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Total Synthesis of (–)-Rosmarinecine by Intramolecular Cycloaddition of (*S*)-Malic Acid Derived Pyrroline *N*-Oxide

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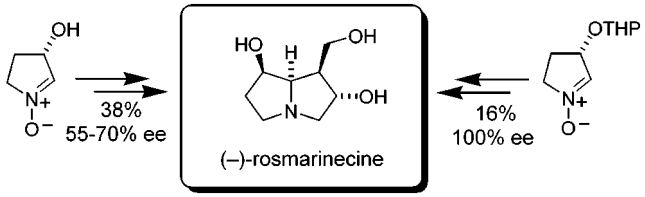
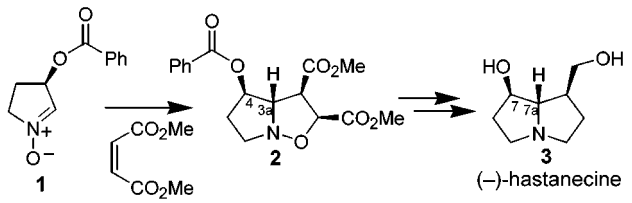
ABSTRACT



Straightforward total syntheses of (–)-rosmarinecine have been achieved from L-malic acid derived pyrroline *N*-oxides by two novel useful cascade processes, which join the family of domino reactions. Both strategies, which furnished the target alkaloid in enantioenriched and enantiopure forms, respectively, allow complete control of configuration at all the three newly created contiguous stereogenic centers.

We recently reported the synthesis of (−)-hastanecine (**3**) (Scheme 1),[1] as well as of related unnatural hydroxypyrrolizidines, based on an intermolecular cycloaddition of nitrone **1** with dimethyl maleate in the key step. The reaction gave with a fair preference compound **2**, with *trans* relative stereochemistry at C3a−C4, derived from an *exo-anti* transition state.[1]

Scheme 1



In this Letter we report the total synthesis of (−)-rosmarinecine by the intramolecular version of this strategy. This variant complements the previous findings, allowing access to the necine bases possessing the C7−C7a *cis* relative stereochemistry with complete control of configuration at all the new stereogenic centers.

(−)-Rosmarinecine (**4**), the necine base portion of several pyrrolizidine alkaloids,[2] has been chosen as a target compound to test the feasibility of this approach. Among the polyhydroxylated necines, (−)-rosmarinecine (**4**) is structurally a considerably challenging target, as proved by only two successful total syntheses reported so far.[3]

Tatsuta and co-workers accomplished the first synthesis of (−)-rosmarinecine (**4**) in 18 steps and 6.9% overall yield starting from D-glucosamine.[3a] Recently, Denmark and coworkers reported the application of their domino double

(1) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633.

(2) Hartmann, T.; Witte L. In *Alkaloids: Chemical & Biological Perspectives*, Vol. 9; Pelletier, S. W., Ed.; Pergamon: Oxford, 1995; p 155.

(3) (a) Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096. (b) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266.

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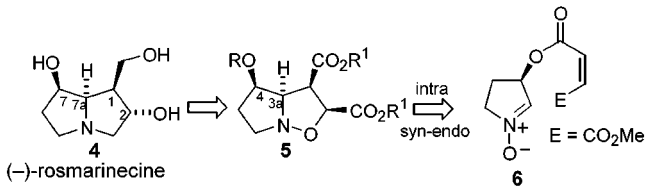
cycloaddition strategy[4] to a ten-step synthesis of (−)-rosmarinecine (**4**) in 97.3% ee and 8.6% overall yield using a chiral auxiliary.[3b]

The retrosynthetic sequence for the application of our strategy (Scheme 2) requires an *endo-syn* approach of the

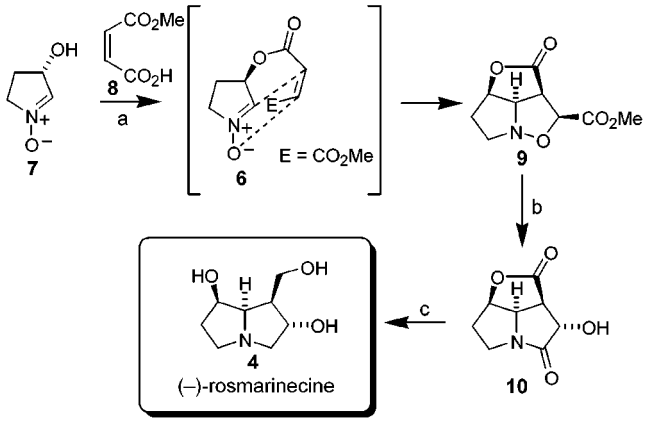
Scheme 2



partners, which is the less favored in the intermolecular reaction.[1] This stereochemical requirement might instead be achieved by an intramolecular process. The appropriate precursor was envisaged in **6**, where the reacting moieties are linked by a removable ester junction. The (*R*) configuration required at C7 of the final alkaloid is available from D-malic acid, but it is cheaper to utilize L-malic acid requiring inversion of configuration at the stereogenic center at some stage of the synthesis.[5] This strategy had been successful in the synthesis of hastanecine, where the inversion was effected at an early stage by a Mitsunobu reaction with benzoic acid on a hydroxydimesylate precursor of the nitrone **1**.[1] Subsequent double nucleophilic displacement with hydroxylamine followed by oxidation cleanly furnished the desired nitrone **1**.[1] An analogous procedure for the synthesis of **6**, utilizing maleic acid monomethyl ester (**8**)[6] in place of benzoic acid, failed in the present case. Indeed, after the Mitsunobu reaction, hydroxylamine gave preferentially conjugate addition to the maleic acid moiety rather than nucleophilic substitution and cyclization.

Then, accomplishment of the inversion after construction of the nitrone moiety was taken into account. Introduction of the maleic acid portion of **6** by a Mitsunobu reaction of **8** on the preformed hydroxy-substituted nitrone **7**, readily accessible from the corresponding trialkylsilyl protected nitrones,[7] was then attempted, albeit nothing was previously reported about the compatibility of a nitrone moiety under Mitsunobu reaction conditions.[8] The reaction afforded exclusively the desired cycloadduct **9** in 70% yield by a clean domino *Mitsunobu−intramolecular nitrone cycloaddition* process (Scheme 3). Structural assignment of the adduct,

Scheme 3[a]



[a] Reagents and conditions: (a) **8** (1.2 equiv), PPh_3 (3 equiv), DEAD (3 equiv), THF, 0 °C, 2 h, 70%; (b) H_2 1 atm, 20% $Pd(OH)_2$/C, MeOH, rt, 24 h, 59%; (c) Red-Al (12 equiv), THF, reflux, 3 h, 90%.

confirmed by NOESY spectra, proved the expected high preference for an *endo-syn* TS in the intramolecular cycloaddition of the intermediate nitrone **6**.[7]

Isoxazolidine reductive ring opening of **9** turned out to be troublesome. Molybdenum hexacarbonyl,[9] H_2/Raney Ni,[10] nickel boride,[11] and Cu/Zn[12] were not able to afford the desired lactam **10**. Hydrogenation over Pd on charcoal[10,13] furnished up to a 40% yield of **10**, but the reaction was not reproducible. Finally, the use of $Pd(OH)_2$[14] resulted in the conversion of **9** to **10** in 55−60% yield. Reduction of lactam **10** was accomplished by the use of Red-Al, which gave (−)-rosmarinecine (**4**) in 90% yield after chromatography. This completes a nine-step, 10.2% overall yield access to this alkaloid from readily accessible starting materials, namely, maleic anhydride, (*S*)-dimethylmalate, and hydroxylamine hydrochloride. Recrystallization provides analytically pure material, with spectroscopic properties identical to those reported for the natural product.[3b] However, to our disappointment, its physical data (mp 155−157 °C, $[\alpha]^{23}_D$ −65.6, c = 0.88 in EtOH) did not match those of the natural compound,[3b] with the optical rotation corresponding to ca. 55% ee. Repetition of the whole process afforded samples of (−)-rosmarinecine only enantiomerically enriched in variable purities, with a 70% ee in the best case. ^{1}H NMR analysis of the enantiomeric composition of the precursor **10** after derivatization as the Mosher ester gave a value of 59% ee, in good agreement with that derived from the optical measurement. Clearly, partial racemization had occurred at an early stage of the process. Finally, after completion of the described sequence, it was ascertained that partial

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(5) D-Malic acid is ca. 30 times as expensive as its L-enantiomer.
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(8) For reviews on the Mitsunobu reaction, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Castro, B. R. *Org. React.* **1983**, *29*, 1. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
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(12) Dhavale, D. D.; Gentilucci, L.; Piazza, M. G.; Trombini, C. *Liebigs Ann. Chem.* **1992**, 1289.
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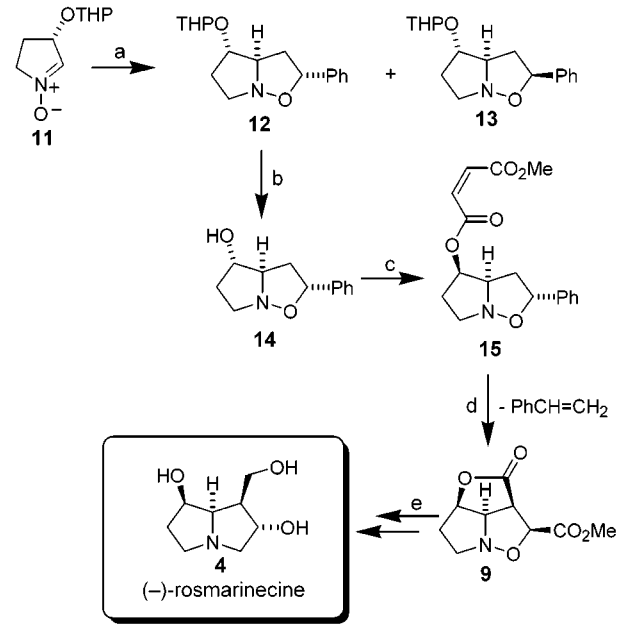
racemization of the starting nitrone **7** had occurred, since it was obtained with different degrees of optical purities.[7] This finding was completely unexpected, contrasting with the behavior previously observed for all the corresponding protected nitrones.[7] It has since been proven that nitrone **7** itself has a low configurational stability, and partial racemization occurs independently on its precursor.[15,16] Loss of stereochemical integrity under Mitsunobu reaction conditions has been ruled out, since direct esterification of nitrone **7** also provided partially racemized material.

An alternative strategy, which considered protection of the nitrone moiety, was then envisaged for accessing enantiopure (−)-rosmarinecine. Only two methods have been suggested, but applied only very occasionally, for such a purpose: addition of HCN (or a silyl cyanide)[17] and cycloaddition of a suitable dipolarophile.[18] The latter method seemed more suitable to our aim, as preliminarily proved in an analogous model process.[15]

Reaction of the tetrahydropyranyl protected nitrone **11**[15] with styrene gave the two diastereomeric cycloadducts **12** and **13** (Scheme 4) which were easily separated by flash column chromatography, albeit in principle they can be used as a mixture, since the stereochemical information at C2 is lost in the following steps. Deprotection of the hydroxyl group of **12** to afford **14**, followed by Mitsunobu reaction with **8**, assembled the dipolarophile for the intramolecular cycloaddition while providing the desired inversion of configuration at C4. On refluxing **15** in *o*-dichlorobenzene, a domino *cycloreversion−intramolecular nitrone cycloaddition* process occurred to afford cleanly **9** in good yield. The optical rotation value of **9** ($[\alpha]^{27}_D$ −53.5, c = 0.39 in $CHCl_3$), compared to that of the same compound obtained by the above process in Scheme 3, was consistent with complete enantiomeric purity of the product. This was confirmed by an ^1H NMR spectrum of the Mosher ester of lactam **10**, which showed only one set of signals. Completion of the synthesis according to the final steps of Scheme 3 gave enantiomerically pure **4**, as confirmed by comparison of its physical data (mp 166−168 °C, $[\alpha]^{20}_D$ −122.3, c = 0.61 in EtOH) with those reported for the natural product (mp 168−170 °C, $[\alpha]^{21}_D$ −119.8, c = 1.01 in EtOH).[3b] The total synthesis of enantiopure (−)-rosmarinecine has been, then, achieved in 11 steps and 7.2% overall yield (based only on major cycloadduct **12**) from diethyl L-malate.

Scheme 4[a]



[a] Reagents and conditions: (a) styrene (2 equiv), toluene, 80 °C, 11 h, 72% of **12** + 17% of **13**; (b) (i) PPTS, absolute EtOH, reflux, 3 h; (ii) Ambersep 900-OH, MeOH, 3 h, 89%; (c) **8** (2.4 equiv), PPh_3 (3 equiv), DEAD (3 equiv), THF, 0 °C then rt, 2 d, 69%; (d) *o*-dichlorobenzene, reflux, 14 h, 70%; (e) same procedure as for steps (b) and (c) in Scheme 3, **10** 56%, **4** 85%.

In conclusion, the intramolecular version of our chiral pyrroline *N*-oxide cycloaddition methodology has been applied to the total synthesis of (−)-rosmarinecine. The alkaloid has been obtained enantiomerically enriched (maximum 70% ee) by a novel domino protocol for inversion of absolute configuration and control of relative configuration via a Mitsunobu−intramolecular nitrone cycloaddition process and enantiomerically pure by protection of the nitrone followed by a Mitsunobu reaction and a cycloreversion−intramolecular nitrone cycloaddition process. The study of the scope and further application of these procedures is underway in our laboratory.

Acknowledgment. We thank MURST (Ministero dell'Università e della Ricerca Scientifica e Tecnologica)−Italy for financial support (Cofin 2000) and CNR (Consiglio Nazionale delle Ricerche)−Italy for a postdoctoral fellowship to F. Cardona.

Supporting Information Available: Experimental procedures and spectral and analytical data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Nitrone **7** obtained by desilylation of the corresponding TBDMS- and TIPS-protected nitrones has been erroneously reported as enantiomerically pure in earlier communications.[7] Studies are in progress in order to ascertain the origin and mechanism of this racemization process.

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