Formal Total Synthesis of (±)-Dimethyl Secologanoside

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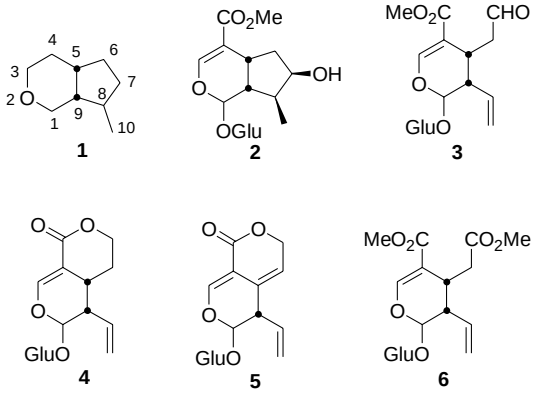
A formal total synthesis of the iridoid monoterpene (±)-dimethyl secologanoside (**6**) is described. The Norrish I type fragmentation of bicyclo[2.2.1]heptannone **9** is the key step.

Keywords: Iridoid monoterpene; Secologanoside; Norrish I type fragmentation; Cyclopentanopyran.

INTRODUCTION

The iridoid monoterpenes represent a large family of cyclopentanopyran natural products.[1] Among the various iridoids, the cyclopenta[*c*]pyran bearing the 2-oxa-*cis*-bicyclo[4.3.0]nonane **1** moiety (Scheme I) as a fundamental ring system is the most widely distributed. Loganin (**2**),[2] one of the most important iridoids, is the biosynthetic precursor to secologanin (**3**),[3] C_7-C_8 *seco* ring. The monoterpene glycoside secologanin plays a central role in the biosynthesis of indole alkaloids.[4] Secologanin is also the biogenetic key intermediate for the biosynthesis of secoiridoids, such as sweroside (**4**)[5] and gentiopicroside (**5**).[6] The synthesis of this physiologically active and structurally appealing class of iridoid monoterpenes continues to be an active area of research even today.[7] Here, we wish to describe an efficient formal total synthesis of (±)-dimethyl secologanoside (**6**),[8] an analogue of secologanin.

Scheme I



RESULTS AND DISCUSSION

Cyclopentene **12** has been reported as a precursor of secologanside (**6**).[8] Our approach to secologanoside (**6**) is based on the Norrish type I cleavage of bicyclo[2.2.1]heptanone derivative **9** for the construction of the all *cis*-trisubstituted cyclopentene ring system in compound **10**.[9] The logical precursor for compound **10** may be the bicyclo[2.2.1]heptanone derivative **8**.[10] Our synthesis began with the commercially available **7**, a substance which "holds" the desired stereochemistry and the same carbon number in the final product.

The key intermediate **8** was easily prepared from dicyclopentadiene **7** on a half molar scale in a one-pot reaction.[10] Oxidative cleavage of the double bond in **8** was carried out using an excess of ozone and an oxidative workup with hydrogen peroxide. Without purification, the resulting diacid was directly treated with excess diazomethane to afford dimethyl ester **9** in 78% yield. Photolysis of **9** produced the Norrish type I cleavage product **10** in 83% yield.[11] With compound **10** in hand, its conversion to **12** is quite straightforward. Reduction of the aldehyde group in **10** with sodium borohydride in methanol at -23 °C gave the corresponding hydroxy ester **11** (94%), which was subsequently tosylate with *para*-toluenesulfonyl chloride to yield tosylate **12** in 89%. The structure of **12** was confirmed by comparison of the ^{1}H and ^{13}C NMR spectra with those of an authentic sample provided by Professor Chang.[8]

In conclusion, we have developed a facile route to the key intermediate **12** for the synthesis of secologanoside (**6**). Efforts directed toward the synthesis of other naturally occurring iridoids are currently under way in our laboratory.

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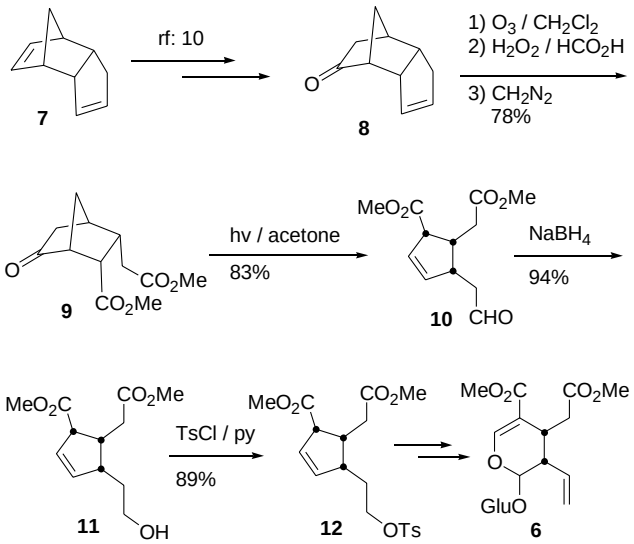
Scheme II



EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial sources and used without further purification. A column chromatograph contained silica gel (70~230 mesh); precoated TLC sheets of silica gel (60 f_{254} plates) were used for thin-layer chromatography. All reactions were performed under an atmosphere of nitrogen in dried (except those concerned with aqueous solutions) spherical flasks and stirred with magnetic bars. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR-2000 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 spectrometer, with TMS as the internal standard. Mass spectra (MS) were measured on a VGQUATTRO 5022 mass spectrometer. High resolution mass (HRMS) values were determined on a JEOL JMSHY 110 mass spectrometer. Elemental analyses (EA) were performed on a Heraeus CHN-O analyzer.

(1*R,2*S**,3*S**,4*R**)-3-Methoxycarbonylmethyl-6-oxo-bicyclo[2.2.1]heptane-2-carboxylic acid methyl ester (9)**

A solution of **8** (1.0 g, 6.8 mmol) in dichloromethane (30 mL) at -60 °C was treated with ozone until the solution turned blue. After it was stirred at -60 °C for an additional 5 min, the mixture was allowed to warm to room temperature and then stripped of solvent *in vacuo*. The residue was redissolved in formic acid (20 mL) with magnetic stirring, and then 5 mL of hydrogen peroxide (33%) was added. The resulting mixture was heated at reflux for 24 h. After it was cooled to room temperature, the mixture was concentrated *in vacuo*. Water (20 mL) was added to the residue and the resulting solution was extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were dried, filtered, and concentrated. After ethyl acetate (20 mL) was added to that residue, the resulting solution was treated with diazomethane at 0 °C for 30 min, after which nitrogen was bubbled into the solution to remove any excess diazomethane. Removal of the solvent by evaporation followed by flash column chromatography on silica gel (elution with 15-30% ethyl acetate in hexane) afforded compound **9** (1.26 g, 78%) as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 3H), 3.36 (s, 3H), 3.24 (dd, *J* = 11.2, 4.5 Hz, 1H), 2.75-2.60 (m, 3H), 2.44 (dd, *J* = 16.4, 7.1 Hz, 1H), 2.27 (dd, *J* = 18.3, 3.0 Hz, 1H), 2.03 (dd, *J* = 18.3, 4.2 Hz, 1H), 1.85-1.78 (m, 2H): ^{13}C NMR ($CDCl_3$) δ 213.2 (s), 172.6 (s), 172,4 (s), 54.1 (d), 51.5 (q), 51.4 (q), 45.1 (d), 38.7 (d), 37.9 (t), 37.8 (t), 36.9 (d), 32.3 (t); IR (neat) 1725 cm^{-1}; MS (EI, 70 eV) *m/z* 240 (11, M^+), 209 (49), 79 (100); HRMS (EI) *m/z* calcd. for $C_{12}H_{16}O_5$ 240.0998, found 240.1000; Anal. calcd. for $C_{12}H_{16}O_5$: C, 60.03; H, 6.72. Found: C, 60.22; H, 6.90.

(1*R,4*S**,5*S**)-5-Methoxycarbonylmethyl-4-(2-oxo-ethyl)-cyclopent-2-enecarboxylic acid methyl ester (10)**

A solution of compound **9** (200 mg, 0.83 mmol) in oxygen-free acetone (100 mL) was irradiated under a nitrogen atmosphere with a 450-W medium pressure mercury lamp using a Pyrex glass filter for 3 h while the progress of the reaction was monitored by GC. The solution was concentrated, and then the residue was purified by flash column chromatography on silica gel (elution with 15-25% ethyl acetate in hexane) to yield compound **10** (166 mg, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.63 (br. s, 1H), 5.91 (ddd, *J* = 5.8, 1.9, 1.8 Hz, 1H), 5.60 (ddd, *J* = 5.8, 2.7, 1.4 Hz, 1H), 3.53 (s, 3H), 3.51 (s, 3H), 3.46 (ddd, *J* = 8.2, 2.7, 1.8 Hz, 1H), 3.20-3.05 (m, 1H), 2.89 (p, *J* = 8.2 Hz, 1H), 2.55-2.45 (m, 2H), 2.36 (dd, *J* = 8.2, 4.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 201.2 (s), 173.50 (s), 172.5 (s), 137.8 (d), 128.6 (d), 52.1 (d), 51.5 (2c, q), 45.7 (t), 40.5 (d), 38.9 (d), 31.7 (t); IR (neat) 2729, 1732, 1716 cm^{-1}; Ms (EI, 70 eV) *m/z* 241 [4, $(m+1)^+$], 208 (24), 180 (76), 77 (100); HRMS (EI) *m/z* $C_{12}H_{16}O_5$ calcd.for 240.0998, found 240.1002.

(1*R,4*S**,5*S**)-4-(2-Hydroxyethyl)-5-methoxycarbonyl-methyl-cyclopent-2-enecarboxylic acid methyl ester (11)**

Sodium borohydride (78 mg, 2.0 mmol) was added gradually to a stirred solution of compound **10** (500 mg, 2.1 mmol) in methanol (15 mL) at -23 °C. After 30 min, the reac-

tion was quenched with saturated ammonium chloride (30 mL) and the aqueous layer was extracted with ethyl acetate (4 × 25 mL). The combined organic layers were washed with brine, and then dried, filtered and stripped of solvent. Purification of the residue by flash column chromatography on silica gel (elution with 20-35% ethyl acetate in hexane) gave 474 mg (94%) of **11** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.15-6.00 (m, 1H), 5.80-5.70 (m, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.80-3.50 (m, 3H), 3.04 (quinq, 1H), 2.90-2.75 (m, 1H), 2.59 (dd, *J* = 8.0, 16.2 Hz, 1H), 2.49 (dd, *J* = 3.6, 16.2 Hz, 1H), 1.94 (br. s, 1H), 1.580-1.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.9 (s), 173.3 (s), 138.3 (d), 128.1 (d), 61.2 (t), 52.2 (d), 51.6 (2C, q), 43.4 (d), 39.8 (d), 34.1 (t), 31.8 (t); IR (neat) 3522, 1732 cm^{-1}; MS (EI, 70 eV) *m/z* 210 (15, $(M\text{-}CH_3OH)^+$), 164 (80), 105 (100); HRMS calcd. for $C_{11}H_{14}O_4$ (M^+-CH_3OH) 210.0892, found 210.0890.

Tosylate 12

A solution of **11** (300 mg, 1.2 mmol) and *p*-toluenesulfonyl chloride (354 mg, 1.9 mmol) in dichloromethane (15 mL) containing 2 mL of pyridine was stirred at room temperature for 4 h. To that mixture we added dichloromethane (60 mL). The organic solution was washed with saturated sodium bicarbonate (15 mL), water (2 × 20 mL), and brine, then dried, filtered, and concentrated to produce crude **12**. Flash column chromatogoraphy on silica gel (elution with 20-30% ethyl acetate in hexane) afforded tosylate **12** (437 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 5.90 (ddd, *J* = 5.9, 2.3, 1.7 Hz, 1H), 5.74 (ddd, *J* = 5.9, 2.7, 1.3 Hz, 1H), 4.15-4.00 (m, 2H), 3.68 (s, 3H), 3.36 (s, 3H), 3.57 (ddd, *J* = 8.1, 2.7, 1.7 Hz, 1H), 2.98 (p, 1H), 2.90-2.70 (m, 1H), 2.54 (dd, *J* = 16.5, 8.1 Hz, 1H), 2.46 (s, 3H), 2.41 (dd, *J* = 16.5, 8.1 Hz, 1H), 1.90-1.60 (m, 2H); ^{13}C NMR ($CDCl_3$ δ 173.6 (s), 172.8 (s), 144.8 (s), 137.1 (d), 132.9 (s), 129.8 (2C, d), 129.3 (d), 127.9 (2C, d), 68.9 (t), 52.1 (d), 51.7 (2C, q), 42.7 (d), 39.6 (d), 31.7 (t), 30.5 (t), 21.6 (d); IR (neat) 1732 cm^{-1}; MS (EI, 70 eV) *m/z* 396 (M^+, 0.1), 364 (9), 91 (100); HRMS calcd. for $C_{19}H_{24}O_7S$ 396.1243, found 396.1248. Anal. calcd. for $C_{19}H_{24}O_7S$: C, 57.60; H, 6.11. Found: C, 57.61; H, 6.21.

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