HETEROCYCLES, Vol. 53, No. 3, 2000, pp. 733 - 737, Received, 22nd November, 1999

SHORT STEP SYNTHESIS OF (4*R*)-4-HYDROXYMETHYL-4-METHYL-2-HEXENE-1,5-DIOL: A USEFUL CHIRAL SYNTHON FOR NATURAL PRODUCT SYNTHESIS WITH QUATERNARY CARBON CENTER

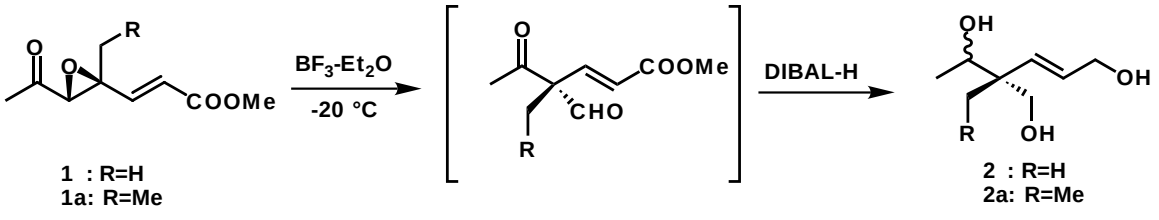
Kunisuke Okada,* Daisuke Nakamura, and Yuhji Hattori

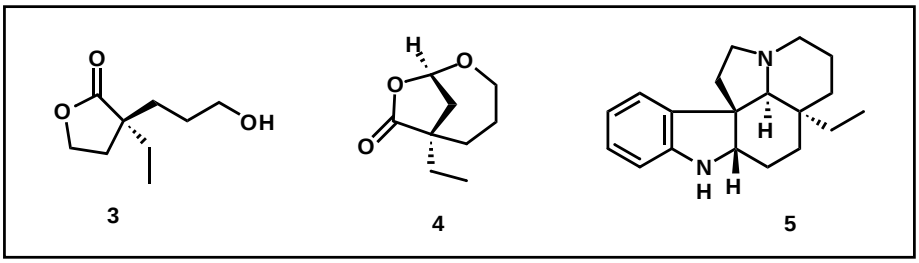
Faculty of Pharmacy, Meijo University, Tenpaku, Nagoya 468-8503, Japan

Abstract - A chiral synthon (**2**), prepared previously *via* 1,2-acyl migration of the optically active α,β-epoxy ketone (**1**), was synthesized from Koga's chiral keto ester (**6**) in 4 steps.

In the previous paper, we reported the synthesis of the titled compound (**2**) *via* 1,2-acyl migration of the optically active α,β-epoxy ketone (**1**) as shown in Figure 1.[1] The triol (**2a**), synthesized *via* similar way, was successfully transformed into lactones (**3**) and (**4**), the key intermediate for *Aspidosperma* and *Hunteria* type indole alkaloids.[2] This C9-chiral synthon (**2a**) was also utilized for the synthesis of pentacyclic ring system of (-)-aspidospermidine (**5**).[3] (Figure 1)

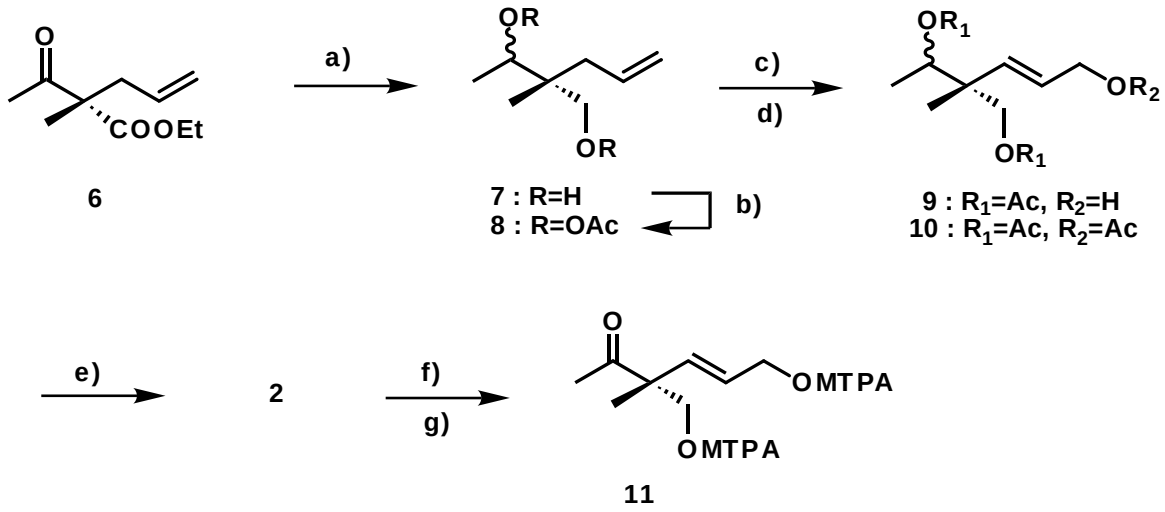
Figure 1





This paper deals with an alternative synthesis of **2** starting from Koga's chiral keto ester (**6**) [4] in 4 steps which is summarized in Scheme 1. Reduction of **6** ($[\alpha]_D^{25}$ -26.8° (c 0.53, $CHCl_3$), 90 % ee; lit.,[4] $[\alpha]_D^{22}$ -27.9° ($CHCl_3$), 94 % ee) with lithium aluminum hydride in ether at 0 ℃ produced the diol (**7**) as a mixture of diastereoisomer (1:1) in 92 % yield. Acetylation of **7** with acetic anhydride in pyridine gave **8** in 94 % yield. Treatment of **8** with mercuric diacetate (1.1 equiv.) in acetic acid at 140 ℃ for 4 h followed by demercuriation mediated by $NaBH_4$-O_2 in *N*,*N*-dimethylformamide afforded a mixture, which was separated by flash column chromatography on silica gel, to give diacetate (**9**) (23.6 %) and triacetate (**10**) (15.8 %) along with starting material (**8**) (52 %).[5] Alkaline hydrolysis of **9** and **10** afforded the desired triol in quantitative yield. The triol (**2**) thus obtained was converted into di-MTPA ester by treatment with 1.9 equiv. of (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride[6] in pyridine and the desired product was followed by oxidation with pyridinium chlorocromate in dichloromethane, giving rise to the ketone (**11**). ^{1}H-NMR spectrum of **11** was in complete agreement with that of the authentic sample derived from **1** *via* 1,2-acyl migration reaction. The optical purity of **11** was also confirmed by an NMR to be 90 % ee, based on two singlets appeared at 2.02 and 2.00 ppm with an integral ratio of 95:5. The epimer at quaternary carbon center of **2** is also available from the enantiomer of **6** under the same conditions.

Scheme 1



Reagents: a) LAH / Et_2O, 0 °C, 3.5 h; b) Ac_2O / py, 40 °C, 2 h; c) $Hg(OAc)_2$ / AcOH, 140 °C, 4 h; d) $NaBH_4$ - O_2 / DMF, rt, 1 h; e) NaOH / MeOH, rt, 2 h; f) MTPA-Cl / py, rt, 1.5 h; g) PCC / CH_2Cl_2, rt, 8 h

EXPERIMENTAL

Spectra were recorded by the following instruments: IR spectra, JASCO IRA-1 spectrophotometer; MS spectra, JEOL MS-700 and HX-110 spectrometer; NMR spectra, JEOL A-400 spectrometer. The chemical shifts are expressed in ppm (δ) downfield from tetramethylsilane as internal standard. Column chromatography was performed on Wakogel C-300 (flash column chromatography). TLC was carried out on Kieselgel 60F254 plates (Art. 5744, Merck). Unless otherwise noted, all reaction mixtures were dried, after work up, over anhydrous Na_2SO_4.

Reduction of 6

To a suspension of LAH (2.30 g, 60.65 mmol) in ether (500 mL) cooled at 0 ℃ was added a solution of **6** (11.16 g, 60.65 mmol) in ether (100 mL) dropwise during 20 min and the mixture was stirred at 0 ℃ for 3.5 h. After acidified with 1N HCl (about 200 mL) at 0 ℃, the water layer of the mixture was further extracted with ether (300 mL x 3). The combined ether extracts were washed with saturated $NaHCO_3$ solution, brine and dried. Evaporation of ether under reduced pressure gave an oil which was purified by flash column chromatography on silica gel with CH_2Cl_2-MeOH (100:3 v/v) as eluent, giving a diastereomeric mixture (1:1) of **7** (8.035 g, 92 %) as an oil. IR (film) 3300 (br), 2960, 1640, 1030 cm^{-1}; MS m/z 144 (M^+); ^{1}H-NMR ($CDCl_3$, 400 MHz) 0.80 and 0.84 (3H, s), 1.19 and 1.21 (3H, d, J=6.9 Hz), 1.97 (1H, dd, J=13.8, 7.4 Hz), 2.33 (1H, dd, J=13.8, 7.4 Hz), 3.45 and 3.50 (1H, d, J=11.0 Hz), 3.66 and 3.70 (1H, d, J=11.0 Hz), 3.82 (1H, m), 5.10 (2H, m), 5.89 (1H, m).

Acetylation of 7

To a solution of **7** (248 mg, 1.72 mmol) in pyridine (2.5 mL) was added acetic anhydride (2 mL) and the mixture was warmed at 40 ℃ for 2 h which was then poured into an ice-water (20 mL) and stirred at rt for 1 h. Extracts of the mixture with ethyl acetate (30 mL x 3) were washed with saturated $NaHCO_3$ solution, brine and dried. Evaporation of the solvent gave an oil which was purified by flash column chromatography on silica gel with hexane-AcOEt (4:1 v/v) as eluent, to give a diastereomeric mixture (1:1) of diacetate (**8**) (368.6 mg, 94 %) as an oil. IR (film) 2960, 1730, 1370, 1230, 1035 cm^{-1}; MS m/z 228 (M^+); ^{1}H-NMR ($CDCl_3$, 400 MHz) 0.917 and 0.931 (3H, s), 1.180 and 1.182 (3H, d, J=6.4 Hz), 2.029 and 2.041 (3H, s), 2.055 and 2.059 (3H, s), 3.836 and 3.840 (1H, d, J=11.5 Hz), 3.984 and 4.022 (1H, d, J=11.5 Hz), 4.906 and 4.929 (1H, q, J=6.4 Hz), 5.03-5.09 (2H, m), 5.74-5.81 (1H, m); *Anal.* Calcd

for $C_{12}H_{20}O_4$: C, 63.12; H, 8.84 %, Found: C, 62.83; H, 8.41 %.

Mercuration and demercuration of 8

To a solution of **8** (563.1 mg, 2.47 mmol) in acetic acid (20 mL) was added mercuric diacetate (866.8 mg, 2.72 mmol) and the mixture was heated at 140 ℃ for 4 h. After evaporation of the solvent, the residue was dissolved in 1N HCl (50 mL) and extracted with ethyl acetate (100 mL x 2). The combined extracts were washed with saturated $NaHCO_3$ solution, brine, dried and concentrated. The solution of the residual oil in *N*,*N*-dimethylformamide (10 mL) was added dropwise to a suspension of $NaBH_4$ (187.0 mg, 4.94 mmol) in *N*,*N*-dimethylformamide (20 mL) under flashing of oxygen gas at rt. After 1 h, the precipitates were filtered by using a short column of Hyflo Super Cel, which was washed with small volume of *N*,*N*-dimethylformamide. The combined filtrates were diluted with ethyl acetate (400 mL) and the mixture was washed with water (80 mL x 5), saturated $NaHCO_3$ solution, brine and dried and then concentrated. The residual mixture was separated by flash column chromatography on silica gel using a mixture of hexane-AcOEt (3:1 v/v) as a solvent, to give a starting material (**8**) (292.8 mg, 52 %), a diastereomeric mixture (1:1) of diacetate (**9**) (142.4 mg, 49.2 %) and triacetate **10** (111.3 mg, 32.8 %) as an oil, respectively. **9:** IR (film) 3400 (br), 2960, 1730, 1370, 1240, 1050, 1035 cm^{-1}; MS m/z 244 (M^+); ^{1}H-NMR ($CDCl_3$, 400 MHz) 1.090 and 1.099 (3H, s), 1.130 and 1.133 (3H, d, J=6.4 Hz), 2.04 (3H, s), 2.05 (3H, s), 3.80 and 3.82 (1H, d, J=11.0 Hz), 4.09-4.18 (3H, m), 4.96 and 5.00 (1H, q, J=6.4 Hz), 5.70-5.76 (2H, m); HRMS (EI) Calcd for $C_{12}H_{20}O_5$ (M^+) 244.1315, Found 244.1344. **10:** IR (film) 2970, 1730, 1725, 1370, 1235, 1050, 1030 cm^{-1}; MS m/z 286 (M^+); ^{1}H-NMR ($CDCl_3$, 400 MHz) 1.089 and 1.098 (3H, s), 1.126 and 1.128 (3H, d, J=6.4 Hz), 2.037 (3H, s), 2.049 (3H, s), 2.076 (3H, s), 3.789 and 3.835 (1H, d, J=11.0 Hz), 4.079 and 4.156 (1H, d, J=11.0 Hz), 4.570 and 4.582 (2H, br.s), 4.956 and 4.994 (1H, q, J=6.4 Hz), 5.63-5.71 (1H, m), 5.749 and 5.811 (1H, d, J=16.0 Hz); HRMS (EI) Calcd for $C_{14}H_{22}O_6$ (M^+) 286.1415, Found 286.1419.

Hydrolysis of acetates (9) and (10)

Diacetate (**9**) (244 mg, 1.0 mmol) was dissolved in 1N KOH in MeOH (10 mL) and the solution was allowed to stand at rt for 2 h. After neutralized with 1N HCl in MeOH, the mixture was concentrated under reduced pressure. The residue was dissolved in 10% MeOH in CH_2Cl_2 and the solution was filtered through a short column of Hyflo Super Cel. The filtrate was concentrated again and the residual

oil was purified by chromatography on silica gel with CH_2Cl_2-MeOH (10:1 v/v) as eluent, yielding a diastereomeric mixture (1:1) of triol (**2**) (157.1 mg, 98%) as an oil. Under the similar way, triacetate (**10**) was converted into **2** in 98% yield. MS m/z 160 (M^+); ^{1}H-NMR ($CDCl_3$, 400 MHz) 0.96 and 1.02 (3H, s), 1.13 and 1.16 (3H, d, J=6.4 Hz), 3.64 (2H, br s), 3.72-3.89 (1H, m), 4.12-4.20 (2H, m), 5.65-5.75 (2H, m).

Di-MTPA ester of 2

To a solution of **2** (5.7 mg, 0.0356 mmol) in CH_2Cl_2 (0.4 mL) was added pyridine (0.02 mL) and MTPA chloride (0.013 mL, 0.069 mmol) at 0 ℃ and the mixture was stirred at rt for 1.5 h. After dilution with CH_2Cl_2, the mixture was washed with 1N HCl, H_2O, saturated $NaHCO_3$ solution, brine and dried and then concentrated. The residue was purified on silica gel TLC (hexane-AcOEt=2:1 v/v) to give a di-MTPA ester of **2** as an oil which was followed by oxidation with PCC (28.4 mg, 0.132 mmol) in dichloromethane (1 mL) at rt for 8 h, providing a ketone (**11**) (oil, 15.6 mg, 74.3 %). IR (film) 2940, 1730, 1705, 1230, 1160, 1020 cm-1; ^{1}H-NMR ($CDCl_3$, 400 MHz) 1.28 (3H, s), 2.02 (3H, s), 3.48 (3H, s), 3.53 (3H, s), 4.33 (1H, d, J=11.1 Hz), 4.40 (1H, d, J=11.1 Hz), 4.73 (1H, dd, J=13.4, 5.4 Hz), 4.81 (1H, dd, J=13.4, 5.4 Hz), 5.72 (1H, m), 5.79 (1H, d, J=16.0 Hz), 7.35-7.51 (10H, m); HRMS (FAB) Calcd for $C_{28}H_{29}O_7F_6$ 591.1816 (MH^+); Found 591.1841.

REFERENCES

1. K. Okada, T. Katsura, H. Tanino, H. Kakoi, and S. Inoue, *Chem., Lett.*, **1994**, 157.
2. K. Okada, K. Murakami, H. Tanino, H. Kakoi, and S. Inoue, *Heterocycles*, **1996**, *43*, 1735.
3. K.Okada, K. Murakami, and H. Tanino, *Tetrahedron*, **1997**, *53*, 14247.
4. K. Tomioka, K. Ando, Y. Takemasa, and K. Koga, *J. Am. Chem. Soc.*, **1984**, *106*, 2718.
5. C. L. Hill and G. M. Whitesides, *J. Am. Chem. Soc.*, **1974**, *96*, 870-876.
6. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **1969**, *34*, 2543.
7. S. W. Mamber, J. D. Mitulski, K. L. Hamelehle, J. C. Frech, G. C. Hokanson, J. L. Shillis, W. R. Leopold, D. D. Von Hoff, and J. B. Tunac, *J. Antibiot.*, **1987**, *40*, 73.