SHORT PAPER

J. Chem. Research (S), 2000, 130–132

Stereoselective synthesis of (+)-ferruginyl methyl ether and (+)-sugiyl methyl ether†

Gan Yonghong and Pan Xinfu*

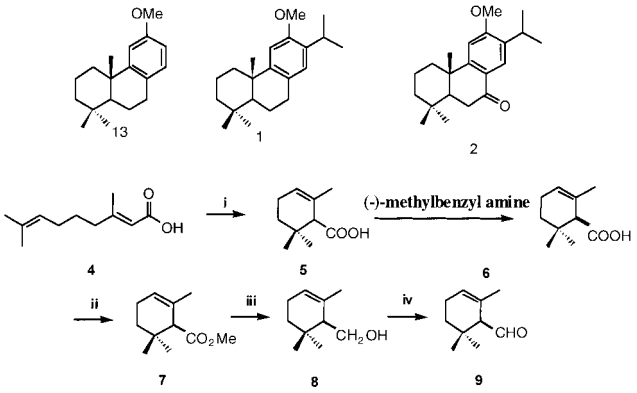
National Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, China

A facile stereoselective synthetic procedure to (+)-ferruginyl methyl ether and (+)-sugiyl methyl ether has been developed with high stereoselectivity and overall yield.

Diterpenoids have attracted particular attention of medicinal chemists and clinicians, because many of them exhibit significant bioactivities, such as antibacterial,[1–3] antidermatophytic,[2,3] antioxidant,[4] antiinflammatory, [3,5] antineoplastic,[6] and antiplatelet aggregation.[7] In 1948, Barton and Schmeidler[8] concluded that the A/B ring junction in the diterpenoids is *trans* and this was confirmed by the first total synthesis of (±)-ferruginol by King *et al.*[9] However, the synthetic route followed by King *et al*. was not stereoselective, and the important intermediate 1,1-dimethyl-4α-methyl-6-methoxy-1:2:3:4:4α:9:10:10α-octahydrophenanthrene **13** was obtained in low yield by a laborious process. In order to achieve a stereoselective synthesis of this compound, an efficient stereospecific method must be developed whereby the *trans* isomer could be obtained predominantly. Herein, we report a facile stereoselective synthesis of (+)-ferruginyl methyl ether **1** and (+)-sugiyl methyl ether **2**.

Our synthetic strategy is AC→ABC, as shown in Scheme 1. In order to obtain the (*S*)-(-)-α-cyclocitral **9**, geranic acid **4** was cylized with 85% H_3PO_4 at 100 °C to give the (α)-cyclogeranic acid **5**. The precursor of compound **9**, (*S*)-(-)-cyclogeranic acid **6**, was obtained by resolution of (α)-cyclogeranic acid **5** with (-)-(α)-methylbenzylamine. Esterification of (*S*)-(-)-cyclogeranic acid **6** with K_2CO_3 / MeI in acetone gave the methyl (*S*)-(-)-cyclogeranate **7**. The compound **7** was reduced by $LiAlH_4$ to give the alcohol **8**. Oxidation of alcohol **8** by PCC at low temperature afforded the ring A starting material, (*S*)-(-)-α-cyclocitral **9** ($[\alpha]_D^{25}$ –700, c 0.03 $CHCl_3$; lit.[10] ($[\alpha]_D^{25}$ –743, c 0.05, $CHCl_3$).

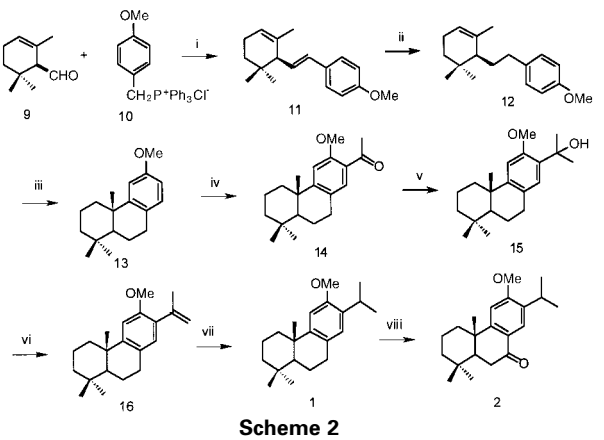
Scheme 1 (i): 85% H_3PO_4 / toluene, (ii): K_2CO_3 / MeI; (iii): $LiAlH_4$, (iv): PCC, CH_2Cl_2.



Scheme 1

As shown in Scheme 2, condensation of (*S*)-(-)-cyclocitral **9** with p-methoxybenzyltriphenylphosphonium **10** in the presence of n-BuLi / hexane gave the styrene derivative **11**. Partial hydrogenation of compound **11** in ethanol over 10% Pd/C afforded the phenethyl derivative **12** several conditions were examined. In order to obtain a better yield and stereoselectivity in the cyclization step. Finally, we found that BF_3 •Et_2O was a good cylization reagent providing a high yield and stereoselectivity for compound **12** (d.e. > 95%, determined by ^{1}H NMR). The cyclized compound **13** (all *trans*) was treated with acetyl chloride and $AlCl_3$ to yield the compound **14**. Treatment of compound **14** with CH_3Li gave the alcohol **15**. The compound **15** was dehydrated by *p*-toluenesulfonic acid in (*p*-Tos)/benzene to give the styrene derivative **16**. Hydrogenation of **16** in methanol over 5% Pd / C gave the (+)-ferruginyl methyl ether **1**. Oxidation of (+)-ferruginhyl methyl ether with CrO_3 / HOAc gave (+)-sugiyl methyl ether **2**. The HNMR spectra confirms the stereochemistry of compound **1** and **2**, and that we have introduced a chiral centre from (*S*)-(-)-α-cyclocitral. If the A/B ring is *cis* junction, the δ value of C4-(α)-methyl group will appear[11] at about 0.4~0.6 ppm because of the shielding effect. If the A/B ring is a *trans* junction, the δ value of C4-(α)-methyl group will appear at about 0.9~1.0 ppm because of the shielding effect. The ^{1}H NMR of compound **1** and **2**, did not contain a signal at 0.4~0.6 ppm and hence the A/B ring junction in the compound **1** and **2** must be *trans*. (+)-Ferruginyl methyl ether and (+)-suginyl methyl ether have been successfully synthesized in high stereoselectivity and overall yield.

Scheme 2 Reagents and conditions: (i) *n*-BuLi, *n*-hexane (60%); (ii) 10% Pd/C, ethanol (98%); (iii) BF_3·Et_2O, CH_2Cl_2 (85%); (iv) acetyl choride, anhydrous $AlCl_3$ (90%); (v) CH_3Li (95%); (vi) *p*-Tos, benzene; (90%); (vii) 5% Pd/C (95%); (viii) CrO_3/HOAc (85%); (ix) $NaBH_4$/ ethanol (95%); (x) *p*-Tos, benzene (90%).



Scheme 2

* To receive any correspondence. E-mail: panxf@lzu.edu.cn

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

The ^{1}H NMR and ^{13}C NMR data were recorded in $CDCl_3$ solution with Bruker AM-80 or AM-400 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS or $CDCl_3$. Optical rotations were determined on a JASCO J-20C polarimeter with 0.2 dm tube. Mass spectra were recorded on a ZAB-HS mass spectrometer (EI). Microanalyses were performed on a MOD-1106 elemental analyser. Column chromatography was generally performed on silica gel (200–300 mesh) eluting with petroleum ether : EtOAc (100:1→ 20:1 v/v) and TLC on silica gel GF_{254} plates with petroleum ether : EtOAc (20 : 1 v/v) unless noted below.

(±)-(α)-Cyclogeranic acid **(5)**: At 100 ºC, 85% H_3PO_4 (0.01 mmol) was added to geranic acid **4** (16g, 0.1mmol) in toluene (30mL). The reaction mixture was stirred for 2 h at this temperature, then the reaction was quenched with saturated $NaHCO_3$. It was extracted with ethyl ether and the combined organic layer was washed with brine and then dried with Na_2SO_4. After evaporation of the solvent under reduced pressure, the precipitate was recrystallized from *n*-hexane to give the pure compound **5** (14g, 90%). m.p. 101–102°C; ^{1}H NMR δ 0.90 (s, 3H), 0.96 (s, 3H), 1.60 (s, 3H), 1.8~2.5 (m, 5H), 5.6 (brs, 1H), 11.0 (s, 1H). MS (EI): 168, 153, 81, and 77. (Found: C, 71.29; H, 9.50. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%).

(S)-(-)-Cyclogeranic acid **(6)**:- (±)-**5** (16.0g) in ether (50mL) was treated with (-)-α-methylbenzylamine (9.0g). The precipitate was recrystallized from *n*-hexane to give the (-)-salt m.p. 110–112°C (needle). The solution of the (-)-salt in methanol was acidified with 5% HCl and extracted with ether. The combined organic layer was washed with brine, then dried with Na_2SO_4. Evaporation of the solvent under reduced pressure, followed by recrystallization from *n*-hexane to give the pure compound **6**. m.p. 101–102°C (as large prisms). ($[\alpha]_D^{25}$ -300° (c 0.5, ethanol) lit.[10] ($[\alpha]_D^{25}$ -319° ethanol)). Other spectra data were same as those of compound **5**.

(S)-Methyl α-cyclogeranate **(7)**: (*S*)-(-)-cyclogeranic acid (5.0 g, 30 mmol) in acetone (30 mL) was treated with anhydrous K_2CO_3 (5.0 g, 36 mmol) and 3 mL MeI (6.0 g, 36 mmol). The mixture was stirred at room temperature for 3 h. Recovery in ether gave the compound **7** (5.0g, 90%) as an oil. ^{1}H NMR δ 0.90 (s, 3H), 0.96 (s, 3H), 1.60 (s, 3H), 1.8~2.5 (m, 5H), 2.1 (s, 3H), 5.6 (brs, 1H). MS (EI): 182, 167, 81 and 77. (Found: C, 72.53; H, 10.00. $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.95%).

(S)-2,6,6-Timethyl-1-cyclohexanemethanol **(8)**: Compound **7** (4.5 g, 25 mmol) in anhydrous ether (10 mL) was added dropwise. At –10°C, to a suspension of $LiAH_4$ (600 mg, 16 mmol) in anhydrous ethyl ether (30 mL). The mixture was stirred at this temperature for 1 h. Then, the reaction was quenched with ice-water, extracted with ether and the combined organic layer was washed with brine, then dried with Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the alcohol **8** (4.5g, 90%). The alcohol was used for the next step immediately without further identification.

(S)-(-)-Cyclocitral **(9)**: The alcohol **8** (4.0g, 23mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) containing 0.3 g 4Å molecular sieve and anhydrous NaOAc (1.5 g). PCC (5.0 g, 26 mmol) in 30 mL anhydrous CH_2Cl_2 was added to above solution portionwise at –10°C. The solution was stirred at this temperature for 1h, then the salt was removed by passing through a short column of Al_2O_3. After purification by column chromatography gave the pure compound **9** (3.0g, 75%). ^{1}H NMR δ 0.92 (s, 3H), 0.98 (s, 3H), 1.60 (s, 3H), 1.8~2.5 (m, 5H), 5.7 (brs, 1H), 9.2 (s, 1H). MS (EI): 152, 123, 137, 77. ($[\alpha]_D^{25}$ –708° (c 0.03, $CHCl_3$) lit.[11] ($[\alpha]_D^{25}$ –743° (c 0.05, $CHCl_3$)), (Found: C, 78.85; H, 10.50. $C_{10}H_{16}O$ requires C, 78.90; H, 10.59%).

3-(4-Methoxystyryl)-2,4,4-trimethyl-1-cyclohexene **(11)**: A solution of *n*-butyllithium in hexane (1.6N, 4mL) was added to a suspension of (4-methoxybenzyl)-triphenylphosphonium chloride (3.2g, 7.55mmol) in dry hexane (20mL) under an atmosphere of argon. The mixture was stirred at room temperature for 1h. Then a solution of **9** (700 mg, 4.6 mmol) in dry hexane (10 mL) was added over 10 min. The solution was stirred for 4 h to complete the reaction. The solution was then poured into dilute HCl, and the mixture was extracted with ether. The combined organic layer was washed with brine and dried with Na_2SO_4, The crude product was purified by column chromatography to give the desired compound **11** as an oil (700 mg, 60%). ^{1}H NMR δ 0.94 and 1.00 (s, each 3H), 1.63 (bs, 3H), 3.83 (s, 3H), 5.50 (brs, 1H), 6.00 (1H, dd, *J*=8, 15Hz), 6.40 (1H, d, *J*=15Hz), 6.88 (2H, d, 8.9Hz), 7.34 (2H, d, 8.9Hz). MS (EI): 256, 200, 185, 121, 91. (Found: C, 89.40; H, 9.40. $C_{18}H_{24}O$ requires C, 84.32; H, 9.44%).

3-(4-Methoxyphenylethyl)-2,4,4-trimethyl-1-cyclohexene **(12)**: A suspension of **11** (500 mg) and 10% Pd/C (250 mg) in anhydrous ethanol (10 mL) was stirred at room temperature in an atmosphere of hydrogen. The reaction was monitored by TLC. When the reaction was complete, the mixture was filtered. The filtrate was evaporated *in vacuo* to yield the desired compound **12** (480 mg, 95%) as colorless oil. ^{1}H NMR δ 0.91 and 1.00 (s, each 3H), 1.70 (bs, 3H), 3.80 (s, 3H), 5.34 (brs, 1H), 6.84 (2H, d, 8.6Hz), 7.13 (2H, d, 8.6Hz). MS (EI): 258, 243, 121. (Found: C, 83.55; H, 10.10. $C_{18}H_{26}O$ requires C, 83.67; H, 10.14%).

12-Methoxy-podocarpane-8,11,13-trene **(13)**: BF_3 Et_20 (0.6 ml was added to a solution of **12** (300mg, 1.2 mmol) in CH_2Cl_2 (15mL) dropwise. The mixture was allowed to stand overnight. Then 30 mL ether was added and the solution was neutralized with saturated $NaHCO_3$. The mixture was extracted with ether and the combined organic layer was washed successively with saturated $NaHCO_3$ and brine, and then dried with Na_2SO_4. It was purified by column chromatography to give the pure *trans* compound **1** (260 mg, 85%) (no *cis* compound was detected by ^{1}H NMR). ^{1}H NMR δ 0.99 (s, 6H), 1.24 (s, 3H), 1.32~ 2.37 (m, 10H), 3.82 (s, 3H), 6.70 (1H, dd, *J*=8.0, 2.0Hz), 6.85 (1H, d, 2.0Hz), 6.93 (1H, d, *J*=8.0Hz). MS (EI): 258, 243, 187, 161, 121,9.. (Found: C, 83.57; H, 10.09. $C_{18}H_{26}O$ requires C, 83.67; H, 10.14%).

13-Acetyl-12-methoxy-podocarpan-8,11,13-triene **(14)**: Anhydrous $AlCl_3$ (350mg) was added portionwise at –10°C, to a solution of **13** (300 mg, 1.2 mmol) in CH_2CL_2 (15 mL). Then acetyl chloride (0.2 mL) was added dropwise maintaining the reaction temperature below –5°C. After stirring overnight, the mixture was poured to ice-water, and extracted with CH_2Cl_2. The combined organic layer was successively washed with saturated $NaHCO_3$ and brine, then dried with Na_2SO_4. After purification by column chromatography, the compound **13** was obtained as a yellowish oil (310 mg, 95%). ^{1}H NMR δ 0.91 (s, 3H), 0.95 (s, 3H), 1.21 (s, 3H), 1.32~ 2.37 (m, 10H), 2.58 (s, 3H), 3.87 (s, 3H), 6.83 (s, 1H), 7.44 (s, 1H). MS (EI): 300, 285, 256, 203, 163, 91. (Found: C, 79.73; H, 9.15. $C_{20}H_{28}O_2$ requires C, 79.96; H, 9.39%).

Alcohol **(15)**: To a solution of **14** (300 mg, 1.1 mmol) in anhydrous THF (5 mL), CH_3Li (1.3 N, 1.5 mL) was added at 0°C. The solution was stirred for 4 h and then poured to ice-water. It was extracted with ether. The combined organic phase was washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give the alcohol **15** (310 mg, 95%). The compound **15** was used for next step without further identification.

13-(Isopropenyl)-12-methoxy-podocarpane-8,11,13-triene **(16)**: A catalytic amount of p-toluenesulfonic acid was added to a solution of **15** (500mg, 1.6mmol) in benzene. The solution was refluxed for 0.5 h. After cooling, saturated $NaHCO_3$ was added to the solution and the mixture was extracted with ether. The combined organic layer was washed with brine and dried with Na_2SO_4. Purification by column chromatography gave the styrene derivative **15** (450 mg, 90%). ^{1}H NMR δ 0.92 (s, 3H), 0.94 (s, 3H), 1.21 (s, 3H), 1.71 (s, 3H), 1.32~ 2.37 (m, 10H), 3.8 (s, 3H), 5.05 (s, 1H), 5.10 (s, 1H), 6.75 (s, 1H), 6.85 (s, 1H). MS (EI): 298, 285, 163, 91. (Found: C, 84.49; H, 10.28. $C_{21}H_{30}O$ requires C, 84.51; H, 10.31%).

(+)-ferruginyl methyl ether **(1)**: A suspension of **16** (300 mg) and 5% Pd/C (150 mg) in ethanol (10 mL) was stirred at room temperature in an atmosphere of hydrogen. The reaction was monitored by TLC. When the reaction was complete, the mixture was filtered. The filtrate was evaporated *in vacuo* to yield the desired compound **16** as colorless heavy oil (280mg, 95%). $[\alpha]_D^{25}$ +30° (c 0.1, MeOH), ^{1}H NMR δ 0.83 and 0.85 (s, each 3H), 1.14 (6H, d, *J*=7.5Hz), 1.17 (s, 3H), 1.10~3.00 (m, 11H), 3.70 (s, 3H), 3.25 (sept, *J*=7.5Hz), 6.75 (s, 1H), 6.69 (s, 1H). MS (EI): 300, 176, 163, 133, 69. (Found: C, 83.75; H, 10.52. $C_{21}H_{32}O$ requires C, 83.94; H, 10.73%)

(+)-suginyl methyl ether **(2)**: A solution of **1** (300mg, 1mmol) in acetic acid (5mL) was treated with CrO_3 (1mmol) in acetic acid (5mL) at room temperature. The mixture was stirred for 0.5 h, then water was added to quench the reaction. After extraction with ether, the combined organic layer was washed with saturated $NaHCO_3$ and brine. Purification by column chromatography gave the compound **2** (280mg, 90%) as white needle crystals. m.p. 130-132°C, ($[\alpha]_D^{25}$ +27° (c 0.1, MeOH) lit.[12] ($[\alpha]_D^{25}$ +32° (c 0.1, MeOH)).^{1}H NMR δ 0.93 and 1.00 (s, each 3H), 1.23 (d, 3H, *J*=7.0Hz), 1.27 (d, 3H, *J*=7.0Hz), 1.28 (s, 3H), 3.88 (s, 3H), 3.25 (sept, *J*=7.0Hz), 6.75 (s, 1H), 7.89 (s, 1H). MS (EI): 300, 285, 189, 163, and 69. (Found: C, 80.10; H, 9.52. $C_{21}H_{30}O_2$ requires C, 80.21; H, 9.62%).

Support from the National Natural Science Foundation of China is gratefully acknowledged.

Received 27 October 1999, accepted 3 January 2000
Paper 99/31

References

1 C.N. Fang, P.L. Cheng and T.P. Hsu, *Acta. Chem. Sinica*, 1976, **34**, 197.
2 G. Honda, Y. Koezuka and M. Tobata, *Chem. Pharm. Bull.*, 1988 **36**, 408.
3 H.W. Luo, S.X. Chen, J.N. Lee and J.K. Synder *Phytochemistry*, 1988, **27**, 290.
4 C.M. Houlihan, C.T Ho and S.S. Chang, *Am. Oil. Chem. Soc.*, 1985, **62**, 96.
5 Y.G. Gao, L.E. Wang and K.S. Chin Tang, *J. Integrated Trade. West. Med.*, 1983, **3**, 300.
6 W.L. Wu, W.L. Chang, A.R. Lee, H.C. Lin and M.L. King, *Med. Sci.*, 1985, **6**, 159.
7 M. Onitsuka, M. Fujin, N. Shinma and H.B. Marayama, *Chem. Pharm. Bull.*, 1983, **31**, 1670.
8 D.H.R. Barton and G.A. Schmeidler, *J. Chem. Soc.*, 1948, 1197.
9 F.E. King, T.J. King and J.G. Toplis, *Chem. Ind.*, 1954, 108, *J. Chem. Soc.*, 1957, 573.
10 C. Fehr, I. Stempf and J. Galindo, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1042.
11 W. Ernst, A. Adriano, B. Peter and W.J. Richard, *Org. Chem.*, 1965, **30**, 713.
12 E. Wenkert, J. De Paiva Campello and J.D. McChesney, *Phytochemistry*, 1974, **13**, 2545.