A Chiral Synthesis of a Unique Secodehydroabietane from Tall Oil

Kaoru FUJI,*[,a] Shang-Zhen ZHENG,[a,1)] Manabu NODE,[b] and Xiao-Jiang HAO[a]

Institute for Chemical Research, Kyoto University,[a] Uji, Kyoto 611, Japan and Kyoto Pharmaceutical University,[b] Yamashina-ku, Kyoto 607, Japan. *Received August 10, 1990*

A total synthesis of naturally occurring (+)-9,10-secoabieta-8,11,13-trien-18,10-olide (1) has been achieved from a chiral building block, (*R*)-2-methyl-2-(2-*E*-nitrovinyl)-5-pentanolide (3).

Keywords asymmetric synthesis; diterpenoid; secoabietane; abietane; total synthesis

In 1977 Conner and Rowe reported the isolation of a novel compound, 9,10-secoabieta-8,11,13-trien-18,10-olide (**1**), from the southern pine tall oil.[2)] Based on a combination of spectral analysis and biogenetic arguments, the relative stereochemistry of **1** was proposed. Unambiguous structure determination including absolute stereochemistry was provided by the conversion of levopimaric acid (**2**) into **1**.[3)]

Here, we report a total synthesis of (+)-**1**. The synthetic scheme utilized 2-(3-isopropylphenyl)ethyl bromide (**6**) prepared from 3-isopropylacetophenone (**4**). The 1,4-addition of a Grignard reagent prepared from **6** to the chiral nitroolefin **3**[4)] proceeded smoothly to afford a 1 : 1 mixture of **7a** and **7b** in 74% yield. Though it was possible to isolate each diastereomer, the mixture was directly used for further transformations. Thus, a three-step sequence involving the treatment with *p*-toluenesulfonic acid (*p*-TsOH) in methanol, mesylation, and substitution with sodium iodide in refluxing acetone provided a mixture **8** in 73% overall yield. Intramolecular alkylation of **8** was followed by the Nef reaction to give **9a** and **9b** in 11 and 51% overall yields from **8**, respectively. The undesired major ketone **9b** was equilibrated by refluxing in methanol with *p*-TsOH to yield approximately a 1.3 : 1 mixture of **9a** and **9b**, from which pure **9a** was isolated in 55% yield. The desired ketone **9a** can be obtained in high yield by recycling through this procedure. Addition of methylmagnesium bromide occurred exclusively from the α-side to afford **10**. Since cyclohexanone **9a** should exist in a chair conformation with the bulky β-arylethyl substituent disposed equatorially, the β-side of the molecule is sterically hindered by an axial methyl group (Fig. 1). Treatment of **10** with a modified polyphosphoric acid[5)] yielded 9,10-secoabieta-8,11,13-trien-18,10-olide (**1**) with inversion of the configuration at C-10. The transformation involves formation of a carbenium ion at C-10 followed by a ring flip to close the lactone ring as shown in Fig. 2.

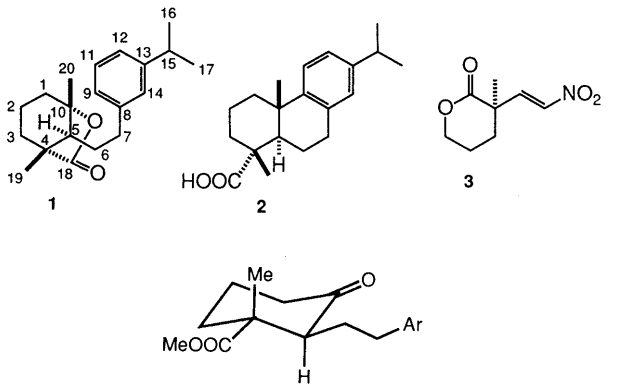


Fig. 1. Conformation of **9a**

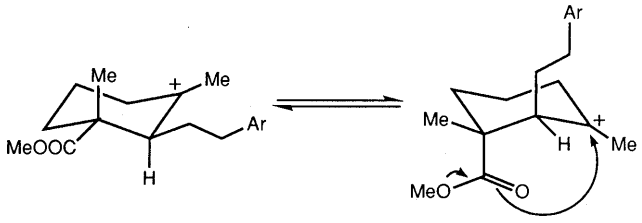
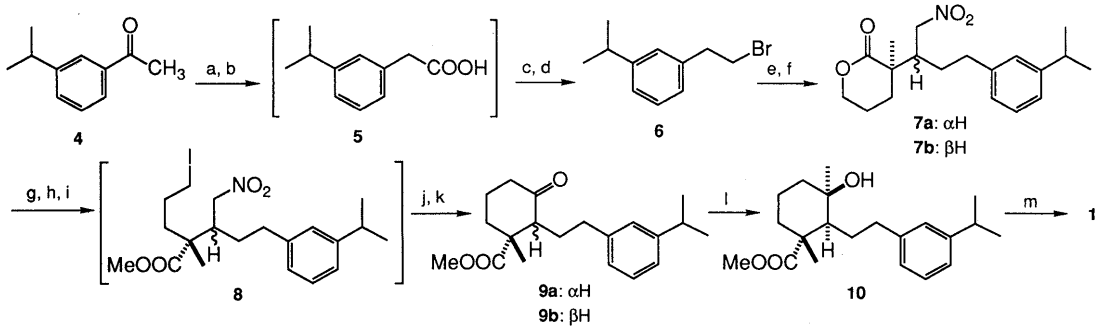


Fig. 2. Ring Flip of Intermediate Carbenium Ion

Experimental

Infrared (IR) spectra were recorded on a JASCO IR-810 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained with a Varian Gemini-200 spectrometer in $CDCl_3$ and signals are given in ppm using tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-DX



a) morpholine–sulfur b) 10% KOH c) $LiAlH_4$ d) PPh_3–NBS e) Mg f) **3** g) TsOH–MeOH h) MsCl–Et_3N i) NaI j) NaH k) NaOMe–MeOH, then $TiCl_3$ l) MeMgBr m) P_2O_5–$MeSO_3H$

Chart 1

300 mass spectrometer. Optical rotations were recorded on a JASCO DIP-181 polarimeter.

2-(3-Isopropylphenyl)ethyl Bromide (6) A mixture of 3-isopropylacetophenone (**4**)[6] (10.0 g, 62 mmol) and sulfur (4.0 g, 124 mmol) in dry morpholine (27 ml) was refluxed for 36 h, poured into ice-water, and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated to give an oil that was chromatographed on silica gel (hexane–AcOEt, 5 : 1) to yield the thioamide (12.5 g). Aqueous 10% KOH (180 ml) was added to the thioamide and the mixture was heated under reflux for 36 h. After addition of 10% hydrochloric acid, the reaction mixture was extracted with ethyl acetate. The organic phase was washed twice with brine, dried (Na_2SO_4), and evaporated under reduced pressure to afford a residue, which was chromatographed over silica gel (hexane–benzene, 1 : 1) to give 3-isopropylphenylacetic acid (**5**, 7.7 g, 69% from **4**).

A solution of **5** (10.0 g, 56 mmol) in 300 ml of dry tetrahydrofuran (THF) was treated with 3.2 g (84 mmol) of $LiAlH_4$, and the solution was refluxed for 1 h. Usual extractive work-up yielded an oil (9.4 g), which was dissolved in 270 ml of THF. After addition of PPh_3 (17.7 g, 67 mmol), the mixture was stirred at room temperature for 1 h followed by the addition of *N*-bromosuccinimide (NBS) (12.0 g, 67 mmol). After being stirred for 2 h, the reaction mixture was extracted with dichloromethane. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to give a crude product. Distillation under reduced pressure afforded 2-(3-isopropylphenyl)ethyl bromide (**6**) (11.2 g, 93%), bp 94—97 °C (3 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2960, 1600, 1460. ^{1}H-NMR δ: 1.25 (6H, d, J=7 Hz), 2.87 (1H, m), 3.14 (2H, m), 3.56 (2H, t, J=7 Hz), 6.89 (1H, d, J=2 Hz), 7.06 (2H, m), 7.25 (1H, t, J=8 Hz). HRMS *m/z*: Calcd for $C_{11}H_{15}Br$: 226.034. Found: 226.036.

(4*R*,5*S*)-7-(2-Isopropylphenyl)-5-nitromethyl-4,1-heptanecarbolactone (7a) and (4*R*,5*R*)-7-(2-Isopropylphenyl)-5-nitromethyl-4,1-heptanecarbolactone (7b) The Grignard reagent (0.52 M solution in THF, 16.6 ml) prepared from **6**, was added dropwise to a solution of (*R*)-2-methyl-2-(2-nitrovinyl)-5-pentanolide (**3**) (1.16 g, 6.3 mmol) in dry THF (60 ml) at −78 °C. The reaction mixture was stirred for 2 h, poured into aqueous NH_4Cl, and extracted with dichloromethane. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated to give an oil, which was purified by passing it through a short silica gel column. Elution with hexane–AcOEt (3 : 1) gave a 1 : 1 mixture of **7a** and **7b** (1.54 g, 74%). A part of the mixture (130 mg) was separated by preparative thin layer chromatography (TLC) (hexane–Et_2O, 2 : 1) to yield **7a** (63 mg) and **7b** (55 mg).

7a: Colorless oil. $[\alpha]_D^{20}$ +17.3 (c=1.43, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1550, 1460, 1260. ^{1}H-NMR δ: 1.24 (6H, d, J=7 Hz), 1.33 (3H, s), 1.50—2.00 (6H, m), 2.75 (2H, m), 2.88 (1H, septet, J=7 Hz), 2.95 (1H, m), 4.15—4.45 (2H, m), 4.35 (1H, dd, J=6, 13 Hz), 4.60 (1H, dd, J=6, 13 Hz), 6.95—7.10 (3H, m), 7.20 (1H, t, J=8 Hz). *Anal.* Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.29; H, 8.33; N, 3.96.

7b: Colorless oil. $[\alpha]_D^{20}$ −8.7° (c=1.24, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1550, 1460, 1260. ^{1}H-NMR δ: 1.22 (6H, d, J=7 Hz), 1.31 (3H, s), 1.50—2.00 (6H, m), 2.35—2.95 (4H, m), 4.20 (1H, dt, J=3, 11 Hz), 4.36 (1H, m), 4.53 (1H, dd, J=6, 13 Hz), 4.92 (1H, dd, J=5, 13 Hz), 6.80—7.10 (3H, m), 7.20 (1H, t, J=8 Hz). *Anal.* Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.08; H, 8.21; N, 4.05.

Methyl (1*R*,2*S*)-2-[2-(2-Isopropylphenyl)ethyl]-1-methyl-4-oxo-1-cyclohexanecarboxylate (9a) and Methyl (1*R*,2*R*)-2-[2-(2-Isopropylphenyl)-ethyl]-1-methyl-4-oxo-1-cyclohexanecarboxylate (9b) Anhydrous *p*-TsOH (91 mg, 0.53 mmol) was added to a stirred solution of the 1 : 1 mixture of **7a** and **7b** (1.5 g, 4.4 mmol) in 60 ml of MeOH, and the solution was refluxed for 10 h. The solvent was removed and the residue was passed through a short column of silica gel with hexane–AcOEt (2 : 1) as an eluent to give 1.56 g of a hydroxy ester. The hydroxyester was dissolved in 80 ml of dichloromethane, and mesyl chloride (0.7 g, 6.2 mmol) was added to the stirred solution. The mixture was stirred at 0 °C for 30 min, then triethylamine (0.6 g, 6.2 mmol) was added and stirring was continued for 1 h. The reaction mixture was poured into ice water and extracted with dichloromethane. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The crude product in dry acetone (120 ml) was treated with NaI (6.2 g, 41 mmol), and the mixture was refluxed for 10 h. The reaction mixture was poured into water and extracted with dichloromethane. The combined organic phase was washed with saturated sodium thiosulfate solution and brine, dried (Na_2SO_4), and evaporated to give a crude material, which was purified by short column chromatography over silica gel eluted with hexane–AcOEt (5 : 1) to afford a mixture **8** (1.5 g, 76%).

A solution of **8** (1.1 g, 2.3 mmol) in 20 ml of dry dimethylformamide (DMF) was added to a well-stirred solution of NaH (60%) (380 mg, 9.5 mmol) in 80 ml of dry DMF under nitrogen at 0 °C and stirring was continued for 24 h. After addition of acetic acid (1.5 ml), the solvent was removed under reduced pressure. The residue was partitioned between 2 N HCl and ether. The combined ether phase was washed, dried, and evaporated to give a crude oil, which was passed through a short column of silica gel. Elution with hexane–AcOEt (5 : 1) gave an oil, which was dissolved in dry methanol (20 ml). Sodium methoxide (1 M in MeOH, 2.3 ml) was added and the mixture was stirred for 1 h followed by addition of 20% aqueous $TiCl_3$ (5.4 ml) and ammonium acetate (2.8 g) in water (12 ml) under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After addition of 2 N hydrochloric acid (50 ml), the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a crude product, which was purified by short column chromatography (hexane–AcOEt, 7 : 1), affording 373 mg (81%) of **9b** as a colorless oil. $[\alpha]_D^{20}$ −2.2° (c=2.0, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1230. ^{1}H-NMR δ: 1.21 (6H, d, J=7 Hz), 1.22 (3H, s), 1.50 (1H, m), 1.60—1.90 (4H, m), 2.00—2.50 (5H, m), 2.70 (1H, m), 2.85 (1H, septet, J=7 Hz), 3.60 (3H, s), 6.90—7.04 (3H, m), 7.18 (1H, t, J=8 Hz). HRMS (FAB) *m/z*: Calcd for $C_{20}H_{28}O_3$+H: 317.213. Found: 317.212. Further elution with the same solvent gave 78 mg (17%) of **9a** as a colorless oil. $[\alpha]_D^{20}$ +9.8° (c=1.56, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1720, 1240. ^{1}H-NMR δ: 1.03 (3H, s), 1.15 (1H, m), 1.24 (6H, d, J=7 Hz), 1.68—2.45 (8H, m), 2.70 (1H, m), 2.90 (2H, m), 3.65 (3H, s), 6.90—7.10 (3H, m), 7.21 (1H, t, J=8 Hz). HRMS (FAB) *m/z*: Calcd for $C_{20}H_{28}O_3$+H: 317.214. Found: 317.212.

Conversion of 9b into 9a Anhydrous *p*-TsOH (41 mg, 0.24 mmol) was added to a stirred solution of **9a** (75 mg, 0.24 mmol) in dry MeOH, and the reaction mixture was refluxed for 3.5 h. After removal of the solvent, the residue was purified by preparative TLC with Et_2O–hexane (1 : 1) to give 41 mg (55%) of **9a** together with 32 mg (43%) of recovered **9b**.

Methyl (1*R*,2*S*,3*R*)-1,3-Dimethyl-1-hydroxy-2[2-(2-isopropylphenyl)-ethyl]cyclohexanecarboxylate (10) A stirred solution of **9a** (78 mg, 0.25 mmol) in 20 ml of dry THF was treated with MeMgBr in THF (0.94 M, 0.54 ml) at 0 °C, and the reaction mixture was stirred for 2 h. After addition of 20 ml of saturated NH_4Cl, the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried, and evaporated to give **10** (82 mg, 100%), which was purified by short column chromatography on silica gel eluted with Et_2O. Colorless oil: $[\alpha]_D^{20}$ −12.2° (c=1.64, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1720, 1260. ^{1}H-NMR δ: 1.13 (1H, br s), 1.24 (6H, d, J=7 Hz), 1.26 (3H, s), 1.34 (3H, s), 1.40—1.95 (8H, m), 1.95 (1H, t, J=5 Hz), 2.57 (2H, m), 2.87 (1H, septet, J=7 Hz), 3.67 (3H, s), 6.96—7.07 (3H, m), 7.22 (1H, t, J=7 Hz). HRMS (FAB) *m/z*: Calcd for $C_{21}H_{31}O_2$ $(M-H_2O+H)^+$: 315.233. Found: 315.232.

9,10-Secoabieta-8,11,1-trien-18,10-olide (1) A mixture of P_2O_5 (200 mg), $MeSO_3H$ (1.36 ml), and **10** (74 mg, 0.2 mmol) was stirred for 30 min, then poured into ice-water and extracted with dichloromethane. The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was purified by preparative TLC on silica gel developed with Et_2O–hexane (1 : 3) to give **1** (43 mg, 65%) as a colorless oil. $[\alpha]_D^{20}$ +9.2° (c=1.85, $CHCl_3$) (lit.[3] $[\alpha]_D^{25}$ +9.5° (c=0.11), $CHCl_3$). *Anal.* Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.92; H, 9.46. Spectroscopic data were identical with the reported data.[3]

References and Notes

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