Cycloaddition of an Enantiopure Cyclic Nitrone to Maleate: Straightforward Synthesis of the Necine Base (–)-Hastanecine

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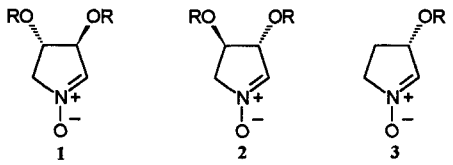
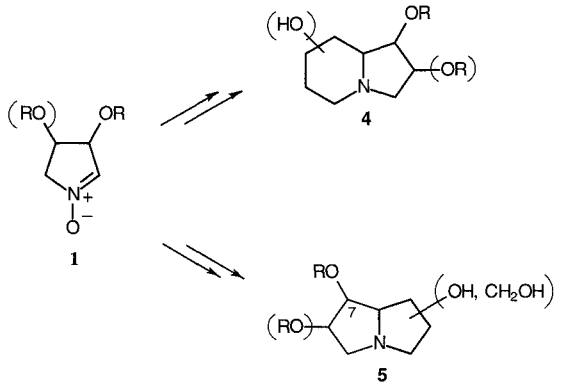
Abstract: A formal synthesis of the necine base (–)-hastanecine, subunit of the pyrrolizidine alkaloids hastacine and punctanecine, is reported. The key intermediate **7** is synthesized in five steps from dimesylate **11**, derived from L-malic acid, in 28.3% overall yield. The correct absolute stereochemistry at C7 in the target compound is attained by means of a Mitsunobu reaction on dimesylate **11**. The desired stereochemistry at the remaining stereogenic centres (C1 and C7a) derives from a highly preferential *exo-anti* approach in the key cycloaddition of nitrone **9** (obtained with complete regiocontrol) to dimethyl maleate.

A project dealing with the application of enantiomerically pure five-membered cyclic nitrones to the synthesis of natural and potentially biologically active compounds has been started in our group a few years ago.[1]



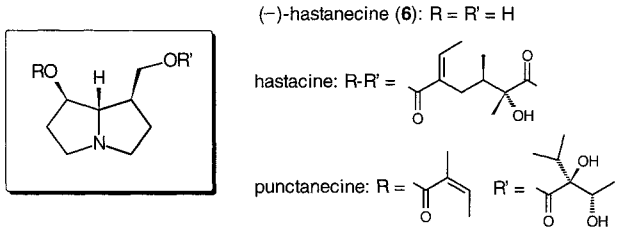
1 **2** **3**

Nitrones of type **1**, **2**, and **3** were conveniently synthesized from L- and D-tartaric acid[1c-d,2] and L-malic acid,[1b,3] respectively, and have been used in several syntheses of polyhydroxyindolizidines **4** (Scheme 1).[1,4] The same nitrones might be employed for the construction of related pyrrolizidine structures **5** (Scheme 1) by use of cycloaddition reactions to maleic or fumaric acid derivatives, analogous to those already applied to the parent, unsubstituted nitrone.[5]

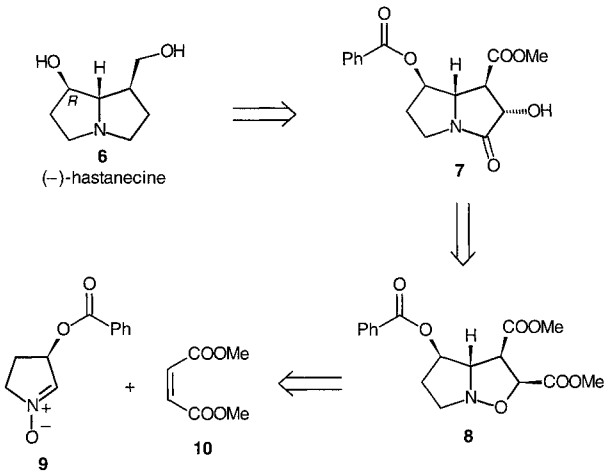


Scheme 1

A perusal of the literature on the structures of 7-hydroxy pyrrolizidine alkaloids found in nature showed that, apart from very few cases, the (*R*) absolute stereochemistry at C7 is required.[6] The obvious choice of D-malic acid as a starting material is unconvenient[7] and a strategy involving inversion at this centre has been attempted. In principle, this could be done at any stage of the synthesis, depending on the relative stereochemistry required at the remaining stereocentres. Indeed, it has already been demonstrated that a high preference for an *anti* transition state is usually secured in the cycloaddition step.[1,2c,4]



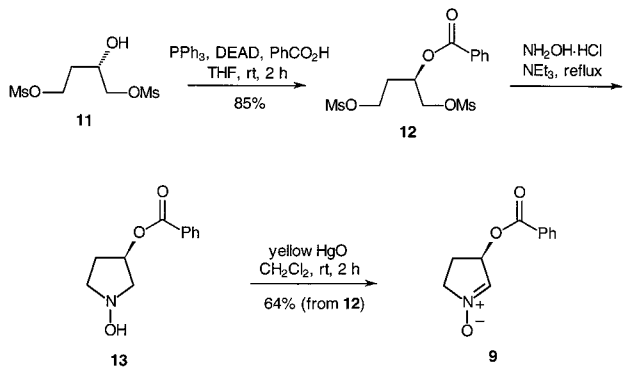
(–)-Hastanecine (**6**), the subunit necine base constituent of the alkaloids hastacine, isolated from *Cacalia hastata* and *Cacalia robusta*,[8] and punctanecine, isolated from *Liatris punctata*,[9] was chosen as a target compound. Hastanecine has been the object of several synthetic efforts in both racemic and optically active forms.[10] Recently, it has been synthesized by Denmark and coworkers in 97.7% e.e. by the use of a domino hetero Diels-Alder-dipolar cycloaddition process employing a chiral auxiliary,[10i] via the intermediate lactam **7**. The same pyrrolizidinone **7** might be readily accessible enantiomerically pure from **9** and **10** according to the retrosynthesis in Scheme 2.



Scheme 2

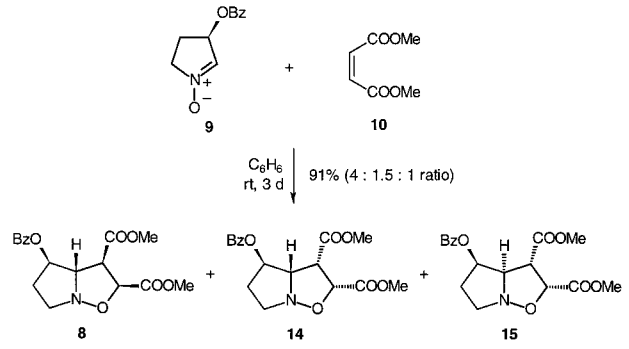
The relative stereochemistry of (–)-hastanecine (**6**) required that the inversion at C7 is operated before the cycloaddition, on the basis of the expected preference for an *exo-anti* transition state in this step.[1,4] The required nitrone **9** would generate the desired stereochemistry as depicted in Scheme 2. Protection of the hydroxyl as the benzoate is convenient, since the enantiomeric nitrone has already been prepared from the parent hydroxylamine without contamination with its regioisomer.[3] Moreover, placement of the benzoate with simultaneous

inversion of absolute configuration at the stereogenic centre of the starting L-malic acid might be possible according to the Mitsunobu protocol.[11] Inversion of configuration by benzoic acid in Mitsunobu conditions was attempted at an early stage of the synthesis, directly on the previously synthesized dimesylate **11** (Scheme 3).[3] Indeed, many functional groups are unaffected by Mitsunobu reaction conditions,[11] including tosylates,[12] and a precedent in the presence of a mesylate moiety has also been reported.[13] Nucleophilic displacement of the hydroxyl group by benzoate in standard Mitsunobu conditions worked very well to give the benzoyloxy dimesylate **12** in high yields (Scheme 3).[14,15] Complete inversion of configuration at the stereogenic centre was proven by comparison of the specific optical rotation with that of its enantiomer (**12**: $[\alpha]_D^{21}$ = +31.1 (*c* 0.98, $CHCl_3$) vs (*ent*)-**12**: $[\alpha]_D^{21}$ = –29.6 (*c* 1.00, $CHCl_3$)).[3] The usual cyclization-oxidation procedure provided exclusively the desired nitrone **9** (Scheme 3), identified by comparison with its known enantiomer (**9**: $[\alpha]_D^{19}$ = +148.8 (*c* 1.10, $CHCl_3$) vs (*ent*)-**9**: $[\alpha]_D^{23}$ = –147.7 (*c* 1.04, $CHCl_3$)),[3] with no trace of the regioisomer, as previously found.[3]



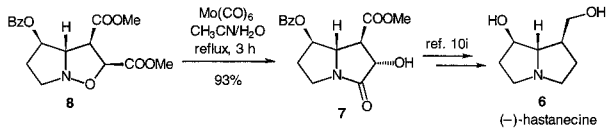
Scheme 3

The cycloaddition of nitrone **9** to dimethyl maleate (**10**) gave three diastereoisomers **8**, **14**, and **15**, out of the possible four, in a 4:1.5:1 ratio, measured by ^1H NMR of the crude reaction mixture (Scheme 4).[14,16] Structural assignment to all the cycloadducts was based on NOESY spectra and on comparison with the analogous cycloaddition to the enantiomeric *tert*-Bu protected nitrone, which gave the related cycloadducts in 5:1:1 ratio.[17] As expected, the major cycloadduct **8** derived from an *exo-anti* transition state, which assembled the correct *trans-trans* relative stereochemistry at C3-C3a-C4 as required for the synthesis of (–)-hastanecine. The diastereomeric mixture was partially resolved by flash column chromatography, affording pure **8** and mixtures of the other adducts.



Scheme 4

Cycloadduct **8** was easily converted to pyrrolizidinone **7** in excellent yield by isoxazolidine ring-opening with $Mo(CO)_6$ in CH_3CN (Scheme 5).[18,14,19] Spectral data of **7** were identical with those reported by Denmark et al. for the same intermediate in their synthesis of (–)-hastanecine,[10i] and its specific optical rotation (**7**: $[\alpha]_D^{26}$ = –69.7 (*c* 1.09, $CHCl_3$)) is completely consistent with the value reported for the compound having a 97.7% e.e. ($[\alpha]_D^{25}$ = –67.8 (*c* 1.02, CH_2Cl_2)).[10i]



Scheme 5

In conclusion, a formal synthesis of the enantiomerically pure necine base (–)-hastanecine starting from low cost, largely available L-malic acid has been accomplished. The overall yield (14% from L-malic acid to **7**) is affected by incomplete control of diastereoselectivity in the cycloaddition of **9** to **10**. However, diastereoisomers **14** and **15** produced in this step might be useful intermediates for the synthesis of other necine bases possessing different relative stereochemistries. For example, the cycloadduct **15** possesses the correct stereochemistry at all stereocentres as presented by (+)-croalbinecine.[6,21,22]

Studies for practical obtainment of cycloadducts having different stereochemical information are in progress in our laboratory.

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References and Notes

(1) (a) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949. (b) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743. (c) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806. (d) Goti, A.; Cardona, F.; Brandi, A.; Picasso, S.; Vogel, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1659. (e) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761.

(2) (a) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274. (b) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316. (c) Brandi, A.; Cicchi, S.; Goti, A.; Koprowski, M.; Pietrusiewicz, K. M. *J. Org. Chem.* **1994**, *59*, 1315.

(3) Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, in press.

(4) (a) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706. (b) Mc Caig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939.

(5) (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Tufariello, J. J.; Tette, J. P. *J. Org. Chem.* **1975**, *40*, 3866.

(6) (a) Hartmann, T.; Witte, L. *Chemistry, Biology and Chemoecology of the Pyrrolizidine Alkaloids In Alkaloids: Chemical & Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1995; vol. 9, p. 155. (b) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: New York, 1986. (c) Liddell, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187. (d) Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413; and preceding reports in the series.

(7) D-Malic acid is ca. 30 times as expensive as its L-enantiomer. Moreover, the commercial product has a lower enantiomeric purity (95% e.e.).

(8) (a) Konovalov, V. S.; Menshikov, G. P. *Zh. Obshch. Khim.* **1945**, *15*, 328. (b) Robins, D. J. *Prog. Chem. Org. Nat. Prod.* **1982**, *41*, 115.

(9) Mead, E. W.; Looker, M.; Gardner, D. R.; Stermitz, F. R. *Phytochemistry* **1992**, *31*, 3255.

(10) (a) Culvenor, C. C. J.; Koretskaya, N. I.; Smith, L. W.; Utkin, L. M. *Aust. J. Chem.* **1968**, *21*, 1671. (b) Aasen, A. J.; Culvenor, C. C. J.; Smith, L. W. *J. Org. Chem.* **1969**, *34*, 4137. (c) Danishefsky, S.; Mckee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 7711. (d) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235. (e) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425. (f) Hart, D. J.; Choi, J.-K. *Tetrahedron* **1985**, *41*, 3959. (g) Hudlicky, T.; Seoane, G.; Lovelace, T. C. *J. Org. Chem.* **1988**, *53*, 2094. (h) Mulzer, J.; Scharp, M. *Synthesis* **1993**, 615. (i) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672. (j) Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187.

(11) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Castro, B. R. *Org. React.* **1983**, *29*, 1. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(12) (a) Mitsunobu, O.; Ebina, M.; Ogihara, T. *Chem. Lett.* **1982**, 373. (b) Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1984**, *49*, 4332. (c) Ferrier, R. J.; Schmidt, P.; Tyler, P. C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 301.

(13) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081.

(14) All new compounds gave satisfactory spectral and analytical data.

(15) (2*R*)-2-benzoyloxy-1,4-bis(methansulfonyloxy)butane (**12**). To a solution of dimesylate **11** (2.0 g, 7.62 mmol) in dry THF (50 mL) were added PPh_3 (6.02 g, 22.87 mmol) and benzoic acid (2.79 g, 22.87 mmol), then DEAD (3.6 mL, 22.87 mmol) dropwise at 0 °C. The mixture was stirred 2 h at rt, then concentrated, diluted with CH_2Cl_2, washed with 1 M NaOH and 1 M HCl and dried over Na_2SO_4. The crude mixture was purified by flash column chromatography, eluent CH_2Cl_2/MeOH 25:1 and the solid product (R_f 0.43) recrystallized from di-*i*-propyl ether to give 2.37 g (6.47 mmol, 85%) of the title compound **12**. M.p. 68-69 °C; $[\alpha]_D^{21}$ = +31.1 (*c* 0.98, $CHCl_3$). Anal. Calcd for $C_{13}H_{18}O_8S_2$: C, 42.62; H, 4.95. Found: C, 42.68; H, 5.07.

(16) (2*S*,3*R*,3a*S*,4*R*)-4-Benzoyloxy-2,3-bis(methoxycarbonyl)hexahydropyrrolo[1,2-*b*]isoxazole (**8**). A solution of nitrone **9** (209 mg, 1.02 mmol) and dimethyl maleate (**10**, 159 µL, 1.22 mmol) in benzene (3.3 mL) was stirred at rt for 3 d. After concentration, a ^{1}H NMR of the crude mixture showed the presence of cycloadducts **8**, **14**, and **15** in a 4:1.5:1 ratio. Flash column chromatography, eluent petroleum ether/ethyl acetate 2:1, gave 199 mg (0.57 mmol, 56%) of the major cycloadduct **8**. M.p. 103-104 °C; R_f 0.26; $[\alpha]_D^{25}$ = +52.8 (*c* 1.02, $CHCl_3$); ^{1}H-NMR: 8.08-8.00 (m, 2H), 7.62-7.40 (m, 3H), 5.31 (dt, *J* = 5.4, 1.4 Hz, 1H), 4.87 (d, *J* = 8.1 Hz, 1H), 4.32 (dd, *J* = 6.2, 1.4 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.62 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.59-3.33 (m, 2H), 2.53-2.34 (m, 2H); ^{13}C-NMR: 169.3 (s), 168.8 (s), 165.9 (s), 133.3 (d), 129.6 (d, 2C), 129.5 (s), 128.4 (d, 2C), 79.9 (d), 77.3 (d), 73.8 (d), 55.5 (t), 55.4 (d), 52.6 (q), 52.5 (q), 30.4 (t); Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.69; H, 5.51; N, 3.70.

(17) Fedi, V. Tesi di Laurea, Università di Firenze 1996.

(18) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.

(19) (1*R*,2*S*,7*R*,7a*S*)-7-Benzoyloxy-2-hydroxy-1-methoxycarbonylhexahydropyrrolizin-3-one (**7**). A mixture of **8** (100 mg, 0.28 mmol) and $Mo(CO)_6$ (53 mg, 0.2 mmol) in CH_3CN (4 mL) and H_2O (0.3 mL) was refluxed for 3 h, then worked as in ref. 20. Flash column chromatography, eluent $CHCl_3$/MeOH 50:1 gave a solid product, which was recrystallized from AcOEt/$(i\text{-Pr})_2O$ to afford 85 mg (0.27 mmol, 93%) of pure **7**, whose spectral data were identical to those reported in ref. 10i. M.p. 143-144 °C; $[\alpha]_D^{26}$ = –69.7 (*c* 1.09, $CHCl_3$). Anal. Calcd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39. Found: C, 59.95; H, 5.48; N, 3.92.

(20) Guarna, A.; Guidi, A.; Goti, A.; Brandi, A.; De Sarlo, F. *Synthesis* **1989**, 175.

(21) Sawhney, R. S.; Atal, C. K.; Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1974**, *27*, 1805.

(22) The corresponding cycloadduct from the enantiomeric *tert*-Bu protected nitrone has been converted to the enantiomer of croalbinecine protected at the hydroxyl on C7.[17]