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# Enantioselective synthesis of senecivernine, a 12-membered dilactonic pyrrolizidine alkaloid

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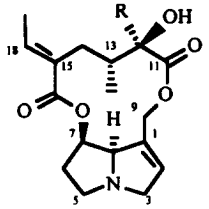
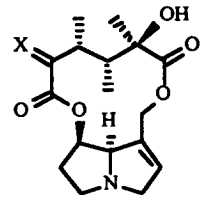
**Abstract**

The first synthesis of the title compound is described using a rigid molecule tricyclodecadienone **8** as the starting material and a retro-Diels–Alder reaction as the key step for the efficient synthesis of a masked seneciverinic acid **20**; the target was prepared using the esterification of two hydroxy groups of (+)-retronecine **7** sequentially with compound **20** in a total of 19 steps and 18% overall yield. 

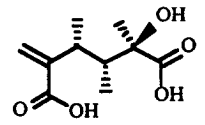
12-Membered dilactonic pyrrolizidine alkaloids have attracted much attention due to their interesting chemical structure and unique biological activities.[1,2] Three members, integerrimine **1**,[3–5] its 15,18-dihydroderivative, yamataimine[6] and usaramine **2**[5] have been synthesized (Scheme 1).



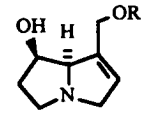
1 integerrimine R = $CH_3$
2 usaramine R = $CH_2OH$



3 senecivernine X = $CH_2$
4 merenskine X = α - OH, β - $CH_2Cl$
5 sceleratine X = α - OH, β - $CH_2OH$



6 senecivernic acid



(+) - 7 a = H
b = TBS

Scheme 1.

Senecivernine **3** was isolated from *Senecio vernalis* Walkstein et Kit by the Roder group[7] in 1979 and its full stereochemistry, showing the same stereochemistry as that in compounds merenskine **4**[9] and sceleratine **5**,[10] was recently determined with X-ray analysis by Parvez.[8] Therefore, senecivernine **3** might be a biogenetic precursor of merenskine **4** and sceleratine **5** even though the corresponding epoxide of senecivernine **3** has not been isolated from nature. In comparison with integerrimine **1** and

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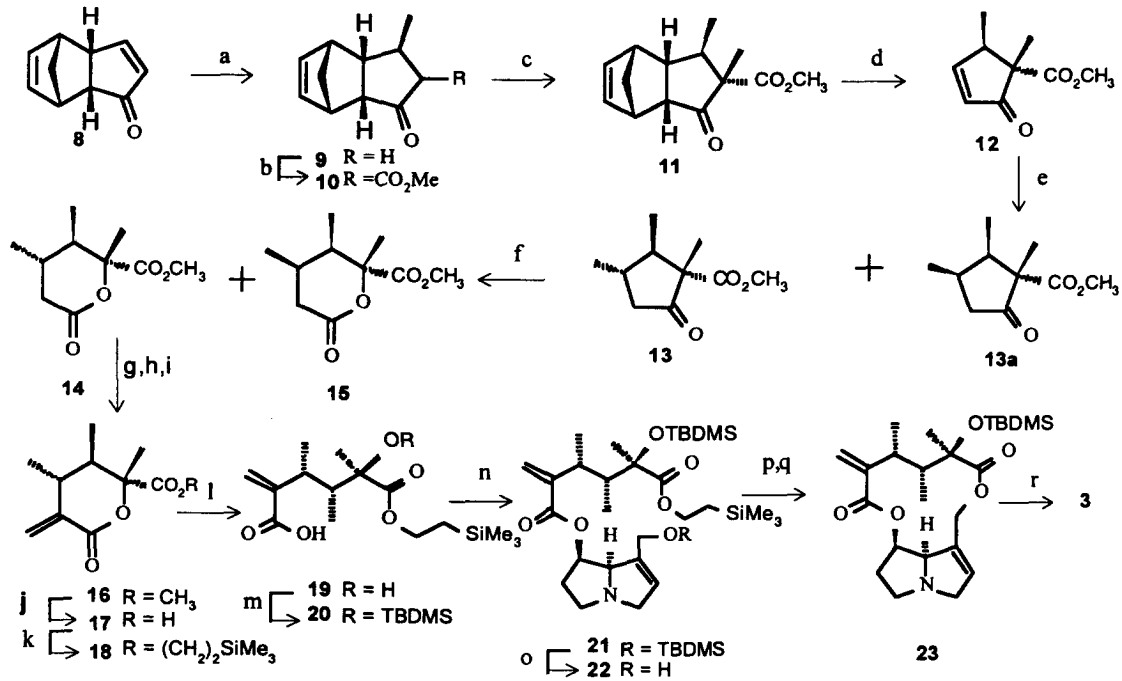
usaramine **2**, senecivernine **3** has an additional chiral center at $C_{14}$ and a more sensitive *exo*-methylene group at $C_{15}$, which is an important moiety in many natural products responsible for antitumor activity. This distinct feature greatly arouses our interest in the possible biological activity of senecivernine **3** and a total synthesis should be highly significant.

A major point for the synthesis of the pyrrolizidine alkaloid senecivernine **3** is the development of efficient methodologies for the introduction of all functional groups in a fully functionalized compound, and in the manner for the coupling of the necic base, a dihydroxy alkaloid (+)-retronecine **7** with the dicarboxylic acid **6** under mild conditions, during which the labile *exo*-methylene group in compound **6** would survive. During the course of our program in natural products synthesis by retro-Diels–Alder reaction,[11–15] a rigid tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one **8** was used as a starting material for stereospecific introduction of the necessary functional groups and substituents, then retro-Diels–Alder reaction released a cyclopentenone derivative, which was a suitable precursor for the natural product synthesis. We now describe using this methodology for the first stereospecific synthesis of the title compound (Scheme 2).




Scheme 2. Reagents and conditions: (a) 4.0 equiv. $CH_3Li$, 2.0 equiv. CuI, THF, −78~ −60°C, 6 h, 94.4%; (b) $CH_3OCO_2CH_3$, 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) 4.0 equiv. $CH_3Li$, 2.0 equiv. CuI, 4 Å molecular sieves, THF, −78°C, 4 h, 95%; (f) 1.3 equiv. *m*-CPBA, cat. $Li_2CO_3$, $CH_2Cl_2$, reflux, 16 h, **14** (71%), **15** (8.6%); (g) 2.0 equiv. LDA, THF, −78°C, HMPA, HCHO(g), −45°C, 3 h; (h) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 10 h; (i) DBU, $CH_2Cl_2$, rt, 24 h, 81.4% from **13**; (j) 1.2 equiv. LiOH, THF:$H_2O$ (1:1), 0°C, 8 h, 91.4%; (k) 2.0 equiv. DCC, 1.5 equiv. 2-trimethylsilylethanol, cat. amount DMAP, $CH_2Cl_2$, 0°C, overnight, 83%; (l) 2.0 equiv. LiOH, $H_2O_2$ THF/$H_2O$, 0°C, overnight, 82%; (m) (I) 3.4 equiv. TBS·OTf, 6.8 equiv. 2,6-lutidine, $CH_2Cl_2$, 0°C, 1 h; (II) $K_2CO_3$, MeOH:THF:$H_2O$ (3:1:1), 25°C, 3 h, 99%; (n) (I) 3.0 equiv. $Et_3N$, 1.5 equiv. $(EtO)_2P(O)Cl$, THF, rt, 3 h; (II) 1.5 equiv. **7b**, cat. amount DMAP, 1.5 equiv. $CH_3Li$, THF, rt, 15 h, 86%; (o) 50 equiv. $NH_4F$, MeOH:$H_2O$ (3:1), 60–65°C, 4 h, 93%; (p) 2.0 equiv. MsCl, 2.3 equiv. $Et_3N$, $CH_2Cl_2$, 0°C, 30 min; (q) 14 equiv. *n*-$Bu_4NF$, THF, 2 h, 93% from **21**; (r) 40% HF, $CH_3CN$, reflux, 6 h, 80%

1,4-Addition of lithium dimethyl cuprate to (−)-**8**[16] gave exclusively *exo*-product **9**. A methoxycarbonyl group was introduced at the less hindered α-position of the carbonyl with dimethyl carbonate

in the presence of excess sodium hydride to afford **10**. In order to minimize the formation of *O*-methylated product, phase transfer methylation was chosen to produce the *exo*-methylated product **11** (91.8%) with a small amount of the corresponding *O*-methylated compound (6.7%). Retro-Diels–Alder reaction was accomplished by thermolysis of **11** at 410°C/340 torr to give the cyclopentenone **12**. β-Methyl controlled 1,4-addition of lithium dimethyl cuprate to **12** produced **13** and a small amount of an isomer **13a**, which could not be isolated by flash chromatography. Fortunately, Baeyer–Villiger oxidation of the above mixture provided isolable **14** (71%) and **15** (8.3%). Reaction of the enolate generated by treatment of **14** with LDA at –78°C, with formaldehyde in THF in the presence of HMPA introduced a hydroxymethyl group, which was then directly acetylated and treated with DBU at room temperature to give methylene lactone **16**. Selective hydrolysis of **16** produced a monoacid **17**, which condensed with 2-trimethylsilylethanol to give the lactone **18**. Carefully opening the lactone **18** with base provided the hydroxy acid **19**, which was treated with *t*-butyl-dimethylsilyltriflate and then selectively hydrolyzed to the desired monoacid **20**. The carboxylic acid in **20** was activated as its acyl phosphate and condensed with the lithium alkoxide of **7b**[17] to give the ester **21**. The primary hydroxy silylether was selectively cleaved under mild conditions to give the alcohol **22**, which was unstable and used directly for the next step without purification. Mesylation of the alcohol **22** and selective cleavage of the trimethylsilylated ester with spontaneous macrolactonization produced dilactone **23**. Finally, removal of the silyl protecting group gave the target molecule **3**, which was identical with data reported by the Roder group[7] by comparison of the spectroscopic data.[18] Therefore, we have finished the first enantioselective synthesis of the highly functionalized 12-membered dilactone pyrrolizidine alkaloid senecivernine **3** from tricyclodecadienone **8** in 19 steps and 18% overall yield.

## Acknowledgements

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18. **3**: m.p. 106–108°C; $[\alpha]_D^{23}$=–34.2 (*c* 0.5 in ethanol) (lit[7] m.p. 103–105°C; $[\alpha]_D^{20}$=–34.9 (in ethanol)); IR (neat): ν=3522, 2928, 1720 (brs), 1633, 1453, 1257, 1166, 1131, 950 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ=0.85 (d, *J*=7.1 Hz, 3H, $CH_3$), 1.08 (d, *J*=7.0 Hz, 3H, $CH_3$), 1.33 (s, 3H, $CH_3$), 1.60–1.79 (m, *J*=1.5, 7.1 Hz, 1H, CH), 2.01–2.31 (m, 1H, $CH_2$), 2.35–2.50 (m, 1H, $CH_2$), 2.50–2.60 (m, 1H, CH), 2.60–2.75 (m, 1H, $CH_2$) 3.15 (m, 1H, OH), 3.28 (m, 1H, $CH_2$), 3.39 (dd, *J*=1.8, 6.0 Hz, 1H, $CH_2$), 3.97 (dd, *J*=1.8, 6.0 Hz, 1H, $CH_2$), 4.07 (dd, *J*=0.7, 11.5 Hz, 1H, $CH_2$), 4.35 (m, 1H, CH), 5.07 (dt, *J*=1.1, 3.8 Hz, 1H, CH), 5.23 (s, 1H, $CH_2$=), 5.51 (d, *J*=11.7 Hz, 1H, $CH_2$), 5.85 (s, 1H, $CH_2$=), 6.21 (m, 1H, –CH=); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ=5.8, 12.1, 26.3, 34.3, 36.0, 40.8, 53.2, 60.8, 62.6, 75.6, 77.5, 77.8, 120.8, 131.5, 136.3, 147.5, 169.0, 178.4; MS (70 eV): *m/z* (%): 336 (14) [$M^+$+1], 291 (7.3) [$M^+$–$CO_2$], 248 (15) [$M^+$–$CO_2$–$CH_3CO$], 220 (31) [$M^+$–$CO_2$–$CH_3CO$–$C_2H_4$], 120 (100) [$C_8H_{10}N$].