COMMUNICATION

Using a rigid molecule tricyclodecadienone for the stereospecific synthesis of the chain compound senecivernic acid[1]

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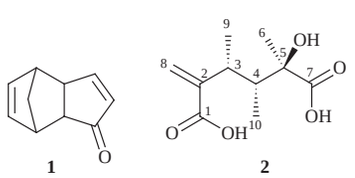
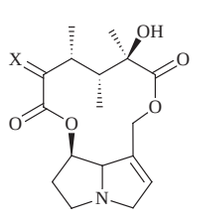
The highly efficient synthesis of a chain compound, senecivernic acid 2, using a rigid molecule, tricyclodecadienone 1, as the starting material *via* a retro-Diels–Alder reaction as the key step and without using any protecting groups is described in a total of ten steps and in 50% overall yield.

During the course of our program into natural products synthesis using retro-Diels–Alder reactions,[2–5] the rigid molecule tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one **1** was used as the starting material for the stereospecific introduction of the necessary functional groups and substituents. A retro-Diels–Alder reaction then released a cyclopentenone derivative which was a suitable precursor for natural product synthesis. Herein we wish to use this methodology for stereospecific synthesis of the chain compound senecivernic acid **2** from a rigid molecule **1** without using any protecting groups.



1 **2**



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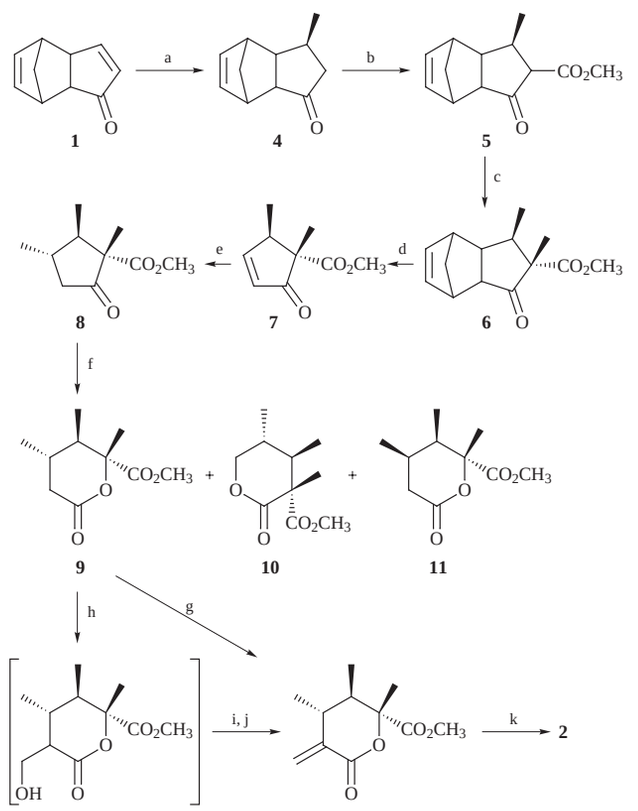
a, Senecivernine X = CH_2
b, Merenskine X = α-OH, β-CH_2Cl
c, Sceleratine X = α-OH, β-CH_2OH

Senecivernic acid **2** is a necic acid of senecivernine **3a** which was first isolated from *Senecio vernalis Walkstein et Kit* by Röder's group[6] in 1979, but without elucidation of the full stereochemistry. The stereochemistry was recently identified[7] to be the same as that in merenskine **3b**[8] and sceleratine **3c**.[9] Therefore, senecivernine **3a** might be a biogenetic precursor of merenskine **3b** and sceleratine **3c**, even though the corresponding epoxide of senecivernine **3a** has not been isolated from nature. As a beginning to our program aimed at the synthesis of this kind of pyrrolizidine alkaloid using our own developed methodology, senecivernic acid **2** became our first synthetic target molecule.

1,4-Addition of lithium dimethylcuprate to **1**[10] gave exclusively *exo*-attacked product **4** (Scheme 1). A methoxycarbonyl group was introduced at the less hindered α-position



Scheme 1 *Reagents and conditions*: a, CH_3Li (4 equiv.), CuI (2 equiv.), THF, −78 ~ −60 °C, 6 h, 94.4%; b, $CH_3O_2CO_2CH_3$, NaH, 50–60 °C, 8 h, 99%; c, CH_3I, CH_2Cl_2, 10% NaOH, cat. Bu_4NI, rt, 30 h, 95%; d, 410 °C, 310 torr, 100%; e, CH_3Li (4 equiv.), CuI (2 equiv.), 4 Å molecular sieves, THF, −78 °C, 4 h, 95%; f, *m*CPBA (1.3 equiv.), cat. Li_2CO_3, CH_2Cl_2, reflux, 16 h, **9**, 78%; **10**, 2.3%; **11**, 6.8%; g, LDA (2 equiv.), THF, −78 °C, gaseous HCHO, −78 °C, 3 h and rt, overnight, 68.6%; h, LDA (2 equiv.), THF, −78 °C, HMPA, gaseous HCHO, −45 °C, 3 h; i, Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 10 h; j, DBU, CH_2Cl_2, rt, 24 h, 81.4% from **9**; k, 1 M NaOH, 60 °C, 3 h, 92%

of the carbonyl using dimethyl carbonate in the presence of an excess of sodium hydride to afford **5**. Ester **5** was methylated with methyl iodide to give **6**. In order to minimize the formation of *O*-methylated product, phase transfer methylation was used and this also produced the *exo*-attacked product **6** (95%) with a trace amount of the corresponding *O*-methylated compound. Retro-Diels–Alder reaction was accomplished by thermolysis of **6** at 410 °C/310 torr to give a cyclopentenone **7**. β-Methyl controlled 1,4-addition of lithium dimethylcuprate to **7** produced **8** and a small amount of an isomer which was not isolable by flash chromatography. Fortunately, Baeyer–Villiger

oxidation of the above mixture provided isolable **9** (78%), **10** (2.3%) and **11** (8.6%), which could be separated by flash chromatography. A solution of **9** in THF was treated with LDA at −78 °C for 90 min, then with excess gaseous formaldehyde at the same temperature and the reaction mixture was stirred for an additional 30 min then allowed to warm to −20 to −40 °C for 3 h, and then finally to room temperature overnight to give **12** directly in 68.6% yield. However, the yield was improved by the following three step procedure. Reaction of the enolate of **9**, generated by treatment of **9** with LDA at −78 °C, with formaldehyde in THF in the presence of HMPA produced hydroxymethylated compound **13** which was directly acetylated to give the corresponding acetate of **13**. Finally treatment of the acetate with DBU at room temperature produced **12** in 81.4% overall yield. Opening the lactone **12** with base afforded crystalline target molecule **2**, mp 134–135 °C. IR and MS spectral data of **2** were identical with those reported in the literature.

However, we found that the ^{1}H NMR spectral data of our synthesized racemic **2** were different from those of the optically active compound **2** obtained by degradation of naturally occurring senecivernine **3a** by Röder's group.[6]† In order to confirm the sterochemistry of our synthesized compound **2**, X-ray analysis‡ was carried out and revealed that our synthesized compound **2**[11] had the correct structure as shown.

In conclusion, an efficiently stereo-, regio- and chemoselective synthesis of a chain compound, senecivernic acid **2**, has been achieved using a rigid molecule, tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one **1**, as the starting material and without using any protecting groups in overall ten steps and in 50% overall yield. As optically active **1** is available,[12] the total synthesis of optically active **2** is guaranteed and the syntheses of senecivernine **3a**, merenskine **3b** and sceleratine **3c** are in progress.

Experimental

2β,3β-Dimethyl-2α-methoxycarbonylcyclopent-4-enone 7

Into the tube of the thermolysis apparatus was placed substrate **6** (200 mg) and the apparatus was evacuated then filled with N_2 and the pressure adjusted to 310 mm Hg. The inside cold finger was cooled to −78 °C with dry ice–acetone and the tube was put into the heating bath previously heated to 420 °C for 3 min. The heating bath was removed and the tube was allowed to warm to room temperature. The thermolysis product, together with the unreacted substrate on the cold finger was collected by washing with EtOAc. The above operation repeated five times with a total amount of **6** of 1.198 g (5.12 mmol). The collected EtOAc solution was concentrated *in vacuo*. The residual yellow oil was separated by flash column chromatography (light petroleum–EtOAc 98 : 2 ~90 : 10) to afford substrate **6** (280 mg) and enone **7** (660 mg). By recycling recovered **6** it can be changed into enone **7** completely, making the final yield of **7** about 100%; ν_{max}(neat)/cm^{-1} 3000, 2950, 1745, 1715, 1600; δ_H 1.18 (d, *J* 7.0 Hz, 3H, C_3-Me), 1.29 (s, 3H, C_2-Me), 3.45 (m, *J* 7.0 Hz, 1H, C_3-H), 3.72 (s, 3H, CO_2Me), 6.18 (dd, *J* 5.2 Hz, *J* 1.8 Hz, 1H, C_5-H), 7.64 (dd, *J* 1.8 Hz, *J* 5.2 Hz, 1H, C_4-H); *m/z* 169 (M^+ + 1, 25.85), 168 (M^+, 17.26), 137 (74.84), 125 (31.19), 109 (91.78), 93 (10.64), 81 (100), 65 (18.30), 59 (15.79), 54 (67.76), 43 (52.78). HRMS: calcd. for $C_9H_{12}O_3$ 168.0786. Found 168.0769.

2β,3β,4α-Trimethyl-2α-methoxycarbonylcyclopentanone 8

A suspension of CuI (1.520 g, 8.0 mmol) and activated molecular sieves (3 g) in dry THF (80 ml) was stirred for 30 min at room temperature, then cooled to −20 °C and CH_3Li in dry diethyl ether (1.89 M, 8.5 ml, 16 mmol) was added dropwise. The reaction solution was stirred at −5 ~ −30 °C for an additional 2 h, then cooled to −78 °C and then compound **7** (671 mg, 3.994 mmol) was added dropwise, in dry THF (20 ml) (cooled with dry ice–acetone in advance) during 80 min and the resulting yellow suspension was stirred at −78 °C for an additional 4 h. To the mixture was added saturated aqueous NH_4Cl (200 ml), filtered through Celite and it was then separated. The aqueous phase was extracted with EtOAc (3 × 100 ml) and the combined organic extracts washed with brine and dried over anhydrous Na_2SO_4. Removal of EtOAc *in vacuo* followed by flash chromatography (light petroleum–EtOAc 98 : 2 ~ 94 : 6) afforded compound **8** (713 mg, 97%) as a colorless oil. The ratio of 4α/4β methyl group was 88 : 12, as determined by GC. ν_{max}(neat)/cm^{-1} 2900, 1745, 1720; δ_H 0.866 (d, *J* 5.65 Hz, $C_{4'}$-Me), 1.014 (d, *J* 6.88 Hz, C_3-Me and $C_{3'}$-Me), 1.157 (d, *J* 5.65 Hz, C_4-Me), 1.167 (s, C_2-Me), 1.772 ~ 1.892 (heptet, *J* 6.34 Hz, C_4-H), 2.078 (dd, *J* 11.96 Hz, *J* 18.48 Hz, C_5-H$_\alpha$), 2.24–2.36 (m, C_3-H), 2.547 (dd, *J* 7.20 Hz, *J* 18.15 Hz, C_5-H$_\beta$), 3.695 (s, $C_{2'}$-CO_2Me), 3.713 (s, C_2-CO_2Me); *m/z* 185 (M^+ + 1, 17.66), 156 (36.48), 141 (7.88), 125 (6.28), 115 (33.16), 109 (7.79), 97 (13.89), 83 (100.00), 70 (21.22), 59 (30.89), 43 (26.53). HRMS: calcd. for $C_{10}H_{16}O_3$ 184.1099. Found 184.1095.

5α-Methoxycarbonyl-3α,4β,5β-trimethyl-5-pentanolide 9, 2α-methoxycarbonyl-2β,3β,4α-trimethyl-5-pentanolide 10 and 5α-methoxycarbonyl-3β,4β,5β-trimethyl-5-pentanolide 11

Under an atmosphere of N_2, compound **8** (with a small amount of the 4β-methyl isomer) (750 mg, 4.076 mmol), MCPBA (1.4 g, purity >70%, 5.68 mmol) and Li_2CO_3 (34 mg, 0.046 mmol) in dry CH_2Cl_2 (20 ml) was refluxed for 40 h and cooled to room temperature. Saturated aqueous Na_2SO_3 was added to decompose excess of MCPBA. After addition of CH_2Cl_2 (200 ml) to the mixture, the organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 50 ml) and brine, dried over anhydrous Na_2SO_4 and concentrated. Purification of the residue on silica gel (light petroleum–EtOAc 98 : 2 ~ 95 : 5) gave compound **9** (620 mg, 78%), compound **10** (18 mg, 2.3%) and compound **11** (68 mg, 8.6%) as colorless oils.

Compound 9. ν_{max}(neat)/cm^{-1} 2900, 1740; δ_H 0.944 (d, *J* 6.69 Hz, 3H, C_4-Me), 1.035 (d, *J* 6.58 Hz, 3H, C_3-Me), 1.509 (s, 3H, C_5-Me), 1.764 ~ 1.941 (m, 1H, C_3-H), 2.024 (m, 1H, C_4-H), 2.127 (dd, *J* 17.65 Hz, *J* 11.44 Hz, 1H, C_2H$_\beta$), 2.662 (dd, *J* 17.78 Hz, *J* 5.42 Hz, 1H, C_2-H$_\alpha$); *m/z* 201 (M^+ + 1, 1.75), 141 (76.59), 113 (21.96), 69 (100.00), 59 (6.52), 56 (35.08); HRMS: calcd. for $C_{10}H_{10}O_4$ 200.1049. Found 200.1074.

Compound 10. ν_{max}(neat)/cm^{-1} 2900, 1740; δ_H 0.918 (d, *J* 6.92 Hz, 3H, C_3-Me), 0.967 (d, *J* 6.62 Hz, 3H, C_4-Me), 1.424 (s, 3H, C_2-Me), 1.865 (m, 1H, C_4-H), 2.276 (m, 1H, C_3-H), 3.770 (s, 3H, CO_2Me), 3.838 (dd, *J* 10.86 Hz, *J* 11.36 Hz, 1H, C_5-H$_\alpha$), 4.268 (dd, *J* 11.36 Hz, *J* 5.29 Hz, 1H, C_5-H$_\beta$); *m/z* 201 (M^+ + 1, 2.48), 175 (3.54), 169 (10.91), 141 (97.50), 127 (75.22), 114 (19.67), 109 (37.21), 95 (30.48), 83 (62.48), 73 (21.93), 69 (60.16), 59 (46.88), 56 (100.00). HRMS: calcd. for $C_{10}H_{16}O_4$ 200.1049. Found 200.1057.

Compound 11. ν_{max}(neat)/cm^{-1} 2900, 1730; δ_H 0.956 (d, *J* 6.94 Hz, 3H, C_4-Me), 0.977 (d, *J* 5.85 Hz, 3H, C_3-Me), 1.549 (s, 3H, C_5-Me), 2.067 ~ 2.168 (m, 2H, C_4-H, C_2-H$_\alpha$), 2.112 (m, 1H,

† δ_H ([^{2}H$_6$]DMSO) 6.00 (1H, s, H-8a), 5.44 (1H, s, H-8b), 5.1–3.5 (3H, D_2O exch., H-1, H-5, H-7), 2.85 (1H, qd, *J* 7.1, 2.9, H-3), 1.88 (1H, qd, *J* 7.1, 2.9, H-4), 1.23 (1H, s, H-6), 0.98 (1H, d, *J* 7.1, H-9) and 0.78 (1H, d, *J* 7.1, H-10). Lit.[6] δ_H ([^{2}H$_6$]DMSO) 7.73 (3H, D_2O exch., H-1, H-5, H-7), 6.50 (1H, s, H-8a), 5.69 (1H, s, H-8b), 2.45 (1H, m, H-3), 2.11 (1H, m, H-4), 1.53 (1H, s, H-6), 1.24 (1H, d, *J* 7, H-9), 1.06 (1H, d, *J* 7, H-10).

‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/226.

C_3-H), 2.522 (dd, *J* 12.2 Hz, 1H, C_2-H_β), 3.789 (s, 3H, CO_2Me); *m*/*z* 201 ($M^+ + 1$, 1.51), 141 (23.68), 113 (12.78), 69 (100.00), 59 (7.57), 56 (36.21). HRMS: calcd. for $C_{10}H_{16}O_4$ 200.1049. Found 200.1047.

5α-Methoxycarbonyl-2-methylene-3α,4β,5β-trimethyl-5-pentanolide 12

Method A. To a cold (−30 °C) THF solution (20 ml) of Pr^i_2NH (0.11 ml, 0.75 mmol) was added a hexane solution of Bu″Li (2.3 M, 0.3 ml, 0.69 mmol). The resulting solution was stirred for 90 min at −40 °C ~ −20 °C, then cooled to −78 °C. A THF solution of compound **9** (100 mg, 0.5 mmol) was added, and the resultant solution was stirred at −78 °C for an additional 90 min. Formaldehyde gas was introduced with the N_2 flow (generated by the thermolysis of paraformaldehyde at 160 °C) and the reaction mixture was stirred at −20 ~ −40 °C for an additional 3 h, then gradually warmed to room temperature and stirred overnight. Saturated aqueous NH_4Cl (50 ml) was added and the mixture filtered through Celite, and extracted with CH_2Cl_2 (4 × 35 ml). The usual work-up gave a residue which was purified on silica gel (light petroleum–EtOAc 95 : 5 ~ 85 : 15) to give lactone **12** (64 mg) as a colorless oil in 68.6% yield according to the recovered starting material **9** (12 mg).

Method B. To a cold (−78 °C) THF solution (10 ml) of Pr^i_2NH (0.24 ml, 1.7 mmol) was added a hexane solution of Bu″Li (0.95 ml, 1.8 M, 1.7 mmol). The mixture was warmed to 0 °C, stirred for 15 min and cooled to −78 °C. A THF solution of compound **9** (190 mg, 0.95 mmol) was added, and the resultant solution was stirred at −78 °C for 1 h. HMPA (0.71 ml, 4.0 mmol) was added. After stirring for 10 min, freshly prepared formaldehyde in THF (30 ml, about 20 mmol, obtained by thermal cracking of paraformaldehyde in the presence of *p*-toluenesulfonic anhydride) was added. The mixture was stirred at −78 °C for 10 min and at −45 °C for 3 h. Saturated aqueous NH_4Cl and Et_2O were added and the mixture separated. The aqueous phase was extracted with Et_2O (3 × 40 ml). The combined organic phase was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was dissolved in CH_2Cl_2 (10 ml) and treated with Ac_2O (0.42 ml, 4.2 mmol), Et_3N (0.56 ml, 4.0 mmol) and a catalytic amount of DMAP. The mixture was stirred at room temperature overnight. To this mixture was added DBU (0.35 ml, 2.32 mmol), and the mixture was stirred at room temperature for a further 24 h. The reaction mixture was diluted with Et_2O and washed with 1% HCl and brine. The organic phase was dried over Na_2SO_4, and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography (light petroleum–EtOAc 95 : 5 ~ 90 : 10) on silica gel gave the product **12** (110 mg) as a colorless oil in 81.4% yield according to the recovered starting material **9** (62 mg). ν_{max}(neat)/cm^{-1} 2900, 1730, 1605, 755; δ_H 1.011 (d, *J* 6.74 Hz, 3H, C_4-Me), 1.216 (d, *J* 7.05 Hz, 3H, C_3-Me), 1.520 (s, 3H, C_5-Me), 2.142 (dq, *J* 6.88 Hz, *J* 9.02 Hz, 1H, C_4-H), 2.466 (m, 1H, C_3-H), 3.778 (s, 3H, CO_2Me), 5.695 (d, *J* 1.84 Hz, 1H, CH_2=), 6.481 (d, *J* 1.98 Hz, 1H, CH_2=); *m*/*z* 213 ($M^+ + 1$, 1.80), 212 (M^+, 1.11), 153 (100.00), 125 (4.52), 111 (17.53), 109 (38.79), 81 (38.42), 67 (16.11), 54 (12.69). HRMS: calcd. for base peak, $C_9H_{13}O_2$ ($M^+ - CO_2Me$) 153.0916. Found 153.0938.

Acknowledgements

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10 All compounds in this paper are racemic.
11 Crystal data for compound **2**: $C_{10}H_{16}O_5$, triclinic, *P*1 with $a = 8.858(3)$ Å, $b = 11.094(3)$ Å, $c = 5.961(2)$ Å, $\alpha = 101.23(3)°$, $\beta = 107.81(2)°$, $\gamma = 89.90(3)°$, $V = 546(3)$ Å^3, $Z = 2$, with 201 parameters refined against 1135 reflections having $I > 3.06(I)$, $R = 0.043$, $R_w = 0.058$.
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