Synthesis of 1-substituted *cis*-bicyclo[3.3.0]octane-3,7-dione derivatives as potential precursors of polyquinanes

Pelayo Camps,* José A. Fernández, and Santiago Vázquez

Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmacia, Universitat de Barcelona, Av. Diagonal 643, E-08028, Barcelona, Spain
E-mail: camps@ub.edu

Dedicated to Prof. James Cook on the occasion of his 65th anniversary

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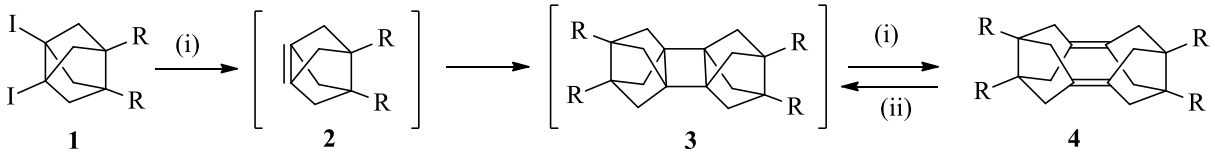
Abstract
The synthesis of several 1-substituted *cis*-bicyclo[3.3.0]octane-3,7-dione derivatives as potential precursors of a triquinacene having a pyramidalized C=C bond from ethyl *cis*-3,7-dioxobicyclo-[3.3.0]octane-1-carboxylate is described.

Keywords: 1-Substituted *cis*-bicyclo[3.3.0]octane-3,7-diones, polycyclic compounds, *cis*-dihydroxylation, Swern oxidation, epoxidation, alkylation

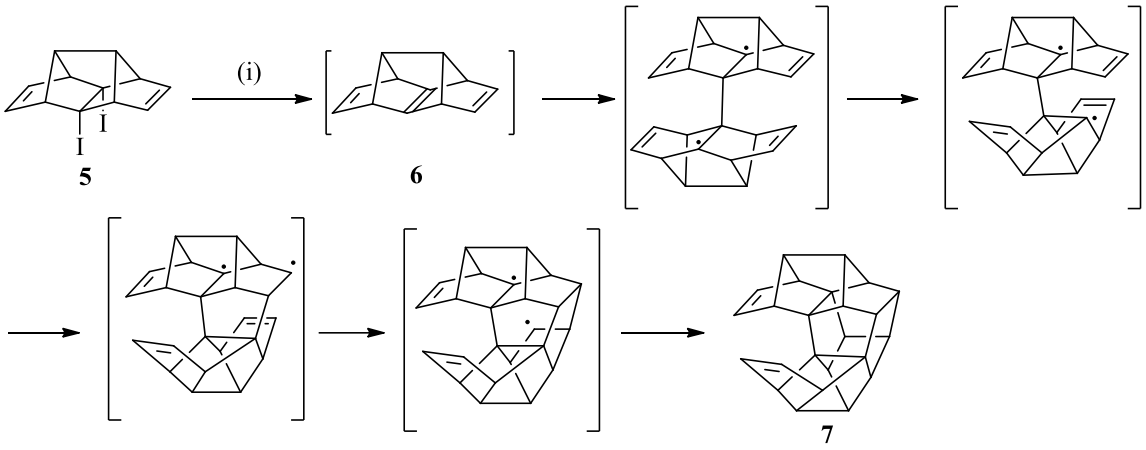
Introduction

For several years, we have been working on the generation, trapping and dimerization of highly pyramidalized alkenes containing the skeleton of tricyclo[3.3.0.0^{3,7}]oct-1(5)-ene **2**.[1] These alkenes are very reactive and can not be isolated, but they can be trapped as Diels-Alder adducts with various dienophiles. In the absence of a dienophile, these pyramidalized alkenes usually dimerize in a [2+2] cycloaddition to give cyclobutane dimers **3**, which under the standard reaction conditions of their generation (molten sodium in boiling 1,4-dioxane) are transformed into diene dimers **4** (Scheme 1).



R = H, Me
R,R = CH_2OCH_2, $CH_2OC(CH_3)_2OCH_2$

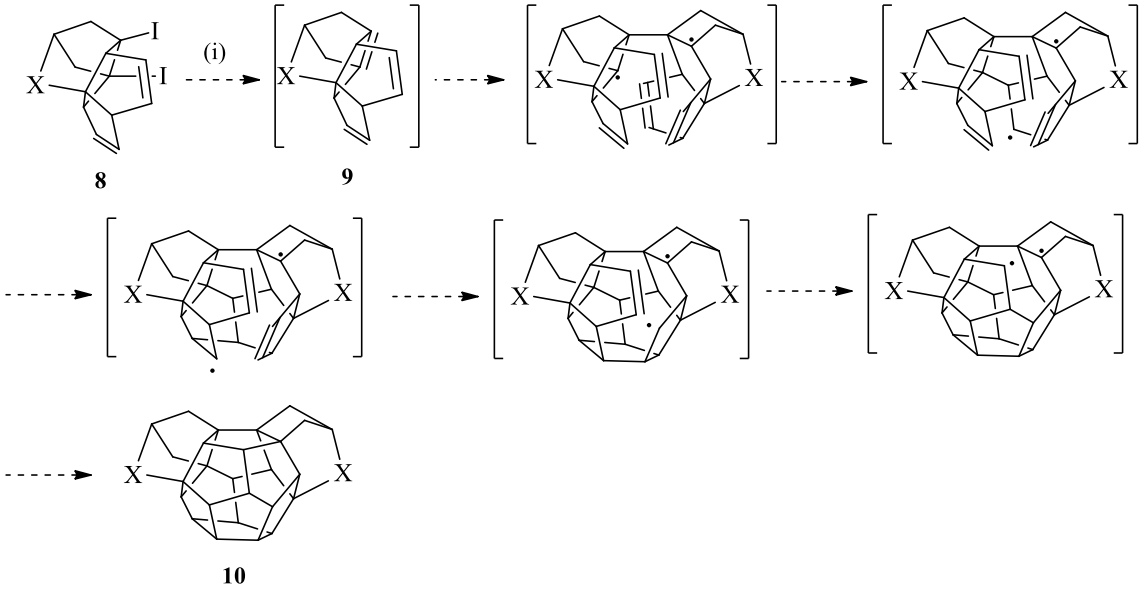
Scheme 1. Generation and dimerization of pyramidalized bicyclo[3.3.0.0^{3,7}]oct-1(5)-ene derivatives **2**. (i) Molten Na, 1,4-dioxane, reflux, 3 h. (ii) *n*-Pentane, hν, 6 h.



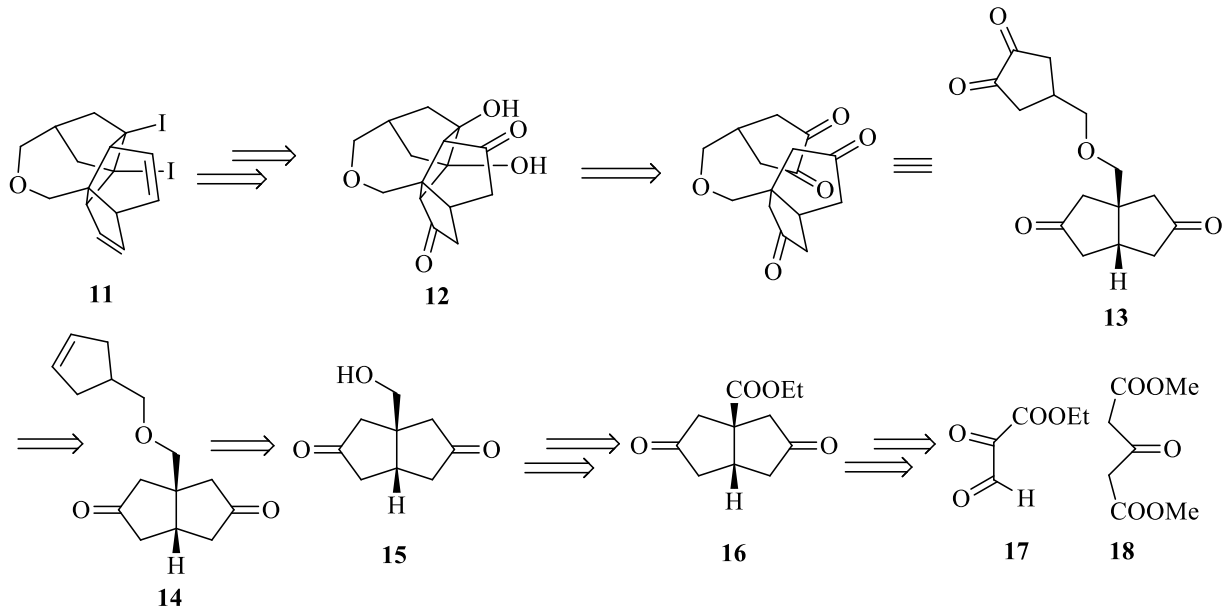
Scheme 2. Generation and [2+2+2+2] dimerization of pentacyclo[6.4.0.0^{2,10}.0^{3,7}.0^{4,9}]dodeca-5,8,11-triene (**6**). (i) Molten Na, 1,4-dioxane, reflux, 3 h.

We were also able to perform [2+2] cross-couplings among different pyramidalized alkenes by simultaneously generating them in the same pot.[1d,e,f,j] However, in one case, in which the pyramidalized alkene contained additional, relatively close alkene functionalities, dimerization took place through a [2+2+2+2] process to give a complex polycyclic product **7** (Scheme 2).[1h]

This observation led us to envision a similar process in a triquinacene derivative containing a pyramidalized C=C bond that might lead to a dodecahedrane derivative **10** (see Scheme 3).



Scheme 3. Potential [2+2+2+2+2+2] dimerization of a bridged triquinacene containing a pyramidalized C=C bond to dodecahedrane derivative **10**. (i) Molten Na, 1,4-dioxane, reflux.

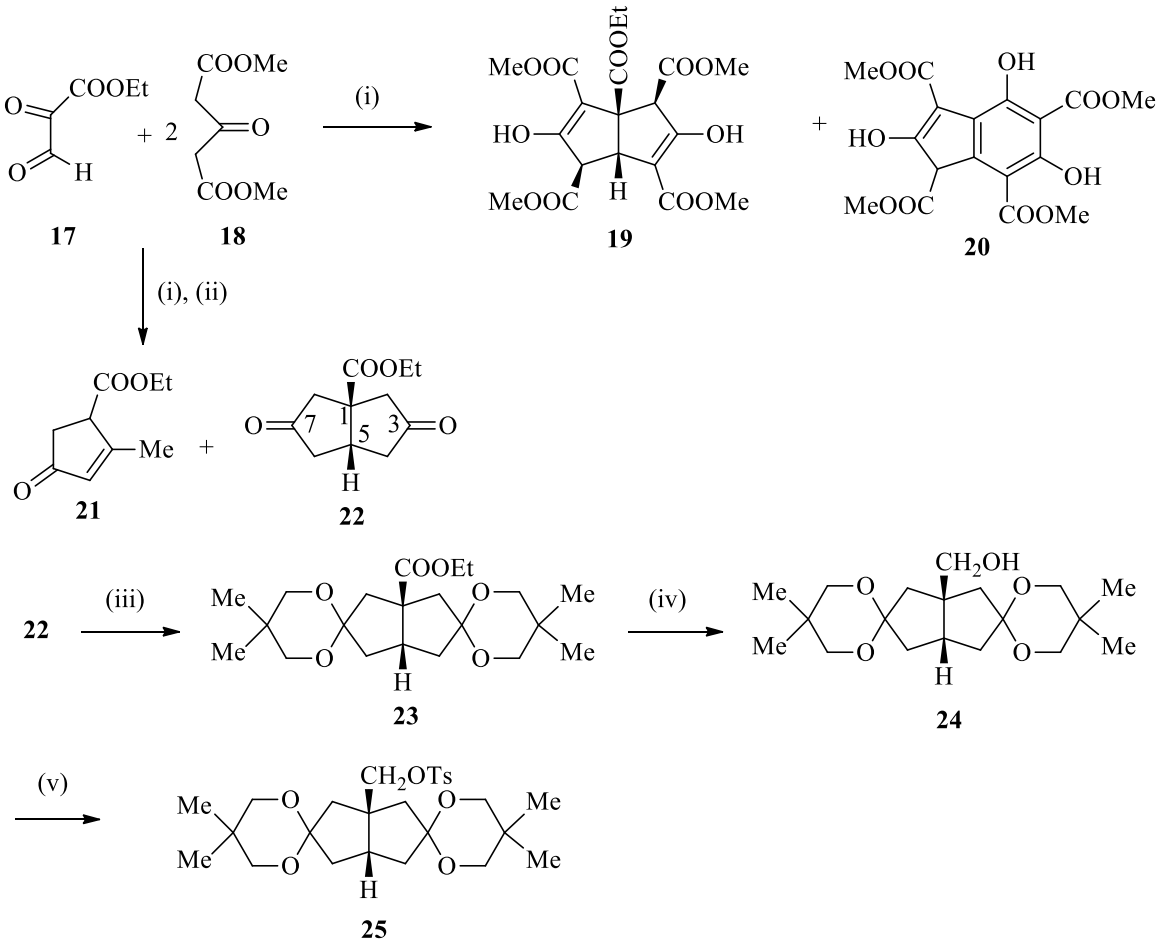


Scheme 4. Retrosynthetic analysis for compound **11** (= **8**, X = CH_2OCH_2).

The preparation of the precursor **11** (= **8**, X = CH_2OCH_2) was envisaged, as shown in Scheme 4, to be formed from dihydroxydione **12**. Substitution of two vicinal bridgehead hydroxyl groups by iodine atoms in related systems has been previously described.[2] Also the conversion of two keto groups into two alkene functions in connection with the preparation of triquinacene derivatives has been described.[3] We envisaged the preparation of dihydroxydione **12** through a double intramolecular condensation from tetraketone **13**, a compound which might be prepared from dimethyl acetonedicarboxylate **18** and ethyl 2,3-dioxopropanoate **17** by standard procedures through the shown intermediates and the required protecting group transformations.

Results and Discussion

Compound **17** was prepared as described[4] from oxalic acid monoethyl ester chloride by reaction with diazomethane, followed by oxidation of the formed α-diazoketone with dimethyldioxirane. Reaction of **17** with dimethyl acetonedicarboxylate **18** in water containing sodium bicarbonate gave a mixture of compounds **19** and **20** as previously described.[5] Analytically pure samples of compounds **19** (9%) and **20** (11%) were isolated from the reaction mixture by column chromatography. For the preparation of diketone **22**, the reaction mixture obtained from **17** and **18** was directly submitted to hydrolysis and decarboxylation under the Krapcho conditions. Column chromatography of the resulting mixture gave the new diketo ester **22** and a compound that was characterized as ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate **21** (Scheme 5).



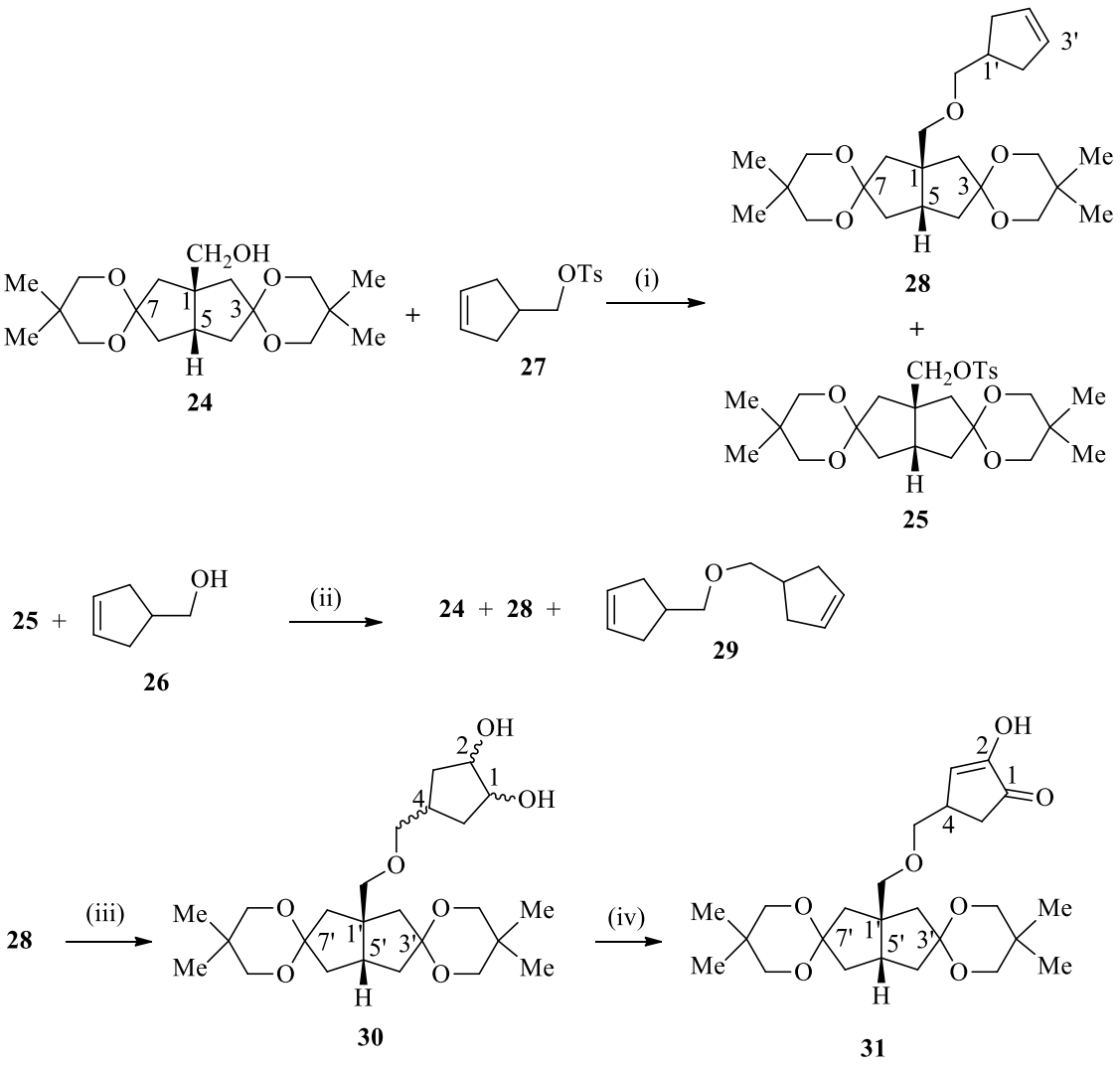
Scheme 5. Preparation of intermediates **24** and **25**. (i) $NaHCO_3$, H_2O, r.t., 4 d, **19** (11%), **20** (9%). (ii) NaCl, H_2O, DMSO, 180 °C, 4 h, **22** (36%), **21** (19%). (iii) 2,2-Dimethylpropane-1,3-diol, *p*-TsOH, toluene, reflux, 2 h, **23** (90%). (iv) LAH, Et_2O, rt, 1.5 h, **24** (98%). (v) TsCl, pyridine, 4 °C, 23 h, **25** (100%).

The keto functions of diketoester **22** were protected with 2,2-dimethylpropane-1,3-diol to give acetal **23** in high yield, which was reduced with lithium aluminum hydride (LAH) to alcohol **24**. Tosylation of alcohol **24** gave the corresponding tosylate **25** (Scheme 5).

For the introduction of the (3-cyclopentenyl)methyl group in alcohol **24**, (3-cyclopentenyl)-methanol **26** and the corresponding tosylate **27** were prepared as described. Reaction of *cis*-1,4-dichloro-2-butene with the lithium salt of dimethyl malonate gave dimethyl 3-cyclopentene-1,1-dicarboxylate.[5] Hydrolysis and decarboxylation of this diester gave 3-cyclopentenecarboxylic acid, which was reduced with LAH to alcohol **26**.[6] Reaction of alcohol **26** with tosyl chloride gave the corresponding tosylate **27**.[7]

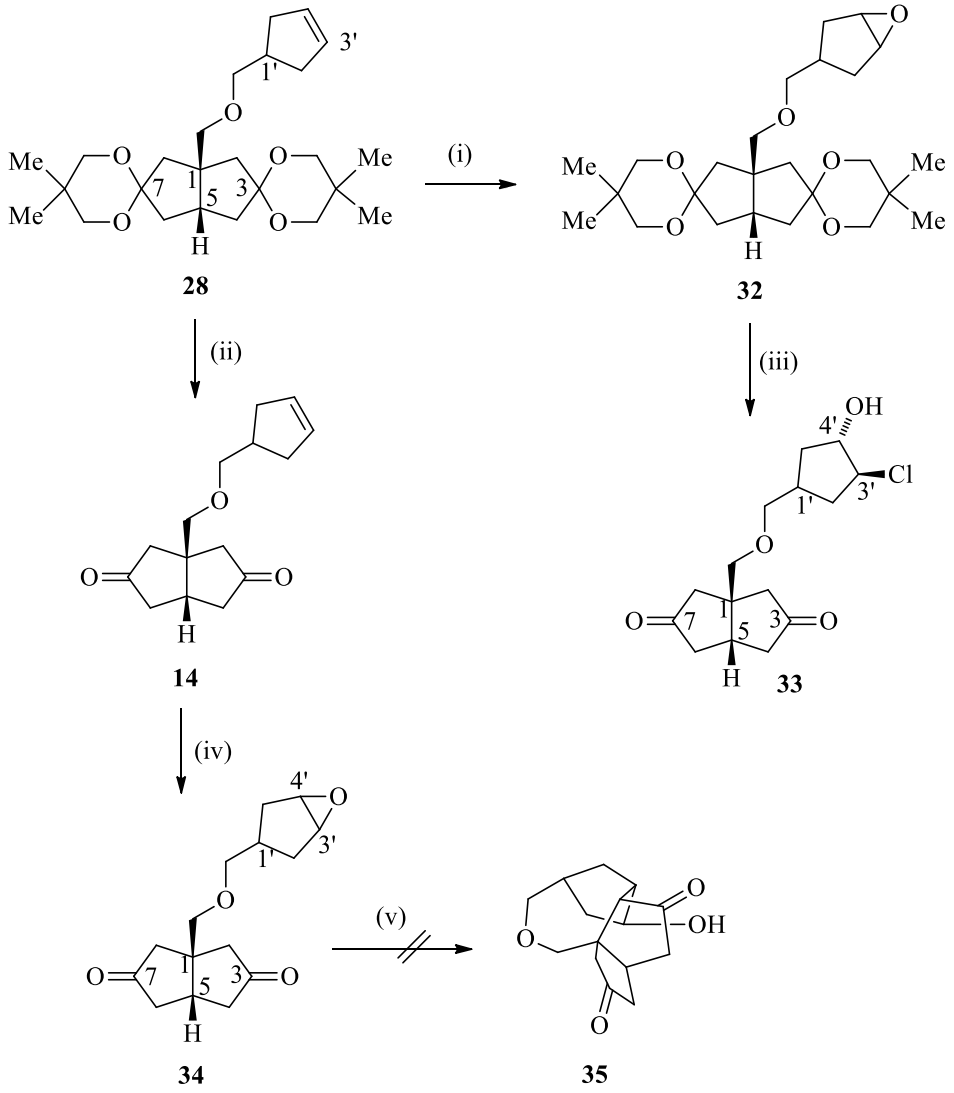
First, we synthesized ether **28** by reaction of alcohol **24** with tosylate **27**. However and to our surprise, the yield of ether **28** was only 19%, tosylate **25** was isolated in 27% yield, and a large

amount of alcohol **24** (38%) was recovered. This means that tosyl transfer between alcohol **24** and tosylate **27** is taking place to a large extent (Scheme 6).



Scheme 6. Preparation of **31**. (i) NaH, toluene, reflux, 3.5 h, **28** (19%), **25** (27%), **24** (38% recovered). (ii) NaH, toluene, reflux, 19 h, **28** (44%, from **25**), **24** (44%, from **25**), **29** (52%, from **26**). (iii) $K_2OsO_4 \cdot 2H_2O$ (0.02 equiv), NMO (1.2 equiv), H_2O/*t*-BuOH, 0 °C, 15 min, r.t., 4 h, **30**. (iv) Oxalyl chloride, DMSO, Et_3N, DCM, **31** (41% from **28**).

Then, we carried out the reaction of alcohol **26** and tosylate **25**. In this case, ether **28** was obtained from **25** with an improved yield (44%), although tosyl transfer was also observed; alcohol **24** and ether **29** were obtained from **25** (44%) and from **26** (52%), respectively. Dihydroxylation of compound **28** using a catalytic amount of dipotassium osmate and *N*-methyl-morpholine *N*-oxide (NMO) as the stoichiometric oxidant gave a mixture of stereoisomeric alcohols (1*r*,2*c*,4*c*)- and (1*r*,2*c*,4*t*)-**35**, which was characterized as such.



Scheme 7. Transformations of **28**. (i) MCPBA, DCM, rt, 1 h, **32** (94%). (ii) $Ce(NH_4)_2(NO_3)_6$, CH_3CN/H_2O, 65 ºC, 5 min, **14** (44%). (iii) 35% HCl, THF, rt, 2 h, **33** (61%). (iv) MCPBA, DCM, rt, 1.5 h, **34** (63%). (v) LiHMDS (2.4 equiv), toluene, –68 ºC to rt, 24 h; or LiHMDS (2.4 equiv), toluene, $Sc(OTf)_3$ (1.2 equiv), –68 ºC to rt, 24 h; or LiHMDS (2.4 equiv), THF, –78 ºC to rt, 24 h; or LiHMDS (2.4 equiv), THF, $BF_3 \cdot Et_2O$ (1.2 equiv), –78 ºC to rt, 24 h.

Swern oxidation of this mixture gave the expected product **31**, which exists essentially in the enol form, as evidenced by the comparison of significant ^{13}C NMR signals of the 2-hydroxy-cyclopent-2-en-1-one moiety of **31** ($\delta_{1\text{-}C}$ 203.0, $\delta_{2\text{-}C}$ 153.2, $\delta_{3\text{-}C}$ 130.5) with the corresponding signals of a model compound, 4-(*n*-hexyl)-2-hydroxycyclopent-2-en-1-one ($\delta_{1\text{-}C}$ 203.3, $\delta_{2\text{-}C}$ 152.0, $\delta_{3\text{-}C}$ 133.3).[8] Attempts to convert enol **31** into dihydroxydione **12** (hydrolysis and two intramolecular aldol condensations) or into the corresponding acetal with *p*-TsOH in acetone gave a mixture, in which **31** had disappeared but the expected products were not detected.

Noteworthy, dihydroxydione **12** is by far the most stable among 12 possible stereoisomers derived from enol **31** by hydrolysis and double intramolecular aldol condensation, as established by theoretical methods (MM3,[9] AM1,[10] and PM3[11]). However, among the 16 stereoisomers of hydrolysis and monocondensation products derived from enol **31**, the precursor of dihydroxydione **12** and several other stereoisomers showed similar stabilities according to the above theoretical methods.

In view of this result and having ether **28** in hand, we attempted an alternative approach to the skeleton of compound **12** in a stepwise way (Scheme 7). To this end, ether **28** was epoxidized with *m*-chloroperoxybenzoic acid (MCPBA) to give a mixture of stereoisomeric epoxides **32** in a ratio close to 1:3 (^{1}H NMR). Attempts to hydrolyze this mixture under various acidic conditions (MsOH, H_2SO_4, *p*-TsOH) gave complex product mixtures with not only the acetal functions hydrolyzed but also the epoxide reacted. When the hydrolysis was carried out with 35% HCl in THF, a stereoisomeric mixture of chlorohydrins **33** was obtained. In order to obtain epoxide **34**, we first carried out the hydrolysis of the acetal functions of compound **28** by reaction with Ce(IV) ammonium nitrate.[12] Under these conditions, diketone **14** was obtained in 44% yield. Epoxidation of diketone **14** with MCPBA gave a mixture of stereoisomeric epoxides **34** in 63% yield. However, all attempts to transform this compound into the tricyclic derivative **35** on reaction with an excess of lithium hexamethyldisilazide (LiHMDS) in toluene or THF, in the presence of Sc(III) triflate or boron trifluoride etherate[13] were fruitless, always leading to complex mixtures of unidentified products.

Conclusions

In conclusion we have prepared a series of 1-substituted *cis*-bicyclo[3.3.0]octane-3,7-dione derivatives as potential precursors of a triquinacene having a pyramidalized C=C bond. In spite of very favorable expectations based on different theoretical calculations, the double aldol condensation of compound **31** that should provide the tetracyclic dihydroxydione **12** failed to give any defined product. Also, the intramolecular condensation of diketoepoxide **34** to diketoalcohol **35** failed to give any defined product. Work is in progress to prepare a derivative of general structure **8** through other synthetic approaches.

Experimental Section

General. Melting points were determined with a MFB 595010 M Gallenkamp melting point apparatus. ^{1}H NMR spectra were recorded on Varian-Gemini 200 (200 MHz), Varian Gemini-300 (300 MHz), Varian Mercury-400 (400 MHz), or Varian VXR-500 (500 MHz) spectrometers. ^{13}C NMR spectra were recorded on Varian Gemini-200 (50.3 MHz) and Varian Gemini-300 (75.4 MHz) spectrometers. The ^{1}H/^{1}H homocorrelation spectra (COSY and NOESY) and the one

bond and long range $^{1}H/^{13}C$ heterocorrelation spectra (gHSQC and gHMBC, respectively) were performed on a Varian VXR-500 spectrometer. Chemical shifts are given in δ scale and the coupling constants in Hz. IR spectra were registered on a FTIR Perkin–Elmer model 1600 or a Perkin–Elmer Spectrum RX1 spectrometer. MS and GC/MS analyses were carried out on a Hewlett-Packard HP-5988A spectrometer, the sample being introduced directly or through a gas chromatograph (Hewlett.Packard model 5890 Series II) using a 30-m column (HP-45, 5% diphenyl-95% dimethylpolysiloxane), conditions: 10 psi, initial temperature 100 °C (2 min), then heating at a rate of 10 ºC/min up to 250 ºC, then isothermic. The electron impact (EI, 70 eV) or chemical ionization (CI, CH_4) techniques were used. Where not indicated, the electron impact ionization technique was used. Only significant ions are given: those with higher relative ratio, except for the ions with higher *m*/*z* values. High resolution MS spectra were performed in an Autospec Micromass spectrometer at the University of Santiago de Compostela. The elemental analyses were determined in a Carlo Erba model 1106 equipment at the IIQAB (CSIC) of Barcelona, Spain. For the column chromatography, silica gel 60 AC (35–70 μM, SDS, ref. 2000027 or 70–200 μM, SDS, ref. 2100027) or neutral aluminum oxide (Macherey-Nagel) were used. Except where otherwise indicated, 35–70 μM silica gel was used. Thin-layer chromatography (TLC) was performed on aluminum-backed sheets with silica gel 60 F_{254} (Merck, ref. 1.05554) and spots were visualized with UV light, a 1% aqueous solution of $KMnO_4$ or by placing the sheets in an iodine atmosphere.

Ethyl *cis*-3,7-dioxobicyclo[3.3.0]octane-1-carboxylate (22) and ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate (21). To a solution of $NaHCO_3$ (6.41 g, 76.3 mmol) in water (460 mL), dimethyl acetone-1,3-dicarboxylate **18 (**23.9 g, 137 mmol) and ethyl 2,3-dioxopropanoate (**17**; 10.2 g, 69 mmol) were added; the mixture was vigorously stirred at room temperature for 4 d. The mixture was acidified to pH 1 with 6N HCl and then extracted with DCM (3×275 mL). The organic extracts were combined, dried (anhydrous Na_2SO_4), and concentrated in vacuo to give a residue (30.8 g). Part of this residue (4.9 g) was subjected to column chromatography (silica gel, 100 g; hexane/EtOAc 85:15); **20** (0.46 g, 9%) and **19** (0.48 g, 11%) were eluted in this order. The ^{1}H and ^{13}C NMR data of compounds **19** and **20** matched those previously described.[5] The rest of the above residue (25.9 g) was taken up in DMSO (47 mL); water (12 mL) and finely ground NaCl (3.5 g) were added, the mixture was heated to 180 °C for 4 h, then allowed to cool to room temperature and concentrated in vacuo. The residue (18.9 g) was subjected to column chromagraphy (silica gel, 190 g; hexane/EtOAc 9:1); **21** (1.9 g, 19%) and **22** (4.3 g, 36%) were eluted in this order. Analytical samples were obtained as colorless oils by distillation in a rotary microdistillation equipment at 130 °C/0.1 Torr and 150 °C/0.1 Torr, respectively.

Compound 21. IR (NaCl): *ν* 2982, 2932, 1732, 1625, 1436, 1409, 1369, 1327, 1257, 1230, 1185, 1031, 857 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.5 Hz, 3H, OCH_2CH_3), 2.14 (s, 3H, 2-CH_3), 2.60 (dd, *J* = 18.5 Hz, *J'* = 7.0 Hz, 1H, 5-H_{trans}), 2.68 (dd, *J* = 18.5 Hz, *J'* = 2.5 Hz, 1H, 5-H_{cis}), 3.63 (dm, *J* = 7.0 Hz, 1H, 1-H), 4.19 (m, 2H, OCH_2CH_3), 6.00 (s, 1H, 3-H). ^{13}C

NMR (50.3 MHz, $CDCl_3$): δ 14.2 ($OCH_2\mathit{C}H_3$), 18.0 (2-CH_3), 39.3 (5-C), 49.9 (1-C), 61.5 ($O\mathit{C}H_2CH_3$), 132.1 (3-C), 171.2, 173.6 (*C*OOEt , 2-C), 206.8 (4-C). GC/MS (t_R = 12.6 min): *m*/*z* (%) 168 ($M^{\cdot+}$, 38), 123 (15), 122 (54), 96 (43), 95 (95), 94 (51), 67 (100). Anal. calcd. for $C_9H_{12}O_3 \cdot 0.2H_2O$: C, 62.92; H, 7.28. Found: C, 62.83; H, 7.09.

Compound 22. IR (NaCl): *v* 2981, 2926, 1744, 1405, 1319, 1289, 1253, 1228, 1178, 1163, 1105, 1059, 1022 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.0 Hz, 3H, $OCH_2C\mathit{H}_3$), 2.19 [ddd, *J* = 19.0 Hz, *J'* = 5.5 Hz, *J''* = 1.0 Hz, 2H, 4(6)-H_{endo}], 2.37 [dd, *J* = 19.0 Hz, *J'* = 1.0 Hz, 2H, 2(8)-H_{endo}], 2.79 [ddd, *J* = 19.0 Hz, *J'* = 9.0 Hz, *J''* = 1.5 Hz, 2H, 4(6)-H_{exo}], 3.05 [dd, *J* = 19.0 Hz, *J'* = 1.5 Hz, 2H, 2(8)-H_{exo}], 3.19 (tt, *J* = 9.0 Hz, *J'* = 5.5 Hz, 1H, 5-H), 4.21 (q, *J* = 7.0 Hz, 2H, $OC\mathit{H}_2CH_3$). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1 ($OCH_2\mathit{C}H_3$), 40.9 (5-C), 43.7 [4(6)-C], 46.4 [2(8)-C], 52.6 (1-C), 62.0 ($O\mathit{C}H_2CH_3$), 174.2 (*C*OOEt), 214.5 [3(7)-C]. GC/MS (t_R = 16.4 min): *m*/*z* (%) 210 ($M^{\cdot+}$, 17), 164 (14), 141 (72), 137 (23), 136 (16), 113 (100), 85 (44). Anal. calcd. for $C_{11}H_{14}O_4 \cdot 0.1H_2O$: C, 62.31; H, 6.75. Found: C, 62.23; H, 6.74.

Ethyl 3,3:7,7-bis(2,2-dimethyl-1,3-propylidenedioxy)-*cis*-bicyclo[3.3.0]octane-1-carboxylate (23). A mixture of diketone **22** (2.31 g, 11.0 mmol), 2,2-dimethyl.1,3-propanediol (4.44 g, 42.6 mmol) and *p*-$TsOH \cdot H_2O$ (72 mg) in toluene (100 mL) was heated under reflux for 2 h with continuous removal of the formed water using a Dean-Stark equipment. The cold solution was washed with water (3×40 mL), dried (anhydrous Na_2SO_4) and concentrated in vacuo to give acetal **23** as a white solid (3.79 g, 90%). White crystals (from Et_2O); mp 86.1–87.4 °C. IR (KBr): $\tilde{\nu}$ 2979, 2951, 2867, 1717, 1473, 1364, 1323, 1304, 1132, 1111, 1043 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (s, 6H, 2 *syn*-CH_3), 1.01 (s, 6H, 2 *anti*-CH_3), 1.25 (t, *J* = 7.0 Hz, 3H, $OCH_2C\mathit{H}_3$), 1.99 [ddd, *J* = 13.0 Hz, *J'* = 6.0 Hz, *J''* = 1.0 Hz, 2H, 4(6)-H_{endo}], 2.02 [dd, *J* = 13.5 Hz, *J'* = 1.0 Hz, 2H, 2(8)-H_{endo}], 2.10 [ddd, *J* = 13.0 Hz, *J'* = 9.0 Hz, *J''* = 1.5 Hz, 2H, 4(6)-H_{exo}], 2.64 [dd, *J* = 13.5 Hz, *J'* = 1.5 Hz, 2H, 2(8)-H_{exo}], 3.02 (tt, *J* = 9.0 Hz, *J'* = 6.0 Hz, 1H, 5-H), 3.39 (dd, *J* = 11.0 Hz, *J'* = 1.0 Hz, 2H, 2 C$H_{\mathit{exo,anti}}$ dioxane substructure), 3.46 (dd, *J* = 11.0 Hz, *J'* = 1.0 Hz, 2H, 2 C$H_{\mathit{endo,anti}}$ dioxane substructure), 3.49 (d, *J* = 11.5 Hz, 2H, 2 C$H_{\mathit{endo,syn}}$ dioxane substructure), 3.51 (dd, *J* = 11.5 Hz, 2H, 2 C$H_{\mathit{exo,syn}}$ dioxane substructure), 4.14 (q, *J* = 7.0 Hz, 2H, $OC\mathit{H}_2CH_3$). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1 (CH_3, $OCH_2\mathit{C}H_3$), 22.4 (CH_3, *syn*-CH_3), 22.6 (CH_3, *anti*-CH_3), 30.0 [C, 2 $\mathit{C}(CH_3)_2$], 40.6 [CH_2, 4(6)-C], 40.7 (CH, 5-C), 42.0 [CH_2, 2(8)-C], 55.0 (C, 1-C), 60.7 (CH_2, $O\mathit{C}H_2CH_3$), 71.9 (CH_2, *exo*-$\mathit{C}H_2$ dioxane substructure), 72.1 (CH_2, *endo*-$\mathit{C}H_2$ dioxane substructure), 108.5 [C, 3(7)-C], 176.9 (C, *C*OOEt). GC/MS (t_R =23.7 min): m/z (%) 382 ($M^{\cdot+}$, 14), 309 (59), 227 (64), 155 (27), 141 (28), 113 (28), 69 (100). Anal. calcd. for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96. Found: C, 66.07; H, 9.02.

[3,3:7,7-Bis(2,2-dimethyl-1,3-propylidenedioxy)-*cis*-bicyclo[3.3.0]oct-1-yl]methanol (24). To a suspension of LAH (0.36 g, 9.5 mmol) in anhydrous Et_2O (12 mL), a solution of acetal **23** (1.18 g, 3.1 mmol) in anhydrous Et_2O (40 mL) was added and the mixture was stirred at room temperature for 1.5 h. Water (3 mL) was slowly added and the formed suspension was filtered. Concentration of the filtrate in vacuo gave alcohol **24** (1.03 g, 98%) as white solid. White crystals (from Et_2O); mp 109.5–110.8 °C. IR (KBr): *v* 3495, 2961, 2932, 2858, 1474, 1323, 1308, 1145, 1108, 1084, 1073, 1042, 1011 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.95 (s, 6H),

0.97 (s, 6H) [2 C(CH_3)$_2$], 1.93 [ddd, *J* = 13.0 Hz, *J'* = 6.5 Hz, *J''* = 1.0 Hz, 2H, 4(6)-H$_{endo}$], 2.01 (dd, *J* = 13.5 Hz, *J'* = 1.0 Hz, 2H) and 2.05 [dd, *J* = 13.5 Hz, *J'* = 1.0 Hz, 2H) [2(8)-H$_{endo}$ and 2(8)-H$_{exo}$], 2.22 [ddd, *J* = 13.5 Hz, *J'* = 8.5 Hz, *J''* = 1.0 Hz, 2H, 4(6)-H$_{exo}$], 2.40 (tt, *J* = 8.5 Hz, *J'* = 6.5 Hz, 1H, 5-H), 2.89 (broad s, 1H, OH), 3.44–3.50 (complex signal, 10H, 4 CH_2 of 2 dioxane substructures plus C*H*$_2$OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.4 (CH_3) and 22.5 (CH_3) [2 C(*C*H_3)$_2$], 30.0 [C, 2 *C*(CH_3)], 39.5 [CH_2, 4(6)-C], 39.8 (CH, 5-C), 44.5 [CH_2, 2(8)-C], 50.4 (C, 1-C), 70.4 (CH_2, CH_2OH), 71.7 (CH_2) and 72.1 (CH_2) (CH_2 2 dioxane substructures), 109.1 [C, 3(7)-C]. GC/MS (t_R = 23.5 min): *m*/*z* (%) 340 ($M^{\cdot+}$, 5), 309 (17), 155 (23), 128 (26), 99 (18), 69 (100). Anal. calcd. for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.93; H, 9.48.

[3,3:7,7-Bis(2,2-dimethyl-1,3-propylidenedioxy)-*cis*-bicyclo[3.3.0]oct-1-yl]methyl tosylate (25). To a cold (0 °C) solution of alcohol **24** (1.00 g, 2.9 mmol) in pyridine (3.5 mL), tosyl chloride (0.71 g, 3.7 mmol) was added in portions for 15 min. The mixture was stirred at 0 °C for 1.5 h and then it was kept at 4 °C for 21 h. The mixture was poured on to a mixture of ice (15 g) and 35% HCl (3 mL) and it was extracted with DCM (2×20 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give tosylate **25** as white solid (1.46 g, quantitative yield). White crystals (from Et_2O); mp 131.9–132.5 °C. IR (KBr): *ν* 2947, 2929, 2853, 1472, 1356, 1174, 1105, 928, 668 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83 (s, 6H) and 0.94 (s, 6H) [2 C(CH_3)$_2$], 1.82 [complex signal, 4H, 4(6)-H$_{endo}$ and 2(8)-H$_{endo}$], 1.98 – 2.12 [complex signal, 5H, 2(8)-H$_{exo}$, 4(6)-H$_{exo}$ and 5-H), 2.42 (s, 3H, Ar-CH_3), 3.26 (s, 4H, 2 CH_2) and 3.38 (s, 4H, 2 CH_2) (4 CH_2 of 2 dioxane substructures), 3.85 (s, 2H, CH_2OTs), 7.32 [d, *J* = 8.5 Hz, 2H, Ar-3(5)-H], 7.77 [d, *J* = 8.5 Hz, 2H, Ar-2(6)-H]. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 21.6 (CH_3, Ar-CH_3), 22.4 (CH_3) and 22.6 (CH_3) [2 C(*C*H_3)$_2$], 30.0 [C, 2 *C*(CH_3)], 39.5 (CH, 5-C), 40.6 (CH_2) and 41.5 (CH_2) [2(8)-C and 4(6)-C], 48.9 (C, 1-C), 71.4 (CH_2) and 72.2 (CH_2) (2×2 CH_2 of 2 dioxane substructures), 77.2 (CH_2, CH_2OTs), 108.7 [C, 3(7)-C], 128.0 [CH, Ar 2(6)-C], 129.8 [CH, Ar 3(5)-C], 132.9 (C, Ar 1-C), 144.6 (C, Ar 4-C). GC/MS (t_R = 21.4 min): *m*/*z* (%) 324 (20), 323 [(M–TsO)$^+$, 100], 322 (20), 321 (39), 237 (45), 151 (57). Anal. calcd. for $C_{26}H_{38}O_7S$: C, 63.13; H, 7.74, S, 6.48. Found: C, 63.28; H, 7.74, 6.40.

1-[(Cyclopent-3-enyl)methoxymethyl]-3,3:7,7-bis-(2,2-dimethyl-1,3-propylidenedioxy)-*cis*-bicyclo[3.3.0]octane (28). Procedure 1. To a magnetically stirred suspension of NaH (12 mg, 60% content, 0.28 mmol) in anhydrous toluene (0.5 mL) under an argon atmosphere, a solution of alcohol **24** (85 mg, 0.25 mmol) in the same solvent (0.5 mL) was added and the mixture was stirred until no more hydrogen was evolved. Then, a solution of tosylate **27** (76 mg, 0.30 mmol) in anhydrous toluene (0.5 mL) was added dropwise and the mixture was heated under reflux for 3.5 h, following the evolution of the reaction by TLC. The mixture was allowed to cool to room temperature, was washed with water (3×2 mL). The organic phase was dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a residue (123 mg) that was subjected to column chromatography (neutral aluminum oxide, 6 g; hexane). In order of elution, ether **28** (20 mg, 19%), tosylate **25** (33 mg, 27%) and starting alcohol **24** (32 mg, 38% recovery) were isolated. **28**: White crystals (sublimed); mp 74.8–76.6 °C. IR (NaCl): *ν* 3054, 2952, 2931, 2852, 1472, 1362, 1324, 1309, 1110, 1042 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (s, 6H) and 0.97 (s, 6H)

[2 C(CH_3)$_2$], 1.86 [dd, *J* = 13.5 Hz, *J'* = 1.0 Hz, 2H, 2(8)-H$_{endo}$], 1.91 [ddd, *J* = 13.0 Hz, *J'* = 7.0 Hz, *J''* = 1.0 Hz, 2H, 4(6)-H$_{endo}$], 2.05 [ddd, *J* = 13.0 Hz, *J'* = 9.0 Hz, *J''* = 1.0 Hz, 2H, 4(6)-H$_{exo}$], 2.08 [m, 2H, 2'(5')-H$_{cis}$], 2.15 [m, 1H, 5-H], 2.20 [dd, *J* = 13.5 Hz, *J'* = 1.5 Hz, 2H, 2(8)-H$_{exo}$], 2.42 [m, 2H, 2'(5')-H$_{trans}$], 2.55 (m, 1H, 1'-H), 3.22 (s, 2H, C1-CH_2O), 3.28 (d, *J* = 7.5 Hz, 2H, C1'-CH_2O), 3.39–3.47 (m, 8H, 4 CH_2 of 2 dioxane substructures), 5.62 [s, 2H, 3'(4')-H]. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 22.5 (CH_3) and 22.7 (CH_3) [2 C(*C*H_3)$_2$], 30.0 [C, 2 *C*(CH_3)], 35.9 [CH_2, 2'(5')-C], 36.5 (CH, 1'-C), 40.3 (CH, 5-C), 40.4 [CH_2, 4(6)-C], 42.5 [CH_2, 2(8)-C], 49.9 (C, 1-C), 71.7 (CH_2) and 72.1 (CH_2) (2×2 CH_2 of 2 dioxane substructures), 75.5 (CH_2, 1'-C-*C*H_2O), 78.1 (CH_2, 1-C-*C*H_2O), 109.4 [C, 3(7)-C], 129.5 [CH, 3'(4')-C]. GC/MS (t_R =28.9 min): *m*/*z* (%) 420 ($M^{\cdot+}$, 9), 341 (13), 309 [(M-$C_5H_7CH_2OCH_2$)$^+$, 94], 128 (26), 81 (54), 79 (32), 69 (100). Anal. calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.84; H, 9.55.

Procedure 2. To a magnetically stirred suspension of NaH (127 mg, 55% content, 2.9 mmol) in anhydrous toluene (1 mL) under an argon atmosphere, a solution of alcohol **26** (228 mg, 2.3 mmol) in anhydrous toluene (1 mL) was added and the mixture was stirred until no more hydrogen was evolved. Then, a solution of tosylate **25** (960 mg, 1.93 mmol) in anhydrous toluene (2 mL) was added dropwise and the mixture was heated under reflux for 19 h, following the evolution of the reaction by TLC. The mixture was allowed to cool to room temperature and was washed with water (2×10 mL). The organic phase was dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a residue (857 mg) that was subjected to column chromatography (neutral aluminum oxide, 35 g; hexane/EtOAc mixtures). Ether **29** (106 mg, 52% from **26**) was eluted with hexane, the expected ether **28** (355 mg, 44% from **25**) was eluted with hexane/EtOAc 95:5 and alcohol **24** (287 mg, 44% from **25**) was eluted with EtOAc.

Compound 29. Oil, bp 120 °C / 1 Torr. IR (NaCl): *v* 2923, 2853, 1459, 1376, 1116 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04–2.15 (m, 4H) and 2.42–2.64 (complex signal, 6H) [2(5)-H_2 and 1-H], 3.32 (d, *J* = 6.9 Hz, 4H, CH_2O), 5.65 [m, 4H, 3(4)-H]. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 36.0 [CH_2, 2(5)-C], 36.6 (CH, 1-C), 75.3 (CH_2, CH_2O), 129.5 [CH, 3(4)-C]. GC/MS (t_R = 12.3 min, CI): *m*/*z* (%) 179 ([M+H]$^+$, 2), 177 ([M–H]$^+$, 2), 111 ([M–C_5H_7]$^+$, 11), 81 ([M–C_6H_9O]$^+$, 100).

Mixture of (1*r*,2*c*,4*t*)- and (1*r*,2*c*,4*c*)-4-{[3,3:7,7-bis-(2,2-dimethyl-1,3-propylidenedioxy)-*cis*-bicyclo[3.3.0]oct-1-yl]methoxymethyl}cyclopentane-1,2-diol (30). To a cold (0 °C) suspension of $K_2OsO_4 \cdot 2H_2O$ (7.6 mg, 0.02 mmol) and *N*-methylmorpholine *N*-oxide (NMO, 161 mg, 1.37 mmol) in a mixture of water/*t*-BuOH 1:1 (1.3 mL), a solution of ether **28** (474 mg, 1.13 mmol) in acetone (3 mL) was added dropwise and the mixture was magnetically stirred for 15 min at 0 °C and then for 4 h at room temperature. The mixture was concentrated in vacuo and the residue (553 mg), containing mainly one stereoisomeric diol, was used as such in the next step. An analytical sample of diol **30** was obtained by taking the product in DCM, filtering the solution through a 0.45 μm polytetrafluoroethylene (PTFE) filter and concentrating the filtrate in vacuo. IR (NaCl): *v* 3435, 2952, 2932, 2855, 1473, 1395, 1362, 1323, 1308, 1107 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (data of the main diastereomer of **30**): δ 0.92 (s, 6H) and 0.98 (s, 6H) [2 C(CH_3)$_2$], 1.50–2.60 [complex signal, 14H, 2'(8')-H_2, 4'(6')-H_2, 5'-H, 3(5)-H_2 and 4-H], 3.23 (s, 2H, C1'-

CH_2O), 3.27 (d, *J* = 6.0 Hz, C4-CH_2O), 3.34–3.50 (complex signal, 10H, CH_2 from 2 dioxane substructures and 1(2)-H, 4.13 (broad t, *J* = 4.2 Hz, 2H, 2 OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): (data of the main diastereomer of **30**): δ 22.4 (CH_3) and 22.5 (CH_3) [2 C(*C*H_3)$_2$], 29.9 [C, 2 *C*(CH_3)$_2$], 34.4 (CH, 4-C), 34.5 (CH_2) and 39.9 (CH_2) [2'(8')-C and 4'(6')-C], 40.3 (CH, 5'-C), 42.7 [CH_2, 3(5)-C], 49.6 (C, 1'-C), 71.6 (CH_2) and 71.9 (CH_2) [1'-C-*C*H_2O and 4-C-*C*H_2O], 73.7 [CH, 1(2)-C], 75.2 (CH_2) and 78.0 (CH_2) (4 CH_2 of 2 dioxane substructures), 109.2 [C, 3'(7')-C]. GC/MS (t_R = 25.8 min): *m*/*z* (%) 454 ($M^{\cdot+}$, 16), 351 (18), 309 [(M−($C_5H_7O_2$)CH_2OCH_2)$^+$, 100], 267 (19), 223 (20), 128 (19), 69 (56). HRMS: calcd. for [$C_{25}H_{42}O_7$+H]$^+$: 455.3009. Found: 455.3007.

4-[[3,3:7,7-Bis(2,2-dimethyl-1,3-propylidenedioxy)-*cis*-bicyclo[3.3.0]oct-1-yl]methoxymethyl]]-2-hydroxycyclopent-2-en-1-one (31). To a magnetically stirred cold (−70 °C, acetone/ CO_2 bath) solution of oxalyl chloride (270 μL, 3.1 mmol) in DCM (7 mL) under an argon atmosphere, a solution of anhydrous DMSO (470 μL, 6.6 mmol) in DCM (1.5 mL) was added. The mixture was stirred for 30 min and then a solution of diol **30** (451 mg, 1.0 mmol) in DCM (2 mL) was added dropwise keeping the temperature below −65 ºC. The mixture was stirred for 2 h at −65 °C, then anhydrous Et_3N (1.5 mL) was added and stirring was continued for 1.5 h at this temperature. The reaction mixture was allowed to warm to room temperature, was acidified with cold 1N HCl (20 mL) and was diluted with DCM (20 mL). The organic phase was separated and the aqueous phase was extracted with DCM (20 mL). The organic phase and extracts were combined, washed with brine (2×20 mL), dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a residue (364 mg) that was subjected to column chromatography (silica gel, 70–200 μm; hexane/EtOAc mixtures). Upon elution with hexane/EtOAc 8:2, slightly impure enol **31** (182 mg, 41%) was isolated as an oil. IR (NaCl): *v* 3448, 2953, 2924, 2859, 1736, 1400, 1267, 1111, 1080, 1045 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (s, 6H), 0.97 (s, 6H) [2 C(CH_3)$_2$], 1.8–2.2 [complex signal, 12H, 2'(8')-H_2, 4'(6')-H_2, 5'-H, 4-H and 5-H_2], 3.27 (s, 2H) and 3.45 (s, 10H) (4 CH_2 of 2 dioxane substructures, C1'-CH_2O and C4-CH_2O), 6.50 (d, *J* = 3.5 Hz, 1H, 3-H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 22.5 (CH_3) and 22.6 (CH_3) [2 C(*C*H_3)$_2$], 30.0 [2 *C*(CH_3)$_2$], 35.1 (CH, 5'-C), 36.4 [CH_2, 4'(6')-C], 39.9 [CH_2, 2'(8')-C], 40.4 (CH, 4-C), 42.8 (CH_2, 5-C), 49.6 (C, 1'-C), 71.7 (CH_2) and 72.0 (CH_2) (4 CH_2 of 2 dioxane substructures), 74.2 (CH_2, 4-C-*C*H_2O), 78.4 (CH_2, 1'-C-*C*H_2O), 109.2 [C, 3'(7')-C], 130.5 (CH, 3-C), 153.2 (C, 2-C), 203.1 (C, 1-C).

Attempted conversion of (31) into (12)

To a solution of enol **31** (45 mg, 0.1 mmol) in acetone (1.4 mL), *p*-TsOH·H_2O (5 mg) was added and the mixture was magnetically stirred at room temperature for 24 h. The solution was concentrated in vacuo, water (5 mL) and EtOAc were added, the organic phase was separated and the aqueous one was extracted with EtOAc (2×2 mL). The combined organic phases were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give and oily residue in which no defined product could be detected (^{1}H NMR).

Mixture of 3,3:7,7-bis(2,2-dimethyl-1,3-propylidenedioxy)-1-[(*trans*-3,4-epoxycyclopentyl) methoxymethyl]-*cis*-bicyclo[3.3.0]octane (*trans*-32) and its stereoisomer (*cis*-32). To a magnetically stirred solution of ether **28** (420 mg, 1.0 mmol) in DCM (10 mL) at room temperature, MCPBA (449 mg, 77% content, 2.0 mmol) was added portionwise in 5 min and stirring was continued for 1 h. The organic solution was washed with saturated aqueous $NaHCO_3$ solution (3×10 mL), was dried (anhydrous Na_2SO_4) and concentrated in vacuo to give an oily residue of the mixture of epoxides **32** (412 mg, 94%) in a ratio close to 1:3 (^{1}H and ^{13}C NMR). IR (NaCl): *v* 2951, 2857, 1473, 1395, 1362, 1308, 1108, 838 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) (data of the main diastereomer of **32**): δ 0.91 (s, 6H) and 0.92 (s, 6H) [2 C(CH_3)$_2$], 1.83–2.22 [complex signal, 14H, 2(8)-H_2, 4(6)-H_2, 5-H, 1'-H and 2'(5')-H_2], 3.21 (s, 2H, C1-CH_2O), 3.34 (broad d, *J* = 4.5 Hz, 2H, C1'-CH_2O), 3.45 (broad s, 10H, 3'(4')-H and 4 CH_2 of 2 dioxane substructures). ^{13}C NMR (75.4 MHz, $CDCl_3$): (data of the main diastereomer of **32**): δ 22.5 (CH_3) and 22.6 (CH_3) [2 C(*C*H_3)$_2$], 30.0 [C, 2 *C*(CH_3)$_2$], 31.1 [CH_2, 2'(5')-C], 33.1 (CH, 1'-C), 40.1 [CH_2, 4(6)-C], 40.4 (CH, 5-C), 42.8 [CH_2, 2(8)-C], 49.7 (C, 1-C 57.0 [CH, 3'(4')-C), 71.7 (CH_2) and 72.0 (CH_2) (4 CH_2 of 2 dioxane substructures), 73.4 (1'-C-*C*H_2O), 78.2 (1-C-*C*H_2O), 109.3 [C, 3(7)-C]. GC/MS (t_R = 28.7 min): *m*/*z* (%) 436 ($M^{\cdot+}$, 2), 309 ([M-(C_5H_5O)CH_2OCH_2]$^+$, 22), 128 (33), 69 (100). HRMS (ESI-TOF): calcd. for [$C_{25}H_{40}O_6$+H]$^+$: 437.2898. Found: 437.2895.

Mixture of (1*r*,3*c*,4*t*)- and (1*r*,3*t*,4*c*)-1-[(3-chloro-4-hydroxycyclopentyl)methoxymethyl]-*cis*-bicyclo[3.3.0]octane-3,7-dione (33). To a solution of the stereoisomeric mixture of epoxides **32** (77 mg, 0.18 mmol) in THF (5 mL), 35% HCl (50 μL) was added and the mixture was stirred for 2 h at room temperature. After diluting with water (5 mL), the mixture was extracted with EtOAc (3×10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (2×5 mL) and brine (2×5 mL), dried (anhydrous Na_2SO_4) and concentrated in vacuo to give an oily residue (67 mg) that was subjected to column chromatography (silica gel, 7 g; hexane/EtOAc mixtures). Upon elution with hexane/EtOAc 2:3 a slightly impure stereoisomeric mixture of chlorohydrins **33** was isolated (51 mg, 61%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.6–3.0 [complex signal, 14H, 2(8)-H_2, 4(6)-H_2, 5-H, 1'-H, 2'-H_2 and 5'-H_2], 3.41 (d, *J* = 6.2 Hz, 2H, C1'-CH_2O), 3.47 (s, 2H, C1-CH_2O), 3.51 (d, *J* = 4.0 Hz, 1H, O-H), 3.95 (m, 1H, 4'-H), 4.20 (m, 1H, 3'-H). ^{13}C NMR (50.3 MHz, $CDCl_3$) (data of the main diastereomer of **33**) δ 34.5 (CH_2, 2'-C), 34.9 (CH, 1'-C), 36.8 (C, 5'-C), 39.7 (CH, 5-C), 44.8 [CH_2, 4(6)-C], 46.7 [CH_2, 2(8)-C], 47.9 (C, 1-C), 64.3 (CH, 3'-C), 75.7 (CH_2, 1'-C-*C*H_2O), 77.3 (1-C-*C*H_2O], 79.4 (CH, 4'-C), 217.0 [C, 3(7)-C]. GC/MS (t_R = 25.0 min): *m*/*z* (%) 264 ([M–HCl]$^{\cdot+}$, 3), 151 (27), 150 (26), 137 (100), 83 (53), 79 (82), 69 (64), 55 (65).

1-[(Cyclopent-3-enyl)methoxymethyl]-*cis*-bicyclo[3.3.0]octane-3,7-dione (14). To a warm (70 °C), magnetically stirred solution of ether **28** (119 mg, 0.28 mmol) in acetonitrile (4 mL), a solution of $Ce(NH_4)_2(NO_3)_6$ (769 mg, 1.4 mmol) in water (4 mL) was added. The stirred mixture was heated to 65 °C for 5 min and was then allowed to cool to room temperature. The mixture was extracted with DCM (3×15 mL), the organic extracts were combined, dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a residue (54 mg) that was subjected to column

chromatography (silica gel, 5.4 g; heptane/EtOAc mixtures). Upon elution with heptane/EtOAc, diketone **14** (31 mg, 44%) was isolated. An analytical sample was obtained by distillation in a rotary microdistillation equipment. Colorless oil, bp 175 ºC/0.1 Torr. IR (KBr): *v* 3052, 2925, 2891, 1740, 1403, 1114 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.02 [broad dd, *J* = 13.5 Hz, *J'* = 5.5 Hz, 2H, 2'(5')-H_{cis}], 2.09 [dd, *J* = 19.0 Hz, *J'* = 5.5 Hz, 2H, 4(6)-H_{endo}], 2.25 [dd, *J* = 18.5 Hz, *J'* = 1.0 Hz, 2H, 2(8)-H_{endo}], 2.39 [dd, *J* = 18.5 Hz, *J'* = 1.5 Hz, 2H, 2(8)-H_{exo}], 2.38–2.45 [m, 2H, 2'(5')-H_{trans}], 2.47–2.54 [m, 1H, 1'-H], 2.72 [ddd, *J* = 19.0 Hz, *J'* = 9.0 Hz, *J''* = 1.5 Hz, 2H, 4(6)-H_{exo}], 2.85 (tt, *J* = 9.0 Hz, *J'* = 5.5 Hz, 1H, 5-H), 3.32 (d, *J* = 7.0 Hz, 2H, C1'-CH_2O), 3.43 (s, 2H, C1-CH_2O), 5.62 [s, 2H, 3'(4')-H]. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 35.8 [CH_2, 2'(5')-C], 36.5 (CH, 1'-C), 39.7 (CH, 5-C), 44.8 [CH_2, 4(6)-C], 46.7 [CH_2, 2(8)-C], 47.9 (C, 1-C), 75.8 (CH_2, 1'-C-*C*H_2O), 77.1 (CH_2, 1-C-*C*H_2O), 129.4 [CH, 3'(4')-C], 216.8 [C, 3(7)-C]. MS (CI): *m*/*z* (%): 250 (30), 249 ([M+H]$^+$, 67), 201 (69), 199 (88), 179 (80), 169 (65), 151 (100), 137 (39), 109 (54), 81 (99), 80 (75). Anal. calcd. for $C_{15}H_{20}O_3 \cdot 0.2H_2O$: C, 71.52; H, 8.16. Found: C, 71.61; H, 8.20. HRMS: calcd. for [$C_{15}H_{20}O_3$+H]$^+$: 249.1491. Found: 249.1492.

1-[(*trans*-3,4-Epoxycyclopentyl)methoxymethyl]-*cis*-bicyclo[3.3.0]octane-3,7-dione (*trans*-34). To a magnetically stirred solution of diketone **14** (99 mg, 0.40 mmol) in DCM (6 mL) at room temperature, MCPBA (359 mg, 77% content, 1.6 mmol) was added portionwise within 5 min and stirring was continued for 1.5 h. The organic solution was washed with 10% aqueous $Na_2S_2O_3$ solution (3×5 mL) and saturated aqueous $NaHCO_3$ solution (3×5 mL), dried (anhydrous Na_2SO_4) and concentrated in vacuo to give an oily residue of the mixture of epoxides *cis*- and *trans*-**34** (96 mg), which was subjected to column chromatography (silica gel, 10 g; heptane/EtOAc mixtures). Upon elution with heptane/EtOAc 1:1, pure epoxide *trans*-**34** (13 mg, 12%) and a mixture of epoxides *trans*-**34**/*cis*-**34** in a ratio close to 1:3 (38 mg, 36%) were isolated. The analytical samples of epoxide *trans*-**34** and of the mixture of epoxides *trans*-**34**/*cis*-**34** were obtained by distillation in a rotary microdistillation equipment at 200 °C/0.1 Torr.

trans-**34.** IR (NaCl): *v* 2924, 2854, 1738, 1401, 1101, 839 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.76–1.84 [m, 4H, 2'(5')-H_2], 2.10 [dd, *J* = 19.0 Hz, *J'* = 5.5 Hz, 2H, 4(6)-H_{endo}], 2.24 [dd, *J* = 19.0 Hz, *J'* = 0.5 Hz, 2H, 2(8)-H_{endo}], 2.22–2.32 (m, 1H, 1'-H), 2.38 [dd, *J* = 19.0 Hz, *J'* = 1.5 Hz, 2H, 2(8)-H_{exo}], 2.71 [ddd, *J* = 19.0 Hz, *J'* = 9.0 Hz, *J''* = 1.5 Hz, 2H, 4(6)-H_{exo}], 2.85 (tt, *J* = 9.0 Hz, *J'* = 5.5 Hz, 1H, 5-H), 3.23 (d, *J* = 8.0 Hz, 2H, C1'-CH_2O), 3.39 (s, 2H, C1-CH_2O), 3.45 [s, 2H, 3'(4')-H]. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 30.3 [CH_2, 2'(5')-C], 35.0 (CH, 1'-C), 39.7 (CH, 5-C), 44.8 [CH_2, 4(6)-C], 46.8 [CH_2, 2(8)-C], 48.0 (C, 1-C), 58.5 [CH, 3'(4')-C], 76.9 (CH_2, 1'-C-*C*H_2O), 77.8 (CH_2, 1-C-*C*H_2O), 216.9 [C, 3(7)-C]. MS (CI): *m*/*z* (%) 265 ([M+H]$^+$, 25), 199 (14), 191 (13), 179 (51), 169 (21), 151 (100), 97 (38), 79 (66). HRMS (CI): calcd. for [$C_{15}H_{20}O_4$+H]$^+$: 265.1440. Found: 265.1440.

Mixture of epoxide stereoisomers *trans*-34/*cis*-34 (ratio of 1:3)**.** IR (NaCl): *v* 2926, 2855, 1739, 1402, 1120, 837 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): (data of *cis*-**34** epoxide from the mixture): δ 1.37 [dd, *J* = 13.0 Hz, *J'* = 9.0 Hz, 2H, 2'(5')-H_{cis}], 2.01 (m, 1H, 1'-H), 2.04–2.12 [m, 4H, 2'(5')-H_{trans} and 4(6)-H_{endo}], 2.24 [d, *J* = 19.0 Hz, 2H, 2(8)-H_{endo}], 2.35 [dd, *J* = 19.0 Hz, *J'* = 1.5 Hz, 2H, 2(8)-H_{exo}], 2.69 [ddd, *J* = 19.0 Hz, *J'* = 8.5 Hz, *J''* = 1.5 Hz, 2H, 4(6)-H_{exo}], 2.83 (tt, *J* =

9.0 Hz, *J'* = 6.0 Hz, 1H, 5-H), 3.36 (d, *J* = 5.5 Hz, 2H, C1'-CH_2O), 3.41 (s, 2H, C1-CH_2O), 3.43 [s, 2H, 3'(4')-H]. ^{13}C NMR (75.4 MHz, $CDCl_3$): (data of epoxide *cis*-**34** from the spectrum of the mixture) δ 31.0 [CH_2, 2'(5')-C], 32.9 (CH, 1'-C), 39.8 (CH, 5-C), 44.8 [CH_2, 4(6)-C], 46.7 [CH_2, 2(8)-C], 47.9 (C, 1-C), 56.9 [CH, 3'(4')-C], 73.9 (CH_2, 1'-C-*C*H_2O), 77.3 (CH_2, 1-C-*C*H_2O), 216.5 [C, 3(7)-C]. HRMS (CI): calcd. for $[C_{15}H_{20}O_4+H]^+$: 265.1440. Found: 265.1443. Anal. calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.77; H, 7.84.

Attempted conversion of epoxide (34) into alcohol (35)

Procedure 1. A solution of (LHMDS) was prepared by adding a solution of *n*-BuLi (2.5 M in hexanes, 90 μL, 0.23 mmol) to a cold (–68 °C, acetone/CO_2 bath) solution of hexamethyldisilazane (HMDS, 56 μL, 0.27 mmol) in anhydrous toluene (0.5 mL). After stirring for 10 min, a solution of the stereoisomeric mixture of epoxide **34** (24 mg, 0.09 mmol) in anhydrous toluene (0.5 mL) was added dropwise. The reaction mixture was stirred at –68 °C for 1 h and then allowed to warm to room temperature for 24 h. The reaction mixture was quenched by addition of saturated aqueous solution of NH_4Cl (1 mL) and was extracted with Et_2O (3×10 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a residue (12 mg) containing mainly epoxide **34** (^1H NMR) The aqueous phase was acidified with 1N HCl (5 mL) and was extracted with Et_2O (3×10 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a residue (19 mg) consisting mainly of epoxide **34**.

Procedure 2. The reaction was carried out as in *procedure 1* and after the addition of **34**, $Sc(OTf)_3$ (1.2 equiv) was added. Epoxide **34** was the main component of the crude product.

Procedure 3. The reaction was carried out as in *procedure 1* using THF instead of toluene as the solvent, with similar result.

Procedure 4. The reaction was carried out as in *procedure 3* and after the addition of **34**, $BF_3 \cdot Et_2O$ in THF (1.2 equiv) was added. Epoxide **34** was the main component of the crude product.

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Supplementary Materials

Possible pathways from **17** and **18** to the side product **21 (**Scheme S1) can be found as supplementary material.

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