Asymmetric Synthesis of (+)-Nemorensic Acid— Revision of the Stereochemistry of the Pyrrolizidine Alkaloid Nemorensine

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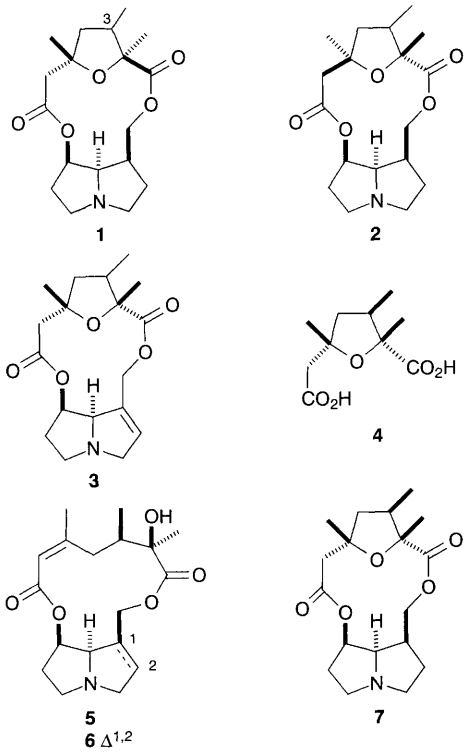
(+)-Nemorensic acid, the necic acid constituent of the pyrrolizidine alkaloid nemorensine, is shown to be (2*R*,3*R*,5*S*)-2-carboxy-2,3,5-trimethyltetrahydrofuranacetic acid by synthesis from (*R*)-(+)-β-citronellol, and a corrected structure for the parent alkaloid nemorensine is established by a single crystal X-ray analysis.

Plants of the *Senecio* family produce a large number of pyrrolizidine-containing alkaloids, many of which are hepatotoxic.[1] Nemorensine, isolated from three varieties of *S. nemorensis*,[2] was initially assigned structure **1**,[3] but this was subsequently revised without explanation to the stereoisomeric 2,5-disubstituted tetrahydrofuran **2**.[4] 'Oxonemorensine' was also isolated in the course of these studies and was postulated as the *N*-oxide of **2**.[4] A related alkaloid from *S. nemorensis*, retroisosenine, has been allocated structure **3** in which a *cis* 2,5-disubstituted tetrahydrofuran was put forward for the dicarboxylic (necic) acid portion.[3] Although the configuration at C-3 was not specified in any of these structures, a synthesis of racemic **4** ['(±)-nemorensic acid'] by Klein[5] established the relative configuration shown. Independently, the same necic acid was found among the saponification products of bulgarsenine **5**[6] and doronenine **6**.[7]

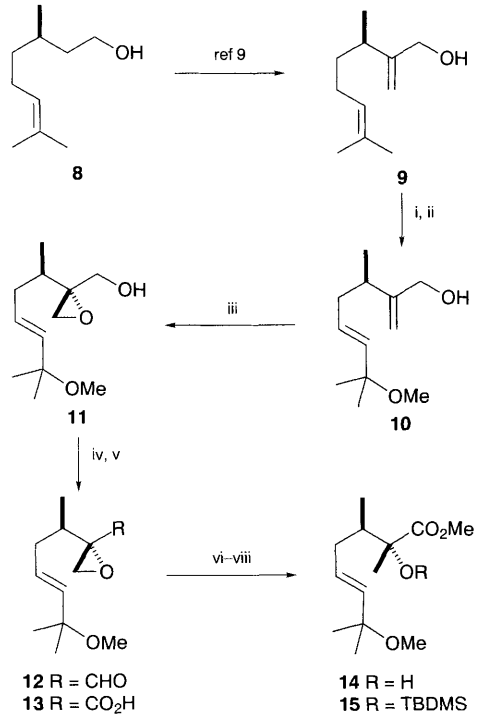
The foregoing results along with inconsistencies in the ^{1}H NMR data reported for 'nemorensic acid'[3] led us to speculate that both structures attributed to the necic acid portion of nemorensine in **1** and **2** were in error. Herein, we describe an asymmetric synthesis of *'cis'* and *'trans'* nemorensic acids which confirms that this is indeed the case. We also report an X-ray crystallographic analysis of the parent alkaloid nemorensine which establishes that its structure, including absolute configuration, is correctly represented by **7**.

Our previous studies on the asymmetric synthesis of necic acid components of the macrolactone pyrrolizidine alkaloids integerrimine[8,9] and usaramine[9,10] have shown that (*R*)-(+)-β-citronellol **8** is a valuable starting material for this purpose.[11]



With the aim of relaying the absolute configuration of this monoterpene into the three stereogenic centers of nemorensic acid,[12] (+)-**8** was first converted to allylic alcohol **9**. Methoxyselenation of **9**,[13] followed by oxidation of the intermediate alkylselenide, gave **10** which was subjected to Katsuki–Sharpless epoxidation with (*R*,*R*)-(−)-diisopropyl tartrate as the chiral adjuvant.[14] The (2*S*,3*R*) epoxide **11**, produced in >98% diastereoisomeric excess, was oxidised under Swern conditions[15] to aldehyde **12** and then to carboxylic acid **13** with sodium chlorite.[16] Selective reduction of the epoxide was accomplished at low temperature with lithium aluminum hydride, and treatment of the resulting α-hydroxy acid with diazomethane yielded **14.** This alcohol was protected as its *tert*-butyldimethylsilyl (TBDMS) ether **15**.

The octenoate chain of **15** was cleanly truncated by ozonolysis to furnish **16**. A carefully controlled Grignard reaction of this aldehyde with methylmagnesium bromide afforded **17**, which after Swern oxidation[15] gave **18**. Wadsworth–Emmons olefination[17] of **18** with phosphonate **19** produced a 5.6:1 mixture of (*E*)- and (*Z*)-α,β-unsaturated esters, **20** and **21**, which were separated by chromatography. Upon exposure of **20** to tetrabutylammonium fluoride, the derived alcohol underwent spontaneous cyclization to a 4.5:1 mixture of tetrahydrofurandicarboxylic esters **22** and **23**, respectively. These isomers were readily separated by HPLC (250 × 4.6 mm silica column, 15:1 hexane–ethyl acetate, 3 ml min^{-1}). The major stereoisomer **22** was shown to possess



Scheme 1 *Reagents and conditions*: i, PhSeCl, MeOH, $NaHCO_3$; ii, H_2O_2, 84% from **8**; iii, $Ti(OPr^i)_4$, (−)-DIPT, Bu^tOOH, 94%; iv, $(COCL)_2$, DMSO, Et_3N, 98%; v, $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, 90%; vi, $LiAlH_4$, THF, 45%; vii, CH_2N_2, 100%; viii, TBDMSOTf, Et_3N, 82%

2,5-*trans* configuration at the tetrahydrofuran nucleus by means of a nuclear Overhauser enhancement experiment in which the *pro-(R)* hydrogen (H_α) at C-4 was correlated with methyl protons at C-5 and the *pro-(S)* hydrogen (H_β) with methyl signals at C-2 and C-3. Saponification of **22** afforded **24**† which exhibited properties clearly different from those recorded for the hydrolysis product of nemorensine.[3] On the other hand, the properties of synthetic **4**,‡ obtained by saponification of **23**, were in excellent agreement with those reported for the necic acid of nemorensine.[3] Conversion of synthetic **4** and **24** to their respective dimethyl esters, **25** and **26**,§ permitted further comparison with the naturally derived substance and again demonstrated that nemorensic acid has the absolute configuration represented by **4**.

Finally, the structure of natural nemorensic acid was confirmed by a single crystal X-ray analysis of its parent alkaloid nemorensine (Fig 1).¶ This determination conclusively established the structure of nemorensine as **7**, in which the necic acid portion is shown to possess (2*R*,3*R*,5*S*) absolute configuration by virtue of its stereochemical relationship to the pyrrolizidine segment [(−)-platynecine][18] present in the alkaloid. Literature data suggest that nemorensine **7** and retroisosenine do not possess the same necic acid constituent.[3,4] Furthermore, the spectral properties of **24** do not correspond to those recorded for the necic acid derived from retroisosenine.[3] Whether this alkaloid is a yet unidentified stereochemical variant based on **3** remains to be determined.

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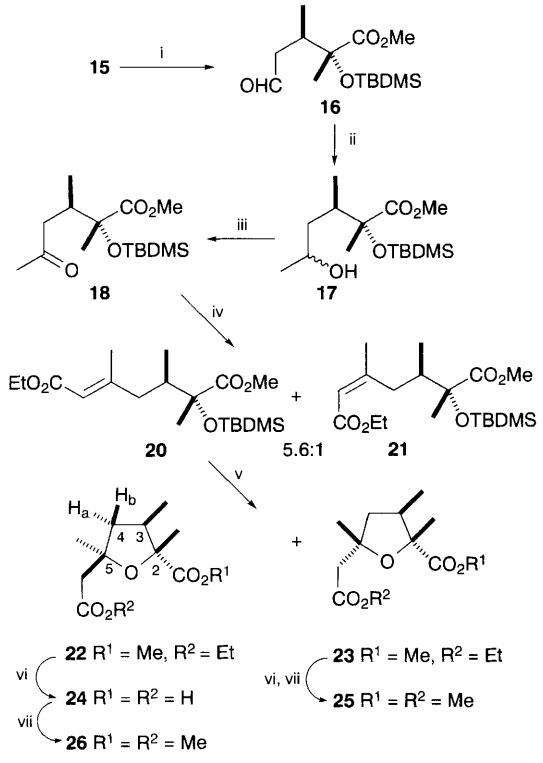

Scheme 2 *Reagents and conditions*: i, O_3, CH_2Cl_2, Me_2S, 77%; ii, MeMgBr, Et_2O, −78 °C, 66%; iii, $(COCl)_2$, DMSO, Et_3N, 98%; iv, $(EtO)_2P(O)CH_2CO_2Et$ **19**, KH, THF, 50%; v, Bu^n_4NF, THF, 77%; vi, LiOH, THF, 98%; vii, CH_2N_2, Et_2O, 100%

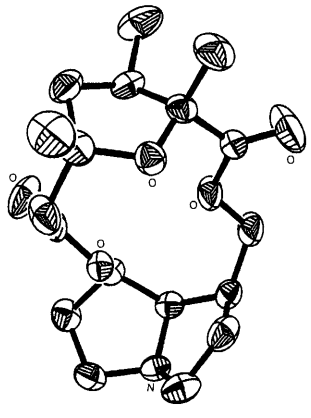

Fig. 1 ORTEP plot of nemorensine **7** with heteroatoms labelled. Thermal ellipsoids are drawn at the 50% probability level.

Footnotes

† Compound **24**: oil; $[\alpha]_D^{23}$ + 55.4 (*c* 0.99, $CHCl_3$).

‡ Compound **4**: mp 174–175 °C (lit.,[3] 174–178 °C); $[\alpha]_D^{23}$ + 87.2 (*c* 0.24, EtOH); {lit.,[3] $[\alpha]_D^{24}$ + 87 (*c* 0.84, EtOH)}.

§ Compound **25**: ^{1}H NMR ($CDCl_3$) δ 1.08 (3 H, d, *J* = 6.9 Hz), 1.29 (3 H, s), 1.43 (3 H, s), 1.56 (1 H, dd, *J* = 12.3, 12.3 Hz), 2.40 (1 H, dd, *J* = 6.9, 7.1 Hz), 2.61 (2 H, dd, *J* = 14.3, 14.6 Hz), 2.61–2.71 (1 H, m), 3.66 (3 H, s), 3.73 (3 H, s). Compound **26**: ^{1}H NMR ($CDCl_3$) δ 1.09 (3 H, d, *J* = 6.8 Hz), 1.24 (3 H, s), 1.34 (3 H, s), 1.92 (1 H, t, *J* = 12.3, 12.5 Hz), 2.05 (1 H, dd, *J* = 6.8, 6.9 Hz), 2.65 (2 H, dd, *J* = 14.4, 14.4 Hz), 2.64–2.77 (1 H, m), 3.66 (3 H, s) and 3.74 (3 H, s).

¶ *Crystal data* for **7**: $C_{18}H_{27}NO_5$, *M* = 337.4, orthorhombic, space group *P*2,2,2, *a* = 6.721(1), *b* = 10.819(2), *c* = 25.003(5) Å, U = 1818.65 Å^3, *Z* = 4, D_c = 1.233 g cm^{-3}, *F*(000) = 728.00, λ(Cu-Kα) = 1.54178 Å, 2002 reflections, 1823 unique (R_{int} = 4.42), 1641 observed [$I > 4\sigma(I)$]; *R* = 0.0549, *R'* = 0.0680. *S* = 1.41. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 A. R. Mattocks, *Chemistry and Toxicology of Pyrrolizidine Alkaloids*, Academic Press: Orlando, Florida, 1986.
2 A. Klasek, P. Sedmera, A. Boeva and F. Santavy, *Coll. Czech. Chem. Commun.*, 1973, **38**, 2504.
3 N. T. Nghia, P. Sedmera, A. Klasek, A. Boeva, S. Dvorakova and F. Santavy, *Coll. Czech. Chem. Commun.*, 1976, **41**, 2952.
4 A. Klasek, P. Sedmera, F. Vokun, A. Boeva, S. Dvorakova and F. Santavy, *Coll. Czech. Chem. Commun.*, 1980, **45**, 548.
5 L. L. Klein, *J. Am. Chem. Soc.*, 1985, **107**, 2573.
6 E. Röder, H. Wiedenfeld and M. Frisse, *Phytochemistry*, 1980, **19**, 1275.
7 A. Kirfel, G. Will, H. Wiedenfeld and E. Roeder, *Acta Crystallogr., Sect C.*, 1980, **9**, 353, 363.
8 J. D. White and S. Ohira, *J. Org. Chem.*, 1986, **51**, 5492.
9 J. D. White, J. C. Amedio, Jr., S. Gut, S. Ohira and L. R. Jayasinghe, *J. Org. Chem.*, 1992, **57**, 2270.
10 J. D. White, J. C. Amedio, Jr., S. Gut and L. R. Jayasinghe, *J. Org. Chem.*, 1989, **54**, 4268.
11 J. D. White and L. R. Jayasinghe, *Tetrahedron Lett.*, 1988, **29**, 2139.
12 T. L. Ho, *Enantioselective Synthesis. Natural Products from Chiral Terpenes*, Wiley; New York, 1992, p 16.
13 A. Toshimitsu, T. Aoai, H. Owada, S. Uenwra and M. Okano, *Tetrahedron*, 1985, **41**, 5301.
14 Y. Gao, R. M. Hanson, J. M. Klunder, A. Y. Do, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765.
15 T. T. Tidwell, *Org. React.*, 1990, **39**, 297.
16 B. O. Lindgren and T. Nilsson, *Acta Chem. Scand.*, 1983, **27**, 888; G. A. Kraus and H. J. Taschner, *J. Org. Chem.*, 1980, **45**, 1175.
17 B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863.
18 H. Rueger and M. Benn, *Heterocycles*, 1983, **20**, 1331.