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A General and Stereoselective Approach to Nonactate Esters and Isomers : A Versatile Synthesis of (+)-Methyl Nonactate

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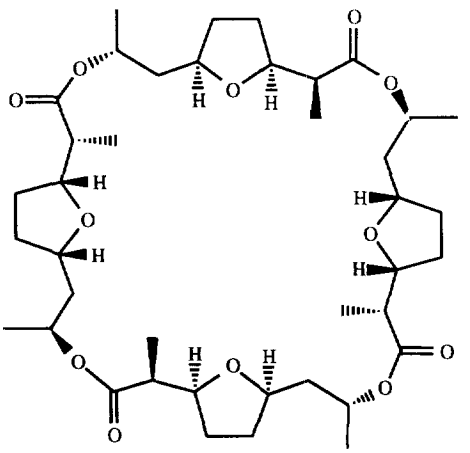
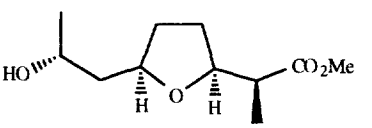
Abstract : A total synthesis of (+)-methyl nonactate from a chiral synthon obtained by enantioselective enzymatic transesterification is described. This new approach involves stereoselective reactions of aldolisation, reduction and intramolecular Michael addition and appears to be quite general since it could be applied as well to the synthesis of both enantiomers of 2- or 8-*epi* nonactate esters or homologues. © 1997 Elsevier Science Ltd.

Nonactin **1** is the lowest homologue of the nactins, a class of macrotetrolide antibiotics which have been isolated from a variety of *Streptomyces* cultures.[1] They are able to mediate cation (particularly potassium) transport and their antibiotic activity can be traced to their ionophoric properties. Structurally, nonactin is composed of two subunits of (-)-nonactic acid and two subunits of (+)-nonactic acid arranged in an alternating order. The interesting biological properties of nonactin as well as the stereochemical challenges contained in the structure of nonactic acid (control of 1,2 and 1,3-acyclic relationships and *cis* stereochemistry around the tetrahydrofuran ring) have, these last years, attracted the attention of organic chemists. Thus, a number of syntheses of nonactic acid (or its methyl ester) and its 8-*epi* isomer have been reported either in racemic or in both enantiomeric forms.[2]



nonactin **1**



(+)-methyl nonactate **2**

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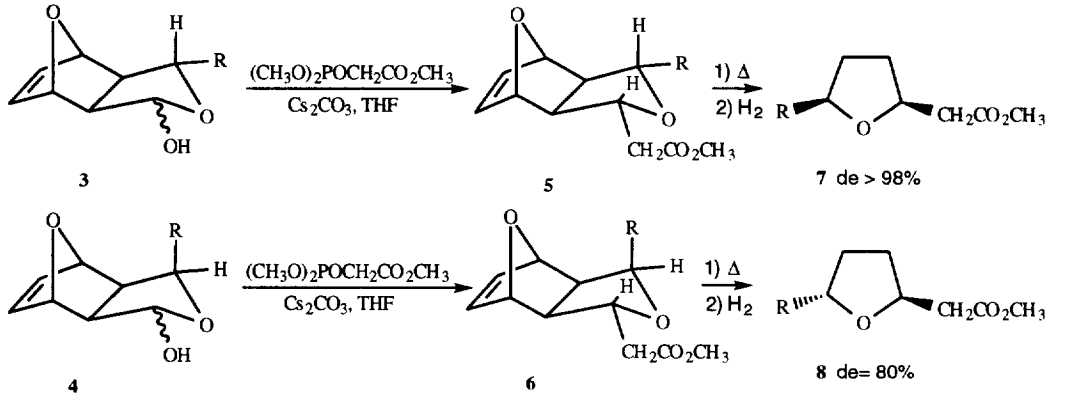
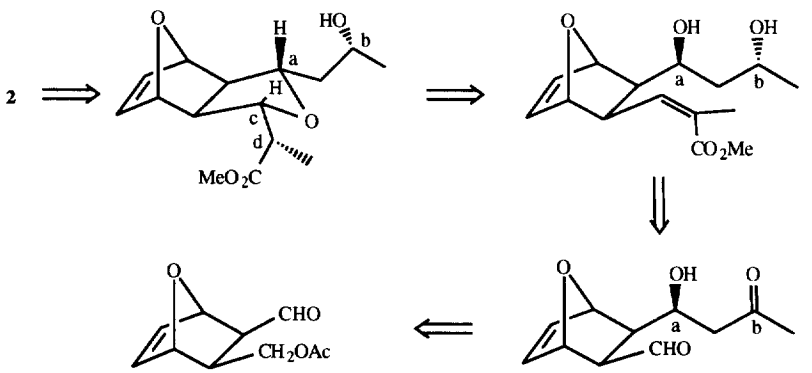
In this paper we report the synthesis of (+)-methyl nonactate **2** by a general and versatile route which involves, as the key step, a stereoselective intramolecular Michael addition for the formation of the requisite *cis*-2,5-disubstituted tetrahydrofuran ring.

A large number of biologically important natural products contain *cis*- as well as *trans*-2,5-disubstituted tetrahydrofuran units and for these reasons, stereoselective synthesis of such structural features has received considerable attention in recent years.[3] If electrophilic cyclisations of γ,δ-unsaturated alcohols have been well developed, reports on cyclisations of such alcohols via a simple Michael reaction are relatively scarce and more or less successful with respect of the degree of stereoselectivity.[4] We have recently shown [5] that the lactols **3** and **4** react with trimethylphosphonoacetate to give with high diastereoselectivity the rigid tricyclic compounds **5** and **6** via a tandem Horner-Emmons/intramolecular Michael reaction.



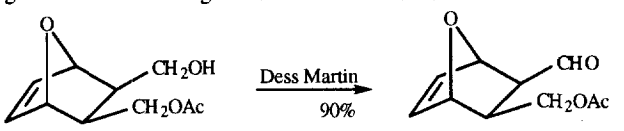
The *cis*- or *trans*-stereochemistry around the created tetrahydrofuran ring is directly related to the configuration of the carbon bearing the hydroxyl group participating in the Michael cyclisation. After retro Diels-Alder reaction followed by hydrogenation, the simple *cis*- or *trans*-2,5-disubstituted furans **7** and **8** are easily obtained. This highly diastereoselective intramolecular Michael addition constitutes the key step of our synthesis of (+)-methyl nonactate **2** and our retrosynthetic analysis is outlined in Scheme 1.



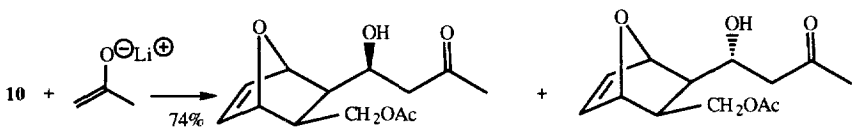
Scheme 1

As is shown in this scheme, the relative and absolute configurations of carbons b and c (corresponding to C_8 and C_3 of nonactate **2**) are entirely controlled by the configuration of carbon a (corresponding to C_6 of nonactate **2**) through the anti reduction of a β-hydroxy ketone on one hand and the intramolecular Michael addition cited above on the other hand.

Our synthesis started from the enantiomerically pure hydroxy acetate **9** easily prepared by trans esterification of the corresponding diol in the presence of lipase PS (Amano).[6] Dess-Martin oxidation gave rise with high yield to the acetoxy aldehyde **10**. Aldol condensation of this aldehyde with the simple lithium enolate of acetone proved to be quite stereoselective, affording as the major product (ratio = 85/15) the stereoisomer **11** possessing the desired *S* configuration for the carbon a.

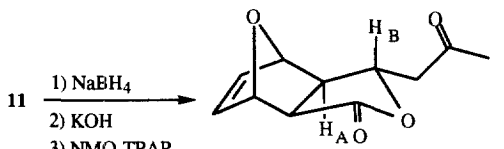


9 **10**



11

The *S* configuration of the carbon bearing the hydroxyl group has been established by ^1H NMR spectroscopy after chemical transformation of **11** to the lactone **12**.



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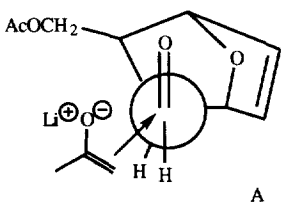
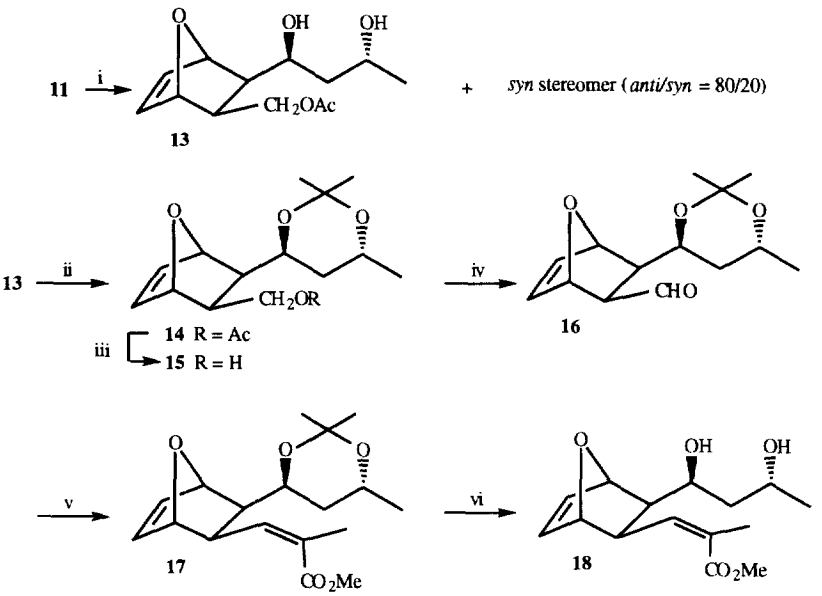
The value of the geminal coupling constant, J_{HAHB} = 3.6 Hz is charateristic of a *trans* arrangement of the two hydrogen (J_{trans} = 3.5 Hz ; J_{cis} = 8 Hz).[7] The stereoselectivity observed in the aldol condensation is well explained by a Felkin-Anh transition state where the conformation A is preferred.



A

Treatment of the β-hydroxy ketone **11** with tetramethylammonium triacetoxy borohydride (scheme 2) under the conditions used by Evans and co-workers [8] resulted in the formation of the *anti*-1,3-diol **13** with good stereoselectivity (*anti/syn* = 80/20). The *anti* configuration of the major 1,3-diol formed was indicated by

the stereoselectivity usually generated by the triacetoxyborohydride reagent.[8] It was confirmed by the relative ^{13}C NMR chemical shifts of the corresponding acetonides which are in very good agreement with the values established by Rychnovsky [9] : the major 1,3-diol acetonide **14** has acetal methyl shifts at 24.2 and 24.9 ppm and acetal carbon shift at 100.4 ppm, whereas the minor acetonide stereomer has acetal methyl shifts at 19.4 and 30.2 ppm and acetal carbon shift at 98.5 ppm. It must be noted that, since several methods have been described for the stereoselective reductions of β-hydroxy ketones to the corresponding *syn*-1,3-diols,[10] our synthesis can be easily adjusted to the formation of 8-*epi*-nonactates.

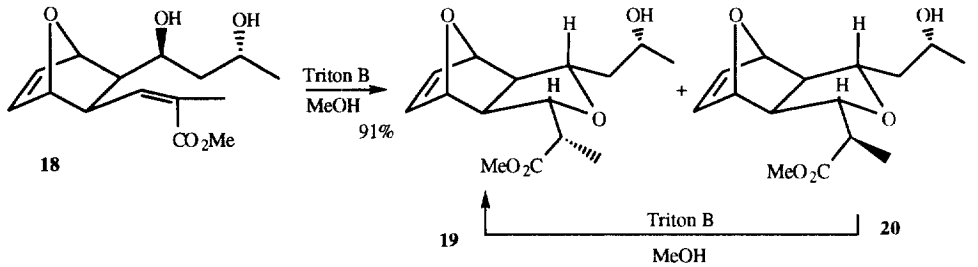


Reagents and conditions : (i) $Me_4N^+(AcO)_3BH^-$, MeCN, AcOH, -30°C, 90% ; (ii) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 80%; (iii) KOH, MeOH, r.t., 95% ; (iv) Triacetoxyperiodinane, pyridine, CH_2Cl_2, 84% ; (v) $(PhO)_2POCH(CH)_3CO_2Me$, NaH, THF, 78% (Z/E = 90/10) ; (vi) HCl 1M, THF, 80%.

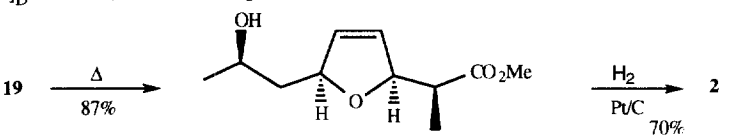
Scheme 2

The transformation of the acetate **13** to the requisite olefin **18** was effected by classical reactions as shown in scheme 2. Treatment of the diol **13** with 2,2-dimethoxypropane in the presence of catalytic amounts of pyridinium p-toluenesulfonate (PPTS) gave the acetonide **14** in excellent yield. After saponification of the acetate function, the free primary hydroxyl group of **15** was oxidized with Dess-Martin periodinane to the aldehyde **16**. Horner-Emmons reaction of the aldehyde **16** with methyl diphenoxyphosphonopropionate [11] afforded the (Z)-α,β-unsaturated ester **17** with high stereoselectivy (*Z/E* = 90/10). The *Z/E* ratio was determined by integration of the vinyl proton signals in the ^1H NMR spectrum. The vinyl proton of the Z-isomer exhibits an upfield signal (5.99 ppm) compared to the vinyl proton resonance of the E-isomer (6.78 ppm).[12] Acidic deprotection of the acetonide **17** gave the free 1,3-diol **18** which was submitted to cyclisation conditions.

The best yield (91%) was obtained by treatment of **18** with benzyltrimethylammonium methoxide (Triton B). As expected, the tetrahydrofuran formation was highly stereoselective since only *cis*-disubstituted tetrahydrofurans were formed. However, as already observed in similar cases,[4a,h,i] the configuration of the carbon bearing the carbomethoxy and the methyl group could not be controlled and a 1 to 1 mixture of compounds **19** and **20** resulted from the cyclisation. The ratio **19/20**, totally independent from the ratio *Z/E* of the starting olefin **18**, is representative of a thermodynamic equilibrium. The desired compound **19** was easily separated on a silica gel column and **20** was converted again to **19** by treatment with Triton B in methanol, so that **19** was obtained in 67% total yield.



The tricyclic compound **19** was then heated under flash thermolysis conditions (450°C, 10^{-3} torr) to give the dihydrofuran **21** which was hydrogenated (H_2, Pt/C) to afford (+)-methyl nonactate **2** structurally identified by its spectral data which were in excellent agreement with those reported [2b,2f,2g] and possessing a specific rotation $[\alpha]_D^{20}$ +21.8 (c 1.04, $CHCl_3$) close to that lastly reported : lit. [2k] $[\alpha]_D^{22}$ +22.5 (c 1.14, $CHCl_3$) ; lit. [2f] $[\alpha]_D^{27}$ +19.6 (c 1.44, $CHCl_3$).



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A novel synthetic route to (+)-methyl nonactate **2** (11 steps from the hydroxyacetate **9**, 6.4% overall yield) has been achieved. Advantages of this route lie in particular in its great versatility since it can be easily adapted, starting from the same synthon **9**, for the synthesis of (-)-methyl nonactate as well as both enantiomers of C_2 or C_8 epimers and of homologues of nonactates. Applications of this research to the total synthesis of pamamycin 607 are now in progress.

EXPERIMENTAL SECTION

General : IR spectra were recorded on a Perkin Elmer 682 spectrophotometer. NMR spectra were recorded on a Bruker AM 250 or AC 200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC/MS R.10-10 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. All reactions were carried out under an inert atmosphere of argon and monitored by thin-layer chromatography (TLC). TLC was performed on Merck silica gel 60F-254 precoated on glass.

(1*R*,2*S*,3*S*,4*S*)-2-Formyl-3-acetoxymethyl-7-oxabicyclo[2.2.1]-5-hepten (10). To a suspension of periodinane (7.64 g, 18 mmol) in CH_2Cl_2 (100 mL) cooled at 0°C was added dropwise a

solution of **9** (2.94 g, 15 mmol) in CH_2Cl_2 (80 mL). After 30 min, the reaction mixture was diluted with ether (250 mL), washed successively with 10% $Na_2S_2O_3$ (30 mL), and a saturated solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with ether (150 mL). The organic layers were dried over $MgSO_4$, filtrated and concentrated. Flash chromatography (ether) gave **10** as a colorless oil (2.62 g, 90% yield) : $[\alpha]_D^{20}$ -47 (c 1.28, $CHCl_3$); IR (neat) 1750, 1725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.36 (dt, J = 7.1, 7.0 Hz, 1H), 2.47 (dd, J = 7.1, 5.1 Hz, 1H), 4.23 (m, 2H), 4.91 (s, 1H), 5.18 (s, 1H), 6.37 - 6.51 (m, 2H), 9.71 (d, J = 5.1 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.5, 41.9, 51.4, 63.3, 79.0, 79.5, 134.5, 136.3, 170.2, 202.5; CIMS (NH_3) m/z (relative intensity) : 214 (MNH_4^+, 100), 197 (MH^+, 11). Anal. calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found : C, 61.02; H, 6.13.

(1*R*,2*S*,3*S*,4*S*,1'*S*)-2-(1'-Hydroxy-3'-oxobutyl)-3-acetoxymethyl-7-oxabicyclo[2.2.1]-5-hepten (11). To a solution of lithium diisopropylamide prepared from diisopropylamine (1.052 g, 10.4 mmol) and BuLi 1.5M in hexane (6.4 mL, 96 mmol) in THF (10 mL) at -78°C was added dropwise propan-2-one (557 mg, 9.6 mmol) in THF (10 mL). The mixture was stirred and after 30 min was added dropwise the aldehyde **10** (1.57 g, 8 mmol) in THF (8 mL). The mixture was stirred for another 30 min and quenched with a solution of saturated ammonium chloride (30 mL), and warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with ether (3X50 mL). The combined organic layers were dried over $MgSO_4$. Concentration in vacuo and purification of the residue by silica gel flash chromatography (AcOEt/petroleum ether : 80/20) gave 1.49 g of a mixture of two stereomers in 85/15 ratio. Recrystallization from hexane/AcOEt 90/10 afforded 1.20 g (60%) of the pure major stereomer **11** as a white solid: mp 86°C; $[\alpha]_D^{20}$ +53 (c 0.965, methanol); IR (KBr) 3420, 3280, 1740, 1120 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.79 (m, 1H), 2.04 (m, 1H), 2.10 (s, 3H), 2.22 (s, 3H), 2.61 (dd, J = 17.9, 9.5 Hz, 1H), 2.91 (dd, J = 17.9, 2.0 Hz, 1H), 3.49 (d, J = 3.1 Hz, 1H), 4.05 (m, 2H), 4.68 (s, 1H), 4.82 (dd, J = 10.8, 4.4 Hz, 1H), 4.88 (s, 1H), 6.39 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.9, 30.7, 39.3, 46.0, 49.0, 64.7, 66.6, 79.7, 80.4, 135.1, 135.9, 170.7, 209.2; CIMS (NH_3) m/z (relative intensity) : 272 (MNH_4^+, 31), 255 (MH^+, 10), 214 (34), 212 (24), 146 (100). Anal. calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found : C, 61.13; H, 7.29.

(1*R*,2*R*,3*S*,4*S*,1'*S*,3'*R*)-2-(1',3'-Dihydroxybutyl)-3-acetoxymethyl-7-oxabicyclo[2.2.1]-5-hepten (13). To a solution of tetramethylammonium triacetoxyborohydride (5.9 g, 22.5 mmol) in CH_3CN (15 mL) was added acetic acid (15 mL) and the mixture was stirred at ambient temperature for 30 min. The mixture was cooled to -30°C, and a solution of **11** (956 mg, 3.76 mmol) in CH_3CN (6 mL) was added dropwise. The mixture was stirred at -30°C for 18 h, quenched at this temperature by the addition of a solution 0.5N of sodium, potassium tartrate (34 mL), and warmed to ambient temperature. The mixture was extracted with CH_2Cl_2 (80 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ to neutrality. The combined aqueous layers were neutralized with solid $NaHCO_3$, then were extracted with CH_2Cl_2 (5x50 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt) to give 900 mg (93%) of a mixture of two stereomers (80/20). Recrystallization from hexane afforded 700 mg (73%) of pure **13** as a white solid: mp 95°C; $[\alpha]_D^{20}$ +39 (c 1.08, $CHCl_3$); IR (KBr) 3570, 3450, 1735, 1125 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (d, J = 6.3 Hz, 3H), 1.80 (m, 1H), 1.86 (m, 1H), 1.98 - 2.14 (m, 3H), 2.11 (s, 3H), 3.14 (d, J = 2.0 Hz, 1H), 3.95 - 4.05 (m, 1H), 4.10 - 4.28 (m, 2H), 4.70 (s, 1H), 4.78 (dd, J = 10.9, 5.0 Hz, 1H), 4.88 (s, 1H), 6.41 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.0, 23.5, 39.3, 43.9, 46.9, 64.7, 65.3, 67.7, 80.3, 80.5, 134.9, 136.3,

171.3; CIMS (NH_3) m/z (relative intensity) : 274 (MNH_4^+, 30), 256 (M^+, 56), 213 (58), 196 (100). Anal. calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found : C, 60.71; H, 7.74.

(1*R*,2*R*,3*S*,4*S*,6'*S*,4'*R*)-2-(1',3'-Dioxa-2',2',4'-trimethylcyclohexyl)-3-acetoxymethyl-7-oxabicyclo[2.2.1]-5-hepten (14). A mixture of **13** (700 mg, 2.73 mmol), 2,2-dimethoxypropane (12 mL) and pyridinium paratoluenesulfonate (15 mg) in CH_2Cl_2 (70 mL) was stirred for 3 h at room temperature. The mixture was washed with a saturated solution of $NaHCO_3$ (5 mL), water (5 mL), dried over $MgSO_4$, filtrated and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/AcOEt : 80/20) gave **14** (647 mg, 80%) as a white solid: mp 105°C; $[\alpha]_D^{20}$ +7.6 (c 1.24, $CHCl_3$); IR (KBr) 3015, 1745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, J = 6.3 Hz, 3H), 1.35 (s, 3H), 1.42 (s, 3H), 1.65 - 2.02 (m, 4H), 2.09 (s, 3H), 3.70 - 4.04 (m, 3H), 4.69 (s, 1H), 4.77 (dd, J = 10.7, 4.2 Hz, 1H), 4.91 (s, 1H), 6.39 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0, 21.4, 24.2, 24.3, 39.2, 40.7, 46.7, 62.4, 64.9, 66.0, 79.1, 80.5, 100.4, 135.3, 136.0, 170.8; CIMS (NH_3) m/z (relative intensity) : 314 (MNH_4^+, 18), 297 (MH^+, 27), 256 (50), 239 (48), 229 (34), 179 (100). Anal. calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found : C, 64.61; H, 8.22.

(1*R*,2*R*,3*S*,4*S*,6'*S*,4'*R*)-2-(1',3'-Dioxa-2',2',4'-trimethylcyclohexyl)-3-hydroxymethyl-7-oxabicyclo[2.2.1]-5-hepten (15). To a solution of **14** (498 mg, 1.68 mmol) in methanol (10 mL) was added dropwise a 1M aqueous solution of KOH (340 µL, 0.34 mmol) and the mixture was stirred at room temperature for 3 h. The solution was concentrated in vacuo. Water (3 mL) was added to the residue and the aqueous phase was extracted with ether (3x30 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated. Chromatography of the residue on silica gel (AcOEt/petroleum ether : 70/30) give **15** as a colorless oil (405 mg, 95%); $[\alpha]_D^{20}$ -46 (c 1.01, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (d, J = 6.3 Hz, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.70 - 1.98 (m, 4H), 3.38 (d, J = 9.1 Hz, 1H), 3.69 (m, 1H), 3.86 (m, 1H), 3.98 (m, 2H), 4.69 (s, 1H), 4.73 (s, 1H), 6.34 (m, 1H), 6.45 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 23.8, 24.9, 40.5, 43.4, 46.6, 62.2, 62.3, 66.7, 79.4, 81.3, 100.4, 135.0, 136.2; CIMS (NH_3) m/z (relative intensity) : 272 (MNH_4^+, 21), 255 (MH^+, 17), 214 (50), 197 (100). Anal. calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found : C, 66.05; H, 8.76.

(1*R*,2*R*,3*S*,4*R*,6'*S*,4'*R*)-2-(1',3'-Dioxa-2',2',4'-trimethylcyclohexyl)-3-formyl-7-oxabicyclo[2.2.1]-5-hepten (16). To a solution of **15** (391 mg, 1.54 mmol) in CH_2Cl_2 (20 mL) and pyridine (250 µl, 3.08 mmol) cooled at 0°C was added triacetoxyperiodinane (852 mg, 2.01 mmol). The mixture was stirred for 30 min then diluted with ether (100 mL), washed successively with saturated solutions of $NaHCO_3$ (10 mL), $Na_2S_2O_3$ (10 mL) and water (10 mL) then dried over $MgSO_4$. Concentration in vacuo at room temperature and purification of the residue by florisil chromatography (ether/petroleum ether : 50/50) gave **16** (328 mg, 84 %) as a colorless oil ; $[\alpha]_D^{20}$ +15 (c 1.145, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, J = 6.3 Hz, 3H), 1.29 (s, 3H), 1.31 (s, 3H), 1.65 - 1.95 (m, 2H), 2.08 (dd, J = 8.1, 10.5 Hz, 1H), 2.43 (dd, J = 5.1, 8.1 Hz, 1H), 3.93 (m, 2H), 4.79 (s, 1H), 5.06 (s, 1H), 6.43 (m, 2H), 9.65 (d, J = 5.1 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.1, 24.0, 24.6, 39.5, 49.6, 51.3, 62.0, 65.6, 78.6, 79.6, 100.1, 135.0, 136.4, 202.4; CIMS (NH_3) m/z (relative intensity) : 253 (MH^+, 4), 185 (25), 167 (14), 144 (22), 127 (100).

(1*R*,2*R*,3*R*,4*S*,6'*S*,4'*R*)-2-(1',3'-Dioxa-2',2',4'-trimethylcyclohexyl)-3-(2"-carbomethoxy-2"-propenyl)-7-oxabicyclo[2.2.1]-5-hepten (17). To a suspension of NaH (43

mg, 1.77 mmol) in THF (1 mL) cooled at -78°C was added methyldiphenoxyphosphonopropionate (487 mg, 1.52 mmol) in THF (1 mL). The mixture was stirred for 30 min and was added **16** (320 mg, 1.27 mmol) in THF (1 mL). The reaction mixture was stirred for another 30 min at -78°C then the temperature was allowed to rise 0°C in 4 h. The reaction was quenched with a solution of saturated NH_4Cl (4 mL). After extraction with ether (3x20 mL), the organic layers were dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by chromatography on silica gel (ether/petroleum ether : 50/50) to give 303 mg (78%) of a mixture of two stereomers (*Z*/*E* : 90/10). A fraction of pure *Z*-**17** was isolated as a colorless oil; $[\alpha]_D^{20}$ -114 (c 0.93, $CHCl_3$); IR (neat) 3080, 1725, 1650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.19 (d, J = 6.3 Hz, 3H), 1.28 (s, 6H), 1.6 - 1.72 (m, 1H), 1.77 - 1.90 (m, 1H), 1.94 (m, 4H), 3.37 (dd, J = 8.1, 10.5 Hz, 1H), 3.72 (s, 3H), 3.78 - 3.99 (m, 2H), 4.63 (s, 1H), 4.80 (s, 1H), 5.99 (dd, J = 1.4, 10.6 Hz, 1H), 6.41 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.8, 21.4, 24.5, 24.9, 39.3, 39.4, 48.5, 51.1, 62.5, 65.7, 79.0, 84.3, 100.0, 126.9, 135.0, 136.6, 144.2, 167.9; CIMS (NH_3) m/z (relative intensity) : 323 (MH^+, 42), 265 (45), 255 (100), 197 (87), 196 (33).Anal. calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found : C, 67.19; H, 7.94.

(1*R*,2*R*,3*R*,4*S*,1'*S*,3'*R*)-2-(1',3',-Dihydroxybutyl)-3-(2"-carbomethoxy-2"-propenyl)-7-oxabicyclo[2.2.1]-5-hepten (18). To a solution of **17** (300 mg, 0.93 mmol) in THF (10 mL) cooled at 0°C was added HCl 1M (4 mL). The mixture was stirred for 30 min, and solid $NaHCO_3$ was carefully added. After extraction with ether (3x10 mL) then CH_2Cl_2 (2x10 mL), the organic layers were dried over $MgSO_4$. Concentration in vacuo and purification of the residue by silica gel chromatography (CH_2Cl_2/MeOH : 95/5) gave 209 mg (80%) of compound **18** as a colourless oil; $[\alpha]_D^{20}$ -153 (c 1.025, $CHCl_3$); IR (neat) 3420, 3080, 1720, 1650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.24 (d, J = 6.3 Hz, 3H), 1.78 (m, 2H), 2.00 (d, J = 1.5 Hz, 3H), 2.06 (dd, J = 7.9, 9.6 Hz, 1H), 3.02 (dd, J = 7.9, 10.6 Hz, 1H), 3.24 (br s, 1H), 3.48 (br s, 1H), 3.78 (s, 3H), 3.92 (m, 1H), 4.15 (m, 1H), 4.64 (s, 1H), 4.79 (s, 1H), 6.06 (dd, J = 10.6, 1.5 Hz, 1H), 6.32 (dd, J = 1.5, 5.8 hz, 1H) 6.48 (dd, J = 1.9, 5.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3, 23.4, 40.8, 42.3, 51.0, 52.0, 64.8, 68.8, 80.0, 83.7, 129.6, 134.1, 137.5, 143.3, 169.6; CIMS (NH_3) m/z (relative intensity) : 283 (MH^+, 100), 282 (M^+, 5), 197 (12), 177 (14).Anal. calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found : C, 63.57; H, 7.83.

(1*R*,2*R*,3*S*,5*S*,6*R*,7*R*,1"*R*,2'*R*)-4,10-Dioxa-3-(1"-carboxymethoxyethyl)-5-(2'-hydroxypropyl)tricyclo[5.2.1.$O^{2,6}$]dec-8-en (19). To a solution of **18** (95 mg, 0.336 mmol) in anhydrous methanol (1.5 mL) was added a solution of benzyltrimethylammonium methoxide 40% in methanol (270 µL). The resulting mixture was stirred for 1 h. After concentration in vacuo at room temperature was added a saturated solution of NH_4Cl (10 mL). The aqueous phase was extracted with ether (3x20 mL). The organic layers were washed with a 1N NaOH solution (3 mL), then brine (5 mL) and dried over $MgSO_4$. Concentration in vacuo and purification by silica gel chromatography (AcOEt/petroleum ether : 80/20) gave the tricyclic adduct **19** (43 mg) and its 3R-diastereomer **20** (43 mg) (91% total yield).

19: $[\alpha]_D^{20}$ -9.5 (c 0.93, $CHCl_3$); IR (neat) 3440, 3080, 1740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, J = 6.3 Hz, 3H), 1.23 (d, J = 7.2 Hz, 3H), 1.72 - 1.92 (m, 2H), 2.27 (m, 2H), 2.70 (m, 1H), 2.90 (br s, 1H), 3.71 (s, 3H), 3.78 (m, 1H), 3.88 (m, 1H), 4.05 (m, 1H), 4.68 (s, 1H), 4.71 (s, 1H), 6.39 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.0, 23.3, 41.8, 43.8, 51.6, 52.1, 53.8, 64.9, 79.7, 79.9, 80.7, 82.4, 136.2, 136.4, 174.6; CIMS (NH_3) m/z (relative intensity) : 300 (MNH_4^+, 51), 283 (MH^+, 100), 109 (41).Anal. calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found : C, 63.75; H, 8.02.

20: $[\alpha]_D^{20}$ -42.5 (c 0.97, $CHCl_3$); IR (neat) 3050, 3080, 1745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (d, J = 6.3 Hz, 3H), 1.27 (d, J = 7.0 Hz, 3H), 1.69 - 1.92 (m, 2H), 2.22 - 2.40 (m, 2H), 2.72 (t, J = 7.1 Hz, 1H), 2.79 (d, J = 4.2 Hz, 1H), 3.71 (s, 3H), 3.73 (t, J = 7.3 Hz, 1H), 3.87 (m, 1H), 4.05 (m, 1H), 4.67 (s, 1H), 4.74 (s, 1H), 6.36 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 23.3, 41.8, 43.8, 51.6, 52.2, 53.8, 64.9, 79.5, 79.9, 80.9, 82.4, 136.1, 136.4, 174.4; CIMS (NH_3) m/z (relative intensity) : 300 (MNH_4^+, 89), 283 (MH^+, 100), 109 (41).Anal. calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found : C, 64.01; H, 7.91.

Epimerisation of 20 to 19

To a solution of **20** (105 mg, 0.372 mmol) in anhydrous methanol (1.5 mL) was added a solution of benzyltrimethylammonium methoxide 40% in methanol (300 µl) and the mixture was stirred for 6 h. After concentration in vacuo at room temperature was added a solution of HCl 1N (4 mL) and the aqueous phase was extracted with ether (3x10 mL). The organic layers was dried over $MgSO_4$, filtrated, treated by a solution of CH_2N_2 in ether. Concentration in vacuo and separation on silica gel as above afforded 48 mg (46%) of cyclised compound **19** and 41 mg of its isomer **20.**

(2*S*,3*S*,6*R*,8*R*)-Methyl-4,5-dehydro nonactate 21. The tricyclic adduct **19** (70 mg, 0.248 mmol) was evaporated through a hot horizontal mullite tube (450°C, 10 $torr^{-3}$) and the thermolysate was collected on a finger cooled to liquid nitrogen temperature. After warming to room temperature the finger was washed with ether and the resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (AcOEt/petroleum ether : 50/50) to give 46 mg (87%) of compound **21** as a colourless oil : $[\alpha]_D^{20}$ +14 (c 0.865, $CHCl_3$); IR (neat) 3420, 3080, 1745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.11 (d, J = 7.1 Hz, 3H), 1.19 (d, J = 6.3 Hz, 1H), 1.54 - 1.80 (m, 2H), 2.58 (q, J = 7.2 Hz, 1H), 2.85 (br s, 1H), 3.67 (s, 3H), 4.02 (m, 1H), 4.90 (m, 1H), 5.00 (m, 1H), 5.82 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.8, 23.4, 44.0, 45.9, 51.7, 64.9, 83.8, 87.4, 127.3, 132.0, 174.7; CIMS (NH_3) m/z (relative intensity) : 232 (MNH_4^+, 93), 215 (MH^+, 100), 214 (M^+, 12). Anal. calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found : C, 61.46; H, 8.38.

(+)-(2*S*,3*S*,6*R*,8*R*)-Methyl nonactate 2. A solution of compound **21** (41 mg, 0.191 mmol) in ethyl acetate (3 mL) was hydrogenated over 5% platinum on coal (5 mg) at atmospheric pressure for 30 min. After filtration, the catalyst was washed with ethyl acetate and the filtrate was concentrated in vacuo. The oily residue was chromatographed on silica gel (AcOEt/petroleum ether : 50/50) to give (+)-methyl nonactate **2** (29 mg, 70%) as a colourless oil : $[\alpha]_D^{20}$ 21.8 (c 1.04, $CHCl_3$); IR (neat) 3440, 1745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.12 (d, J = 7.0 Hz, 3H), 1.19 (d, J = 6.3 Hz, 3H), 1.55 - 1.80 (m, 4H), 1.9 - 2.06 (m, 2H), 2.53 (m, 1H), 2.96 (br s, 1H), 3.69 (s, 3H), 3.92 - 4.18 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.5, 23.2, 28.8, 30.5, 42.7, 45.3, 51.7, 65.1, 77.2, 81.0, 175.2; CIMS (NH_3) m/z (relative intensity) : 234 (MNH_4^+, 19), 217 (MH^+, 100), 199 (14), 134 (12), 117 (30). Anal. calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found : C, 61.13; H, 9.25.

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