3.85 (m, 5H, OCH_2CH_2O, H-2), 3.74 (s, 3H, OCH_3), 3.70-3.35 (m, 3H, H-7, H-6-*THP*), 3.32-3.06 (m, 1H, H-9), 3.02-2.85 (bm, 1H, H-3), 2.62-2.21 (m, 4H, H-1, H-6, H-10), 2.06 (s, 3H, O=CCH_3), 1.79-0.77 (bm, 8H, H-12, H-3-*THP*, H-4-*THP*, H-5-*THP*). Mass-spectrum: Calculated for $C_{23}H_{30}O_{10}$: 466.1838; found: 466.1812.

Methyl *endo*-11-acetoxy-*exo*-3,4-epoxy-5,5-ethylenedioxy-7-hydroxy-*exo*-2-methoxytricyclo-[7.2.1.0^{4,10}]dodecane-8-carboxylate (9a) and methyl *exo*-3,4-epoxy-5,5-ethylenedioxy-7-hydroxy-*endo*-11-hydroxy-*exo*-2-methoxytricyclo[7.2.1.0^{4,10}]dodecane-8-carboxylate (9b)

A solution of **8a** (crystallized diastereomer)(381.5 mg, 0.96 mmole) and dry *tert*-butanol (296 mg, 4 mmole) in dry THF (16 ml) was added within a few *seconds* to a vigorously stirred solution of Li (28 mg, 4 mmole) in liquid NH_3 (60 ml, distilled from Na) at –78 °C. Immediately after decolouration (*ca.* 2 sec) a large excess of NH_4Cl was added. Then NH_3 was evaporated and THF was removed *in vacuo* at room temperature. Saturated aqueous $NaHCO_3$ was added with ice-cooling, and, after saturation with solid NaCl, the mixture was extracted with EtOAc (3x). The combined extracts were dried over $MgSO_4$ and evaporated to give a mixture of compounds which were separated by column chromatography (SiO_2) yielding **8a** (108 mg, 28 %), **9a** (104 mg, 27 %)

and **9b** (75 mg, 22 %)(based on converted **8a** the yield of **9a** and **9b** is 38 and 30 %, respectively). **9a** is an amorphous compound; **9b** could be crystallized by slow evaporation of a CH_2Cl_2-solution, m.p. 138-143 °C.

9a ^{1}H-NMR: 4.70 (dd, ^3J = 4.5, ^3J = 4.5, 1H, H-11), 4.50-4.29 (m, 1H, H-7), 4.23-3.81 (m, 4H, OCH_2CH_2O), 3.76 (s, 3H, CO_2CH_3), 3.45 (s, 3H, OCH_3), 3.43 (m, 2H, H-2, H-3), 3.30 (dd, ^3J = 5.0, ^3J = 5.0, 1H, H-9), 2.97-2.74 (m, 1H, OH), 2.74-1.84 (m, 6H, H-1, H-6, H-8, H-10, H-12-*exo*), 2.08 (s, 3H, O=CCH_3), 1.11-0.74 (m, 1H, H-12-*endo*). ^{13}C-NMR(off-resonance): 174.5 (s, CO_2CH_3), 171.3 (s, O=CCH_3), 105.8 (s, C-5), 81.1 (d, C-2), 74.7 (d, C-11), 66.5 and 65.6 (2xt, OCH_2CH_2O), 66.1 (d, C-7), 60.6 (s, C-4), 56.9 (q, OCH_3), 53.9 (d, C-8), 52.0 (q, CO_2CH_3), 49.9 (d, C-3), 47.3 (t, C-6), 39.3 and 36.5 (2xd, C-1, C-9), 35.4 (d, C-10), 32.7 (t, C-12), 21.3 (q, O=CCH_3). IR: 3520 (OH), 1730 (methyl ester and acetoxy C=O). Mass-spectrum: Calculated for $C_{19}H_{26}O_9$: 398.1577; found: 398.1692 (1.69 %), 115 (100 %).

9b ^{1}H-NMR: 4.44-4.26 (m, 1H, H-7), 4.38 (d, ^3J = 12.0, 1H, OH-11), 4.24-3.80 (m, 5H, OCH_2CH_2O, H-11), 3.72 (s, 3H, CO_2CH_3), 3.67-3.37 (m, 2H, H-2, H-3), 3.49 (s, 3H, OCH_3), 3.08 (dd, ^3J = 5.0, ^3J = 5.0, 1H, H-9 or H-10), 2.92 (bd, ^3J = 5.5, 1H, OH-7), 2.71-2.14 (m, 5H, H-1, H-6, H-8, H-9 or H-10), 2.03-1.68 (m, 1H, H-12-*exo*), 1.10-0.78 (m, 1H, H-12-*endo*). ^{13}C-NMR (off-resonance): 174.7 (s, CO_2CH_3), 107.6 (s, C-5), 81.4 (d, C-2), 77.3 (d, C-11), 76.7 (d, C-7), 67.4 (s, C-4), 66.1 and 66.0 (2xt, OCH_2CH_2O), 57.0 (q, OCH_3), 56.2 (d, C-3 or C-8), 53.6 (d, C-3 or C-8), 52.3 (q, CO_2CH_3), 44.1 (t, C-6), 39.3 (d, C-9), 37.0 (d, C-1 or C-10), 33.2 (C-1 or C-10), 32.6 (t, C-12).

Methyl *endo*-11-acetoxy-*exo*-3,4-epoxy-5,5-ethylenedioxy-7-hydroxy-*exo*-2-(2-tetrahydropyranyloxy)-tricyclo[7.2.1.0^{4,10}]dodecane-8-carboxylate (9c) and methyl *exo*-3,4-epoxy-5,5-ethylenedioxy-7-hydroxy-*endo*-11-hydroxy-*exo*-2-(2-tetrahydropyranyloxy)tricyclo[7.2.1.0^{4,10}]dodecane-8-carboxylate (9d)

Prepared from **8b** according to the procedure described for **9a,b**.

After column chromatography, **9c** (48 %) and **9d** (36 %) were obtained as oily products which were mixtures of diastereomeric compounds.

(**9c**) ^{1}H-NMR: 4.90 (bm, 0.4H, OCHO), 4.66 (bm, 1.6H, OCHO, H-11), 4.35 (bm, 1H, H-7), 4.15-3.78 (m, 5H, OCH_2CH_2O, H-2), 3.71 (s, 3H, OCH_3), 3.64-3.14 (m, 4H, H-9, H-10, H-6-*THP*), 2.65-2.14 (m, 5H, H-1, H-3, H-6, H-8), 2.04 (s, 3H, O=CCH_3), 1.96-0.78 (bm, 8H, H-12, H-3-*THP*, H-4-*THP*, H-5-*THP*). IR: 3540 (OH), 1728 (C=O, methyl ester and acetoxy group).

(**9d**) ^{1}H-NMR: 4.96 (bm, 0.4H, OCHO), 4.82 (bm, 0.6H, OCHO), 4.57, 4.44 and 4.30 (3xs, 1H, OH), 4.26-3.77 (m, 7H, OCH_2CH_2O, H-2, H-7, H-11), 3.74 (s, 3H, OCH_3), 3.71-3.40 (m, 3H, H-9, H-6-*THP*), 3.08 (dd, ^3J = 4.5, 1H, H-10), 2.88 (bm, 1H, OH), 2.60-1.95 (m, 6H, H-1, H-3, H-6, H-8, H-12-*exo*), 1.91-0.72 (bm, 7H, H-12-*endo*, H-3-*THP*, H-4-*THP*, H-5-*THP*).

Methyl *endo*-11-acetoxy-*exo*-3,4-epoxy-5,5-ethylenedioxy-*exo*-2-methoxy-7-oxotricyclo[7.2.1.0^{4,10}]-dodecane-8-carboxylate (10a)

To a stirred solution of **9a** (159.2 mg, 0.4 mmole) in dry benzene (1.3 ml) and dry DMSO (1.3 ml) was added dicyclohexylcarbodiimide (744 mg, 1.2 mmole) and pyridinium trifluoroacetate (38.4 mg, 0.2 mmole). After 24 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, filtered and washed with H_2O (2x), dried over $MgSO_4$, and evaporated to dryness to give a slightly coloured oil (165 mg, 100 %), which partly crystallized. According to ^{1}H-NMR, the reaction product was largely one isomer (single resonances for methyl ester and acetoxy group), but gave a *ca.* 2:1 mixture of epimers after heating or purification over SiO_2 (double resonances for methyl ester and acetoxy group). Crystals could be separated and purified by slow evaporation of an Et_2O-solution, yielding one of the epimers, m.p. 127-130 °C. ^{1}H-NMR: 4.71 (dd, ^3J = 4.5, ^3J = 4.5, 1H, H-11), 4.20-3.88 (m, 4H, OCH_2CH_2O), 3,78 (s, 3H, CO_2CH_3), 3.62 (d, ^3J = 8.2, 1H, H-8), 3.44 (bs, 5H, OCH_3, H-2, H-3), 3.11 (dd, ^3J = 5, ^3J = 4.5, 1H, H-9), 2.99 and 2,93 (2xs, 2H, H-6-*endo*, H-6-*exo*), 2.80-2.15 (m, 3H, H-1, H-10, H-12-*exo*), 2.08 (s, 3H, O=CCH_3), 1.09-0.77 (m, 1H, H-12-*endo*). ^{13}C-NMR (off-resonance): 200.7 (s, C-7), 171.3 (s, O=CCH_3), 168.6 (s, CO_2CH_3), 105.0 (s, C-5), 80.8 (d, C-2), 75.0 (d, C-11), 66.0 and 65.9 (2xt, OCH_2CH_2O), 62.5 (s, C-4), 61.8 (d, C-8), 57.2 (q, OCH_3), 52.5

(t, C-6), 52.0 (d, C-3), 51.9 (q, $CO_2\underline{C}H_3$), 36.6 and 35.6 (2xd, C-1, C-9), 33.8 (d, C-10), 30.6 (t, C-12), 21.2 (q, O=C$\underline{C}H_3$). Mass-spectrum: Calculated for $C_{19}H_{24}O_9$: 396.1420; found: 396.1422 (4.13 %), 113 (100 %).

Methyl *exo*-3,4-epoxy-5,5-ethylenedioxy-*endo*-11-hydroxy-*exo*-2-methoxy-7-oxotricyclo[7.2.1.$0^{4,10}$]-dodecane-8-carboxylate (10b)

Oxalyl chloride (9.5 mg, 75 μmole) in anhydrous CH_2Cl_2 (170 μl) was added dropwise to a stirred solution of dry DMSO (11.7 mg, 150 μmole) in dry CH_2Cl_2 (35 μl) at –55 °C. After 5 min, a solution of **9b** (24 mg, 67.4 μmole) in dry CH_2Cl_2 (70 μl) was added dropwise in 5 min, followed, after stirring during 15 min at –55 °C, by Et_3N (47 μl, 337 mmole). After another 5 min, the temperature was raised to room temperature and H_2O (500 μl) was added. The organic layer was separated and the water layer was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give an oily residue (24 mg, 100 %) which was purified by TLC (SiO_2, EtOAc). **10b** (15.0 mg, 63 %) was obtained as a colourless oil consisting of a mixture of two epimers (ratio *ca.* 3:2). ^{1}H-NMR: 4.29-3.83 (m, 5H, H-11, OCH_2CH_2O), 3.76 (60 %) and 3.70 (40 %) (2xs, 3H, CO_2CH_3), 3.67-3.55 (m, 1H, H-8), 3.50 (60 %) and 3.47 (40 %) (2xs, 3H, OCH_3), 3.55-3.34 (m, 1H, H-2), 3.34-3.08 (m, 1H, H-9), 3.08-2.14 (bm, 7H, H-1, H-3, H-6, H-10, H-12-*exo*, OH), 1.14-0.67 (m, 1H, H-12-*endo*).

Methyl *endo*-11-acetoxy-*exo*-3,4-epoxy-5,5-ethylenedioxy-7-oxo-2-(2-tetrahydropyranyloxy)tricyclo-[7.2.1.$0^{4,10}$]dodecane-8-carboxylate (10c)

Prepared from **9c** according to the procedure described for **10a**. After TLC (SiO_2), **10c** was obtained as a colourless foam (79 % yield) consisting of a 3:2 mixture of isomeric β-ketoesters. ^{1}H-NMR: 4.92 (bm, 0.4H, OCHO), 4.67 (bm, 1.6H, OCHO, H-11), 4.19-3.65 (bm, 6H, OCH_2CH_2O, H-2, H-8), 3.76 (60%) and 3.69 (40%) (2xs, 3H, OCH_3), 3.65-3.36 (bm, 2H, H-6-*THP*), 3.26-2.12 (bm, 6H, H-1, H-3, H-6, H-9, H-10), 2.05 (bs, 3H, O=C$\underline{C}H_3$), 2.03-0.75 (bm, 8H, H-12, H-3-*THP*, H-4-*THP*, H-5-*THP*). IR: 1730 (C=O, methyl ester, acetate and ketone, very strong), 1650 (C=O, methyl ester enol, very weak). Mass-spectrum: Calculated for $C_{23}H_{30}O_{10}$: 466.1838; found: 466.1847; 356 (1.7 %), 55 (100 %).

Methyl *endo*-11-acetoxy-8-(2-benzyloxycarbonylethyl)-*exo*-3,4-epoxy-5,5-ethylenedioxy-*exo*-2-methoxy-7-oxotricyclo[7.2.1.$0^{4,10}$]dodecane-8-carboxylate (11a)

To a stirred solution of *t*-BuOK (7.5 mg) in dry *t*-BuOH (345 μl), **10a** (132 mg, 0.33 mmole) in dry dimethoxyethane (2.3 ml) was added at room temperature, followed by benzyl acrylate (130 μl, 0.85 mmole). After 20 h, the reaction mixture was diluted with EtOAc and washed with concentrated aqueous $NaHCO_3$. The water layer was extracted once with EtOAc, the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The oily residue was extracted several times with pentane to remove the excess benzyl acrylate giving **11a** as a partly crystalline compound (139 mg, 75 %). Recrystallization, first from CH_2Cl_2/pentane and then from Et_2O, gave pure **11a**, m.p. 142-145 °C. An identical product was obtained in quantitative yield by acetylation[16] of **11b**. ^{1}H-NMR: 7.37 (bs, 5H, C_6H_5), 5.15 (s, 2H, $C\underline{H}_2C_6H_5$), 4.65 (bdd, ^3J = *ca.* 4, ^3J = *ca.* 4, 1H, H-11), 4.13-3.81 (m, 4H, OCH_2CH_2O), 3.65 (s, 3H, CO_2CH_3), 3.40 (s, 3H, OCH_3), 3.38-3.13 (m, 3H, H-2, H-3, H-9), 3.15 (AB-system, δ_A = 3.37 and δ_B = 2.93, J_{AB} = 15.0, 2H, H-6), 3.13-2.78 (m, 1H, H-10), 2.76-2.16 (m, 6H, H-1, H-12-*exo*, $C\underline{H}_2C\underline{H}_2CO_2CH_2C_6H_5$), 2.06 (s, 3H, O=C$\underline{C}H_3$), 1.76-0.76 (m, 1H, H-12-*endo*). ^{13}C-NMR: 204.4 (s, C-7), 171.9 (s, $\underline{C}O_2CH_2C_6H_5$), 171.3 (s, O=$\underline{C}CH_3$), 170.9 (s, $\underline{C}O_2CH_3$), 135.6 (C-1-*phenyl*), 128.5 (2xC-3-*phenyl*), 128.3 (C-4-*phenyl*), 128.2 (2xC-2-*phenyl*), 104.6 (s, C-5), 80.5 (d, ^3J = 139, C-2), 75.8 (d, ^3J = 152, C-11), 66.6 (t, ^3J = 148.5, $\underline{C}H_2C_6H_5$), 65.8 and 65.6 (2xt, ^3J = 151, ^3J = 151, OCH_2CH_2O), 65.2 (s, C-4), 60.8 (s, C-8), 57.1 (q, ^3J = 141, OCH_3), 52.3 (dd, ^3J = 129, ^3J = 129, C-6), 52.2 (q, ^3J = 148, $CO_2\underline{C}H_3$), 50.4 (d, ^3J = 181, C-3), 39.1 (d, ^3J = 134, C-9), 35.4 (d, ^3J = 143, C-1), 34.8 (d, ^3J = 142, C-10), 29.8 (t, ^3J = 129, $CH_2\underline{C}H_2CO_2CH_2C_6H_5$), 28.4 (t, ^3J = 134, C-12), 26.4 (t, ^3J = 134, $\underline{C}H_2CH_2CO_2CH_2C_6H_5$), 21.3 (q, ^3J = 129, O=C$\underline{C}H_3$). IR (KBr): 1740 and 1730 (C=O of ester groups), 1702 (C=O of ketone) Mass-spectrum: Calculated for $C_{29}H_{34}O_{11}$: 558.2101; found: 558.2097 (9.84%), 91 (100%).
Calculated for $C_{29}H_{34}O_{11}$: C 62.35, H 6.14; found: C 62.17, H 6.20 %.

Methyl 8-(2-benzyloxycarbonylethyl)-*exo*-3,4-epoxy-5,5-ethylenedioxy-*endo*-11-hydroxy-*exo*-2-methoxy-7-oxotricyclo[7.2.1.$0^{4,10}$]dodecane-8-carboxylate (11b)

Prepared from **10b** according to the procedure described for the synthesis of **11a**; yield 76 %, m.p. 160-163 °C (crystallization from Et_2O). ^{1}H-NMR: 7.37 (s, 5H, C_6H_5), 5.15 (s, 2H, $CH_2C_6H_5$), 4.20-3.75 (m, 6H, H-11, OH, OCH_2CH_2O), 3.65 (s, 3H, CO_2CH_3), 3.44 (s, 3H, OCH_3), 3.37 (bs, 2H, H-2, H-3), 3.12 (AB-system, δ_A = 3.40, δ_B = 2.84, J_{AB} = 15.0, 2H, H-6), 3.06-2.74 (m, 2H, H-9, H-10), 2.74-1.90 (m, 6H, H-1, H-12-*exo*, $CH_2CH_2CO_2CH_2C_6H_5$), 1.27-0.80 (m, 1H, H-12-*endo*). ^{13}C-NMR: 204.4 (C-7), 171.9 ($CO_2CH_2C_6H_5$), 135.6 (C-1-*phenyl*), 128.6 (2xC-3-*phenyl*), 128.3 (C-4-*phenyl*), 128.2 (2xC-2-*phenyl*), 104.4 (C-5), 80.4 (C-2), 77.2 (C-11), 66.7 ($C_6H_5CH_2$), 65.8 and 65.7 (OCH_2CH_2O), 65.4 (C-4), 64.1 (C-8), 57.0 (OCH_3), 52.43 and 52.39 (C-6 and C-3), 52.2 (CO_2CH_3), 39.3 (C-9), 37.6 and 36.2 (C-10 and C-11), 29.8 (CH_2CH_2CO), 28.6 (C-12), 26.4 (CH_2CH_2CO). IR (KBr): 3505 (OH), 1744 and 1737 (C=O of ester groups), 1693 (C=O of ketone). Mass-spectrum: Calculated for $C_{27}H_{32}O_{10}$: 516.1995; found: 516.1971 (8.89%), 91 (100%).

Methyl *endo*-11-acetoxy-8-(2-carboxyethyl)-*exo*-3,4-epoxy-5,5-ethylenedioxy-*exo*-2-methoxy-7-oxotricyclo[7.2.1.$0^{4,10}$]dodecane-8-carboxylate (12)

A suspension of 10% Pd/C (6.5 mg) in EtOAc (250 µl) was added to a solution of **11a** (55.8 mg, 0.1 mmole) in EtOAc (500 µl) under a H_2-atmosphere and stirred vigorously until the calculated amount of H_2 (*ca.* 2.5 ml) had been absorbed. Filtration and evaporation of solvent gave 47 mg of **12** (100 %) as a solid product which was recrystallized from Et_2O, m.p. 191-194 °C. ^{1}H-NMR: 4.71 (bdd, 1H, ^3J = *ca.* 4, ^3J = *ca.* 4, H-11), 4.24-3.80 (m, 4H, OCH_2CH_2O), 3.69 (s, 3H, CO_2CH_3), 3.41 (s, 3H, OCH_3), 3.37-3.10 (m, 3H, H-2, H-3, H-9), 3.12 (AB-system, δ_A = 3.33, δ_B = 2.91, J_{AB} = 15, 2H, H-6), 3.10-2.77 (m, 1H, H-10), 2.77-2.15 (m, 6H, H-1, H-12-*exo*, $CH_2CH_2CO_2H$), 2.07 (s, 3H, O=CCH_3), 1.40-0.91 (m, 1H, H-12-*endo*). ^{13}C-NMR: 204.3 (C-7), 176.7 (CO_2H), 171.5 (O=CCH_3), 170.9 (CO_2CH_3), 104.6 (C-5), 80.5 (C-2), 75.8 (C-11), 65.9 and 65.7 (OCH_2CH_2O), 65.2 (C-4), 60.8 (C-8), 57.2 (OCH_3), 52.33 (C-6), 52.28 (CO_2CH_3), 50.5 (C-3), 39.2 (C-9), 35.4 and 34.9 (C-1 and C-10), 29.4 ($CH_2CH_2CO_2H$), 28.3 and 26.5 (C-12 and $CH_2CH_2CO_2H$), 21.3 (O=CCH_3). IR (KBr): 3430 (CO_2H), 1740, 1715 and 1703 (carbonyl groups).

Methyl *endo*-11-acetoxy-8-(4-*tert*-butyloxycarbonyl-3-oxobutyl)-*exo*-3,4-epoxy-5,5-ethylenedioxy-*exo*-2-methoxy-7-oxotricyclo[7.2.1.$0^{4,10}$]dodecane-8-carboxylate (13)

To a stirred solution of **12** (117 mg, 0.25 mmole) in a mixture of dry THF (1.4 ml) and dry petroleum ether 40-60 (0.9 ml), Et_3N (38.5 µl, 0.275 mmole) was added at –30 °C in 5 min, followed by freshly distilled methyl chloroformate (19 µl, 0.275 mmole) in the course of 15 min. After 3 h at *ca.* –25 °C, the reaction mixture was warmed to 0°C and added in one lot to a stirred solution of the Li-salt of *tert*-butyl trimethylsilyl malonate [prepared by addition of BuLi in hexane (625 µl, 1.6 M) to *tert*-butyl trimethylsilyl malonate (290 mg, 1.25 mmole) in dry Et_2O (1.25 ml) at –78 °C, followed by stirring during 10 min at this temperature and then warming to 0°C]. After 45 min at 0°C, a 5% aqueous solution of $NaHCO_3$ (1.25 ml) was added and the mixture was stirred vigorously during 10 min. Then, the water layer was extracted with EtOAc (3x) and the combined organic extracts were washed with brine. Drying over Na_2SO_4 and evaporation of the solvents gave **13** as a solid product (106.1 mg) which was crystallized from CH_2Cl_2/petroleum ether 40-60, m.p. 122-126 °C. By acidification of the water layer and extraction with EtOAc, starting material **12** (19.5 mg) could be recovered. Based on conversion of **12**, the yield of **13** is 90 %. ^{1}H-NMR: 4.68 (bdd, ^3J = *ca.* 4, ^3J = *ca.* 4, 1H, H-11), 4.29-3.89 (m, 4H, OCH_2CH_2O), 3.66 (s, 3H, CO_2CH_3), 3.40 (s, 3H, OCH_3), 3.37 (s, 2H, $COCH_2CO_2$), 3.37-2.82 (m, 4H, H-2, H-3, H-9, H-10), 3.14 (AB-system, δ_A = 3.36, d_B = 2.92, J_{AB} = 15, 2H, H-6), 2.77-2.16 (m, 6H, H-1, H-12-*exo*, CH_2CH_2CO), 2.06 (s, 3H, O=CCH_3), 1.47 (s, 9H, $OC(CH_3)_3$), 1.41-1.03 (m, 1H, H-12-*endo*). ^{13}C-NMR: 204.5 (C-7), 201.0 (CH_2CH_2C=O), 171.3 (O=CCH_3), 171.1 (CO_2CH_3), 166.1 ($CO_2C(CH_3)_3$), 104.6 (C-5), 82.2 ($CO_2C(CH_3)_3$), 75.8 (C-2), 77.5 (C-11), 65.8 and 65.7 (OCH_2CH_2O), 65.0 (C-4), 60.8 (C-8), 57.2 (OCH_3), 52.4 (C-6), 52.2 (CO_2CH_3), 50.6 (O=CCH_2CO_2C), 50.5 (C-3), 39.4 (C-9), 38.1 (CH_2CH_2CO), 35.5 and 34.8 (C-1 and C-10), 28.0 ($CO_2C(CH_3)_3$), 27.0 (CH_2CH_2CO), 26.5 (C-12), 21.3 (O=CCH_3). IR (KBr): 1735, 1720, 1693 (C=O).

Methyl 8-*tert*-butoxycarbonyl-*exo*-3,4-epoxy-5,5-ethylenedioxy-*endo*-15-hydroxy-*exo*-2-methoxy-9-oxotetracyclo[11.2.1.$0^{4,14}$.$0^{7,12}$]hexadec-7-ene-12-carboxylate (14)

A solution of **13** (85 mg, 0.15 mmole) in dry MeOH (7.5 ml) was mixed with a solution of MeONa in dry MeOH (187.5 µl,

0.2N) and heated with stirring at 50 °C during 9 h. After cooling to room temperature, the mixture was neutralized with 4N HOAc (10 µl) and evaporated *in vacuo* to dryness. The residue was purified by liquid chromatography (SiO_2, EtOAc/petroleum ether 40-60 4/1) and crystallization from CH_2Cl_2/petroleum ether 40-60. **14** (55mg, 72 % yield) was recrystallized from MeOH to yield crystals, m.p. 184-188 °C, suitable for X-ray crystal structure determination. ^{1}H-NMR: 4.23 (d, ^3J = 11.7, 1H, OH), 4.11-3.89 (m, 5H, H-15, OCH_2CH_2O), 3.72 (s, 3H, CO_2CH_3), 3.67 (m, 2H, H-2, H-13), 3.51 (s, 3H, OCH_3), 2.87 (AB-system, δ_A = 3.00, δ_B = 2.73, J_{AB} = 14, 2H, H-6), 2.78 (bdd, ^3J = 4, 1H, H-14), 2.58-1.93 (m, 7H, H-1, H-3, H-10, H-11, H-16-*exo*), 1.53 (s, 9H, $CO_2C(CH_3)_3$), 1.49-1.19 (m, 1H, H-16-*endo*). ^{13}C-NMR: 193.6 (s, C-9), 172.2 (s, $\underline{C}O_2CH_3$), 165.3 (s, $\underline{C}O_2C(CH_3)_3$), 151.2 (s, C-8), 137.9 (s, C-7), 105.8 (s, C-5), 82.4 (s, $CO_2\underline{C}(CH_3)_3$), 80.3 (d, ^1J = 161, C-2), 77.6 (d, ^1J = 154, C-15), 66.7 and 65.7 (2xt, J = 151, J = 151, OCH_2CH_2O), 65.9 (s, C-4), 57.1 (q, J = 141, OCH_3), 53.8 (d, J = 182, C-3), 52.5 (q, ^1J = 148, $CO_2\underline{C}H_3$), 51.8 (s, C-12), 44.1 (d, ^1J = 128, C-13), 42.1 (dd, ^1J = 128.8, ^1J = 128.5, C-6), 37.6 and 37.0 (2xd, ^1J = 142, ^1J = 141, C-1, C-14), 34.8 (t, ^1J = 139, C-10), 34.3 (t, ^1J = 130, C-11), 28.8 (t, ^1J = 134, C-16), 28.1 (q, ^1J = 127, $CO_2C(\underline{C}H_3)_3$). IR: 3500 (OH), 1730 (C=O of ester groups), 1680 (C=O of ketone), 1618 (C=C). Mass-spectrum: Calculated for $C_{26}H_{34}O_{10}$: 506.2152; found: 506.2174 (9.45%), 56 (100%).

Crystal data for (**14**): $C_{26}H_{34}O_{10}$, M = 506.55, monoclinic, space group $P2_1/c$, a = 12.613(4), b = 19.138(2), c = 10.118(2) Å, β = 95.41(2)°, V = 2431.5(9) Å^3, Z = 4, d_x = 1.384 gcm^{-3}. X-ray data were collected on an ENRAF-NONIUS CAD4-diffractometer using Zr-filtered Mo-Kα-radiation up to Θ_{max} = 25°. The structure was solved by direct methods (SHELXS-86) and refined on F with SHELX-76. Convergence was reached at R = 0.075 (wR = 0.084, w = 1) for 1874 reflections with $I > 3\sigma(I)$.
All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were accounted for at calculated positions except for the hydroxyl hydrogen which was located from a difference map and its position and isotropic thermal parameter refined. Structural data have been deposited at the Cambridge Crystallographic Data Centre.

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