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A NOVEL ROUTE TO A KEY PRECURSOR IN THE SYNTHESIS OF (+)-ISOCARBACYCLIN

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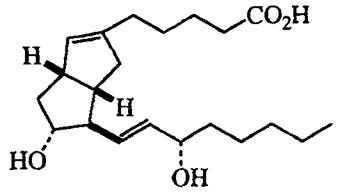
Abstract: A new synthetic route to a key intermediate for the synthesis of (+)-isocarbacyclin is described.

Isocarbacyclin[9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1] **1** has been shown to be the most attractive analog of prostacyclin (PGI_2), a potent inhibitor of human platelet aggregation.[1] Due to its therapeutic utility as an antithrombotic agent, a number of synthetic methods for **1** have been reported.[2~4] In connection with our efforts to develop new synthetic methods for prostaglandins, we report herein a new synthesis of a key precursor **10**.[5]



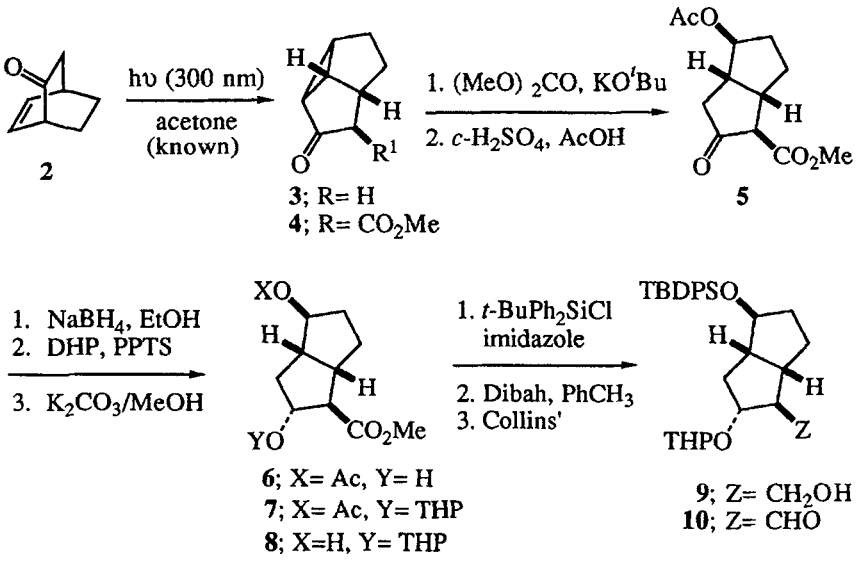
1; (+)-Isocarbacyclin

A key feature of our approach is to utilize (-)-tricyclo[3.3.0.$0^{2,8}$]octan-3-one **3**,[6] which contains a preexisting bicyclo[3.0.0]octane skeleton and is readily available in optically pure form by the triplet sensitized oxadi-π-methane rearrangement of enantiomerically pure bicyclo[2.2.2]oct-5-en-2-one **2**.[6a]

Regio- and stereoselective introduction of the carbomethoxy group, a unit which is necessary for the construction of ω-side chain of isocarbacyclin, was achieved in 67% yield by simply treating **3** with dimethyl carbonate in the presence of potassium *t*-butoxide. Upon treatment of **4** with acetic acid and concentrated sulfuric acid, the oxygen functionality was introduced with concomitant opening of the cyclopropane ring to produce **5** in 75% yield.

Subsequent reduction of **5** with $NaBH_4$ in ethanol proceeded with excellent stereoselectivity to give **6** in 90% yield. Protection of the alcohol **6**

Scheme



2

3; R= H
4; R= CO_2Me

5

6; X= Ac, Y= H
7; X= Ac, Y= THP
8; X=H, Y= THP

9; Z= CH_2OH
10; Z= CHO

as its THP ether followed by deacetylation (K_2CO_3/MeOH) afforded the alcohol **8** in 95% yield. Alcohol **8** was then converted into the aldehyde **10**[5] in 82% overall yield by a standard three-step sequence of reactions as indicated in the scheme.

In this way a new chiral route to a key precursor for the synthesis of (+)-isocarbacyclin was developed.

EXPERIMENTAL

(1*R*,4*R*,5*S*)-(-)-4-Carbomethoxytricyclo[3.3.0.0^{2,8}]octan-3-one (4)

A solution of of tricyclooctanone **3**[6a] (3.75 g, 30.6 mmol) in THF (100 mL) at 0 °C was treated with potassium *t*-butoxide (5.16 g, 45.9 mmol), and dimethyl carbonate (48.1 g, 53.4 mmol) was added dropwise. The resulting solution was stirred for 1 h at the same temperature and for 3 h at the room temperature. The reaction mixture was cooled to 0 °C, quenched with a saturated NH_4Cl solution (50mL). The mixture was extracted with methylene chloride (5 x 20 mL). The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford 3.68 g (66.5%) of **4** as a light yellow oil; $[\alpha]_D$ -69.6° (c 0.03, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H), 2.93-3.33 (m, 3H), 1.40-2.40 (m, 6H); IR (neat) 2955, 2874, 1743, 1718, 1435, 1313, 1251, 1159 cm^{-1}; MS 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 (5)

A solution of carbomethoxytricyclooctanone **4** (818 mg, 4.53 mmol) in glacial acetic acid (15 mL) was treated with concentrated H_2SO_4 (0.3 mL) at

room temperature for 10 min. After 3 h, additional concentrated H_2SO_4 (0.3 mL) was added and the mixture stirred for 2 h. The reaction mixture was diluted with methylene chloride (30 mL) and neutralized carefully with a saturated Na_2CO_3 solution. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexane) to afford 816 mg (75%) of 2-acetoxybicyclooctanone **5** as a light yellow oil, which solidified on standing in the refrigerator; m.p. 59-60 °C; $[\alpha]_D$ +59° (c 0.22, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.90 (m, 1H), 3.76 (s, 3H), 2.03 (s, 3H); IR (KBr) 2957, 2915, 1727, 1658, 1623, 1450, 1253 cm^{-1}; MS 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-carbomethoxy-bicyclo[3.3.0]octane (6)

A solution of bicyclooctanone **5** (816 mg, 3.39 mmol) in 95% ethanol (20 mL) was treated with $NaBH_4$ (257 mg, 6.79 mmol) at -50 °C for 4 h. The reaction mixture was diluted with methylene chloride (20 mL) and quenched with brine (20 mL). The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chreomatography (25% ethyl acetate in hexane) to afford 743 mg (90%) of **6** as a colorless oil: [α] +21° (c 0.03, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.92 (br s, 1H), 4.20 (br s, 1H), 3.73 (s, 3H), 3.56 (br s, 1H), 2.00 (s, 3H); IR (neat) 3445, 2958, 1737, 1437, 1377, 1247, 1201 cm^{-1}; MS m/e 182 (M^+ - AcOH), 149 (M^+ - OMe), 43 (base).

(1*S*,2*S*,5*S*,6*R*,7*R*)-2-Acethoxy-6-carbomethoxy-7-tetrahydropyranyloxybicyclo[3.3.0]octane (7)

A solution of 7-hydroxybicyclooctane **6** (400 mg, 1.65 mmol) and pyridinium *p*-toluenesulfonate (41 mg, 0.16 mmol) in methylene chloride (3 mL) was treated with dihydropyran (164 mg, 1.95 mmol) for 24 h. The reaction mixture was diluted with methylene chloride (20 mL) and washed with a saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (20% ethyl acetate in hexane) to afford 533 mg (99%) of **7** as a colorless oil: ^1H NMR ($CDCl_3$) δ 4.87 (br s, 1H), 4.58 (br s, 1H), 3.68 (s, 3H), 1.98 (s, 3H); IR (neat) 2947, 2871, 1735, 1458, 1376, 1246, 1202, 1135 cm^{-1}; MS 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 (8)

A solution of 2-acetoxybicyclooctane **7** (2.50 g, 7.66 mmol) in absolute methanol (10 mL) was treated with anhydrous potassium carbonate (0.16 g, 1.2 mmol) for 8 h. The mixture was diluted with diethyl ether (30 mL), and quenched with cold saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 30 mL). The combine organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (50% ethyl acetate in hexane) to afford 2.08 g (96.5%) of **8** as a colorless oil: ^1H NMR ($CDCl_3$) δ 4.65 (br s, 1H), 4.03 (br s, 1H), 3.70 (s, 3H); IR (neat) 3442, 2947, 2871, 1735, 1439, 1345, 1271, 1202 cm^{-1}; MS m/e 253 (M^+ - OMe), 200 (M^+ - THP), 85 (base).

(1*S*,2*S*,5*S*,6*R*,7*R*)-2-*t*-Butyldiphenylsilyloxy-6-hydroxymethyl-7-tetrahydropyranyloxybicyclo[3.3.0]octane (9)

A solution of 2-acetoxyme-6-carbomethoxybicyclooctane **8** (394 mg, 1.38 mmol), imidazole (300 mg, 4.41 mmol), and catalytic amount of *N,N*-dimethylamino-pyridine in *N,N*-dimethylformamide (2 mL) was treated with chloro *t*-butyl-diphenylsilane (607 mg, 2.21 mmol) at the room temperature for 24 h. Water (10 mL) was added, and the mixture was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue, without further purification, was dissolved in dry toluene (10 mL), and cooled to -30 °C. To this solution was added dropwise diisobutylaluminum hydride (3.24 mL of 1 M in toluene, 3.24 mmol) and the solution was stirred for 2 h. The reaction mixture was quenched by successive and slow addition of ethyl acetate (2 mL), methanol (2 mL), and water (2 mL). The mixture was stirred vigorously at room temperature for 30 min. The resulting solid was filtered off with the aid of Celite 545. The filtrate was dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (25% ethyl acetate in hexane) to afford 596 mg (82%) of **9** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.27-7.65 (m, 5H), 4.60 (s, 1H), 4.60 (s, 1H), 3.60-3.81 (m, 4H), 3.42-3.49 (m, 1H), 3.14 (s, 9H); IR (neat) 3422, 2941, 2858, 1467, 1430, 1361 cm^{-1}; MS 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*-Butyldimethylsilyloxy-6-formyl-7-tetrahydropyranyloxybicyclo[3.3.0]octane (10)

To a suspension of 3 Å molecular sieves (2 g) and chromium trioxide (1.12 g, 11.25 mmol) in methylene chloride (50 mL) was added pyridine (1.82

ml, 20.25 mmol) and the mixture was stirred at room temperature for 30 min. A solution of 6-hydroxymethylbicyclooctanone **9** (596 mg, 1.20 mmol) in methylene chloride (50 mL) was added and the mixture was stirred for additional 2 h. The reaction mixture was diluted with diethyl ether (150 mL), and filtered through Celite 545. The filtrate was concentrated, and the residue was purified by filtration though a short silica gel column to afford 596 mg (quantitative yield) of **10**: ^{1}H NMR ($CDCl_3$) δ 9.63 (d, J = 2.8 Hz, 1H), 7.21-7.40 (m, 10H), 4.48 (br s, 1H), 1.05 (s, 9H); IR (neat) 2932, 2857, 1723, 1466, 1430, 1362, 1260, 1201, 1111 cm^{-1}; MS 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.

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5. Compound **10** has been transformed into (+)-isocabacyclin methyl ester in this group. The physical and spectral data of (+)-isocarbacyclin methyl ester synthesized in this group were in complete agreement with those reported earlier.[3e]

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