Tandem [4 + 2]/[3 + 2] Cycloadditions of Nitroalkenes. 9. Synthesis of (−)-Rosmarinecine

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Abstract: (−)-Rosmarinecine (**2**) is the necine base portion of the pyrrolizidine alkaloid (−)-rosmarinine. (−)-Rosmarinecine is a representative of the group of pyrrolizidines that show a cis relationship between adjacent stereocenters C(1), C(7), and C(7a), in addition to a highly oxygenated skeleton. (−)-Rosmarinecine (**2**) has been synthesized in eight steps and 14.8% overall yield, as an illustration of a general approach for the construction of pyrrolizidines having this stereochemical feature. The key step in the asymmetric synthesis is a Lewis acid-promoted, tandem inter-[4 + 2]/intra-[3 + 2] cycloaddition between a fumaroyloxy nitroalkene and a chiral vinyl ether.

Introduction and Background

Pyrrolizidine alkaloids have long attracted the interest of synthetic organic chemists due to their diverse biological properties and their structural complexity.[1] Rosmarinine (**1**) was isolated from *S. rosmarinifolius* Linn. (family Compositae) and upon hydrolysis afforded the necine base (−)-rosmarinecine (**2**).[2] Warren and co-workers[3] determined the structure of (−)-rosmarinecine by synthesis from retronecine (**9**), the structure of which had already been determined by Adams and Hamlin.[4] In addition, an X-ray crystal structure of rosmarinine (**1**) has been reported for the purpose of examining the folding of the macrolactone and the necine nucleus.[5] The X-ray crystal structure serves to establish independently the stereostructure of (−)-rosmarinecine (**2**) with respect to the configurations at C(1), C(6), C(7), and C(7a).

The necine portion of **1** has been found in other pyrrolizidine alkaloids with different acid chains attached to the hydroxyl groups: e.g., angularine (**3**), 12-*O*-acetylrosmarinine (**4**), neorosmarinine (**5**), and petitianine (**6**) (Figure 1).[12,13]

Rosmarinecine has since been isolated from various plants in the Compositae family, including *S. pleitocephalus*,[6] *S. triangularis*,[7] *S. taiwanensis* Hayata,[8] *S. pterophorus*,[9] *S. hygrophilus*,[10] *S. adnatus* D.C.,[11] *S. angulatus* L.,[12] *S. hadiensis* and *S. syringifolius*.[13] In addition, rosmarinine, among other alkaloids, has been isolated from butterflies in Southern Australia of the *Danaus plexippus* L. and *Danaus chrysippus* L species.[9] It was demonstrated that the butterflies mainly obtained rosmarinine by consumption of *S.pterophorus*. The butterflies can store the alkaloids for extended period of time, and it is speculated that the purpose is to make the insects distasteful to predators. Finally, the biosynthesis of (−)-rosmarinecine is now well understood.[14,15]

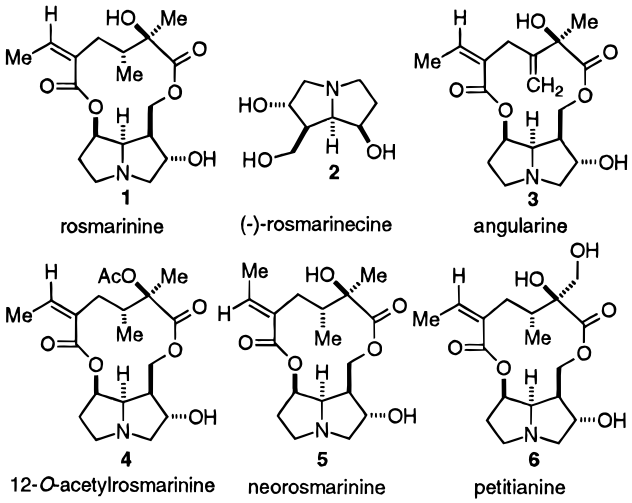

Figure 1. Pyrrolizidine alkaloids that contain rosmarinecine.

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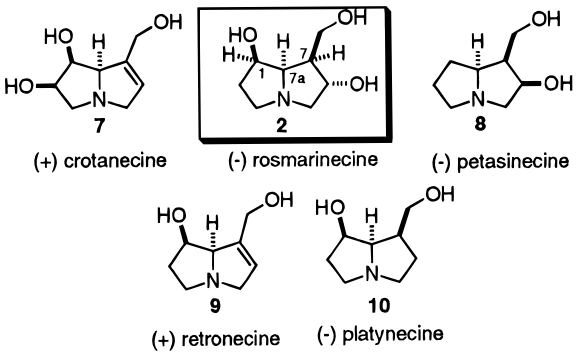


Figure 2. Structure of several cis-substituted necines.

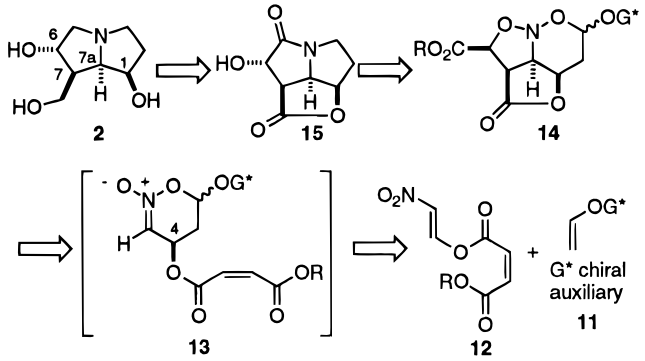
The simpler necines such as isoretronecanol have served as common targets to demonstrate new synthetic methodology, as witnessed by the myriad of synthetic approaches on record.[1,16] (−)-Rosmarinecine, on the other hand, is structurally one of the more complex necines bases, with four stereogenic centers on the eight atoms that form the 1-azabicyclo[3.3.0]octane ring system. It is, therefore, not very surprising that, prior to our effort, there was only one synthesis of this natural product, reported by Tatsuta et al., who prepared (−)-rosmarinecine in 17 steps from D-glucosamine.[17]

Synthesis Design

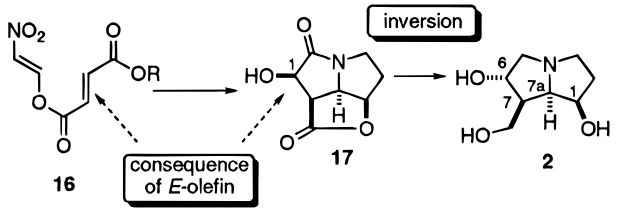
The asymmetric, tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition reaction has been explored extensively in recent years.[18,19] This transformation is ideally suited for the synthesis of necine bases since the core pyrrolizidine skeleton arises from hydrogenation of the bicyclic nitroso acetals, which are the end products of the tandem cycloaddition. As an illustration of the power of the asymmetric tandem [4 + 2]/[3 + 2] nitroalkene cycloaddition reaction, we recently disclosed the synthesis of (−)-hastanecine.[20] This constituted the first example of the use of nitroalkene cycloaddition chemistry in the synthesis of natural products. Herein, we disclose a general approach to necines which bear a cis relationship between any or all of the stereocenters at C(1), C(7), and C(7a), as can be seen in examples **2** and **7**−**10** (Figure 2).[21]

The retrosynthetic analysis for (−)-rosmarinecine is summarized in Scheme 1. It was proposed that rosmarinecine could be obtained from the corresponding α-hydroxy lactam **15** by exhaustive reduction. The α-hydroxy lactam would arise from hydrogenolytic cleavage of nitroso acetal **14**, which itself originates from a tandem inter-[4 + 2]/intra-[3 + 2] cycloaddition of nitroalkene **12** and a chiral vinyl ether **11**. The geometrical constraints imposed by the tether require that the intramolecular [3 + 2] cycloaddition must occur in an endo

Scheme 1



Scheme 2



mode on the same face of the nitronate dipole **13** to which the tether is attached. This would give rise to a cis relationship between the stereocenters at C(1) and C(7). Furthermore, the stereocenter at C(7a) would be cis to those at C(1) and C(7) and would establish the correct relative configuration between C(1), C(7), and C(7a) for (−)-rosmarinecine. The configuration at C(6) is established as a consequence of the dipolarophile geometry, which in this case must be cis. Finally, the absolute stereochemical outcome is established by the appropriate combination of chiral auxiliary and Lewis acid for the intermolecular [4 +2] process to engender the correct configuration at C(4) in the intermediate nitronate **13** (C(1) in (−)-rosmarinecine). This center, in turn, will dictate the creation of all the other required stereocenters in both a relative and an absolute sense. Thus, the synthesis precursors simplify to the maleate-derived β-acyloxy nitroalkene **12** and a nonracemic chiral vinyl ether **11**.

This initial and highly direct approach had to be abandoned due to the instability of the nitroalkene **12,** which rapidly isomerized to the fumarate isomer **16**. After many unsuccessful attempts to employ **12**, it was recognized that **16** could also serve as a suitable precursor for (−)-rosmarinecine (Scheme 2). This more tractable nitroalkene would lead to an α-hydroxy lactam **17,** by analogy to the maleate series, in a tandem [4 + 2]/[3 + 2] cycloaddition, followed by hydrogenolysis. Since the two-dimensional stereochemistry of the fumarate will translate into the incorrect configuration at C(6) in **17** for (−)-rosmarinecine, an inversion at this center is necessitated. While a strategic inelegance, the inversion of the hydroxyl at C(1) should elongate the synthesis by only one or two steps, and therefore, this would still constitute an efficient synthesis.

Results and Discussion

Use of Achiral Dienophiles. To evaluate the feasibility of the approach outlined in Scheme 2, the nitroalkene **21** was prepared by analogy with 2-(benzoyloxy)-1-nitroethene that was used in the synthesis of (−)-hastanecine.[20,22] The commercially available ethyl ester **18** was easily converted to the acid chloride

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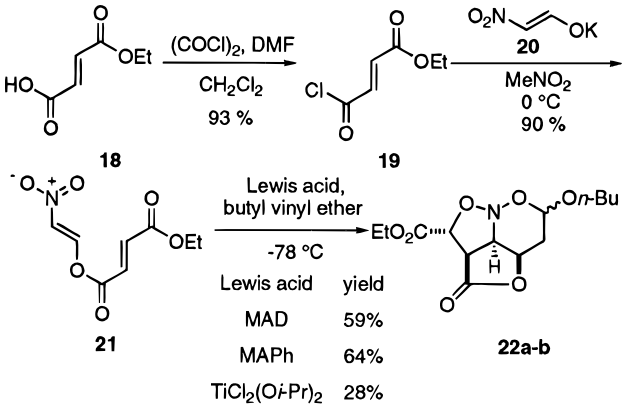
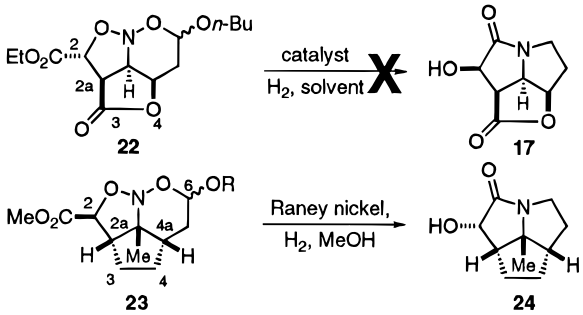
Scheme 3



Scheme 4



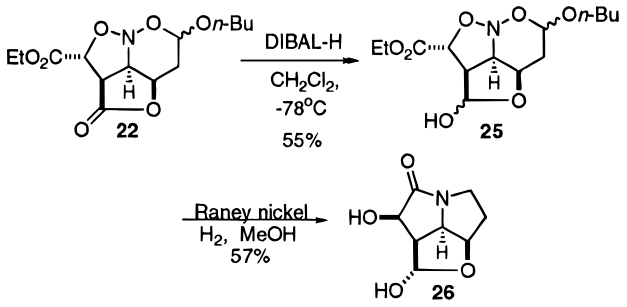
19 (93%), which was subsequently treated with **20**[23] to afford the nitroalkene **21** as a yellow solid in 90% yield (Scheme 3).

For orienting experiments, butyl vinyl ether was selected as the test dienophile, in order to simplify product analysis by ^{1}H NMR spectroscopy. Addition of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[24] to a solution of nitroalkene **21** and butyl vinyl ether at −78 °C afforded the nitroso acetal **22** in 59% yield as a 1.9:1 mixture of diastereomers, with the endo diastereomer (α-anomer) predominating. Changing the Lewis acid to methylaluminum bis(2,6-diphenylphenoxide) (MAPh) gave **22** in 64% yield as a 1:1 mixture of diastereomers. If $TiCl_2$(O-*i*Pr)$_2$ was used as the Lewis acid, a single isomer of **22** was obtained. However, the yield was poor (28%), and the reaction was found to give a number of byproducts that made purification difficult.

With ready access to multigram quantities of **22**, an extensive study was then undertaken to establish the optimal conditions for hydrogenolysis of the nitroso acetal **22** to α-hydroxy lactam **17** (Scheme 4). This study focused on four different catalysts (PtO_2, Raney nickel, Pd/C, and $Pd(OH)_2$) in six different solvents (methanol, 2-propanol, ethyl acetate, THF, toluene, and chloroform) at three different pressures (1 atm, 100 psi, and 200 psi) for periods of time between 14 and 40 h. Disappointingly, none of these conditions afforded the desired product **17**. Either decomposition to a number of unidentified byproducts occurred or starting material was recovered. The inability to effect the desired hydrogenolytic cleavage of **22** to **17** stands in sharp contrast to the facile hydrolysis of nitroso acetals such as **23** to the α-hydroxy lactam **24 (**Scheme 4).

The key structural difference between **22** and **23** is clearly the lactone function, and several reasons for the failure of **22** to be converted to **17** can be formulated. First, it is possible that the lactone undergoes competitive reduction under the hydrogenolysis conditions. Second, the shorter C−O bonds and sp^2-hybridized carbonyl group in the γ-lactone could be creating strain in the tricyclic nitroso acetal. This strain may disfavor recyclization after N−O bond cleavage, thus allowing unwanted side reactions to occur preferentially. Third, unmasking the aldehyde at C(6) may lead to β-elimination of the lactone oxygen, also relieving ring strain. A potential solution to this problem is to relieve the strain (and leaving group ability) engendered by the carbonyl group in the five-membered ring by changing the hybridization of C(3) in **22** from sp^2 to sp^3. This could be accomplished by selectively reducing the carbonyl function. Gratifyingly, treatment of the nitroso acetal **22** with 1 equiv of diisobutylaluminum hydride (DIBAL-H) at −78 °C gave the lactol **25** in 55% yield (Scheme 5). Treatment of this product with Raney nickel at 150 psi of hydrogen for 36 h gave the α-hydroxy lactam **26** in 57% yield as a highly crystalline, white solid after chromatography. Having thus established the feasibility for the creation of a key intermediate in our planned synthesis of (−)-rosmarinecine, we turned to the use of chiral vinyl ethers.

Scheme 5



Optimization of Reaction Parameters for the [4 + 2]/[3 + 2] Cycloaddition. The tandem [4 + 2]/[3 + 2] cycloaddition is the centerpiece in the planned synthesis of (−)-rosmarinecine. In that reaction, all of the stereogenic centers are installed in the correct relative and absolute sense, except that at C(6). To assure both a high yielding and a highly selective sequence of cycloadditions, we examined a number of permutations of Lewis acids and chiral vinyl ethers. To maximize efficiency, the entire synthesis was initially performed employing racemic auxiliaries. Initial experiments employed MAPh and $TiCl_2$(O-*i*Pr)$_2$ as the Lewis acids. MAD was not considered due to its generally low selectivity as the Lewis acid in tandem [4 + 2]/[3 + 2] cycloadditions.[18] The use of nitroalkene **21** and vinyl ether **27** (3 equiv) in reactions promoted by MAPh (3 equiv) led to a 93% yield of nitroso acetal **30** (Table 1). The use of less than 3 equiv of either the Lewis acid or the vinyl ether resulted in low yields (Table 1, entries 1−3).

Although a high yield of the tandem cycloaddition product could be obtained, the nitroso acetal **30** was produced as a 6.3:1 exo/endo mixture of diastereomers, (entry 1, Table 2). The use of $TiCl_2$(O-*i*Pr)$_2$ as the promoter improved the selectivity to 1:10 exo/endo, but this reaction was rather low yielding. More importantly, the product isolated from this cycloaddition was contaminated with unseparable impurities. We therefore turned our attention to the vinyl ether (−)-**28** derived from *trans*-2-(1-methyl-1-phenylethyl)cyclohexanol with MAPh as the promoter.[25,26] The nitroso acetal **31** was isolated in excellent yield

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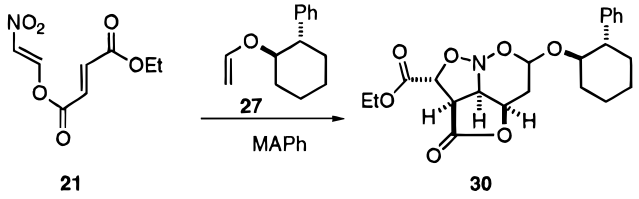
Table 1. Cycloaddition with Vinyl Ether **27** Promoted by MAPh

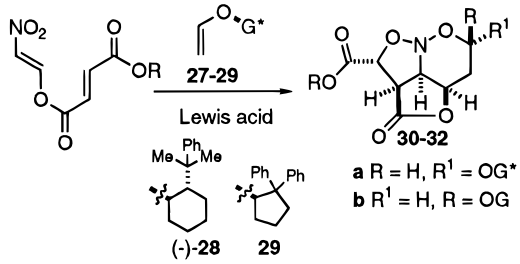


21 **30**

entry	MAPh, equiv	**27**, equiv	yield,[a] %
1	4.0	1.5	69
2	1.1	3	37
3	2.0	3	64
4	3.0	3	93

[a] Yield after chromatographic purification.

Table 2. Cycloaddition with Vinyl Ethers **27**−**29**



30-32 (-)-**28** **29**

entry	R	auxiliary	promoter	diastereo-selectivity, exo/endo	nitroso acetal	yield, %
1	Et	**27**	MAPh[a]	6.3:1	**30**	93
2	Et	**27**	$TiCl_2(Oi\text{-}Pr)_2$	1:10	**30**	57[c]
3	*i*-Pr	**28**	MAPh[a]	12.2:1[d]	**31**	95
4	*i*-Pr	**28**	$TiCl_2(Oi\text{-}Pr)_2$	6.6:4.1:1[e]	**31**	16
5	Et	**29**	MAPh[a]	41:1	**32**	95
6	Et	**29**	$TiCl_2(Oi\text{-}Pr)_2$	>10:1[b]	**32**	37[c]

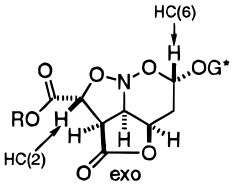
[a] All cycloadditions promoted by MAPh utilized 3 equiv of MAPh and 3 equiv of vinyl ether. [b] Minor could not be detected due to impurities. [c] Contaminated by an unknown impurity. [d] Minor assumed to be the other exo diastereomer. [e] The major diastereomer was the same as that from entry 3.

(95%) and with an improved exo/exo selectivity of 12.2:1. To determine if the two diastereomeric nitroso acetals **31** belonged to the same or opposite enantiomeric families, the mixture was converted to an intermediate in the synthesis of (−)-rosmarinecine.[27] The enantiomeric purity for this intermediate (12.9:1 enantiomeric ratio by chiral HPLC analysis) was shown to correspond well with the observed diasteromeric ratio of 12.2:1. Thus, the two diasteromeric nitroso acetals **31** do, in fact, belong to the opposite enantiomeric families. Unfortunately, they could not be separated by chromatography or recrystallization; consequently, it was not possible to enrich the mixture.

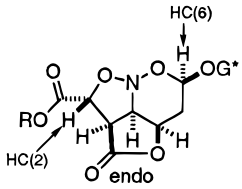
The third vinyl ether to be examined was derived from (*R*)-2,2-diphenylcyclopentanol **29**.[19e] Cycloaddition of **21** and **29** promoted by MAPh afforded the nitroso acetal **32** in both excellent yield (95%) and high diastereoselectivty (Table 2, entry 5). In repeated experiments, the diastereoselectivty was found to be variable (41:1 to 20:1), probably due to unintentional enrichment during chromatographic purification. The minor diasteromer **32b** was confirmed to be an endo-derived cycloadduct, since it was formed preferentially from the cycloaddition with $TiCl_2(Oi\text{-}Pr)_2$ as the promoter. Under these conditions, mainly **32b** was produced but in rather low yield (Table 2, entry 6). We have demonstrated that cycloadditions promoted by $TiCl_2(Oi\text{-}Pr)_2$ are generally endo selective, even with **29** as the vinyl ether.[19e]

(27) The enantiomeric ratio was determined on the 4-nitrobenzoate **50** by a sequence analogous to Scheme 11.

Table 3. Selected ^{1}H NMR Data of the Major Diasteromeric Nitroso Acetals **30**−**32**



30-32a



30-32b

entry	nitroso acetal	HC(6) ppm (*J*, Hz)	HC(2) ppm (*J*, Hz)
1	**30a**	*a*	5.25 (d, 3.7)
2	**30b**	*a*	5.28 (d, 3.6)
3	**31a**	4.72 (t, 6.9)	5.20 (d, 3.6)
4	**32a**	4.64 (t, 7.1)	5.30 (d, 3.7)
5	**32b**	4.95 (dd, 2.2, 6.9)	5.30 (d, 3.9)

[a] Obscured by ethyl ester signal.

Configurational Assignment. In nitroso acetals of the general structure **23**, it had been observed that the relative configuration of the anomeric center, C(6), with respect to the ring junction carbon, C(4a), could be determined by analysis of the splitting pattern of HC(6).[28] In the cycloaddition promoted by MAPh, the relationship should be trans if the exo product were generated kinetically, and the anomeric proton should be observed as a triplet. In contrast, with $TiCl_2(Oi\text{-}Pr)_2$ as the promoter, a cis relationship is dictated by the endo approach of the vinyl ether in the [4 + 2] cycloaddition. In this scenario, the anomeric proton should be observed as a doublet of doublets. It is therefore interesting that the coupling pattern of HC(6) in the nitroso acetals **30**−**32** displayed the same behavior. The anomeric proton appeared as a triplet in the nitroso acetal obtained from a MAPh-promoted reaction, supporting a trans relationship to C(4a) (Table 3, entries 3 and 4). On the other hand, the anomeric proton appeared as a doublet of doublets when the cycloaddition was promoted by a titanium Lewis acid, confirming a cis relationship between C(6) and C(4a) (entry 5). Interestingly, the chemical shift of the anomeric proton is also very sensitive to the auxiliary employed, while all the other protons on the tricyclic ring system are only slightly affected. The coupling pattern of the anomeric proton provided a means to identify the different diastereomeric nitroso acetals that were obtained in each cycloaddition. Armed with the knowledge that **29** behaved in a predictable and selective fashion with MAPh, it was easy to choose the appropriate configuration of 2,2-diphenylcyclopentanol for the synthesis of natural (−)-rosmarinecine.

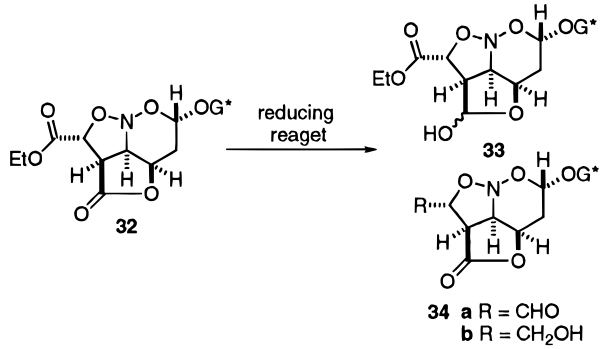
Unmasking of the Nitroso Acetal. From our experience with lactone **22**, it was anticipated that reduction of the lactone **32** would be required to allow the ring closure to occur.[29] Diisobutylaluminum hydride, which had been successfully employed previously, afforded the lactol **33** in, at best, 38% yield (Table 4).[30] The transformation was complicated by the competitive reduction of the ethyl ester, affording a mixture of aldehyde **34a** and alcohol **34b**. Thus, a survey was undertaken

(28) Schnute, M. E. Ph.D. Thesis, University of Illinois at Urbana−Champaign, Urbana, IL, 1995; pp 21−23.

(29) This was verified by the failure of **32** to undergo the desired hydrogenolysis.

(30) (a) Hijfte, L. V.; Little, R. D.; Petersen, J. L.; Moeller, K. D. *J. Org. Chem.* **1987**, *52*, 4647. (b) Ley, S. V.; Santafianos, D.; Blaney, W. M.; Simmonds, M. S. J. *Tetrahedron Lett.* **1987**, *28*, 221. (c) Nakata, T.; Saito, K.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 6345. (d) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490. (e) Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443. Review: (f) Winterfeldt, E. *Synthesis* **1975**, 617.

Table 4. Survey of Reducing Agents for the Reduction of **32**



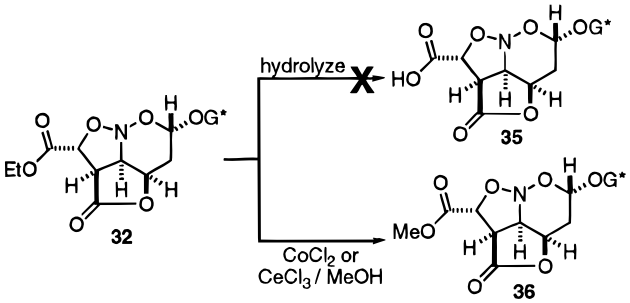
		mass recovery, %		
entry	reagent	lactol **33**	overreduction **34**	starting material **32**
1[a]	DIBAL-H	38	18	33
2[a]	Red-Al·EtOH	24	26	22
3[b]	$LiAlH(Ot\text{-}Bu)_3$	trace	trace	82
4[b]	Red-Al	0	29	58
5[b]	Red-Al·*N*-methyl piperazine	0	85[c]	0
6[a]	L-Selectride	55	0	0
7[d]	LS-Selectride	0	0	quantitative

[a] Isolated yield. [b] Ratios determined by ^{1}H NMR. [c] Numerous side products also observed. [d] No reduction product could be detected by ^{1}H NMR.

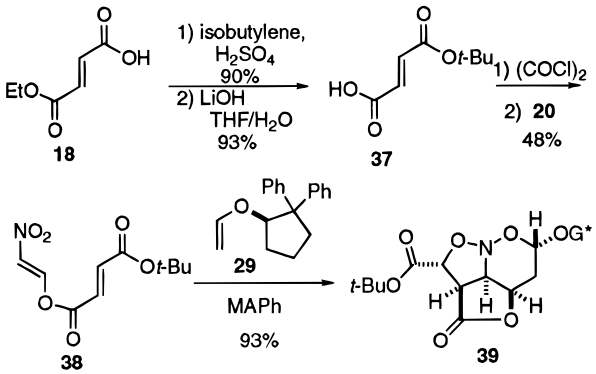
with reagents capable of effecting the lactone-to-lactol conversion:[31] sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al),[32] Red-Al·EtOH,[33] Red-Al·amine,[34] and lithium tris(*tert*-butoxy)aluminum hydride ($LiAlH(Ot\text{-}Bu)_3$).[35] Red-Al reduction of the lactone provided none of the desired product; instead, both overreduction products **34a** and **34b** (29%) were obtained. The ethanol-modified reagent afforded some of the desired product **33** (24%), but the mass recovery was very poor. The use of the *N*-methylpiperazine-modified Red-Al was ineffective. More promising was the use of lithium tris(*sec*-butyl)borohydride (L-Selectride), which afforded the desired lactol **33** in 55% yield. These results were still rather unsatisfactory for such a simple functional group transformation, and two separate strategies were undertaken to differentiate these groups: (1) hydrolysis of the ester to a carboxylic acid and (2) increasing the size of the ester to disfavor sterically reduction.

The simple hydrolysis of the ethyl ester **32** to the carboxylic acid **35** was more difficult than expected. The nitroso acetal **32** was found to be extremely base sensitive, and, in most instances, the free auxiliary was the only recovered material. Also unsuccessful were various reagents that have been

Scheme 6



Scheme 7



employed to cleave ethyl or methyl esters and ethers, such as potassium trimethylsilanolate,[36] iodotrimethylsilane,[37] lithium ethane thiolate,[38] dimethyl sulfide aluminum tribromide,[39] and sodium hydroxide in methanol.[40] The only reaction that showed even moderate success was the transesterification of **32** to a methyl ester (**36**) in methanol promoted by $CeCl_3$ or $CoCl_2$ (Scheme 6).[41]

Increasing the bulk of the ester group proved to be a successful strategy. Our initial approach was to use the corresponding *tert*-butyl ester. From **18**, the *tert*-butyl ester was prepared in 90% yield by esterification with isobutylene promoted by sulfuric acid (Scheme 7).[42,43] Selective hydrolysis of the ethyl ester with 1 equiv of LiOH in THF afforded the acid **37** in 93% yield.[44] The formation of the acid chloride from **37**, and coupling with the potassium salt **20**, afforded the nitroalkene **38** in 48% yield.

(31) (a) Walker, E. R. H. *Chem. Soc. Rev.* **1976**, *5*, 23. (b) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. (c) Barrett, A. G. M. In *Comprehensive Chemistry, Reductions*; Fleming, I., Ed.; Pergamon Press: Oxford 1991; Vol. 8, Chapter 1.10.

(32) (a) Doria, C.; Gaio, P.; Gandolfi, C. *Tetrahedron Lett*. **1972**, 4307. (b) Klötzer, W.; Teitel, S.; Brossi, A. *Helv. Chim. Acta* **1971**, *54*, 2057. (c) Disselnkötter, H.; Lieb, F.; Oediger, H.; Wendisch, D. *Liebigs Ann. Chem.* **1982**, 150. (d) Hohlbrugger, R.; Klötzer, W. *Chem. Ber*. **1979**, *112*, 849.

(33) (a) Hung, H.-K.; Lam, H.-Y.; Niemczura, W.; Wang, M.-C.; Wong, C.-M. *Can. J. Chem.* **1978**, *56*, 638. (b) Tokoroyama, T.; Matsuo, K.; Kotsuki, H.; Kanazawa, R. *Tetrahedron* **1980**, *36*, 3377.

(34) (a) Bartsch, H.; Schwarz, O. *J. Heterocycl. Chem.* **1982**, *19*, 1189. (b) Kanazawa, R.; Tokoroyama, T. *Synthesis* **1976**, 526.

(35) (a) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett*. **1975**, 227. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222. (c) Tsuda, Y.; Yoshimoto, K.; Yamashita, T.; Kaneda, M. *Chem. Pharm. Bull*. **1981**, *29*, 3238. (d) Cassidy, F.; Moore, R. W.; Wootton, G.; Baggaley, K. H.; Geen, G. R.: Jennings, L. J. A.; Tyrrell, A. W. R. *Tertahedron Lett.* **1981**, *22*, 253. (e) Stevens, R. V.; Vinogradoff, A. P. *J. Org. Chem.* **1985**, *50*, 4056. (f) Skattebøl, L.; Stenstrøm, Y. *Acta Chem. Scand. B* **1985**, *39*, 291.

(36) (a) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett*. **1984**, *25*, 5831. (b) Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B. *J. Chem. Soc., Chem. Commun.* **1993**, 1332.

(37) (a) Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247. (b) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495. (c) Ho, T.-L.; Olah, G. A. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 774. (d) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968. (e) Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 874.

(38) (a) Vaughan, W. R.; Baumann, J. B. *J. Org. Chem.* **1962**, *27*, 739. (b) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1731. (c) Kornblum, N.; Scott, A. *J. Am. Chem. Soc.* **1974**, *96*, 590. (d) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459. For a review of dealkylation methods, see: (e) McMurray, J. *Org. React.* **1976**, *24*, 187.

(39) (a) Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 1991. (b) Node, M.; Nishide, K.; Sai, M.; Fujita, E. *Tetrahedron Lett*. **1978**, 5211. (c) Williard, P. G.; Fryhle, C. B. *Tetrahedron Lett*. **1980**, *21*, 3731.

(40) (a) Liu, H.-W.; Auchus, R.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 5335. (b) Gawronski, J. K.; Reddy, S. M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1987**, *109*, 6726.

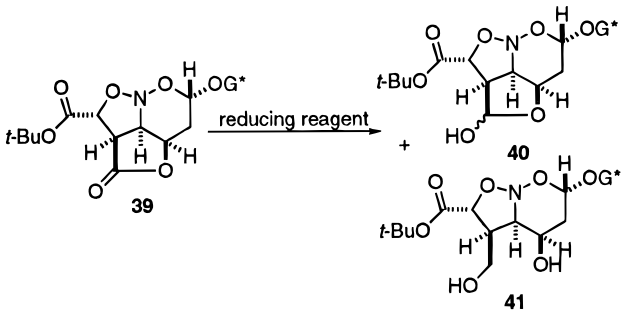
(41) (a) Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976. (b) Gemal, A. L.; Luche, J.-L. *J. Org. Chem*. **1979**, *44*, 4187. For a review of transesterification, see: (c) Otera, J. *Chem. Rev.* **1993**, *93*, 1449.

(42) Nelsen, S. F.; Gillespie, J. P. *J. Org. Chem.* **1975**, *40*, 2391.

(43) An alternative method for the preparation of this compound has been reported: Neises, B.; Steglich, W. *Org. Synth.* **1985**, *63*, 183.

(44) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603.

Table 5. Reductions of **39** with Various Hydride Reagents



		mass recovery, %[a]			
		lactol	side product		starting material
entry	reagent	**40**	**34**	**41**	**39**
1	DIBAL-H	31	14		33
2	$LiAlH(Ot\text{-}Bu)_3$	65		21	0
3	L-Selectride	86	0	0	0

[a] Isolated yield after chromatography.

The nitroalkene **38** was then combined in a cycloaddition with vinyl ether **29** promoted by MAPh. The desired nitroso acetal **39** was isolated in 93% yield as a 19:1 mixture of exo/endo diastereomers. The nitroso acetal could be enriched by a simple recrystallization from ethanol to a 31:1 exo/endo diastereomeric mixture. Surprisingly, DIBAL-H was still a rather nonselective reducing agent, affording only 31% yield of the desired lactol **40** with considerable reduction of the *tert*-butyl ester to **34** (Table 5). Lithium tris(*tert*-butoxy)aluminum hydride (2 equiv) afforded the desired lactol **40** in 65% yield, along with the unwanted diol **41** in 21% yield. However, when L-Selectride was employed as the reducing agent, the lactol **40** was isolated cleanly in 86% yield, with no overreduction detected.

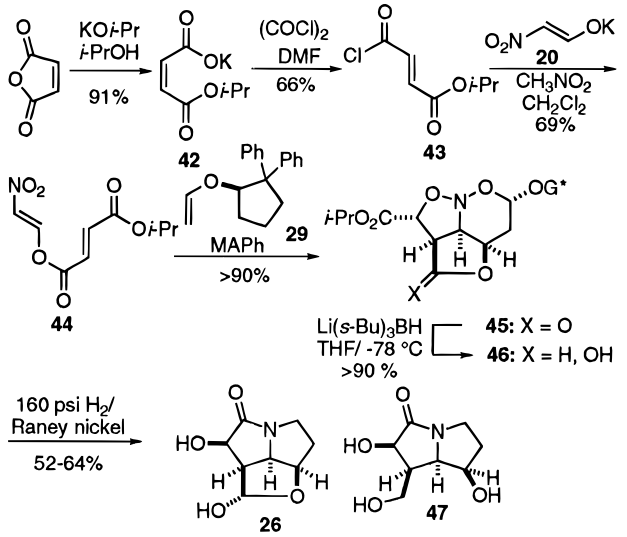
Subjecting of lactol **40** to the standard hydrogenolysis conditions, employing Raney nickel as the catalyst, *afforded none of the desired product* **26** after workup. The isolated product was very polar, as judged by TLC analysis, and seemed to include the *tert*-butyl ester by ^{1}H NMR spectroscopy. It appeared that the initial stages of the hydrogenolysis had been successful, but the final lactamization required to give the desired product did not occur. All attempts to cyclize the suspected intermediate failed. Apparently, the *tert*-butyl group was too bulky to allow the pyrrolidine to attack the carbonyl group in the strained bicyclic framework. We thus elected to test the corresponding isopropyl ester in the hope that it would serve effectively in both stages of the unmasking processes.

The requisite nitroalkene **44** was easily prepared from maleic anhydride (Scheme 8). Reaction of maleic anhydride with potassium isopropoxide, according to the procedure of Veibel and Pedersen, afforded the potassium maleate salt **42** in excellent yield (91%).[45] Treatment of **42** with $(COCl)_2$/DMF as before resulted in the formation of the desired acid chloride **43** (66%).[46] The attendant isomerization of the double bond was assured by the 15.4 Hz vicinal coupling constant, which is in good agreement with that observed in the nitroalkenes derived from **18**. The acid chloride **43** was coupled with **20** to afford the target nitroalkene **44** in 69% yield.

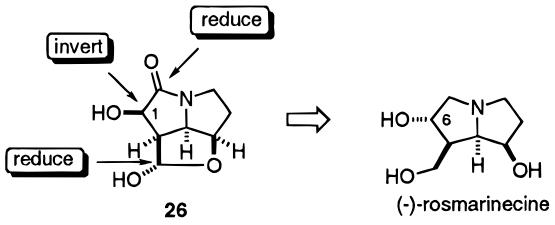
(45) Veibel, S.; Pedersen, C. *Acta Chem. Scand.* **1955**, *9*, 1674.

(46) For alternative methods for the preparation of the acid chloride, see: (a) Oiwa, M.; Matsumoto, A. Jpn. Kokai Tokkyo Koho JP 62 45,561, 1987; *Chem. Abstr.* **1987**, *107*, 176634b. Several methods exist for the preparation of the monoisopropyl fumaric acid, as an example: (b) Zecher, W.; Merten, R. Eur. Pat. Appl. EP 69926 A1, 1983. (c) Gordinskii, B. Y.; Shimanskii, V. M.; Vishnyakova, R. S. *Zh. Prikl. Kim.* **1967**, *40*, 1881. (d) Ushakov, S. N.; Nikolaev, A. F.; Toroptseva, A. M.; Trizno, M. S. *Zh. Prikl. Kim.* **1959**, *32*, 667.

Scheme 8



Scheme 9



The nitroalkene **44** was then transformed into the corresponding nitroso acetal **45** by a tandem cycloaddition with **29** in excellent yield. The reduction of the lactone to the lactol **46** was consistently achieved in greater than 90% yield with L-Selectride, with no evidence of overreduction. Moreover, subjecting the lactol **46** to the hydrogenolytic conditions with Raney nickel gratifyingly afforded the desired product **26** in 59% yield.

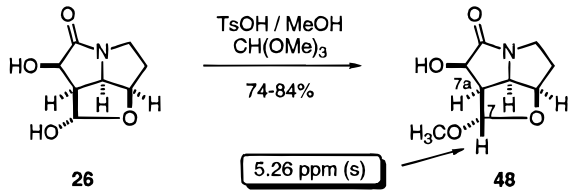
To optimize the yield of **26**, a survey of hydrogen pressure was undertaken. In this system, higher pressures afforded lower yields, though little difference was observed between 14.6 and 160 psi. In some instances, a very small amount of overreduction was detected wherein the lactol had been reduced to a diol (**47**). The optimum conditions employed 160 psi of hydrogen pressure for 48 h. In addition, following removal of the catalyst, the filtrate was heated at 60 °C for 1 h to ensure complete ring closure to the lactam.

Correction of the Configuration at C(6). The lactam **26** possessed all of the correct structural features of (−)-rosmarinecine. However, to convert the lactam to (−)-rosmarinecine, inversion of the configuration at C(1) (which becomes C(6) of (−)-rosmarinecine) was required (Scheme 9). In addition, it remained to reveal the free amino triol by reduction of the lactam and the lactol.

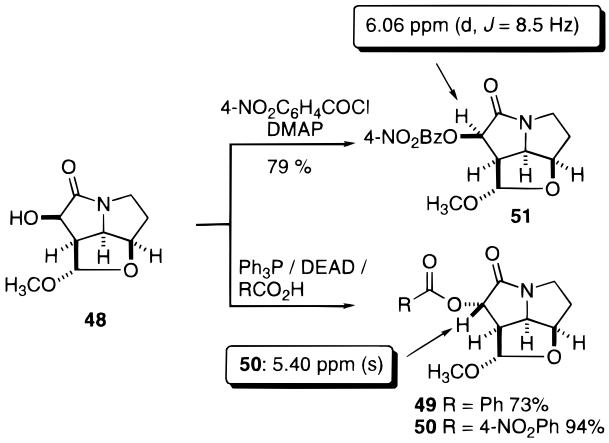
The free hydroxyl at C(1) makes the Mitsunobu reaction the perfect choice to correct the configuration of C(1).[47] In addition, the resulting ester could be deprotected under the same reducing conditions in which the amino triol would be revealed. Initial attempts to selectively invert the stereocenter at C(1) in the presence of the free lactol in **26** were foiled. The only isolated product (54%) contained one benzoate group; unfortunately, it was as a result of an inversion of the lactol, not the C(1) hydroxyl. The selective protection of the lactol as a methyl

(47) Review of the Mitsunobu reaction: Hughes, D. L. *Org. React.* **1992**, *42*, 335.

Scheme 10



Scheme 11



acetal was easily accomplished (MeOH/pTsOH/HC(OMe)$_3$/reflux) to afford **48** in 74−84% yield as a single anomer, as judged by ^{1}H NMR spectrocopy (Scheme 10). If the reaction was carried out for a shorter time, or at room temperature, a mixture of anomeric methyl acetals was obtained.[48] The assignment of configuration of the acetal is made on the assumption of thermodynamic control; the most stable methyl acetal should be of the α configuration due to steric interaction on the concave side of the tricyclic structure. In addition, the acetal proton appeared as a singlet, indicating a trans relationship between HC(7) and HC(7a). The minor anomer appeared at 5.14 ppm as a doublet (J = 5.6 Hz), indicating a cis relationship between HC(7) and HC(7a).

The configuration at C(1) was now easily corrected under standard Mitsunobu reaction conditions utilizing benzoic acid as the nucleophile. The product **49** was isolated in 73% yield (Scheme 11). Recent reports have demonstrated that more acidic nucleophiles, such as 4-nitrobenzoic acid, afforded higher yield in reactions with sterically hindered alcohols.[49] This simple modification dramatically improved the yield in the inversion with **48**, affording the inverted lactam **50** in 94% yield. The only complication in this reaction was the similar polarity of the substitution product and the byproduct triphenylphosphine oxide, requiring multiple purifications by silica gel chromatography to obtain **50** cleanly.

As confirmation that the methyl acetal **48** had, indeed, undergone invertive substitution and was not simply acylated in the Mitsunobu reaction, the α-hydroxy lactam **48** was treated with 4-nitrobenzoyl chloride to obtain the 4-nitrobenzoate **51** in 79% yield (Scheme 11). Comparison of the ^{1}H NMR spectra of the two esters confirmed that the Mitsunobu reaction had occurred with inversion. The ^{1}H NMR spectrum of lactam **50** has a singlet at 5.40 ppm, indicating a trans relationship between HC(7a) and HC(1), while the lactam **51** displayed a doublet at 6.06 ppm (J = 8.5 Hz), indicating a cis relationship between HC(7a) and HC(1).

(48) The production of a single anomer or a high anomeric ratio was important to achieve good yield in the subsequent reaction, as the minor component could never be isolated after workup (vide infra).

(49) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234.

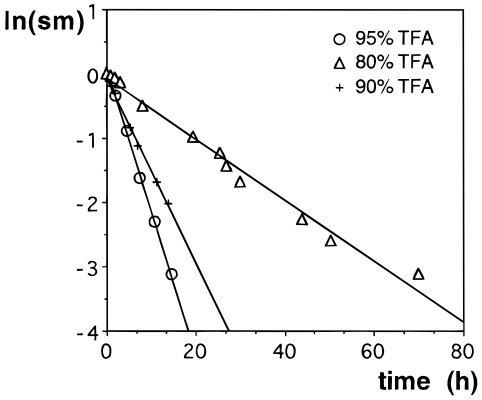
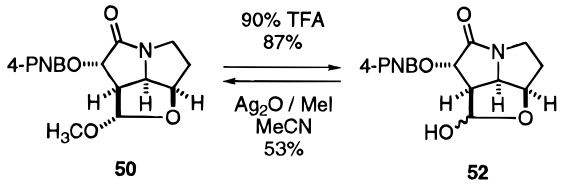
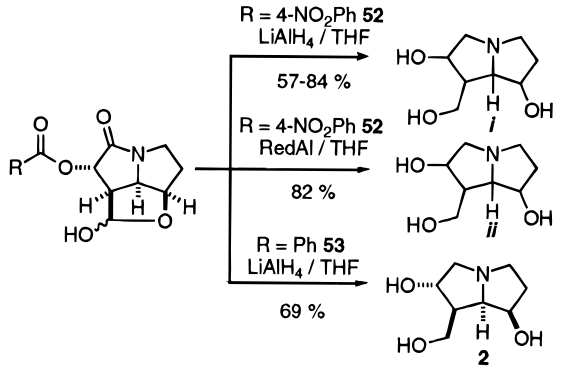


Figure 3. Hydrolysis of **50** as a function of TFA concentration.

Scheme 12



Scheme 13



Synthesis of Rosmarinecine. The final production of amino triol **2** by deprotection of the 4-nitrobenzoate and reduction of the lactam lactol required that the methyl acetal first be cleaved. Simple hydrolysis with 1 N HCl provided the desired product in very low yield, and iodotrimethylsilane[37] or boron trifluoride etherate/tetrabutyl ammonium iodide[50] afforded no reaction at all. More promising results were obtained with the use of trifluoroacetic acid (TFA), which provided the desired product **51** in variable yield.[51] Since the reaction appeared to be very sluggish, the TFA concentration was optimized in a series of ^{1}H NMR experiments. The approximate half-life of the hydrolysis was determined at three different acid concentrations: 80%, 90%, and 95% TFA. All the reactions were performed at room temperature in TFA-*d*, diluted with D_2O to the appropriate concentration. As can be seen in Figure 3[12], all of the reactions displayed pseudo-first-order kinetics. The 80% TFA reaction was very slow, with a $t_{1/2}$ of 14.5 h. Under these reaction conditions, only a trace amount of byproducts was generated, even after a long reaction time. The use of 95% TFA increased the rate dramatically ($t_{1/2}$ = 3.1 h) and afforded a more tolerable reaction time. Unfortunately, under these strongly acidic conditions, a large number of byproducts were observed in the ^{1}H NMR spectrum. The 90% TFA solution provided an excellent balance between rate and selectivity, with

(50) Mandal, A. K.; Soni, N. R.; Ratnam, K. R. *Synthesis* **1985**, 274.

(51) Nakajima, N.; Uoto, K.; Yonemitsu, O.; Hata, T. *Chem. Pharm. Bull.* **1991**, *39*, 64.

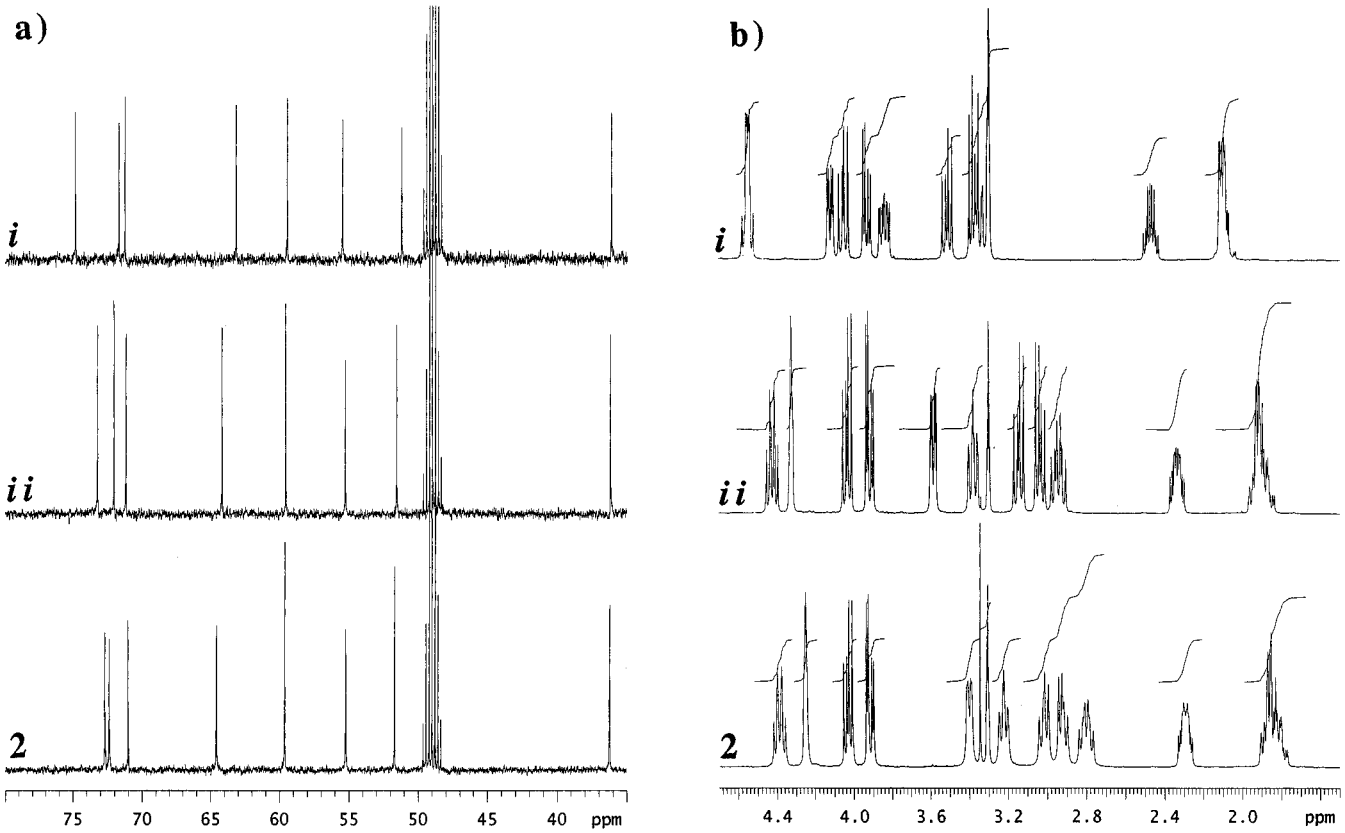
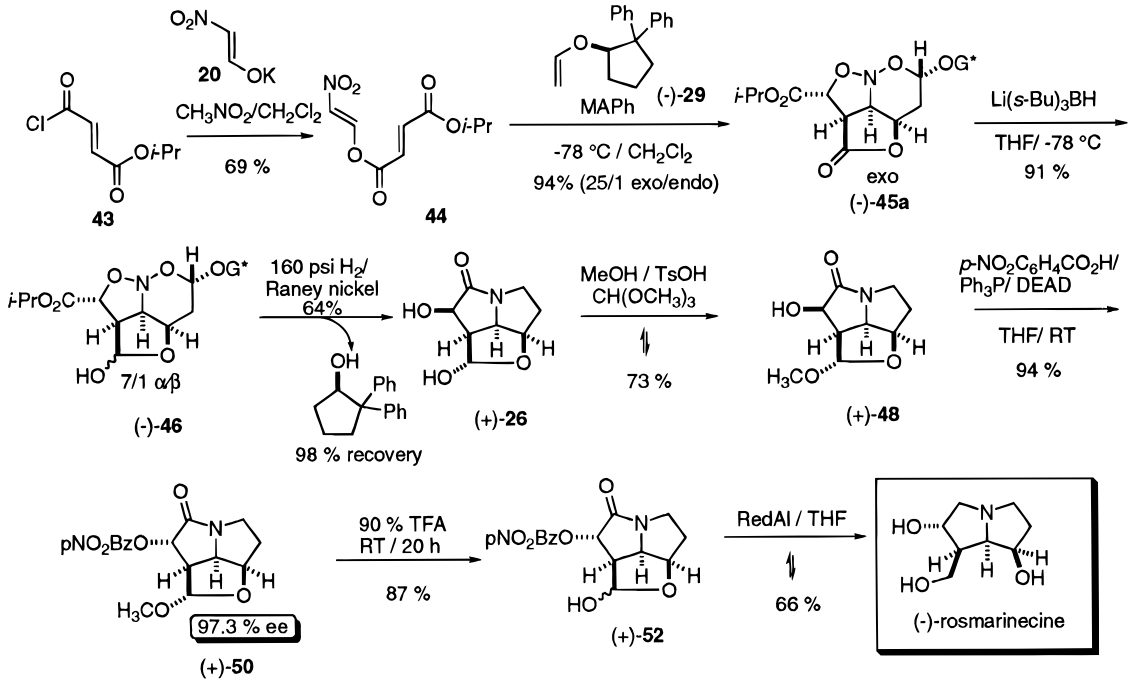


Figure 4. (a) ^{13}C NMR and (b) ^{1}H NMR spectra of ***i***, ***ii***, and rosmarinecine **2** after silica gel chromatography.

Scheme 14

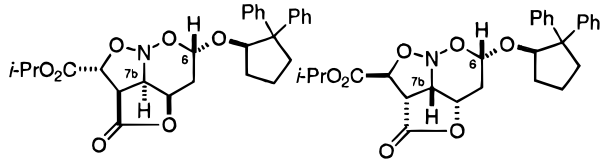


a $t_{1/2}$ of 4.8 h and a byproduct profile similar to that obtained with the 80% TFA reaction.

The isolation, purification, and identification of **52** proved to be challenging. The ^{1}H NMR spectra of the lactol **52** usually contained broad peaks with little fine structure, regardless of the solvent employed. Therefore, to ensure that our assignment of the lactol structure was correct, **52** was methylated with iodomethane and silver oxide (Scheme 12). The methyl acetal **50** was isolated in 53% yield, along with 28% of recovered **52**. The product isolated was the same methyl acetal **50** used in the hydrolysis by comparision of the ^{1}H and ^{13}C NMR spectra; thus, the assignment of the lactol structure as **52** was secured.

The final transformation involved an exhaustive reduction of the lactam, ester, and latent lactol carbonyl groups. In our (−)-hastanecine synthesis, a similar reduction with lithium aluminum hydride revealed the desired amino diol. To complete the synthesis of (−)-rosmarinecine, the 4-nitrobenzoate **52** was treated with lithium aluminum hydride to afford compound ***i*** in 66−84% yield after silica gel chromatography (Scheme 13). The ^{1}H and ^{13}C NMR spectra of ***i*** differed significantly from

Table 6. Selected ^{1}H NMR Data for Nitroso Acetals **45a**,**b**



(-)-45a **(+)-45b**

nitroso acetal	HC(6) ppm (*J*, Hz)	HC(7b) ppm (*J*, Hz)
(−)-**45a**	4.63 (t, 7,2)	4.39 (dd, 6.6, 8.6)
(+)-**45b**	4.95 (dd, 2.2, 6.8)	4.26 (dd, 6.4, 8.6)

those reported for natural (−)-rosmarinecine.[52] In only one instance under these reaction conditions was (−)-rosmarinecine isolated from **52** (45%). Employing Red-Al instead as the reducing agent with **52** afforded an 82% yield of yet another amino triol ***ii***, which differed from both rosmarinecine and ***i***. Still more surprising was the fact that $LiAlH_4$ reduction of the *benzoate* lactol **53** (prepared by TFA hydrolysis of **49**) produced **2** in moderate yield (69%) after silica gel chromatography. The dissimilarity of the NMR spectra of ***i***, ***ii***, and **2** is easily seen, as depicted in Figure 4.

This unanticipated outcome caused considerable consternation. The gross similarity of the NMR spectra of ***i***, ***ii***, and **2** suggested that epimeric forms of the desired product were being generated.[1,53] Some of these possibilities could be eliminated, and we eventually realized that the anomalies in the spectra were caused by variable concentrations of hydrates or *N*-complexes of rosmarinecine itself. This was proven by additional *purification of each of the three substances* ***i***, ***ii***, *and* **2** *on basic alumina to afford the same compound, which in each instance possessed the same* ^{1}*H and* ^{13}*C NMR spectra as those reported for natural (−)-rosmarinecine*.[52]

Total Synthesis of (−)-Rosmarinecine: Summary. The synthesis of enantiomerically pure (−)-rosmarinecine employing the optically active vinyl ether **29** is detailed in Scheme 14, where the yields refer to homogenous, analytically pure material. The requisite nitroalkene **44** was subjected to the tandem [4 + 2]/[3 + 2] cycloaddition sequence, utilizing MAPh as the Lewis acid promoter and (−)-**29**. Reaction of the nitroalkene with 3 equiv of the chiral vinyl ether in the presence of 3 equiv of MAPh afforded the nitroso acetal **45** in 94% yield. The nitroso acetal **45** was isolated as a 25:1 exo/endo mixture of diastereomers that could not be enriched by recrystallization. The diastereomers **45a,b** were, therefore, separated by silica gel chromatography. The chromatographic fractions containing the desired product (−)-**45a** were concentrated in two separate portions. The composition of the major portion (74%) was determined by ^{1}H NMR spectroscopy to be approximatly 95:1 exo/endo mixture of diastereomers, and the minor portion consisted of a 6.3:1 exo/endo mixture. The stereochemical assignment of the diastereomers was based, ^{1}H NMR: the anomeric proton in the exo diastereomer (−)-**45a** appears as a triplet, while the same proton in the endo diastereomer (+)-**45b** appears as a doublet of doublets (Table 6).

The lactone was then reduced with L-Selectride to afford the lactol (−)-**46** in excellent yield (91%). The lactol (−)-**46** was then submitted to the standard hydrogenation conditions to afford the tricyclic α-hydroxy lactam−lactol (+)-**26** in a satisfying 64% yield with a small amount of an overreduced lactol. The chiral auxiliary (*R*)-2,2-diphenylcyclopentanol was recovered in 98% yield after the hydrogenation. Protection of the lactol (+)-**26** as its methyl acetal (+)-**49** (73%), followed by inversion at C(2) by a Mitsunobu reaction utilizing 4-nitrobenzoic acid as the nucleophile, afforded the 4-nitrobenzoate (+)-**50** (94%), which was determined to be 97.3% by chiral HPLC. The deprotection of (+)-**50** was accomplished with 90% trifluoroacetic acid, to afford the lactol (+)-**52** in 87% yield. Reduction of lactol (+)-**52** with Red-Al in THF at reflux afforded, after extensive chromatographic purification on both silica gel and basic alumina, a white solid, which was recrystallized from acetone/pentane to afford (−)-rosmarinecine (**2**) as an analytically pure, white solid in 66% yield. The physical properties matched those of the reported values: mp 169−170 °C, $[\alpha]^{21}_D$ −117.6° (EtOH, c = 0.96), lit.[52] mp 170−172 °C, $[\alpha]^{23}_D$ −119.1° (EtOH, c = 0.94); lit.[10] mp 171−172 °C, $[\alpha]^{25}_D$ −118.5 °; lit.[12] mp 171−172 °C, $[\alpha]^{25}_D$ −116.5° (EtOH, c = 0.01); lit.[17] $[\alpha]^{21}_D$ −121° (EtOH, c = 0.01). Importantly, the ^{1}H NMR and ^{13}C NMR data of the synthetic product are nearly identical to those of the natural compound (mp 168−170 °C, $[\alpha]^{21}_D$ −119.8° (EtOH, c = 1.01)) obtained by hydrolysis of rosmarinine (see supporting information).

Conclusion. The synthesis of (−)-rosmarinecine was accomplished in eight steps and 14.8% overall yield from the fumaroyl acid chloride **43**. All the stereocenters were installed in a single transformation with high selectivity, which demonstrates the utility of the tandem [4 + 2]/[3 + 2] cycloaddition strategy and serves to illustrates the predictive power of the various stereochemical features of the reaction sequence. Since (−)-rosmarinecine is among the more complex necine bases containing an all-cis relationship, this synthesis demonstates the generality of the tandem [4 + 2]/[3 + 2] cycloaddition chemistry for the synthesis of this class of compounds.

Experimental Section

General Experimental. See supporting information for details.

(*E*)-4-Chloro-4-oxo-2-butenoic Acid 1-Methylethyl Ester (43). In a three-neck, 500 mL, round-bottom flask fitted with a Schlenk filtration tube was placed the potassium isopropoxy maleate **42** (15.0 g, 76.5 mmol) in CH_2Cl_2 (120 mL). To the solution was added oxalyl chloride (16.7 mL, 191 mmol, 2.49 equiv), followed by dimethylformamide (0.90 mL, 11.6 mmol, 0.15 equiv), whereupon massive evolution of gas was observed. The resulting solution was stirred at room temperature in an aluminum foil-covered flask for 22 h. Pentane (210 mL) was added, and the precipitated salts were filtered off and washed with pentane (30 mL). The filtrate was concentrated in vacuo, and the black residue was filtered again and fractionally distilled to afford 8.90 g (66%) of **43** as a clear, colorless oil: bp 44−45 °C (0.8 Torr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 15.4 Hz, 1H), 6.92 (d, J = 15.4 Hz, 1H), 5.12 (septet, J = 6.3 Hz, 1H, HC(5)), 1.30 (d, J = 6.1 Hz, 6H, HC(6)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.42 (C(1)), 163.22 (C(4)), 138.49 (C(3)), 136.44 (C(2)), 69.92 (C(5)), 21.62 (C(6)); IR (neat) ν 2985 (m), 2940 (w), 1766 (s), 1726 (s), 1376 (m), 1352 (m), 1337 (m), 1303 (s), 1278 (s), 1262 (s), 1239 (m), 1184 (s), 1146 (m), 1104 (s), 1024 (s), 984 (s), 972 (s), 907 (m); MS (70 eV) *mz* (relative intensity) 176 (M^+, 1), 141 (27), 135 (14), 119 (17), 118 (10), 117 (54), 99 (40), 91 (19), 89 (62), 85 (10), 83 (16), 82 (26), 59 (31), 55 (29), 54 (36), 53 (16), 43 (100), 42 (86). Anal. Calcd for $C_7H_9ClO_3$ (176.59): C, 47.60; H, 5.13. Found: C, 47.45; H, 5.17.

(*E*)-[(2-(Nitroethenyl)oxy]-4-oxo-2-butenoic Acid 1-Methylethyl Ester (**44**). To a slurry of potassium nitroacetaldehyde **20** (2.20 g, 17.3 mmol) in nitromethane (32 mL) at −6 °C was added rapidly a solution of **43** (3.09 g, 17.3 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL). The mixture was allowed to stir for 45 min at −6 °C. During this time, the color changed to light brown, with precipitation of a white solid. Dichloromethane (250 mL) was then added, and the resulting suspension was filtered through Whatman No.1 filter paper. The filtrate was

(52) Denholm, A. A. Ph.D. Thesis, University of Glasgow, 1990. We gratefully acknowledge professor David J. Robins for the copies of this experimental procedure.

(53) We are not aware of a report in the open literature discussing this phenomena, but considering the enormous numbers of papers in this field, a report could have been unintentionally missed.

concentrated by rotary evaporation, and the remaining nitromethane was removed under high vacuum with a water bath at room temperature to give 3.77 g of the crude nitroalkene. The crude product was recrystallized from hexane/Et_2O 10:1 (118 mL) with hot gravity filtration to afford 2.80 g (69%) of **44** as yellow, crystalline solid: mp 67−68 °C (hexane/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 11.0 Hz, 1H, HC(2)), 7.37 (d, J = 11.2 Hz, 1H, HC(1)), 7.07 (d, J = 15.6 Hz, 1H, HC(5)), 6.92 (d, J = 15.9 Hz, 1H, HC(6)), 5.14 (septet, J = 6.3 Hz, 1H, HC(9)), 1.32 (d, J = 6.4 Hz, 6H, HC(10)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.23 (C(7)), 160.07 (C(4)), 147.40 (C(2)), 138.87 (C(5)), 130.30 (C(1)), 129.16 (C(6)), 69.80 (C(9)), 21.59 (C(10)); IR (KBr) ν 3131 (m), 3081 (m), 2981 (m), 1744 (s), 1711 (s), 1671 (m), 1648 (w), 1532 (m), 1373 (m), 1362 (m), 1340 (w), 1315 (m), 1283 (w), 1189 (m), 1147 (w), 1109 (w), 1007 (w), 945 (w); MS(CI, CH_4) *m*/*z* (relative intensity) 230 (M^+ + H, 2), 159 (12), 142 (9), 141 (100), 117 (6), 99 (9). Anal. Calcd for $C_9H_{11}NO_6$ (229.18): C, 47.16; H, 4.83; N, 6.11. Found: C, 47.17; H, 4.84; N, 6.12.

(2*R*,2a*S*,4aR,6*S*,7b*R*)- and (2*S*,2a*R*4aS,6*S*,7b*S*)-6-[(1*R*)-(2-Diphenylcyclopentyl)oxy]-3-oxooctahydro-1,4,7-trioxa-7a-azabicyclopent-[*cd*]indene-2-carboxylic Acid 1-Methylethyl Ester (45). To a solution of 2,6-diphenylphenol (8.202 g, 33.30 mmol, 6.0 equiv) in CH_2Cl_2 (61 mL) was added trimethylaluminum (2.0 M in toluene, 8.3 mL, 17 mmol, 3.0 equiv). Gas evolution was observed, and the resulting light yellow solution was stirred at room temperature for 40 min.

To a solution of **44** (1.272 g, 5.550 mmol) in CH_2Cl_2 (22 mL) at −75 °C was added a solution of (*R*)-2,2-diphenylcyclopentoxyethene ((−)-**29**)[19e] (4.402 g, 16.65 mmol, 3.0 equiv) in CH_2Cl_2 (13 mL). MAPh was added slowly to the resulting mixture over 36 min, keeping the internal temperature below −70 °C. During the addition, the solution changed color from light yellow to deep, dark brown. The brown solution was stirred for additional 1.5 h and then was quenched with MeOH (15.6 mL), poured into CH_2Cl_2 (1 L), and washed with water (2 × 0.6 L). The aqueous phases were back-extracted with CH_2Cl_2 (2 × 0.5 L), and the combined organic extracts were dried (Na_2SO_4), filtered through Celite, and concentrated in vacuo. The crude product was purified by silica gel (330 g) column chromatography, eluting with hexane/EtOAc (1:0 (0.9 L), 30:1 (0.9 L), 8:1 (0.9 L), 4:1 (1.8 L), 2:1 (0.9 L), 1:1 (0.9 L), 0:1(0.9 L)). The first fractions contained 2,6-diphenylphenol, which was recrystallized from hexane (300 mL) to afford 7.00 g (85%) of recovered phenol. The chromatographic fractions containing the desired product were concentrated in two separate portions. The major portion afforded 2.051 g (74.7%) of a white foam, the composition of which was determined by ^{1}H NMR to be a 95:1 exo/endo mixture of diastereomers ((−)-**45a**/(+)-**45b**). The minor portion afforded 0.574 g (20.9%) as a white foam, which consisted of a 6.3:1 exo/endo mixture. An analytically pure sample of the endo diastereomer (+)-**45b** was obtained by radial chromatography (1 mm silica plate), eluting with hexane/EtOAc (4:1, 2:1, 1:1).

For (−)-45a: mp 81−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.09 (m, 10H), 5.25 (d, J = 3.6 Hz, 1H, HC(2)), 5.09 (septet, J = 6.3 Hz, 1H, HC(9)), 4.79 (ddd, J = 2.2, 3.6, 6.4 Hz, 1H, HC(4a)), 4.72 (d, J = 4.1 Hz, 1H, HC(1′)), 4.63 (t, J = 7.2 Hz, 1H, HC(6)), 4.39 (dd, J = 6.6, 8.6 Hz, 1H, HC(7b)), 3.90 (dd, J = 3.4, 8.3 Hz, 1H, HC(2a)), 2.64−2.56 (m, 1H, HC(3′)), 2.30−2.26 (m, 2H, HC(5′ and 3′)), 2.14−2.06 (m, 1H, HC(5′)), 1.89−1.85 (m, 2H, HC(5 and 4′)), 1.54 (ddd, J = 2.0, 7.2, 13.5 Hz, 1H, HC(5)), 1.45−1.38 (m, 1H, HC(4′)), 1.30 (d, J = 6.1 Hz, 3H, HC(10)), 1.29 (d, J = 6.4 Hz, 3H, HC(10)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.81 (C(3)), 166.97 (C(8)), 146.13 (C), 145.25 (C), 128.31 (CH), 128.16 (CH), 127.65 (CH), 126.82 (CH), 125.92 (CH), 125.59 (CH), 99.55 (C(6)), 86.05 (C(1′)), 84.84 (C(2)), 74.04 (C(7b)), 73.98 (C(4a)), 70.60 (C(9)), 60.09 (C(2′)), 49.13 (C(2a)), 35.01 (C(3′)), 31.72 (C(5′)), 28.30 (C(5)), 21.59 (C(10)), 21.55 (C(10)), 20.44 (C(4′)); IR (KBr) ν 3056 (w), 3023 (w), 2979 (m), 2876 (w), 1783 (s), 1740 (s), 1494 (m), 1447 (m), 1385 (m), 1375 (m), 1356 (m), 1287 (s), 1237 (s), 1205 (m), 1176 (s), 1147 (m), 1106 (s), 1067 (s), 1049 (s), 1032 (m), 1012 (m), 932 (m), 914 (s); MS (FAB) *m*/*z* (relative intensity) 532 (M^+ + K, 2), 494 (M^+ + H, 4), 309 (15), 274 (17), 223 (100), 221 (100), 155 (60), 154 (17), 153 (21), 152 (10), 149 (10), 143 (12), 137 (11), 135 (48), 120 (16), 118 (99), 117 (37), 102 (49); $[\alpha]^{21}_D$ −80.1° ($CHCl_3$, c = 1.00); TLC R_f = 0.45 (hexane/EtOAc 1:1). Anal. Calcd for $C_{28}H_{31}NO_7$ (493.55): C, 68.13; H, 6.33; N, 2.83. Found: C, 68.28; H, 6.42; N, 3.01.

For (+)-45b: mp 80−84 °C (hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.09 (m, 10H), 5.28 (d, J = 3.9 Hz, 1H, HC(2)), 5.10 (septet, J = 6.3 Hz, 1H, HC(9)), 4.95 (dd, J = 2.2, 6.8 Hz, 1H, HC-(6)), 4.79 (ddd, J = 3.0, 6.0, 9.3 Hz, 1H, HC(4a)), 4.72 (d, J = 5.4 Hz, 1H, HC(1′)), 4.26 (dd, J = 6.4, 8.6 Hz, 1H, HC(7b)), 3.93 (dd, J = 3.7, 8.6 Hz, 1H, HC(2a)), 2.63−2.55 (m, 1H, HC(3′)), 2.26−2.13 (m, 2H, HC(3′ and 5′)), 1.94−1.86 (m, 1H, HC(5′)), 1.84−1.72 (m, 2H, HC(5 and 4′)), 1.50 (ddd, J = 3.1, 6.9, 16.0 Hz, 1H, HC(5)), 1.37−1.25 (m, 1H, HC(4′)), 1.31 (d, J = 6.1, 3H, HC(10)), 1.30 (d, J = 6.1 Hz, 3H, HC(10)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.72 (C(3)), 166.88 (C(8)), 146.04 (C), 145.25 (C), 128.42 (CH), 128.12 (CH), 127.61 (CH), 126.88 (CH), 125.90 (CH), 125.54 (CH), 101.07 (C(6)), 87.40 (C(1′)), 84.48 (C(2)), 74.54 (C(4a)), 72.56 (C(7b)), 70.54 (C(9)), 60.25 (C(2′)), 49.46 (C(2a)), 34.78 (C(3′)), 32.33 (C(5′)), 29.85 (C(5)), 21.60 (C(10)), 21.56 (C(10)), 20.39 (C(4′)); IR (KBr) ν 3056 (w), 3023 (w), 2979 (m), 2878 (w), 1781 (s), 1741 (s), 1494 (w), 1447 (w), 1386 (w), 1375 (m), 1359 (m), 1346 (w), 1297 (s), 1288 (m), 1238 (s), 1209 (m), 1180 (s), 1154 (s), 1105 (s), 1082 (m), 1072 (m), 1046 (m), 1012 (m), 919 (m); MS (FAB) *m*/*z* (relative intensity) 494 (M^+ + H, 4) 307 (31), 289 (14), 258 (10), 237 (12), 221 (43), 155 (27), 154 (100), 139 (13), 138 (29), 137 (55), 136 (62), 123 (10), 119 (10), 116 (20), 106 (17); $[\alpha]^{21}_D$ +12.9° ($CHCl_3$, c = 0.54); TLC R_f = 0.45 (hexane/EtOAc 1:1). Anal. Calcd for $C_{28}H_{31}NO_7$ (493.55): C, 68.13; H, 6.33; N, 2.83. Found: C, 68.12; H, 6.32; N, 2.99.

(2*R*,2a*S*,4aR,6*S*,7b*R*)-6-[(1*R*)-(2-Diphenylcyclopentyl)oxy]-3-hydroxyoctahydro-1,4,7-trioxa-7a-azabicyclopent[*cd*]indene-2-carboxylic Acid 1-Methylethyl Ester ((−)-(46)). To a solution of (−)-**45a** (1.965 g, 3.981 mmol) in THF (71 mL) at −74 °C was added dropwise lithium tri(*sec*-butyl)borohydride (0.95 M in THF, 4.20 mL, 3.98 mmol, 1.0 equiv) over 5 min. The resulting solution was stirred for 1 h and then quenched with a solution of aqueous phosphate buffer (pH 6.9)/glycerol (1:1, 70 mL). The mixture was immediately poured into CH_2Cl_2 (0.5 L) and then washed with water (150 mL) and brine (2 × 150 mL) and back-extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography, eluting with hexane/EtOAc (8:1, 4:1, 2:1, 1:1, 0:1) to afford 1.810 g (91.8%) of (−)-**46** as a white foam: mp 82−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.09 (m, 10H), 5.49 (s, 0.88H, HC(3α)), 5.41 (dd, J = 6.8, 12.7 Hz, 0.12H, HC(3β)), 5.21 (d, J = 3.4 Hz, 0.12H, HC(2β)), 5.11 (septet, J = 6.3 Hz, 1H, HC(9)), 4.96 (d, J = 6.6 Hz, 0.88H, HC(2α)), 4.74−4.73 (m, 1.12H, HC(1′ and 6β)), 4.63 (t, J = 7.1 Hz, 0.88H, HC(6α)), 4.52−4.49 (m, 0.88H, HC(4aα)), 4.46 (d, J = 13.0 Hz, 0.12H, OH(β)), 4.33 (dd, J = 6.0, 8.9 Hz, 1.12H, HC(7b and 4aβ)), 3.56 (ddd, J = 3.4, 6.9, 8.5 Hz, 0.12H, HC(2aβ)), 3.28 (ddd, J = 1.5, 5.3, 9.0 Hz, 0.88H, HC(2aα)), 3.04 (d, J = 2.6 Hz, 0.88H, OH(α)), 2.64−2.56 (m, 1H, HC(3′)), 2.30−2.20 (m, 2H, HC(3′ and 5′)), 2.16−2.10 (m, 1H, HC(5′)), 1.85−1.80 (m, 2H, HC(4′ and 5)), 1.69 (ddd, J = 3.4, 7.4, 15.3 Hz, 1H, HC(5)), 1.46−1.36 (m, 1H, HC(4′)), 1.28 (d, J = 6.2 Hz, 5.3H, HC(10α)), 1.27 (d, J = 6.3 Hz, 0.7H, HC(10β)); ^{13}C NMR (100 MHz, $CDCl_3$) 164.46 (C(8β)), 168.19 (C(8α)), δ 146.43 (C(α)), 146.22 (C(β)), 145.39 (C(α)), 145.22 (C(β)), 128.42 (CH(α)), 128.28 (CH(β)), 128.15 (CH(β)), 128.07 (CH(α)), 127.63 (CH(β)), 127.52 (CH(α)), 126.91 (CH(α)), 126.80 (CH(β)), 125.89 (CH(β)), 125.80 (CH(α)), 125.57 (CH(β)), 125.48 (CH(α)), 102.00 (C(3α)), 100.53 (C(6β)), 99.38 (C(6α)), 98.34 (C(3β)), 86.20 (C(1′β)), 85.51 (C(1′α)), 84.24 (C(2α)), 83.85 (C(2β)), 78.22 (C(7bβ)), 77.53 (C(7bα)), 73.16 (C(4aα)), 73.03 (C(4aβ)), 69.97 (C(9β)), 69.80 (C(9α)), 60.05 (C(2′)), 58.57 (C(2aα)), 53.63 (C(2aβ)), 35.10 (C(3′α)), 35.05 (C(3′β)), 31.74 (C(5′α)), 31.67 (C(5′β)), 29.48 (C(5β)), 28.05 (C(5α)), 21.60 (C(10)), 20.41 (C(4′)); IR (KBr) ν 3441 (w, br), 3022 (w), 2978 (m), 2946 (m), 2874 (m), 1736 (s), 1494 (m), 1446 (m), 1384 (m), 1376 (m), 1322 (m), 1286 (m), 1267 (m), 1241 (m), 1218 (m), 1198 (m), 1147 (m), 1106 (s), 1073 (s), 1064 (s), 1036 (s), 1019 (m), 974 (m), 949 (m), 926 (m); MS (FAB) *m*/*z* (relative intensity) 496 (M^+ + H, 10), 309 (13), 276 (11), 222 (19), 221 (100), 186 (11), 155 (57), 154 (14), 153 (18), 152 (27), 144 (14), 143 (15), 137 (10), 134 (43), 120 (15), 118 (88), 117 (45), 102 (42); $[\alpha]^{21}_D$ −42.1° ($CHCl_3$,

$c = 0.90$); TLC $R_f = 0.40$ (hexane/EtOAc 1:1). Anal. Calcd for $C_{28}H_{33}NO_7$ (495.57): C, 67.86; H, 6.71; N, 2.82. Found: C, 67.80; H, 6.86; N, 3.18.

(1*R*,5a*S*,7*S*,7a*R*,7b*R*)-1,7-Dihydroxy-6-oxaoctahydro-2*H*-cyclopenta-[*gh*]pyrrolizin-2-one ((+)-(26)) and (1*R*,6*S*,6a*R*,7*S*)-1,6-Dihydroxy-7-(hydroxymethyl)hexahydro-1*H*-pyrrolizin-2-one (47). To a solution of (−)-**46** (1.783 g, 3.598 mmol) in methanol (100 mL) was added a catalytic amount of methanol-washed (6 × 80 mL) W-2 Raney nickel. The suspension was stirred at room temperature in a 300 mL flask inside a steel autoclave for 48 h under 160 psi atmosphere of H_2. The catalyst was filtered off through Celite and washed with methanol (200 mL), and the solution was stirred at 65 °C for 1 h and then concentrated in vacuo. The residue was separated by silica gel column chromatography, eluting with $CHCl_3$/MeOH (1:0, 99:1, 19:1, 9:1, 6:1, 4:1, 2:1) into three fractions. The first fraction contained a mixture of (+)-**26** and (*R*)-2,2-diphenylcyclopentanol. The second portion contained 0.406 g of pure (+)-**26**, and the third fraction contained 0.040 g of a mixture of (+)-**26** and **47**. The first fraction was repurified by silica gel column chromatography, eluting with $CHCl_3$/MeOH (1:0, 99:1, 19:1, 9:1, 4:1, 2:1) to afford 0.836 g (98% recovery) of (1*R*)-2,2-diphenylcyclopentanol and 0.037 g of (+)-**26.** The pure fractions of α-hydroxy lactam (+)-**26** were combined and recrystallized from pentane/$CHCl_3$/MeOH to give 0.428 g of (+)-**26** (64%) as a white amorphous solid. The third fraction was repurified by basic alumina (activity II) column chromatography, eluting with $CHCl_3$/MeOH (19:1, 6:1, 4:1, 2:1 followed by $CHCl_3$/MeOH/NH_4OH 10:5:1), to afford 0.029 g of an 8:1 mixture (as determined by ^{1}H NMR) of **47** and (+)-**26**.

For (+)-26: mp (sealed tube) 153 °C dec (pentane/$CHCl_3$/MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 5.61 (s, 1H, HC(7)), 4.76 (d, $J = 8.1$ Hz, 1H, HC(1)), 4.71 (t, $J = 3.7$ Hz, 1H, HC(5a)), 4.19 (dd, $J = 3.1$, 5.5 Hz, 1H, HC(7b)), 3.80 (ddd, $J = 6.8$, 8.9, 11.6 Hz, 1H, HC(4)), 3.08−3.01 (m, 2H, HC(7a and 4)), 2.21−2.03 (m, 2H, HC(5)); ^{13}C NMR (100 MHz, CD_3OD) δ 178.90 (C(2)), 100.12 (C(7)), 82.80 (C(5a)), 72.66 (C(1)), 67.65 (C(7b)), 54.12 (C(7a)), 43.31 (C(4)), 30.36 (C(5)); IR (KBr) ν 3385 (s), 3279 (m), 3178 (s), 3008 (w), 2994 (m), 2967 (m), 2936 (m), 2900 (m), 1678 (s), 1481 (m), 1443 (s), 1360 (m), 1338 (m), 1323 (m), 1308 (m), 1281 (m), 1231 (m), 1221 (m), 1203 (m), 1127 (s), 1091 (m), 1075 (s), 1031 (m), 983 (m), 968 (m), 949 (m), 924 (m), 917 (m); MS (70 eV) *m*/*z* (relative intensity) 185 (M^+, 16), 168 (48), 167 (18), 141 (22), 140 (19), 139 (14), 138 (20), 128 (16), 123 (13), 122 (31), 112 (11), 111 (57), 110 (70), 96 (37), 95 (59), 86 (10), 85 (16), 84 (43), 83 (100), 82 (25), 73 (29), 70 (19), 69 (17), 68 (33), 67 (30), 58 (10), 57 (30), 56 (19), 55 (45), 54 (16), 53 (16), 45 (10), 44 (11), 43 (21), 42 (32); $[\alpha]^{21}_D$ +130.9° (MeOH, $c = 0.61$); TLC $R_f = 0.20$ ($CHCl_3$/MeOH 9:1). Anal. Calcd for $C_8H_{11}NO_4$ (185.17): C, 51.89; H, 5.99; N, 7.56. Found: C, 51.88; H, 5.96; N, 7.39.

For 47: ^{1}H NMR (400 MHz, CD_3OD) δ 4.42 (d, $J = 7.6$ Hz, 1H, HC(1)), 4.27 (t, $J = 2.8$ Hz, 1H, HC(6)), 3.91 (dd, $J = 5.9$, 11.2 Hz, 1H, HC(8)), 3.80−3.72 (m, 2H, HC(8 and 6a)), 3.61−3.54 (m, 1H, HC(4)), 3.17 (dd, $J = 10.0$, 11.0 Hz, 1H, HC(4)), 2.91−2.83 (m, 1H, HC(7)), 2.25−2.14 (m, 1H, HC(5)), 2.09−2.03 (m, 1H, HC(5)); ^{13}C NMR (100 MHz, CD_3OD) δ 177.46 (C(2)), 73.76 (CH), 69.33 (CH), 66.69 (C(6a)), 58.09 (C(8)), 44.22 (C(7)), 40.68 (C(4)), 36.54 (C(5)).

(1*R*,5a*S*,7*S*,7a*R*,7b*R*) 1-Hydroxy-7-methoxy-6-oxaoctahydro-2*H*-cyclopenta[*gh*]pyrrolizin-2-one ((+)-(48)). To a solution of (+)-**26** (0.213 g, 1.150 mmol) and *p*-toluenesulfonic acid (0.060 g, 0.345 mmol, 0.33 equiv) in MeOH (90 mL) was added trimethyl orthoformate (13 mL). The resulting solution was heated at reflux for 5 h and then cooled to room temperature and quenched with poly(vinylpyridine) (0.085 g). The suspension was filtered, and the filtrate was concentrated in vacuo. The resulting crude product was purified by basic alumina (activity II) column chromatography eluting with hexane/EtOAc (1:1, 0:1) followed by $CHCl_3$/MeOH (19:1, 9:1, 6:1, 2:1), to afford 0.185 g of (+)-**48**. The methyl acetal was recrystallized from acetone/Et_2O/pentane to provide 0.169 g (73%) of (+)-**48** as a white amorphous solid: mp 159−160 °C (acetone/Et_2O/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H, HC(7)), 4.71 (dd, $J = 1.9$, 8.3 Hz, 1H, HC(1)), 4.61 (t, $J = 3.6$ Hz, 1H, HC(5a)), 4.12 (dd, $J = 3.1$, 5.5 Hz, 1H, HC(7b)), 4.08 (d, $J = 3.0$ Hz, 1H, OH), 3.92 (ddd, $J = 7.0$, 8.8, 11.7 Hz, 1H, HC(4)), 3.31 (s, 3H, HC(8)), 3.13 (dd, $J = 5.8$, 8.2 Hz, 1H, HC(7a)), 3.08−3.02 (m, 1H, HC(4)), 2.22−2.07 (m, 2H, HC(2)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.41 (C(2)), 105.57 (C(7)), 81.31 (C(5a)), 71.41 (C(1)), 66.56 (C(7b)), 54.84 (C(8)), 51.26 (C(7a)), 42.53 (C(4)), 29.50 (C(5)); IR (KBr) ν 3355 (s), 2989 (m), 2972 (m), 2953 (m), 1702 (s), 1477 (m), 1432 (m), 1320 (m), 1306 (m), 1279 (m), 1233 (m), 1197 (m), 1162 (m), 1129 (s), 1106 (s), 1079 (m), 1069 (m), 1032 (m), 1006 (s), 964 (m), 926 (m); MS *m*/*z* (relative intensity) (70 eV) 199 (M^+, 15), 168 (25), 167 (46), 142 (58), 140 (42), 139 (15), 138 (25), 122 (19), 112 (18), 111 (27), 110 (79), 100 (11), 98 (15), 96 (23), 95 (100), 94 (12), 87 (25), 86 (10), 84 (19), 83 (67), 82 (24), 71 (20), 70 (12), 69 (15), 68 (38), 67 (24), 57 (12), 56 (14), 55 (31), 54 (11), 53 (13), 45 (15), 43 (17), 42 (20), 41 (49); $[\alpha]^{21}_D$ +186.4° ($CHCl_3$, $c = 0.69$); TLC $R_f = 0.45$ ($CHCl_3$/MeOH 9:1). Anal. Calcd for $C_9H_{13}NO_4$ (199.20): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.15; H, 6.67; N, 7.01.

(1*S*,5a*S*,7*S*,7a*R*,7b*R*)-7-Methoxy-1-[(4-nitrobenzoyl)oxy]-6-oxaoctahydro-2*H*-cyclopenta[*gh*]pyrrolizin-2-one ((+)-(50)). To a solution of (+)-**48** (0.158 g, 0.793 mmol) and triphenylphosphine (0.312 g, 1.190 mmol, 1.5 equiv) in THF (7.6 mL) was added rapidly a solution of 4-nitrobenzoic acid (0.199 g, 1.190 mmol, 1.5 equiv) and diethyl azodicarboxylate (DEAD, 0.187 mL, 1.190 mmol, 1.5 equiv) in THF (2.1 mL). The resulting yellow solution was stirred in an aluminum foil-covered flask for 21.5 h and then poured into CH_2Cl_2 (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 30 mL) and brine (30 mL) and then was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was then purified by silica gel column chromatography, eluting with hexane/EtOAc (6:1, 4:1, 2:1, 1:1, 1:2, 1:4, 1:0) to afford 0.398 g of (+)-**50**, which was further purified by silica gel column chromatography, eluting $CHCl_3$/MeOH (1:0, 99:1, 19:1, 9:1). The product was then recrystallized from acetone/Et_2O/pentane to give 0.280 g (94%) of (+)-**50** as a yellow solid. The 4-nitrobenzoate (+)-**50** was determined to be of 97.3% ee by chiral HPLC analysis: mp 124−126 °C (acetone/Et_2O/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, $J = 1.9$, 7.1 Hz, 2H), 8.24 (dd, $J = 2.0$, 6.9 Hz, 2H), 5.40 (s, 1H, HC(1)), 5.12 (s, 1H, HC(7)), 4.66−4.64 (m, 1H, HC(5a)), 4.50 (dd, $J = 3.4$, 5.9 Hz, 1H, HC(7b)), 4.08 (ddd, $J = 6.1$, 8.1, 12.0, Hz, 1H, HC(4)), 3.37 (s, 3H, HC(6′)), 3.22 (ddd, $J = 6.8$, 8.9, 12.1 Hz, 1H, HC(4)), 2.89 (d, $J = 6.1$ Hz, 1H, HC(7a)), 2.33−2.28 (m, 2H, HC(5)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.68 (C(2)), 163.93 (C(1′)), 150.78 (C(5′)), 134.27 (C(2′)), 131.03 (C(3′)), 123.61 (C(4′)), 109.19 (C(7)), 80.79 (C(5a)), 78.40 (C(1)), 69.06 (C(7b)), 54.68 (C(6′)), 51.32 (C(7a)), 43.93 (C(4)), 31.42 (C(5)); IR (KBr) ν 3069 (w), 2960 (w), 1742 (s), 1727 (m), 1701 (s), 1607 (m), 1530 (s), 1443 (w), 1402 (m), 1385 (w), 1361 (m), 1350 (m), 1296 (m), 1272 (s), 1259 (s), 1242 (m), 1217 (m), 1200 (m), 1097 (s), 1083 (s), 1052 (s), 1013 (s), 997 (m), 960 (w); MS (FAB) *m*/*z* (relative intensity) 349 ($M^+ + H$, 2), 307 (44), 289 (18), 155 (27), 154 (100), 139 (12), 138 (32), 137 (60), 136 (61), 123 (10), 106 (15); $[\alpha]^{21}_D$ +37.1° ($CHCl_3$, $c = 0.49$); TLC $R_f = 0.18$ (hexane/EtOAc 1:1); HPLC (Daicel, Chiralcel OJ cellulose tris(4-methylbenzoate) (25 cm × 4.6 mm), hexane/EtOH 70:30, 0.9 mL/min) t_R (1*S*,5a*R*,7*S*,7a*R*,7b*R*)-(+)-**50**, 20.0 min (98.6%), t_R (1*R*,5a*S*,7*R*,7a*S*,7b*S*)-(−)-**50**, 26.2 min (1.3%). Anal. Calcd for $C_{16}H_{16}N_2O_7$ (348.31): C, 55.17; H, 4.62; N, 8.04, Found: C, 55.06; H, 4.50; N, 7.91.

(1*S*,5a*S*,7a*R*,7b*R*)-7-Hydroxy-1-[(4-nitrobenzoyl)oxy]-6-oxaoctahydro-2*H*-cyclopenta[*gh*]pyrrolizin-2-one ((+)-(52)). A solution of (+)-**50** (0.330 g, 0.947 mmol) in 90% aqueous trifluoroacetic acid (TFA) (16.8 mL) was stirred at room temperature for 20 h. The solution was then concentrated under high vacuum to ca. 3 mL and then was repeatedly diluted with benzene (25 mL) and concentrated in vacuo. The crude product was then purified by silica gel column chromatography, eluting with hexane/EtOAc (4:1, 2:1, 1:1, 1:2, then acetone), to afford 0.308 g of (+)-**52**. The lactol was recrystallized from acetone/Et_2O/pentane to give 0.275 g (87%) of (+)-**52** as a white amorphous solid: mp (sealed tube) 145 °C dec (acetone/Et_2O/pentane); ^{1}H NMR (400 MHz, THF-d_8, major only) δ 8.34−8.30 (m, 2H), 8.26−8.23 (m, 2H), 5.69 (d, $J = 3.2$ Hz, 1H), 5.51 (d, $J = 4.0$ Hz, 1H), 5.34 (s, 1H, OH), 4.70 (t, $J = 4.2$ Hz, 1H, HC(5a)), 4.48 (dd, $J = 3.4$, 5.9 Hz, 1H, HC(7b)), 3.90 (ddd, $J = 5.4$, 9.3, 12.0 Hz, 1H, HC(4)), 3.09 (ddd, $J = 5.4$, 10.0, 11.7 Hz, 1H, HC(4)), 2.82 (d, $J = 5.8$ Hz, 1H, HC(7a)), 2.24 (ddd, $J = 5.1$, 10.0, 19.2 Hz, 1H, HC(5)), 2.14−2.07 (m, 1H, HC(5)); ^{13}C NMR (100 MHz, THF-d_8, major only) δ 172.35 (C(2)), 164.57 (C(1′)), 151.87 (C(5′)), 135.85 (C(2′)), 131.72 (C(3′)), 124.36

(C(4′)), 104.00 (C(7)), 81.62 (C(5a)), 79.49 (C(1)), 69.98 (C(7b)), 53.08 (C(7a)), 44.37 (C(4)), 30.08 (C(5)); IR (KBr) ν 3354 (m, br) 2940 (m), 1745 (s), 1702 (s), 1611 (m), 1535 (m), 1438 (m), 1412 (m), 1362 (m), 1347 (s), 1319 (m), 1301 (m), 1268 (s), 1204 (m), 1118 (s), 1100 (m), 1086 (m), 1053 (m), 1041 (m), 1015 (m), 1008 (m), 997 (m); MS (FAB) *m*/*z* (relative intensity) 335 ($M^+ + H$, 4), 309 (11), 155 (63), 154 (20), 153 (27), 152 (41), 149 (13), 137 (14), 135 (59), 121 (17), 118 (100); $[\alpha]^{21}_D$ +16.2° (THF, $c = 0.48$); TLC $R_f = 0.14$ (hexane/EtOAc 1:2). Anal. Calcd for $C_{15}H_{14}N_2O_7$ (334.28): C, 53.89; H, 4.22; N, 8.38. Found: C, 53.80; H, 4.20; N, 8.38.

Synthetic (−)-Rosmarinecine (2). To a solution of (+)-**52** (0.203 g, 0.607 mmol) in THF (40 mL) was added Red-Al (1.24 M in THF, 5.8 mL, 7.2 mmol, 12 equiv). The clear solution was stirred at room temperature for 0.5 h, during which time the solution changed color from to yellow to red. The resulting solution was then heated at reflux for 3 h, during which time the color changed from purple to black-yellow. The mixture was cooled to room temperature and quenched with water (0.68 mL), 2 N NaOH (0.60 mL), and water (1.36 mL), and then it was diluted with THF (30 mL) and stirred for 5 min. The resulting solution was concentrated to ca. 5 mL, and the crude product was purified by silica gel chromatography, eluting with ($CHCl_3$/MeOH/NH_4OH 10:5:1). The silica gel column was prepared with a large Celite plug (half the height of the silica gel) at the bottom of the column, to give 93 mg of a white-yellow solid. The solid required further purification by chromatography on basic alumina (activity II) eluting with $CHCl_3$/MeOH (6:1, 4:1, 2:1, followed by $CHCl_3$/MeOH/NH_4OH 10:5:1), to give 81 mg of a white solid, which was recrystallized from acetone/pentane to provide 69 mg (66%) of (−)-rosmarinecine as a highly crystalline, white solid: mp (sealed tube) 169−170 °C (acetone/pentane); ^{1}H NMR (400 MHz, CD_3OD) δ 4.37 (ddd, $J = 7.7, 7.7, 9.7$ Hz, 1H, HC(6)), 4.23−4.22 (m, 1H, HC(1)), 4.02 (dd, $J = 6.8, 11.0$ Hz, 1H, HC(8)), 3.90 (dd, $J = 3.7, 11.0$ Hz, 1H, HC(8)), 3.37 (dd, $J = 3.0, 8.1$ Hz, 1H, HC(7a)), 3.19 (ddd, $J = 1.7, 8.1, 9.8$ Hz, 1H, HC(3)), 2.99 (dd, $J = 8.1, 11.0$ Hz, 1H, HC(5)), 2.90 (dd, $J = 7.3, 11.2$ Hz, 1H, HC(5)), 2.77 (ddd, $J = 6.8, 10.0, 11.4$ Hz, 1H, HC(3)), 2.31−2.24 (m, 1H, HC(7)), 1.89−1.76 (m, 2H, HC(2)); ^{13}C NMR (100 MHz, CD_3OD) δ 72.59 (C(7a)), 72.38 (C(1)), 70.96 (C(6)), 64.61 (C(5)), 59.63 (C(8)), 55.21 (C(3)), 51.70 (C(7)), 36.24 (C(2)); IR (KBr) ν 3296 (s, br), 2971 (s), 2934 (s), 2895 (s), 2877 (s), 2859 (s), 1479 (m), 1470 (m), 1458 (m), 1434 (m), 1358 (w), 1323 (m), 1310 (w), 1241 (w), 1166 (m), 1139 (m), 1099 (s), 1087 (s), 1063 (s), 1051 (m), 1034 (m), 1013 (m), 1002 (s), 986 (w); MS (70 eV) *m*/*z* (relative intensity) 173 (M^+, 10), 129 (34), 99 (13), 98 (100), 82 (16), 68 (11); $[\alpha]^{21}_D$ −117.6° (EtOH, $c = 0.96$); TLC $R_f = 0.23$ ($CHCl_3$/MeOH/NH_4OH 10:5:1); Anal. Calcd for $C_8H_{15}NO_3$ (173.21): C, 55.47; H, 8.72; N, 8.09. Found: C, 55.36; H, 8.82; N, 8.07.

Natural (−)-Rosmarinecine (2). A solution of rosmarinine (**1**) (0.177 g, 0.50 mmol) in 1 N aqueous NaOH (3.8 mL) was heated at reflux for 3 h. The resulting yellow solution was cooled to room temperature, diluted with EtOH (50 mL), and concentrated in vacuo. The solid residue was triturated with boiling EtOH (2 × 25 mL), and the extracts were filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography, eluting with $CHCl_3$/MeOH/NH_4OH (10:5:1), to give 81 mg of a yellow oil. The silica gel column was prepared with a large Celite plug (half the height of the silica gel) at the bottom of the column. The oil required further purification by chromatography on basic alumina (activity II) ($CHCl_3$/MeOH 6:1, 4:1, 2:1, followed by $CHCl_3$/MeOH/NH_4OH 10:5:1), to give 61 mg of white solid, which was recrystallized from acetone/pentane to give 50 mg (58%) of (−)-rosmarinecine as a highly crystalline, slightly yellow-white solid: mp (sealed tube) 168−170 °C (acetone/pentane); ^{1}H NMR (400 MHz, CD_3OD) δ 4.37 (ddd, $J = 7.8, 7.8, 9.6$ Hz, 1H, HC(6)), 4.23−4.21 (m, 1H, HC(1)), 4.02 (dd, $J = 6.8, 11.0$ Hz, 1H, HC(8)), 3.90 (dd, $J = 3.7, 11.0$ Hz, 1H, HC(8)), 3.35 (dd, $J = 2.8, 8.2$ Hz, 1H, HC(7a)), 3.18 (ddd, $J = 1.5, 8.1, 9.7$ Hz, 1H, HC(3)), 2.99 (dd, $J = 8.0, 11.0$ Hz, 1H, HC(5)), 2.89 (dd, $J = 7.3, 11.2$ Hz, 1H, HC(5)), 2.76 (ddd, $J = 7.0, 10.0, 11.5$ Hz, 1H, HC(3)), 2.31−2.24 (m, 1H, HC(7)), 1.88−1.75 (m, 2H, HC(2)); ^{13}C NMR (100 MHz, CD_3OD) δ 72.56 (C(7a)), 72.41 (C(1)), 70.96 (C(6)), 64.64 (C(5)), 59.63 (C(8)), 55.21 (C(3)), 51.71 (C(7)), 36.24 (C(2)); IR (KBr) ν 3337 (s, br), 2971 (s), 2965 (s), 2935 (s), 2910 (s), 2895 (s), 2878 (m), 2859 (m), 2758 (m), 2654 (m), 2643 (m), 1479 (w), 1469 (m), 1458 (m), 1444 (m), 1437 (m), 1379 (w), 1359 (m), 1321 (w), 1241 (w), 1206 (w), 1165 (m), 1139 (w), 1096 (s), 1063 (s), 1051 (s), 1034 (s), 1002 (s), 973 (w); MS (70 eV) 173 *m*/*z* (relative intensity) (M^+, 11), 129 (35), 99 (13), 98 (100), 82 (17), 68 (10); $[\alpha]^{21}_D$ −119.8° (EtOH, $c = 1.01$); TLC $R_f = 0.22$ ($CHCl_3$/MeOH/NH_4OH 10:5:1). Anal. Calcd for $C_8H_{15}NO_3$ (173.21): C, 55.47; H, 8.72; N, 8.09. Found: C, 55.44; H, 8.91; N, 8.01.

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Supporting Information Available: Experimental and spectroscopic data for **19**, **21**, **22**, **25**, **26**, **30**, **31**, **32**, **37**, **38**, **39**, **50**, and **51**, along with ^{1}H NMR, ^{13}C NMR, IR, and MS spectra of natural and synthetic (−)-rosmarinecine (30 pages). See any current masthead page for ordering and Internet access instructions.

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