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Cyclopentenone Annulation of 1,4-Diketones with Potassium Phosphate Tribasic: A Synthesis of a Monoterpene Alkaloid, (±)-Tecomanine

Masaaki Miyashita, Daisuke Tanaka, Tomonori Shiratani, and Hiroshi Irie*

Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852, Japan. *Received December 16, 1991*

Conjugate addition of cyclohexanone lithium enolate to 2-nitro-2-butene and the Nef reaction on the resulting nitronate gave 2-(2-oxopropyl)cyclohexanone in good yield. Treatment of the 2-(2-oxopropyl)cyclohexanone thus obtained with potassium phosphate tribasic (K_3PO_4) in isopropanol gave 2,3,4,5,6,7-hexahydro-3-methyl-3a*H*-inden-2-one (8). Application of the procedure to 1,3-dimethyl-4-piperidone (11) gave the 1,3,4,6,7,7a-hexahydro-6-oxo-2,4,7-trimethyl-2*H*-2-pyrindine (12). Epimerization of 12 with basic alumina gave (±)-tecomanine (1). The short synthesis of the alkaloid demonstrates the usefulness of K_3PO_4 as a base for cyclopentenone annulation of 1,4-diketones without migration of the double bond.

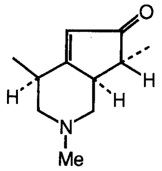
Keywords nitroolefin; conjugate addition; Nef reaction; intramolecular aldol reaction; cyclopentenone; potassium phosphate tribasic; monoterpene alkaloid; tecomanine

Although there have been several syntheses[1] of the monoterpene alkaloid, tecomanine (**1**),[2] which shows hypoglycemic activity,[3] they require long reaction sequences. We aimed at a short synthesis of this alkaloid by applying the synthetic method for 1,4-diketones from nitroolefins and cycloalkanones.[4]

Now, the cyclization reaction of 2-(2-oxopropyl)cycloalkanones has been applied for the construction of cyclopentenone derivatives. The cyclization of 2-(1-methyl-2-oxopropyl)cyclohexanone (**2**) (a mixture of two diastereoisomers) under usual basic conditions, however, gave 2,3,4,5,6,7-hexahydro-1-methyl-3a*H*-inden-2-one (**3**) as the sole product by the migration of a double bond formed by the dehydration of the intramolecular aldol condensation product.[5] Practically, it is not so easy to prevent the migration reaction. When 1,3-dimethyl-5-(1-methyl-2-oxopropyl)-4-piperidone (**4**) was selected as a key intermediate for the alkaloid synthesis, we had to find an appropriate reagent and solvent for the cyclization reaction without migration of the double bond formed by the dehydration reaction of the aldol product. Eventually, we found that potassium phosphate tribasic (K_3PO_4) in isopropanol was suitable for the desired cyclization.

Prior to the synthesis of the alkaloid, we tested several kinds of reagents (K_2CO_3, KOH, and pyrrolidine) for aldol cyclization using the hexanone (**2**) as a substrate. The latter was readily prepared by the conjugate addition of cyclohexanone lithium enolate, generated from cyclohexanone and lithium diisopropylamide (LDA) in tetrahydrofuran (THF), to 2-nitro-2-butene (**5**) followed by an acid-treatment (10% hydrochloric acid, Nef reaction), in 78% yield.[4,5] In a similar manner, the ketones **6** and **7** were prepared from 2-methylcyclohexanone and cycloheptanone, each in 89% yield. The cyclization reaction of **2** using the reagents mentioned above gave exclusively the hydroindenone (**3**) having a tetra-substituted double bond, while treatment of **2** with K_3PO_4 in isopropanol at 45 °C for 32 h gave a mixture of 2,3,4,5,6,7-hexahydro-3-methyl-3a*H*-inden-2-one (**8**) and **3** in a ratio of 90 : 10 in 87% yield. The ratio of the two products was determined from the signal ratio of olefinic (δ, 5.80) and vinyl methyl (δ, 1.68) protons corresponding to each product, respectively, observed in the proton magnetic resonance (^{1}H-NMR) spectrum and by gas chromatographic analysis of the mixture. Similarly, cyclization reactions of the ketones **6** and **7** with K_3PO_4 in isopropanol gave a mixture of the ketones **9a** and **9b** in a ratio of 75 : 25 and **10a** and **10b** in a ratio of 83 : 17, respectively.

Based on the above findings, the synthesis of tecomanine (**1**) was carried out in the following way. Treatment of the dimethylpiperidone (**11**)[6] with LDA followed by the nitroolefin **5** gave the lithium nitronate, which was subjected to the Nef reaction with 10% hydrochloric acid in an one-pot operation, giving the 1,4-diketone (**4**) in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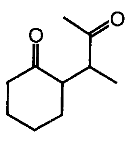
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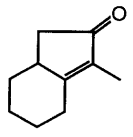
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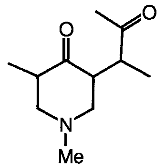
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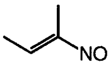
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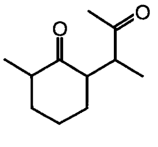
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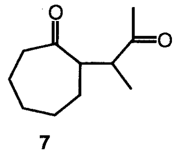
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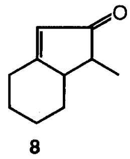
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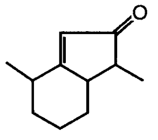
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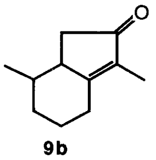
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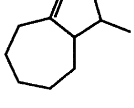
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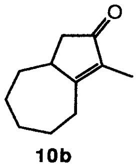
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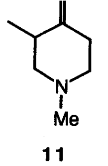
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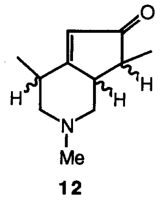
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87% yield as a mixture of diastereoisomers (revealed by the ^{1}H-NMR spectrum). Treatment of the mixture with K_3PO_4 in isopropanol at 55 °C for 55 h gave the annulation product **12** in 49% yield as a single compound. The product, however, was not identical with (±)-tecomanine, suggesting that the ketone **12** was a stereoisomer of tecomanine, though its stereo-structure has not been elucidated so far.[7] Treatment of **12** with basic alumina in benzene with efficient stirring at 40 °C overnight furnished (±)-tecomanine (**1**) in 50% yield, the ^{1}H-NMR and infrared (IR) spectra being identical with those of (±)-tecomanine provided by Professors M. Hanaoka (Kanazawa University) and T. Imanishi (Osaka University). This short synthesis of the alkaloid exemplifies the usefulness of K_3PO_4 for cyclopentenone annulation without migration of the double bond.

Experimental

IR spectra were recorded on a Shimadzu IR-408 spectrometer in chloroform. ^{1}H-NMR spectra were recorded on a JEOL FX 90Q spectrometer with tetramethylsilane as an internal standard and chemical shifts are given in δ (ppm). High-resolution mass spectra (HR-MS) and gas chromatography–mass spectra (GC-MS) were taken with a JEOL JMS-DX 303 instrument. Flash column chromatography was performed with Kieselgel 60G (Art 7731, Merck).

2-(1-Methyl-2-oxopropyl)cyclohexanone (2) A solution of cyclohexanone (98 mg, 1 mmol) in THF (1 ml) was added dropwise to a stirred solution of LDA (1.2 mmol) in THF (2 ml), and the mixture was stirred at −78 °C for 30 min. Then a solution of 2-nitro-2-butene (152 mg, 1.5 mmol) in THF (1 ml) was added. The mixture was stirred for 2 h at the same temperature, then 10% hydrochloric acid was added at 0 °C and the whole was stirred for 2 h at room temperature. The reaction mixture was extracted with AcOEt and the extract was washed with water and saturated brine, dried over $MgSO_4$, and concentrated to dryness to leave an oil, which was chromtographed on silica gel in hexane–AcOEt (5:1). Elution with the same solvent gave the diketone **2** in 78% yield, bp 95 °C (bath temperature)/4 mmHg. IR ($CHCl_3$): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.01 and 1.16 (3H in total, d each, J=7.0, 6.8 Hz, respectively), 1.26—2.16 (6H, m), 2.16—2.45 (2H, m), 2.19 and 2.28 (3H in total, s each), 2.52—3.00 (2H, m). MS m/z: 168 (M^+).

2-(1-Methyl-2-oxopropyl)-6-methylcyclohexanone (6) and 2-(1-Methyl-2-oxopropyl)cycloheptanone (7) The cycloalkanones **6** and **7** were prepared in the same manner as mentioned above, each in 89% yield. **6**: bp 105 °C (bath temperature)/7 mmHg. IR ($CHCl_3$): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.97 (3H, d, J=6.4 Hz), 1.00 and 1.16 (3H in total, d each, J=6.8 Hz, respectively), 1.23—2.18 (6H, m), 2.21 and 2.23 (3H in total, s each), 2.38—2.72 (1H, m), 2.72—2.83 (2H, m). HR-MS m/z: Calcd for $C_{11}H_{18}O_2$ (M^+): 182.1307. Found: 182.1312. **7**: bp 150 °C (bath temperature)/10 mmHg. IR ($CHCl_3$): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.09 (3H, d, J=6.8 Hz), 1.47—2.08 (8H, m), 2.18 and 2.20 (3H in total, s each), 2.36—2.62 (2H, m), 2.73—3.03 (2H, m). HR-MS m/z: Calcd for $C_{11}H_{18}O_2$ (M^+): 182.1307. Found: 182.1306.

2,3,4,5,6,7-Hexahydro-3-methyl-3a*H*-inden-2-one (8) A mixture of the ketone **2** (100 mg, 0.6 mmol), K_3PO_4 (160 mg, 0.6 mmol), and isopropanol (20 ml) was stirred at 45 °C (bath temperature) for 32 h. After addition of NaH_2PO_4 (192 mg, 1.2 mmol), the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was taken up in AcOEt. The organic solution was washed with water and brine, dried ($MgSO_4$), and concentrated to dryness to leave an oil. The oily product was subjected to preparative thin layer chromatography (PTLC) developed with hexane–AcOEt (5:1) to give a mixture of the cyclic products **8** and **3** (90:10, revealed by GC and ^{1}H-NMR) in 87% yield. IR ($CHCl_3$): 1690, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.16 (2.7H, d, J=7.3 Hz), 1.25—1.63 (2.9H, m), 1.68 (0.3H, t, J=2.9 Hz), 1.75—2.52 (6H, m), 2.52—3.00 (1.2H, m), 5.80 (0.9H, s). HR-MS (GC) m/z: **8**: Calcd for $C_{11}H_{14}O$ (M^+): 150.1045. Found: 150.1055. **3**: Calcd for $C_{11}H_{14}O$ (M^+): 150.1045. Found: 150.1076.

Cyclization of the Diketones (6 and 7) Treatment of the diketones **6** and **7** with the same reagent and in the same solvent as for **8** gave a mixture of the hydroindenones **9a** and **9b** (75:25), and **10a** and **10b** (83:17) in 87% and 77% yields, respectively. **9a** and **9b**: IR ($CHCl_3$): 1695, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.02—1.27 (5.25H, m), 1.39—2.56 (8H, m), 1.69 (0.75H, t, J=3.5 Hz), 2.56—3.23 (1.25H, m), 5.81 (0.75H, s). HR-MS (GC) m/z: **9a**: Calcd for $C_{11}H_{16}O$ (M^+): 164.1201. Found: 164.1192. **9b**: Calcd for $C_{11}H_{16}O$ (M^+): 164.1201. Found: 164.1195. **10a** and **10b**: IR ($CHCl_3$): 1690, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.17 (2.49H, d, J=7.3 Hz), 1.21—2.20 (8H, m), 1.65 (0.51H, t, J=2.0 Hz), 2.20—3.02 (4.17H, m), 5.85 (0.83H, d, J=1.5 Hz). HR-MS (GC) m/z: **10a**: Calcd for $C_{11}H_{16}O$ (M^+): 164.1201. Found: 164.1211. **10b**: Calcd for $C_{11}H_{16}O$ (M^+): 164.1201. Found: 164.1213.

1,3-Dimethyl-5-(1-methyl-2-oxopropyl)-4-piperidone (4) A solution of 1,3-dimethyl-4-piperidone (**11**) (3.15 g, 16 mmol) in THF (15 ml) was added dropwise to a solution of LDA (18 mmol) in THF (45 ml) at −78 °C under argon and the mixture was stirred for 30 min. Then a solution of 2-nitro-2-butene (2.27 g, 22.5 mmol) in THF (8 ml) was added. The mixture was stirred at −78 °C for 3 h, then 10% hydrochloric acid was added at 0 °C and the whole was stirred for 3 h. The reaction mixture was basified with $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent gave an oily residue, which was chromatographed (flash) in $CHCl_3$ and isopropylamine (30:1) over silica gel. Elution with the same solvent gave a mixture of diastereoisomers of 1,3-dimethyl-5-(1-methyl-2-oxopropyl)-4-piperidone (**4**) (2.57 g, 87%). IR ($CHCl_3$): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 0.90—1.31 (6H, m), 2.17—2.45 (6H, m), 2.49—2.95 (3H, m), 2.84—3.32 (4H, m). HR-MS m/z: Calcd for $C_{11}H_{19}O_2N$ (M^+): 197.1416. Found: 197.1418.

Cyclization of the 4-Piperidone (4) A mixture of the foregoing 4-piperidone (**4**) (150 mg, 0.76 mmol), K_3PO_4 (203 mg, 0.76 mmol), and isopropanol (30 ml) was stirred at 55 °C for 55 h. After addition of NaH_2PO_4 (243 mg, 1.5 mmol), the mixture was filtered. The filtrate was concentrated *in vacuo* to dryness to leave an oil, which was dissolved in AcOEt. The organic solution was washed with brine and dried ($MgSO_4$). Removal of the solvent gave a mixture (128 mg) consisting of the stereoisomer **12** of (±)-tecomanine (**1**) and the starting material **4**, which was separated by flash column chromatography with hexane–AcOEt (1:2) to give **12** (66 mg, 49%) and the recovered **4** (29 mg, 20%) in that order. IR ($CHCl_3$): 1690, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.18 (3H, d, J=7.3 Hz), 1.34 (3H, d, J=7.0 Hz), 1.56—2.25 (3H, m), 2.29 (3H, s), 2.55—3.12 (2H, m), 3.12—3.30 (2H, m), 5.84 (1H, d, J=1.5 Hz). HR-MS m/z: Calcd for $C_{11}H_{17}ON$ (M^+): 179.1311. Found: 179.1306.

Epimerization of the Stereoisomer (12) to (±)-Tecomanine (1) A mixture of **12** (46 mg, 0.26 mmol), basic alumina (1 g), and benzene (25 ml) was stirred overnight at 40 °C. The alumina was filtered off, and the filtrate was concentrated to dryness to leave a mixture of (±)-tecomanine (Rf=0.1) and a minute amount of the starting material (Rf=0.3). (±)-Tecomanine (**1**) was purified by preparative thin layer chromatography with hexane–AcOEt (1:4) to give 23 mg (50%) of the pure compound. IR ($CHCl_3$): 1690, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.16 (3H, d, J=6.4 Hz), 1.18 (3H, d, J=7.5 Hz), 1.73 (3H, t, J=21.3 Hz), 2.34 (3H, s), 2.41—2.85 (2H, m), 2.91—3.33 (2H, m), 5.85 (1H, s). MS m/z: 179 (M^+).

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References and Notes

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7) Exposure to potassium carbonate in ethanol for a short period was used for the cyclization of *N*-carboethoxy-2-methyl-5-(1-methyl-2-oxopropyl)piperid-4-one, culminating in the synthesis of (±)-tecomanine,[1a] but its application to the piperidone **4** did not give any cyclization product.