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Prostanoids and Related Compounds. V.[1] Synthesis of 6-Aza-5-oxo-2,3,4-trinor-1,5-inter-*m*-phenylene Prostacyclin Derivatives

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6-Aza-5-oxo-2,3,4-trinor-1,5-inter-*m*-phenylene prostacyclin derivatives were synthesized by use of 1,3-dipolar cycloaddition as a key step.

Keywords 6-aza-5-oxo-2,3,4-trinor-1,5-inter-*m*-phenylene prostacycline derivative; 1,3-dipolar cycloaddition; Wittig reaction; prostacycline; inhibitory activity; blood platelet aggregation; Prins reaction; Pfitzer–Moffat oxidation

Prostacyclin (PGI_2) displays a wide range of biological properties,[2] including inhibition of human blood platelet aggregation,[3,4] deaggregation of platelet thrombi,[5] vasodilation,[3] and inhibition of gastric secretion.[6] However, PGI_2 is a rather unstable molecule, whose instability arises from the presence of an enol ether functionality. Therefore, a wide range of stable analogues of prostacyclin have been prepared.

Prostacyclin analogues prepared to date may be regarded as involving formally the following general structural modifications of the natural compound[7]: (1) stabilization of the acid-labile enol ether 5,6-double bond by substitution at the 5-, 7-, or 10-positions; (2) modification of the tetrahydrofuran ring by replacement of the enol ether oxygen with a different atom, by introduction of an aromatic ring or by ring expansion; (3) manipulation of the 5,6-double bond by changing its position or altering the oxidation level.

Of these analogues, we have been interested in carbacyclines and 6-azacarboprostacyclin analogues as potential antithrombotic agents. H. Nakai *et al.*[8] have reported the synthesis of *dl*-6-aza-6,9-methano PGI_1 with weak inhibitory activity in blood platelet aggregation, and B. Horst *et al.*[9] have reported the synthesis of CG 4305.

On the other hand, K. Achiwa and his co-workers[10] have applied the 1,3-dipolar cycloaddition of azomethine ylides to some pyrrolizidine alkaloids.

Thus, we have designed *dl*-6-aza-5-oxo-2,3,4-trinor-1,5-inter-*m*-phenylene prostacyclin derivatives, **1a** and **1b**, whose skeletons can be constructed by 1,3-dipolar cycloaddition developed in our laboratory.[10] In this paper, we wish to report the synthesis of **1a** and **1b**.

As shown in Chart 1, we planned to construct the 6-azaprostacyclin skeleton by 1,3-dipolar cycloaddition developed in our laboratory. Retrosynthetically, **1a** and **1b** might be derived from aldehyde **2** by the Wittig reaction and benzoylation. The aldehyde **2** should be easily synthesized from diol **3** which, in turn, might be obtained by the Prins reaction of **4** followed by hydrolysis. The compound **4** should be obtained by reduction of the carbonyl group of *N*-benzyl-3-azabicyclo[3.3.0]octa-8-one (**5**) and following dehydrogenation, which should be obtained by 1,3-dipolar cycloaddition of *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (**6**) and 2-cyclopenten-1-one (**7**).

The actual synthetic route was shown in Chart 2. The compound **5** was synthesized by the 1,3-dipolar cycloaddition of an intermediary iminium ylide formed from **6** to **7** in the presence of a catalytic amount of trifluoroacetic acid in 79% yield. In order to introduce the C_2-double bond of the compound **5**, reduction of **5** to the alcohol compound by lithium aluminum hydride ($LiAlH_4$) was first attempted, but the dehydrogenation of the alcohol compound by $POCl_3$ did not proceed. On the other hand, protection of the hydroxyl group (the alcohol compound) with *p*-toluenesulfonyl chloride, followed by elimination under various reaction conditions was performed, but the reaction resulted in the recovery of the alcohol compound. Then, compound **5** was treated with *p*-toluenesulfonylhydrazide in ethanol containing a catalytic amount of trifluoroacetic acid to give tosylhydrazone (**8**), which was decomposed by disodium

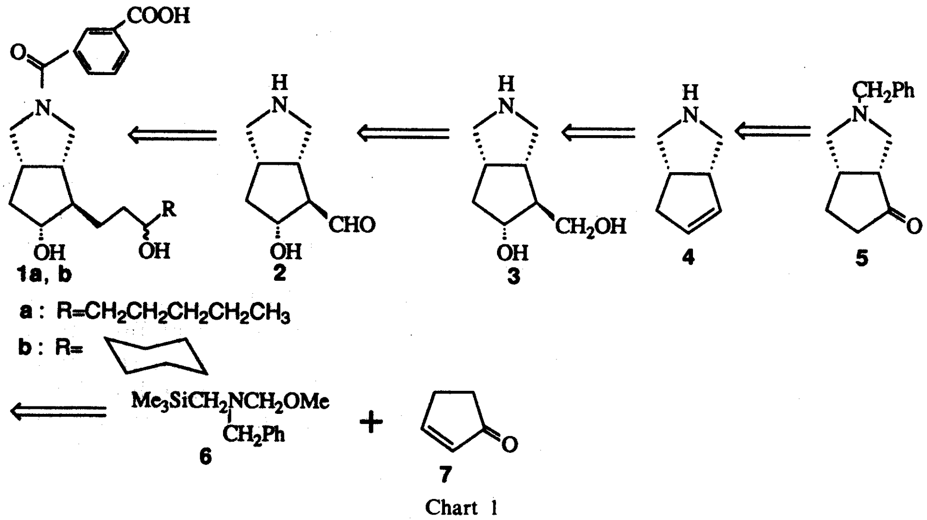

Chart 1

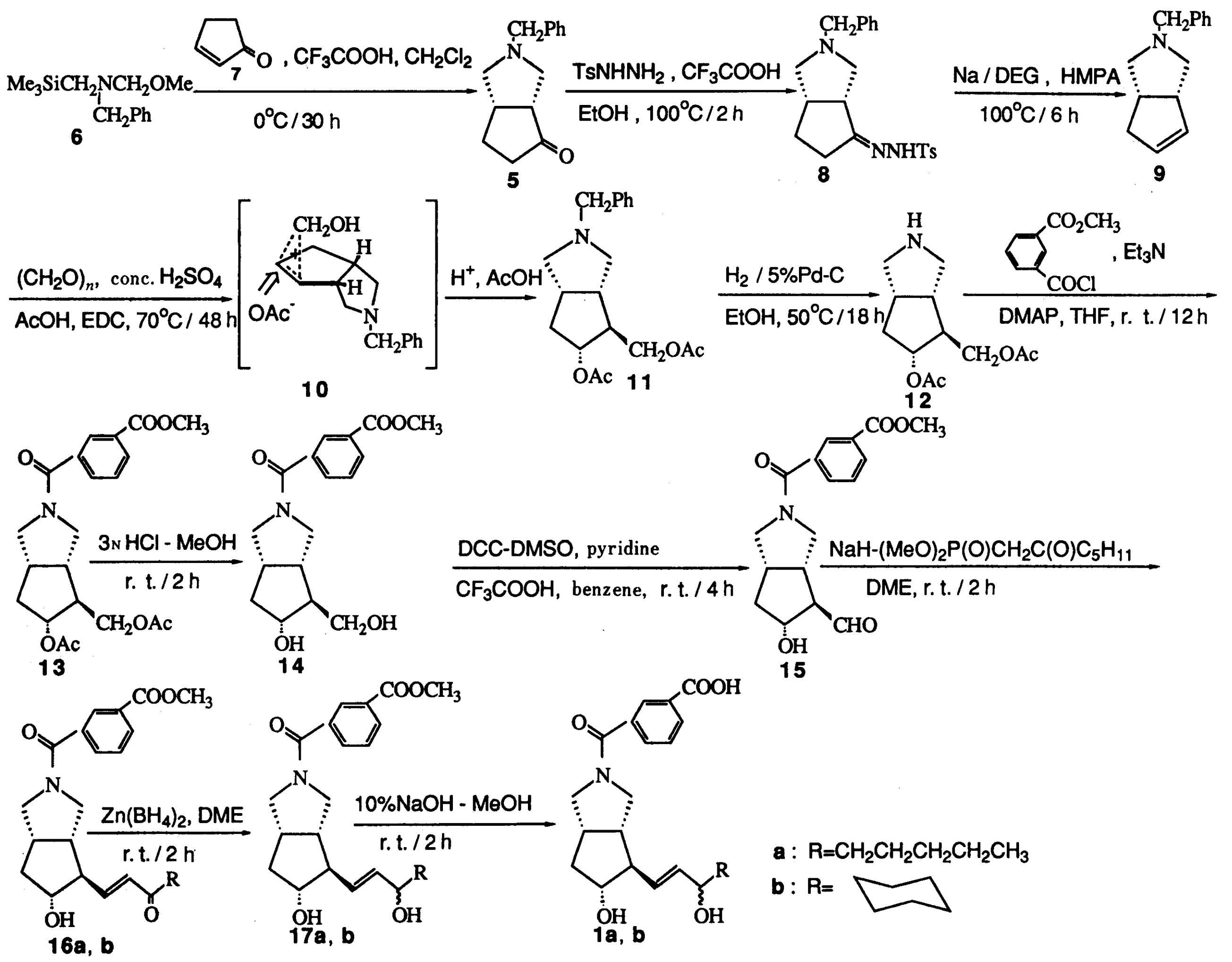

Chart 2

ethylene glycolate in diethylene glycol in the presence of a catalytic amount of hexamethylphosphoramide (HMPA) under reflux[11,12] to afford *N*-benzyl-3-azabicyclo[3.3.0]-oct-7-ene (**9**) (57% from **5**). Decomposition of **8** was initially performed under various reaction conditions, but no reaction occured with *n*-butyl lithium or *tert*-butyl lithium. On the other hand, treatment with NaH or sodium alkoxide in HMPA afforded **9** in poor yield.

The diacetate **11** was obtained by a regio- and stereospecific addition of formaldehyde on the olefinic double bond of **9**, followed by an attack of the acetate anion under the conditions of the Prins reaction.[13] The reaction of the compound **9** with excess paraformaldehyde monomerized *in situ* with sulfuric acid in glacial acetic acid took place at 70 °C to afford **11** in a 57% yield. The structure of **11** was confirmed by the mechanism of the Prins reaction and proton nuclear magnetic resonance (^{1}H-NMR) spectral data. No other regio- or stereoisomeric product could be detected in the reaction mixture. It is thought that the formation of a cyclopropenium cation (**10**) occurred at the less hindered face due to the steric influence of a bicyclo ring, and the following opening of the alleged three-center carbonium ion (**10**) by an attack of an acetate anion occured at the sterically less hindered position, *i.e.* the α-face at the C-7 position, which seems to account for both regio- and stereospecificity.

N-Debenzylation of the diacetate **11** was performed by hydrogenation with palladium on carbon in ethanol to afford key intermediate compound **12**. The carbon appendage to the compound **12** was introduced by acylation.

Treatment of **12** with isophthalic acid monomethyl ester chloride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) in tetrahydrofuran (THF) afforded **13** (86% from **11**). Isophthalic acid monomethyl ester chloride was prepared in two steps from dimethylisophthalate. Dimethylisophthalate was hydrolyzed with 1 N barium hydroxide in methanol to afford isophthalic acid monomethyl ester, which was halogenated with thionyl chloride to give isophthalic acid monomethyl ester chloride.

Methanolysis of **13** with 3 N hydrochloric acid in methanol gave the diol **14** in 80% yield. The diol **14** posseses prim- and *sec*-hydroxyl groups. Then, in order to selectively oxidate a primary alcohol, **14** was treated with Pfitzer–Moffatt[14] reagent to give the corresponding aldehyde **15**, which was used without further purification.The Wittig reaction of **15** with dimethyl (2-oxoheptyl)phosphonate[15] in dimethoxyethane (DME) proceeded smoothly to afford **16a** (67% from **15**). The reduction of **16a** with 1.5 eq zinc borohydride in DME gave the C-15 (prostanoic numbering) epimeric mixture **17a** in 85% yield. Hydrolysis of **17a** with 10% NaOH aq. in methanol afforded **1a** in 80% yield.

In the same route, the compound **1b** was synthesized by using cyclohexyl(triphenylphosphoranyliden)methyl ketone[16] in place of dimethyl(2-oxoheptyl)phosphonate. The Wittig reaction of **15** with cyclohexyl(triphenylphosphoranylidene)methyl ketone in THF afforded the compound **16b** (33% from **14**). Reduction of **16b** with zinc borohydride in DME gave the C-15 epimeric mixture **17b** in 83% yield. Hydrolysis of **17b** with 10% NaOH aq. in methanol afforded **1b** in 73% yield.

The structures of **1a** and **1b** were supported by elemental analysis and confirmed by analysis of the IR, ^{1}H-NMR and fast atom bombardment-mass spectrometry (FAB-MS) spectra. These compounds **1a** and **1b** showed weak inhibitory activities in blood platelet aggregation.

Experimental

Melting points were determined on a micro-melting point apparatus (Yanagimoto) and are uncorrected. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Infrared (IR) spectra were taken on JASCO A-202 IR spectrophotometers and are given in cm^{-1}. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX90q (90 MHz) spectrophotometer in $CDCl_3$. Chemical shifts are given in δ (ppm) downfield from tetramethylsilane, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Thin layer chromatography (TLC) was performed on silica gel (Kieselgel $60F_{254}$ on aluminium sheets, Merck). All compounds were located by splaying the TLC plate with sulfuric acid and heating it on a hot plate. Preparative TLC (PTLC) was performed on a preparative layer chromatography plate (Kieselgel $60F_{254}$ 2 mm and 0.5 mm, Merck). Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck).

Preparation of (1*R,5*S**)-*N*-Benzyl-3-azabicyclo[3.3.0]octan-8-one (5)** A solution of trifluoroacetic acid in CH_2Cl_2 (0.8 ml, 1 mol/l) was added to a stirred solution of *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine (**6**) (2.4 g, 10 mmol) and 2-cyclopenten-1-one (**7**) (0.7 g, 8.3 mmol) in CH_2Cl_2 (20 ml) at 0 °C. The mixture was stirred for 3 h at the same temperature. The reaction mixture was washed with a saturated $NaHCO_3$ aqueous solution (20 ml × 3) and brine (20 ml × 2) and dried over $MgSO_4$. The CH_2Cl_2 solution was concentrated *in vacuo* and the residue was subjected to column chromatography on SiO_2 using a 9 : 1 mixture of hexane–AcOEt as the eluent to give **5** as a yellow oil (1.4 g, 78.6%). bp 117—118 °C (0.5 mmHg). *Anal.* Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.81; H, 7.96; N, 6.44. ^{1}H-NMR: 1.94—3.06 (10H, m, H-1, H-2, H-4, H-5, H-6, H-7), 3.60 (2H, s, $C\underline{H}_2Ph$), 7.13 (5H, s, $CH_2\underline{Ph}$). ^{13}C-NMR: 27.4 (t, C-6), 38.6 (d, C-7), 39.0 (d, C-5), 50.6 (d, C-1), 58.0, 59.5 (each t, C-2, C-4), 61.4 (t, $\underline{C}H_2Ph$), 126.9, 128.2, 128.5 (each d, Ph), 138.9 (s, Ph), 193.0 (s, C=O).

Preparation of (1*R,5*S**)-*N*-Benzyl-3-azabicyclo[3.3.0]oct-7-ene (9)** A catalytic amount of trifluoroacetic acid was added in portions to a solution of **5** (0.13 g, 1 mmol) and *p*-toluenesulfonylhydrazide (0.19 g, 1 mmol) in 5 ml of ethanol. The mixture was refluxed for 2 h. After being cooled, the mixture was concentrated *in vacuo* to afford a yellow residue (**8**), which was used without further purification. Na (0.084 g, 3.6 mmol) was added in 2.4 ml of diethylene glycol and the mixture was refluxed for 2 h. **8** (0.46 g, 1.2 mmol) was added to the mixture in the presence of HMPA (a catalytic amount). The reaction mixture was refluxed for 6 h. After being cooled, H_2O (30 ml) was added to the mixture. The reaction mixture was extracted with CH_2Cl_2 (20 ml × 10). The CH_2Cl_2 layer was washed with brine (20 ml × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on Al_2O_3 using a 4 : 1 mixture of hexane–AcOEt as the eluent to give **9** (0.10 g, 57% from **5**), bp 47—50 °C (2 mmHg). *Anal.* Calcd for $C_{14}H_{17}N$: C, 84.56; H, 8.75; N, 6.82. Found: C, 84.37; H, 8.60; N, 7.03. ^{1}H-NMR: 1.91—3.06 (8H, m, H-1, H-2, H-4, H-5, H-6), 3.60 (2H, s, $C\underline{H}_2Ph$), 5.62 (2H, m, H-7, H-8), 7.30 (5H, s, $CH_2\underline{Ph}$). ^{13}C-NMR: 39.0 (t, C-6), 39.9 (d, C-5), 50.3 (d, C-1), 59.9, 62.2 (t, t, C-2, C-4), 60.2 (t, $\underline{C}H_2Ph$), 126.8, 128.1, 128.8 (d, d, d, Ph), 130.1, 132.8 (d, d, C-7, C-8).

Preparation of (1*S,5*S**,7*R**,8*S**)-8-{7-acetoxy-*N*-benzyl-3-azabicyclo[3.3.0]oct-8-yl}methyl Acetate (11)** A mixture of monomerized paraformaldehyde (0.27 g, 8.6 mmol), ethylene dichloride (EDC) (8 ml) and sulfuric acid (0.46 ml, 8.6 mmol) was stirred for 20 min at 70 °C in a sealed tube. After being cooled to 20 °C, **9** (0.68 g, 3.4 mmol) and dioxane (a catalytic amount) in EDC (2 ml) was added and the mixture was stirred for 48 h at 70 °C in a sealed tube. The reaction mixture was cooled to 10 °C and sodium acetate (0.70 g, 8.6 mmol) in H_2O was added. The reaction mixture was extracted with EDC (20 ml × 2). The EDC extracts were washed with 10% $NaHCO_3$ aq. (40 ml × 2) and H_2O (30 ml × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on Al_2O_3 using a 4 : 1 mixture of hexane–AcOEt as the eluent to give **11** (0.64 g, 57%) as a white crystal, mp 75—80 °C. IR (KBr): 1740 (C=O). *Anal.* Calcd for $C_{19}H_{25}NO_4$: C, 68.85; H, 7.64; N, 4.30. Found: C, 68.86; H, 7.60; N, 4.23. ^{1}H-NMR: 2.01 (3H, s, $OCOCH_3$), 2.04 (3H, s, $OCOCH_3$), 2.08—2.77 (9H, m, H-1, H-2, H-4, H-5, H-6, H-8), 3.59 (2H, s, $C\underline{H}_2Ph$), 4.06 (2H, d, *J* = 5 Hz, $C\underline{H}_2OAc$), 4.52—5.03 (1H, m, H-7), 7.29 (5H, s, $CH_2\underline{Ph}$). ^{13}C-NMR: 20.8, 21.0 (q, q, $OCO\underline{C}H_3 \times 2$), 37.3 (d, C-5), 37.8, (t, C-6), 42.3 (d, C-1), 49.0 (d, C-8), 59.3 (t, $\underline{C}H_2OAc$), 60.1 (t, CH_2Ph), 59.2, 64.4 (t, t, C-2, C-4), 76.0 (d, C-7), 126.9, 128.2, 128.6, 138.9 (d, d, d, s, Ph), 170.5, 170.8 (s, s, $O\underline{C}OCH_3$).

Preparation of Isophthalic Acid Monomethyl Ester Chloride In a flask fitted with a NaOH tube were placed dimethyl isophthalate (7.8 g, 0.02 mmol) and 1 N $Ba(OH)_2$ in methanol (20 ml, 0.02 mmol) and the mixture was stirred for 15 h. The solvent was removed under reduced pressure and the residue was washed with ether. The filtrate and washings were concentrated *in vacuo* to afford the residue, which was washed with ether. The residue was put together. To a solution of the residue in CH_2Cl_2 (20 ml), 3 N HCl aq. was added to create acidity. The CH_2Cl_2 layer was separated and the H_2O layer was extracted with CH_2Cl_2 (20 ml × 2). The CH_2Cl_2 layer and extracts were washed with H_2O (20 ml × 2) and brine (20 ml × 2), and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded isophthalic acid monomethyl ester (3.6 g), which was used without further purification. Thionyl chloride (4.2 g, 36 mmol) was added to isophthalic acid monomethyl ester (3.6 g, 20 mmol) in $CHCl_3$ (20 ml) and the mixture was refluxed for 2 h at 80 °C. The solvent was concentrated *in vacuo* to afford a residue, which was recrystallized from petr. ether to give a white powder isophthalic acid monomethyl ester chloride (3.1 g, 80%), mp 43—45 °C. IR (KBr): 1768 (COCl), 1731 ($COOCH_3$). ^{1}H-NMR: 3.98 (3H, s, CH_3), 7.50—8.89 (4H, m, $\underline{Ph}$). ^{13}C-NMR: 52.61 (q, $COOCH_3$), 129.3, 132.4, 135.0, 135.9 (d, Ph), 133.8, 137.0 (s, s, Ph) 165.46 (s, COCl), 167.74 (s, $COOCH_3$). MS *m/z*: 198 (M^+), 200 $(M+2)^+$.

Preparation of (1*S,5*S**,7*R**,8*S**)-8-{7-Acetoxy-*N*-(*m*-methoxycarbonylbenzoyl-3-azabicyclo[3.3.0]oct-8-yl}methylacetate (13)** 5% Pd–C (0.12 g) was added to a solution of **11** (0.24 g, 0.72 mmol) in ethanol (10 ml). Hydrogen was charged at ordinary pressure and the reaction mixture was vigorously stirred for 18 h at 50 °C. Removal of the catalyst by suction filtration and concentration of the filtrate under reduced pressure gave oily **12** (0.16 g, 93%), which was used without further purification. Isophthalic acid monomethyl ester chloride (1.3 g, 6.7 mmol) was added to **12** (0.91 g, 3.8 mmol) in dry THF (20 ml) at 0 °C. Triethylamine (0.46 ml, 4.5 mmol) and DMAP (0.46 g, 3.8 mmol) was added to the reaction mixture, which was stirred for 18 h at room temperature. After removal of the solvent *in vacuo*, the residue was extracted with CH_2Cl_2 (20 ml × 2). The CH_2Cl_2 layer was washed with aq. $NaHCO_3$ (30 ml × 2) and brine (15 ml × 2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 4 : 1 mixture of AcOEt–hexane as the eluent to give **13** (1.3 g, 86%). IR (neat): 1629 (N–C=O), 1723 (C=O). High-resolution MS Calcd for $C_{21}H_{25}NO_7$ (M^+): 403.1600. Found: 403.1606. ^{1}H-NMR: 2.03 (3H, s, $OCOC\underline{H}_3$), 2.05 (3H, s, $OCOC\underline{H}_3$), 2.12—3.07 (9H, m, H-1, H-2, H-4, H-5, H-6, H-8), 3.92 (3H, s, $COOC\underline{H}_3$), 4.09 (2H, d, *J* = 5 Hz, $C\underline{H}_2OAc$), 4.77—5.11 (1H, m, H-7), 7.36—8.24 (4H, m, Ph). ^{13}C-NMR: 20.8, 21.1 (q × 2, $OCO\underline{C}H_3$), 36.9 (t, C-6), 49.4 (d, C-8), 52.3 (q, $COO\underline{C}H_3$), 64.3 (t, $\underline{C}H_2OAc$), 77.1 (d, C-7), 128.3, 128.7, 130.4, 131.0, 131.7, 137.1 (d, d, s, d, d, s, Ph), 166.3 (s, N–$\underline{C}$=O), 168.6 (s, $\underline{C}OOCH_3$), 170.5, 170.8 (d, d, $O\underline{C}OCH_3$).

Preparation of (1*S,5*S**,7*R**,8*S**)-3-{7-Hydroxy-8-hydroxymethyl-3-azabicyclo[3.3.0]octanyl}-*m*-methoxycarbonylphenylketone (14)** **13** (0.17 g, 0.42 mmol) was added to 20 ml of 3 N HCl in methanol. The mixture was stirred for 2 h at room temperature and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 10 : 1 mixture of $CHCl_3/CH_3OH$ as the eluent to give **14** (0.11 g, 80%). IR (neat): 1630 (N–C=O), 1723 (C=O), 3390 (OH). High-resolution MS Calcd for $C_{17}H_{21}NO_5$ (M^+): 319.1389. Found: 319.1386. ^{1}H-NMR: 1.99—2.82 (9H, m, H-1, H-2, H-4, H-5, H-6, H-8), 3.17—4.21 (5H, m, $C\underline{H}$–$O\underline{H}$, $C\underline{H}_2O\underline{H}$), 3.92 (3H, s, $COOCH_3$), 7.43—8.22 (4H, m, Ph). ^{13}C-NMR: 39.1 (t, C-6), 50.9 (d, C-8), 52.2 (q, $COO\underline{C}H_3$), 63.8 (t, $\underline{C}H_2OAc$), 76.2 (d, C-7), 128.1, 128.5, 130.1, 130.8, 131.4, 136.8 (d, d, s, d, d, s, Ph), 166.2 (s, N–$\underline{C}$–O), 168.7 (s, $O\underline{C}OCH_3$).

Preparation of (1*S,5*S**,7*R**,8*R**)-8-{7-Hydroxy-*N*-(*m*-methoxycarbonylbenzoyl)-3-azabicyclo[3.3.0]octanyl}carbaldehyde (15)** **14** (0.099 g, 0.31 mmol) was dissolved in anhydrous dimethylsulfoxide (DMSO) (0.47

ml) and benzene (2 ml) containing pyridine (0.025 ml, 0.31 mmol) and trifluoroacetic acid (0.012 ml, 0.31 mmol), and the mixture was stirred for 20 min. After the addition of *N*,*N*′-dicyclohexylcarbodiimide (0.19 g, 0.93 mmol), the sealed reaction was stirred for 30 min at 0 °C and for 4 h at room temperature. AcOEt (20 ml) was added followed by a solution of oxalic acid (0.12 g, 0.93 mmol) in methanol (0.8 ml). After gas evolution had ceased (about 30 min), H_2O (10 ml) was added and the insoluble dicyclohexylurea was removed by filtration. The organic layer was washed with 5% aq. Na_2CO_3 (20 ml × 2), 1% HCl aq. (20 ml × 1) and brine (20 ml × 2), dried over $MgSO_4$ and concentrated *in vacuo* to afford **15** (0.098 g), which was used without further purification.

Preparation of (1*S,5*S**,7*R**,8*R**)-7-Hydroxy-*N*-*m*-methoxycarbonylbenzoyl-8-(3-oxo-1-octenyl)-3-azabicyclo[3.3.0]octane (16a)** A suspension of sodio dimethyl (2-oxoheptyl)phosphonate (0.12 g, 0.56 mmol) was prepared under an argon atmosphere from NaH (23 mg as 60% dispersion in mineral oil, *ca*. 0.56 mmol) and dimethyl 2-oxoheptyl phosphonate (0.12 g, 0.56 mmol) in 2 ml of DME at room temperature for 0.5 h. To the suspension was added a solution of **15** (90 mg, 0.28 mmol) in DME (1 ml) at 0 °C, and the whole was stirred for 2 h at room temperature. After dilution of the suspension with brine (10 ml), the mixture was extracted with CH_2Cl_2 (15 ml × 3), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 4 : 1 mixture of AcOEt–hexane as the eluent to afford **16a** (57 mg, 49%). IR (neat): 1630 (N–C=O), 1728 (C=O), 3390 (OH). FAB-MS *m*/*z*: $(M)^+$ 413. ^{1}H-NMR: 0.88 (3H, br t, *J* = 6.3 Hz, CH_3), 1.24 (6H, br s, $-CH{=}CH{-}C(O)CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.88—2.81 (11H, m, H-1, H-2, H-4, H-5, H-6, H-8, $-CH{=}CH{-}C(O)C\underline{H}_2-$), 3.60—4.23 (2H, m, H-7, OH), 3.92 (3H, s, $COOC\underline{H}_3$), 6.02—6.32 (2H, m, $-CH{=}CH-$), 7.32—8.21 (4H, m, ph). ^{13}C-NMR: 13.9 (q, CH_3), 22.5, 24.3, 29.7, 31.5 (t, $CH{=}CHC(O)\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_2CH_3$), 34.35 (t, C-6), 49.1 (d, C-8), 52.3 (q, $COO\underline{C}H_3$), 77.1 (d, C-7), 127.1, 128.5 (d, d, $\underline{C}H{=}\underline{C}H$), 128.1, 128.5, 130.3, 130.8, 131.5, 136.9 (d, d, s, d, d, s, Ph), 166.2 (s, N–C=O), 168.4 (s, $\underline{C}OOCH_3$), 173.23 (s, $CH{=}CH{-}\underline{C}O-$).

Preparation of (1*S,5*S**,7*R**,8*R**)-8-(3-Hydroxy-1-octenyl)-7-hydroxy-*N*-*m*-methoxycarbonylbenzoyl-3-azabicyclo[3.3.0]octane (17a)** Freshly fused zinc chloride (0.31 g) was added to sodium borohydride (0.18 g) in redistilled DME (4.1 ml) under argon. The mixture was stirred overnight at 0—5 °C. To a solution of **16a** (0.057 g, 0.14 mmol) in anhydrous DME (0.1 ml) was added 0.42 ml of the above solution of zinc borohydride. The mixture was stirred at room temperature for 2 h, then saturated sodium tartrate solution was added dropwise until no further evolution of gas was observed. Methylene chloride was then added and the solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to dryness. The residue was purified by PTLC with a solvent system ($CHCl_3$–methanol, 10 : 1) to give **17a** (49 mg, 85%, colorless oil). IR (neat): 1625 (N–C=O), 1723 (C=O), 3380 (OH). FAB-MS *m*/*z*: $(M)^+$ 415. ^{1}H-NMR: 0.88 (3H, br t, *J* = 6.3 Hz, CH_3), 1.25 (8H, br s, $-CH{=}CHCH(OH)C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.86—2.95 (9H, m, H-1, H-2, H-4, H-5, H-6, H-8), 3.30—4.69 (4H, m, H-7, OH, $-C\underline{H}{-}O\underline{H}$), 3.92 (3H, s, $COOCH_3$), 5.54—5.78 (2H, m, $-CH{=}CH-$), 7.38—8.21 (4H, m, Ph). ^{13}C-NMR: 14.0 (q, CH_3), 22.6, 24.3, 29.7, 31.8 (each t, $-CH{=}CHCH(OH)\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_2CH_3$), 35.6 (t, C-6), 49.1 (d, C-8), 52.3 (q, $COO\underline{C}H_3$), 72.8 (d, C–OH), 76.6 (d, C-7), 129.1, 131.1 (each d, $-\underline{C}H{=}\underline{C}H-$), 128.2, 128.6, 130.5, 130.9, 131.7, 137.2 (d, d, s, d, d, s, Ph), 166.3 (s, $N{-}\underline{C}{=}O$), 168.5 (s, $\underline{C}OOCH_3$).

Preparation of (1*S,5*S**,7*R**,8*R**)-*N*-*m*-Carboxybenzoyl-7-hydroxy-8-(3-hydroxy-1-octenyl)-3-azabicyclo[3.3.0]octane (1a)** A solution of **17a** (20 mg, 0.048 mmol) in methanol (1 ml) and 10% aq. KOH (0.8 ml) was stirred at room temperature for 2 h. The reaction mixture was acidified by the addition of 10% aq. HCl followed by extraction with CH_2Cl_2 (15 ml × 2). The CH_2Cl_2 extracts were washed with brine (20 ml × 2), and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded a residue, which was purified by PTLC with a solvent ($CHCl_3$–methanol, 4 : 1) to afford a colorless oil **1a** (15 mg, 80%). IR (neat): 1626 (N–C=O), 1724 (C=O), 3382 (OH). FAB-MS *m*/*z*: $(M)^+$ 401. ^{1}H-NMR: 0.88 (3H, br t, *J* = 6.3 Hz, CH_3), 1.26 (8H, br s, $-CH{=}CHC(OH)C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.86—2.95 (9H, m, H-1, H-2, H-4, H-5, H-6, H-8), 3.36—4.65 (4H, m, H-7, OH, $C\underline{H}{-}O\underline{H}$), 5.54—5.78 (2H, m, $-CH{=}CH-$), 7.36—8.21 (4H, m, Ph). ^{13}C-NMR: 14.0 (q, CH_3), 22.7, 25.3, 29.7, 31.9 (each t, $CH{=}CHC(OH)\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_3$), 36.9 (t, C-6), 49.7 (d, C-8), 72.0 (d, C–OH), 77.4 (d, C-7), 129.3, 131.7 (each d, $-CH{=}CH-$), 128.5, 128.9, 130.6, 131.4, 132.1, 135.1 (d, d, s, d, d, s, Ph), 166.8 (s, N–C=O), 169.9 (s, COOH).

Preparation of Cyclohexyl(triphenylphosphoranylidene)methylketone 6.7 ml of 1.5 mol/l *n*-butyl lithium (0.01 mol) was added to a solution of triphenylphosphine bromide (3.57 g, 0.01 mol) in dry toluene (20 ml) at 0 °C under argon. The mixture was stirred for 30 min at 0 °C and for 4 h at room temperature. To the mixture, ethyl thiolcyclohexanoate (77.4 mg) was added. The reaction mixture was stirred under reflux for 18 h, then extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried over $MgSO_4$ and concentrated *in vacuo* to give the desired product.

Preparation of (1*S,5*S**,7*R**,8*R**)-8-(3-Cyclohexyl-3-oxo-1-propenyl)-7-hydroxy-*N*-*m*-methoxycarbonylbenzoyl-3-azabicyclo[3.3.0]octane (16b)** The compound **15** (0.18 g, 0.58 mmol) was added to a solution of cyclohexyl (triphenylphosphoranylidene) methyl ketone (0.89 g, 2.30 mmol) in dry THF (15 ml) at room temperature under argon. The mixture was refluxed at 80 °C for 3 h, then concentrated *in vacuo*. To the residue, petr. ether was added. Deposited triphenyl-phosphine oxide was filtered off and washed with petr. ether. The filtrate and washings were dried over $MgSO_4$, concentrated *in vacuo* and the residue was subjected to PTLC (silica gel) with a mixture of hexane and AcOEt (1 : 4) to give **16b** (0.088 g, 33%). IR (neat): 3330 (OH), 1724 (C=O), 1629 (N–C=O). FAB-MS *m*/*z*: $(M)^+$ 425. ^{1}H-NMR: 0.73—2.18 (11H, m, cyclohexyl), 2.18—3.23 (10H, m, H-1, H-2, H-4, H-5, H-6, H-8, H-12), 3.23—4.05 (2H, m, H-7, OH), 3.93 (3H, s, $COOCH_3$), 6.07—6.40 (2H, m, $-CH{=}CH-$), 7.34—8.24 (4H, m, Ph), ^{13}C-NMR: 25.7, 25.8, 28.7, 29.6, 29.9 (each t, cyclohexyl), 33.9 (t, C-6), 49.0 (d, C-8), 52.3 (q, $COO\underline{C}H_3$), 77.6 (d, C-7), 125.6, 133.1 (each d, $-CH{=}CH-$), 128.2, 128.6, 130.3, 130.9, 131.6, 136.9 (d, d, s, d, d, s, Ph), 166.3 (s, N–C=O), 168.4 (s, $\underline{C}OOCH_3$), 179.4 (s, $CH{=}CH{-}\underline{C}O$).

Preparation of (1*S,5*S**,7*R**,8*R**)-8-(3-Cyclohexyl-3-hydroxy-1-propenyl)-7-hydroxy-*N*-*m*-methoxycarbonylbenzoyl-3-azabicyclo[3.3.0]-octane (17b)** Freshly fused zinc chloride (0.31 g) was added to sodium borohydride (0.18 g) in redistilled DME (4.1 ml) under argon. The mixture was stirred overnight at 0—5 °C. To a solution of **16a** (0.03 g, 0.071 mmol) in anhydrous DME (1 ml) was added 0.5 ml (0.11 mmol) of the above solution of zinc borohydride at 0 °C. The mixture was stirred at room temperature for 2 h, then a saturated sodium tartrate solution was added dropwise until no further evolution of gas was observed. Methylene chloride was then added and the solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to dryness. The residue was purified by PTLC with a solvent system (hexane–AcOEt, 1 : 4) to give **17b** (24 mg, 80%, colorless oil). IR (neat): 1623 (N–C=O), 1730 (C=O), 3334 (OH). FAB-MS *m*/*z*: $(M)^+$ 427. ^{1}H-NMR: 0.71—2.21 (11H, m, cyclohexyl), 2.21—3.15 (9H, m, H-1, H-2, H-4, H-5, H-7, H-8), 3.91 (3H, s, $COOCH_3$), 3.15—4.84 (4H, m, H-7, OH, $C\underline{H}{-}O\underline{H}$), 5.26—5.76 (2H, m, $-CH{=}CH-$), 7.32—8.21 (4H, m, Ph). ^{13}C-NMR: 25.0, 25.7, 28.2, 29.4, 29.8 (each t, cyclohexyl), 34.0 (t, C-6), 49.1 (d, C-8), 53.3 (q, $COO\underline{C}H_3$), 69.4 (d, CH–OH), 75.8 (d, C-7), 126.5, 131.2 (each d, $-CH{=}CH-$), 128.3, 128.7, 130.4, 130.9, 131.7, 137.4 (d, d, s, d, d, s, Ph), 166.5 (s, N–C=O), 168.1 (s, $COOCH_3$).

Preparation of (1*S,5*S**,7*R**,8*R**)-*N*-*m*-Carboxybenzoyl-8-(3-cyclohexyl-3-oxo-1-propenyl)-7-hydroxy-3-azabicyclo[3.3.0]octane (1b)** A solution of **17b** (0.016 g, 0.037 mmol) in methanol (1 ml) and 10% aq. KOH (1 ml) was stirred at room temperature for 2 h. The reaction mixture was acidified by the addition of 10% aq. HCl followed by extraction with CH_2Cl_2 (15 ml × 3). The CH_2Cl_2 extract was washed with brine (20 ml × 2), and dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded a residue, which was purified by PTLC with a solvent ($CHCl_3$–methanol, 10 : 1) to afford colorless oil **1b** (12 mg, 73%). IR (neat): 1621 (N–C=O), 1719 (C=O), 3400 (OH). FAB-MS *m*/*z*: $(M+Na)^+$ 435. ^{1}H-NMR: 0.72—2.11 (11H, m, cyclohexyl), 2.11—3.35 (9H, m, H-1, H-2, H-4, H-5, H-6, H-8), 3.35—4.38 (4H, m, H-7, OH, $C\underline{H}{-}O\underline{H}$), 5.25—5.72 (2H, m, $-CH{=}CH-$), 7.46—8.25 (4H, m, Ph). ^{13}C-NMR: 25.2, 25.7, 28.2, 29.4, 29.9 (each t, cyclohexyl), 34.2 (t, C-6), 49.7 (d, C-8), 69.5 (d, –CH–OH), 77.0 (d, C-7), 126.7, 131.3 (each d, $-CH{=}CH-$), 128.2, 128.6, 130.4, 130.8, 131.8, 137.2 (d, d, s, d, d, s, Ph), 167.4 (s, N–C=O), 169.9 (s, COOH).

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