# Design and Synthesis of a New 4-Oxa-8ω-11-deoxy-5,6-dihydroprostacyclin Analogue[1)]

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Received February 13, 1996; accepted June 3, 1996

**(±)-5-[5β-(((*E*)-1-Octen-3-ol)-1)-2-oxabicyclo[3.3.0]octan-3-yl]-4-oxapentanoic acid (±)-(1a,b), designed as a chemically and biologically stable prostacyclin analogue, was synthesized in 15% yield overall, *via* the (±)-3-hydroxymethyl-5-carbethoxy-2-oxabicyclo[3.3.0]octane (4) as the key intermediate.**

**Key words** prostacyclin; stable prostacyclin analogue; antithrombotic agent; 2-oxabicyclo[3.3.0]octane derivative

Prostacyclin ($PGI_2$, **2**) is an important autacoid, bioformed from arachidonic acid (AA) cascade, which was characterized byMoncada *et al.*[2)] as the more potent natural antithrombotic agent,[3)] displaying still vasodilator properties.[4)] Unfortunately, the therapeutic use of **2** is drastically limited by its short *in vivo* half-life (*ca.* 3.0 min) owing to the chemical lability of the cyclic enol ether moiety under acidic or neutral hydrolytic conditions,[5)] as well as by the enzymatic metabolic pathways of natural prostaglandins,[6)] involving oxidation of the 15-hydroxyl group, ω-oxidation of the ω-side-chain and β-oxidation of the upper side-chain.

Many $PGI_2$ analogues with structural modifications in the bicyclic system, ω-side-chain and upper side-chain have been prepared in the search for more stable, orally useful and highly selective antithrombotic compounds.[7,8)] As part of a research program aiming at the development of new bioactive prostanoidal compounds derived from functionalized 2-oxabicyclo[3.3.0]octane derivatives,[9)] we describe in this paper the synthesis and antiaggregatory activity of a new (±)-4-oxa-8ω-11-deoxy-5,6-dihydro-$PGI_2$ derivative[1a)] (**1a, b**). This compound was designed as a chemically and metabolically more stable $PGI_2$ analogue, which would retain high intrinsic activity, by introducing an oxygen atom in place of carbon in the upper side-chain at the C-4 position in order to prevent enzymatic β-oxidation.[10)] As a second structural modification we reduced the labile enol ether function, maintaining a *trans* arrangement between the upper and β-chains, as in the natural prostaglandins[8e)] (Fig. 1). Further structural modifications to impede metabolic inactivation were removal of the hydroxyl group at C-11 and moving the ω-side chain from C-12 to the neopentylic C-8 position (Fig. 1). It is known that 11-deoxy-$PGI_2$ analogues retain the antithrombotic properties,[11)] whereas the effect of transposition of the ω-side chain on the biological activity and metabolic stability has not yet been explored, to our knowledge.

**Synthesis** As shown in Chart 1, we planned to obtain the new $PGI_2$ analogue (**1**), using the 3-hydroxymethyl-5-carbethoxy-2-oxabicyclo[3.3.0]octane (**4**), as the key intermediate, which could be prepared in diastereomerically pure form from 2-carbethoxycyclopentanone (**3**),[12)] in 17% overall yield in a three-step process, as previously described.[9)]

The initial approach to the construction of the upper side-chain was the *O*-alkylation of **4**, in 65% yield, by reaction with potassium hydride in tetrahydrofuran (THF) followed by treatment with allyl bromide. The product (**5**) was submitted to regioselective terminal oxidation of the double bond employing the classical sequence of hydroboration–oxidation,[13)] furnishing the desired primary alcohol (**6**) in 78% yield.

The next step in the synthetic route was performed to protect the terminal hydroxyl group of **6**, in order to permit the subsequent chemical manipulation of the neopentylic ester function for the introduction of the ω-side chain. Thus, the reaction of **6** with 4 eq of *tert*-butyldimethylsilyl chloride (TBDMSiCl) in dimethylformamide (DMF) containing 2.5 eq of imidazole was carried out to

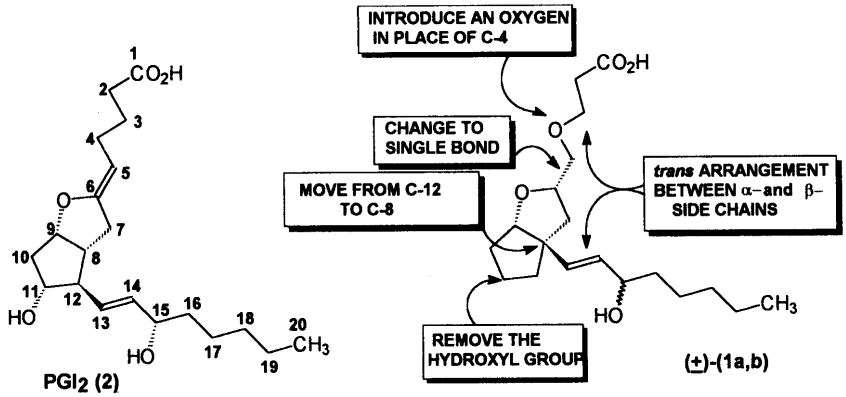


Fig. 1

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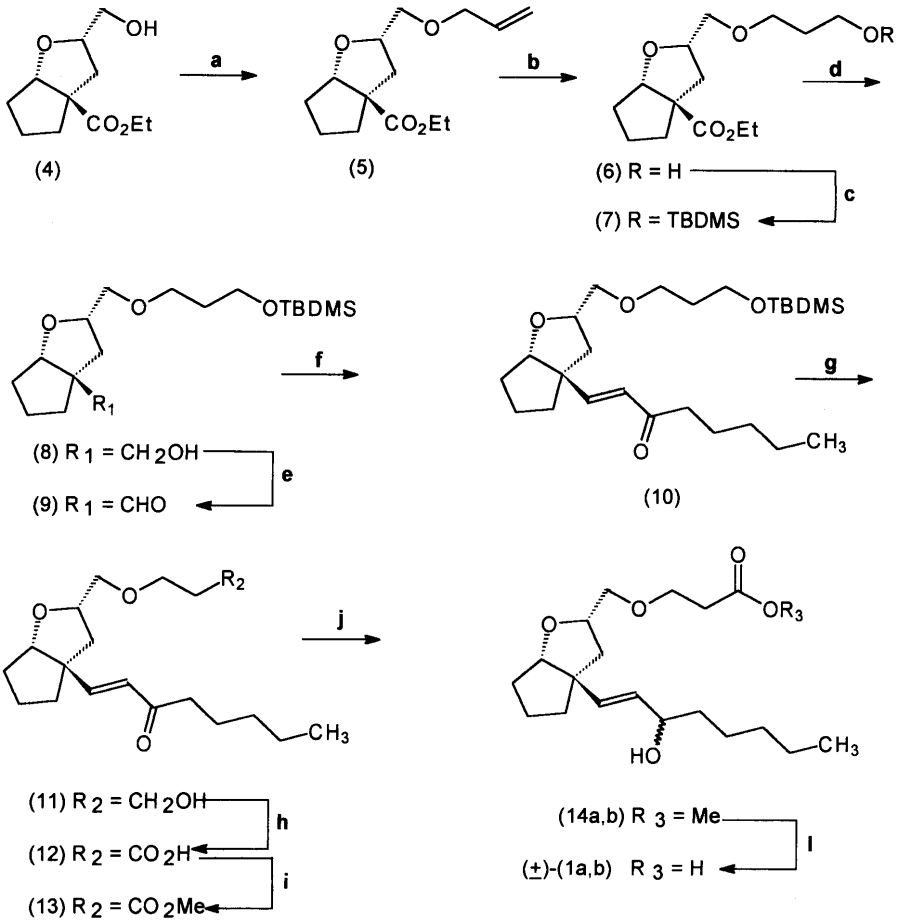


a) KH, THF, 0 °C; $BrCH_2CHCH_2$, 65%. b) $1\text{-}BH_3$, THF, 0 °C, 2- 30% $H_2O_2$, 10% aq. NaOH, 60 °C, 12h, 78%. c) TBDMSiCl, imidazole, DMF, r.t., 16h, 90%. d) $LiAlH_4$, THF, r.t., 3h, 82%. e) $1\text{-}(CO)_2Cl_2$, $CH_2Cl_2$, DMSO, -78 °C; 30 min; $Et_3N$, -78 °C, 15 min, 77%. f) KH, DME, $(MeO)_2POCH_2CO(CH_2)_4CH_3$, -78 °C, 2h; 24h, r.t., 65%. g) HF 5%, MeCN, 100%. h) $H_2CrO_4$, acetone, -10 °C, 88%. i) $CH_2N_2$, $Et_2O$, 5 min., 100%. j) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, r.t., 30 min, 90%. l) $K_2CO_3$, MeOH:$H_2O$ (1:1), r.t., 24 h, 100%.

Chart 1

Table 1. Effect of 4-Oxa-8ω-11-deoxy-5,6-dihydro-$PGI_2$ Analogue (±)-(**1a, b**) on Blood Platelet Aggregation[21]

| Compounds | C (μM) | ADP (5 μM) | | | Collagen (5 μg ml$^{-1}$) | | | AA (100 μM) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $n$[a] | Aggregation[a] (%) | Inhibition (%) | $n$[a] | Aggregation[a] (slope) | Inhibition (%) | $n$[a] | Aggregation[a] (%) | Inhibition (%) |
| Control | 0 | 3 | 41.0±4.5 | — | 3 | 6.9±1.7 | — | 6 | 50.7±5.7 | — |
| Indomethacin | 10 | 3 | 44.3±2.0 | 0.0 | 8 | 0.5±0.1 | 92.0[b] | 2 | 0.0±0.0 | 100.0[b] |
| **1a, b** | 100 | 3 | 38.7±4.2 | 5.6 | 3 | 6.9±2.9 | 0.0 | 5 | 44.8±5.5 | 11.6 |

*a*) The values of aggregation represent the means±S.D. $C$=final concentration. $n$=number of triplicate experiments. *b*) Significantly different from the control at $p<0.05$ (Student's $t$); indomethacin was used as the standard.

afford the silyl ether derivative (**7**) in 90% yield.[14] Compound **7** was subsequently reduced with $LiAlH_4$ in THF to furnish the monoprotected dihydroxy compound (**8**) in 82% yield. The Swern oxidation[15] of the alcohol (**8**) gave the unstable aldehyde intermediate (**9**; 77% yield), which was characterized by the carbonyl group absorption at $\nu$ 1720 cm$^{-1}$ in the infrared (IR) spectra. The compound (**9**) was used immediately in the next synthetic step without further purification.

The Wadsworth–Emmons–Horner reaction of **9** with dimethyl (2-oxoheptyl)phosphonate in 1,2-dimethoxyethane (DME)[16] proceeded smoothly to afford the diastereomerically pure enone (**10**), in 65% yield, which showed, in the $^1$H-NMR spectrum, a characteristic AB pattern centered at 6.98 and 6.12 ppm ($J$=16 Hz) due to the vinyl protons of the expected $E$-configuration of the enone system at C-13/C-15.

With the enone silyl ether (**10**) in hands, the synthesis

of the new $PGI_2$ analogue (±)-(**1a, b**) was concluded by deblocking the primary OTBDMS group by treatment with aqueous 5% HF in acetonitrile[17] to give the desired hydroxy-enone compound (**11**), in quantitative yield. Subsequently, the oxidation of the alcohol (**11**) with Jones' reagent[18] furnished, in 88% yield, the carboxylic acid (**12**), which was esterified to the corresponding methyl ester (**13**) by treatment with diazomethane in diethyl ether.

The regioselective reduction of (**13**) with a methanolic solution of sodium borohydride in the presence of 1.0 eq of cerium trichloride heptahydrate[19] afforded an inseparable mixture[20] of C-15 alcohols (**14a, b**). Finally, mild hydrolysis of **14a, b** in aqueous methanolic potassium carbonate completed the synthetic route, furnishing quantitatively, the new desired $PGI_2$ analogue (±)-(**1a, b**).

## Results

The preliminary data on the antiplatelet activity of the $PGI_2$ analogue (±)-(**1a, b**) synthesized above are given in Table 1. The inhibitory activities of (±)-(**1a, b**) on blood platelet agreggation,[21] in rabbit platelet-rich plasma stimulated with AA, adenosine diphosphate (ADP) and collagen, were poor, with only moderate inhibition in the AA-induced model.

### Experimental

$^1$H- and $^{13}$C-NMR spectra were determined in deuterochloroform containing *ca.* 1% tetramethylsilane as an internal standard with Brucker AC200 and Varian VXR 300 spectrometers. Splitting patterns were as follows: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; st, sextet; dd, double doublet; m, multiplet. IR spectra were obtained with a Perkin-Elmer 1600 spectrophotometer as neat films on sodium chloride plates. The mass spectra (MS) were obtained on a GC/VG Micromass 12 at 70 eV. Ultraviolet (UV) spectra were determined in methanol solution on a Beckman DU-70 spectrophotometer.

Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate powder. The progress of all reactions was monitored by TLC performed on 2.0 × 6.0 cm aluminum sheets precoated with Silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were visualized under UV light or by spraying with molybdatophosphoric acid in ethanol. For column chromatography Merck silica gel (70—230 mesh) was used. Solvents used in the reactions were dried, redistilled prior to use and stored over 3—4 A molecular sieves. Reaction mixture were generally stirred under a dry nitrogen atmosphere.

**Ethyl (1*RS*,3*RS*,5*RS*)-3-Allyloxymethyl-5-(2-oxabicyclo[3.3,0]octane)carboxylate (5)** A 35% suspension of potassium hydride in mineral oil (0.24 g; 2.1 mmol) was washed with dry *n*-hexane to afford a white solid, which was suspended in dry THF (12 ml). Then, a solution of the bicyclic alcohol[9] **4** (0.35 g; 1.6 mmol) in dry THF (12 ml) was added and the resulting mixture was stirred at 0 °C for 1 h. Allyl bromide (2.3 ml; 26.5 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 30 min. After this time, most of the solvent was evaporated and the residue was diluted with water (10 ml) and extracted with methylene chloride (5 × 15 ml). The organic extracts were dried and evaporated, and the resulting oil was chromatographed on Silica gel G with a mixture of *n*-hexane–ethyl acetate (9 : 1) to furnish 0.27 g (65%) of the *O*-allyl product **5** as a colorless oil. IR (film) $cm^{-1}$: 3090 (C=C-H), 1730 (C=O), 1650 (C=C), 1280 (C-O), 1185 (C-O), 1110 (C-O). $^1$H-NMR (300 MHz) $\delta$: 5.98—5.85 (1H, m, $-CH_2C\underline{H}=CH_2$), 5.30—5.15 (2H, m, $-CH_2CH=C\underline{H}_2$), 4.48 (1H, d, $J$=5 Hz, C1-H), 4.13 (2H, q, $J$=7 Hz, $-OC\underline{H}_2CH_3$), 4.03 (3H, m, –O–C<u>H</u>–C<u>H</u>$_2$–O-allyl), 3.6—3.45 (2H, m, $-OC\underline{H}_2CH=CH_2$), 2.55 (1H, dd, $J$=5 Hz, C4-$\beta$H), 2.05—1.9 (2H, m), 1.8—1.67 (2H, m), 1.65—1.5 (1H, m), 1.48 (1H, m), 1.23 (3H, t, $J$=7 Hz, $-OCH_2C\underline{H}_3$) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 176.0 (C=O), 134.5 ($-CH_2\underline{C}H=CH_2$), 116.9 ($-CH_2CH=\underline{C}H_2$), 89.2 (C(1)), 78.6 (C(3)), 72.2 (–O–CH–<u>C</u>H$_2$–O-allyl), 71.7 ($-O\underline{C}H_2CH=CH_2$), 60.6 ($O\underline{C}H_2CH_3$), 59.6 (C(5)), 40.5 (C(4)), 37.2 (C(8)), 33.4, 23.9, 14.0 ($OCH_2\underline{C}H_3$) ppm. MS *m/z* (rel. int. %): 209 ($M^+-OEt$, 10%), 197 ($M^+-OCH_2CHCH_2$, 14%), 183 ($M^+-CH_2OCH_2CHCH_2$, 72%), 137 ($M^+-CH_2OCH_2CH-CH_2-OEt$, 33%), 109 ($M^+-CH_2OCH_2CHCH_2-CO_2Et$, 100%).

**Ethyl (1*RS*,3*RS*,5*RS*)-3-(3-Hydroxypropyloxymethyl)-5-(2-oxabicyclo-[3.3,0]octane)carboxylate (6)**[13] A solution of the allyl-ether **5** (0.182 g; 0.71 mmol) in 5 ml of dry THF at 0 °C was treated with 1 ml (*ca.* 1 mmol) of a 1 M solution of $B_2H_6$ in dry THF. The resulting mixture was stirred at 0 °C for 2 h. Then, methanol was added dropwise until no further gas was evolved, and 0.35 ml of a 10% aqueous NaOH solution (1 mmol) and 0.35 ml of 30% aqueous $H_2O_2$ solution were added at 0 °C. The suspension formed was maintained at 60 °C for 12 h. After cooling, the reaction mixture was partitioned between ethyl ether (10 ml) and water (5 ml), followed by separation of the organic phase. The aqueous layer was further extracted with ethyl ether (3 × 10 ml) and the organic extracts were combined, treated with 10 ml of a 10% aqueous HCl solution, dried and evaporated to give 0.149 g (78%) of the primary alcohol derivative **6** as a colorless oil. IR (film) $cm^{-1}$: 3440 (O-H), 1727 (C=O), 1284 (C-O), 1185 (C-O), 1113 (C-O). $^1$H-NMR (300 MHz) $\delta$: 4.53 (1H, d, $J$=5 Hz, C1-H), 4.20 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 4.05 (1H, m, C3-H), 3.85—3.50 (6H, m, $-C\underline{H}_2OC\underline{H}_2CH_2C\underline{H}_2OH$), 2.58 (1H, dd, $J$=5 Hz, C4-$\beta$H), 2.10—1.55 (10H, m), 1.29 (3H, t, $J$=7 Hz, $-OCH_2C\underline{H}_3$) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 176.0 (C=O), 89.2 (C(1)), 78.6 (C(3)), 72.1 ($-\underline{C}H_2OCH_2CH_2CH_2OH$), 70.5 ($-CH_2O\underline{C}H_2CH_2CH_2OH$), 61.6 ($-CH_2OCH_2CH_2\underline{C}H_2OH$), 60.8 ($O\underline{C}H_2CH_3$), 59.7 (C(5)), 40.2 (C(4)), 37.2 (C(8)), 33.5, 31.7, 24.07, 14.0 ($OCH_2\underline{C}H_3$) ppm. MS *m/z* (rel. int. %): 196 ($M^+-HO(CH_2)OH$, 9%), 183 ($M^+-CH_2O(CH_2)_3OH$, 88%), 137 ($M^+-CH_2O(CH_2)_3OH-OEt$, 37%), 109 ($M^+-CH_2O(CH_2)_3OH-CO_2Et$, 100%).

**Ethyl (1*RS*,3*RS*,5*RS*)-3-(3-*tert*-Butyldimethylsilyloxypropyloxymethyl)-5-(2-oxabicyclo[3.3.0]octane)carboxylate (7)**[14] A solution of 0.33 g (2.2 mmol) of TBDMSiCl and 0.094 g (1.38 mmol) of imidazole in 0.5 ml of dry DMF was added to 0.15 g (0.55 mmol) of the alcohol ester **6** in 0.5 ml of dry DMF under nitrogen at room temperature. The mixture was stirred for 16 h and poured into saturated aqueous NaCl at room temperature. The mixture was stirred for 30 min, then the product was extracted with dichloromethane (3 × 15 ml) to yield 0.19 g (90%) of the silyl ether **7** as a viscous oil. IR (film) $cm^{-1}$: 1729 (C=O), 1250 (C-O), 1180 (C-O), 1105 (C-O), 838 (Si-O). $^1$H-NMR (300 MHz) $\delta$: 4.50 (1H, d, $J$=5 Hz, C1-H), 4.15 (2H, q, $J$=7 Hz, $OC\underline{H}_2CH_3$), 4.02 (1H, m, C3-H), 3.68 (2H, t, $J$=6 Hz, $-CH_2OC\underline{H}_2CH_2CH_2OSi$), 3.54 (2H, t, $J$=6 Hz, $-CH_2OCH_2C\underline{H}_2C\underline{H}_2OSi$), 3.50 (2H, m, $C\underline{H}_2OCH_2CH_2-CH_2OSi$), 2.56 (1H, dd, $J$=5 Hz, C4-$\beta$H), 2.02—1.78 (2H, m), 1.75—1.66 (6H, m), 1.63—1.5 (1H, m), 1.25 (3H, t, $J$=7 Hz, $-OCH_2CH_3$), 0.88 (9H, s, $-Si(CH_3)_2C(C\underline{H}_3)_3$), 0.03 (6H, s, $-Si(C\underline{H}_3)_2C(CH_3)_3$) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 176.1 (C=O), 89.2 (C(1)), 78.7 (C(3)), 72.4 ($-\underline{C}H_2OCH_2CH_2CH_2OSi$), 68.1 ($-CH_2O\underline{C}H_2CH_2CH_2OSi$), 62.2 ($-CH_2OCH_2CH_2\underline{C}H_2OSi$), 60.7 ($O\underline{C}H_2CH_3$), 59.7 (C(5)), 40.6 (C(4)), 37.3 (C(8)), 33.5, 32.6, 25.7, 25.5, 24.0, 14.0 ($OCH_2\underline{C}H_3$), −5.4 ($-Si(\underline{C}H_3)_2C(CH_3)_3$) ppm.

**(1*RS*,3*RS*,5*RS*)-3-(3-*tert*-Butyldimethylsilyloxypropyloxymethyl)-(2-oxabicyclo[3.3.0]octan)-5-yl Methanol (8)** To a suspension of 0.165 g (4.34 mmol) of lithium aluminum hydride in 7.7 ml of dry THF was added 0.167 g (0.43 mmol) of the silyl ester **7** diluted in 7.7 ml of dry THF, under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 3 h, then water (0.4 ml) and 10% aqueous NaOH solution (0.4 ml) was added dropwise and stirring was continued for 1 h. The precipitate was filtered off and washed with ethyl acetate. The combined organic layers were dried and the solvent was removed under vacuum to give 0.12 g (82%) of the neopentylic alcohol **8** as a colorless oil. IR (film) $cm^{-1}$: 3390 (O-H), 1250 (C-O), 1100 (C-O), 1070 (C-O), 1045 (C-O), 835 (Si-O). $^1$H-NMR (300 MHz) $\delta$: 4.11 (1H, d, $J$=5 Hz, C1-H), 3.93 (1H, st, $J$=5 Hz, C3-H), 3.68 (2H, t, $J$=7 Hz, $-CH_2OC\underline{H}_2-CH_2CH_2OSi$), 3.60—3.33 (4H, m, $-CH_2OC\underline{H}_2CH_2CH_2OSi$), 2.25 (1H, br s, OH), 2.05 (1H, dd, $J$=5 Hz, C4-$\beta$H), 1.95—1.20 (9H, m), 0.88 (9H, s, $-Si(CH_3)_2C(C\underline{H}_3)_3$), 0.03 (6H, s, $-Si(C\underline{H}_3)_2C(CH_3)_3$) ppm. $^{13}$C-NMR (75 MHz, $CDCl_3$) $\delta$: 87.1 (C(1)), 77.2 (C(3)), 72.8 ($-\underline{C}H_2OCH_2CH_2-CH_2OSi$), 68.0 ($-CH_2O\underline{C}H_2CH_2CH_2OSi$), 67.6 ($-CH_2OH$), 59.7 ($-CH_2OCH_2CH_2\underline{C}H_2OSi$), 55.6 (C(5)), 40.1 (C(4)), 36.1 (C(8)), 33.3, 32.6, 29.4, 25.7, 23.5, −5.6 ($-Si(\underline{C}H_3)_2C(CH_3)_3$) ppm. MS *m/z* (rel. int. %): 327 ($M^+-OH$, 1%), 287 ($M^+-$*tert*-Bu, 4%), 154 ($M^+-CH_2-CH_2CH_2OTBDMS-OH$, 11%), 141 ($M^+-CH_2O(CH_2)_3OTBDMS$, 100%), 123 ($M^+-CH_2O(CH_2)_3OTBDMS-H_2O$, 39%).

**(1*RS*,3*RS*,5*RS*)-3-(3-*tert*-Butyldimethylsilyloxypropyloxymethyl)-5-**

**(2-oxabicyclo[3.3.0]octane)carbaldehyde (9)**[15] Dry dimethyl sulfoxide (DMSO) (0.09 ml, 1.26 mmol) was added to a solution of 0.07 ml (0.8 mmol) of oxalyl chloride in 17 ml of dry dichloromethane, under nitrogen at −78 °C. After 10 min, 0.2 g (0.58 mmol) of the hydroxy silyl ether **8** diluted in 2 ml of dry dichloromethane was added and the resulting solution was stirred for 30 min at −78 °C. Then, 0.4 ml (3 mmol) of triethylamine was added, and stirring was continued for an additional 15 min at −78 °C. After this time, 1.2 ml of water was added and the mixture was extracted with dichloromethane (5 × 10 ml). The organic extracts were combined, dried and evaporated to give 0.15 g (77%) of the neopentylic aldehyde **9**, as a colorless oil which was used for the next step without further purification. IR (film) $cm^{-1}$: 2719 (O=C-H), 1720 (C=O), 1250 (C-O), 1100 (C-O), 840 (Si-O).

**(*E*)-1-((1*RS*,3*RS*,5*RS*)-3-((3-*tert*-Butyldimethylsilyloxypropyloxymethyl)-(2-oxabicyclo[3.3.0]octan))-5-yl)-1-octen-3-one (10)**[16] A solution of the aldehyde **9** (0.18 g; 0.52 mmol) in 3 ml of dry DME was added to a mixture of potassium dimethyl (2-oxoheptyl)phosphonate in DME [from 0.071 g (35% dispersion in mineral oil, 0.624 mmol) of potassium hydride and 0.15 g (0.67 mmol) of dimethyl (2-oxoheptyl)phosphonate in 14 ml of dry DME stirred under nitrogen at room temperature for 1 h] at −78 °C. The mixture was stirred for 1 h at −78 °C and 16 h at 25—30 °C, then the reaction mixture was cooled to 0 °C and *ca.* 0.4 ml of acetic acid was added dropwise. The solvent was evaporated and the resulting syrup was diluted with water (10 ml) and extracted with ethyl ether (5 × 10 ml). The organic extracts were dried and evaporated to afford a light yellow oil, which was chromatographed on silica gel G with a mixture of *n*-hexane–ethyl acetate (95 : 5) to furnish 0.15 g (65%) of the enone **10**, as a light yellow oil. IR (film) $cm^{-1}$: 1705 (C=O), 1670 (C=C), 1250 (C-O), 1030 (C-O), 830 (Si-O). $^1$H-NMR (200 MHz) $\delta$: 6.98 (1H, d, $J$=16 Hz, –CH=CHCO), 6.12 (1H, d, $J$=16 Hz, –CH=CHCO), 4.23 (1H, d, $J$=5 Hz, C1-H), 3.97 (1H, qt, $J$=5 Hz, C3-H), 3.68 (2H, t, $J$=7 Hz, $-CH_2OCH_2CH_2CH_2OSi$), 3.60—3.45 (4H, m, $-CH_2OCH_2CH_2CH_2OSi$), 2.54 (2H, t, $J$=7 Hz, –CH=CHCOCH$_2$–), 2.10 (1H, dd, $J$=4.7 Hz, C4-$\beta$H), 1.78—1.48 (17H, m), 0.88 (12H, s, $-Si(CH_3)_2C(CH_3)_3$, $-CO(CH_2)_4CH_3$), 0.045 (6H, s, $-Si(CH_3)_2C(CH_3)_3$) ppm. $^{13}$C-NMR (50 MHz) $\delta$: 201.0 (C=O), 151.8 (–CH=CHCOCH$_2$), 126.5 (–CH=CHCOCH$_2$–), 90.6 (C(1)), 78.1 (C(3)), 73.0 ($-CH_2OCH_2CH_2CH_2OSi$), 68.5 ($-CH_2OCH_2CH_2CH_2OSi$), 60.0 ($-CH_2OCH_2CH_2CH_2OSi$), 45.5 (C(5)), 42.7, 41.0, 38.9, 36.0, 33.0, 31.8, 29.9, 26.0, 24.0, 22.8 ppm. MS *m/z* (rel. int. %): 438 ($M^+$, 0.5%), 381 ($M^+$ − *tert*-Bu, 3%), 149 ($M^+ - O(CH_2)_3OTBDMS - OC(CH_2)_4CH_3 - H$, 100%), 99 (+O=C(CH$_2$)$_4$CH$_3$, 34%), 71 ($+CH_2(CH_2)_3CH_3$, 36%), 57% (+*tert*-Bu, 9%). UV $\lambda_{max}$ (MeOH) nm: 228 (log $\varepsilon$ 4.01).

**(*E*)-1-((1*RS*,3*RS*,5*RS*)-3-((3-Hydroxypropyloxymethyl)-(2-oxabicyclo[3.3.0]octan))-5-yl)-1-octen-3-one (11)**[17] A solution of 0.126 g (0.288 mmol) of the enone silyl ether **10** in 9.5 ml of acetonitrile was treated at room temperature with 0.5 ml of 40% aqueous HF solution and the resulting mixture was stirred for 4 h. Then, 10 ml of saturated aqueous NaCl solution and 10 ml of dichloromethane were added. The organic layer was separated, dried and evaporated and the resulting oil was chromatographed on Silica gel G with a mixture of *n*-hexane–ethyl acetate (8 : 2) to furnish 0.0935 g (100%) of the alcohol enone derivative **11** as a light yellow oil. IR (film) $cm^{-1}$: 3405 (O-H), 1675 (C=O), 1625 (C=C), 1290 (C-O), 1100 (C-O). $^1$H-NMR (200 MHz) $\delta$: 6.93 (1H, d, $J$=16 Hz, –CH=CHCO), 6.12 (1H, d, $J$=16 Hz, –CH=CHCO), 4.23 (1H, s, C1-H), 3.85—3.40 (6H, m), 2.80—2.45 (2H, m), 2.06 (1H, m), 1.95—0.88 (20H, m) ppm. $^{13}$C-NMR (50 MHz) $\delta$: 200.8 (C=O), 151.5 (–CH=CHCOCH$_2$), 126.3 (–CH=CHCOCH$_2$–), 90.3 (C(1)), 77.9 (C(3)), 72.5 ($-CH_2OCH_2CH_2CH_2OH$), 70.3 ($-CH_2OCH_2CH_2CH_2OH$), 61.3 ($-CH_2OCH_2CH_2CH_2OH$), 55.9 (C(5)), 41.9, 40.8, 38.4, 33.3, 32.0, 31.4, 29.7, 28.9, 23.8, 23.0, 22.4, 13.9 ppm.

**3-(5-((*E*)-3-Oxo-1-octenyl)-((1*RS*,3*RS*,5*RS*)-2-oxabicyclo[3.3.0]-octan-3-yl)methoxypropionic Acid (12)**[18] An 8 N solution of Jones' reagent (*ca.* 0.5 ml) was added dropwise to a solution of 0.08 g (0.247 mmol) of the alcohol enone **11** in 5 ml of acetone, at −10 °C. After 30 min, 2 ml of isopropanol was added and the reaction mixture was filtered. The filtrate was concentrated under reduced pressure to obtain a residue, which was diluted with 10 ml of a mixture of diethyl ether–water (2 : 1). The organic layer was separated, dried and evaporated to give 0.073 g (88%) of the acid **12** as a colorless oil. IR (film) $cm^{-1}$: 3450 (O-H), 1705 (C=O), 1620 (C=C), 1185 (C-O), 990 (C-O).

**Methyl 3-(5-((*E*)-3-Oxo-1-octenyl)-((1*RS*,3*RS*,5*RS*)-2-oxabicyclo-[3.3.0]octan-3-yl)methoxy)propionate (13)** An ethereal solution of diazomethane was added dropwise to a solution of 0.05 g (0.148 mmol) of the acid enone **12** in ethyl ether (2 ml) until the evolution of gas ceased. Then, 0.2 ml of acetic acid was added and the resulting organic solution was dried with anhydrous potassium carbonate and concentrated under reduced pressure to furnish 0.052 g (100%) of the methyl ester derivative **13**, as a light yellow oil. IR (film) $cm^{-1}$: 1710 (C=O), 1678 (C=C), 1190 (C-O), 990 (C-O). $^1$H-NMR (200 MHz) $\delta$: 6.97 (1H, d, $J$=16 Hz, –CH=CHCO), 6.14 (1H, d, $J$=16 Hz, –CH=CHCO), 4.50 (1H, d, $J$=5 Hz, C1-H), 3.98 (1H, st, $J$=5 Hz, C3-H), 3.77 (2H, t, $J$=6 Hz, $-CH_2OCH_2CH_2COOMe$), 3.66 (3H, s, –COOCH$_3$), 3.54 (2H, d, $J$=4 Hz, $-CH_2OCH_2CH_2COOMe$), 2.61 (2H, t, $J$=6 Hz, $-CH_2OCH_2CH_2$-COOMe), 2.54 (2H, t, $J$=7 Hz, –CH=CHCOCH$_2$–), 2.11 (1H, dd, $J$=5 Hz, C4-$\beta$H), 1.95—1.48 (9H, m), 1.50—1.20 (6H, m), 1.00—0.85 (3H, m) ppm. $^{13}$C-NMR (50 MHz) $\delta$: 200.7 (CH=CH–C=O), 173.0 (–COOMe), 151.6 (–CH=CHCOCH$_2$–), 126.3 (–CH=CHCOCH$_2$–), 90.3 (C(1)), 77.9 ($-CH_2OCH_2CH_2COOMe$), 66.9 (–COOCH$_3$), 55.9 (C(5)), 42.1, 40.8, 38.4, 34.8, 33.3, 31.4, 29.7, 24.1, 23.8, 22.4, 18.4 ppm. MS *m/z* (rel. int. %): 321 ($M^+$ − OMe, 5%), 296 ($M^+ - CH_2$=$CHCH_2CH_3$, 4%), 191 ($M^+ - CH_2O(CH_2)_2COOMe - CH_2CH_2CH_3$ − H, 100%), 99 (+O=C(CH$_2$)$_4$CH$_3$, 39%), 71 ($+CH_2(CH_2)_3CH_3$, 21%).

**Methyl 3-(5-(3-Hydroxy-1-octenyl)-((1*RS*,3*RS*,5*RS*)-2-oxabicyclo-[3.3.0]octan-3-yl) methoxy)propionate (14a, b)**[19] A solution of the enone **13** (0.025 g; 0.07 mmol) in 1 ml of methanol containing 0.022 g (0.059 mmol) of heptahydrated cerium trichloride was treated at room temperature with a solution of 0.003 g (0.08 mmol) of sodium borohydride in 1 ml of methanol. The reaction mixture was stirred at room temperature for 30 min, then saturated aqueous ammonium chloride solution (2 ml) was added. The product was isolated with methylene chloride, dried and evaporated to furnish 0.022 g (90%) of the C-15 epimeric alcohols **14a**, **14b** as a colorless oil. IR (film) $cm^{-1}$: 3400 (C-O), 1735 (C=O), 1650 (C=C), 1110 (C-O). $^1$H-NMR (200 MHz) $\delta$: 5.82 (1H, d, $J$=16 Hz, –CH=CHCHOH), 5.47 (1H, d, $J$=16 Hz, –CH=CHCHOH), 4.15 (1H, d, $J$=5 Hz, C1-H), 4.07 (1H, d, $J$=6 Hz, –CH=CHCHOH), 3.98 (1H, m, C3-H), 3.76 (2H, t, $J$=6 Hz, $-CH_2OCH_2CH_2$-COOMe), 3.68 (3H, s, –COOCH$_3$), 3.52 (2H, d, $J$=4 Hz, $-CH_2OCH_2$-$CH_2COOMe$), 2.61 (2H, t, $J$=6 Hz, $-CH_2OCH_2CH_2COOMe$), 2.01 (1H, dd, $J$=5 Hz, C4-$\beta$H), 1.91—1.20 (15H, m), 0.92—0.84 (3H, m) ppm. $^{13}$C-NMR (50 MHz) $\delta$: 172.4 (–COOMe), 137.6 (–CH=CHCH(OH)–), 129.6 (–CH=CHCH(OH)), 90.7 (C(1)), 77.7 (C(3)), 73.2 (–CH=CH–CH(OH)–), 73.1 ($-CH_2OCH_2CH_2COOMe$), 66.8 ($-CH_2OCH_2CH_2$-COOMe), 55.1 (C(5)), 51.6 (–COOCH$_3$), 42.76 (42.70), 38.91 (38.81), 37.4, 34.8, 33.2, 31.7, 29.7, 25.1, 23.9, 22.6, 14.0 ppm. MS *m/z* (rel. int. %): 336 ($M^+ - H_2O$, 28%), 283 ($M^+ - CH_2CH_2CH_2CH_2CH_3$, 65%). *Anal.* Calcd for $C_{20}H_{34}O_5$: C, 67.77; H, 9.67. Found: C, 67.71; H, 9.69.

**3-(5-(3-Hydroxy-1-octenyl)-((1*RS*,3*RS*,5*RS*)-2-oxabicyclo[3.3.0]-octan-3-yl)methoxy)propionic Acid (1a, b)** A solution of 0.008 g (0.022 mmol) of the alcohols **14a**, **14b** and 0.1 g of potassium carbonate in 1.5 ml of 35% aqueous methanol was stirred for 24 h at room temperature. Then, the reaction mixture was neutralized with 10% aqueous HCl solution and extracted with ethyl acetate (4 × 5 ml). The organic extracts were combined, dried and evaporated under reduced pressure to furnish 0.0076 g (100%) of the desired acid **1a**, **1b**, as a colorless oil. IR (film) $cm^{-1}$: 3350 (O-H), 1718 (C=O), 1250 (C-O), 1185 (C-O), 1035 (C-O). MS *m/z* (rel. int. %): 340 ($M^+$, 1%), 305 ($M^+ - OH - H_2O$, 100%), 252 ($M^+ - CH_2CH_2CH_2CH_2CH_3 - OH$, 59%). Compound (±)-(**1a, b**) was also characterized by $^1$H- and $^{13}$C-NMR after esterification with an ethereal solution of diazomethane, showing the same pattern as **14a, b**. *Anal.* Calcd for $C_{19}H_{32}O_5$: C, 67.02; H, 9.47. Found: C, 67.03; H, 9.45.

**Acknowledgment** We thank CNPq (Br., No. 50.1105/94-3, No. 52.0011/94-5) for financial suport and CNPq (Br.) for fellowships (to CAMF, ALPM & EJB).

**References and Notes**

1) *a*) Taken in part from the PhD Thesis of C.A.M.F., Instituto de Química/LASSBio, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Br., 1994; *b*) This work represents contribution No. 11 from LASSBio, UFRJ.
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