A General Strategy for the Synthesis of Cis-Substituted Pyrrolizidine Bases. The Synthesis of (−)-Rosmarinecine†

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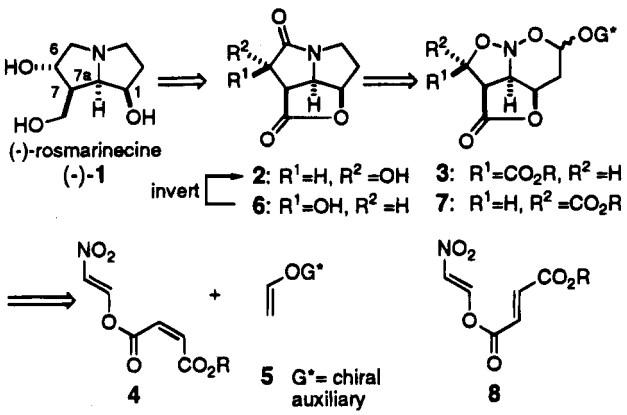
Pyrrolizidine alkaloids have represented an enduring challenge for organic synthesis due to their diverse biological properties and compact structural complexity.[1] One of the critical stereochemical features of these compounds is the relationship of the three contiguous centers C(1), C(7), and C(7a). A number of pyrrolizidine bases possess an all cis relationship of these centers as illustrated by (−)-rosmarinecine (**1**), the necine base portion of the alkaloid rosmarinine. Rosmarinine was isolated in 1940 from *S. rosmarinifolius* Linn.[2] and its structure was established by an independent synthesis from retronecine.[3,4] Interestingly, the necine portion has been found with different diacid chains esterified to the hydroxyl groups such as in petitianine and angularine.[5] Rosmarinecine has been synthesized once previously in 17 steps from D-glucosamine.[6]

In formulating a *general* strategy for the synthesis of necine bases, we recognized the potential of the tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition reaction to generate substituted pyrrolizidines with a high degree of stereocontrol.[7] On the basis of previous methodological studies, we anticipated that (−)-rosmarinecine could arise from reduction of the fused tricyclic lactam lactone **2**, Scheme 1. This familiar structure could be formed from hydrogenolysis of the key intermediate, nitroso acetal **3**, which contains all of the requisite stereochemical information. The all cis configurational relationship of C(1), C(7a), and C(7) in (−)-rosmarinecine dictates that **3** must arise from a tandem *inter* [4 + 2]/ *intra* [3 + 2] cycloaddition.[7a] The geometrical constraints imposed by the tether require that the intramolecular [3 + 2] cycloaddition occurs in an exo mode on the same face of the nitronate dipole to which the tether is disposed. The

Scheme 1



configuration at C(6) then arises as a consequence of the dipolarophile geometry, in this case, cis.[7a] Finally, the absolute stereochemical outcome is established by the appropriate combination of chiral auxiliary and Lewis acid for the intermolecular [4 + 2] process.[7c] Thus, the synthesis simplifies to the two components, β-acyloxy (*Z*)-nitroalkene **4** and chiral vinyl ether **5**. Unfortunately, this initial approach had to be abandoned due to the instability of the maleate-derived nitroalkene. In view of the instability of **4**, we next considered a less direct approach which utilizes the fumarate-derived nitroalkene **8**. Although this would lead to the wrong configuration at C(6) for (−)-rosmarinecine (via **7**), thus necessitating a hydroxyl inversion of intermediate **6**, the synthesis would still be remarkably efficient.

The synthesis of (−)-rosmarinecine is detailed in Scheme 2. The starting nitroalkene **10** was prepared in 69% yield by combining potassium nitroacetaldehyde[8] with isopropyl fumaroyl chloride[9] **9** . The nitroalkene was then subjected to the tandem [4 + 2]/[3 + 2] cycloaddition sequence using methylaluminum bis(2,6-diphenylphenoxide) (MAPh) as the promoter.[7c] The reaction of **10** with 3 equiv of the chiral vinyl ether (−)-**11** derived from (*R*)-2,2-diphenylcyclopentanol[10] in the presence of 3 equiv of MAPh afforded the nitroso acetal **12** in 96% yield and an overall 25/1, exo/endo ratio of diastereomers. A major portion (75%) of (−)-**12a** was determined by ^{1}H NMR integration to be a 95/1 (exo/endo) mixture of diastereomers and was taken forward in the synthesis.[11] The tandem cycloaddition thus installed all the stereocenters for (−)-rosmarinecine with the correct absolute configuration (except at HC(6)) in a single operation.

Orienting experiments which employed *n*-butyl vinyl ether as the dienophile revealed that the fused tricyclic nitroso acetal could not be directly reduced under several different conditions to the expected α-hydroxy lactam **6**. We suspected that the failure of the unmasking process was due to the presence of the lactone for two reasons. First, the shorter bonds in the lactone (compared to the saturated hydrocarbon[7a]) made the nitroso acetal more

† Dedicated with greatest respect and appreciation to Professor Nelson J. Leonard, a pioneer in pyrrolizidine alkaloid chemistry.

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(11) A minor fraction (21%) consisted of a 6.3/1 exo/endo ratio.

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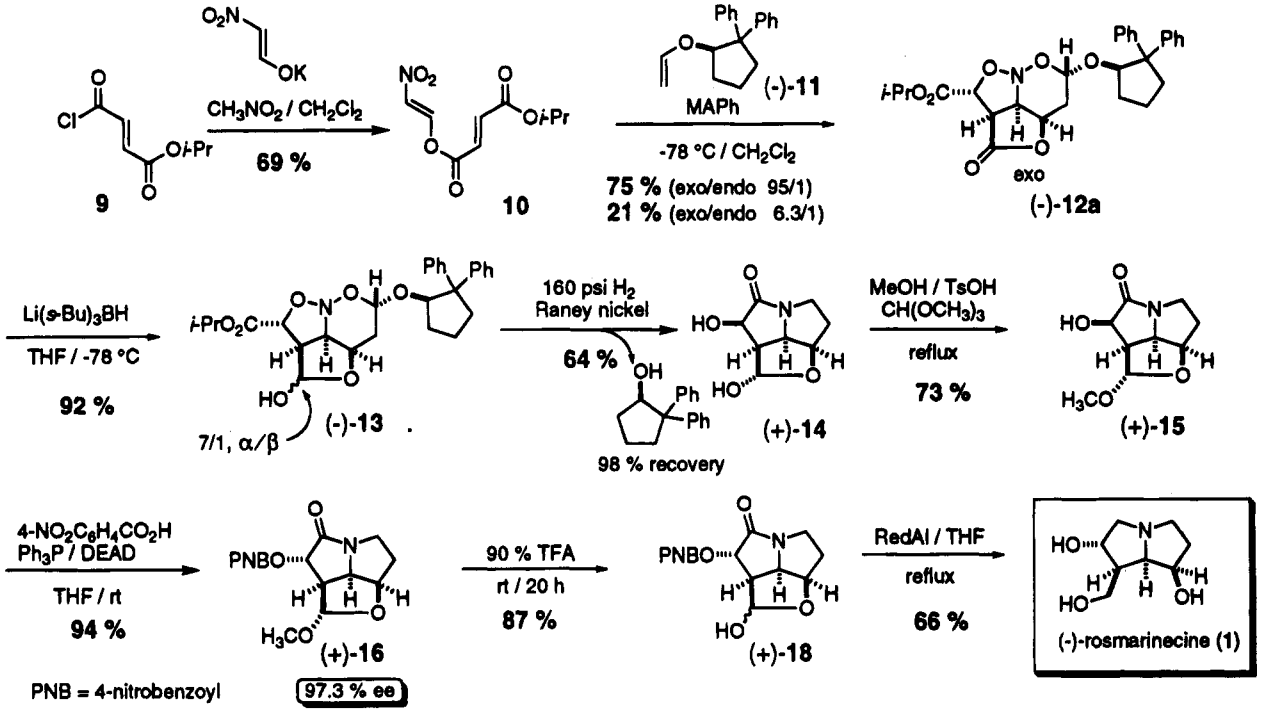
Scheme 2



strained, so that after hydrogenolysis, reclosure to form the tricyclic core would be inhibited. Second, the lactone itself might be reactive under the reducing conditions. After considerable optimization, we found that the nitroso acetal isopropyl ester (−)-**12a** could be reduced very selectively with lithium tri(*sec*-butyl)borohydride to afford the lactol (−)-**13** in excellent yield (92%).[12] The lactol (−)-**13** was then subjected to the hydrogenolysis conditions to afford the tricyclic α-hydroxy lactam-lactol (+)-**14** in a very satisfying 64% yield together with a small amount of an over-reduced lactam-triol. The chiral auxiliary (*R*)-2,2-diphenylcyclopentanol was recovered in 98% yield.

Since the lactam was derived from a fumarate dipolarophile, an inversion at C(6) was required for the correct configuration in (−)-rosmarinecine. First, the lactol was protected as a methyl acetal by heating in methanol at reflux for 5 h with a catalytic amount of acid to afford (+)-**15** in 73% yield. The inversion at C(6) was then accomplished in excellent yield (94%) by a Mitsunobu reaction with 4-nitrobenzoic acid as the nucleophile.[13] The enantiomeric excess of the 4-nitrobenzoate (+)-**16** was determined to be 97.3% by chiral HPLC analysis (Chiralcel OJ column).[14]

The completion of the synthesis of (−)-rosmarinecine required the deprotection of the methyl acetal (+)-**16** and the reduction of the resulting lactol (+)-**18**. The deprotection was accomplished with 90% trifluoroacetic acid (20 h/rt) to afford the lactol (+)-**18** in 87% yield. From our experience in the final reduction step in the synthesis of (−)-hastanecine,[7e] we did not anticipate any difficulty in the analogous transformation here. Thus, reduction of lactol (+)-**18** with Red-Al in refluxing tetrahydrofuran afforded (after chromatographic purification on both silica gel and basic alumina)[15] a white solid which was recrystallized from acetone/pentane to provide (−)-rosmarinecine as an analytically pure, white solid in 66% yield. The physical and spectroscopic data of the synthetic product (mp, R_f, ^{1}H and ^{13}C NMR, IR, MS, and $[\alpha]_D$) matched those of the natural compound obtained by hydrolysis of (−)-rosmarinine.[16,4]

Thus, the synthesis of (−)-rosmarinecine has been accomplished in eight steps and 14.8% overall yield from acid chloride **9**. All of the stereocenters were installed in a single transformation with high selectivity clearly demonstrating the utility of the tandem [4 + 2]/[3 + 2] cycloaddition strategy. The synthesis of more complex pyrrolizidine alkaloids using the nitroalkene cycloaddition approach is in progress.

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Supplementary Material Available: Complete experimental and spectroscopic data for all described compounds along with ^{1}H NMR and ^{13}C NMR spectra of (+)-**18** and both natural and synthetic (−)-rosmarinecine (27 pages).

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(12) Other combinations of ester groups and reducing agents were less successful (unselective reduction, slow closure). Details of this optimization will be given in a full account.

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(14) The inversion of configuration was confirmed by acylation of (±)-**15** to produce (±)-**17** a diastereomer of (±)-**16**, see supplementary material.

(15) The rosmarinecine obtained after silica gel chromatography, although apparently pure, gave ^{13}C NMR spectra with variable chemical shifts for C(1), C(5), and C(7a) perhaps due to rapid equilibration of hydrates or salts. Only after basic alumina chromatography could consistent spectroscopic data be collected.

(16) Synthetic (−)-**1**: mp 169−170 °C, $[\alpha]^{21}_D$ −117.6° (EtOH, *c* = 0.96). Natural (−)-**1**: mp 170−172 °C, $[\alpha]^{23}_D$ −119.1° (EtOH, *c* = 0.94);[16a] mp 171−172 °C, $[\alpha]^{25}_D$ −118.5°;[16b] mp 171−172 °C, $[\alpha]^{25}_D$ −116.5° (EtOH, *c* = 0.01);[5c] lit. $[\alpha]^{21}_D$ −121° (EtOH, *c* = 0.01).[6] (a) Denholm, A. A. Ph. D Thesis, University of Glasgow; 1990. (b) Richardson, M. F.; Warren, F. L. *J. Chem. Soc.* **1943**, 452.

(17) The natural sample had mp 168−170 °C and $[\alpha]^{21}_D$ −119.8° (EtOH, *c* = 1.01).