Tetrahedron Vol. 37, pp. 2079 to 2084, 1981
Printed in Great Britain.

0040-4020/81/112079-06$02.00/0
Pergamon Press Ltd.

THE SYNTHESIS OF FUNCTIONALIZED CIS-BICYCLO|3.3.0|OCTANES

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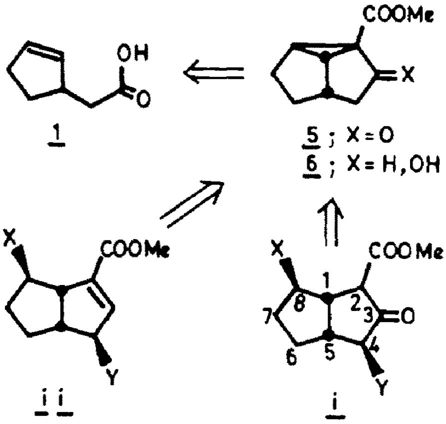
(Received in UK 3 April 1981)

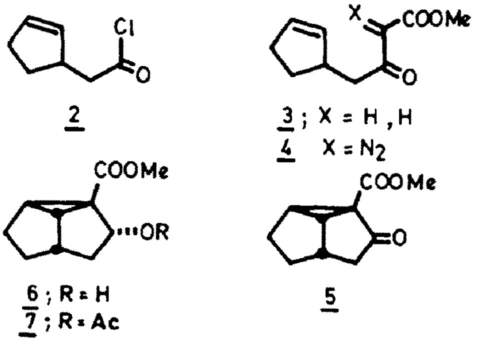
Abstract - A number of polyfunctionalized cis-bicyclo|3.3.0|octanes have been synthesized starting from the tricyclic key intermediate 5 which was obtained by the intramolecular cyclopropanation reaction of the diazo keto ester 4. Selected stereocontrolled transformations of 5 using nucleophiles and electrophiles have been studied for the preparation of the title compounds.

The increasing number of natural products carrying fused cyclopentane rings has stirred considerable interest in the synthesis of these compounds. We have embarked on a program for the synthesis of such polyquinanes[1] and of iridoid monoterpenes[2]. One of our strategies (scheme 1) centers about the intermediate 2-methoxycarbonyl tricyclo $|3.3.0.0^{2,8}|$octan-3-one (5), obtained from commercially available 2-cyclopentene-1-acetic acid (1) via an intramolecular carbinoid cyclopropanation reaction.



Scheme 1

It seemed worthwhile to investigate the properties of this tricyclic intermediate for the formation of polyfunctionalized bicyclo|3.3.0| octanes. The rigid structure of 5 allows for stereocontrol; electrophilic attack will introduce substituents (Y) at C-4 while the nucleophilic opening (i) of the cyclopropane ring is facilitated by the presence of two electron withdrawing functions. The 2-methoxycarbonyl group is present in many iridoids and can also be used as a handle in the synthesis of other target molecules. Depending on the nature of X, carbon atoms 6 and 7 can be functionalized. Reduction of the keto function will lead to the cyclopropyl alcohol 6 which can also be studied as a substrate for cyclopropane ring cleavage (ii). Ultimately, with suitably functionalized side chains Y present, one may consider additional ring annulation on carbon atom 3 at an appropriate stage in a synthetic sequence.

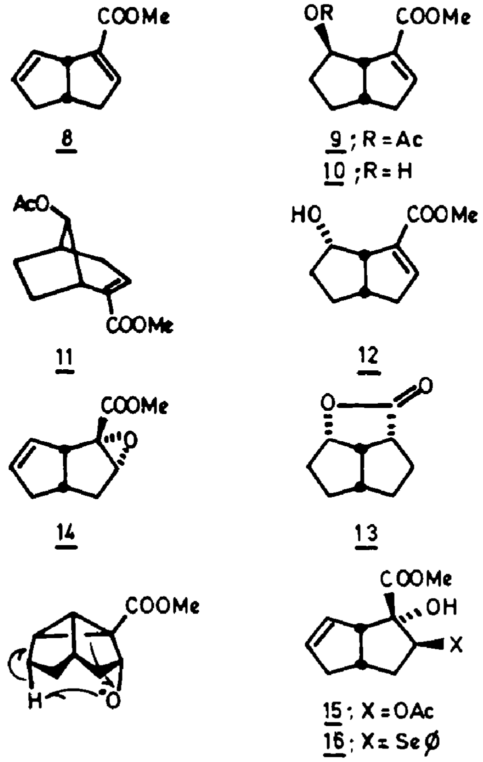


Scheme 2

In the present paper we describe the synthesis of the tricyclic intermediates 5 and 6 and some illustrative examples of their transformation to functionalized bicyclo|3.3.0|octanes. Starting from 2-cyclopentene-1-acetic acid (1) the intermediate 5 was constructed through a four-step sequence (55 % overall) (scheme 2). Transformation to the acid chloride 2, followed by condensation with Meldrums acid in pyridine-dichloromethane and solvolysis with dry methanol[3] afforded β-keto ester 3.

Subsequent treatment with p.tosylazide and triethylamine[4] gave the diazo compound 4; finally the cyclopropanation reaction (65 %) was performed in refluxing toluene with copper(II)acetylacetonate as the catalyst[5]. As expected, reduction of ketone 5 with sodium borohydride yielded the endo alcohol 6 (82 %) (δ HCOH = 5.37; d, J = 9.5 Hz).

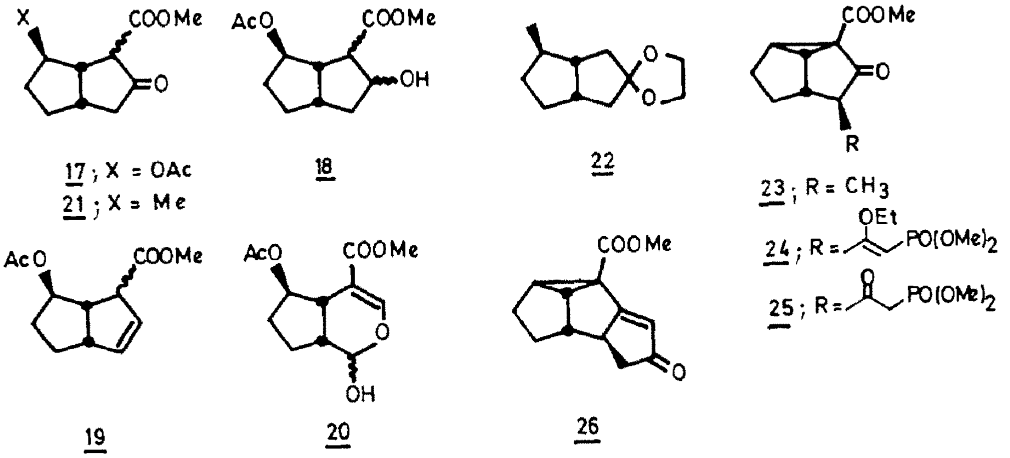
With both compounds 5 and 6 at hand we first studied the cyclopropane ring cleavage of 6 which in principle would provide the shortest route to 8 and/or 9, diquinanes possessing structural features of primary interest to us (scheme 3).



Scheme 3

Sulfuric acid promoted solvolysis of 6 in acetic acid led to a mixture of four products 7, 9, 11 and 8 from which only latter could be obtained pure by column chromatography (18 %). The other fraction consisted of isomeric acetates 7, 9 and 11; the bicyclo|3.2.1|octenol 11 was always a minor isomer. The ratio of 7 and 9 heavily depended on reaction conditions, 9 being favoured with increasing concentration of sulfuric acid. The desired 9 could not be obtained pure for structure elucidation. However, starting from 5 (vide infra) pure 9 was available via 17 and has been converted into lactone 13, thus proving the relative configuration at C-8. Oxidation of the alcohol 10 (from 9 with sodium bicarbonate in methanol) led to the corresponding ketone which upon reduction with sodium borohydride afforded two epimeric alcohols 10 and 12 (ratio 1:3). Catalytic hydrogenation (Pd/C) of this mixture yielded lactone 13 (49 %) as the major product. Although unpractical for preparative work, the outcome of the solvolysis of 6 indicated that indeed the 1,8 bond in 6 is most prone to cleave as only a small amount of the bicyclo|3.2.1|octene 11 arising from 1,2 bond cleavage was found. Solvolysis of 6 with perchloric acid in acetone gave a cleaner reaction and allowed the isolation of alcohol 10 (60 %) still contaminated with the bicyclo|3.2.1|oct-2-en-8-ol. Attempts to obtain diene 8 as the sole product have met only with limited success; treatment of 6 with mesyl chloride in pyridine yielded 8 in 30 %. The spatial proximity of the α-hydrogen at C-7 and the endo oriented alcohol group in 6 provided an opportunity for remote functionalization at C-7; lead tetraacetate oxidation of 6 in the presence of calcium carbonate yielded epoxide 14 (71 %) as the sole product. The ^1H NMR spectrum displayed vinylic absorptions at δ = 5.67 and δ = 5.78 and a broad singlet at δ = 3.84; the endo orientation of the epoxide is based on mechanistic considerations. Facile opening of the epoxide 14 upon treatment with acetic acid or with phenylselenide ion yielded respectively 15 and 16. The scope of the usefulness of the propitious epoxide 14 will be the subject of later studies.

We then focussed our attention on the ring opening of the doubly activated cyclopropane in 5 (scheme 4). It has been shown that in these cases the bond which is cleaved is the one best situated for simultaneous overlap with both carbonyl groups and that the nucleophilic attack occurs with inversion[6]. Inspection of molecular models of 5 indicates that the homoconju-



Scheme 4

gate addition should occur at C-8. Solvolysis with acetic acid at room temp , in the presence of sulfuric acid, afforded the acetate 17 (80 %). We were gratified to observe that the methoxycarbonyl group is not only a desirable substituent for subsequent transformations but also enhances the regioselectivity. Indeed this result contrasts with those observed for acid promoted solvolysis of tricyclo|3.3.0.0^{2,8}|octan-3-ones, lacking the additional activating group. In these cases bicyclo|3.3.0|octan-3-ones and bicyclo|3.2.1|octan-3-ones were obtained in a 4:1 ratio[7,8].

As already mentioned the α,β unsaturated ester 9 was at the origin an important target. The following four-step sequence from 5 is a more practical route to generate pure 9 than the one via 6 (vide supra). The solvolysis of 5 and subsequent sodium cyanoborohydride reduction could be performed as a one pot procedure (51 %). Treatment of the resulting alcohol 18 with mesyl chloride and triethylamine[9] followed by 1,5-diazabicyclo|5.4.0|undec-5-ene (DBU) afforded 9 (94 %). Transformation of the bicyclo|3.3.0|oct-2-ene system to the iridoid skeleton will necessitate double bond migration prior to ozonolysis. The α,β unsaturated ester 9 was taken as a model. Although base induced isomerisations[10] failed, 9 could nicely be converted to 19 via treatment with N-bromosuccinimide to the allylic bromide and subsequent zinc-acetic acid reduction[11] (77 %). Ozonolysis of 12 followed by reductive workup directly led to the nor iridoid 20 (82 %).

We were gratified to observe that lithiumdimethylcuprate cleanly transformed ketone 5 into keto ester 21, stereohomogeneous at C-8 (85 %). Hydrolysis, decarboxylation and acetal formation led to 22; the δ value (19.6) for the methyl group in the ^{13}C NMR spectrum[12] strongly supports the indicated stereochemistry.

Further transformations of 5 involved substitution at C-4 prior to cyclopropane ring cleavage. Reaction of the enolate anion of 5 (lithium diisopropylamide, tetrahydrofuran) with methyl iodide afforded the stereohomogeneous 23 (85 %). The exo orientation of the methyl group was tentatively proposed for steric reasons; transformation of 23 to (±)-iso-iridomyrmecin[13] confirmed this assignment. Similarly alkylating the lithium enolate of 5 with dimethyl-2-ethoxy-3-iodo-1-propenylphosphonate (obtained from Piers' reagent* [14] with sodium iodide in acetone) yielded 24 (79 %); we have observed that Piers' reagent (the 3-bromo analogue) reacts only sluggishly with enolates of cyclopentanones. Subsequent hydrolysis of the enolether gave the keto phosphonate 25 (87 %), which underwent an intramolecular Horner-Wittig reaction (sodium hydride in dimethylformamide) to the tetracyclic enone 26, albeit in low yield. Some of the functionalized cis-bicyclo|3.3.0|octanes described here open perspectives for selective transformations at all positions of the skeleton. Work directed to the total synthesis of some natural products is presently undertaken.

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* We thank Prof. E. Piers for kindly providing us with the detailed experimental procedure.

EXPERIMENTAL

The m.ps are uncorrected. The NMR spectra were recorded at 90 MHz (Varian EM-390) or at 360 MHz (Brucker-WH200) in CDCl$_3$ unless otherwise stated with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. The MS data were recorded on an AEI MS-50 spectrometer. Rf values are quoted for Merck silica gel 60 GF$_{254}$ the plates of thickness 0.25 mm with EtOAc-isooctane (ratio given between brackets) as eluent unless otherwise stated. Reaction products were isolated by the addition of water and extraction. The combined extracts were washed with saturated brine and dried over MgSO$_4$. The solvent was removed from the filtered solns on a rotary evaporator. Column chromatographic separations were performed on silica gel with EtOAc-isooctane (ratio given between brackets) as eluent unless otherwise stated.

Methyl-3-oxo-4-(2-cyclopentenyl)-butyrate (3)

A soln of 2-cyclopentene-1-acetic acid 1 (80 g; 0.63 mol) in SOCl$_2$ (80 ml; 1.1 mol) was stirred at 60° for 1 hr. The acid chloride 2 was distilled (b.p. 65°C; 15 mm Hg; 98 %). To a soln of Meldrums acid (92 g; 0.74 mol) in pyridine (100 mL) and CH$_2$Cl$_2$ (150 mL) was at 0° slowly added 2 (90 g; 0.62 mol) in CH$_2$Cl$_2$ (150 mL); stirring was continued for 2 hr at 20°. CH$_2$Cl$_2$ (800 mL) was added; the soln was washed with 4 N HCl aq and with water and dried on MgSO$_4$. The solvent was evaporated and the residue was refluxed in dry MeOH (600 mL) for 2 hr. Distillation gave 3 (b.p. 75°; 0.01 mm Hg; 97 g; 85 %).
IR (film) 1760, 1730, 1660, 1640 cm^{-1}; NMR 5.45-5.25 (m, 2), 3.5 (s, 3), 3.1 (s < 2), 2.95 (m, 1), 2.45-1.80 (m, 5), 1.35 (m, 1); MS m/z 182 (M$^{+\cdot}$, 17), 67 (100).

2-Methoxycarbonyltricyclo|3.3.0.0^{2,8}|octan-3-one (5)

To a soln of 3 (23.6 g; 0.13 mol) in dry acetonitrile (195 mL) and Et$_3$N (18.1 mL; 0.13 mol) was added at 0° p.TsSO$_2$N$_3$ (25.61 g; 0.13 mol) in acetonitrile (100 mL). The mixture was stirred overnight at 20° under N$_2$, concentrated in vacuo and the residue taken up in ether. The soln was washed with KOH aq and water and dried (MgSO$_4$). After stripping of the solvent, the residue (26.5 g; 127 mmol) was taken up in dry toluene (2.5 L) and Copper(II)acetylacetonate (2.65 g) was added. The mixture was heated at reflux under vigorous stirring for 2 hr and was then concentrated in vacuo. The residue was dissolved in CHCl$_3$ and washed with 10 % H$_2$SO$_4$ aq and water. Workup and column chromatography (3:7) yielded 5 (14.87 g; 65 %). Rf (3:7) 0.18; IR (film) 1750-1720 cm^{-1}; NMR (300 MHz) 3.72 (s, 3), 3.18 (dd, J = 6.8 and 5.6 Hz, 1), 2.94 (ddd, J = 9.5, 5.8 and 5 Hz, 1), 2.74 (ddd, J = 6.8, 6 and 1 Hz, 1), 2.70 (ddd, J = 19.7, 9.5 and 1.5 Hz, 1), 2.19 (ddd, J = 11, 10 and 6 Hz, 1), 2.80 (ddddd, J = 11, 10, 10, 5 and 1.5 Hz, 1), 1.89 (d, J = 17.5 Hz, 1), 1.68 (dddd, J = 11, 10, 6.5 and 1 Hz, 1), 1.55 (dd, J = 11 and 6.5 Hz, 1); HRMS m/z (52 %) 180.0791, calc for C$_{10}$H$_{12}$O$_3$, 180.0786.

2-Methoxycarbonyl tricyclo|3.3.0.0^{2,8}|octan-3-ol (6)

To a stirred soln of 5 (180 mg; 1 mmol) in MeOH (5 mL) at 0°, was slowly added NaBH$_4$ (50 mg). Stirring was continued for 30 min. Workup and column chromatography (3:7) yielded 6 (128 mg; 82 %). Rf (benzene/EtOAc 6:10) 0.44; IR (film) 3600-3300, 1720, 1700 cm^{-1}; NMR 5.37 (d, J = 9.5 Hz, 1), 3.72 (s, 3), 2.75-2.45 (m, 5), 2.32 (t, J = 6.5 Hz, 1), 2.10-1.90 (m, 2), 1.58 (dd, J = 10.5 and 6.5 Hz, 1), 1.32 (d, J = 14 Hz, 1); HRMS m/z (2 %) 182.0939; calc for C$_{10}$H$_{14}$O$_3$, 182.0942.

Solvolysis of 6 in HOAc

To a soln of 6 (1.8 g; 10 mmol) in HOAc (13.5 mL) at 10° was added 10 % H$_2$SO$_4$ in HOAc (4.5 mL). After stirring for 2 hr at 20° the soln was cooled and NaOAc (2.05 g; 25 mmol) was added. The soln was poured in water. After workup, column chromatography (1:9) gave two fractions; (1) pure 8 (300 mg, 18 %) and (2) a mixture of 7, 9, 11 (1270 mg; 57 %) in a ratio 4:6:1 as determined by NMR.
9 : Rf (2:8) 0.46; IR (film) 1720, 1630 cm^{-1}; NMR (360 MHz) 6.66 (dt, J = 2.0 and 2.5 Hz, 1), 5.88 (dq, J = 5.75 and 2.33 Hz, 1), 5.66 (dq, 5.75 and 2.25 Hz, 1), 3.97 (bd, J = 8.0 Hz, 1), 3.74 (s, 3), 3.08 (m, ΣJ = 35.0 Hz, 1), 2.83 (dddd, J = 19.0, 9.5, 2.5 and 1.25 Hz, 1), 2.68 (dddt, J = 16.75, 9.0, 1.5 and 2.25 Hz, 1), 2.25 (ddt, J = 19.0, 4.5 and 2.75 Hz, 1), 2.14 (ddq, J = 16.75, 3.5 and 2.4 Hz, 1); HRMS m/z (58 %) 164.0834, calc for C$_{10}$H$_{12}$O$_2$, 164.0837.

Lactone 13

To a soln of 10 (728 mg; 4.0 mmol) in acetone (40 mL) at -10° is added Jones reagent (2M; 4 mL). Stirring is continued for 1 hr at 20° and iPrOH (2 mL) is added. Workup and column chromatography (ether/hexane 1:1) afforded the corresponding ketone (504 mg; 69 %).
Rf (ether/benzene 1:1) 0.42; IR (KBr) 1740, 1725, 1720-1690, 1615 cm^{-1}; NMR 6.78 (q, J = 2.4 Hz, 1), 3.78 (s, 3), 3.6-1.7 (m, 8); MS m/z 180 (M$^+$, 100). To a soln of the ketone (182 mg; 1.0 mmol) in MeOH (2 mL) at 0° is added NaBH$_4$ (22 mg; 0.55 mmol). After 15 min the mixture is poured into H$_2$O (20 mL); workup and column chromatography (ether/hexane 1:1) afforded an inseparable mixture of 10 and 12 (1:3)(167 mg; 92 %).
12 : Rf (benzene/ether 1:1) 0.30; NMR 6.82 (q, J = 2.0 Hz, 1), 4.34 (q, J = 5.5 Hz, 1), 3.76 (s, 3), 3.5-1.5 (m, 9).
A portion of this mixture 10 and 12 (1:3) (72 mg; 0.4 mmol), and 10 % Pd/C (24 mg) in MeOH (4 mL) was stirred for 2 hr at 20° under H$_2$ (1 atm.); filtration, evaporation and column chromatography (benzene/ether 9:1) gave 13 (30 mg; 49 %). Rf (benzene/ether 1:1) 0.48; IR (film) 1770-1750 cm^{-1}; NMR 4.95 (bt, J = 6.0 Hz, 1), 3.18 (td, J = 9.25 and 7.25 Hz, 1), 3.06 (td, J = 9.25 and 5.0 Hz, 1), 2.63 (m, ΣJ = 36.0 Hz, 1), 2.3-1.3 (m, 8); MS m/z 152 (M, 2), 80 (100).

2α,3α-Epoxy-2β-methoxycarbonyl-cis-bicyclo|3.3.0|oct-7-ene (14)

A mixture of 6 (5 g; 34.4 mmol) Pb(OAc)$_4$ (16.75 g; 31.8 mmol) and CaCO$_3$ (4.3 g; 43 mmol) in benzene (50 mL) was refluxed for 3 hr. Additional Pb(OAc)$_4$ (3.3 g; 7.45 mmol) and CaCO$_3$ (1 g; 10 mmol) were added and reflux was continued for 1 hr. After cooling and dilution with ether (50 mL) the mixture was filtered through silica gel. The solid was washed with ether (3 x 20 mL). Workup and column chromatography (2:8) yielded epoxide 14 (3.5 g; 71 %). Rf (25:75) 0.25; IR (film) 1745, 1735 cm^{-1}; NMR (300 MHz) 5.78-5.67 (m, 2), 3.84 (bs, FWHM = 3 Hz, 1), 3.77 (s, 3), 3.70 (dtd, J = 9.2, 2.8 and 1.3 Hz, 1), 2.98 (ddddd, J = 10.4, 10.2, 9.2, 9.2 and 1.6 Hz, 1), 2.50 (ddt, J = 16.5, 10.2 and 2.2 Hz, 1), 2.14 (ddd, J = 15.0, 9.2 and 1.6 Hz, 1), 2.07 (m, J = 32 Hz, 1), 2.00 (dd, J = 15.0 and 1.6 Hz, 1); HRMS m/z (M-H$_2$O) (68 %) 162.0677, calc for C$_{10}$H$_{10}$O$_2$, 162.0681.

3β-Acetoxy-2α-hydroxy-2β-methoxycarbonyl-cis-bicyclo|3.3.0|oct-7-ene (15)

To a soln of epoxide 14 (784 mg; 4.35 mmol) in HOAc (2.2 mL) at 20° was added dropwise

H_2SO_4 (10 %) in HOAc (2.2 mL). After 1 hr the mixture was poured into a sat $NaHCO_3$ aq. Workup and column chromatography (3:7) yielded 15 (570 mg; 55 %). Rf (3:7) 0.16; IR (film) 3550-3400, 1745, 1730 cm^{-1}; NMR (360 MHz) 5.85 (dq, J = 5.7 and 2.2 Hz, 1), 5.67 (dq, J = 5.7 and 2.2 Hz, 1), 5.07 (t, J = 7.5 Hz, 1), 3.83 (s, 3), 3.57 (s, 1), 3.53 (dq, J = 8.6 and 2.2 Hz, 1), 2.99 (m, J = 9.4, 9.0, 8.6, 4.3 and 2.0 Hz, 1), 2.72 (ddq, J = 17.0, 9.0 and 2.2 Hz, 1), 2.21 (dq, J = 17.0 and 2.2 Hz, 1), 2.17 (ddd, J = 13.4, 9.4 and 7.4 Hz, 1), 2.02 (s, 3), 1.87 (ddd, J = 13.4, 7.2 and 4.3 Hz, 1); MS m/z 240 (M^+, < 1), 43 (100).

6β-Acetoxy-4β-methoxycarbonyl-cis-bicyclo |3.3.0|octan-3-one (17)

To a soln of 5 (200 mg; 5 mmol) in HOAc (9 mL) at 20° was added dropwise 20 % H_2SO_4 soln in HOAc (1.2 mL). After 5 min HOAc was added, the mixture was concentrated in vacuo and then taken up in ether. Workup and column chromatography (15:85) afforded the acetate 17 (960 mg; 80 %). Rf (35:65) 0.37; IR (KBr) 1745, 1685, 1650 cm^{-1}; NMR 5.15 (m, 1), 3.78 (s, 3), 2.02 (s, 3), 3.30-1.30 (m, 9); MS m/z 209 (1), 180 (30), 165 (10), 148 (100), 121 (30).

6β-Acetoxy-3-hydroxy-4-methoxycarbonyl-cis-bicyclo|3.3.0|octane (18)

A soln of 5 (10.5 g; 58.3 mmol) and H_2SO_4 (3 mL) in HOAc (45 mL) at 20° was stirred for 2 hr; solid NaOAc (20 g; 240 mmol) was then slowly added. After dilution with THF (100 mL) $Na(CN)BH_3$ (6.3 g; 0.1 mol) was added (portionwise over a period of 1 hr), followed by water (50 mL) and solid $NaHCO_3$ (42 g; 0.5 mol). Workup and column chromatography (hexane/ether 1:1) yielded 18 (7.2 g; 51 %). Rf (ether) 0.35; IR (film) 3600-3300, 1740-1725 cm^{-1}; NMR 5.03 (bs, 1), 4.20 (m, 1), 3.70 (s, 3), 3.15 (s, 1), 2.70-1.10 (m, 9), 2.00 (s, 3); MS m/z 242 (M^+, < 1), 43 (100).

6β-Acetoxy-4-methoxycarbonyl-cis-bicyclo |3.3.0|oct-3-ene (9)

To a soln of 18 (7.2 g; 30 mmol) and Et_3N (6.3 mL; 45 mmol) in CH_2Cl_2 (150 mL) at -10° was added a soln of MesCl (2.8 ml; 36 mmol) in CH_2Cl_2 (7 mL). After 30 min DBU (13.7 mL; 90 mmol) was added and the mixture was stirred at 20° for 18 hr. Workup and column chromatography (hexane/ether 8:2) yielded 9 (6.3 g; 94 %). Rf (ether) 0.57; IR (film) 1735, 1720, 1710, 1625 cm^{-1}; NMR (360 MHz) 6.75 (q, J = 2.3 Hz, 1), 5.18 (bs, FWHM = 9 Hz, 1), 3.74 (s, 3), 3.39 (bd, J = 8.8 Hz, 1), 3.01 (qt, J = 9.0 and 3.4 Hz, 1), 2.81 (dddd, J = 19.5, 9.5, 2.5 and 1.75 Hz, 1), 2.19 (dq, J = 19.5 and 3.2 Hz, 1), 2.05 (s, 3), 2.00 (m, 1), 1.80-1.61 (m, 2), 1.45 (m, ΣJ = 25.5 Hz, 1); HRMS m/z (M-HOAc) 164.0834 (100 %) calc. for $C_{10}H_{12}O_2$, 164.0837.

6β-Acetoxy-4-methoxycarbonyl-cis-bicyclo |3.3.0|oct-2-ene (19)

A mixture of 9 (112 mg; 0.5 mmol), NBS (100 mg; 0.55 mmol) and a trace of AIBN in CCl_4 (25 mL) was refluxed for 3 min. After cooling to 0° the succinimide was filtered off and was washed with cold CCl_4 (1 mL). After evaporation in vacuo and the bromide was dissolved in CH_2Cl_2 (1 mL) and HOAc (1 mL) and Zn powder (130 mg; 20 mmol) was added at -10°. After 1 hr the mixture was diluted with ether (5 mL) and filtered. Workup and column chromatography (hexane/ether 1:1) yielded 19 (84 mg; 75 %). Rf (hexane/ether 1:1) 0.38; NMR 5.8-5.5 (m, 2), 4.83 (m, 1), 3.75 and 3.70 (s, 3), 2.05 and 2.00 (s, 3); MS m/z 224 (M^+, 1), 43 (100).

7β-Acetoxy-2-hydroxy-5-methoxycarbonyl-3-oxa-cis-bicyclo|4.3.0|non-4-ene (20)

In a soln of 19 (678 mg; 3 mmol) in CH_2Cl_2 (25 mL) at -60° was passed O_3. The excess ozone was stripped off with N_2. After evaporation in vacuo the residue was taken up in HOAc (10 mL). Under stirring Zn powder (520 mg; 8 mmol) was added slowly; stirring was continued for 1 hr at 20° and for 2 hr at 80°. After cooling, ether (50 mL) was added and the mixture was worked up. Column chromatography (1:1) yielded 20 (642 mg; 82 %). Rf (7:3) 0.37; IR (film) 3600-3300, 1730, 1700, 1630 cm^{-1}; NMR (CCl_4) 7.35 (d, J = 1.0 Hz, 1), 5.30-5.00 (m, 2), 3.70 (s, 3), 2.90 (dd, J = 3.6 and 7.2 Hz, s), 2.5-1.5 (m, 6), 2.00 (s, 3); HRMS m/z (M-HOAc) (5 %) 196.0731, calc for $C_{10}H_{12}O_2$ 196.0735.

3,3-Ethyleendioxy-6β-methyl-cis-bicyclo |3.3.0|octane (22)

To Me_2CuLi (3.15 mmol) in ether (3 mL) at -80° was slowly added a soln of 5 (180 mg; 1.0 mmol) in ether (1 mL). The mixture was warmed up to -30° and after 15 min poured into sat NH_4Cl aq. Workup and column chromatography (3:7) yielded 21 (170 mg; 88 %). Rf (3:7) 0.63; NMR 3.77 and 3.73 (s, 3), 3.1-1.0 (m, 10), 1.06 (d, J = 6.6 Hz, 3).

A soln of 21 (170 mg; 0.88 mmol) in 1 % H_2SO_4/HOAc (2 mL) was refluxed for 2 hr. After cooling, the mixture was diluted with ether/pentane (1:2; 25 mL) and worked up, affording a volatile ketone (87 mg; 72 %), which is dissolved in benzene (5 mL). After addition of glycol (0.5 ml) and p.TsOH (trace) this mixture was refluxed for 2 hr, H_2O being removed with a Dean-Stark separator. Workup and column chromatography (1:9) yielded 22 (95 mg; 82 %). IR (film) 1240, 1150, 1115, 1040, 1025, 1010 cm^{-1}; ^1H NMR 3.90 (s, 4), 2.7-1.1 (m, 11), 0.97 (d, J = 6.0 Hz, 3); ^{13}C NMR 119.6, 64.6, 64.0, 49.0, 42.3, 41.9, 40.7, 40.6, 35.7, 32.8, 19.6; MS m/z 182 (M^+, 31), 125 (100).

Phosphonate 24

To a soln of LDA (1.47 mmol) in THF (1.25 mL) at -80° was slowly added a soln of 5 (221 mg; 1.24 mmol) in THF (1.25 mL). After 20 min the mixture was warmed to 0° and a soln of dimethyl 2-ethoxy-3-iodo-1-propenylphosphonate (432 mg; 1.35 mmol) in THF (1.25 mL) was quickly added. Stirring was continued for 10 min at 0° and 20 min at 20°. Quenching with sat NH_4Cl aq, extraction with EtOAc (3 x 10 ml), workup and column chromatography (hexane/acetone 7:3) yielded 24 (360 mg; 79 %). Rf (hexane/acetone 1:1) 0.28; IR (film) 1750, 1725, 1610 cm^{-1}; NMR 4.51 (d, J = 5.4 Hz, 1), 3.82 (q, J = 6.6 Hz, 2), 3.71 (s, 3), 3.71 (d, J = 11.1 Hz, 6), 3.3-1.4 (m, 10), 1.30 (t, J = 6.6 Hz, 3); MS m/z 372 (M^+, 0.2), 151 (100).

Phosphonate 25

A soln of 24 (254 mg; 0.68 mmol) in HCl-acetone (0.5 M; 3.5 mL) was stirred for 30 min at 0°; Et_3N (300 μl, 2.2 mmol), CH_2Cl_2 (5 mL) and solid $MgSO_4$ were then added. After filtration, evaporation of the solvents and column chromatography (hexane/acetone 1:1) 25 was obtained (205 mg; 87 %). Rf (hexane/acetone 1:1) 0.34; IR (film) 1750, 1725 cm^{-1}; NMR 3.78 (d, J = 10.8 Hz, 6), 3.71 (s, 3), 3.09 (d, J = 22.8 Hz, 2), 3.2-1.5 (m, 10); MS m/z 344 (M^+, 0.1), 151 (100).

2-Methoxycarbonyl-1,11-dehydrotetracyclo |6.3.0.0^{2,4}0^{3,7}|undecan-10-one (26)

To a soln of 25 (34 mg; 0.1 mmol) in DMF (1.0 mL) at 20° was added NaH (5 mg; 0.1 mmol). Stirring is continued for 2 hr at 20° and 2 hr at 60°. After cooling the reaction was quenched with a sat NH_4Cl aq (5 mL). Extraction with ether (3 x 10 ml), workup and column chromatography (ether) afforded 26 (4 mg; 20 %; m.p. 110-111° from hexane). Rf (Et_2O) 0.37; IR (KBr) 1720, 1700, 1600 cm^{-1}; NMR 6.37 (d, J = 2.2 Hz, 1), 3.73 (s, 3), 3.17 (dd, J = 7.0 and 5.0 Hz, 1), 3.02 (td, J = 7.0 and 2.2 Hz, 1), 2.74 (dd, J = 15.6 and 6.8 Hz, 1), 2.69 (m, J = 16 Hz, 1), 2.50 (m, J = 19 Hz, 1), 2.3-1.85 (m, 4), 1.71 (dd, J = 10.8 and 5.0 Hz, 1); HRMS m/z 218.0948 (24 %), calc for $C_{13}H_{14}O_3$ 218.0942.

Acknowledgements : We thank the N.F.W.O. and the "Ministerie voor Wetenschapsbeleid" for financial help to the laboratory. P.C. is indepted to the I.W.O.N.L. for a graduate scolarship.

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