Enantioselective Total Synthesis of (+)-Isoboonein

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Enantioselective total synthesis of (+)-isoboonein, an iridoid lactone, was accomplished from (−)-dimenthyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate, which was synthesized by diastereoselective Diels–Alder reaction of dimenthyl fumarate with cyclopentadiene.

Key words asymmetric; synthesis; isoboonein; iridoid

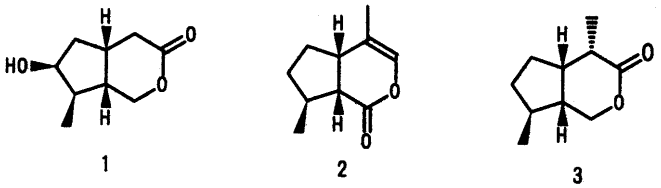
More than 600 iridoids have been isolated from medicinal, toxic, edible or other plants, however the biological activities of most iridoids are unreliable.[1] (+)-Isoboonein (**1**) was isolated from *Rauwolfia grandiflora* by A. Bianco *et al.* in 1994.[2] The same compound, named as abelialactone, had been obtained earlier by hydrolysis of abelioside A from *Abelia grandiflora*,[3] and the structure was correlated with loganin.[4] Although the biological activity of **1** has not been reported, analogous cyclopentano-δ-lactone iridoids have been reported with unique biological activities, *e.g.* nepetalactone (**2**) with excitative activity toward cats,[5] and iridomyrmecin (**3**) with strong insecticide activity against preying insects, from ants (*Iridomyrmex humilis* MAYR.).[6] As the absolute stereochemistry of (+)-isoboonein (**1**) is similar to typical iridoids, enantioselective synthesis of **1** may provide not only a possible synthetic route to these iridoid lactones, but also useful synthetic intermediates to many other iridoids. In this paper, we describe an enantioselective total synthesis[7] of (+)-isoboonein from the diastereoselective Diels–Alder adduct (**7**) of dimenthyl fumarate (**5**) with cyclopentadiene.[8]

Results and Discussion

There are several reports of iridoid synthesis starting from bicyclo[2.2.1]heptanes.[9—13] Facile and highly diastereoselective reaction should be chosen to provide the first asymmetric intermediate for our enantioselective synthesis of iridoids. Diels–Alder reaction of dimenthyl fumarate (**5**) with cyclopentadiene has been reported to give (−)-dimenthyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**7**) diastereoselectively.[8] Since the stereochemistry at C1, C2 and C3 of (−)-**7** is comparable to the stereochemistry at C4a, C7a and C7 of (+)-isoboonein (**1**), respectively, we planned to create the δ-lactone ring of **1** *via* the cleavage of the cyclopentene ring of **7**.

Synthesis of racemic isoboonein was examined first from racemic bicyclo[2.2.1]heptane derivative **6** and the same synthetic route was then applied for the synthesis of optically active (+)-isoboonein (**1**). The optically active diol **8** was synthesized *via* Diels–Alder reaction (92%) of **5**,[8] followed by reduction of **7** (78%) in 97% ee.[14,15] The optical yield was calculated from the $[\alpha]_D$ value of our synthetic **8** and the reported value.[14] The diol **8** was then converted to ketone **12** [optically active **8**→**9** (85%)→**10** (89%)→**11** (89%)→**12** (86%) in Fig. 2] according to the literature for the synthesis of (±)-**12**.[16] Oxidation of **12** with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane provided lactone **13** [(±)-**13**, 97%; optically active **13**, 82%] which could be formed *via* Baeyer–Villiger oxidation of **12** followed by successive reactions of opening of the lactone ring in the oxidation product (A) and recyclization to lactone **13**. Since **13** has a carbon skeleton similar to isoboonein (**1**), with the same stereochemistry at C4a and C7a, the functional groups on the cyclopentane ring of **13** were modified to give **1** as follows. Since the stereochemistry at C6 of **13** is opposite to that of **1**, the hydroxy group was oxidized with pyridinium chlorochromate on alumina (PCC–Al_2O_3) in CH_2Cl_2[17] to afford ketone **14** [(±)-**14**, 80%; optically active **14**, 80%] which was then treated with trifluoroacetic acid–water–CH_2Cl_2 to give enone **15** [(±)-**15**, 55%; optically active **15**, 65%]. Hydrogenation of **15** with H_2 and 5% Pd–C in ethyl acetate (EtOAc) gave a mixture (5 : 1) of ketones **16** and **17** [(±)-**16** and **17**, 79%; optically active compounds **16** and **17**, 97%]. As the stereochemistry at C-7 of the major ketone **16** is opposite to **1**, the mixture was treated with pyridinium *p*-toluenesulfonate in refluxing benzene to give a mixture (1 : 8) of **16** and **17** [(±)-**16** and **17**, 75%; optically active **16** and **17**, 65%]. The major isomer **17** has the same stereochemistry as **1**. The mixture of **16** and **17** was then reduced with $NaBH_4$ in isopropanol and the product purified to give **18** [(±)-**18**, 68%; optically active **18**, 78%], an epimeric alcohol of isoboonein (**1**) at C6. The alcohol **18** was epimerized by sequential Mitsunobu reaction with azodicarboxylic acid diethyl ester, triphenylphosphine, and acetic acid in tetrahydrofuran (THF)[18] and hydrolysis with K_2CO_3 in methanol, and the resulting product was heated in refluxing benzene to recyclize to the lactone ring, to give isoboonein (**1**) [(±)-**1**, 22% from **18**; optically active **1**, 13% from **18**]. The synthetic (+)-**1**, $[\alpha]_D$ +65.0° (c=0.08, methanol) was identical with natural isoboonein (**1**), $[\alpha]_D$ +65.0° (c=0.2, methanol).

Since (+)-isoboonein (**1**) has similar absolute stereochemistry at C5, C8 and C9 to those of typical iridoids, this synthetic route should be useful for enantioselective synthesis of various iridoids.



1 2 3

Fig. 1.

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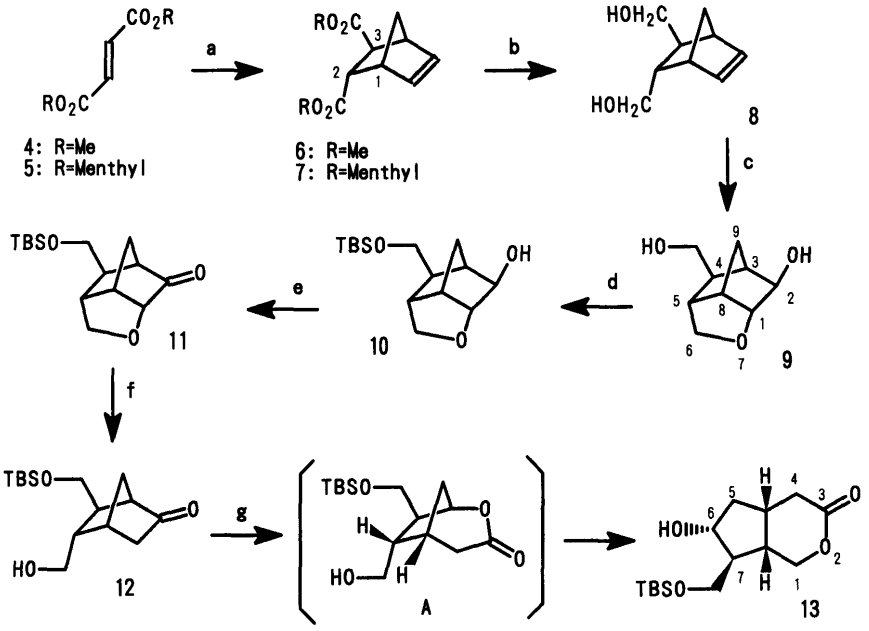

Fig. 2

a, cyclopentadiene, Et_2AlCl; b, $LiAlH_4$; c, MCPBA; d, TBSCl; e, oxalyl chloride, DMSO, Et_3N in CH_2Cl_2; f, $HgCl_2$, Al, THF–EtOH; g, MCPBA.

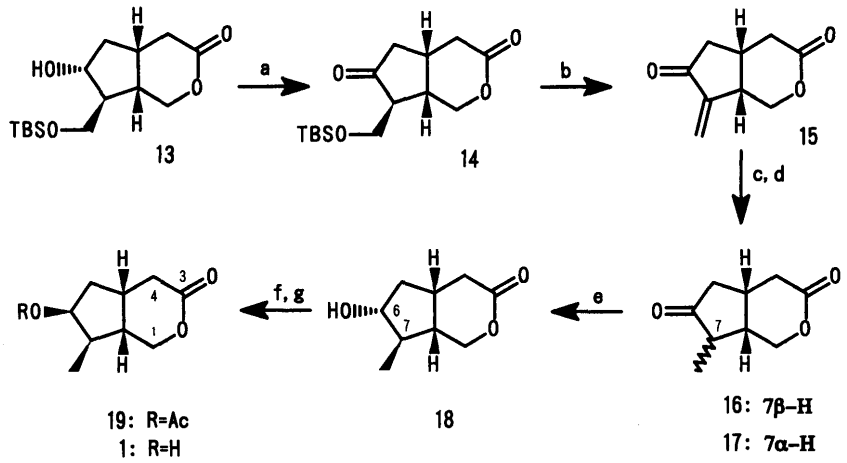

Fig. 3

a, PCC–Al_2O_3; b: TFA–H_2O; c, H_2–5% Pd/C; d, reflux, PPTS in PhH; e, $NaBH_4$ in isopropanol; f, Ph_3P, $(NCO_2C_2H_5)_2$, CH_3CO_2H in THF; g, K_2CO_3 in CH_3OH, HCl.

Experimental

All melting points were measured on a MEL-TEMP (Laboratory Device) without correction. IR and UV spectra were measured on a JEOL JIR-WINSPEC50 Fourier transform (FT)-infrared spectrometer and a JASCO UVDEC-460 spectrometer, respectively. Mass spectra were recorded on a JEOL JMS-SX-102A spectrometer. Nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra were measured on a JEOL JNM-EX270 spectrometer in $CDCl_3$ containing tetramethylsilane as internal standard, and J values are reported in Hz. TLC was carried out on Kiesel-gel GF_{254} (0.25 mm thickness). Silica gel 60 (70—230 mesh ASTM) was used for column chromatography.

5,6-Di(hydroxymethyl)bicyclo[2.2.1]hept-2-ene (8) Optically active **8** was synthesized from **5** by similar procedures to those described in the literature (78%, 97% ee). Optically active **8**, white crystals, mp 40 °C, $[\alpha]_D$ −22.2° (c=2.1, $CHCl_3$ at 23 °C).

4-Hydroxymethyl-7-oxatricyclo[3.2.1.1^{3,8}]nonan-2-ol (9) Optically active **9** (85%), white crystals, mp 87 °C, $[\alpha]_D$ −52.5° (c=2.1, CH_3OH).

4-*tert*-Butyldimethylsilyloxymethyl-7-oxatricyclo[3.2.1.1^{3,8}]nonan-2-ol (10) Optically active **10** (89%), oil, $[\alpha]_D$ −20.0° (c=0.1, $CHCl_3$).

4-*tert*-Butyldimethylsilyloxymethyl-7-oxatricyclo[3.2.1.1^{3,8}]nonan-2-one (11) Optically active **11** (89%), oil, $[\alpha]_D$ −63.0° (c=0.1, $CHCl_3$).

5-Hydroxymethyl-6-(*tert*-butyldimethylsilyloxymethyl)bicyclo[2.2.1]-heptan-2-one (12) Optically active **12** (86%), oil, $[\alpha]_D$ −25.0° (c=0.1, $CHCl_3$).

4a*R*,6*R*,7*S*,7a*S*-Tetrahydro-6-hydroxy-7-(*tert*-butyldimethylsilyloxymethyl)cyclopenta[*c*]pyran-3(1*H*)-one (13) A solution of **12** (420 mg, 1.48 mmol) and MCPBA (1.28 g, 5.94 mmol) in 40 ml of CH_2Cl_2 was stirred for 3 d at ambient temperature. An excess amount of a solution of diazomethane in ether was added to the reaction mixture and the products were separated by silica gel column chromatography to give 433 mg (1.44 mmol) of **13** (97%). (±)-**13**, oil. MS *m/z*: 300 (M^+, 1%), 285 (5), 243 (100), 195 (25), 183 (43), 151 (50), 105 (86). IR (neat) cm^{-1}: 3450, 2952, 2931, 2850, 1764, 1473, 1250, 1089. ^{1}H-NMR δ: 4.28 (1H, dd, J=5.0, 11.5 Hz), 4.20 (1H, dd, J=5.5, 11.5 Hz), 3.96 (1H, m), 3.80—3.65 (2H, m), 2.87 (1H, br), 2.62 (1H, dd, J=6.5, 13.8 Hz), 2.44 (1H, dd, J=5.5, 13.8 Hz), 2.52 (1H, m), 2.29 (1H, m), 2.13 (1H, m), 1.88 (1H, m), 1.39 (1H, m), 0.89 (9H, s), 0.07 (6H, s). ^{13}C-NMR δ: 173.4, 74.7, 69.3, 64.5, 50.6, 40.8, 37.2, 34.6, 30.5, 25.8, 18.1, −5.57.

Optically active **13** (82%), oil, $[\alpha]_D$ +38.0° (c=0.1, $CHCl_3$).

4a*R*,7*S*,7a*S*-Tetrahydro-6-oxo-7-(*tert*-butyldimethylsilyloxymethyl)cyclopenta[*c*]pyran-3(1*H*)-one (14) To a solution of hydroxy lactone **13** (574 mg, 1.91 mmol) in dry CH_2Cl_2 (50 ml), PCC–alumina (10.3 g, 9.55 mmol) was added and the mixture was stirred for 6 h. After filtration and washing of the alumina with CH_2Cl_2, the combined CH_2Cl_2 solution was evaporated and the residue was chromatographed on silica gel eluting with hexane–ethyl acetate to give 467 mg (1.56 mmol) of ketolactone **14** (80%). (±)-**14**: white crystals, mp 88 °C. MS *m/z*: 298 (M^+, 3%), 283 (5), 257 (25),

241 (100), 181 (43). IR (KBr) cm^{-1}: 2973, 1749, 1727, 1245, 1037. ^{1}H-NMR δ: 4.40 (1H, m), 4.18 (1H, dd, J=5.1, 11.8 Hz), 3.79 (1H, m), 3.71 (1H, m), 2.87—2.65 (3H, m), 2.51 (1H, m), 2.33 (1H, m), 2.26—2.03 (2H, m), 0.77 (9H, s), −0.05 (3H, s), −0.06 (3H, s). ^{13}C-NMR δ: 215.5, 171.7, 76.4, 61.7, 51.8, 44.5, 36.5, 34.6, 28.5, 25.4, 17.7, −6.00, −6.08.

Optically active **14** (79%), oil, $[\alpha]_D$ −10.0° (c=0.1, $CHCl_3$).

4a*R*,7a*S*-Tetrahydro-6-oxo-7-methylenecyclopenta[*c*]pyran-3(1*H*)-one (15) A solution of **14** (21.0 mg, 0.07 mmol) in 6 ml of CH_2Cl_2 and 4 ml of trifluoroacetic acid–H_2O (9 : 1) was stirred for 12 h at ambient temperature. The solution was neutralized with saturated aqueous $NaHCO_3$ and the CH_2Cl_2 layer was washed with brine, dried over $MgSO_4$, and evaporated. After purification by column chromatography (silica gel, hexane–ethyl acetate), enone **15** (6.40 mg, 0.039 mmol, 55%) was obtained. (±)-**15**: white crystals, mp 86 °C. MS *m/z*: 166 (M^+, 36%), 136 (95), 108 (33), 94 (100). IR (neat) cm^{-1}: 2973, 1749, 1727, 1635, 1245, 1037. ^{1}H-NMR δ: 6.23 (1H, d, J=2.3 Hz), 5.52 (1H, d, J=2.3 Hz), 4.52 (1H, dd, J=4.6, 10.9 Hz), 4.21 (1H, dd, J=6.9, 10.9 Hz), 3.44 (1H, m), 3.00—2.80 (3H, m), 2.42 (1H, dd, J=6.3, 14.4 Hz), 2.24 (1H, dd, J=5.3, 16.4 Hz). ^{13}C-NMR δ: 204.0, 171.6, 143.4, 121.6, 69.3, 43.6, 38.2, 34.8, 27.5.

Optically active **15** (65%), mp 101 °C, $[\alpha]_D$ +100.0° (c=0.1, $CHCl_3$).

4a*R*,7a*S*-Tetrahydro-6-oxo-7-methylcyclopenta[*c*]pyran-3(1*H*)-one (16 and 17) A mixture of the enone **15** (58.5 mg, 0.352 mmol) and 5% Pd–C (19.8 mg) in ethyl acetate (8 ml) was stirred under H_2 for 72 h. After filtration through celite, the solution was evaporated and the residue was chromatographed over silica gel eluting with hexane–ethyl acetate to afford a mixture of **16** and **17** (5 : 1, 46.5 mg, 0.276 mmol, 79%). This mixture was then refluxed with 4.3 mg (0.017 mmol) of pyridinium *p*-toluenesulfonate in benzene (10 ml) for 5 h. After evaporation, the residue was chromatographed over silica gel to give a mixture of **16** and **17** (1 : 8, 34.9 mg, 0.208 mmol, 75%). (±)-**16**: oil. MS *m/z*: 168 (M^+, 25%), 152 (40), 139 (40), 126 (100), 111 (71), 97 (74). IR (neat) cm^{-1}: 2967, 1733, 1255, 1178. ^{1}H-NMR δ: 4.32 (1H, dd, J=4.5, 12.0 Hz), 4.08 (1H, dd, J=9.3, 12.0 Hz), 3.00—2.23 (6H, m), 2.04 (1H, m), 1.10 (3H, d, J=6.5 Hz). ^{13}C-NMR δ: 208.3, 175.6, 66.4, 45.3, 42.4, 37.3, 34.8, 28.0, 9.16. (±)-**17**: white crystals, mp 79 °C. MS *m/z*: 168 (M^+, 100%), 153 (8), 140 (20), 127 (55), 96 (10). IR (neat): 2973, 2931, 1743, 1286, 1245, 1089 cm^{-1}. ^{1}H-NMR δ: 4.53 (1H, dd, J=4.0, 11.6 Hz), 4.29 (1H, dd, J=4.3, 11.6 Hz), 3.00—2.78 (3H, m), 2.63 (1H, dd, J=9.2, 18.9 Hz), 2.45 (1H, dd, J=5.7, 15.4 Hz), 2.38—2.18 (2H, m), 1.14 (3H, d, J=6.5 Hz). ^{13}C-NMR δ: 216.0, 171.8, 68.8, 43.7, 43.2, 40.6, 34.8, 27.9, 13.2.

Optically active **16** and **17** (1 : 8, 65%).

4a*R*,6*R*,7a*S*-Tetrahydro-6-hydroxy-7-methylcyclopenta[*c*]pyran-3(1*H*)-one (18) To a solution of **17** (35.3 mg, 0.21 mmol) in isopropanol (6 ml), $NaBH_4$ (48.1 mg, 1.26 mmol) was added at 0 °C and the solution was stirred for 10 min. After addition of saturated aqueous NH_4Cl, the products were extracted with $CHCl_3$ repeatedly and the solution was washed with brine, dried over $MgSO_4$, and evaporated to give alcohol **18** (24.4 mg, 0.143 mmol, 68%). (±)-**18**: oil. MS *m/z*: 170 (M^+, 28%), 152 (69), 139 (28), 126 (100), 111 (71). IR (neat) cm^{-1}: 3460, 2962, 2925, 1737, 1255, 1162, 1062. ^{1}H-NMR δ: 4.30 (1H, dd, J=4.8, 11.5 Hz), 4.18 (1H, dd, J=5.6, 11.5 Hz), 3.70 (1H, m), 2.68—2.40 (3H, m), 2.27 (1H, m), 1.99 (1H, m), 1.72 (1H, m), 1.58 (1H, br s), 1.34 (1H, ddd, J=9.3, 12.9, 12.9 Hz), 1.09 (3H, d, J=6.6 Hz). ^{13}C-NMR δ: 173.9, 78.0, 68.7, 43.9, 42.1, 40.9, 34.8, 30.3, 16.5.

Optically active **18** (78%), $[\alpha]_D$ +64.0° (c=0.1, $CHCl_3$).

Mitsunobu Inversion of Alcohol 18 to Isoboonein (1) To a solution of alcohol **18** (32.2 mg) in THF (4 ml), Ph_3P (71.2 mg, 0.271 mmol), CH_3CO_2H (0.022 ml, 0.384 mmol), and $(NCO_2C_2H_5)_2$ (0.036 ml, 0.228 mmol) were added successively at 0 °C, and the solution was stirred at ambient temperature for 24 h. After evaporation, the residue was chromatographed over silica gel eluting with hexane–ethyl acetate to give crude acetate **19** (16.9 mg). **19**: oil. MS *m/z*: 212 (M^+, 7%), 170 (65), 152 (100), 126 (64), 110 (53), 93 (61). IR (neat) cm^{-1}: 2967, 2931, 1737, 1245. ^{1}H-NMR δ: 5.19 (1H, t, J=2.8 Hz), 4.33 (1H, dd, J=4.0, 12.1 Hz), 4.17 (1H, dd, J=3.0, 12.1 Hz), 2.86 (1H, m), 2.64 (1H, dd, J=6.8, 14.9 Hz), 2.38 (1H, dd, J=4.1, 14.9 Hz), 2.06 (3H, s), 2.22—2.00 (3H, br), 1.49 (1H, ddd, J=3.4, 11.5, 14.2 Hz), 1.02 (3H, d, J=5.4 Hz). ^{13}C-NMR δ: 173.0, 170.6, 78.4, 68.3, 42.4, 40.3, 39.2, 34.4, 32.6, 21.1, 12.9. The crude acetate **19** was hydrolyzed without further purification. To a solution of **19** in methanol (5 ml), K_2CO_3 (25 mg, 0.255 mmol) was added and the mixture was stirred for 12 h at ambient temperature. After neutralization of the mixture with 1 M HCl, the solvent was evaporated and the residue was extracted with benzene. The benzene solution was refluxed for 2 h to complete the lactonization and then evaporated. The residue was chromatographed over silica gel to give isoboonein (**1**) (6.6 mg, 0.039 mmol, 22% from **18**). (±)-**1**: oil. MS *m/z*: 170 (M^+, 38%), 152 (33), 139 (100), 124 (60), 111 (55), 97 (45). IR (neat) cm^{-1}: 3466, 3309, 2962, 2931, 1727, 1234, 1068. ^{1}H-NMR δ: 4.32 (1H, dd, J=4.0, 12.1 Hz), 4.16 (1H, dd, J=3.0, 12.0 Hz), 4.15 (1H, m), 2.95 (1H, m), 2.65 (1H, dd, J=7.3, 15.1 Hz), 2.38 (1H, dd, J=3.9, 15.1 Hz), 2.16 (1H, m), 2.06 (1H, ddd, J=1.0, 8.2, 13.6 Hz), 1.94 (1H, ddq, J=4.0, 7.0, 10.2 Hz), 1.43 (1H, ddd, J=4.0, 9.6, 13.3 Hz), 1.08 (3H, d, J=7.0 Hz). ^{13}C-NMR δ: 173.5, 75.6, 68.6, 41.7, 41.6, 41.5, 34.5, 32.7, 12.7.

Optically active **1** (13% from **18**), oil, $[\alpha]_D$ +65.0° (c=0.08, CH_3OH).

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