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Asymmetric Synthesis of the Azabicyclic Core of the *Stemona* Alkaloids

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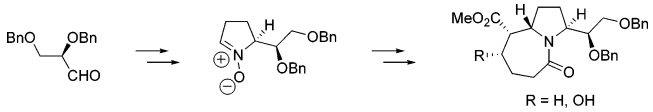

A general strategy for the construction of the 1-azabicyclo[5.3.0]decane core of *Stemona* alkaloids is developed. Our diversity-oriented approach exploits 1,3-dipolar cycloaddition of five-membered cyclic nitrones to C_6 olefins, followed by N−O reductive cleavage and azepine closure. The use of various enantiopure pyrroline *N*-oxides allows for a practical, stereoselective preparation of several putative precursors of different *Stemona* alkaloids.

Introduction

The deep knowledge of plant curative properties acquired by traditional folk medicine has motivated the scientific community toward the isolation and characterization of their bioactive components and the development of new drugs. The extracts of several plants of the *Stemonaceae* family (*Stemona* and *Croomia* genera) have been used for years in China and Japan as treatments for bronchitis, pertussis, and tuberculosis and as antihelmintics.[1] Significant constituents of these extracts are a series of structurally related alkaloids, which may be responsible for their medicinal properties, although studies on the specific biological activity of individual members of this alkaloid family are quite limited.[2] Nowadays, around 60 *Stemona* alkaloids are known, which have been classified in six groups attending to structural criteria.[3] The structures of 20 of them (tuberostemonine,[4] oxotuberostemonine,[5] stemonine (**1**),[6] protostemonine,[7] stemofoline,[8] stemonamine,[9] stemospironine (**2**),[10] croomine (**3**),[11] tuberostemonone,[12] tuberostemoninol,[13] tuberostemoamide,[13] tuberostemonine LG,[14] protostemotinine,[15] neotuberostemonol,[16] neotuberostemoninol,[16] stemocurtisine,[17] stemokerrin,[18] sessilifoliamide A,[19] 1′,2′-didehy-

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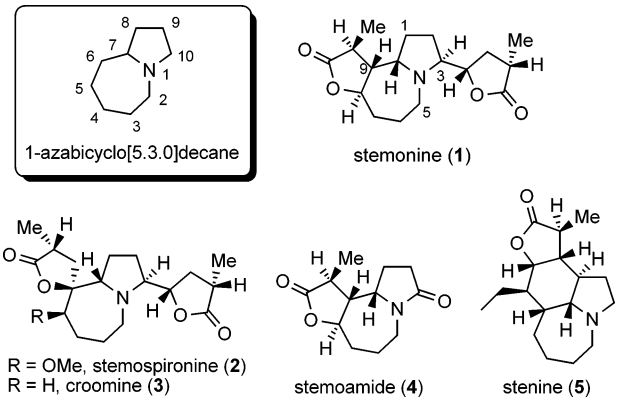
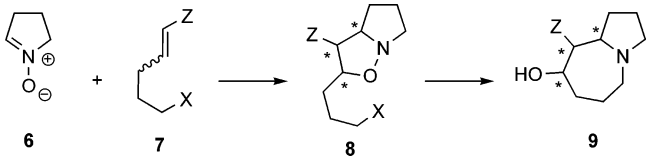
CHART 1



drostemofoline,[20] 2′-hydroxystemofoline,[20] and stemocurtisinol[21]) were elucidated by X-ray analyses, whereas those of the remaining alkaloids were determined from their spectroscopic data and/or by chemical correlation.[22] All of the *Stemona* alkaloids are polycyclic and, except for a small miscellaneous group, all of them present a central 1-azabicyclo[5.3.0]decane system as the most characteristic structural feature. Most of them also incorporate at least one substructure of α-methyl-γ-butyrolactone, which can be linked to the azabicyclic core in a spiro or fused manner or as a substituent.

The challenging molecular architecture of the *Stemona* alkaloids has attracted considerable interest among synthetic organic chemists, and several total syntheses have been published recently, although they are limited to a quite small number of targets.[23−31] In most of these

SCHEME 1. Cyclic Nitrone Approach to the 1-Azabicyclo[5.3.0]decane System



synthetic approaches, the azabicyclodecane nucleus is formed by exo-tet or exo-trig cyclization of either a substituted pyrrolidine[23b,c,24a,b,d,e,g,25a,c,27] or azepine,[23a,28,31] although some authors make use of ring-closing metathesis chemistry[25d,e,g,29] or intramolecular cycloaddition processes[24c,d,25b,f] and, except for two syntheses[25e,f] of stemoamide (**4**), the structurally simplest member of the family, the azabicyclic core is always generated from an advanced synthetic intermediate, generally holding multiple stereocenters and specifically assembled for the target alkaloid.

We thought that it would be desirable to develop a new synthetic strategy for *Stemona* alkaloids in which the 1-azabicyclo[5.3.0]decane ring system was generated at an early stage of the sequence and the α-methyl-γ-butyrolactone motifs and other specific fragments were then integrated. Such an approach would benefit from flexibility because the same intermediate could be common to various alkaloids, providing molecular diversity. Accordingly, we set up the methodology shown in Scheme 1,[32] emulating a highly effective procedure for the synthesis of indolizidine and pyrrolizidine frameworks.[33] One of the attractive features of this methodology is the high degree of stereoselectivity accomplished in the 1,3-dipolar cycloadditions of nitrone **6** to 1,2-disubstituted olefins of type **7**.[34] Thus, the relative configuration of the three contiguous stereogenic centers of the final azepine can

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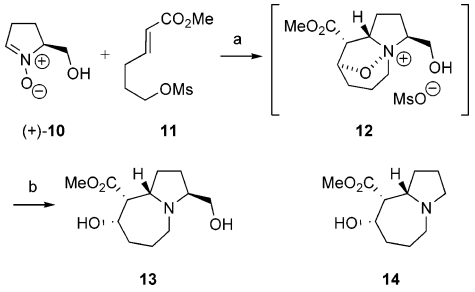
be controlled through the *E* or *Z* configuration of the starting dipolarophiles, favoring the formation of *endo*- or *exo*-isoxazolidines (referred to the electronwithdrawing group Z), respectively. Moreover, incorporation of any substituent at the nitrone counterpart may induce facial discrimination and hence a means to enantioselectivity because several substituted pyrroline *N*-oxides are available in the enantiopure form.[35] In this article, we present the results of a study aimed to prepare 1-azabicyclo[5.3.0]-decane compounds suitably substituted for further elaboration to various enantiomerically pure *Stemona* alkaloids, according to the abovementioned strategy.

Results and Discussion

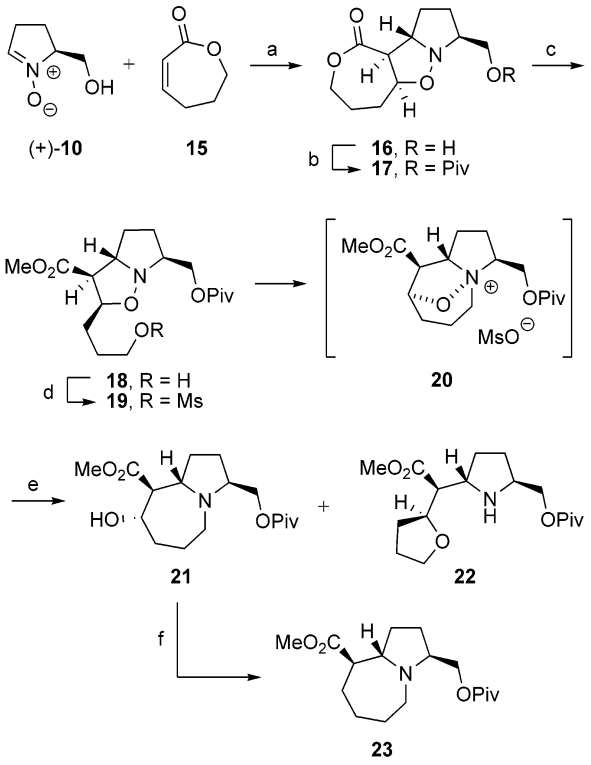
Stereoselective Preparation of 1-Azabicyclo[5.3.0]-decane Intermediates. In a previous paper, we described the results of model studies performed with achiral nitrone **6** and various olefins (**7**) as starting materials, leading to several 1-azabicyclo[5.3.0]decane compounds in excellent yields.[32] Accordingly, we decided to extend the methodology depicted in Scheme 1 to substituted 1-pyrroline *N*-oxides that were accessible enantiomerically pure. Initially, nitrone (+)-**10** (Scheme 2) was visualized as a suitable precursor for the synthesis of *Stemona* alkaloids bearing an α-methyl-γ-butyrolactone substituent at C-3, as **1**−**3**. Nitrone (+)-**10** can be synthesized by the direct oxidation of L-prolinol with dimethyldioxirane (DMD) in 32% yield.[35g] As expected, when (+)-**10** was treated with an equimolar amount of α,β-unsaturated ester **11**[32] in refluxing $CHCl_3$, a primary adduct (derived from an endo transition state with antifacial approach) was formed, which cyclized spontaneously to deliver the corresponding tricyclic isoxazolidinium mesylate (**12**). Removal of the solvent and treatment of the residue with Zn in 10% aqueous HCl furnished azabicycle **13** in 42% overall yield, along with 46% of unreacted olefin. Unfortunately, compound **13** proved to be quite unstable, decomposing even at freezer temperatures. This fact was not totally unforeseen because the model compound (**14**), which has the same relative stereochemistry, had shown a manifest feasibility to dehydrate.[32]

SCHEME 2. Preparation of Enantiopure Bicyclic Intermediate 13 from Nitrone (+)-10[a]



[a] Reagents and conditions: (a) $CHCl_3$, reflux, 2 days; (b) Zn, 10% HCl, sonication, 30 min, 42% for the two steps (79% over unrecovered **11**).

SCHEME 3. Preparation of Enantiopure Bicyclic Intermediates 21 and 23 from Nitrone (+)-10[a]



[a] Reagents and conditions: (a) ref 28 g; (b) PivCl, pyr, DMAP, CH_2Cl_2, rt, overnight, 96%; (c) MeOH, TsOH, reflux, 6 h, 90%; (d) MsCl, pyr, rt, overnight; (e) Zn, 10% HCl, sonication, 40 min, then 30% NH_4OH, 70% of **21** and 15% of **22** from **18**; (f) TCDI, THF, rt, overnight, then Bu_3SnH, AIBN, toluene, 100 °C, 30 min, 96%.

A stable analogue of **13**, epimeric at C-6, was prepared as outlined in Scheme 3 from isoxazolidine **16**, derived from nitrone (+)-**10** and oxepinone **15**.[35g] Hydroxyl group

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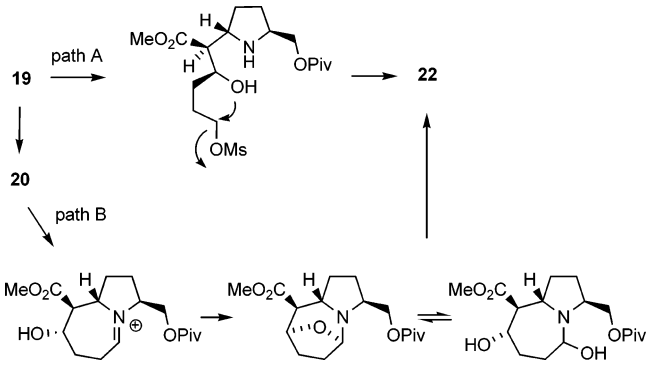
TABLE 1. Addition of Organometallic Reagents (1.6 equiv) to D-Glyceraldehyde Derivatives 24 and 31

entry	substrate	nucleophile	solvent	temperature	yield	anti:syn (**26** or **32**)
1	**31**	**25**	THF	rt	43%	2.5:1 (**32**)
2	**31**	**25**	THF	−78 °C	59%	4:1 (**32**)
3	**24**	**25**	THF	−78 °C	60%	1.4:1 (**26**)
4	**24**	**25**	THF	rt	67%	1.2:1 (**26**)
5	**24**	**25**·CuBr·DMS	THF/DMS	−20 °C	45%	1:2 (**26**)
6	**24**	**25**·CuBr·DMS	THF/DMS	−50 °C	42%	1:2.5 (**26**)
7	**24**	**25**·CuBr·DMS	THF/DMS	−78 °C	no reaction	
8	**24**	**25**·CuI	THF	−78 °C	31%	1:2 (**26**)
9	**24**	**25**·CuBr·DMS	Et_2O	−78 °C	25%	1:1 (**26**)
10	**24**	**25**·CuBr·DMS[a]	THF	−78 °C	34%	1:1 (**26**)

[a] LiCl (1.6 equiv) was added to the reaction media.

SCHEME 4. Mechanistic Proposal for the Formation of 22

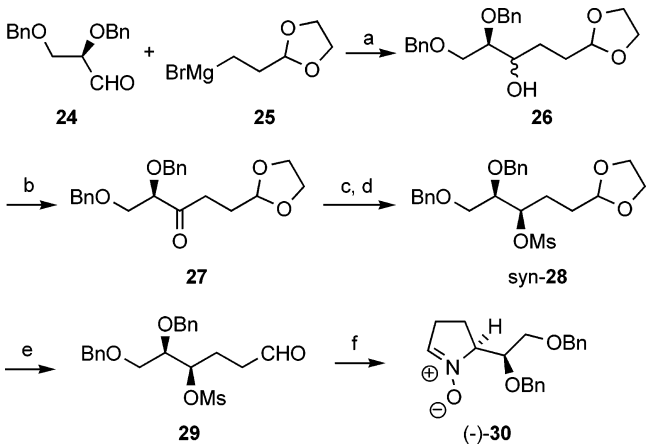


protection as the pivaloyl ester followed by methanolysis of the lactone and then mesylation provided tricyclic isoxazolidinium mesylate **20**, which was reduced without previous isolation to furnish azabicyclodecane **21** in 60% overall yield from **16** and a minor quantity of furane **22** (13%). Initially, we thought that incomplete cyclization of sulfonate **19** before the N−O bond-reductive cleavage may account for the formation of **22** through a competitive displacement of the mesylate by the newly generated hydroxyl group instead of the amine (Scheme 4, path A), but the isolation of aminal intermediates in related model compounds[32] led us to consider a second possibility (path B) with the intermediacy of an iminium cation. Reductive deoxygenation of **21**, which is required for the synthesis of croomine, was accomplished in 96% yield following the Barton-McCombie procedure.[32,36]

The preparation of compounds **21** and **23** evidenced the reliability of the "cyclic nitrone approach" to the *Stemona* alkaloids, but to develop practical syntheses of diverse alkaloids, two main difficulties had to be overcome: (i) although the preparation of (+)-**10** was straightforward, this nitrone was difficult to purify, and scale-up of the procedure was problematic; as a consequence, the available amounts of cycloadducts were quite limited; (ii) because of its basic and nucleophilic character, the unprotected amine caused the instability of some intermediates and, occasionally, interfered in subsequent transformations.

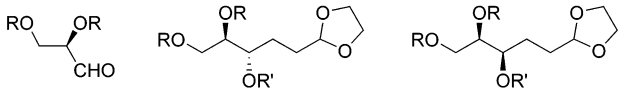
Synthesis and Reactivity of (5*S*)-[(1*S*)-1,2-Dibenzyloxyethyl]-1-pyrroline *N*-oxide, (−)-30.[35r] Our search for a more convenient preparation of an enantiopure, suitably substituted pyrroline *N*-oxide resulted in the synthesis of (−)-**30**, which is shown in Scheme 5.

SCHEME 5. Synthesis of Nitrone (−)-30[a]



[a] Reagents and conditions: (a) THF, rt, 4 h, 67%; (b) Dess−Martin, CH_2Cl_2, 2 h, 95%; (c) L-Selectride, THF, −78 °C, 87%; (d) MsCl/pyr, CH_2Cl_2, rt, 3 days, 89%; (e) 2 M HCl/THF, 55 °C, 1 day, 96%; (f) NH_2OH·HCl/pyr, ^{t}BuOH, 80 °C, 3 days, 69%.

CHART 2. Representative Examples of *Stemona* Alkaloids



24, R = Bn
31, RR = CMe_2

anti-**26**, R = Bn, R' = H
anti-**32**, RR = CMe_2, R' = H
anti-**33**, RR = CMe_2, R' = Ms

syn-**26**, R = Bn, R' = H
syn-**28**, R = Bn, R' = Ms
syn-**32**, RR = CMe_2, R' = H
syn-**33**, RR = CMe_2, R' = Ms

The sequence begins with the addition of Grignard reagent **25**[37] to a protected D-glyceraldehyde, generating a new stereogenic center that will determine the relative configuration of the nitrone and, ultimately, that of the target alkaloid at C-3. We therefore studied in some detail the stereoselectivity of the reaction between **25** and D-glyceraldehyde derivatives **24**[38] and **31** (Chart 2),[39] readily prepared from D-mannitol. Table 1 shows the results of this study.

(36) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(37) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.

(38) Ashton, W. T.; Canning, L. F.; Reynolds, G. F.; Tolman, R. L.; Karkas, J. D.; Liou, R.; Davies, M.-E. M.; DeWitt, C. M.; Perry, H. C.; Field, A. K. *J. Med. Chem.* **1985**, *28*, 926.

(39) Mann, J.; Parlett, N. K.; Thomas, A. *J. Chem. Res. (S)* **1987**, 369.

The reaction of **25** with isopropylidene derivative **31** in THF at room temperature (entry 1) furnished an inseparable 2.5:1 mixture of the alcohols (**32**, whose configuration could not be initially assigned) in 43% yield. Lowering the temperature (entry 2) improved both the yield and the diasteroselectivity. The configuration of the major diastereomer of **32** was later established as anti by X-ray analysis of the corresponding mesylate anti-**33**,[40] which was isolated from a mixture of anti- and syn-**33** by fractional crystallization from Et_2O/hexane. The anti diastereoselectivity of the addition of **25** to **31** is in agreement with a chairlike transition state with the metal center coordinated to the carbonyl and β-dioxolane oxygen atoms and the Grignard reagent approaching the less-hindered face of the aldehyde, as previously proposed for the addition of other organometallic reagents to this substrate.[41] The addition of **25** to dibenzylderivative **24** at low temperature (entry 3) afforded a 1.4:1 mixture of the anti and syn alcohols (**26**) in 60% yield. Attempts were made to modify the selectivity by varying the temperature (entry 4) or by in situ formation of mixed Cu−Mg nucleophilic reagents in various solvents[42] (entries 5−10), but we found only modest selectivity improvements with lower overall yields.

The synthetic problem was solved by oxidizing the mixture of anti- and syn-**26** and then reducing the resulting ketone (**27**) with L-Selectride. This procedure rendered alcohol syn-**26** (vide infra) exclusively in 55% overall yield from **24**. Mesylation of syn-**26** followed by acetal hydrolysis and then treatment of the resulting aldehyde (**29**) with hydroxylamine provided the target nitrone ((−)-**30**) in 59% yield. This sequence may be performed easily on a multigram scale, and batches of up to 9 g of (−)-**30** have been prepared in a single operation. The enantiomeric purity of alcohol syn-**26** was established by ^{1}H NMR analysis of its corresponding diastereomeric Mosher esters.

The 1,3-dipolar cycloadditions of (−)-**30** to dipolarophiles **34**−**39** (Chart 3) were then investigated, with the aim of determining the scope of this chiral nitrone as an asymmetric inductor in such processes. Except for diester **37**, whose preparation is described below and which was selected for synthetic purposes, all of the dipolarophiles used in this study were commercially available. The results of the cycloadditions are summarized in Table 2.

The relative configuration of the newly generated stereogenic centers in isolated products **40**−**48** was determined by ^{1}H NMR analyses, including NOE experiments. For the tricyclic adducts (**41**, **42**, and **46**−**48**), a small value of $J_{8a,8b}$ (0−2 Hz) indicates a trans relationship between H_{8a} and H_{8b},[35g,43] whereas larger values (8−10 Hz) denote a cis relative geometry. For bicyclic adducts **43** and **44**, $J_{3,3a}$ values of 8.1 and 5.9 Hz are in agreement with a cis and trans relationship between H_3 and H_{3a}, respectively.[44] The relative configurations at C-6 were established by the following NOE correlations: H_{3a} and H_6 for **42**, H_2 and H_6 for **43** and **45**, and from H_{8b} and H_6 to the same proton at C-8 for **47**. Finally, an X-ray analysis of a single crystal of compound **42**[35r] provided evidence for the relative configuration of the chiral centers (C-6 and C-1′) already present in the starting nitrone (−)-**30**. Consequently, the configurations of all of the new compounds (**26**−**30** and **40**−**48**) were undoubtedly secured.

In general, both the facial and endo/exo selectivity of the cycloadditions of nitrone (−)-**30** followed the expected bias,[34,45] being very high in all cases except for vinylene carbonate (**39**), which showed a moderate preference for the exo reaction course (entry 6) and, among the dipolarophiles studied, was also unique in affording a detect-

CHART 3

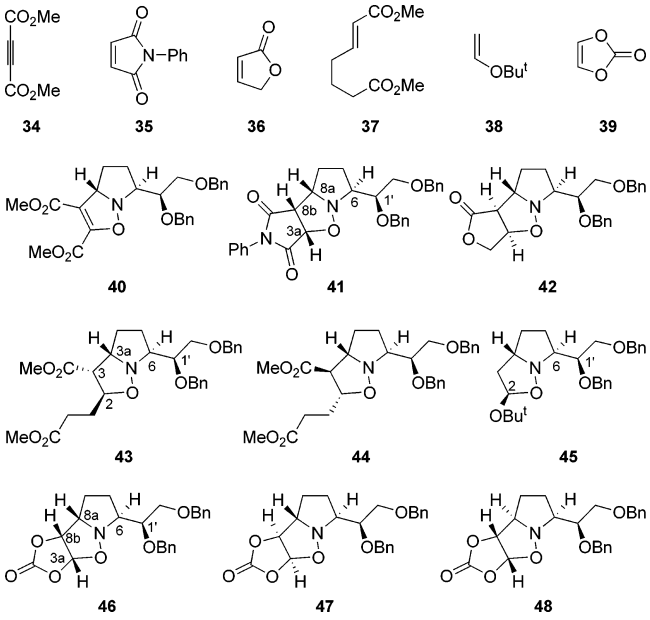


TABLE 2. Cycloaddition of nitrone (−)-30 to dipolarophiles 34−39

entry	dipolarophile[a]	solvent[b]	time[c]	endo-anti[d]	exo-anti[d]	exo-syn[d]
1	**34**	$CHCl_3$	30 min	**40** (89%)[e]		
2	**35**	toluene	2 h	**41** (87%)		
3	**36**	toluene	2 h		**42** (89%)	
4	**37**	toluene	2 h	**43** (83%)[f]	**44** (7%)	
5	**38**	$CHCl_3$	6 h		**45** (89%)	
6	**39**	toluene	20 h	**46** (23%)	**47** (36%)	**48** (11%)

[a] A 10% excess of dipolarophile was used in all runs, except for **39**, which was used in a 10 molar excess. [b] The reactions were performed at the reflux temperature, except for entry 1, which was run at room temperature. [c] The reactions were run until nitrone (−)-**30** was completely consumed, according to TLC analysis. [d] Yields are referred to isolated pure products. [e] Endo/exo selectivity does not apply to this case. [f] Endo related to the conjugated ester of the starting olefin.

(40) The crystal structure of anti-**31** has been deposited at the Cambridge Crystallographic Data Centre and was allocated the deposition number CCDC 257171.

(41) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843.

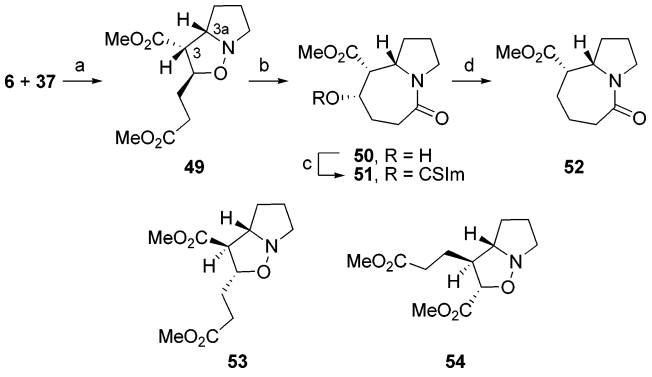
(42) For an exhaustive study of the addition of organometallic reagents to **24** see: Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422.

(43) Alonso-Perarnau, D.; de March, P.; Figueredo, M.; Font, J.; Soria, A. *Tetrahedron* **1993**, *49*, 4267.

(44) Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Monsalvatje, M.; Virgili, A.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 8578.

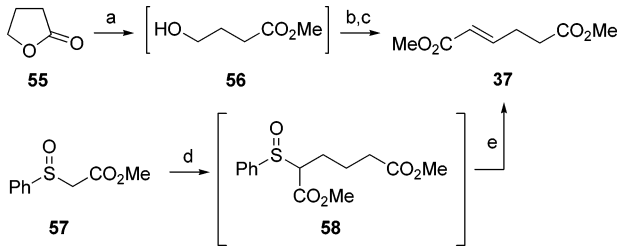
(45) (a) Tufariello, J. J. Chapter 9. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 2. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; VCH Verlagsgesellschaft: Weinheim, Germany, 1988. (c) Frederickson, M.; *Tetrahedron* **1997**, *53*, 403. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (e) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

SCHEME 6. Preparation of Lactam 52[a]



[a] Reagents and conditions: (a) toluene, reflux, 4 h, 71%; (b) H_2, Pd/C, EtOAc, HOAc, rt, 20 h; then Na_2CO_3, $H_2O-CHCl_3$, 95%; (c) TCDI, THF, rt, overnight; (d) Bu_3SnH, AIBN, toluene, reflux, 45 min, 66% for the two steps.

SCHEME 7. Synthesis of Ester 37[a]

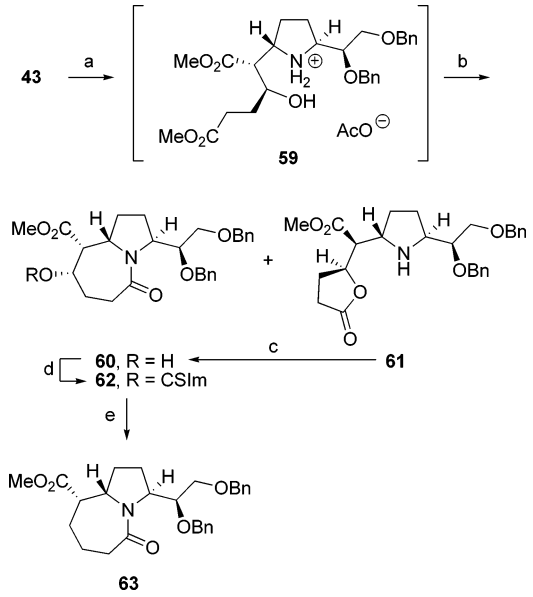


[a] Reagents and conditions: (a) MeOH, cat. H_2SO_4, reflux, 5 h, 75%; (b) PCC, CH_2Cl_2, rt, 5 h; (c) Ph_3PCHCO_2Me, CH_2Cl_2, rt, overnight, 46% from **56**; (d) NaH, DME, HMPA, rt, 45 min, then $BrCH_2CH_2CH_2CO_2Me$, rt, 24 h; (e) 100 °C, 16 h, 63% from **57**.

able amount of a cycloadduct (**48**) derived from a synfacial approach. The cycloaddition to *N*-phenylmaleimide (entry 2) is noteworthy because it furnished endo cycloadduct **41** exclusively in excellent yield,[46] which is in contrast with the lack of endo-exo selectivity previously observed in the cycloaddition of this dipolarophile to the related nitrone (+)-**10**.[35g] For our synthetic purposes related to the *Stemona* alkaloids, the isolation of endo-anti cycloadduct **43** in 83% yield (entry 4) was particularly gratifying.

Preparation of *N*-Protected 1-Azabicyclo[5.3.0]decane Intermediates. Next, we focused our attention on the preparation of 1-azabicyclo[5.3.0]decane derivatives holding a lactam functionality instead of the highly reactive amine, and the proper conditions were first established for the model nitrone (**6**, Scheme 6). Although a synthesis of the required diester (**37**) through dimerization of methyl acrylate had been reported previously,[47] we explored alternative approaches. Our first preparation of **37** (Scheme 7) was accomplished from γ-butyrolactone (**55**) by methanolysis[48] followed by PCC oxidation and then Wittig olefination in 35% overall yield. Scale-up of this sequence met with some difficulties, mainly because of the manifest tendency of the intermediate hydroxyester (**56**) to relactonize. Therefore, a more practical

SCHEME 8. Synthesis of Lactam 63[a]



[a] Reagents and conditions: (a) Zn, HOAc, sonication, rt, 2.5 h; (b) $CHCl_3$, aqueous NH_4OH; (c) toluene, reflux, 14 h, 86% from **43**; (d) TCDI, THF, reflux, 2.5 h; (e) Bu_3SnH, AIBN, toluene, reflux, 2 h, 63% for the two steps.

synthesis of **37** was developed starting from methyl phenylsulfinylacetate (**57**) by alkylation with methyl 4-bromobutanoate and subsequent pyrolytic elimination in 63% overall yield, which is perfectly reproducible on a multigram scale.

The cycloaddition of **6** to diester **37** in refluxing toluene furnished a mixture of the expected endo adduct (**49**), its exo diastereomer (**53**), and the regioisomer (**54**), in an approximate ratio of 33:3:1 and 86% overall yield, from where the major product (**49**) could be isolated in 71% yield. The relative configuration of **49** and **53** was deduced from the value of the coupling constant, $J_{3,3a}$ (7.9 Hz for **49** and 5.2 Hz for **53**). The most representative signal of the ^1H NMR spectrum of **54** was a doublet at δ 4.10 assigned to H_2 ($J_{2,3}$ = 7.7 Hz). The reduction with activated Zn in 10% aqueous HCl, which had proved to be the most effective procedure for the N−O bond cleavage in closely related amine substrates,[32] when applied to **49**, led to an important loss of material. Similar results were found using $Mo(CO)_6$ as the reducing agent or hydrogen in MeOH in the presence of Pd/C. By contrast, hydrogenation in EtOAc containing acetic acid (5 equiv) and 10% Pd/C as the catalyst was very efficient and, after treatment of the crude reduction material with Na_2CO_3 in a biphasic system (CH_2Cl_2/H_2O), the bicyclic lactam (**50**) was isolated in 95% yield. The Barton−McCombie protocol that was applied to **50** afforded **52** in 66% yield.

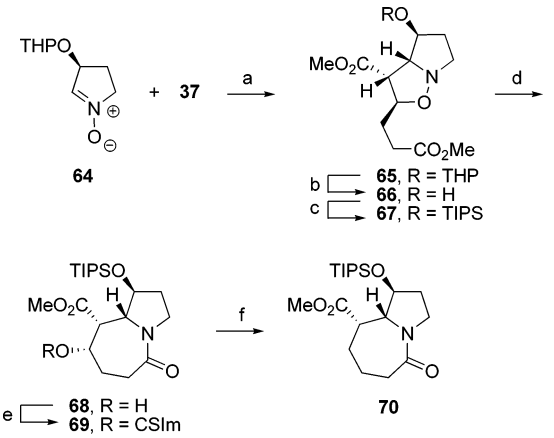
In isoxazolidine **43**, derived from the enantiopure nitrone (−)-**30**, the presence of benzyl ether residues prevented the use of catalytic hydrogenation for the N−O bond cleavage. Fortunately, we found out that this reduction can be very efficiently performed with activated Zn in glacial acetic acid (instead of 10% aqueous HCl) under sonication (Scheme 8). Alkalinization with aqueous NH_4OH furnished an intermediate hydroxylamine, which cyclized spontaneously, leading to a mixture of lactam

(46) In a preliminary communication (ref 35r) the relative configuration of this adduct was erroneously assigned as exo.

(47) (a) Alderson, T.; Jenner, E. L.; Lindsey, R. V. *J. Am. Chem. Soc.* **1965**, *87*, 5638. (b) Nugent, W. A.; Hobbs, F. W., Jr. *J. Org. Chem.* **1983**, *48*, 5364.

(48) (a) Brown, H. C.; Keblys, K. A. *J. Org. Chem.* **1966**, *31*, 485. (b) Huckstep, M.; Taylor, R. J. K. *Synthesis* **1982**, 881.

SCHEME 9. Synthesis of Lactam 69[a]



[a] Reagents and conditions: (a) toluene, reflux, 2 h, 87%; (b) MeOH, TsOH, reflux, overnight, 95%; (c) TIPSOTf, Et_3N, CH_2Cl_2, rt, overnight, 87%; (d) H_2, Pd/C, EtOAc, HOAc, rt, 24 h; then toluene, reflux, overnight, 85%; (e) TCDI, THF, rt, overnight; (f) Bu_3SnH, AIBN, toluene, reflux, 30 min, 77% for the two steps.

60 and lactone **61**, but heating this mixture in refluxing toluene for 14 h delivered the more stable product (**60**) exclusively in 86% yield from **43**. Deoxygenation of **60** provided **63** in 63% yield.

The substitution pattern in compound **60** makes it a suitable intermediate for the synthesis of stemonine (**1**) and stemospironine (**2**), whereas **63** may be an appropriate precursor of croomine (**3**). To extend the scope of the synthetic approach to the group of alkaloids related to stenine (**5**), we performed an analogous sequence (Scheme 9) starting from nitrone **64**, whose preparation from (*S*)-malic acid on a multigram scale has been described recently by Brandi and co-workers.[35q]

Because of the stereogenic center at the THP protecting group, nitrone **64** is obtained as a mixture of two epimers. Consequently, although its cycloaddition to diester **37** in refluxing toluene occurred with complete stereoselectivity (endo-anti), a mixture of two isoxazolidines (**65**) with identical relative configurations at the newly formed stereogenic centers was isolated in 87% yield. To gain analytical simplicity in the subsequent steps, we removed the THP group, and a silyl ether protection was placed instead. Catalytic hydrogenation in the conditions established for the model isoxazolidine (**49**) and then heating in refluxing toluene overnight furnished lactam **68** (85% yield), which was converted into the corresponding deoxygenation product (**70**) in 77% yield.

Conclusions

In summary, a new strategy for the construction of the 1-azabicyclo[5.3.0]decane core common to most *Stemona* alkaloids has been explored. Our diversity-oriented approach exploits 1,3-dipolar cycloaddition of five-membered cyclic nitrones to C_6 α,β-unsaturated esters followed by N−O reductive cleavage and azepine closure. Starting from a D-glyceraldehyde derivative, a new 5-substituted pyrroline *N*-oxide ((−)-**30**) has been prepared in an enantiopure form on a multigram scale. The cycloaddition of this nitrone to diester **37** occurs with very high stereoselectivity and yield, providing a very practical access to putative precursors of different alkaloids of the tuberostemospironine group (such as **2** and **3**). When the same protocol is applied to the related nitrone (**64**),[35q] it gives access to suitable intermediates for alkaloids of the stenine group (such as **5**), evidencing the high flexibility of this protocol. Work is in progress to complete the synthesis of several *Stemona* alkaloids.

Experimental Section

Methyl (5*S*,6*R*,7*S*,10*S*)-5-Hydroxy-10-hydroxymethyl-1-azabicyclo[5.3.0]decane-6-carboxylate (13). A solution of nitrone (+)-**10**[35g] (330 mg, 1.49 mmol) and olefin **11**[32] (172 mg, 1.49 mmol) in $CHCl_3$ (12 mL) was heated at reflux for 2 days. The solvent was removed, 10% aqueous HCl (20 mL) and activated Zn (6.2 g, 94.8 mmol) were added to the residue, and the mixture was sonicated for 30 min. Then it was filtered, and the solid was washed with 10% aqueous HCl and water. The combined filtrates were brought to pH 9−10 by addition of 30% aqueous NH_4OH and then extracted with $CHCl_3$ (5 × 5 mL). The organic extracts were dried (Na_2SO_4), and the solvent was removed under vacuum to furnish an oily residue. Purification of this material by column chromatography (silica gel, 9:1 $CHCl_3$−MeOH) rendered 153 mg (46% recovering) of the starting olefin (**11**) and 153 mg (0.63 mmol, 42% yield, 79% over unrecovered **11**) of **13**: yellow oil; $[\alpha]_D$ −34 (*c* 1.29, $CHCl_3$); IR (film): 3374 (br), 2952, 2924, 2861, 1729, 1159, 1047; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.90 (dt, *J* = 8.8, 4.4 Hz, 1H), 3.71 (s, 3H), 3.70 (m, 1H), 3.63 (dd, *J* = 10.9, 3.3 Hz, 1H), 3.39 (dd, *J* = 10.9, 1.8 Hz, 1H), 3.14 (m, 1H), 3.01 (br dd, *J* = 12.6, 7.5 Hz, 1H), 2.87 (t, *J* = 2.9 Hz, 1H), 2.75 (br t, *J* ≈ 10.9 Hz, 1H), 2.40 (br s, 1H), 1.92 (m, 7H), 1.60 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.5, 73.7, 65.6, 60.6, 60.3, 54.1, 51.7, 48.9, 35.3, 30.0, 26.9, 22.9; MS (EI) *m/z*: 244 (MH^+, 2), 226 (2), 212 (100). Compound **13** decomposes rapidly even at freezer temperatures.

(5a*S*,8*S*,10a*S*,10b*S*)-8-Pivaloyloxymethyloctahydrooxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-one (17). Pyridine (72 μL, 0.88 mmol) and DMAP (108 mg, 0.88 mmol) were added to a stirred solution of **16**[35g] (100 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) under nitrogen, and the mixture was cooled to 0 °C. Pivaloyl chloride (110 μL, 0.88 mmol) was added dropwise, and the reaction mixture was stirred at room temperature overnight. Then it was washed with brine (3 mL), the organic phase was dried (Na_2SO_4), and the solvent was removed under vacuum. Purification of the residue by column chromatography (silica gel, EtOAc) afforded **17** (131 mg, 0.42 mmol, 96% yield): mp 99−101 °C (white solid from $CHCl_3$-hexane); $[\alpha]_D$ −121 (*c* 1.35, $CHCl_3$); IR (film): 2966, 1729, 1159; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (ddd, *J* = 12.2, 9.5, 3.3 Hz, 1H), 4.35 (td, *J* = 6.7, 3.1 Hz, 1H), 4.28 (dd, *J* = 12.8, 6.7 Hz, 1H), 4.18 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.15 (td, *J* = 12.8, 4.3 Hz, 1H), 4.06 (dd, *J* = 11.0, 6.7 Hz, 1H), 3.31 (m, 1H), 3.30 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.24 (m, 1H), 2.06 (m, 3H), 1.78 (m, 1H), 1.62 (m, 3H), 1.18 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 178.3, 171.5, 74.2, 67.1, 66.4, 64.9, 61.5, 57.2, 38.7, 27.2, 27.1, 25.6, 25.5, 22.5; MS (EI) *m/z*: 312 (MH^+, 7), 311 (M^+, 5), 209 (13), 196 (100). HRMS (EI, 70 eV): calcd for $C_{16}H_{25}NO_5$, 311.1733; found, 311.1729.

Methyl (2*S*,3*S*,3a*S*,6*S*)-2-(3-Hydroxyprop-1-yl)-6-pivaloyloxymethylhexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (18). A solution of **17** (130 mg, 0.42 mmol) and $TsOH·H_2O$ (238 mg, 1.25 mmol) in MeOH (13 mL) was heated at reflux for 6 h. Then the methanol was evaporated under vacuum, the remaining oil was redissolved in CH_2Cl_2 (6 mL), and the solution was washed with saturated aqueous $NaHCO_3$ and then dried (Na_2SO_4). Removal of the solvent furnished an oil, which, after purification by column chromatography (silica gel, Et_2O), afforded **18** (129 mg, 0.38 mmol, 90% yield): oil; $[\alpha]_D$ −100 (*c* 3.65, $CHCl_3$); IR (film): 3409 (br), 2959, 2875, 1729, 1159; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (m, 1H), 4.19 (dd, *J* = 11.0, 5.5 Hz, 1H), 4.12 (td, *J* = 7.3, 3.7 Hz, 1H), 4.08 (dd, *J* = 11.0, 6.7 Hz, 1H), 3.71 (s, 3H), 3.64 (m, 2H), 3.28 (dq,

J = 9.5, 6.1 Hz, 1H), 3.01 (dd, J = 6.1, 3.7 Hz, 1H), 2.16 (m, 1H), 1.99 (m, 1H), 1.60 (m, 6H), 1.18 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 178.4, 171.4, 78.1, 67.1, 66.5, 65.0, 62.3, 58.1, 52.0, 38.7, 29.7, 29.6, 27.1, 26.9, 25.8; MS (EI) *m/z:* 344 (MH^+, 20), 228 (64), 210 (51), 200 (27), 184 (31), 57 (100). Anal. Calcd for $C_{17}H_{29}NO_6$: C, 59.46; H, 8.51; N, 4.08. Found: C, 59.10; H, 8.54; N, 4.16.

Methyl (5*S*,6*S*,7*S*,10*S*)-5-Hydroxy-10-pivaloyloxymethyl-1-azabicyclo[5.3.0]decane-6-carboxylate (21). A solution of alcohol **18** (278 mg, 0.81 mmol) in CH_2Cl_2 (22 mL) was added dropwise to a solution of mesyl chloride (320 μL, 4.11 mmol) in anhydrous pyridine (2 mL) at 0 °C under nitrogen, and the mixture was stirred at room temperature overnight. The solvent was removed, 10% aqueous HCl (19 mL) and activated Zn (2.65 g, 40.5 mmol) were added to the residue, and the mixture was sonicated for 40 min. Then it was filtered, and the solid was washed with 10% aqueous HCl and water. The combined filtrates were brought to pH 9−10 by addition of 30% aqueous NH_4OH and then extracted with $CHCl_3$ (5 × 35 mL). The organic extracts were dried (Na_2SO_4), and the solvent was removed under vacuum to furnish an oily residue. Purification of this material by column chromatography (silica gel, 4:1 EtOAc−hexanes) rendered **21** (187 mg, 0.57 mmol, 70% yield) and methyl (2*S*)-2-[(2*S*,5*S*)-5-pivaloyloxymethyl-2-pyrrolidinyl]-2-[(2*S*)-tetrahydrofur-2-yl]acetate (**22**) (39 mg, 0.12 mmol, 15% yield). **21**: oil; $[\alpha]_D$ −24 (*c* 1.74, $CHCl_3$); IR (film): 3472 (br), 2945, 2875, 1729, 1159; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (dd, J = 11.0, 4.6 Hz, 1H), 4.00 (m, 1H), 3.96 (dd, J = 11.0, 6.1 Hz, 1H), 3.67 (s, 3H), 3.38 (ddd, J = 9.1, 7.3, 4.3 Hz, 1H), 3.19 (m, 1H), 2.86 (m, 2H), 2.64 (dd, J = 9.1, 7.9 Hz, 1H), 1.95 (m, 5H), 1.71 (m, 1H), 1.55 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 178.4, 173.9, 73.2, 65.1, 62.7, 61.2, 57.6, 51.4, 50.1, 38.6, 34.7, 30.4, 27.5, 27.1, 23.3; MS (EI) *m/z*: 310 ($[M-OH]^+$, 1), 296 (5), 212 (100), 210 (37), 57 (25). Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.10; H, 9.03; N, 4.25. **22**: oil; $[\alpha]_D$ −4 (*c* 1.43, $CHCl_3$); IR (film): 2959, 2875, 1729, 1159; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.06 (q, J = 7.3 Hz, 1H), 3.98 (dd, J = 11.0, 4.9 Hz, 1H), 3.90 (dd, J = 11.0, 6.9 Hz, 1H), 3.80 (dt, J = 8.3, 6.9 Hz, 1H), 3.69 (m, 1H), 3.68 (s, 3H), 3.45 (td, J = 8.1, 6.3 Hz, 1H), 3.40 (qd, J = 6.9, 4.9 Hz, 1H), 2.52 (t, J = 7.6 Hz, 1H), 1.99 (m, 1H), 1.87 (m, 4H), 1.72 (m, 1H), 1.70 (br s, 1H), 1.56 (m, 1H), 1.42 (m, 1H), 1.18 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 178.4, 173.0, 78.8, 67.7, 67.2, 56.7, 56.2, 55.8, 51.5, 38.8, 29.7, 29.4, 27.7, 27.1, 25.6; MS (EI) *m/z*: 328 (MH^+, 5), 327 (M^+, 2), 212 (94), 184 (100), 110 (54), 82 (67), 71 (44), 57 (79). Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.42; H, 9.04; N, 4.39.

Methyl (6*R*,7*S*,10*S*)-10-Pivaloyloxymethyl-1-azabicyclo-[5.3.0]decane-6-carboxylate (23). TCDI (49 mg, 0.27 mmol) was added to a stirred solution of **21** (50 mg, 0.15 mmol) in anhydrous THF (5 mL) under nitrogen, and the mixture was stirred at room temperature overnight. Then the solvent was evaporated under vacuum, and the residue was redissolved in $CHCl_3$ (6 mL). This solution was washed with water (3 × 4 mL), dried (Na_2SO_4), and the solvent was removed, affording a residue (82 mg) that was used in the next step without further purification. A solution of this crude material in anhydrous toluene (4 mL) was added dropwise to a solution of Bu_3SnH (165 μL, 0.61 mmol) and AIBN (4 mg, 0.02 mmol) in anhydrous toluene (1 mL) at 100 °C under nitrogen, and the mixture was heated at this temperature for 30 min. The cold solution was diluted by the addition of toluene (4 mL) and extracted with 10% aqueous HCl (3 × 6 mL). The combined aqueous extracts were made basic to pH 9−10 with 30% aqueous NH_4OH and extracted with $CHCl_3$ (3 × 10 mL). These organic extracts were dried (Na_2SO_4), and the solvent was evaporated under vacuum affording an oily residue, which furnished **23** (45 mg, 0.36 mmol, 96% yield) after purification by column chromatography (silica gel, 7:3 hexanes−EtOAc): oil; $[\alpha]_D$ −38 (*c* 0.53, $CHCl_3$); IR (film): 2931, 2860, 1729, 1159; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.05 (dd, J = 10.9, 4.9 Hz, 1H), 3.95 (dd, J = 10.9, 5.8 Hz, 1H), 3.63 (s, 3H), 3.33 (dt, J = 9.5, 6.4 Hz, 1H), 3.15 (qn, $J \approx$ 5.6 Hz, 1H), 2.86 (m, 2H), 2.41 (td, J = 9.5, 3.2 Hz, 1H), 1.65 (m, 10H), 1.17 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 178.5, 175.9, 65.8, 64.8, 62.3, 51.4, 50.1, 49.8, 38.7, 31.5, 30.3, 28.2, 27.7, 27.2, 26.6; MS (EI) *m/z*: 280 (2), 210 (5), 196 (100), 57 (13). HRMS (EI, 70 eV): calcd for $C_{17}H_{29}NO_4$, 311.2096; found, 311.2083.

(2*R*,3*S*)-1,2-Dibenzyloxy-5-(1,3-dioxolan-2-yl)pentan-3-ol (anti-26) and its (2*R*,3*R*) Isomer (syn-26). A solution of aldehyde **24**[38] (1.0 g, 3.7 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred solution of Grignard reagent **25**[37] (5.9 mmol) in anhydrous THF (15 mL) at 0 °C under nitrogen, and the mixture was stirred at room temperature for 4 h. Then the reaction mixture was treated with saturated aqueous NH_4Cl (10 mL), the organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The organic extracts were dried ($MgSO_4$) and concentrated to render a residue, which furnished a 1.2:1 mixture of alcohols anti-**26** and syn-**26**, respectively (930 mg, 2.48 mmol, 67% yield), after purification by column chromatography (silica gel, 7:3 hexanes−EtOAc). anti-**26**: ^{1}H NMR (250 MHz, $CDCl_3$, data extracted from the mixture): δ 4.88 (t, J = 4.4 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 3.88 (m, 4H), 3.66 (m, 2H), 3.51 (m, 1H), 2.80 (br s, 1H). syn-**26**: vide infra.

(2*R*)-1,2-Dibenzyloxy]-5-(1,3-dioxolan-2-yl)pentan-3-one (27). A solution of alcohols **26** (400 mg, 1.07 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to a stirred solution of Dess−Martin periodinane (773 mg, 1.83 mmol) in anhydrous CH_2Cl_2 (15 mL) at room temperature under nitrogen, and the mixture was stirred for 2 h. Then the reaction mixture was diluted with Et_2O (20 mL), and a saturated aqueous solution of $NaHCO_3$ (10 mL) containing $Na_2S_2O_3$ (1.0 g) was added to the resulting suspension. The mixture was stirred for several minutes until complete dissolution of the solid was achieved, the organic layer was separated, washed with water, and dried ($MgSO_4$), and the solvent was removed under vacuum. Purification of the residue by column chromatography (silica gel, 7:3 hexanes−EtOAc) furnished **27** (360 mg, 0.97 mmol, 95% yield): oil; $[\alpha]_D$ −22 (*c* 1.32, $CHCl_3$); IR (film): 2944, 2883, 1718, 1454, 1097; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30 (m, 10H), 4.89 (t, J = 4.3 Hz, 1H), 4.64 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.52 (m, 2H), 4.03 (t, J = 4.5 Hz, 1H), 3.84 (m, 6H), 2.72 (t, J = 7.3 Hz, 2H), 1.96 (dt, J = 7.3, 4.3 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 209.9, 137.7, 137.4, 128.4, 128.3, 127.8, 127.63, 127.60, 103.2, 83.7, 73.4, 72.5, 70.3, 64.7, 33.3, 26.9; MS (EI) *m/z*: 129 (25), 91 (100). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.37; H, 7.08.

(2*R*,3*R*)-1,2-Dibenzyloxy-5-(1,3-dioxolan-2-yl)pentan-3-ol (syn-26). L-Selectride (1 M in THF, 10.5 mL, 10.5 mmol) was added dropwise to a solution of ketone **27** (3.52 g, 9.50 mmol) in anhydrous THF (60 mL) at −78 °C under nitrogen, and the mixture was stirred at this temperature for 2 h. Then the reaction mixture was quenched with saturated aqueous NH_4Cl solution (4 mL), water (50 mL) was added, the organic layer was separated, and the aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under vacuum. Purification of the residue by column chromatography (silica gel, 7:3 hexanes−EtOAc) furnished syn-**26** (3.08 g, 8.27 mmol, 87% yield): oil; $[\alpha]_D$ −9 (*c* 1.70, $CHCl_3$); IR (film): 3457 (br), 2914, 2872, 1454, 1100; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28 (m, 10H), 4.92 (t, J = 4.4 Hz, 1H), 4.81 (d, J = 11.6 Hz, 1H), 4.59 (m, 3H), 3.93 (m, 4H), 3.72 (m, 3H), 3.54 (q, J = 4.8 Hz, 1H), 2.65 (s, 1H), 1.79 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 135.6, 135.4, 126.1, 125.7, 125.4, 103.2, 80.2, 73.6, 73.1, 71.6, 70.4, 65.31, 65.26, 32.0, 29.6; MS (ESI, MeOH) *m/z*: 395 (MNa^+), 373 (MH^+, 100). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.46; H, 7.55.

(1*R*,2*R*)-2,3-Dibenzyloxy-1-[2-(1,3-dioxolan-2-yl)]ethylpropyl Methanesulfonate (syn-28). A solution of syn-**26** (2.91 g, 7.85 mmol) in CH_2Cl_2 (60 mL) was added dropwise to

a stirred solution of mesyl chloride (1.2 mL, 15.7 mmol) in pyridine (3.2 mL, 39.2 mmol) at 0 °C under nitrogen, and the mixture was stirred at room temperature for 3 days. Then 0.5 M aqueous HCl (25 mL) was added to the reaction mixture and the organic phase was separated, washed with water (25 mL), and dried ($MgSO_4$). Removal of the solvent under vacuum rendered a residue, which furnished syn-**28** (3.15 g, 6.99 mmol, 89% yield) after purification by column chromatography (silica gel, 1:1 hexanes−EtOAc): oil; $[\alpha]_D$ −3 (*c* 4.55, $CHCl_3$); IR (film): 3030, 2873, 1959, 1725, 1351; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28 (m, 10H), 4.87 (m, 2H), 4.77 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.53 (d, J = 11.8 Hz, 1H), 3.80 (m, 7H), 2.96 (s, 3H), 1.97 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.3, 138.2, 128.88, 128.86, 128.5, 128.4, 128.2, 104.1, 82.6, 78.7, 73.9, 73.4, 69.1, 65.4, 38.9, 26.9, 25.4; MS (EI) *m/z*: 91 (100), 73 (29). Anal. Calcd for $C_{23}H_{30}O_7S$: C, 61.31; H, 6.71; S, 7.12. Found: C, 61.70; H, 6.53; S, 6.85.

(5*S*)-[(1*S*)-1,2-Dibenzyloxyethyl]-1-pyrroline *N*-Oxide ((−)-30). HCl (2 M, 5.6 mL, 11.2 mmol) was added to a stirred solution of syn-**28** (1.01 g, 2.24 mmol) in THF (25 mL), and the mixture was stirred at 55 °C for 1 day. The cool reaction mixture was neutralized by the addition of $NaHCO_3$, the organic layer was separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under vacuum. Purification of the remaining oil by column chromatography (silica gel, 3:2 hexanes−EtOAc) furnished a product (0.88 g, 2.15 mmol, 96% yield) that was identified as (1*R*,2*R*)-2,3-dibenzyloxy-1-(3-oxo)propylpropyl methanesulfonate (**29**) according to NMR analysis: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (s, 1H), 7.28 (m, 10H), 4.79 (m, 1H), 4.71 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 3.65 (m, 3H), 2.90 (s, 3H), 2.58 (t, J = 7.3 Hz, 2H), 2.07 (m, 1H), 1.89 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.7, 137.5, 128.4, 128.0, 127.7, 81.4, 78.5, 73.4, 72.7, 68.1, 39.3, 38.2, 25.5. Aldehyde **29** was quite unstable and was rapidly submitted to the next synthetic step: Pyridine (350 μL, 4.33 mmol) and NH_2OH·HCl (68 mg, 0.98 mmol) were added to a solution of **29** (200 mg, 0.49 mmol) in ^{t}BuOH (4 mL), and the mixture was stirred at 80 °C for 3 days. Then the solvent was evaporated under vacuum, CH_2Cl_2 (10 mL) was added to the remaining residue, and the solution was washed with water (2 mL), dried ($MgSO_4$), and the solvent was removed. Purification of the remaining oil by column chromatography (silica gel, 39:1 $CHCl_3$-MeOH) furnished nitrone (−)-**30** (105 mg, 0.33 mmol, 69% yield): oil; $[\alpha]_D$ −27 (*c* 1.84, $CHCl_3$); IR (film): 3028, 2920, 2854, 1710, 1586, 1453, 1203, 1091; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 10H), 6.90 (dd, J = 4.6, 2.5 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.63 (m, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H) 4.13 (m, 1H), 3.57 (dd, J = 10.2, 5.6 Hz, 1H), 3.47 (dd, J = 10.2, 6.3 Hz, 1H), 2.58 (m, 2H), 2.40 (m, 1H), 2.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 137.7, 135.7, 128.2, 127.5, 74.9, 74.1, 73.5, 73.1, 69.6, 27.2, 18.8; MS (EI) *m/z*: 112 (28), 91 (100). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.63; H, 7.40; N, 4.33.

Dimethyl (*E*)-Hex-2-enedioate (37). A solution of ester **57** (12.0 g, 60.5 mmol) in anhydrous DME (80 mL) was slowly added to a stirred suspension of NaH (3.63 g, 90.8 mmol) in anhydrous DME (160 mL) containing HMPA (16 mL) at room temperature, under nitrogen. After 45 min of stirring, a solution of methyl 4-bromobutanoate (15 mL, 119.2 mmol) in anhydrous DME (90 mL) was added to the reaction flask, and the mixture was allowed to evolve for 24 h and was then heated at 100 °C for 16 h. The solvent was removed under vacuum, the residue was dissolved in EtOAc (150 mL), and the solution was washed with water (50 mL). The aqueous phase was separated and extracted with EtOAc (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated, affording an oil, which furnished **37**[47] (6.57 g, 38.4 mmol, 63% yield) after purification by column chromatography (silica gel, from hexanes to 85:15 hexanes−EtOAc): ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.93 (dt, J = 15.8, 6.5 Hz, 1H), 5.84 (dt, J = 15.8, 1.4 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.48 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 172.6, 166.7, 146.8, 121.8, 51.8, 51.5, 32.2, 27.2.

Methyl (2*S*,3*R*,3a*S*,6*S*)-(6-[(1*S*)-1,2-Dibenzyloxyethyl]-2-(2-methoxycarbonylethyl)perhydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (43) and its (2*R*,3*S*,3a*S*,6*S*) Isomer (44). A solution of **37** (87 mg, 0.51 mmol) in toluene (1.5 mL) was added to a solution of nitrone (−)-**30** (150 mg, 0.46 mmol) in toluene (1 mL), and the mixture was heated at reflux for 2 h. Removal of the solvent under vacuum followed by column chromatography (silica gel, 4:1 hexanes−EtOAc) of the residue afforded, by elution order, **43** (190 mg, 0.38 mmol, 83% yield) and **44** (16 mg, 0.03 mmol, 7% yield). **43**: oil; $[\alpha]_D$ −74 (*c* 1.85, $CHCl_3$); IR (film): 3029, 2950, 1733, 1436, 1367, 1202; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28 (m, 10H), 4.81 (d, J = 11.6 Hz, 1H), 4.68 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.17 (ddd, J = 9.3, 8.3, 3.8 Hz, 1H), 4.00 (q, $J \approx$ 8.1 Hz, 1H), 3.68 (m, 3H), 3.68 (s, 3H), 3.64 (s, 3H), 3.26 (m, 1H), 3.11 (t, $J \approx$ 9.3 Hz, 1H), 2.42 (m, 2H), 2.06 (m, 2H) 1.84 (m, 2H), 1.57 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.3, 170.4, 138.8, 138.4, 128.2, 128.1, 127.6, 127.5, 127.4, 127.3, 80.5, 75.0, 73.2, 73.0, 71.3, 68.6, 66.1, 55.9, 51.8, 51.5, 30.5, 27.0, 26.4; MS (ESI, MeOH) *m/z*: 520 (MNa^+), 498 (MH^+, 100). Anal. Calcd for $C_{28}H_{35}NO_7$: C, 67.59; H, 7.09; N, 2.81. Found: C, 67.60; H, 7.08; N, 2.82. **44**: oil; $[\alpha]_D$ −58 (*c* 2.30, $CHCl_3$); IR (film): 2950, 1734, 1436, 1367, 1271, 1173; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28 (m, 10H), 4.73 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 12.7 Hz, 1H), 4.50 (d, J = 12.7 Hz, 1H), 4.14 (td, J = 8.1, 4.1 Hz, 1H), 3.91 (q, $J \approx$ 6.5 Hz, 1H), 3.63 (m, 3H), 3.72 (s, 3H), 3.53 (s, 3H), 3.43 (m, 1H), 2.74 (dd, J = 8.7, 5.9 Hz, 1H), 2.43 (m, 2H), 1.91 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.3, 171.7, 138.8, 138.4, 128.3, 128.2, 127.8, 127.6, 127.5, 127.4, 80.7, 79.6, 73.3, 73.0, 71.2, 69.5, 69.0, 58.2, 52.2, 51.6, 30.8, 30.2, 29.0, 26.3; MS (ESI, MeOH) *m/z*: 520 (MNa^+), 498 (MH^+, 100). Anal. Calcd for $C_{28}H_{35}NO_7$: C, 67.59; H, 7.09; N, 2.81. Found: C, 67.71; H, 7.24; N, 2.85.

Methyl (2*RS*,3*SR*,3a*RS*)-2-(2-Methoxycarbonylethyl)-hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (49). A solution of nitrone **6** (1.49 g, 17.5 mmol) and diester **37** (1.77 g, 10.3 mmol) in toluene (10 mL) was heated at reflux for 4 h. Removal of the solvent under vacuum followed by purification of the residue by column chromatography (silica gel, EtOAc) afforded, by elution order, a 10:1 mixture of **49** and its (2*RS*,3*SR*,3a*SR*) diastereomer (**53**, 1.79 g, 6.96 mmol), a 7:1 mixture of **49** and methyl (2*RS*,3*RS*,3a*RS*)-3-(2-methoxycarbonylethyl)hexahydropyrrolo[1,2-*b*]isoxazole-2-carboxylate (**54**) (472 mg, 1.84 mmol), and a fraction of pure **49** (29 mg, 0.11 mmol). The overall yield was 86%. A second column chromatography of the combined first two fractions (silica gel, from 5:1 to 2:1 hexanes−EtOAc) furnished pure **49** (1.85 g, 7.20 mmol). The overall yield of isolated **49** was 71%. **49**: oil; IR (film): 2954, 2875, 1738, 1439, 1367, 1247, 1202, 1172; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24 (td, J = 8.2, 4.1 Hz, 1H), 3.87 (q, $J \approx$ 7.9 Hz, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 3.26 (t, J = 8.0 Hz, 1H), 3.12 (m, 2H), 2.42 (ddd, J = 16.0, 9.1, 6.2 Hz, 1H), 2.35 (ddd, J = 16.0, 9.1, 6.2 Hz, 1H), 1.93 (m, 4H), 1.68 (m, 1H), 1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 170.7, 76.4, 67.2, 56.87, 56.83, 52.0, 51.6, 30.5, 28.6, 27.3, 24.2; MS (EI) *m/z*: 257 (M^+, 7), 141 (12), 110 (21), 86 (53), 85 (100), 55 (36). Anal. Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.03; H, 7.22; N, 5.11. **53**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.02 (td, J = 8.4, 3.9 Hz, 1H), 3.9 (m, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.28 (m, 1H), 2.85 (m, 1H), 2.66 (dd, J = 8.4, 5.2 Hz, 1H), 2.43 (m, 2H), 1.95 (m, 6H). **54**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.10 (d, J = 7.7 Hz, 1H), 3.74 (s, 3H), 3.49 (s, 3H), 3.58 (m, 1H), 3.43 (m, 1H), 3.02 (m, 1H), 2.38 (m, 2H), 1.85 (m, 6H).

Methyl (5*RS*,6*SR*,7*RS*)-5-Hydroxy-2-oxo-1-azabicyclo-[5.3.0]decane-6-carboxylate (50). Glacial HOAc (1.1 mL,

19.5 mmol) and 10% Pd/C (260 mg) were added to a solution of **49** (1.00 g, 3.89 mmol) in EtOAc (16 mL), and the mixture was stirred under hydrogen at atmospheric pressure and room temperature for 20 h. The reaction mixture was filtered through Celite, and the solvent was evaporated under vacuum. The remaining oil was dissolved in water (15 mL), $CHCl_3$ (50 mL) was added, and small portions of Na_2CO_3 were successively added while stirring until permanent alkaline pH (around 9) of the aqueous phase was achieved. After 5 h of stirring, the organic layer was separated, and the aqueous phase was extracted with $CHCl_3$ (4 × 30 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under vacuum, furnishing a solid that was identified as **50** (843 mg, 3.72 mmol, 95% yield): mp 153−155 °C (white solid from EtOAc−hexane); IR (KBr): 3277 (br), 2979, 2881, 1732, 1618, 1475, 1436; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (t, J = 7.1 Hz, 1H), 3.81 (dt, J = 6.2, 4.7 Hz, 1H), 3.69 (m, 1H), 3.69 (s, 3H), 3.26 (dt, J = 11.4, 7.6 Hz, 1H), 3.04 (d, J = 4.7 Hz, 1H), 2.85 (br s, 1H), 2.55 (dd, J = 13.5, 6.5 Hz, 1H), 2.36 (t, J = 13.5 Hz, 1H), 2.27 (m, 1H), 2.21 (m, 1H), 2.12 (m, 1H), 1.93 (m, 1H), 1.74 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 172.0, 171.2, 74.1, 56.0, 53.3, 52.0, 47.1, 33.8, 32.3, 28.0, 23.1; MS (EI) *m/z*: 227 (M^+, 9), 70 (100). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.97; H, 7.54; N, 6.07.

Methyl (6*RS*,7*RS*)-2-Oxo-1-azabicyclo[5.3.0]decane-6-carboxylate (52). (i) TCDI (1.06 g, 5.95 mmol) was added to a solution of **50** (750 mg, 3.30 mmol) in anhydrous THF (66 mL), and the mixture was stirred at room temperature overnight. The solvent was removed under vacuum, CH_2Cl_2 (30 mL) was added to the residue, and the solution was washed with water (2 × 15 mL). The organic phase was separated and dried ($MgSO_4$), and the solvent was evaporated, furnishing a white solid that was identified as methyl (5*RS*,6*SR*,7*RS*)-5-imidazolylthiocarbonyloxy-2-oxo-1-azabicyclo[5.3.0]decane-6-carboxylate (**51**) and used in the next step without further purification: mp 169−171 °C (white solid from CH_2Cl_2-pentane); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.46 (s, 1H), 6.97 (s, 1H), 5.63 (m, 1H), 4.02 (m, 1H), 3.68 (s, 3H), 3.65 (m, 1H), 3.30 (m, 2H), 2.63 (m, 3H), 2.35 (m, 1H), 2.15 (m, 1H), 2.00 (m, 1H), 1.70 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 182.4, 171.0, 169.3, 136.8, 131.1, 117.8, 83.3, 55.5, 52.3, 49.6, 47.1, 32.9, 32.4, 23.7, 22.9. (ii) A solution of crude **51** (prepared from 750 mg, 3.30 mmol, of **50**) in anhydrous toluene (70 mL) was added to a refluxing solution of Bu_3SnH (3.5 mL, 13.2 mmol) and AIBN (81 mg, 0.50 mmol) in anhydrous toluene (25 mL) under nitrogen, and the mixture was heated at reflux for 45 min. The cold solution was concentrated under vacuum, and the residue was purified by column chromatography (silica gel, EtOAc), furnishing **52** (460 mg, 2.18 mmol, 66% yield): mp 52−55 °C (white solid from CH_2Cl_2-pentane); IR (KBr): 2934, 2868, 1732, 1618, 1436, 1258, 1159; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.96 (br t, J = 7.25, 1H), 3.75 (ddd, J = 11.5, 7.9, 3.9 Hz, 1H), 3.65 (s, 3H), 3.31 (dt, J = 11.5, 3.9 Hz, 1H), 2.76 (m, 1H), 2.57 (dt, J = 14.1, 7.1 Hz, 1H), 2.42 (ddd, J = 14.1, 11.6, 2.5 Hz, 1H), 2.17 (m, 3H), 1.75 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.1, 172.4, 59.0, 51.6, 47.1, 46.1, 37.9, 32.5, 32.4, 23.2, 19.8; MS (EI) *m/z*: 211 (M^+, 7), 183 (6), 70 (100). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.48; H, 8.41; N, 6.43.

Methyl (5*S*,6*R*,7*S*,10*S*)-10-[(1*S*)-1,2-Dibenzyloxyethyl]-5-hydroxy-2-oxo-1-azabicyclo[5.3.0]decane-6-carboxylate (60). Activated zinc powder (40.5 g, 0.62 mol) was added to a solution of **43** (4.40 g, 8.9 mmol) in acetic acid (90 mL), and the mixture was sonicated for 2.5 h. The mixture was then filtered, the solid was thoroughly washed with toluene, and the solvent was evaporated under vacuum. The remaining oil was identified as the salt **59**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28 (m, 10H), 4.81 (d, J = 11.9 Hz, 1H), 4.56 (m, 3H), 4.11 (td, J = 8.9, 2.8 Hz, 1H), 3.70 (s, 3H), 3.61 (m, 4H), 3.36 (m, 1H), 2.66 (dd, J = 8.6, 4.4 Hz, 1H), 2.52 (m, 2H), 2.39 (s, 3H), 1.77 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 174.2, 172.7, 138.3, 137.9, 128.3, 127.8, 127.7, 127.6, 127.5, 78.6, 73.4, 72.6, 71.2, 69.4, 59.2, 58.4, 52.6, 51.5, 30.9, 30.0, 28.2, 26.9. This oil was dissolved in $CHCl_3$ (60 mL), water was added, and the mixture was brought to an alkaline pH (around 11) by the addition of 30% aqueous NH_4OH. The organic layer was separated, and the aqueous phase was extracted with $CHCl_3$ (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under vacuum. The remaining oil was dissolved in toluene (110 mL) and heated at reflux for 14 h. The toluene was evaporated under vacuum, and the residue was purified by column chromatography (silica gel, EtOAc), furnishing lactam **60** (3.55 g, 7.6 mmol, 86% yield): mp 123−5 °C (white solid from EtOAc−hexane); $[\alpha]_D$ −64 (*c* 1.51, $CHCl_3$); IR (KBr): 3366 (br), 2946, 2854, 1729, 1610, 1447, 1151, 1070; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28 (m, 10H), 4.62 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 4.37 (d, J = 1.4 Hz, 1H), 4.36 (d, J = 12.0 Hz, 1H), 4.11 (d, J = 9.3 Hz, 1H), 3.73 (m, 2H), 3.59 (s, 3H), 3.54 (d, J = 5.5 Hz, 2H), 2.91 (d, J = 5.0 Hz, 1H), 2.62 (m, 1H), 2.36 (m, 1H), 1.97 (m, 5H), 1.57 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 171.8, 171.3, 139.0, 138.31, 128.28, 128.0, 127.5, 127.4, 76.9, 73.7, 73.6, 73.1, 71.2, 60.6, 56.8, 54.8, 51.9, 33.9, 32.7, 27.5, 23.5; MS (ESI, MeOH) *m/z*: 490 (MNa^+). Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.77; H, 7.23; N, 3.00.

Methyl (6*S*,7*S*,10*S*)-10-[(1*S*)-1,2-Dibenzyloxyethyl]-2-oxo-1-azabicyclo[5.3.0]decane-6-carboxylate (63). (i) TCDI (1.08 g, 6.05 mmol) was added to a solution of **60** (1.28 g, 2.74 mmol) in anhydrous THF (50 mL), and the mixture was stirred at reflux for 2.5 h. The solvent was removed under vacuum, CH_2Cl_2 (60 mL) was added to the residue, and the solution was washed with water (2 × 30 mL). The organic phase was separated and dried ($MgSO_4$), and the solvent was evaporated, furnishing a yellow oil (1.36 g, 2.36 mmol, 86% yield) that was identified as methyl (5*S*,6*R*,7*S*,10*S*)-10-[(1*S*)-1,2-dibenzyloxyethyl]-5-imidazolylthiocarbonyloxy-2-oxo-1-azabicyclo[5.3.0]-decane-6-carboxylate (**62**). Compound **62** showed low stability and was used in the next step without further purification: ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.45 (s, 1H), 7.28 (m, 10H), 6.98 (s, 1H), 5.56 (dt, J = 11.6, 5.2 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.49 (d, J = 12.1 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 4.34 (m, 1H), 4.13 (d, J = 9.3 Hz, 1H), 3.83 (d, J = 9.3 Hz, 1H), 3.65 (s, 3H), 3.52 (m, 2H), 3.14 (d, J = 5.2 Hz, 1H), 2.68 (m, 1H), 2.43 (m, 2H), 2.04 (m, 3H), 1.79 (m, 1H), 1.50 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 182.3, 170.9, 169.8, 138.9, 138.2, 136.7, 131.0, 128.34, 128.27, 128.0, 127.49, 127.46, 117.7, 83.3, 76.7, 73.4, 73.1, 71.0, 60.7, 56.5, 52.3, 50.7, 33.1, 32.7, 23.4, 23.3. (ii) A solution of crude **62** (460 mg, 0.80 mmol) in anhydrous toluene (15 mL) was added to a refluxing solution of Bu_3SnH (640 μL, 2.39 mmol) and AIBN (26 mg, 0.16 mmol) in anhydrous toluene (2 mL) under nitrogen, and the mixture was heated at reflux for 2 h. The cold solution was concentrated under vacuum, and the residue was purified by column chromatography (silica gel, 1:1 hexanes−EtOAc), furnishing **63** (264 mg, 0.58 mmol, 73% yield): oil; $[\alpha]_D$ −54 (*c* 0.71, $CHCl_3$); IR (ATR): 2950, 2859, 1719, 1617, 1452, 1249, 1152; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (m, 10H), 4.68 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.41 (td, J = 5.5, 1.8 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.13 (br d, J = 9.4 Hz, 1H), 3.86 (br d, J = 9.4 Hz, 1H), 3.61 (s, 3H), 3.53 (d, J = 5.5 Hz, 2H), 2.62 (br s, 1H), 2.55 (ddd, J = 12.3, 9.0, 3.4 Hz, 1H), 2.39 (dd, J = 13.5, 6.8 Hz, 1H), 2.05 (m, 4H), 1.70 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.1, 139.1, 138.3, 128.2, 128.0, 127.9, 127.5, 127.4, 76.9, 73.6, 73.0, 71.3, 60.7, 59.9, 51.7, 47.4, 38.4, 32.6, 32.3, 23.3, 19.3; MS (ESI, MeOH) *m/z*: 474 (MNa^+). Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.55; H, 7.19; N, 2.93.

Methyl (2*S*,3*R*,3a*R*,4*S*)-2-(2-Methoxycarbonylehyl)-4-(tetrahydropyran-2-yloxy)hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (65). A solution of diester **37** (3.3 g, 18.0 mmol) in anhydrous toluene (35 mL) was added to a solution

of nitrone **64**[35q] in anhydrous toluene (35 mL) under nitrogen, and the mixture was stirred at reflux for 2 h. The solvent was removed under vacuum, and the residue was purified by column chromatography (silica gel, 1:1 hexanes−EtOAc), furnishing **65** (5.6 g, 15.7 mmol, 87% yield): oil; IR (ATR): 2947, 1732, 1436, 1199, 1162, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.52 (m, 1H), 4.25−3.70 (complex, 5H), 3.72 and 3.71 (s, 3H), 3.67 (s, 3H), 3.50−3.15 (complex, 3H), 2.53−1.40 (complex, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.6, 170.8, 98.7, 97.7, 78.8, 78.2, 74.5, 73.9, 62.9, 55.9, 52.4, 51.9, 33.0, 31.5, 31.1, 30.7, 28.8, 28.6, 25.7, 19.8; MS (ESI, MeOH) *m/z*: 396 (MK^+), 380 (MNa^+, 100), 358 (MH^+). Anal. Calcd for $C_{17}H_{27}NO_7$: C, 57.08; H, 7.61; N, 3.92. Found: C, 56.70; H, 7.55; N, 3.84.

Methyl (2*S*,3*R*,3a*R*,4*S*)-4-Hydroxy-2-(2-methoxycarbonylethyl)hexahydropyrrolo[1,2-*b*]isoxazol-3-carboxylate (66). A solution of **65** (5.6 g, 15.7 mmol) and TsOH (1.2 g, 6.3 mmol) in MeOH (150 mL) was heated at reflux overnight. The solvent was evaporated under vacuum, the residue was dissolved in CH_2Cl_2 (100 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (100 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated. Purification of the crude reaction product by column chromatography (silica gel, EtOAc) furnished **66** (4.0 g, 14.6 mmol, 95% yield): oil; $[\alpha]_D$ −38 (*c* 1.25, $CHCl_3$); IR (ATR): 3368 (br), 2952, 1730, 1437, 1199, 1169; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.22 (dt, J = 7.3, 5.9 Hz, 1H), 4.13 (td, J = 8.5, 3.5 Hz, 1H), 3.75 (s, 3H), 3.65 (s + m, 4H), 3.37 (t, J = 8.5 Hz, 1H), 3.39 (m, 1H), 3.16 (dt, J = 12.9, 7.0 Hz, 1H), 2.39 (m, 3H), 2.05 (m, 1H), 1.93 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.8, 171.6, 76.8, 75.1, 74.6, 56.0, 55.2, 52.8, 52.0, 33.5, 30.8, 29.2; MS (ESI, MeOH) *m/z*: 296 (MNa^+, 100), 274 (MH^+). Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.69; H, 7.01; N, 5.13. Found: C, 52.33; H, 6.70; N, 5.01.

Methyl (2*S*,3*R*,3a*R*,4*S*)-2-(2-Methoxycarbonylethyl)-4-(triisopropylsilyloxy)hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (67). Et_3N (4 mL, 28.6 mmol) and TIPSOTf (5 mL, 18.6 mmol) were added to a solution of alcohol **66** (4.0 g, 18.0 mmol) in anhydrous CH_2Cl_2 (80 mL) at 0 °C, under nitrogen. The reaction mixture was stirred overnight as it came to room temperature and was then washed with saturated aqueous $NaHCO_3$. The organic phase was separated, dried (Na_2SO_4), and concentrated under vacuum. Purification of the residue by column chromatography (silica gel, 4:1 EtOAc−hexanes) furnished **67** (5.5 g, 12.8 mmol, 87% yield): oil; $[\alpha]_D$ −17 (*c* 1.40, $CHCl_3$); IR (ATR): 2944, 2865, 1735, 1436, 1197, 1168; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.25 (m, 1H), 4.12 (td, J = 9.3, 4.5 Hz, 1H), 3.83 (dd, J = 9.3, 1.6 Hz, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 3.35 (m, 1H), 3.24 (t, J = 9.3 Hz, 1H), 3.23 (m, 1H), 2.37 (m, 2H), 2.03 (m, 1H), 1.86 (m, 2H), 1.71 (m, 1H), 0.99 (br s, 21H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.3, 170.7, 78.4, 76.9, 74.4, 56.1, 55.4, 51.9, 51.5, 35.4, 30.2, 28.0, 17.9, 12.1; MS (ESI, MeOH) *m/z*: 452 (MNa^+, 100), 430 (MH^+). Anal. Calcd for $C_{21}H_{39}NO_6Si$: C, 58.71; H, 9.15; N, 3.26. Found: C, 58.54; H, 9.33; N, 3.20.

Methyl (5*S*,6*R*,7*R*,8*S*)-5-Hydroxy-2-oxo-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decane-6-carboxylate (68). Glacial HOAc (400 μL, 6.3 mmol) and 10% Pd/C (1.1 g) were added to a solution of **67** (5.5 g, 12.8 mmol) in EtOAc (190 mL), and the mixture was stirred under hydrogen at atmospheric pressure and room temperature for 24 h. The reaction mixture was filtered through Celite, and the solvent was evaporated under vacuum. The remaining oil was dissolved in CH_2Cl_2 (150 mL) and washed with saturated aqueous Na_2CO_3. The organic phase was dried (Na_2SO_4), the solvent was removed under vacuum, the residue was dissolved in toluene (150 mL), and the solution was heated at reflux overnight. Evaporation of the solvent and purification of the residue by column chromatography (silica gel, 3:1 EtOAc−hexanes) furnished **68** (4.3 g, 10.9 mmol, 85% yield) as a white solid: mp 131−134 °C; $[\alpha]_D$ +0.9 (*c* 1.50, $CHCl_3$); IR (ATR): 3413 (br), 2945, 2863, 1739, 1621, 1460, 1435, 1147, 1041, 1022; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.64 (td, J = 5.2, 3.1 Hz, 1H), 3.79 (m, 2H), 3.70 (s, 3H), 3.58 (br d, J = 3.1 Hz, 1H), 3.31 (dt, J = 11.6, 7.2 Hz, 1H), 3.24 (br d, J = 5.0 Hz, 1H), 2.57 (br dd, J = 14.2, 7.5 Hz, 1H), 2.49 (br d, J = 7.5 Hz, 1H), 2.37 (br t, J = 14.2 Hz, 1H), 2.25 (br q, J = 14.2 Hz, 1H), 1.95 (m, 2H), 1.77 (m, 1H), 1.03 (br s, 21 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 172.1, 170.7, 77.8, 74.2, 65.6, 51.9, 51.2, 45.0, 33.8, 32.7, 28.1, 17.9, 12.1; MS (ESI, MeOH) *m/z*: 422 (MNa^+). Anal. Calcd for $C_{20}H_{37}NO_5Si$: C, 60.12; H, 9.33; N, 3.51. Found: C, 60.17; H, 9.61; N, 3.42.

Methyl (6*S*,7*R*,8*S*)-2-Oxo-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decane-6-carboxylate (70). (i) A solution of TCDI (2.4 g, 13.5 mmol) in anhydrous THF (40 mL) was added to a solution of **68** (3.0 g, 7.5 mmol) in anhydrous THF (60 mL), under nitrogen, and the mixture was stirred at room temperature overnight. The solvent was removed under vacuum. Purification of the residue by column chromatography (silica gel, EtOAc) furnished a white solid (3.8 g, 7.4 mmol, 98% yield) that was identified as methyl (5*S*,6*S*,7*R*,8*S*)-5-imidazolylthiocarbonyloxy-2-oxo-8-triisopropylsilyloxy-1-azabicyclo[5.3.0]decane-6-carboxylate (**69**): IR (ATR): 2942, 2865, 1735, 1645, 1392, 1288, 1097; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.22 (m, 1H), 7.50 (m, 1H), 7.00 (m, 1H), 5.64 (dt, J = 11.1, 4.8 Hz, 1H), 4.48 (td, J = 4.8, 3.1 Hz, 1H), 3.76 (dt, J = 11.7, 7.5 Hz, 1H), 3.73 (m, 1H), 3.67 (s, 3H), 3.54 (br d, J = 5.0 Hz, 1H), 3.49 (dt, J = 11.7, 6.8 Hz, 1H), 2.60 (m, 3H), 2.15 (m, 1H), 1.82 (m, 2H), 1.04 (br s, 21H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 182.3, 171.1, 168.9, 136.8, 131.1, 117.8, 83.2, 77.7, 65.0, 52.3, 47.1, 45.0, 33.0, 32.5, 23.8, 18.0, 12.0. Compound **69** showed low stability and was immediately submitted to the next synthetic transformation. (ii) A solution of AIBN (81 mg, 0.5 mmol) in anhydrous toluene (20 mL) and another solution of **69** (840 mg, 1.6 mmol) in anhydrous toluene (20 mL) were successively added to a refluxing solution of Bu_3SnH (1.8 mL, 6.6 mmol) in anhydrous toluene (20 mL), and the mixture was heated at reflux for 30 min. The solvent was removed under vacuum, and the residue was purified by column chromatography (silica gel, 1:1 hexanes−EtOAc), furnishing **70** (490 mg, 1.3 mmol, 79% yield) as a white solid: mp 50−54 °C; $[\alpha]_D$ +26 (*c* 1.40, $CHCl_3$); IR (ATR): 2953, 2930, 2862, 1736, 1641, 1429, 1191, 1145, 1102, 1034; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.61 (td, J = 6.1, 4.5 Hz, 1H), 3.82 (m, 1H), 3.65 (br d, J = 4.7 Hz, 1H), 3.60 (s, 3H), 3.32 (dt, J = 11.6, 8.1 Hz, 1H), 2.97 (br t, J = 3.4 Hz, 1H), 2.57 (m, 1H), 2.38 (m, 2H), 2.00 (m, 1H), 1.72 (m, 4H), 1.01 (br s, 21 H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 173.2, 172.1, 78.0, 68.2, 51.9, 45.0, 43.9, 37.8, 32.8, 32.5, 19.8, 17.9, 12.1; MS (ESI, MeOH) *m/z*: 406 (MNa^+). Anal. Calcd for $C_{20}H_{37}NO_4Si$: C, 62.62; H, 9.72; N, 3.75. Found: C, 62.56; H, 9.88; N, 3.57.

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Supporting Information Available: General experimental procedures, preparation and analytical data of compounds anti-**32**, syn-**32**, anti-**33**, syn-**33**, **40**−**42**, **45**, and **48**, and crystal data of compound anti-**33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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