Asymmetric synthesis of dimethyl swazinecate and structural confirmation of its parent alkaloid (−)-swazine

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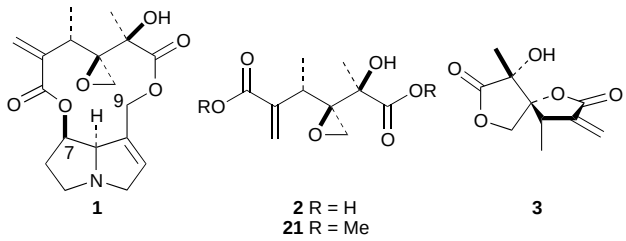
Synthesis of dimethyl swazinecate, a principal component of the pyrrolizidine alkaloid swazine, was completed from (*S*)-(−)-β-citronellal; an X-ray crystallographic analysis of natural swazine confirmed its absolute stereostructure.

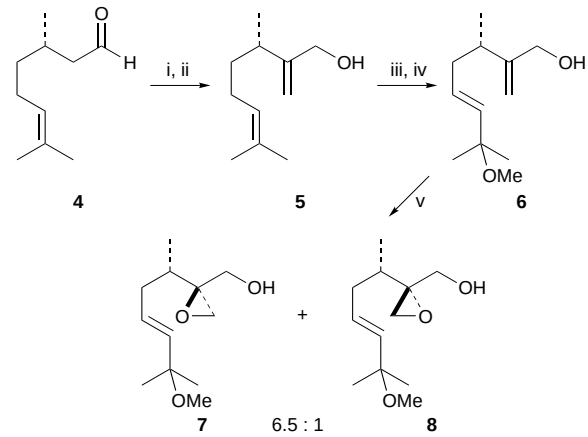
Pyrrolizidine alkaloids are widespread among plants of the *Senecio* family, many of which possess toxic properties that pose serious risk to human and animal health.[1] (−)-Swazine **1**, first isolated from *Senecio swaziensis* Compton,[2] is among the more complex members of this class of alkaloids, consisting of a functionalized adipic acid derivative **2** (swazinecic acid) that bridges the C7 and C9 hydroxy groups of the pyrrolizidine retronecine to form a twelve-membered dilactone. Neither acidic nor careful basic hydrolysis of **1** has permitted isolation of intact **2**. Instead, the constitution of this dicarboxylic (necic) acid was inferred from the spirolactone **3** obtained upon treatment of **1** with hot, 1.5 M sulfuric acid. The structure of **3** was established by X-ray crystallographic analysis of its *p*-bromobenzoate.[2] Initially, swazine was formulated as the dilactone isomeric with **1**, in which swazinecic acid **2** was connected to retronecine in the reverse orientation to that shown. This assignment was subsequently revised,[3] and the revision was accepted after a more complete degradative and spectroscopic investigation.[4] Herein, we report the first synthesis of swazinecic acid, characterized as its dimethyl ester, which confirms its absolute stereostructure as **2**. We also describe an X-ray crystallographic analysis of natural swazine which now substantiates the designation of this alkaloid as **1**.



1 **2** R = H, **21** R = Me **3**

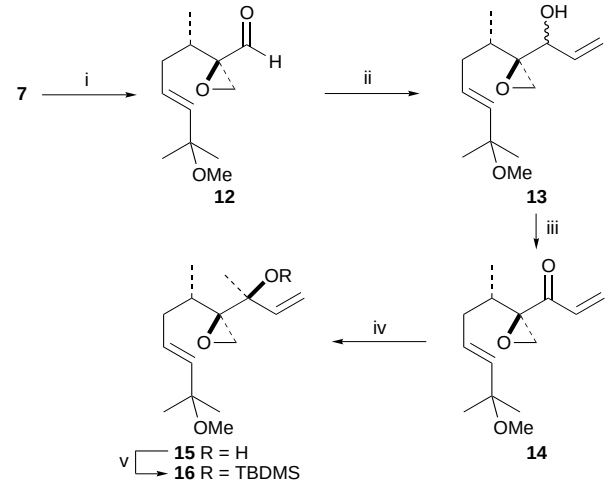
Our approach, which employs β-citronellal as the starting material,[5] hinges upon oxidative truncation of an elaborated terpenoid structure to generate a dicarboxylic acid having the requisite functionality and configuration of the necic acid.[6–10] Since our planned route to **2** involved early introduction of a relatively sensitive epoxide, it was essential that later steps in the sequence avoid reagents which would destroy this function.

α-Methylenation of (−)-**4**, followed by Luche reduction of the resultant α,β-unsaturated aldehyde (as described for the enantiomeric series),[9] gave the allylic alcohol **5** (Scheme 1). The trisubstituted olefin of this diene underwent selective methoxyselenation using Toshimitsu's conditions,[11] and the intermediate alkyl selenide was oxidized to afford **6** in good yield. Asymmetric epoxidation of **6** using (*S*,*S*)-(+)-diisopropyl tartrate (DIPT) as the chiral adjuvant[12] gave **7** and **8** in the ratio 6.5 : 1.

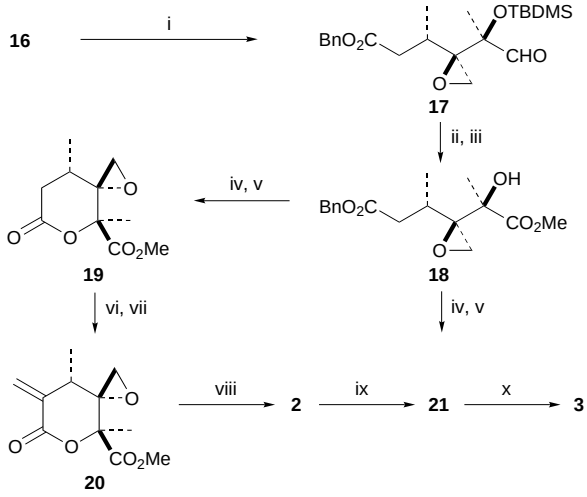


Scheme 1 *Reagents and conditions*: i, LDA, $CH_2{=}N^+Me_2I^-$, MeI, $NaHCO_3$, 94%; ii, $NaBH_4$, $CeCl_3{\cdot}7H_2O$, 93%; iii, PhSeCl, $NaHCO_3$, THF–MeOH; iv, H_2O_2, $NaHCO_3$, THF–H_2O, 82% (from **5**); v, Bu^tOOH, $Ti(OPr^i)_4$, (+)-DIPT, CH_2Cl_2, 92%

After chromatographic separation, **7** was oxidized to aldehyde **12** which was converted to alcohol **13** upon treatment with vinylmagnesium bromide at low temperature (Scheme 2). Further oxidation with Dess–Martin periodinane produced α,β-unsaturated ketone **14**. Chelation-controlled Grignard addition to this ketone was expected to occur selectively at the *re* face of the carbonyl group, and when **14** was treated carefully with methylmagnesium bromide at low temperature a single alcohol,



Scheme 2 *Reagents and conditions*: i, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 95%; ii, vinylmagnesium bromide, THF, −78 °C, 72%; iii, Dess–Martin periodinane, 100%; iv, methylmagnesium bromide, Et_2O, −78 °C, 60%; v, TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −35 °C, 76%



Scheme 3 *Reagents and conditions*: i, O_3, $(CF_3CO)_2O$, BnOH–CH_2Cl_2, $NaHCO_3$, Et_3N, −78 °C; ii, $NaClO_2$, Bu^{t}OH, Me_2C=CHMe; iii, CH_2N_2, Et_2O, 65% from **16**; iv, H_2, Pd/C; v, 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent), 99% from **18**; vi, LDA, CH_2O, 55%; vii, MsCl, Et_3N, 96%; viii, KOH, MeOH–H_2O; ix, CH_2N_2, Et_2O, 63% from **20**; x, H_2SO_4

assigned structure **15**, was obtained accompanied by the product of conjugate addition.

Alcohol **15** was protected as its *tert*-butyldimethylsilyl ether **16** in a process that retained the epoxide intact. Ozonolytic cleavage of **16** in the presence of benzyl alcohol, trifluoroacetic anhydride and triethylamine at low temperature gave the aldehyde ester **17** in excellent yield (Scheme 3).[13] Unfortunately, the inherent instability of **17** resulting from its propensity towards intramolecular aldol condensation demanded immediate oxidation of this aldehyde to a carboxylic acid, during which the silyl ether was cleaved. Treatment of the resultant α-hydroxy acid with diazomethane afforded **18** which underwent hydrogenolysis of the benzyl ester followed by lactonization with Mukaiyama's reagent[14] to give **19**. Condensation of the lithium enolate of **19** with formaldehyde produced a stereoisomeric mixture of hydroxymethyl lactones which, when exposed to methanesulfonyl chloride and base, led directly to *exo* methylene δ-lactone **20**. Saponification of **20** furnished swazinecic acid **2** which was characterized as its dimethyl ester **21**.‡

Since there is no record of either **2** or **21** having been obtained by degradation of swazine **1**, the structure of synthetic dimethyl swazinecate was confirmed by its conversion to the spirodilactone **3** upon treatment with sulfuric acid in hot THF. The spectroscopic properties of **3** obtained by this method matched those recorded for the same substance derived from **1**.

Final confirmation of the structure, including absolute configuration, of swazinecic acid was obtained by X-ray crystallographic analysis of swazine itself (Fig. 1).§ Since hydrolysis of swazine is known to yield (+)-retronecine, whose absolute configuration has been determined by independent synthesis,[15] the full structure of **1** and hence **2** is as shown.

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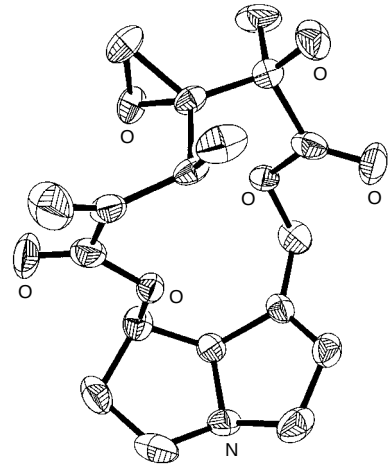

Fig. 1 ORTEP plot of the crystal structure of swazine **1**. Thermal ellipsoids are drawn at the 50% probability level.

Notes and References

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‡ *Selected data* for **21**: $[\alpha]_D^{27}$ −38.4 (*c* 0.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.19 (3 H, d, *J* 7), 1.47 (3 H, s), 2.44 (1 H, d, *J* 4), 2.91 (1 H, d, *J* 4), 3.62 (1 H, q, *J* 7), 3.77 (3 H, s), 3.81 (3 H, s), 5.52 (1 H, s), 6.17 (1 H, s); δ_C (100 MHz, C_6D_6) 17.2, 22.8, 30.5, 45.2, 51.9, 52.7, 63.8, 77.8, 123.0, 141.3, 168.0, 175.0; ν_{max}/cm^{-1} 3472, 2959, 1733, 1450, 1269, 1156, 1103, 1035; *m*/*z* (CI) 259 (M^+ + 1), 241, 227, 209, 199, 181, 177, 167, 155, 125.

§ *Crystal data* for **1**: $C_{18}H_{23}NO_6$, (MW = 349.37), orthorhombic, space group $P2_12_12_1$ (No. 19), *a* = 8.940(2), *b* = 12.229(2), *c* = 16.706(3) Å, *V* = 1826.4(6) Å^3, *Z* = 4, D_c = 1.271 Mg m^{-3}. A total of 1936 data were collected on a Siemens P4 diffractometer equipped with Cu-Kα radiation (λ = 1.54178 Å, μ = 0.795 mm^{-1}) of which 1775 were unique (R_{int} = 0.0335). A solution was obtained using direct methods as programmed in SHELXS-90 and refined against all data using the program SHELXL 97. The final residuals are *R*1 = 0.0366 (all data), *wR*2 = 0.0990 (all data) with a GoF = 1.071. Supplementary materials in electronic format (CIF file) are available from the authors upon request. CCDC 182/758.

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