to be freely rotating in all case, except in its Ag^+ complex.

Because of the combined effects of disorder (the averaging of Al and Si positions into a single (Si, Al) position and of the oxide ion positions as though the coordination spheres of Si and Al were the same size) and moderately high thermal motions, the ethylenic double bond length 1.27(3) Å is a little bit shorter and inaccurately determined. However the esd of this bond length is high, so may be acceptable. This result is very similar to those found in the ethylene sorption complexes of Co_4Na_4-A, 1.21(11) Å and that Ag_{12}-A, 1.19(12) Å.[3,6] For comparison, the C=C bond length in ethylene gas is 1.334 Å.[21].

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A New Chiral Synthetic Route to (+)-Isocarbacyclin

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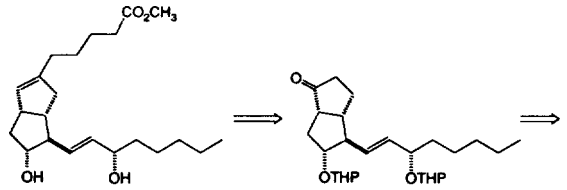
A synthetic route to (+)-isocarbacyclin starting from (−)-tricyclo[3.3.0.$0^{2,8}$]octan-3-one **6** is described. The key intermediate **4** has been synthesized from **6** by a sequential introduction of methoxycarbonyl group at C-12 and the oxygen functionality at C-9α (PG numbering) for the construction of α- and ω-side chain, and then converted to isocarbacyclin methyl ester 2.

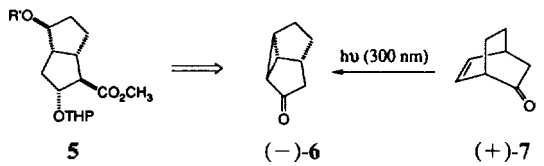
Introduction

Prostacyclin **3** is a potent inhibitor of platelet aggregation.[1] In human platelet-rich plasma, prostacyclin is 50 and 20 times more active than PGE_2 and PGD_2, respectively. However, prostacyclin can not be used for therapeutic purposes as it is, since it is very unstable due to the presence of an enol ether group.

Since the discovery of prostacyclin, considerable attention has been focused on the design of stable prostacyclin analogues which still retain the sufficient biological activity. Among them, isocarbacyclin [**1**, 9(O)-methano-$\Delta^{6,9(\alpha)}$-PGI_1] has recently been introduced as a promising therapeutic agent for cardiovascular disease.[2] Afterwards, a number of



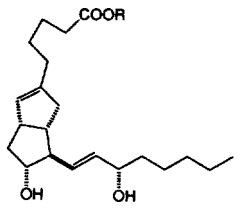
2, (+)-Isocarbacyclin methyl ester 4

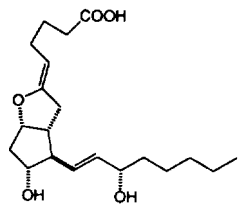


5 (−)-6 (+)-7

Scheme 1.

synthetic methods for **1** have been reported by several groups.[3] In most cases, the synthetic route to optically active isocarbacyclin **1** involve, for the construction of bicyclo[3.3.0] octane skeleton, the annulation of a five-membered ring on to the preexisting cyclopentenone rings derived usually from the "Corey lactone" or from (R)-4-hydroxy-2-cyclopentenone.



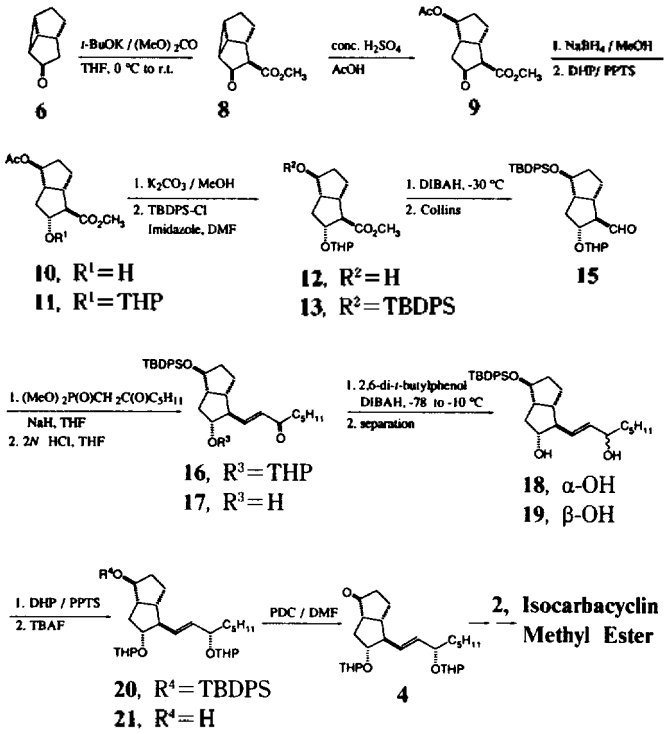


Isocarbacyclin **1**, R=H Prostacyclin **3**
2, R=Me

In connection with our efforts to develop an efficient synthesis for isocarbacyclin **1**, we embarked on the formal total synthesis of (+)-isocarbacyclin methyl ester **2** from a conceptually new starting material. In this paper, we wish to disclose the details of a new synthetic approach to isocarbacyclin **1**.

Retrosynthetic Analysis. It was expected that tricyclooctanone **6** would be a good starting material on several reasons: (1) it already has a bicyclo[3.3.0]octane skeleton necessary for isocarbacyclin synthesis, (2) regio- and stereocontrolled introduction of methoxycarbonyl group at C-4 for the formation of ω-side chain can be easily achieved since cyclopropyl group exist at C-2 position, (3) cyclopropyl ring would readily be opened by oxygen nucleophile for the introduction of α-side chain of isocarbacyclin, and (4) tricyclooctanone **6** is readily available in racemic or in optically active form from bicyclo[3.3.0]oct-5-en-2-one **7**.[4] Accordingly, a key feature of our approach to **2** is to utilize (−)-tricyclo[3.3.0.$0^{2,8}$]-octan-3-one **6**, which contains a preexisting bicyclo[3.3.0]octane skeleton, as shown in Scheme 1.

Based on these expectations, tricyclooctanone **6** can be transformed into **5** without difficulty. The bicyclooctanone **4** can also be derived from **5** by introducing ω-side chain through Horner-Emmons reaction pathway. Finally, isocarbacyclin methyl ester **2** can be obtained from **4** by Ikegami's procedure.[3e]



Scheme 2.

Synthesis of Isocarbacyclin Methyl Ester 2. The bicyclooctanone **4**, a key precursor for the synthesis of **2**, was synthesized by the reaction pathway shown in Scheme 2.

Firstly, introduction of methoxycarbonyl group was attempted on standard conditions[5] by treating **6** with dimethyl carbonate in the presence of NaH as a base in dioxane (90℃, 24 hr). Unfortunately, the reaction did not proceed at all. Several attempts under such conditions as NaH/dimethyl carbonate (r.t, reflux), NaH/ethyl chloroformate/dioxane were fruitless. Finally, regio- and stereoselective methoxycarbonylation at C-4 proceeded smoothly by using potassium *t*-butoxide as a base to afford β-ketoester **8** in 67% yield. Upon treatment of **8** with acetic acid and concentrated sulfuric acid, the acetoxy functionality was introduced smoothly at C-8 with concomitant opening of cyclopropane ring to produce **9** in 75% yield. Subsequent reduction of **9** with $NaBH_4$ proceeded on the less hindered exo face with excellent steroselectivity to give **10** in 90% yield. Protection of the alcohol **10** with dihydropyran followed by deacetylation with potassium carbonate in methanol provided the alcohol **12** in 96% yield. The alcohol **12** was then converted into the aldehyde **15** in 82% overall yield by a three step sequence; protection of C-8 alcohol as *t*-butyldiphenylsilyl (TBDPS) ether, reduction of methyl ester to alcohol with diisobutylaluminum hydride (DIBAH), and Collins oxidation of the corresponding alcohol. The aldehyde **15** was also obtained in 70% yield by selective reduction of methyl ester with 1.1 eq of DIBAH at −78℃ accompanied by the alcohol **14** in 22% yield.

The aldehyde **15**, also a useful intermediate for the synthesis of isocarbacyclin analogues by variation of ω-side chain, was subjected to Hornor-Emmons reaction by treating with NaH and dimethyl (2-oxoheptyl)phosphonate to provide

the enone **14** in 92% yield. Prior to reduction of the enone **14**, the tetrahydropyranyl (THP) group of the enone at C-11 (PG numbering) was deprotected by 2 N HCl in tetrahydrofuran (THF) to give **15** in 92% yield. Subsequent reduction of the hydroxyenone **17** with excess of diisobutylaluminum 2,6-di-butyl-4-methylphenoxide[6] yielded a mixture of the epimers at C-15 (PG numbering). These two epimers were separated by flash column chromatography to provide the desired and more polar isomer **18** in 67% yield with the less polar isomer **19** in 21% yield. The diol **18** was protected as di-THP ether **20** and then desilylated by tetra-*n*-butylammonium fluoride to give the corresponding alcohol **21**. Subsequent oxidation of the alcohol with pyridinium dichromate (PDC) afforded the key intermediate **4** in 90% yield.

The completion of the synthesis of isocarbacyclin methyl ester **2** was accomplished by attachment of α-side chain following Ikegami's procedure.[3e,7] The spectral data of **2** thus obtained were in complete agreement with those reported earlier.[3a,c]

In summary, we have developed a new chiral synthetic route to (+)-isocarbacyclin methyl ester **2** starting from tricyclo[3.3.0.$0^{2,8}$]octan-3-one **6**, which is readily available in optically pure form by the triplet sensitized oxadi-π-methane rearrangement from enantiomerically pure bicyclo[3.3.0]oct-5-en-2-one. The efficacy of our synthetic strategy relies upon easy introduction of α-and ω-side chain to a preexisting bicyclo[3.3.0]octane skeleton. The whole synthesis of (+)-isocarbacyclin methyl ester **2** has been carried out in ~10% overall yield starting from tricyclo[3.3.0.$0^{2,8}$]octan-3-one **6**.

Experimental

The ^{1}H-NMR spectra were recorded either on a Gemini Varian-300 (300 MHz), a Bruker AM-200 (200 MHz), or a JEOL JNM-60 (60 MHz) spectometer. Infrared (IR) spectra were obtained on a Analect FX-6160 FT-IR spectrometer using potasium bromide pellet and sodium chloride cell. Mass spectra were recorded on a HP 5988A GC-Mass by electron impact method (EI) at 70 eV. Optical rotations were measured using a Perkin-Elmer 241 Polarimeter at room temperature using the sodium D line. Melting points (mp) were determined on a Thomas-Hoover capillary melting apratus. Elemental analysis was performed by a Perkin-Elmer 240 DS analyzer.

(1*R*, 4*R*, 5*S*)-(−)-4-Carbomethoxytricyclo[3.3.0.$0^{2,8}$]octan-3-one (8). A solution of tricyclooctanone **6**[4a] (3.75 g, 30.6 mmol) in THF (100 m*l*) was treated with potassium-*t*-butoxide (5.16 g, 45.9 mmol) at 0℃, and then treated dropwise with dimethyl carbonate (48.1 g, 534 mmol) for 1 h at the same temperature. The resulting solution was warmed to room temperature and stirred for 3 h. The reaction mixture was cooled to 0℃, quenched with saturated NH_4Cl solution (50 m*l*), and extracted with methylene chloride (20 m*l*×4). The combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford **8** (3.68 g, 67%) as a light yellow oil; $[\alpha]_D$−69.6° (c 0.03, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 3.68 (3H, s), 2.93-3.33 (3H, m), 1.40-2.40 (6H, m); IR (neat) 2955, 2874, 1743, 1718, 1435, 1313, 1251, 1195 cm^{-1}; mass spectrum m/e 180 (M^+), 149, 80 (base) Anal. Calcd. for $C_{10}H_{12}O_3$: C 66.65, H 6.71 found C 66.43, H 6.79.

(1*S*, 2*S*, 5*S*, 6*R*)-(+)-2-Acetoxy-6-carbomethoxybicyclo[3.3.0]octan-7-one (9). A solution of carbomethoxytricyclooctanone **8** (818 mg, 4.53 mmol) in glacial acetic acid (15 m*l*) was treated with conc. H_2SO_4 (0.30 m*l*) at room temperature for 10 min with stirring. After 3 h, conc. H_2SO_4 (0.30 m*l*) was added again to the mixture and stirred further for 2 h. The reaction mixture was diluted with methylene chloride (30 m*l*) and neutralized carefully with saturated Na_2CO_3 solution. The organic layer was separated and the aqueous layer was extracted with methylene chloride (10 m*l*×2). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) to afford 2-acetoxybicloctanone **9** (816 mg, 75%) as a light yellow oil, which solidifies on standing in refrigerator; mp 59-60℃; $[\alpha]_D$+59° (c 0.22 $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 4.90 (1H, m), 3.76 (3H, s), 2.03 (3H, s); IR (KBr) 2957, 2915, 1727, 1658, 1623, 1450, 1253 cm^{-1}; mass spectrum m/e 240 (M^+), 209, 197, 180, 152, 148, 120, 108, 43 (base), 39; Anal. Calcd. for $C_{12}H_{16}O_5$: C 59.99, H 6.71 found C 60.02, H 6.83.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-(+)-2-Acetoxy-7-hydroxy-6-carbomethoxybicyclo[3.3.0]octane (10). A solution of bicyclooctanone **9** (816 mg, 3.39 mmol) in 95% ethanol (20 m*l*) was treated with $NaBH_4$ (257 mg, 6.79 mmol) at −50℃ and stirred for 4 h at the same temperature. The reaction mixture was diluted with methylene chloride (20 m*l*) and quenched with brine. The organic layer was separated and the aqueous layer was extracted with methylene chloride (30 m*l*×2). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (25% ethyl acetate in hexane) to afford **10** (743 mg, 90%) as a colorless oil; $[\alpha]_D$+21° (c 0.03, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 4.92 (1H, bs), 4.20 (1H, bs), 3.73 (3H, s), 3.56 (1H, bs), 2.00 (3H, s); IR (neat) 3445, 2958, 1737, 1437, 1377, 1247, 1201 cm^{-1}; mass spectrum m/e 182 (M^+-AcOH), 149, 43 (base); Anal. Calcd. for $C_{12}H_{18}O_5$: H 7.49 found C 59.11, H 7.62.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-2-Acetoxy-6-carbomethoxy-7-tetrahydropyranyloxybicyclo[3.3.0]octane (11). A solution of 7-hydroxybicyclooctane **10** (400 mg, 1.65 mmol) and pyridinium *p*-toluenesulfonate (41 mg, 0.16 mmol) in methylene chloride (3 m*l*) was treated with dihydropyran (164 mg, 1.95 mmol) and stirred for 24 h. The mixture was diluted with methylene chloride (20 m*l*) and washed successively with saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford **11** (533 mg, 99%) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 4.87 (1H, bs), 4.58 (1H, bs), 3.68 (3H, s), 1.98 (3H, s); IR (neat) 2947, 2871, 1735, 1458, 1376, 1246, 1202, 1135 cm^{-1}; mass spectrum m/e 242 (M^+-THP), 182 (M^+-THP-AcOH), 85.43 (base); Anal. Calcd. for $C_{17}H_{26}O_6$: C 62.56, H 8.03 found: C 62.46, H 8.18.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-6-Carbomethoxy-2-hydroxy-7-tetrahydropyranyloxybicyclo[3.3.0]octane (12). A solution of 2-acetoxybicyclooctane **11** (2.50 g, 7.66 mmol) in absolute methanol (10 m*l*) was treated with anhyd. potassium carbonate (0.16 g, 1.2 mmol) and stirred for 8 h. The mixture

was diluted with diethyl ether (30 m*l*) and quenched with cold NH_4Cl saturated solution (30 m*l*). The organic layer was separated and the aqueous layer was extracted with methylene chloride (30 m*l*×2). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% ethyl acetate in hexane) to afford **12** (2.08 g, 96%) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 4.65 (1H, bs), 4.03 (1H, bs), 3.70 (3H, s); IR (neat) 3442, 2947, 2871, 1735, 1439, 1345, 1271, 1202 cm^{-1}; mass spectrum m/e 253 (M^+-OMe), 200 (M^+-THP), 85 (base); Anal. Calcd. for $C_{15}H_{25}O_5$: C 63.36, H 8.51 found: C 62.98, H 8.69.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-2-*t*-Butyldiphenylsilyloxy-6-hydroxymethyl-7-tetrahydropyranyloxybicyclo[3.3.0]octane (14). A solution of 2-acetoxy-6-methoxycarbonylbicyclooctane **12** (394 mg, 1.38 mmol), imidazole (300 mg, 4.41 mmol) and catalytic amount of 4-dimethylaminopyridine in *N,N*-dimethylformamide (2 m*l*) was treated with chloro *t*-butyldiphenylsilane (607 mg, 2.21 mmol) and stirred at room temperature for 24 h. To the mixture was added water (10 m*l*) and extracted twice with diethyl ether (20 m*l*). The combined organic layer was washed with water (10 m*l*), dried ($MgSO_4$), and concentrated under reduced pressure. The residue, without further purification, was treated with dry toluene (10 m*l*) and cooled to −30℃. To this solution was added dropwise 3.24 m*l* (3.24 mmol) of diisobutylaluminum hydride solution (1 M solution in toluene) and stirred for 2 h. The reaction mixture was quenched by successive and slow addition of ethyl acetate (2 m*l*), methanol (2 m*l*), and water (2 m*l*). The mixture was stirred vigorously at room temperature for 30 min. The resulting solid was filtered through Celite-545 and washed several times with diethyl ether. The combined organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (25% ethyl acetate in hexane) to afford **14** (596 mg, 82% from **12**) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.27-7.65 (5H, m), 4.60 (1H, s), 4.60 (1H, s), 3.60-3.81 (4H, m), 3.42-3.49 (1H, m), 3.14 (9H, s); IR (neat) 3422, 2941, 2858, 1467, 1430, 1361 cm^{-1}: mass spectrum m/e 438 (M^+-*t*-butyl), 283, 199, 85 (base), 77.57; Anal. Calcd. for $C_{30}H_{42}O_4Si$: C 72.83, H 8.56 found: C 72.84, H 8.72.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-2-*t*-Butyldiphenylsilyloxy-6-formyl-7-tetrahydropyranyloxybicyclo[3.3.0]octane (15). To a solution of 2 g of 3 Å molecular sieve and chromium trioxide (1.12 g, 11.25 mmol) in methylene chloride (50 m*l*) was added pyridine (1.82 m*l*, 20.25 mmol) and stirred at room temperature for 30 min. To the mixture was added a solution of hydroxymethylbicyclooctanone **14** (596 mg, 1.20 mmol) in methylene chloride (50 m*l*) and stirred for 2 h. The reaction mixture was diluted with diethyl ether (150 m*l*) and filtered through Celite-545 and washed several times with ether. The combined organic layer was concentrated at low temperature and filtered again through short length (*ca.* 5 cm) silica gel column by washing with diethyl ether. The ether solution was concentrated under reduced pressure to afford **15** (596 mg) in quantitative yield: ^{1}H-NMR ($CDCl_3$) δ 9.63 (1H, d, *J*=2.8 Hz), 7.21-7.40 (10H, m), 4.48 (1H, bs), 1.05 (9H, s); IR (neat) 2932, 2857, 1723, 1466, 1430, 1362, 1260, 1201, 1111 cm^{-1}; mass spectrum m/e 435 (M^+-*t*-butyl), 333, 283, 199 (base), 85, 57, 43, 41; Anal. Calcd. for $C_{30}H_{40}O_4Si$: C 73.13, H 8.18 found: C 73.28, H 8.27.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-2-*t*-Butyldiphenylsilyloxy-6-(3-oxo-(E)-1-octenyl)-7-tetrahydropyranyloxybicyclo[3.3.0]octane (16). A solution of 60% sodium hydride (12 mg, 0.36 mmol) in THF (2 m*l*) was treated with dimethyl (2-oxoheptyl)phosphonate (80 mg, 0.36 mmol) at room temperature and stirred for 30 min. To the mixture was added a solution of aldehyde **15** (127 mg, 0.25 mmol) in THF (2 m*l*) and stirred for 3 h. The reaction mixture was quenched by addition of brine (10 m*l*) and extracted with diethyl ether (20 m*l*×2). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromtography (10% ethyl acetate in hexane) to afford **16** (140 mg, 92%) as a colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.10-7.73 (10H, m), 6.73 (1H, dd, *J*=7.6 Hz, 16.0 Hz), 6.09 (1H, d, *J*=16.0 Hz); IR (neat) 2934, 2856, 1696, 1673, 1628, 1463, 1430, 1363, 1200, 1111 cm^{-1}; mass spectrum m/e 532 (M^+-*t*-butyl), 199, 85 (base) 57, 43, 41; Anal. Calcd. for $C_{37}H_{52}O_4Si$: C 75.47 H, 8.90 found: C 75.23, H 8.0.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-2-*t*-Butyldiphenylsilyloxy-7-hydroxy-6-(3-oxo-(*E*)-1-octenyl)bicyclo[3.3.0]octane (17). To a stirred solution of THP ether **16** (209 mg, 0.35 mmol) in THF (9 m*l*) was added 2 N HCl solution (2 m*l*). After 22 h, the mixture was diluted with CH_2Cl_2 (20 m*l*) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford **17** (170 mg, 96%) as an oil; $[\alpha]_D$ +25° (c 0.016, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.26-7.76 (10H, m), 6.76 (1H, dd, *J*=8 Hz, *J*=16 Hz), 6.25 (1H, d, *J*=16 Hz), 4.03 (1H, bs), 3.13-3.80 (1H, m), 1.06 (9H, s); mass spectrum m/e 486 (M^+-H_2O), 447 (M^+-*t*-butyl), 199 (base), 85, 57, 43, 41.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-(+)-*t*-Butyldiphenylsilyloxy-7-hydroxy-6-[3*S*-hydroxy-(*E*)-octenyl]bicyclo[3.3.0]octane (18). To a stirred solution of 2,6-*t*-butyl-4-methylphenol (413 mg, 1.87 mmol) in dry toluene (5 m*l*) at −4℃ was added diisobutylaluminum hydride (1.87 m*l*, 1 M solution in toluene, 1.87 mmol) for 5 min under N_2 atmosphere. The resulting colorless solution was stirred at −5-5℃ for 1 h, then cooled to −78℃. To this solution was added a solution of enone **17** (94 mg, 0.187 mmol) in dry toluene (1 m*l*). The solution was changed to orange color. The mixture was gradually raised to −10℃ over 2 h, and changed to pale yellow. The reaction mixture was quenched by addition of water (1 m*l*), and vigorously stirred at room temperature for 2 h. The precipitate was removed by filtration and washed with EtOAc (15 m*l*). The combined filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was separated by flash column chromatography (30% ethyl acetate in hexane) to give the desired 15α-diol **18** (64 mg, 67%) as a more polar fraction and the 15β-diol **19** (21 mg, 22%) as a less polar fraction. Spectral data of **18**: $[\alpha]_D$ +10° (c 0.02, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.24-7.65 (10H, m), 5.34-5.45 (2H, m), 3.96 (2H, m), 3.47 (1H, m), 2.22 (2H, m), 1.04 (9H, s), 0.76 (3H, t, *J*=6 Hz); IR (neat) 3300, 2932, 2859, 1465, 1429, 1109, 1061, 1029 cm^{-1}; mass spectrum m/e 450 (M^+-*t*-butyl), 233, 199 (base), 91, 57, 43, 41. The spectral data of **19** were nearly identical with those of **18** except the optical rotation.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-2-*t*-Butyldiphenylsilyloxy-7-tetrahydropyranyloxy-6-[3*S*)-tetrahydropyranyloxy-(*E*)-1-octenyl]bicyclo[3.3.0]octane (20). To a stirred solution of diol **18** (196 mg, 0.38 mmol) and pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol) in CH_2Cl_2 (1 m*l*) was added dihydropyran (98 mg, 1.16 mmol). After 12 h, the mixture was concentrated under reduced pressure and purified by flash column chromatography (5% ethyl acetate in hexane) to give the di-THP ether **20** in quantitative yield: ^{1}H-NMR ($CDCl_3$) δ 7.32-7.65 (10H, m), 5.28-5.59 (2H, m), 4.55-4.69 (2H, m), 2.22-2.26 (2H, m), 1.03 (9H, s); IR (neat) 2933, 2857, 1463, 1433, 1201, 1112, 1069, 1024 cm^{-1}; mass spectrum m/e 515, 431, 199, 85 (base, THP), 57, 43, 41.

(1*S*, 2*S*, 5*S*, 6*R*, 7*R*)-2-Hydroxy-7-tetrahydropyranyloxy-6-[(3*S*)-tetrahydropyranyloxy-(*E*)-1-octenyl]bicyclo[3.3.0]octane (21). To a stirred solution of TBDPS-ether **20** (261 mg, 0.38 mmol) in THF (1 m*l*) was added tetra-*n*-butylammonium fluoride (1 m*l*, 1M solution in THF, 1 mmol). After 24 h, the mixture was concentrated under reduced pressure and purified by flash column chromatography (60% ethyl acetate in hexane) to give the alcohol **21** in quantitative yield: ^{1}H-NMR ($CDCl_3$) δ 5.29-5.65 (2H, m), 4.64-4.73 (2H, m), 3.45-4.02 (7H, m), 0.88 (3H, t, J=3 Hz); IR (neat) 3400 cm^{-1}; mass spectrum m/e 317, 250, 232, 206, 85, 43, 41.

(1*S*, 5*R*, 6*R*, 7*R*)-2-oxo-7-tetrahydropyranyloxy-6-[(3*S*)-tetrahydropyranyloxy-(*E*)-1-octenyl]bicyclo[3.3.0]octane (4). To a stirred solution of the alcohol **21** (168 mg, 0.38 mmol) in *N,N*-dimethylformamide (2 m*l*) was added pyridinium dichromate (447 mg, 1.18 mmol). After 19 h, the mixture was poured into ice water and washed with ether (2×20 m*l*). The combined ethereal layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford the ketone **4** (147 mg, 90%): ^{1}H-NMR ($CDCl_3$) δ 5.25-5.56 (2H, m), 4.56-4.65 (2H, m), 3.75-4.05 (m, 2H); IR (neat) 2933, 2870, 1789, 1457, 1345, 1201, 1130 cm^{-1}.

(1*S*, 5*R*, 6*R*, 7*R*)-2-Oxo-7-tetrahydropyranyloxy-6-[(3S)-tetrahydropyranyloxy-(*E*)-1-octenyl]bicyclo[3.3.0]octane-$\Delta^{3,5}$-pentanoate (23). To a stirred solution of diisopropylamine (80 μ*l*, 0.46 mmol) in THF (1 m*l*) was added a 1.6 M solution of *n*-butyl lithium in hexane (288 μ*l*, 0.46 mmol) at −78℃ for 30 min. After 10 min, a solution of ketone **4** (100 mg, 0.23 mmol) in THF (5 m*l*) was added slowly. After 10 min, hexamethylphosphoramide (HMPA) (82 mg, 0.46 mmol) was added to the enolate mixture. After additional 30 min at −78℃, a solution of methyl 5-oxopentanoate[8] **22** (60 mg, 0.46 mmol) in THF (1 m*l*) was added. The mixture was stirred at −78℃ for 1 h and then slowly warmed to −40℃ for 2 h. The mixture was quenched by addition of NH_4Cl saturated solution (3 m*l*) and diluted with ether (10 m*l*). The mixture was washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in benzene (3 m*l*) and treated with triethylamine (64 μ*l*, 0.46 mmol) and methanesulfonyl chloride (33 μ*l*, 0.46 mmol). After 1 h, the mixture was treated with 1,5-diazabicyclo[5.4.0]undec-7-ene (DBU, 146 μ*l*, 1.46 mmol) and stirred overnight. The reaction mixture was diluted with ether and washed with saturated $NaHCO_3$ solution, water, brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% ethyl acetate in hexane) to afford the enone **23** (88 mg, 70%): ^{1}H-NMR ($CDCl_3$); δ 6.35-6.58 (1H, m), 5.30-5.62 (2H, m), 4.61-4.69 (2H, m), 4.03 (2H, m), 3.87 (2H, m), 3.67 (3H, s), 3.47 (2H, m); IR (neat) 2933, 2865, 1739, 1645, 1440, 1376 cm^{-1}.

Methyl 5-(phenoxycarbonylthio)-5-[(1*S*, 5*S*, 7*R*, 8*R*)-7-tetrahydropyranyloxy-8-((3*S*)-tetrahydropyranyloxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-en-3-yl]pentanoate (24). A solution of the enone **23** (42 mg, 0.076 mmol) and cerium chloride heptahydrate (28 mg, 0.076 mmol) in MeOH (2 m*l*) was cooled to −30℃ and treated with $NaBH_4$ (3 mg, 0.077 mmol). After 30 min, the reaction mixture was quenched by addition of brine and washed with ether (2×10 m*l*). The ethereal solution was dried ($MgSO_4$) and concentrated under reduced pressure to give the nearly pure allylic alcohol (**23-1**). Without further purification, the allylic alcohol dissolved in CH_3CN (1 m*l*) and treated with phenyl thionochlorocarbonate (23 mg, 0.135 mmol) and 4-dimethylaminopyridine (DMAP, 83 mg, 0.67 mmol) and stirred overnight. The mixture was diluted with ether (5 m*l*) and filtered to remove DMAP and its salt. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (15% ethyl acetate in hexane) to afford a rearranged thiol-carbonate (**24**, 48 mg, overall 92%). **23-1**: ^{1}H-NMR ($CDCl_3$) δ 5.27-5.67 (2H, m), 3.67 (3H, s); IR (neat) 3455, 2932, 2856, 1741, 1440, 1132 cm^{-1}: **24**; ^{1}H-NMR ($CDCl_3$) δ 7.15-7.40 (5H, m), 5.35-5.63 (3H, m), 3.93-4.12 (2H, m), 3.74-3.91 (3H, m), 3.67 (3H, s), 3.43-3.50 (2H, m), 3.00-3.05 (1H, m), 2.51-2.57 (1H, m), 0.88 (3H, t, J=6 Hz); IR (neat) 2932, 2865, 1795, 1490, 1440, 1347, 1255, 1192 cm^{-1}; mass spectrum m/e 498, 454, 345, 85 (base), 77, 67, 57, 55, 43.

Methyl 5-[(1*S*, 5*S*, 7*R*, 8*R*)-7-tetrahydropyranyloxy-8-((3*S*)-tetrahydropyranyloxy-(*E*)-1-octenyl)bicyclo[3.3.0]oct-2-ene-3-yl]pentanoate (25). To a solution of thiol-carbonate (**24**, 15 mg, 0.02 mmol) and catalytic amount of azobisisobutyronitrile (AIBN) in benzene (2 m*l*) was added tributyltin hydride (17 mg, 0.06 mmol) and refluxed overnight. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (15% ethyl acetate in hexane) to give the reduced product (**25**, 10 mg, 86%): ^{1}H-NMR ($CDCl_3$) δ 5.25-5.60 (3H, m), 4.66-4.72 (2H, m), 3.69-4.06 (m, 4H), 3.67 (3H, s), 3.42-3.45 (2H, m), 2.92-3.03 (1H, m), 0.88 (3H, t, J=6 Hz); IR (neat) 2937, 2870, 1741, 1440, 1350, 1201, 1162 cm^{-1}.

9(O)-Methano-$\Delta^{6,9(a)}$-PGI$_1$ methyl ester (Isocarbacyclin methyl ester) (2). The di-THP ether **25** (15 mg, 0.028 mmol) was dissolved in 1 m*l* of AcOH/THF/H_2O (3 : 1 : 1) and stirred at room temperature for 36 h. The solvent was removed *in vacuo* and purified by flash column chromatography (50% ethyl acetate in hexane) to afford the isocarbacyclin methyl ester **2** (8 mg, 84%): ^{1}H-NMR ($CDCl_3$) δ 5.54-5.57 (2H, m), 5.30 (1H, s), 4.07-4.10 (1H, m), 3.69-3.79 (1H, m), 3.68 (3H, s), 3.00 (1H, m), 0.90 (3H, t, J=6 Hz); IR (neat) 3321, 2926, 2860, 1740, 1442, 1256, 1203, 1170, 1085, 970 cm^{-1}; mass spectrum m/e 346 (M^+-H_2O), 328 (M^+-2H_2O), 315 (M^+-H_2O-OMe), 302, 180, 179, 178, 148, 145, 133, 132, 131, 129, 119, 107, 106, 105, 99, 95, 94, 92, 91, 81, 80, 779, 71, 67, 55, 43 (base), 41, 39.

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7. The key intermediate enone **4** was converted to isocarbacyclin methyl ester **2** by the following method.[3e] 1. LDA/THF-HMPA/methyl 5-oxopentanoate[8], MsCl/DBU; 2. $NaBH_4/CeCl_3$; 3. phenyl thionochlorocarbonate/CH_3CN; 4. n-Bu_3SnH/AIBN; 5. AcOH/THF/H_2O. In the aldol condensation step, the yield could be improved up to 70% by the use of HMPA (42% in the absence of HMPA); see experimentals.
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A Study on Spin-Lattice Relaxation of ^{19}F Spins in Benzotrifluoride: Contributions from Dipole-Dipole Interaction and Spin-Rotation Interaction

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In this work we have studied the spin-lattice relaxation of ^{19}F spins in benzotrifluoride in our quest for a reliable method of discriminating the contribution due to dipolar relaxation mechanism from that due to spin-rotational mechanism for nuclear spins located on methyl or substituted methyl group in organic molecules. Over the temperature range of 248-268 K the decay of normalized longitudinal magnetization was found to be well described by a two-parameter equation of the form

$$R(t)=\exp(-st)\left\{\frac{5}{6}\exp(-s_1t)+\frac{1}{6}\right\}$$

which was derived under the assumption that interactions in the A_3 spin system are modulated randomly and predominantly by internal rotational motions of $-CF_3$ top, and it was shown that the separation of contribution due to dipolar interactions from that due to spin-rotation interaction could be successfully achieved by least-square fitting of observed data to this equation. The results indicate that the spin-rotational contribution is overwhelmingly larger than that of dipolar origin over the given temperature range and becomes more deminating at higher temperature.

Introduction

Study of the magnetic relaxation mechanisms for a nuclear spin (or spins) located on a molecule often yields invaluable information regarding the dynamics of this molecule in bulk phase.[1,2] Among several relaxation mechanisms for a nuclear spin (or spins) of $I=1/2$ those due to intra- and intermolecular magnetic dipole-dipole interactions are usually dominant ones, but for a spin (or spins) in a rapidly rotating small molecule or internal rotor such as methyl group the spin-rotation interaction is also known to make appreciable contribution to its (or their) relaxation.[3] Study of dipolar mechanism is well known to provide us with the information related to the modulation of internuclear distance vectors whereas that of spin-rotation mechanism unveils the dynamics of modulation of molecular rotational angular momentum vectors.[4] Therefore, it is important to separate the contribution due to the former from that originating from the latter. Previously, this separation was often achieved in liquid by means of observing the nuclear magnetic relaxation as a function of temperature and then relating this temperature dependence to that of the solvent (or solution) viscosity.[5,6] However, there has been lingering skepticism, or even criticism, over the use of macroscopic quantities like viscosity

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