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TOTAL SYNTHESIS OF C_{19}-DITERPENE ALKALOIDS: CONSTRUCTION OF A FUNCTIONALIZED BCD-RING SYSTEM

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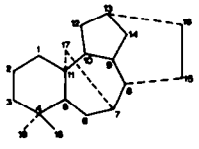
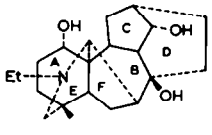
Abstract - The construction of the BCD-ring system of C_{19}-diterpene alkaloids was initiated by development of a ring expansion reaction of cyclic enamino-esters with propiolic acid esters, leading from the 5-membered ring ketone **3** to the 7-membered ring ketone **10**. Epoxidation and stereospecific reductive epoxide ring opening to give hydroxy ester **18** were subsequent key-steps which eventually furnished cyclic β-keto ester **22**. This versatile intermediate has a full potential of functional groups suited for further elaboration into the A-, E- and F-rings and substituents of a variety of C_{19}-diterpene alkaloids.

INTRODUCTION

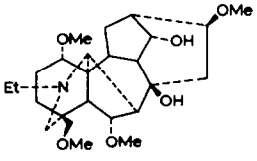
C_{19}-diterpene alkaloids constitute a class of natural products, mainly isolated from plants of the Delphinium and Aconitum genera, which are characterized by an intricate hexacyclic ring system, heavily substituted by hydroxy, methoxy and acyloxy groups. Differences among the numerous members of this alkaloid family are determined by type, number and position of these substituents on the basic skeleton which mostly is modelled on the carbon frame work of aconane.[1]



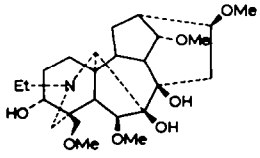
aconane



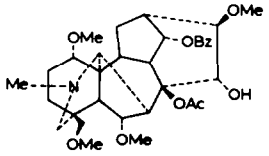
cardiopetaline



chasmanine



isodelphinine

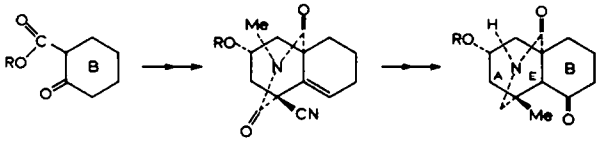


acomonine

Some typical representatives with varying complexity in the substitution pattern of the aconane skeleton are shown above. Many of these alkaloids are of interest because of their complex structures, unique chemistry and varied applications that range from human poisons to traditional medical uses.[2]

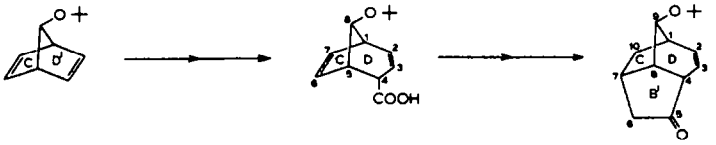
The total synthesis of the C_{19}-diterpene alkaloids is a conspicuous challenge. The most important and impressive contributions have undoubtedly been made by Wiesner and his colleagues who have developed some highly efficient methods for the construction of these compounds, culminating in the total synthesis of chasmanine.[3]

Our own (published) work in this area, sofar, has been directed on the one hand to the development of a general building principle for the attachment of the A- and E-ring to an existing BC-ground skeleton, providing sufficient functionality, properly situated, to enable elaboration of the other rings and substituents as well. As a part of this programme, we investigated the Knoevenagel reaction of cyclic β-keto esters (as a model for the B-ring) and malononitrile, and succeeded in the construction of compounds of type **1**[4]; **1** recently has been transformed into **2** as a model for the ABE-ring system of C_{20}-diterpene alkaloids.[5]



1 **2**

On the other hand, early efforts in this laboratory to develop methods for the synthesis of substituted bicyclo[3.2.1]octane derivatives (CD-ring system) starting from 7-*tert*-butoxy-norbornadiene have led to an efficient synthesis of **3**.[6]



3

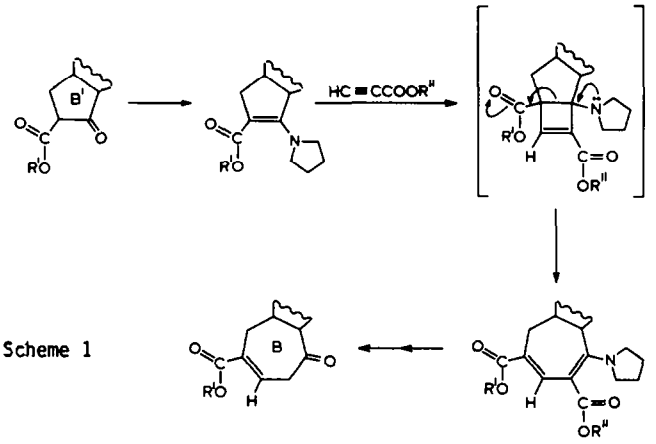
In our synthetic strategy, the tricyclic compound **3** can be regarded as a favourable relay for the construction of the BCD-ring system provided that the cyclopentanone ring B' can be transformed into a properly functionalized seven-membered cyclic β-keto ester system, to link up with the synthetic methodology summarized above.

In the present paper[7] we wish to describe a synthetic procedure leading to a tricyclic β-keto ester as a BCD-ring system, in which the attachment of the A-, E- and F-ring can be achieved according to methodology already developed in model systems and in which the D-ring can be provided with a variety of oxygen functions present in many types of C_{19}-diterpene alkaloids.

RESULTS AND DISCUSSION

Inspection of the literature with respect to ring enlargement reactions of a five-membered ring with a two carbon fragment, revealed that the addition of esters of propiolic acid to enamines derived from cyclic ketones[8] was in fact the only reaction known to meet our synthetic requirements, at least in principle. In our approach, this reaction ought to be feasible with

a cyclic enamino-ester as a reaction partner (Scheme 1) because the carbonyl group of the ester, in a later stadium of the synthesis, had to serve as a juncture (C-17) for the E- and F-ring.

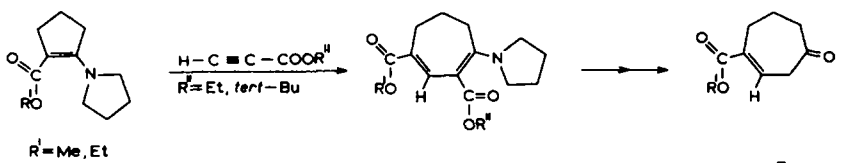


Scheme 1

However, while many reactions between simple cyclic enamines and acetylenic mono- and dicarboxylic acid esters are known, a similar reaction of an enamino-ester has only been described for an acyclic case.[9]

Mechanistically, the ring enlargement of cyclohexenyl-enamines (without ester group) is described as an addition of the enamine to the triple bond forming a zwitterionic intermediate which cyclizes to a cyclobutene adduct.[8,9,10] Ring opening of the latter can proceed thermally via a concerted conrotatory process; this has been shown[10] to give primarily a strained *cis, trans*-1,3-cyclooctadiene which isomerizes subsequently to the more stable *cis, cis*-1,3-cyclooctadiene. With cyclopentenyl-enamines, the intermediacy of the primary highly strained *cis, trans*-1,3-cycloheptadiene could not be proved.[10] In our view, the ring opening of the cyclobutene intermediate formed by reaction of enamines of cyclic β-ketoesters and propiolic acid esters, can easily occur *via* a polar mechanism of retro-aldol type (Scheme 1) leading directly to the final stable *cis,cis*-reaction product; in this mechanism the ester group is expected to facilitate the ring enlargement reaction.

Execution of this reaction with ethyl propiolate and the pyrrolidine-enamine of ethoxycarbonyl-cyclopentanone (as a model for the B-ring) indeed gave the ring enlargement product **4** (R'=R"=Et) in 36% yield, characterized by a typical singulet in the ^{1}H-NMR spectrum at δ 7.9 ppm, which we assign to the vinylic proton. Variation of solvent (benzene, diethyl ether, DME, DMF), reaction time and temperature had no beneficial effect on the yield. Use of *tert*-butyl propiolate lowered the yield to 22%.

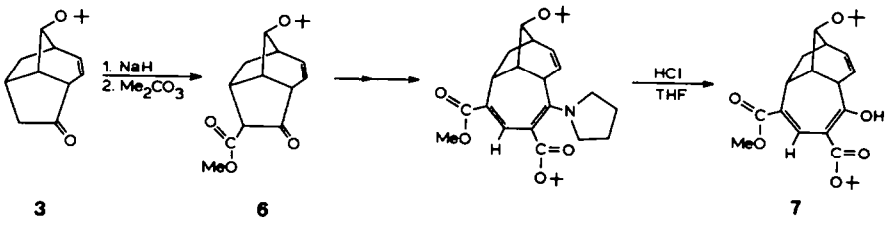


4 **5**

Conversion to the desired **5** could, however, be accomplished in high overall-yield by hydrolysis of the enamine **4** (R" = *tert*-butyl) with dilute hydrochloric acid in THF at room temperature followed by removal of the *tert*-butyl group and simultaneous decarboxylation by boiling during 4 min. in glacial acetic acid with a catalytic amount of p-toluenesulfonic acid. The resulting oily product **5** was identified by its ^{1}H-NMR spectrum (tt of 1H at δ 6.86, ^3J = 6, ^3J = 1, and dt of 2H at δ 3.33, ^3J = 6, ^4J = 1) which confirmed the presence of a C=CH-CH_2-C=O moiety. The

The isomer in which the C=C- bond is conjugated to the keto-carbonyl group was not found.

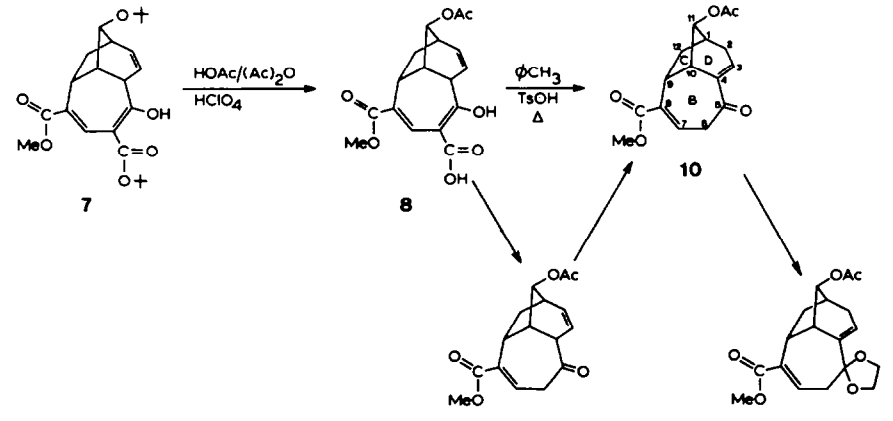
In spite of the moderate success met with the model compound, it was decided to apply the ring expansion reaction to the tricyclic β-keto ester 6 derived from ketone 3.



3 6 7

Reaction of 3 with dimethyl carbonate and NaH[11] gave a 96% yield of β-keto ester 6 as starting material. The crude product was converted to the enamino-ester by reaction with pyrrolidine and magnesium sulfate in a mixture of THF and diethyl ether.[12] Without purification, the enamine was treated with *tert*-butyl propiolate in toluene at 80°C to yield a brown-yellow solid which again in crude form was hydrolyzed by stirring overnight with dilute hydrochloric acid in THF. After crystallization, the ring expansion product 7 was obtained in 58% yield together with 38% of starting material 6. Taking into account the amount of recovered starting material, the ring expansion of the tricyclic compound is almost quantitative! We here have encountered one of the rare examples where the model reaction (to 5) turned out to be much worse than the real case, and actually misleading.

Direct conversion of 7 to the desired keton 10 with boiling glacial acetic acid, as applied in the model system, did not give useful results. Therefore, a stepwise procedure was followed. Treatment of 7 with a mixture of acetic acid, acetic anhydride and 70% perchloric acid during a few minutes at room temperature furnished an almost quantitative yield of the fully enolized β-keto acid 8 in which the *tert*-butoxy substituent at the bridge position had been replaced by an acetoxy group. Probably as a consequence of the complete enolization, β-keto acid 8 was surprisingly stable, but could be decarboxylated by heating in boiling toluene. In the presence of p-toluenesulfonic acid during 3 hours, the double bond in the D-ring shifted into conjugation with the developing carbonyl group in ring B to give 10. Without acid, the slightly unstable β,γ-unsaturated ketone 9 was formed which in turn could be converted to the conjugated isomer 10 by heating in toluene in the presence of acid.



7 8 10

9 11

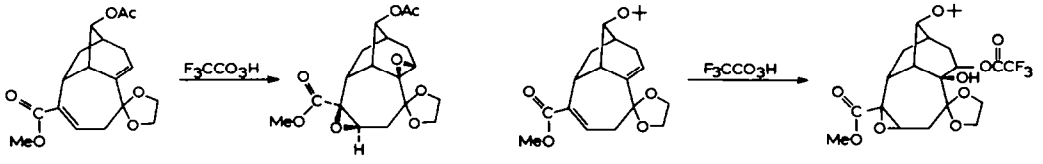
Structural assignment of **10** was established by its ^{1}H- and ^{13}C-NMR spectra and comparison with those of the model compound **5**.

Finally, the carbonyl group in ring B (which is both the position of juncture of ring F in a later stage and a precursor of the OH-group present at this position in many C_{19}-diterpene alkaloids) was protected by dioxolane formation to give **11**.

With **11** in hand, the stage was set for attachment of the required oxygen functions in the D-ring *via* the double bond, and for transformation of the α,β-unsaturated ester group of the B-ring into a β-keto ester system as a versatile starting point[4,5] for the construction of the A-, E- and F-rings including their proper substituents. In principle, many oxidative pathways are suited to functionalize the B- and D-ring individually. Although such a sequential approach would give more flexibility in terms of synthetic variation, functionalization of both rings simultaneously by epoxidation also seemed to be an attractive route for the following reasons. Introduction of an epoxy group into ring D, followed by reductive cleavage at an appropriate stage, would furnish an oxygen function at C-8, which is present in practically all C_{19}-diterpene alkaloids known.[1] By hydrolysis of the epoxide, the 1,2-diol function at C-8 and C-15, present in some of these alkaloids, would also be attainable.

Furthermore, by allylic oxidation at C-16 before epoxidation (and reductive and/or hydrolytic manipulation) the oxygen function present at this position in most C_{19}-alkaloids[1] might be introduced. Epoxidation of ring B, followed by reductive cleavage, would give access to a β-hydroxy ester which is expected to readily give the desired β-keto ester.

Epoxidation of **11** with peroxytrifluoroacetic acid at 40°C in dichloromethane and dipotassium hydrogen phosphate as a solid buffer,[13] gave di-epoxide **12** in 75% yield. From TLC, ^{1}H-NMR and ^{13}C-NMR data it was concluded that only one stereoisomer was formed (by X-ray crystal structure determination of the derivative **18** from **12**, *vide infra*, the structure of **12** was established as depicted). Probably as a consequence of the required high reaction temperature, epoxidation with m-chlorobenzoic acid gave a mixture of isomeric epoxides in a lower yield.

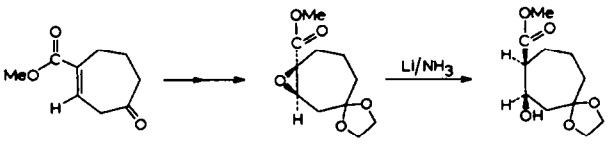


11 **12** **13** **14**

The course of the epoxidation reaction was unexpectedly influenced by the nature of the substituent on the bridge (C-14). Epoxidation of the *tert*-butoxy compound **13**[7] with peroxytrifluoroacetic acid, in the presence of dipotassium hydrogen phosphate or even sodium carbonate as a strongly basic buffer, gave a product which, according to IR [absorption at 3335 (OH) and 1783 cm^{-1} (CF_3COO)], ^{1}H-NMR (resonance of broad doublet at δ 5.18 ppm indicative of CF_3COOCH) and ^{13}C-NMR spectra (resonances at δ 155.5 (C=O) and δ 114.3 ppm (CF_3) as quartets with a C-F coupling of 42.5 Hz and of 287 Hz, respectively), was the trifluoroacetate **14** of unknown configuration. An analogous result was obtained with m-chloroperbenzoic acid. Although the origin of the difference in behaviour of **11** and **13** is not clear, it seems likely that precoordination of the peroxy acid to the basic ether oxygen of **13** rather than attack of trifluoroacetate on an intermediate epoxide is a key factor in the mechanism of formation of **14**.

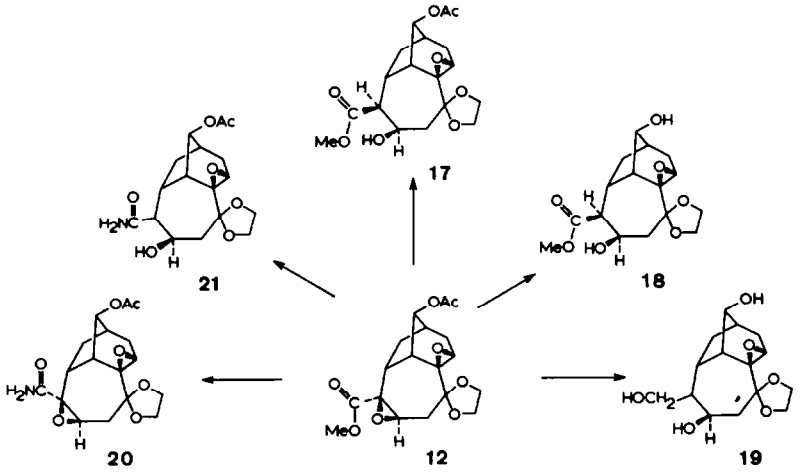
Reductive ring opening of di-epoxide **12** was tested with model **15** obtained by dioxolane protection and subsequent epoxidation of **5**. Several methods (compatible with the presence of additional functional groups in **12**) such as reaction with sodium iodide in acetone[14] and with organocuprates[15] were applied to **15**, however without useful results.

Reaction with lithium in liquid ammonia at -78°C (mentioned once in the literature[16] for the conversion of β,β-pentamethyleneglycidate into the corresponding β-hydroxy ester) was more successful. Application of an improved version of this method to 15 gave the β-hydroxy ester 16 as a single reaction product in *ca.* 70% yield (on the analogy of results with tricyclic compounds, the configuration of the ester and hydroxy group in 16 is assumed to be cis, *vide infra*).



5 15 16

However, when applied to 12, this reaction gave a mixture of several closely related products which were separated by column chromatography and identified by ^{1}H-, ^{13}C-NMR and IR spectroscopy. While it was immediately clear that the epoxy group in the D-ring was not affected (probably as a consequence of steric hindrance), it turned out (Scheme 2) that the two useful reaction products 17 and 18, with and without acetyl group at the bridge, were formed in only 20-25% combined yield, besides the overreduction product 19 and the two amides 20 and 21 (10-20% yield). Usually, the combined yield of identified reaction products in this capricious reaction was not better than 60%.



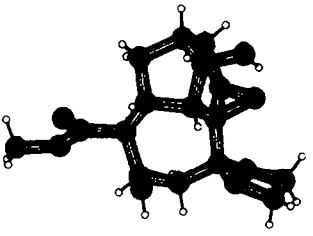
Scheme 2

In a detailed study, it was determined that the overreduction product 19 only arises by the action of an excess of lithium in ammonia, *i.e.* when the substrate is added slowly to the solution of lithium or when deliberately a very large excess of lithium is used. In the latter case, using 10 equivalents of lithium, only 18 and 19 were found in the reaction mixture, indicating that the formation of amides is a relatively slow process which becomes prominent only if a deficient amount of lithium is used for the reduction of the glycidate. The amides 20 and 21 probably originate from the attack of lithium amide (which in its turn is formed by the action of ammonia on carbanions initially formed in the reaction mixture) on the very reactive glycidate ester group; this undesired side reaction can be avoided by addition of a stronger proton donor. On the basis of these considerations reaction conditions could be devised which gave a good and reproducible yield of the desired products 17 and 18 without formation of the side products 19, 20 and 21. Thus, the substrate 12 dissolved in THF and a large excess of

tert-butanol as a proton source, was added very rapidly (within 5 seconds) to an intensively stirred blue solution of 4 equivalents of lithium in liquid ammonia at -78°C. Immediately after the disappearance of the colour (which occurred within seconds) the reaction mixture was quenched with an excess of ammonium chloride. In this way, after a normal work-up procedure including column chromatography, a 1:2 mixture of the β-hydroxy esters **17** and **18** was obtained in *ca.* 75% yield. The acetoxy compound **17** subsequently could be transformed into the hydroxy compound **18** in almost quantitative yield by potassium carbonate in aqueous methanol.[17]

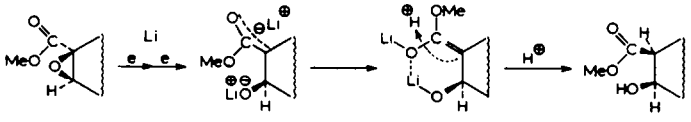
The relative configuration of the hydroxy compound **18** was determined by X-ray crystal structure determination; the details of the structure determination will be published elsewhere.[18] The ORTEP drawing of the structure of **18**, portrayed in Fig. 1, clearly shows as the

Figure 1
ORTEP drawing of 18



most salient feature that both the hydroxy and methoxycarbonyl group, originating from reductive ring opening of the glycidate, have the *exo*-configuration. Assuming that opening of the epoxide group proceeds with retention of configuration at the hydroxyl bearing carbon, it follows that the configuration of di-epoxide **12** is as shown.

The *cis*-relationship of hydroxy and ester group of **18** is not important from a synthetic point of view; however, it gives a decisive clue to the mechanism and stereochemistry of the epoxide ring opening and subsequent protonation. On the analogy of the reaction of lithium in ammonia with α,β-epoxyketones[19] and with α,β-unsaturated ketones[20], it is plausible that reductive ring opening starts with single electron transfer to the ester carbonyl group; this is followed by opening of the epoxide ring, and by transfer of a second electron to give a β-hydroxy ester dianion (Scheme 3).

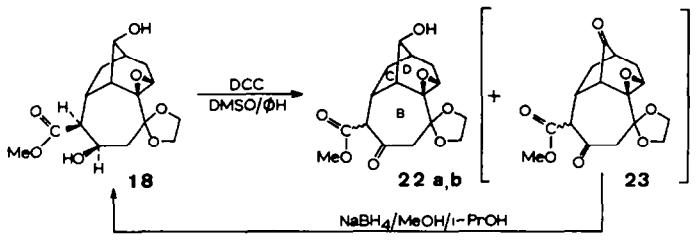


Scheme 3

Fráter et al. [21] and Kraus et al. [22] assume that lithium dianions of β-hydroxy esters have a stable chelate structure as a consequence of electrostatic interactions between the anionic oxygen atoms and the lithium cations. Electrophilic attack on this 6-ring chelate is postulated to occur from the less hindered side in order to explain the observed stereoselectivity in the alkylation of these dianions. Similarly, we suppose that protonation of the β-hydroxy ester dianion formed by ring opening of glycidate **12** with lithium in ammonia takes place from the less hindered side; inspection of molecular models shows this to be the *endo*-side. This brings about the *exo*-configuration of the ester group in **18**.

The last operation to be tackled in the present synthesis was the oxidation of **18** to the β-keto ester **22**. As it turned out, it was not necessary to protect the OH at the bridge; as a consequence of steric hindrance and of ring strain, oxidation at this position was much slower than that of the hydroxyl group in ring B. The best results were obtained by the Pfitzner-Moffat method[23] (DCC, DMSO, pyridinium trifluoroacetate) which gave **22** in 65% isolated yield, besides a small amount of the di-oxidation product **23** (which could be recycled by $NaBH_4$-reduction). Before column chromatography purification on silica, **22** is a single com-

pound which, *via* the keto-enol equilibrium, is converted to a 2:1 mixture of isomeric β-keto esters **22a** + **22b**, with **22a**, the isomer with the original *exo*-configuration, prevailing.



β-Keto ester **22** comprises the BCD-ring system with a full potential of functional groups suitable for further elaboration into the A-, E- and F-rings and substituents of C_{19}-diterpene alkaloids. The formation of a mixture of isomers of **22** is not of importance with respect to future synthetic operations leading to attachment of the A-ring, since use of the (planar) anion of **22** is anticipated.

The synthetic possibilities of the seven-membered cyclic β-keto ester **22** have been explored in model systems and have successfully led to the construction of the A-ring with oxygen functions at C-1 or C-3.

Application of this methodology will be the subject of future publications.

Acknowledgement

We thank Dr. A.L. Spek, Rijksuniversiteit Utrecht, for the crystal structure determination which was financed by the Netherlands Foundation for Chemical Research (SON) with funds obtained from the Netherlands Organization for the Advancement of Pure Research (ZWO).

EXPERIMENTAL

General

IR spectra of *ca.* 4% solutions in $CHCl_3$ were recorded with a Perkin-Elmer 580B spectrophotometer; relevant resonances are given in cm^{-1}. ^{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 internal reference. ^{13}C-NMR spectra of $CDCl_3$-solutions were measured with a Bruker WH-90 (22.63 MHz) or a Bruker WM-250 (62.8 MHz) spectrometer with $CDCl_3$ (δ = 77.0 ppm) as internal reference. Chemical shifts δ 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. Melting points were determined on a Kofler hot stage apparatus under a Reichert microscope and are uncorrected.

All reactions were performed with purified reagents in a N_2 atmosphere.

endo-9-*tert*-Butoxytricyclo[5.2.1.$0^{4,8}$]dec-2-en-5-one (3)

A brief account of the synthesis of **3** has been published[6]; full details are described below. To a stirred solution of *endo*-8-*tert*-butoxybicyclo[3.2.1]octa-2,6-diene-4-*endo*-carboxylic acid[6] (39.25 g, 0.177 mole) in dry Et_2O (525 ml) and dry pyridine (16 ml), a solution of $SOCl_2$ (20 ml) in dry Et_2O (66 ml) was added in 1 hr (temperature 0-5°C). After stirring for 4.5 hr at room temperature, the reaction mixture was filtered and the filtrate concentrated *in vacuo*. The oily residue (42.5 g, 0.177 mole), dissolved in dry Et_2O (260 ml), was added dropwise in 1.5 hr to an ice-cooled stirred solution of CH_2N_2 in Et_2O (1 l of a 0.4 M solution). After stirring overnight at 5°C, the reaction mixture was concentrated *in vacuo* to yield the diazoketone [43.5 g; IR: 2105 ($-CH_2=N_2$)] which was dissolved in cyclohexane (400 ml) and added in 0.5 hr to a boiling suspension of copper-bronze (12 g) in cyclohexane (900 ml). During this addition, additional copper-bronze (36 g) was added in 5 equal portions. After boiling for an additional hr, the cooled reaction mixture was filtered over hyflo and evaporated *in vacuo* to yield a dark brown residue (43.25 g; IR: no absorbance at 2105) which was sublimed at 140-150°C/10^{-2} mm Hg and recrystallized from Et_2O to furnish *exo*-10-*tert*-butoxytetracyclo[4.4.0.$0^{2,4}$.$0^{3,9}$]-dec-7-en-5-one {12.42 g, 32.2%), m.p. 89-91°C; ^{1}H-NMR: 6.24 - 5.56 (m, 2H, H-7, H-8), 4.11 (dd, ^{3}J = 5.5, ^{3}J = 2.5, 1H, H-10), 3.07 - 2.41 (m, 4H, H-1, H-4, H-6, H-9), 2.19 - 1.63 (m, 2H, H-2, H-3), 1.16 (s, 9H, *tert*-butyl); IR: 1701 (C=O).

The cyclopropane ring of this ketone (4.6 g, 21.1 mmole) was opened by dropwise addition of a solution in dry THF (100 ml) to a vigorously stirred solution of Li (4.0 g, 0.57 mole) in NH_3 (1000 ml) at -65°C over a period of 0.5 hr. After additional stirring under reflux during 3 hr, solid NH_4Cl was added in small portions until the blue colour had disappeared. The NH_3 was evaporated overnight and, after addition of Et_2O (400 ml), H_2O was added until all salts had dissolved. Separation of the organic layer, extraction with Et_2O (3x), drying and evaporation of solvent *in vacuo*, gave a yellow oil (4.8 g) which according to IR was a mixture of ketone and alcohol. This was dissolved in dry DMF (110 ml) and to the stirred solution, cooled in ice, pyridinium dichromate[24] (30.2 g, 86.6 mmole) was added in 10 min. After stirring during 7 hr at 0°C, the homogeneous dark-brown mixture was poured into H_2O (1100 ml) and extracted with Et_2O (6x). The combined organic layers were washed with 1 N NH_4OH, dried and concentrated *in vacuo* to yield **3** (4.47 g, 96%), m.p. 53-57°C (after sublimation at 40-70°C/0.4-0.5 mm Hg); ^{1}H-NMR: 6.03 (dd, ^3J = 9.5; ^3J = 6.5, 1H, H-2), 5.59 (dd, ^3J = 9.5, ^3J = 4, 1H, H-3), 4.04 (dd, ^3J = 4, ^3J = 4. 1H, H-9), 3.13 (m, 1H, H-4), 2.70 (m, 2H, H-7, H-8), 2.47 - 2.08 (m, 3H, H-1, H-6), 1.64 - 1.14 (m, 2H, H-10), 1.22 (s, 9H, *tert*-butyl); IR: 1740 (C=O).
(Found: C, 75.75; H, 9.21. Calc. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15%).

O^3-*tert*-Butyl O^1-methyl 4-N-pyrrolidinylcyclohepta-1,3-diene-1,3-dicarboxylate (**4**)

A solution of *tert*-butyl propiolate (23.9 g, 0.19 mole) in dry toluene (90 ml) was added dropwise in 15 min. to a stirred solution of methyl 2-N-pyrrolidinylcyclopent-1-ene-1-carboxylate[25] (36.9 g, 0.19 mole) in dry toluene (90 ml). After 10 min. at room temperature, the mixture was heated for 1 hr at 80°C, cooled and evaporated *in vacuo*. The brown oily residue was dissolved in Et_2O upon which **4** (13.4 g, 22%) crystallized as bright-yellow crystals, m.p. 152-154°C; ^{1}H-NMR: 7.74 (s, 1H, H-2), 3.75 (s, 3H, OCH_3), 3.59 - 3.38 (m, 4H, CH_2NCH_2), 2.47 - 2.16 (m, 6H, H-5, H-6, H-7), 2.06 - 1.86 (m, 4H), 1.51 (s, 9H, *tert*-butyl); IR: 1680 (C=O), 1655 (C=C).

Methyl 4-oxocyclohept-1-ene-1-carboxylate (**5**)

A solution of **4** (23.0 g, 72 mmole) in THF (275 ml) and 1 N HCl (275 ml) was stirred vigorously overnight. After evaporation of THF *in vacuo* at 50°C, the hydrolyzed compound crystallized from the water layer, was collected and dried (18.3 g, 95%), m.p. 89-90°C; ^{1}H-NMR: 14.09 (s, 1H,OH), 7.65 (bs, 1H, H-2), 3.77 (s, 3H, OCH_3), 2.66 - 2.44 (m, 4H, H-5, H-7), 2.32 - 1.92 (m, 2H, H-6), 1.56 (s, 9H, *tert*-butyl).
The dry compound, dissolved in glacial acetic acid (400 ml) and p-toluenesulfonic acid (2.75 g), was heated in an oil bath of 150°C and boiled for 4 min. After cooling and evaporation at 45-50°C *in vacuo*, the residue was diluted with Et_2O and H_2O, and neutralized with solid $NaHCO_3$. Extraction with Et_2O, drying and evaporation of solvent *in vacuo* yielded **5** as a yellow oil (10.72 g, 94%), pure according to TLC (SiO_2, $CHCl_3$); ^{1}H-NMR: 6.86 (tt, ^3J = 6, ^3J = 1, 1H, H-2), 3.69 (s, 3H, OCH_3), 3.33 (dt, ^3J = 6, ^4J = 1, 2H, H-3), 2.72 - 2.48 (m, 4H, H-5, H-7), 2.15 - 1.87 (m, 2H, H-6); IR: 1708 (broad signal of C=O, ester and ketone), 1646 (C=C).

Methyl *endo*-9-*tert*-butoxy-5-oxotricyclo[5.2.1.$0^{4,8}$]dec-2-ene-6-carboxylate (**6**)

A suspension of NaH (2.16 g, 90 mmole) and **3** (6.60 g, 30 mmole in Me_2CO_3 (150 ml, freshly distilled) was boiled with stirring for 4 hr. After cooling, acidification with 4 N HOAc and extraction of the H_2O-layer with Et_2O (2x), the combined organic layers were washed with sat. $NaHCO_3$- and NaCl-solution, respectively, dried and concentrated *in vacuo*. The oily residue (8.35 g, 100%) solidified on standing and was pure according to TLC. It could be sublimed, or crystallized from p.e. 40-60 to yield **6** as light-yellow crystals, m.p. 71-76°C; ^{1}H-NMR: 6.07 (dd, ^3J = 9, ^3J = 7, 1H, H-2), 5.60 (ddd, ^3J = 9, ^3J = 4.5, ^4J = 1, 1H, H-3), 4.05 (dd, ^3J = 4.5, ^3J = 4.5, 1H, H-9), 3.75 (s, 3H, OCH_3), 3.43 - 3.19 (m, 2H, H-4, H-6), 3.16 - 2.71 (m, 1H, H-7), 2.52 - 2.24 (m, 2H, H-1, H-8), 1.75 - 1.09 (m, 2H, H-10), 1.22 (s, 9H, *tert*-butyl); IR: 1750, 1725 (C=O, ester and ketone). (Found: C, 69.06; H, 7.94. Calc. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97%.

O^6-*tert*-Butyl O^8-methyl 5-hydroxy-*endo*-11-*tert*-butoxytricyclo[7.2.1.$0^{4,10}$]dodeca--2,5,7-triene-6,8-dicarboxylate (**7**)

To an ice-cold stirred suspension of **6** (13.44 g, 48.3 mmole) and $MgSO_4$ (2.83 g) in dry Et_2O (70 ml) and dry THF (42 ml), pyrrolidine (5.75 ml) was added dropwise in 5 min. Then 3 portions of $MgSO_4$ (2.12 g each) were added at room temperature with intervals of 30 min., and stirring was continued for 1.5 hr. Filtration and concentration *in vacuo* yielded the enamino-ester (15.55 g, 97%) as a brown foam.
This was dissolved in dry toluene (60 ml) and treated with a solution of *tert*-butyl propiolate (5.92 g, 47 mmole) in dry toluene (60 ml) during 15 min. at room temperature. After heating for 1 hr. at 80°C, the cooled reaction mixture was concentrated *in vacuo*, and the residue was dissolved in THF (250 ml) and 0.3 N HCl (250 ml). After stirring overnight at room temperature, THF was evaporated *in vacuo* and the remaining water layer was extracted with Et_2O (3x). After washing with $NaHCO_3$- and NaCl-solution, respectively, drying and evaporation of solvent, Et_2O was added and crystalline **7** was collected. The filtrate was concentrated and chromatographed over SiO_2. The total yield of **7** was 11.29 g (58%), besides 5.16 g of starting material **6** (38%). M.p. of **7**: 122-124°C; ^{1}H-NMR: 14.33 (s, 1H, OH), 7.56 (d, ^4J = 2, 1H, H-7), 5.98 - 5.68 (m, 1H, H-2), 5.27 (ddd, ^3J = 9.5, ^3J = 2, ^4J = 2, 1H, H-3), 4.11 (broad signal, 2H, H-4, H-11), 3.74 (s, 3H, OCH_3), 3.58 - 3.16 (m, 1H, H-9), 2.63 - 2.11 (m, 3H, H-1, H-10, H-12-*exo*), 1.74 - 1.34 (m, 1H, H-12-*endo*), 1.56 (s, 9H, *tert*-butyl ester) , 1.23 (s, 9H, *tert*-butyl ether). (Found: C, 68,49; H, 8.01. Calc. for $C_{23}H_{32}O_5$; C, 68.29; H, 7.97%).

O^6-Hydrogen O^8-methyl *endo*-11-acetoxy-5-hydroxytricyclo[7.2.1.$0^{4,10}$]dodeca-2,5,7-triene-6,8-dicarboxylate (8)

$HClO_4$ (70%, 2.02 ml) was added to an ice-cold stirred solution of 7 (2.02 g, 5 mmole), in glacial acetic acid (40.4 ml) and acetic anhydride (10.1 ml). The cooling bath was then replaced by a bath of room temperature, and stirring was continued for 4 min. The reaction mixture was poured into ice-water (400 ml) and, after standing in the cold for 2 hr., the precipitate was collected and dried *in vacuo* to yield 8 (1.63 g, 97.5%), m.p. 121-123°C (dec.); ^{1}H-NMR: 13.78 (s, 1H, OH), 7.59 (d, ^4J = 2, 1H, H-7), 6.01 - 5.75 (m, 1H, H-2), 5.42 - 5.11 (m, 2H, H-3, H-11), 3.98 (broad signal, 1H, H-4), 3.77 (s, 3H, OCH_3), 3.63 - 3.30 (m, 1H, H-9), 2.80 - 2.36 (m, 3H, H-1, H-10, H-12-*exo*), 2.14 (s, 3H, acetoxy), 1.90 - 1.25 (m, 1H, H-12-*endo*). (Found: C, 60.85; H, 5.42. Calc. for $C_{17}H_{18}O_7$: C, 61.07; H, 5.42%).

Methyl *endo*-11-acetoxy-5-oxotricyclo[7.2.1.$0^{4,10}$]dodeca-2,7-diene-8-carboxylate (9)

A suspension of 8 (83.5 mg, 0.25 mmole) in dry toluene (2 ml) was heated to boiling. After 20 min., the homogeneous mixture was cooled, diluted with Et_2O and washed with $NaHCO_3$- and NaCl-solution, respectively. Drying and evaporation *in vacuo* yielded 9 as a yellow foam (66.6 mg, 92%), pure according to TLC; ^{1}H-NMR: 6.79 - 6.60 (m, 1H, H-7), 5.89 (broad signal, 2H, H-2, H-3), 5.17 (dd, ^3J = 4, ^3J = 4. 1H, H-11), 3.71 (s, 3H, OCH_3), 3.84 - 3.40 (m, 2H, H-6, H-9), 3.12 (dd, ^2J = 15.5, ^3J = 8.5, 1H, H-6), 3.21 - 3.00 (m, 1H, H-10), 2.71 - 2.17 (m, 2H, H-1, H-5), 2.07 (s, 3H, acetoxy), 1.68 - 1.06 (m, 2H, H-12); ^{13}C-NMR (22.63 MHz; off-resonance): 203.9 (s, C-5), 171.0 (s, acetoxy-*carbonyl*), 167.4 (s, methoxycarbonyl), 136.9 (s, C-8), 131.1 (d, C-7), 127.6 (d, C-2), 123.7 (d, C-3), 75.1 (d, C-11), 52.1 (q, methoxycarbonyl), 51.9 (d, C-4), 41.0 (t, C-6), 38.7 (2 x d, C-9, C-10), 35.1 (d, C-1), 29.4 (t, C-12), 21.0 (q, acetoxy-methyl).

Methyl *endo*-11-acetoxy-5-oxotricyclo[7.2.1.$0^{4,10}$]dodeca-3,7-diene-8-carboxylate (10)

A suspension of 8 (5.83 g, 17.5 mmole) and p-toluenesulfonic acid (205 mg) in dry toluene (221 ml) was heated to reflux for 3 hr. The work-up procedure as for 9 yielded a brown oil which was crystallized from a small amount of EtOAc to furnish 10 as colourless crystals (4.24 g, 84%), m.p. 116-118°C; ^{1}H-NMR: 6.82 (ddd, ^3J = 9, ^3J = 4, ^4J = 1.5, 1H, H-7), 6.61 (m, 1H, H-3), 5.11 (dd, ^3J = 4, ^3J = 3.5, 1H, H-11), 3.78 (ddd, ^2J = 16, ^3J = 4, ^5J(H-6-*exo*, H-9)? = 4, 1H, H-6-*exo*), 3.73 (s, 3H, OCH_3), 3.54 - 3.21 (m, 2H, H-9, H-10), 3.02 (dd, ^2J = 16, ^3J = 9, 1H, H-6-*endo*), 2.89 - 2.34 (m, 3H, H-1, H-2), 2.17 - 1.83 (m, 1H, H-12-*exo*), 2.05 (s, 3H, acetoxy), 1.45 - 1.15 (m, 1H, H-12-*endo*); ^{13}C-NMR (22.63 MHz; off-resonance): 198.7 (s, C-5), 170.8 (s, acetoxy-*carbonyl*), 167.3 (s, methoxy*carbonyl*), 138.1 (s, C-4), 135.6 (s, C-8), 135.0 (d, C-7), 131.3 (d, C-3), 73.7 (d, C-11), 51.8 (q, *methoxy*carbonyl), 43.8 (d, C-10), 40.2 (d + t, C-9, C-6), 36.1 (t, C-2), 31.7 (d + t, C-1, C-12), 21.0 (q, acetoxy-*methyl*); IR (KBr): 1730, 1709, 1690 (C=O), 1626 (C=C). (Found: C, 66.24; H, 6.28. Calc. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25%).

Methyl *endo*-11-acetoxy-5,5-ethylenedioxytricyclo[7.2.1.$0^{4,10}$]dodeca-3,7-diene-8-carboxylate (11)

A solution of 10 (7.25 g, 25 mmole), ethanediol (7.75 g, 125 mmole) and p-toluenesulfonic acid (250 mg) in benzene (220 ml) was refluxed *via* a Dean-Stark apparatus filled with mol-sieves 4 Å. After 6 hr. the mixture was cooled, diluted with Et_2O, washed with sat. $NaHCO_3$- and NaCl-solution, respectively, dried and concentrated *in vacuo*. The residue was purified by column chromatography and crystallization from Et_2O, yielding 11 as colourless crystals (6.89 g, 82.5%), m.p. 118-121°C; ^{1}H-NMR: 6.76 (ddd, ^3J = 9, ^3J = 5, ^4J = 2, 1H, H-7), 5.78 (broad signal, 1H, H-3), 4.99 (dd, ^3J = 4.5, ^3J = 4.5, 1H, H-11), 4.10 - 3,69 (m, 4H, OCH_2CH_2O), 3.68 (s, 3H, OCH_3), 3.41 - 2.82 (m, 3H, H-6-*exo*, H-9, H-10), 2.75 - 2.25 (m, 4H, H-1, H-2, H-6-*endo*), 2.06 (s, 3H, acetoxy), 1.96 - 1.62 (m, 1H, H-12-*exo*), 1.33 - 1.02 (m, 1H, H-12-*endo*); ^{13}C-NMR (off-resonance): 170.7 (s, acetoxy-*carbonyl*), 167.8 (s, methoxy*carbonyl*), 136.8 (s, C-4), 135.8 (s, C-8), 133.6 (d, C-7), 121.0 (d, C-3), 111.4 (s, C-5), 73.8 (d, C-11), 65.5 and 62.7 (2 x t, OCH_2CH_2O), 51.4 (q, *methoxy*-carbonyl), 43.7 (d, C-10), 39.3 (d, C-9), 36.9 (t, C-6), 35.4 (t, C-2), 32.0 (d, C-1), 30.9 (t, C-12), 20.8 (q, acetoxy-*methyl*). (Found: C, 64.24; H, 6.55 . Calc. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63%).

Methyl *endo*-11-acetoxy-3,4,7,8-diepoxy-5,5-ethylenedioxytricyclo[7.2.1.$0^{4,10}$]dodecane-8-carboxylate (12)

To a mixture of 11 (1.61 g, 4.8 mmole) and K_2HPO_4 (13.36 g, 76.8 mmole, dried at 50°C *in vacuo* for 20 hr) in CH_2Cl_2 (20 ml), stirred and heated at 40°C, peroxytrifluoroacetic acid [prepared by dropwise addition of trifluoroacetic anhydride (6.05 g, 28.8 mmole) in 10 min. to a stirred mixture of H_2O_2 (655 µl 90%, 24 mmole) and CH_2Cl_2 (5 ml)] was added dropwise in 20 min. After additional stirring for 30 min. at 40°C, the mixture was cooled, and enough H_2O was added to dissolve all salts present. The water layer was extracted with CH_2Cl_2 (2x) and the combined organic layers were washed with $NaHCO_3$- and NaCl-solution, respectively. Drying and evaporation *in vacuo*, column chromatography over SiO_2, followed by crystallization from EtOAc gave 12 (1.32 g, 75%) as a colourless solid, m.p. 147-149°C; ^{1}H-NMR: 4.71 (dd, ^3J = 4, ^3J = 4, 1H, H-11), 4.13 - 3.77 (m, 4H, dioxolane), 3.74 (s, 3H, OCH_3), 3.59 (dd, ^3J = 5, ^3J = 1, 1H, H-7), 3.18 - 2.89 (m, 3H, H-3, H-9, H-10), 2.77 - 2.13 (m, 5H, H-1, H-2, H-6), 2.05 (s, 3H, acetoxy), 1.86 - 1.08 (m, 2H, H-12); ^{13}C-NMR: 170.6 (s, acetoxy-*carbonyl*), 170.4 (s, methoxy*carbonyl*), 106.2 (s, C-5), 76.2 (d, C-11), 65.9 and 65.0 (2 x t, OCH_2CH_2O), 62.5 and 62.2 (2 x s, C-4, C-8), 57.4 (d, C-7), 52.4 (q, *methoxy*carbonyl), 50.2 (d, C-3), 36.7 (d, C-10), 35.6 (t, C-6), 35.2 (d, C-9), 31.6 (t, C-2), 31.0 (d, C-1), 29.7 (t, C-12), 21.0 (q, acetoxy-*methyl*); IR: 1732 (C=O). (Found: C, 58.95; H, 5.98. Calc. for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05%).

Methyl 1,2-epoxy-4,4-ethylenedioxycycloheptane-1-carboxylate (15)

A solution of 5(336 mg, 2 mmole), ethanediol (155 mg, 2.5 mmole), and p-toluenesulfonic acid (20 mg) in benzene (15 ml) was heated to reflux for 4.5 hr with continueous removal of H_2O. After the usual work-up, the dioxolane was isolated as an oil (400 mg, 94%), homogeneous according to TLC (SiO_2, $CHCl_3$); ^{1}H-NMR: 6.94 (bt, ^3J = 7, 1H, H-2), 3.96 (s, 4H, OCH_2CH_2O), 3.73 (s, 3H, OCH_3), 2.65 - 2.47 (m, 4H, H-3, H-7), 2.08 - 1.86 (m, 2H, H-5), 1.82 - 1.51 (m, 2H, H-6); IR: 1698 (C=O, ester), 1642 (C=C).
This compound was epoxidized as described for 12, yielding (without further purification) 15 as a colourless solid (381 mg, 89%), m.p. 31-33°C; ^{1}H-NMR: 3.96 (bs, 4H, OCH_2CH_2O), 3.76 (s, 3H, OCH_3), 3.27 (dd, ^3J = 6.5, ^3J = 3.5, 1H, H-2), 2.89 - 2.38 (m, 2H, H-3), 2.05 - 1.45 (m, 6H, H-5, H-6, H-7); ^{13}C-NMR (22.63 MHz; off-resonance): 171.3 (s, methoxy*carbonyl*), 109.1 (s, C-4), 64.5 and 64.0 (2 x t, OCH_2CH_2O), 59.5 (s, C-1), 56.1 (d, C-2), 52.4 (q, *methoxy*carbonyl), 40.0 (t, C-3), 38.6 (t, C-5), 28.7 (t, C-7), 19.8 (t, C-6); IR: 1735 (C=O).
Mass-spectrum: Calc. for $C_{11}H_{16}O_5$: 228.0997.
Found: 228.0988 (2.1%), 169 (80%), 99 (100%).

Methyl 4,4-ethylenedioxy-2-hydroxycycloheptane-1-carboxylate (16)

To a vigorously stirred solution of 15 (1.14 g, 5 mmole) in dry THF (20 ml), ammonia (150 ml, distilled from Na) was added, followed (after cooling to -78°C) by Li (87.5 mg, 12.5 mmole). After all Li had dissolved, an excess of NH_4Cl was added, and ammonia was evaporated. The residue was concentrated *in vacuo*, dissolves in conc. $NaHCO_3$-solution (100 ml), saturated with solid NaCl, and extracted with Et_2O (3x). Drying and evaporation of solvent gave 16 (802 mg, 70%), which was further purified by column chromatography, furnishing 16 as colourless crystals, m.p. 66-73°C; ^{1}H-NMR: 4.28 - 4.00 (m, 1H, H-2), 3.95 (m, 4H, OCH_2CH_2O), 3.71 (s, 3H, OCH_3), 2.81 (d, ^3J = 6, 1H, OH), 2.83 - 2.48 (m, 1H, H-1), 2.10 (bd, ^3J = 5, 2H, H-3), 2.03 - 1.56 (m, 6H, H-5, H-6, H-7); ^{13}C-NMR (23.63 MHz; off-resonance): 175.7 (s, methoxy*carbonyl*), 109.8 (s, C-4), 68.2 (d, C-2), 64.0 and 63.9 (2 x t, OCH_2CH_2O), 53.9 (d, C-1), 51.6 (q, *methoxy*carbonyl), 44.3 (t, C-3), 38.5 (t, C-5), 28.3 (t, C-7), 21.6 (t, C-6). IR: 3450 (br, OH), 1720 (C=O). (Found: C, 57.23; H, 7.94. Calc. for $C_{11}H_{18}O_5$: C, 57,38; H, 7.88%).

Methyl *endo*-11-acetoxy-3,4-epoxy-5,5-ethylenedioxy-*exo*-7-hydroxytricyclo[7.2.1.0^{4,10}]dodecane--8-carboxylate (17) and methyl 3,4-epoxy-5,5-ethylenedioxy-*exo*-7-*endo*-11-dihydrotricyclo-[7.2.1.0^{4,10}]dodecane-8-carboxylate (18)

A solution of 12 (732 mg, 2 mmole) in dry THF (16 ml) and dry *tert*-BuOH (3.2 ml) was added very fast (within 5 sec.) to a vigorously stirred solution of Li (56 mg, 8 mmole) in NH_3 (120 ml, distilled from Na). Immediately after decolorization, the addition was stopped, and the reaction mixture treated as fast as possible with a large excess of NH_4Cl (in this typical example, the blue colour disappeared after addition of 494.5 mg of 12 so that 237.5 mg of 12 was not added). Then, NH_3 was evaporated and the residue concentrated *in vacuo* at room temperature. Conc. $NaHCO_3$-solution (120 ml) was added with ice-cooling, and, after saturation with solid NaCl, the mixture was extracted with EtOAc (3x). The combined extracts were dried and evaporated, leaving a mixture of 12, 17 and 18 which was separated by column chromatography, giving 12 (47 mg,10%),17 as a colourless foam (98.5 mg, 20%) and 18 (204.8 mg, 46.5%), m.p. 179-181°C.

17. ^{1}H-NMR: 4.68 (dd, ^3J = 4, ^3J = 4, 1H, H-11), 4.34 (dd, ^3J = 6, ^3J = 4, 1H, H-7), 4.29 - 3.78 (m, 4H, OCH_2CH_2O), 3.74 (s, 3H, OCH_3), 3.28 (bdd, ^3J = 4.5, ^3J = 4.5, 1H, H-9), 3.11 (bd, ^3J = 4, 1H, H-10), 2.98 - 2.50 (m, 3H, H-3, H-8, OH), 2.48 - 2.01 (m, 5H, H-1, H-2, H-6), 2.05 (s, 3H, acetoxy), 1.94 - 1.58 (m, 1H, H-12-*exo*), 1.36 - 0.99 (m, 1H, H-12-*endo*); ^{13}C-NMR: 174.8 (s, methoxy*carbonyl*), 170.0 (s, acetoxy-*carbonyl*), 107.8 (s, C-5), 76.0 (d, ^1J = 154, C-11), 67.2 (d, ^1J = 149, C-7), 66.0 and 65.8 (2 x t, ^1J = 149, ^1J = 150, OCH_2CH_2O), 64.0 (s, C-4), 55.6 (d, ^1J = 127, C-3), 52.2 (q, ^1J = 148, *methoxy*carbonyl), 51.4 (d, ^1J = 180, C-8), 43.9 (t, ^1J = 128, C-6), 36.4 (d, ^1J = 144, C-10), 36.1 (t, ^1J = 130, C-2), 33.3 (d, ^1J = 134, C-9), 32.2 (d, ^1J = 139, C-1), 30.5 (t, ^1J = 127, C-12), 21.2 (q, ^1J = 129, acetoxy-*methyl*); IR: 3541 (OH), 1728 (C=O).

18. ^{1}H-NMR: 4.71 (d, ^3J = 11. 1H, OH), 4.34 (m; after exchange with D_2O; dd, ^3J = 5.5, ^3J = 3, 1H, H-7), 4.18 - 3.76 (m, 5H, H-11, OCH_2CH_2O), 3.74 (s, 3H, OCH_3), 3.31 (bd, ^3J = 4, 1H, H-9), 3.01 (bdd, ^3J = 4.5, ^3J = 4.5, 1H, H-10), 2.94 (d, ^3J = 5, 1H, OH), 2.74 - 1.66 (m, 8H, H-1, H-2, H-3, H-6, H-8, H-12-*exo*), 1.29 - 0.96 (m, 1H, H-12-*endo*); ^{13}C-NMR: 174.8 (s, methoxy*carbonyl*), 107.4 (s, C-5), 77.0 (d, ^1J = 147, C-11), 67.8 (s, C-4), 67.2 (d, ^1J = 143, C-7), 65.9 and 65.8 (2 x t, ^1J = 150, ^1J = 151, OCH_2CH_2O), 56.1 (d, ^1J = 128, C-3), 54.2 (d, ^1J = 174, C-8), 52.1 (q, ^1J = 148, *methoxy*carbonyl), 44.0 (t, ^1J = 130, C-6), 36.9 (d and t, ^1J = 143, ^1J = 132, C-10, C-2), 34.6 (d, ^1J = 136, C-9), 33.0 (d, ^1J = 134, C-1), 30.2 (t, ^1J = 127, C-12); IR: 3530 and 3455 (OH); 1730 (C=O). (Found: C, 58.84; H, 6.74. Calc. for $C_{16}H_{22}O_7$: C, 58.88; H, 6.80%.

Methyl 3,4-epoxy-5,5-ethylenedioxy-*endo*-11-hydroxy-7-oxotricyclo[7.2.1.0^{4,10}]dodecane--8-carboxylate (22)

To a solution of 18 (285.8 mg, 0.88 mmole) in dry benzene (2.9 ml) and dry DMSO (2.9 ml), dicyclohexylcarbodiimide (199.7 mg, 0.968 mmole) and pyridinium trifluoroacetate (85 mg, 0.44 mmole) was added. After stirring at room temperature for 40 hr, the reaction mixture was diluted with EtOAc, filtered, and washed with H_2O (3x). The H_2O layer was extracted with EtOAc (2x) and the combined organic extracts were washed with H_2O, dried and evaporated to dryness. Column chromatography yielded 18 (51.4 mg, 18%), 22 as a colourless foam (150 mg, 53%), and 23 (29.0 mg, 9%). Calculated on converted 18 the yield of 22 is 65%.

22 (mixture of isomers). ^{1}H-NMR: 4.46 (d, ^3J = 11, 1H, OH), 4.36 - 3.85 (m, 5H, H-11, OCH_2CH_2O), 3.89 - 3.58 (m, 1H, H-8), 3.74 (65%) and 3.67 (35%)(2 x s, total 3H, OCH_3), 3.36 (bd, ^3J = 4.5, 0.65H, H-9), 3.14 - 2.70 (m, 4.35H, H-6, H-3, H-9, H-10), 2.71 - 2.01 (m, 3H, H-1, H-2), 1.98 - 1.55 (m, 1H, H-12-*exo*), 1.39 - 0.92 (m, 1H, H-12-*endo*); IR: 3460 (OH), 1745 (C=O, ester), 1713 (C=O, keton), 1652 (C=O of enol, very weak), 1615 (C=C of enol, very weak).

23 (mixture of isomers). ^{1}H-NMR: 4.22 - 3.84 (m, 4H, OCH_2CH_2O), 3.83 - 3.67 (m, 1H, H-8), 3.77 (65%) and 3.71 (35%) (2 x s, total 3H, OCH_3), 3.34 (bd, ^3J = 3, 0.65H, H-9), 3.14 - 2.78 (m, 4.35H, H-3, H-6, H-9, H-10), 2.80 - 1.97 (m, 3H, H-1, H-2), 1.76 - 0.94 (m, 2H, H-12); IR: 1760 (broad signal at 1725, C=O of ester and ketones).

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