Synthesis of Polyhydroxylated Pyrrolizidine Alkaloids of the Alexine Family by Tandem Ring-Closing Metathesis−Transannular Cyclization. (+)-Australine

James D. White* and Peter Hrnciar

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

james.white@orst.edu

Received August 22, 2000

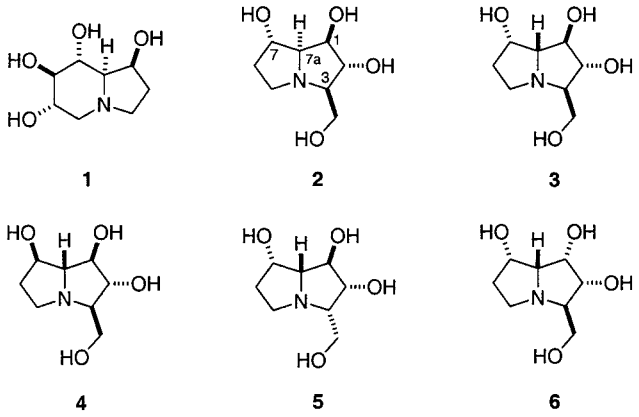
Dienes **23** and **54**, prepared from epoxy alcohol **9** via oxazolidinones **15** and **51**, respectively, underwent ring-closing metathesis with Grubbs's catalyst to give azacyclooctenes **26** and **55**. Treatment of each azacyclooctene with *m*-chloroperoxybenzoic acid afforded *β*-epoxide **28** from **26** and α-epoxide **61** from **60**. Basic hydrolysis of each of these oxazolidinones was accompanied by transannular attack at the epoxide by nitrogen, resulting in 2-(*O*-benzyl)-7-deoxyalexine (**29**) and 1,2-di-(*O*-benzyl)australine (**62**). The latter was converted to the alkaloid australine (**3**) upon hydrogenolysis. Attempts to effect ring-closing metathesis of dienes **37**, **38**, and **46** were unsuccessful, suggesting that, while one allylic oxygen substituent can be tolerated by Grubbs's catalyst, two cannot.

Introduction

Castanospermum australe, a rainforest tree found in Queensland, Australia, and *Alexa leiopetala*, a leguminous tree indigenous to Guyana, Surinam, Venezuela, and the Amazon basin, are rich sources of polyhydroxylated pyrrolizidine and indolizidine alkaloids. The major alkaloidal component of these species is castanospermine (**1**),[1,2] a powerful inhibitor of several glucosidases,[3] including mammalian intestinal sucrosidase and the glucosidase involved in lysomal glycoprotein procession.[4] The wide variety of biological activities described for castanospermine[5] has drawn interest toward other alkaloids present in the pods and seeds of *C. australe* and *A. leiopetala*. Alexine (**2**), isolated in 1987,[6] was the first example of a polyhydroxylated pyrrolizidine alkaloid with a C3 hydroxymethyl branch; subsequently, several other tetrahydroxypyrrolizidines were isolated from *C. australe*, including australine (**3**),[7] 7,7a-diepialexine (**4**),[8] 3,7a-diepialexine (**5**),[9] and 1,7a-diepialexine (**6**) (Chart 1).[8,10]

The pyrrolizidines **2**−**6** are potent glycosidase inhibitors which appear to be more selective in their binding

Chart 1



to specific enzymes than **1**. For example, while alexine (**2**) and its stereoisomer **5** are only poor inhibitors of mammalian glucosidases,[9] they display the powerful amyloglucosidase inhibition seen with castanospermine.[8] Alexine is also an effective thioglucosidase inhibitor.[11] Australine (**3**) is a specific inhibitor of fungal amyloglucosidase and glycoprotein-processing glucosidase 1, but on the other hand no significant inhibition of *β*-glucosi-

(1) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Price, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.

(2) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Striton, C. H.; Carter, D.; Hegarty, M. P. Bell, E. A. *Phytochemistry* **1988**, *27*, 1403.

(3) (a) Saul, R.; Chambers, J. P.; Molyneux, R. J.; Elbein, A. D. *Arch. Bioch. Biophys.* **1983**, *221*, 539. (b) Elbein, A. D. *CRC Crit. Rev. Biochem.* **1984**, *16*, 21. (c) Cenci diBello, I.; Mamm, D.; Nash, R.; Winchester, B. in *Lipid Storage Disorders*; Salvayre, R.; Douste-Blazy, L.; Gatt, S., Eds.; Plenum: New York 1988; Vol. 150, p 635.

(4) (a) Saul, R.; Ghoidoni, J. J.; Molyneux, R. J.; Elbein, A. D. *Proc. Natl. Acad.Sci. USA* **1985**, *82*, 93. (b) Pan, Y. T.; Hori, H.; Saul, R.; Standford, B. A.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1983**, *22*, 3975.

(5) (a) Walker, B. D.; Kowalski, M.; Rosen, W. C.; Rohrschneider, L. R.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120. (b) Sunkara, P. S.; Bowlin, T. L.; Liu, P. S.; Svoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206. (c) Ostrauder, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res.* **1988**, *48*, 1091.

(6) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487.

(7) (a) Harris, C. H.; Harris, T. M.; Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. *Tetrahedron Lett.* **1989**, *30*, 5685. (b) Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198. (c) Nash, R. J.; Fellows, L. E.; Plant, A. C.; Fleet, G. W. J.; Derome, A. E.; Baird, P. D.; Hegarty, M. P.; Scofield, A. M. *Tetrahedron* **1988**, *44*, 5959.

(8) Simmonds, M. S. J.; Blaney, W. M.; Fellows, L. E. *J. Chem. Ecol.* **1990**, *16*, 3167.

(9) (a) Robins, D. J. *J. Nat. Prod. Rep.* **1990**, *7*, 377. (b) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, N. G.; Peach, J. V.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 114.

(10) (a) Fellows, L.; Nash, R. *Chem. Abstr.* **1990**, *114*, 143777s. (b) Elbein, A. D.; Tropea, J. E.; Molyneux, R. J. *Chem. Abstr.* **1989**, *113*, 91444p.

(11) (a) Scofield, A. M.; Rossiter, J. T.; Witham, P.; Kitre, G. C.; Nash, R. J.; Fellows, L. E. *Phytochemistry* **1990**, 29, 107. (b) Tropea, J. E.; Molyneux, R. J.; Kaushal, C. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1984**, *28*, 2027.

10.1021/jo0012748 CCC: $19.00
Published on Web 11/28/2000

dase, α- and β-mannosidase, or α- and β-galactosidase was observed for this alkaloid.[12] 1,7a-Diepialexine (**6**) showed only modest glucosidase 1, β-glucosidase, and α-mannosidase inhibition but, like **4**, it displayed strong activity in a mouse gut digestive α-glucosidase assay.[10] Recently, it has been shown that **3**, **4**, and **6** inhibit HIV-induced synostia formation in JM cells.[8,10]

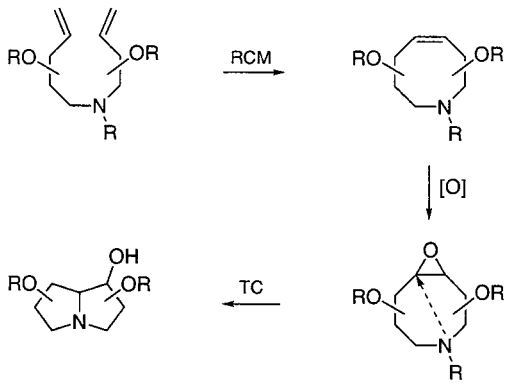
Structural assignments to **2**,[6] **3**,[7] and **5**[9] were made by X-ray crystallographic analysis. Comparison of proton−proton coupling constants in these structures showed characteristic patterns which could be correlated with the configuration and conformation of these molecules. However, the NMR data for australine (**3**), as reported by Molyneux,[9b] did not fit these spectral trends and thus prevented the formulation of more general rules which could be used for structural assignments to other members of this class. Although the anomalies were originally explained by a conformational change in **3**, further investigation cast doubt on the authenticity of the published data for this alkaloid.[13] This placed the structural assignments to **4** and **6** in question since these were made exclusively on the basis of NMR data.

The first synthetic approach toward australine (**3**) was reported by Pearson,[14] but due to an unfortunate error the data which was supplied to Pearson and which was thought to be that of natural australine was in fact that for **4**. As a consequence, Pearson mistakenly concluded that he had synthesized 7,7a-diepialexine along with a second stereoisomer, 7-epialexine. As later work has revealed, Pearson had in fact prepared australine (**3**). After Pearson's synthesis, a short sequence transforming natural castanospermine (**1**) to australine (**3**) was described by Tyler[15] which possibly mimics the proposed biogenetic conversion of this indolizidine to the corresponding C3-branched polyhydroxylated pyrrolizidine. A synthesis of 1,7a-diepialexine (**6**) has been reported by Fleet starting from L-gluconolactone,[16] and recently Denmark has completed syntheses of several members of the class of polyhydroxylated pyrrolizidine alkaloids employing an elegant tandem nitroalkene-cycloaddition strategy.[17]

The foregoing studies indicated that, while the structure of **6** was assigned correctly, that of 7,7a-diepialexine (**4**) was not. It could be surmised, based on the results of Pearson,[14] that the data originally assigned to 7,7a-diepialexine belonged to australine (**3**), but the nature of Pearson's synthesis did not allow definitive structural interpretation. It was this ambiguity which initially provoked our interest in a general synthetic route to the alexine family of polyhydroxylated pyrrolizidine alkaloids and which directed our attention toward australine (**3**) in particular.

Our plan for synthesizing polyhydroxylated pyrrolizidines was based on two key constructions. The first of these is ring-closing metathesis (RCM) which creates an azacyclooctene from a functionalized dialkylamine; the second is a transannular cyclization (TC) which leads from the derived azacyclooctene epoxide to the bicyclic framework of a pyrrolizidine. Our RCM-TC strategy is outlined in Scheme 1, and in a preliminary report we described its successful application to a synthesis of australine (**3**).[18]

Scheme 1

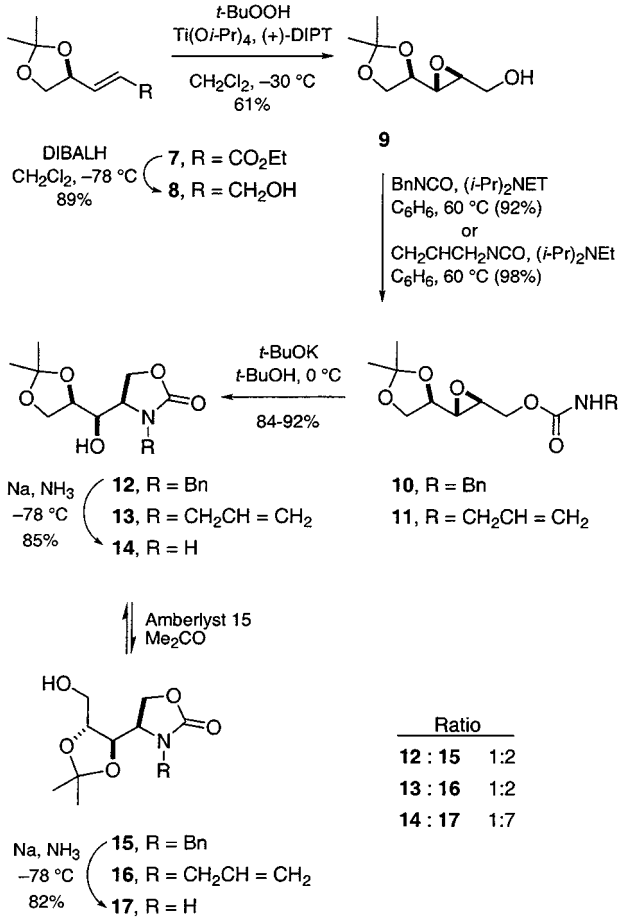


Results and Discussion

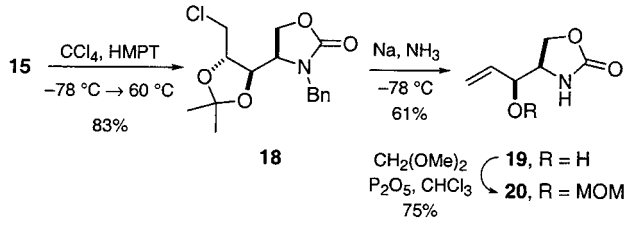
In designing a synthesis of our olefin metathesis precursor, we sought a route which permitted flexibility in the incorporation of oxygen functionality. α,β-Unsaturated ester **7**, obtained from oxidative cleavage of 1,2;5,6-di-*O*-isopropylidene-D-mannitol[19] followed by Wadsworth−Emmons condensation of the derived glyceraldehyde with ethyl diethylphosphonoacetate (Scheme 2), appeared to be an ideal starting point for this objective. Reduction of **7** with diisobutylaluminum hydride gave allylic alcohol **8**[20] which upon Sharpless asymmetric epoxidation in the presence of diisopropyl L-tartrate produced epoxy alcohol **9**.[21] Treatment of **9** with benzyl isocyanate yielded the urethane **10**, which upon exposure to potassium *tert*-butoxide underwent regiospecific intramolecular opening of the epoxide to afford oxazolidinone **12**.[22] Our plan at this stage was to utilize a known rearrangement of glycerol acetonide derivatives in which the acetonide migrates from a terminal to an internal 1,2-diol, thereby liberating a primary alcohol.[23] The rearrangement, which is only successful where migration furnishes a trans disubstituted acetonide, i.e., where oxygen substituents in the precursor bear a syn relationship as in **12**, would position **15** for homologation to one of the two components required for RCM. Unfortunately, the rearrangement of **12** catalyzed by Amberlyst 15 led to only a 2:1 ratio of **15**:**12**, respectively. Although this pair of acetonides could be separated by column chromatography and **12** recycled through the equilibration process, it was hoped that a more favorable ratio could be obtained by placing a less sterically demanding substituent at the nitrogen atom. To this end, the *N*-allyl urethane **11** was prepared by reaction of **9** with allyl isocyanate, and **11** was converted

(12) Fleet, G. W. J.; Haraldsson, M.; Nash. R. J.; Fellows, L. E. *Tetrahedron Lett.* **1988**, *29*, 5441.
(13) Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron Asymm.* **1998**, *9*, 2549.
(14) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513.
(15) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 213.
(16) Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. M.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517.
(17) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046.
(18) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, 120, 7359.
(19) Fischer, H. O. L.; Baer, E. *Helv. Chim. Acta* **1934**, *17*, 622.
(20) Marshall, J. A.; Trometer, J. D.; Cleary, D. G. *Tetrahedron* **1989**, *45*, 391.
(21) Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607.
(22) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.
(23) Mulzer, J.; de Lasalle, P.; Friessler, A. *Justus Liebigs Ann. Chem.* **1986**, 1152.

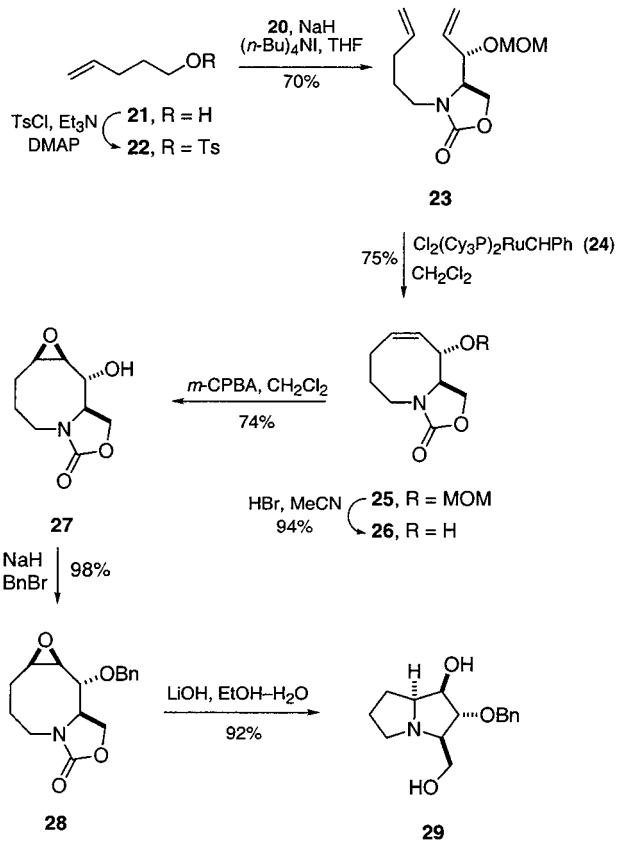
Scheme 2



Scheme 3



Scheme 4



to oxazolidinone **13** by the same procedure used with **10**. Exposure of **13** to Amberlyst 15 again gave a 2:1 ratio of rearranged (**16**) to unrearranged acetonides. Since the blocking group at the oxazolidinone nitrogen of **12** or **13** must eventually be replaced by a substituent which provides the second alkene needed for RCM, it was decided to explore the acetonide rearrangement of **14** in which no substituent is present at nitrogen. The latter was obtained by debenzylation of **12** with sodium–ammonia,[24] and when exposed to Amberlyst 15 it was found to undergo rearrangement to **17** with the improved ratio of 7:1. However, **17** (which could also be obtained by debenzylation of **15**) could not be separated from **14**, and for this reason it was concluded that *N*-benzyl derivative **15** would provide a more satisfactory route with pure materials. Thus, **15** was first converted to chloro acetonide **18**,[25] and subsequent reaction of this substance with sodium–ammonia removed the *N*-benzyl substituent and reductively cleaved the chloro acetonide to furnish the allylic alcohol **19** (Scheme 3).[26] This was protected as its methoxymethyl (MOM) ether **20** prior to the next phase of the synthesis.

The pentenyl chain to be attached to the nitrogen atom of **20** was obtained from 4-penten-1-ol (**21**) which was first converted to its tosylate **22** (Scheme 4). Alkylation of the sodium salt of **20** with **22** in the presence of tetra-*n*-butylammonium iodide afforded **23** which underwent clean ring-closing metathesis using Grubbs's catalyst **24**[27] to give the azacyclooctene **25**. We believe the efficiency of this RCM is due, at least in part, to the presence of the basal oxazolidinone to which the reacting alkenes are tethered,[28] since 1,9-azadienes in which this ring is not present are relatively poor RCM substrates. A useful inference drawn from the successful RCM of **23** is that Grubbs's catalyst **24** can tolerate at least one allylic oxygen substituent in this system.[29]

A pivotal issue which now came to the fore was the facial selectivity in epoxidation of the azacyclooctene, since the configuration at C1 of **2** requires that oxygen enter the β face of **25**, whereas access to other pyrrolizidines would necessitate epoxidation at the α face. The

(24) (a) Annis, G. D.; Hebblethwaite, E. M.; Hodgson, S. T.; Hollisshead, D. M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2851. (b) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3488.

(25) Angyal, S. J.; Pickles, V. A.; Ahluwalia, R. *Carbohydr. Res.* **1967**, *3*, 300.

(26) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.

(27) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

(28) For a recent discussion of the templating effect on tethered dienes in RCM to form medium-sized rings, see Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

(29) (a) Levisalles, J.; Rudler, H.; Villemin, D. *J. Organomet.* **1979**, *164*, 251. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.

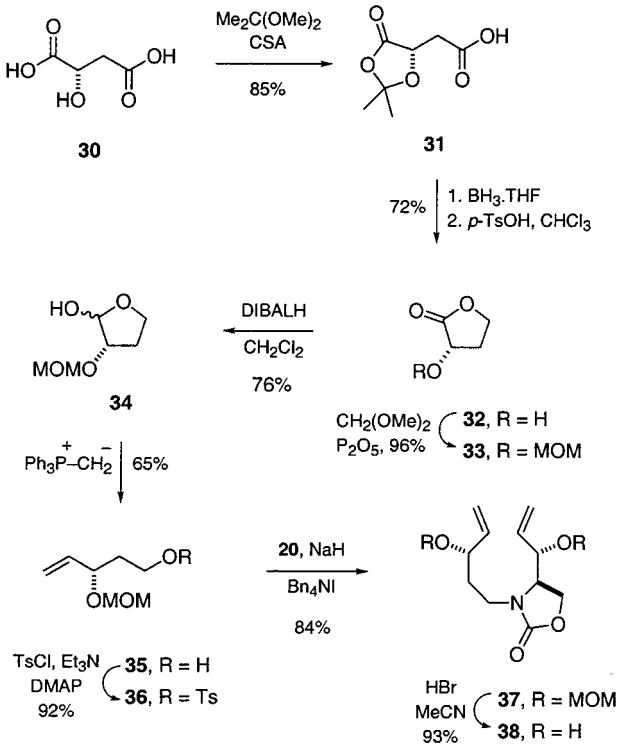
preferred conformation of **25** according to an energy minimization routine is one in which the double bond is orthogonal to the allylic oxygen substituent. A directed a syn epoxidation is therefore not possible, and in fact the face of the double bond anti to the allylic substituent is the more exposed. In accord with this assessment, epoxidation of MOM ether **25** with *m*-chloroperoxybenzoic acid gave exclusively the epoxide of β configuration (vide infra). Although, this favorable outcome was countered by difficulty in removing the MOM protecting group without damage to the epoxide, reversal of the epoxidation−deprotection sequence easily solved this problem. Alcohol **26**, obtained in quantitative yield after removal of the MOM ether from **25**, underwent epoxidation to give **27** as the sole product.

Our intention with **27** was to effect a one-pot cleavage of the oxazolidinone and transannular attack at the epoxide with the derived nitrogen anion to yield a pyrrolizidine directly. Unfortunately, the free hydroxyl group of **27** interfered with this plan, and all efforts to complete the transannular cyclization phase of our RCM-TC agenda from this epoxide were unsuccessful. Benzylation of **27** not only circumvented this obstacle but gave us a crystalline derivative **28** whose exposure to lithium hydroxide in aqueous ethanol led in high yield to **29**, the benzyl ether of 7-deoxyalexine.[30] The crystal structure of **28** is shown in Figure 1.

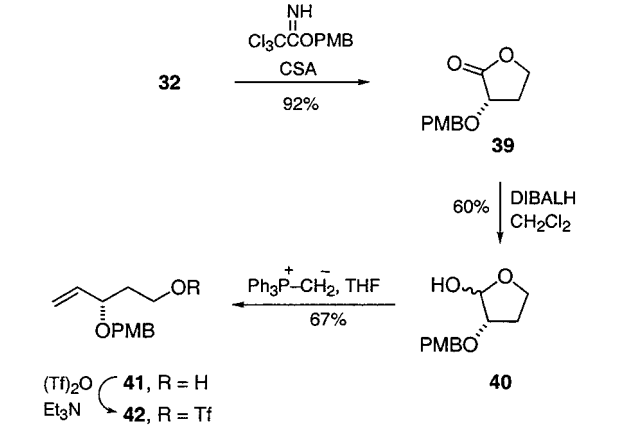
Although 7-deoxyalexine has not been reported as a member of the family of naturally occurring hydroxylated pyrrolizidines, the success exemplified in our synthesis of **29** encouraged us to launch our RCM-TC strategy at alexine (**2**) itself. In principle, this requires only a minor modification to **22** which incorporates an additional oxygen substituent at C3 prior to N-alkylation of **20**. The revised plan was put into motion starting from (*S*)-malic acid (**30**) which was first transformed to acetonide **31** and then to α-hydroxy-γ-lactone **32** by a known procedure (Scheme 5).[31] After protection of the hydroxyl group of **32** as its MOM ether **33**, the lactone was reduced to lactol **34**, and this was reacted with triphenylphosphonium methylide to afford the pentenol **35**. Tosylation of this alcohol gave **36** which was used in an efficient N-alkylation of oxazolidinone **20** to furnish RCM substrate **37**. A parallel route in which **32** was converted to a *tert*-butyldimethylsilyl ether rather than **33** was less successful and met its demise when silyl migration to the liberated primary alkoxide was found to occur during the Wittig reaction. With expectations of emulating the successful RCM of **23**, diene **37** was exposed to Grubbs's catalyst **24** under a variety of conditions. No azacyclooctene was produced, nor was an attempted RCM with diol **38** any more productive.

Suspecting that the pair of allylic MOM ethers could be responsible for the failure of **37** to undergo RCM,[29] a new metathesis substrate was designed in which these protecting groups were no longer present. A further modification was made in which the oxazolidinone template was replaced by a cycle linking the two oxygen substituents in the butenyl chain, thus providing a more rigid platform at one terminus of the RCM candidate.[28] First, (*S*)-3-*p*-methoxybenzylpent-4-en-1-ol (**41**) was prepared from lactone **39** via **40** and was converted to its triflate **42** (Scheme 6). Next, oxazolidinone **19** was protected at both the nitrogen and the hydroxyl function as its bis-Boc derivative **43** (Scheme 7). Treatment of **43** with sodium ethoxide effected cleavage of both the oxazolidinone and the carbonate (but not the urethane) to yield diol **44**, which was transformed to benzylidene acetal **45**. Alkylation of **45** with triflate **42** afforded RCM substrate **46** in excellent yield; however, this substance like **37** and **38** was completely unreactive toward Grubbs's catalyst **24**. The failure of **37**, **38**, and **46**, in contrast to **23**, to undergo RCM must be attributed to interference by the bis allylic oxygen functionality with initial formation of the ruthenium−olefin complex from which subsequent metathesis must flow. It emphasizes the care with which RCM substrates must be designed,[32] and in the context of a general RCM-TC strategy for synthesis of pyrrolizidines such as **2**−**6** it stipulates that oxygen

Scheme 5



Scheme 6

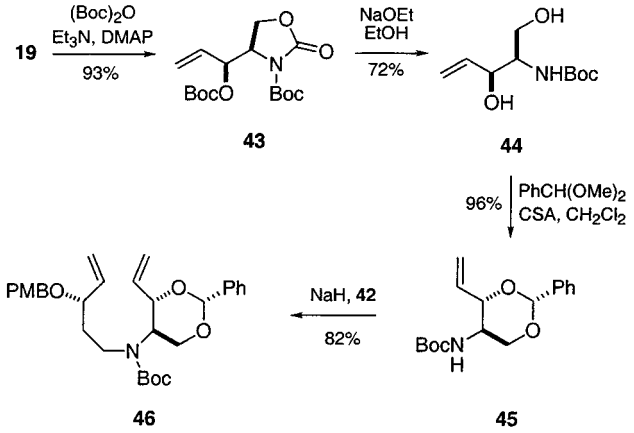


(30) For a recent synthesis of 7-deoxyalexine, see Yoda, H.; Asai, F.; Takabe, K. *Synlett* **2000**, 1001.

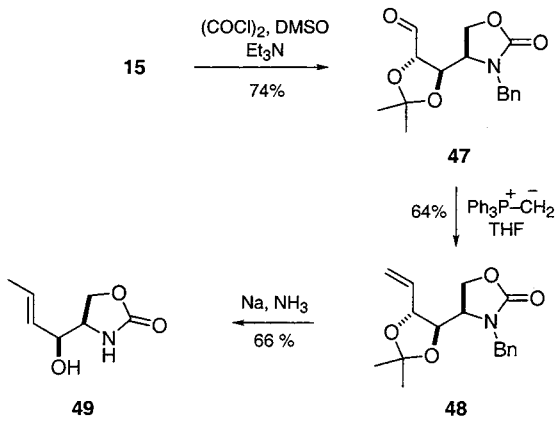
(31) Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2865.

(32) For discussion of this point, see Armstrong, S. K. *J. Chem. Soc., Perkin Trans 1* **1998**, 371.

Scheme 7



Scheme 8

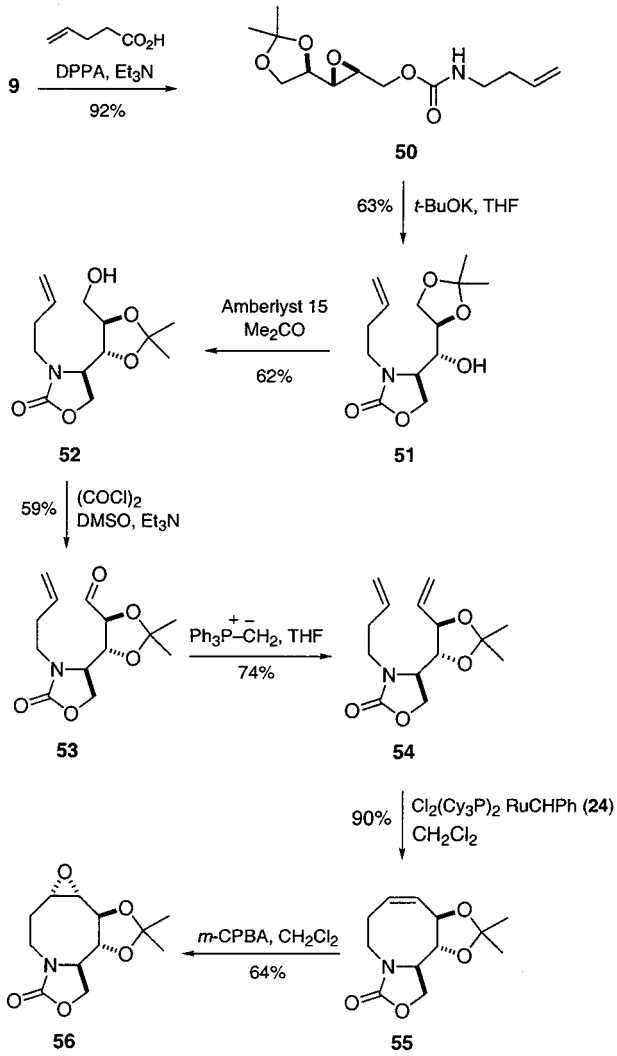


substitution should be positioned at only one of the two allylic sites in the alkenyl chains of the RCM candidate.

The disappointing RCM results with **37**, **38**, and **46** caused us to realign an earlier plan for synthesis of australine (**3**), and alcohol **15** was selected as the starting point for a new approach to our RCM substrate. Swern oxidation[33] of **15** afforded aldehyde **47** which upon Wittig olefination gave **48** (Scheme 8). Unfortunately, the intended N-debenzylation of **48** with sodium−ammonia was complicated by reductive elimination of the acetonide,[24] resulting in the useless allylic alcohol **49**. In an attempt to circumvent this problem, debenzylation was carried out on **15**, but the primary alcohol of this unprotected oxazolidinone proved exceptionally difficult to oxidize to an aldehyde.

The impasse presented by **48** was circumvented by incorporating the butenyl chain required for RCM prior to formation of the oxazolidinone, so that removal of a protecting group at the nitrogen atom was no longer required. The isocyanate from Curtius rearrangement[34] of the acyl azide prepared from 4-pentenoic acid was reacted in situ with **9** to give the urethane **50** in excellent yield (Scheme 9). Upon exposure to potassium *tert*-butoxide, **50** underwent smooth intramolecular displacement of the epoxide to form oxazolidinone **51**[22] in which the stereogenic oxygen substituents are in the same syn relationship as in **14**. This configuration set the stage for migration of the acetonide from the terminal position

Scheme 9



to the internal dioxolane,[23] a rearrangement which was again efficiently catalyzed by Amberlyst 15 resin and which yielded a 2:1 mixture favoring **52** over **51**. The primary alcohol of **52** released in this migration was oxidized[33] to aldehyde **53**, and Wittig olefination then furnished the RCM substrate **54**.

It was hoped that the two five-membered rings of **54** would impose a degree of conformational immobilization on this structure which would be advantageous for RCM,[28] and indeed treatment of the diene with Grubbs's catalyst **24** led to azacyclooctene **55** in excellent yield. The extent to which the acetonide of **54** assists RCM can be gauged by comparison of the conditions used in this case (room temperature, 5 h) with those necessary for RCM of **25** (60 °C, 18 h). The conformation of **55** now became a matter of importance, since in contrast to **26** an epoxide must be introduced from the α face of the double bond. Molecular modeling suggested that the eight-membered ring of **55** exists preferentially in a conformation which places all of the substituents in an equatorial orientation, and an AM 1 optimized geometry for the diol derived from **55** clearly shows that the α face of the double bond is more exposed to attack in this conformation.[18] In fact, epoxidation of **55** with *m*-chloroperoxybenzoic acid produced a single epoxide whose structure was confirmed as **56** by X-ray crystallographic analysis (Figure 2).

(33) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(34) Smith, P. A. S. *Org. React.* **1946**, *3*, 337.

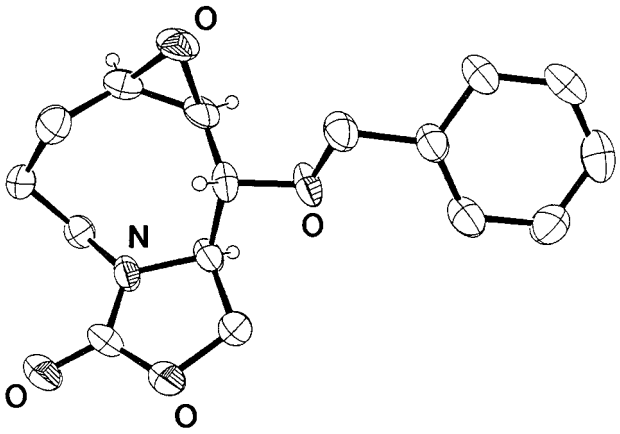


Figure 1. ORTEP diagram for **28**. Ellipsoids are drawn at the 30% probability level.

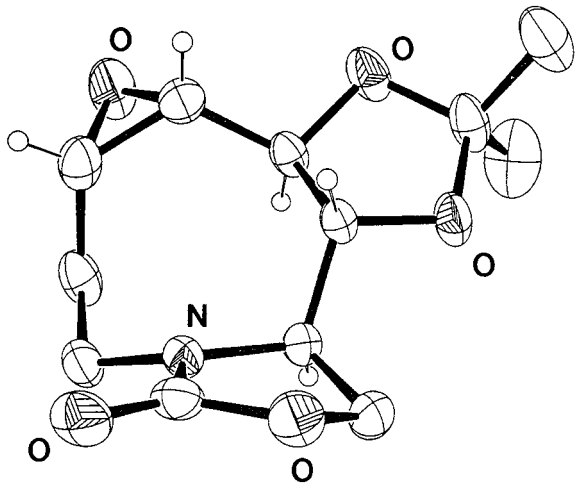
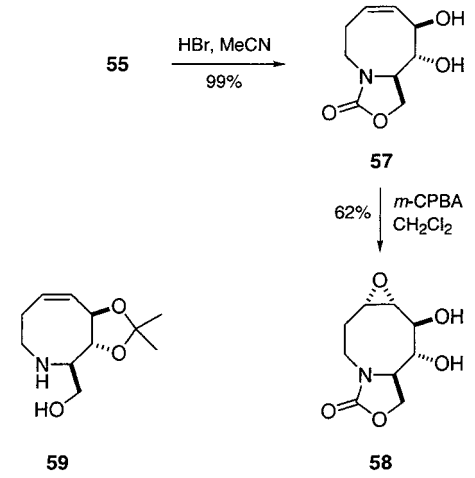


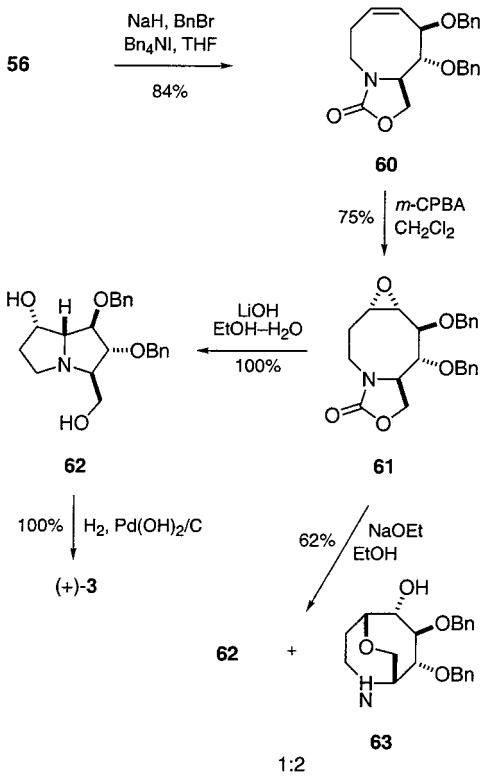
Figure 2. ORTEP diagram for **56**. Ellipsoids are drawn at the 30% probability level.

The acetonide which had provided impetus to the RCM of **54** now proved to be an encumbrance for the transannular cyclization of **56**. A conformational reorganization of the eight-membered ring shown in Figure 1 must take place in order to orient the nitrogen for internal displacement of the epoxide, and while this would be quite feasible if the acetonide were not present, the trans fusion of a five-membered ring imposes a significant barrier on this process. Not surprisingly, removal of the acetonide from **56** without compromising the epoxide proved to be impossible, and it was therefore decided to return to **55** in order to avoid this cul-de-sac. Diol **57**, obtained by hydrolysis of **55** with 48% aqueous hydrobromic acid (Scheme 10), now became the substrate for epoxidation, and based on the conformation shown in Figure 1, it was again predicted that attack by peracid would take place from the α side of the double bond. This assertion would appear to run counter to the generally accepted dictum of Henbest[35] who demonstrated that allylic alcohols exert a strong directing influence upon epoxidation with peracids. However, it is known that the Henbest rule is inoperative in medium rings, and that a trans orientation of epoxide and alcohol is often the result even in systems with significantly more flexibility than **57**.[36] In line with this reasoning, epoxidation of **57** gave a single product

Scheme 10



Scheme 11



58 whose configuration was established by correlation with acetonide **56**. Unfortunately, **58** resisted all attempts at opening the oxazolidinone, so that an unlatched nitrogen never had the opportunity for transannular attack on the epoxide in this molecule. This failure is to be contrasted with base treatment of **55**, which readily yielded amino alcohol **59**, and it was concluded from this result that successful TC would only be possible where the vicinal diol of **58** was blocked.

Revision of the final steps to **3** necessitated a return to **56** which was converted to its bis benzyl ether **60** (Scheme 11). Epoxidation of **60** again gave a single stereoisomer which, in this case, was nicely crystalline; X-ray crystallographic analysis confirmed the anticipated stereochemistry of **61** as shown.[18] With the stage now set

(35) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.

(36) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.

for transannular cyclization to a pyrrolizidine, **61** was reacted with a variety of bases which were expected to first open the oxazolidinone. Of these, only lithium hydroxide was fully satisfactory, and this led to a quantitative yield of di-*O*-benzylaustraline (**62**). The facile conversion of **61** to **62** would imply that the transient lithiated amino alcohol generated upon exposure of **61** to hydroxide places the nucleophilic nitrogen in an especially favorable orientation for 1,5-displacement at the epoxide, so that inversion at the epoxide center undergoing attack and conservation of the other C−O bond results in the (7*S*,7a*R*) configuration of australine. This stereochemical arrangement is also characteristic of other pyrrolizidine alkaloids such as **5** and **6** which could therefore be accessed via a similar TC strategy. The importance of a lithiated species for the TC step became evident when the analogous sodio derivative, prepared from **61** with sodium ethoxide, underwent transannular reaction. In this case, bicyclic amino ether **63** was the major product resulting from attack at the epoxide by the liberated alkoxide rather than by nitrogen. Interestingly, the attack by alkoxide occurs in the opposite regio sense to that operating along the pathway to **62**. The divergent behavior of lithio and sodio intermediates derived from **61** can be rationalized in terms of the diminished affinity of sodium (compared to lithium) cation for coordination with oxygen, thus rendering the alkoxide more nucleophilic.

Final hydrogenolysis of **62** over Pearlman's catalyst removed both benzyl groups and furnished (+)-australine (**3**) in quantitative yield. The synthesized material was identical in all respects, including optical rotation, with a sample of natural australine provided by Professor G. W. J. Fleet of Oxford University. It was also clear from careful comparison of our NMR data for **3** that this substance was distinct from stereoisomers **4**, **5**, and **6**, a point which has recently received more detailed scrutiny.[13] Comparison of our australine with the substance which Pearson had synthesized and which he had erroneously believed to be 7,7a-diepialexine[14] showed that they were identical.

In summary, a general strategy for synthesis of hydroxylated pyrrolizidines bearing a C3 alkyl substituent has been devised in which an azacyclooctene precursor is generated by ring-closing metathesis. Stereoselective epoxidation of this azacyclooctene and transannular opening by nitrogen produces a pyrrolizidine in which hydroxyl configurations are set unambiguously. A limitation of this strategy is the inability of RCM to accommodate two allylic oxygen substituents in the diene substrate. Future attempts to remove this deficiency will focus on RCM of precursors bearing hydroxyl surrogates such as silicon substituents.

Experimental Section

Melting points are uncorrected. Chemical ionization (CI) high and low resolution mass spectra (HRMS and MS) were obtained using a source temperature of 120 °C and CH_4 as the ionizing source. Perfluorokerosene was used as a reference. Column chromatography was carried out on silica gel 60 (70−230 mesh). Unless otherwise indicated, reactions were carried out under a nitrogen atmosphere. Solvents were dried by distillation over sodium/benzophenone (Et_2O, THF) or over CaH_2 (CH_2Cl_2).

(4*R*)-3-Benzyl-4-[(2*R*)-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl](hydroxy)methyl]-1,3-oxazolidin-2-one (12). To a solution of **10** (41.8 mg, 0.136 mmol) in dry THF (10 mL) maintained at −10 °C was added a 1 M solution of potassium *tert*-butoxide in *tert*-BuOH (272 mL, 0.272 mmol), and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with a saturated solution of NH_4Cl (1 mL), and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (4 g of silica gel, EtOAc−hexane, 2:1) afforded 53.1 mg (84%) of **12** as a pale yellow solid: mp 70−73 °C; $[\alpha]_D^{23}$ −14.6 (*c* 4.55, $CHCl_3$); IR (neat) 3433, 2994, 1738, 1445, 1382, 1269, 1220, 1147, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.43 (s, 3H), 2.45 (d, J = 6 Hz, 1H), 3.62−3.68 (m, 1H), 3.75−3.86 (m, 2H), 3.94−3.99 (m, 2H), 4.18−4.28 (m, 2H), 4.51 (dd, J = 7, 9 Hz, 1H), 4.84 (d, J = 15 Hz, 1H), 7.29−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.3, 46.6, 58.0, 63.1, 66.0, 67.5, 75.7, 110.3, 128.2, 128.3, 129.2, 136.0, 159.2; MS (CI) *m*/*z* 308 (M^+ + 1), 278, 250, 176, 151, 129, 91; HRMS (CI) *m*/*z* 308.1500 (calcd for $C_{16}H_{22}NO_5$: 308.1498).

(4*R*)-3-Allyl-4-[(2*R*)-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl](hydroxymethyl]-1,3-oxazolidin-2-one (13). To a solution of **11** (40 mg, 0.16 mmol) in dry THF (15 mL) maintained at −10 °C was added a 1 M solution of potassium *tert*-butoxide in *tert*-BuOH (280 mL, 0.28 mmol), and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with a saturated solution of NH_4Cl, and the product was extracted with EtOAc (3 × 8 mL). The combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (6 g of silica gel, EtOAc−hexane, 2:1) afforded 36.8 g (92%) of **13** as a colorless oil: $[\alpha]_D^{23}$ −18.6 (*c* 2.12, $CHCl_3$); IR (neat) 3438, 2989, 2935, 1733, 1450, 1367, 1264, 1230, 1147, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.44 (s, 3H), 2.81 (d, J = 6 Hz, 1H), 3.67 (dd, J = 8, 19 Hz, 1H), 3.78−3.85 (m, 2H), 3.87−3.96 (m, 1H), 4.02−4.06 (m, 2H), 4.14−4.23 (m, 1H), 4.28 (t, J = 9 Hz, 1H), 5.23 (s, 1H), 5.26−5.28 (m, 1H), 5.72−5.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 26.3, 45.2, 58.3, 63.1, 66.1, 67.3, 75.9, 110.2, 119.0, 132.4, 158.8; MS (CI) *m*/*z* 258, 228, 199, 170, 140, 125; HRMS (CI) *m*/*z* 258.1340 (calcd for $C_{12}H_{20}NO_5$: 258.1341).

(4*R*)-4-[(2*R*)-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl](hydroxy)methyl]-1,3-oxazolidin-2-one (14). Anhydrous ammonia (100 mL) was condensed into a 250 mL two-necked flask containing a solution of **12** (1.14 g, 3.71 mmol) in THF (7 mL) maintained at −78 °C. To this mixture was added sodium metal until a blue color persisted. The solution was stirred for 2 h at −78 °C and was quenched with solid NH_4Cl. The ammonia was evaporated, and the residue was extracted with a EtOAc−MeOH (5%) mixture (3 × 10 mL). The extract was filtered through Celite, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (40 g of silica gel, EtOAc−hexane, 2:1) afforded 0.69 (85%) of **14** as a colorless solid: mp 109−112 °C; $[\alpha]_D^{23}$ −2.5 (*c* 1.96, $CHCl_3$); IR (neat) 3198, 2983, 1772, 1440, 1381, 1244, 1059, 946 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.44 (s, 3H), 3.20 (d, J = 7 Hz, 1H), 3.58−3.64 (m, 1H), 3.92−3.97 (m, 2H), 4.06 (t, J = 7 Hz, 1H), 4.14−4.19 (m, 1H), 4.45 (t, J = 9 Hz, 1H), 4.48−4.59 (m, 1H), 6.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 26.3, 55.3, 65.8, 67.3, 71.3, 75.5, 110.0, 160.9; MS (CI) *m*/*z* 218 (M^+ + 1), 202, 188, 160, 142, 116, 109, 98, 88, 86, 84, 73; HRMS (CI) *m*/*z* 218.1029 (calcd for $C_9H_{16}NO_5$: 218.1028).

(4*S*)-3-Benzyl-4-[(4*R*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one (15). To a solution of **12** (1.19 g, 3.87 mmol) in dry acetone (80 mL) was added Amberlyst 15 resin (ca. 100 mg), and the mixture was stirred for 18 h at room temperature. The mixture was filtered and the filtrate was neutralized with solid $NaHCO_3$ (2 g). The resulting solution was concentrated, and the residue was chromatographed (160 g of silica gel, EtOAc−hexane, 1:1) to afford 761 mg (64%) of **15** as a colorless solid: mp 89−92 °C; $[\alpha]_D^{23}$ −6.30 (*c* 1.73, $CHCl_3$); IR (neat) 3438, 2984, 1743, 1440, 1250, 1098, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.44 (s, 3H), 3.57−3.62 (m, 1H), 3.62−3.73 (m, 2H), 3.78−

3.83 (m, 1H), 4.18 (dd, J = 2, 8 Hz, 1H), 4.25 (d, J = 17 Hz, 1H), 4.27 (d, J = 15 Hz, 1H), 4.34 (dd, J = 6, 9 Hz, 1H), 4.83 (d, J = 15 Hz, 1H), 7.28−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 27.2, 46.9, 54.5, 62.3, 62.7, 75.2, 110.1, 128.2, 128.5, 129.0, 135.0, 158.6; MS (CI) m/z 308 ($M^+ + 1$), 250, 176, 151, 129, 114, 91, 84; HRMS (CI) m/z 308.1500 (calcd for $C_{16}H_{22}NO_5$: 308.1498). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, C, 62.26; H, 6.86; N, 4.80.

(4*R*)-3-Allyl-4-[(4*R*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one (16). To a solution of **13** (35.0 mg, 0.136 mmol) in dry acetone (20 mL) was added Amberlyst 15 resin (ca. 10 mg), and the mixture was stirred for 18 h at room temperature. The mixture was filtered, and the filtrate was neutralized with solid $NaHCO_3$ (20 mg). The mixture was filtered through a short column of silica gel, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (5 g of silica gel, EtOAc−hexane, 1:1) gave 22.4 mg (64%) of **16** as a colorless oil: $[\alpha]_D^{23}$ −13.9 (*c* 1.10, $CHCl_3$); IR (neat) 3443, 2989, 2925, 1738, 1450, 1377, 1259, 1084, 1044, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.45 (s, 3H), 3.65−3.84 (m, 4H), 3.97−4.02 (m, 1H), 4.18−4.24 (m, 2H), 4.29−4.38 (m, 2H), 5.24−5.32 (m, 2H), 5.73−5.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 27.2, 45.4, 54.8, 62.3, 62.7, 75.1, 110.1, 119.0, 132.2, 158.2; MS (CI) m/z 258 ($M^+ + 1$), 242, 228, 200, 182, 156, 141, 131, 126; HRMS (CI) m/z 258.1341 (calcd for $C_{12}H_{20}NO_5$: 258.1341).

(4*S*)-4-[(4*R*,5*R*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one (17). Anhydrous ammonia (25 mL) was condensed into a 50 mL, two-necked flask containing a solution of **15** (130 mg, 0.423 mmol) in THF (2 mL) maintained at −78 °C. To the mixture was added sodium metal until a blue color persisted. The mixture was stirred for 2 h at −78 °C and quenched with solid NH_4Cl. The ammonia was evaporated, and the residue was extracted with a EtOAc-MeOH (5%) mixture (3 × 5 mL). The extract was filtered through Celite and the filtrate was concentrated under reduced pressure. Chromatography of the residue (10 g of silica gel, EtOAc−hexane, 2:1) yielded 75 mg (82%) of **17** as a colorless oil: $[\alpha]_D^{23}$ −1.0 (*c* 1.50, $CHCl_3$); IR (neat) 3365, 2984, 2940, 1793, 1255, 1044 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 11.38 (s, 6H), 3.68−3.71 (m, 1H), 3.79−3.94 (m, 4H), 4.41 (dd, J = 5, 9 Hz, 1H), 4.52 (t, J = 8 Hz, 1H), 6.85 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 54.8, 62.7, 68.3, 79.9, 81.1, 109.8, 160.5; HRMS (CI) m/z 218.1030 (calcd for $C_9H_{16}NO_5$: 218.1028

(4*R*)-3-Benzyl-4-[(4*R*,5*S*)-5-(chloromethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one (18). To a solution of **15** (261 mg, 0.850 mmol) and HMPT (0.310 mL, 1.70 mmol) in THF (30 mL) maintained at −78 °C under an argon atmosphere was added CCl_4 (0.82 mL, 8.50 mmol), and the mixture was stirred for 4 h at −78 °C. The temperature of the reaction mixture was gradually raised to 60 °C, and stirring was continued for 12 h. The mixture was filtered through a short column of silica gel and the filtrate was concentrated under reduced pressure. Chromatography of the residue (10 g of silica gel, EtOAc−hexane, 1:4) afforded 230 mg (83%) of **18** as a colorless oil: $[\alpha]_D^{23}$ −100.0 (*c* 0.87, $CHCl_3$); IR (neat) 1758, 1437, 1375, 1242, 1071 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.44 (s, 3H), 3.44 (dd, J = 7, 11 Hz, 1H), 3.60 (dd, J = 4, 11 Hz, 1H), 3.70−3.76 (m, 1H), 3.86−3.91 (m, 1H), 4.17 (dd, J = 2, 7 Hz, 11H), 4.24−4.33 (m, 2H), 4.81 (d, J = 15 Hz, 1H), 7.28−7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 27.2, 44.2, 46.8, 55.2, 62.3, 76.2, 77.0, 110.9, 127.8, 128.3, 128.5, 129.0, 135.8, 158.3; MS (CI) m/z 326 ($M^+ + 1$), 268, 213, 176, 169, 91; HRMS (CI) m/z 326.1160 (calcd for $C_{16}H_{21}ClNO_4$: 326.1159). Anal. Calcd for $C_{16}H_{20}ClNO_4$: C, 58.99; H, 6.19; Cl, 10.88. Found: C, 59.26; H, 6.30; Cl, 10.52.

(4*R*)-4-[(1*S*)-1-Hydroxy-2-propenyl]-1,3-oxazolidin-2-one (19). Anhydrous ammonia (40 mL) was condensed into a 100 mL, two-necked flask containing a solution of **18** (44 mg, 0.145 mmol) in THF (2 mL) maintained at −78 °C. To the mixture was added sodium metal until the blue color persisted. The reaction was stirred for 3 h at −78 °C and was quenched with solid NH_4Cl. The ammonia was evaporated, and the residue was extracted with a EtOAc−MeOH (5%) mixture. The extract was filtered through a short column of silica gel, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (15 g of silica gel, EtOAc−hexane, 2:1) gave 54 mg (61%) of **19** as a colorless solid: mp 85−89 °C; $[\alpha]_D^{23}$ −10.1 (*c* 1.36, $CHCl_3$); IR (neat) 3345, 1743, 1421, 1250, 1064 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (br s, 1H), 3.89−3.95 (m, 1H), 4.23−4.27 (m, 1H), 4.32−4.41 (m, 2H), 5.30 (d, J = 10 Hz, 1H), 5.41−5.47 (m, 1H), 5.72−5.83 (m, 1H), 6.60 (s br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.4, 66.0, 72.7, 118.6, 135.1, 161.1; MS (CI) m/z 144 ($M^+ + 1$), 131, 129, 114, 109, 103, 86, 71; HRMS (CI) m/z 144.0660 (calcd for $C_6H_{10}NO_3$: 144.0661).

(4*R*)-4-[(1*S*)-1-(Methoxymethoxy)-2-propenyl]-1,3-oxazolidin-2-one (20). To a solution of **19** (20 mg, 0.140 mmol) and dimethoxymethane (123 μL, 1.40 mmol) in dry $CHCl_3$ (15 mL) was added P_2O_5 (25 mg), and the mixture was stirred at ambient temperature until TLC analysis indicated ca. 80% conversion to a new product. The supernatant was decanted from the solid residue and was neutralized with solid $NaHCO_3$ (30 mg). The mixture was filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (3 g of silica gel, EtOAc−hexane, 1:1) afforded 20 mg (75%) of **20** as a colorless solid: mp 140−144 °C; $[\alpha]_D^{23}$ +80.8 (*c* 0.73, $CHCl_3$); IR (neat) 3306, 2915, 1758, 1240, 1142, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 3H), 3.89−3.94 (m, 1H), 4.02 (t, J = 6 Hz, 1H), 4.41 (dd, J = 5.9 Hz, 1H), 4.47 (t, J = 7 Hz, 1H), 5.41−5.47 (m, 3H), 5.62−5.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.3, 55.4, 67.1, 78.7, 94.1, 122.3, 133.1, 159.5; MS (CI) m/z 188 ($M^+ + 1$), 170, 158, 156, 140, 126, 82; HRMS (CI) m/z 188.0923 (calcd for $C_8H_{14}NO_4$: 188.0928).

4-Pentenyl 4-Methylbenzenesulfonate (22). A solution of 4-penten-1-ol (**21**, 45 mL, 0.24 mmol), *p*-toluenesulfonyl chloride (81.2 mg, 0.426 mmol), triethylamine (77 mL, 0.55 mmol), DMAP (4 mg), and $CHCl_3$ (2 mL) was stirred for 3 h at ambient temperature. An aqueous solution of HCl (5%, 2 mL) was added, and the organic phase was separated, washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield pure as an oil **22**: IR (neat) 3070, 2911, 1648, 1604, 1360, 1177, 1097, 988, 928, 824 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68−1.76 (m, 2H), 201−2.10 (m, 2H), 2.44 (s, 3H), 4.02 (t, J = 6 Hz, 1H), 4.93 (s, 1H), 4.95−4.97 (m, 1H), 5.63−5.73 (m, 1H), 7.34 (d, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 28.2, 29.5, 70.0, 116.0, 128.1, 130.0, 133.4, 136.1, 144.9; MS (CI) m/z 3070, 2911, 1648, 1604, 1360, 1177, 1097, 988, 928, 824; HRMS (CI) m/z 241.0899 (calcd for $C_{12}H_{17}O_3S$: 241.0894). This compound was used immediately for alkylation of **20**.

(4*R*)-4-[(1*S*)-1-(Methoxymethoxy)-2-propenyl]-3-(4-pentenyl)-1,3-oxazolidin-2-one (23). To a solution of **20** (7.3 mg, 0.039 mmol) in dry THF (2 mL) were added NaH (50 wt % dispersion in mineral oil, 8 mg, 0.390 mmol), tetra-*n*-butylammonium iodide (1 mg), and **22** (12.2 mg, 0.055 mmol). The mixture was stirred for 16 h at 70 °C, and the reaction was quenched with a saturated solution of NH_4Cl. The organic phase was separated, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (2 g of silica gel, EtOAc−hexane, 3:1) yielded 7.0 mg (70%) of **23** as a colorless oil: $[\alpha]_D^{23}$ +91.3 (*c* 0.53, $CHCl_3$); IR (neat) 2920, 1753, 1435, 1235, 1167, 1044, 922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61−1.79 (m, 2H), 2.08−2.13 (q, J = 7 Hz, 1H), 2.99−3.19 (m, 1H), 3.32 (s, 3H), 3.58−3.66 (m, 1H), 3.85−3.89 (m, 1H), 4.21−4.29 (m, 3H), 4.55 (d, J = 7 Hz, 1H), 4.69 (d, J = 7 Hz, 1H), 4.99−5.08 (m, 2H), 5.39−5.45 (m, 2H), 5.62−5.71 (m, 1H), 5.79−5.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 26.4, 31.0, 41.7, 56.2, 57.8, 62.8, 75.0, 94.4, 115.6, 120.7, 133.0, 137.6, 158.6; MS (CI) m/z 256 ($M^+ + 1$), 226, 224, 196, 194, 180, 170, 156, 154, 126, 110, 100, 95, 86; HRMS (CI) m/z 256.1550 (calcd for: $C_{13}H_{22}NO_4$: 256.1549).

(10*S*,10a*R*)-10-(Methoxymethoxy)-1,5,6,7,10,10a-hexahydro[1,3]oxazolo[3,4-*a*]azocin-3-one (25). To a solution of **23** (6.30 mg, 0.025 mmol) in CH_2Cl_2 (4 mL) under an argon

atmosphere was added Grubbs's catalyst (**24**, 4.5 mg, 5.50 mmol), and the mixture was stirred for 18 h at 60 °C. The mixture was concentrated under reduced pressure, and the residue was chromatographed (3 g of silica gel, EtOAc−hexane, 1:1) to give 4.12 mg (75%) of **25** as a colorless oil: $[\alpha]_D^{23}$ +89.7 (*c* 0.38, $CHCl_3$); IR (neat) 2931, 2847, 1758, 1455, 1420, 1375, 1241, 1162, 1112, 1042, 993 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40−1.48 (m, 1H), 2.10−2.31 (m, 3H), 2.85−2.93 (m, 1H), 3.42 (s, 3H), 3.46−3.52 (m, 1H), 3.73 (dd, J = 5, 14 Hz, 1H), 4.29 (dd, J = 5, 9 Hz, 1H), 4.38−4.46 (m, 2H), 4.78 (d, J = 7 Hz, 1H), 4.57 (d, J = 6 Hz, 1H), 5.58 (dd, J = 6 Hz, 1H), 5.77−5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) d 24.0, 26.5, 42.9, 56.5, 61.3, 66.8, 76.1, 94.9, 131.8, 132.2, 159.1; MS (CI) *m*/*z* 228 (M^+ + 1), 214, 198, 194, 182, 166, 154, 138, 122, 97, 83; HRMS (CI) *m*/*z* 228.1236 (calcd for $C_{11}H_{18}NO_4$: 228.1236).

(10*S*,10a*R*)-10-Hydroxy-1,5,6,10,10a-hexahydro[1,3]-oxazolo[3,4-*a*]azocin-3-one (26). To a solution of **25** (6.0 mg, 0.026 mmol) in CH_3CN (1 mL) was added an aqueous solution of HBr (48%, 1 drop), and the mixture was stirred for 2 h at ambient temperature. The mixture was neutralized with solid $NaHCO_3$ and filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (2 g of silica gel, EtOAc−hexane, 2:1) to furnish 4.5 mg (94%) of **26** as a colorless oil: $[\alpha]_D^{23}$ +28.6 (*c* 1.26, $CHCl_3$); IR (neat) 3321, 2935, 1738, 1465, 1377, 1245, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37−1.47 (m, 1H), 2.08−2.24 (m, 3H), 2.17 (s, 3H), 2.58 (br s, 1H), 2.85−2.95 (m, 1H), 3.39−3.47 (m, 1H), 3.69 (dd, J = 5, 14 Hz, 1H), 33.39−4.46 (m, 2H), 5.64−5.72 (m, 2H); ^{13}C NMR (75 MHZ, $CDCl_3$) δ 23.9, 26.3, 42.7, 62.4, 67.0, 71.7, 129.9, 134.2, 159.4; MS (CI) *m*/*z* 184 (M^+ + 1), 170, 140, 122, 96, 88, 70; HRMS (CI) *m*/*z* 184.0971 (calcd for $C_9H_{14}O_3N$: 184.0974).

(1a*R*,8a*R*,9*R*,9a*S*)-9-Hydroxyoctahydro[1,3]oxazolo[3,4-*a*]oxireno[2,3-*d*]azocin-6-one (27). To a solution of **26** (12.0 mg, 0.066 mmol) in CH_2Cl_2 (2 mL) was added *m*-chloroperoxybenzoic acid (50 wt %, 56.5 mg, 0.162 mol), and the mixture was stirred for 7 h at ambient temperature. Methyl sulfide (50 μL) and solid $NaHCO_3$ (40 mg) were added, and the reaction was stirred for a further 1 h at ambient temperature. The mixture was filtered through a short column of silica gel, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (2 g of silica gel, EtOAc−hexane, 3:1) gave 9.6 mg (74%) of **27** as a colorless crystalline solid: $[\alpha]_D^{23}$ +34.2 (*c* 0.88, CH_3CN); IR (neat) 3292, 2915, 1714, 1450, 1264, 1250, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.19−1.38 (m, 1H), 1.61−1.68 (m, 1H), 2.14−2.23 (m, 1H), 2.96−3.04 (m, 2H), 3.06−3.11 (m, 1H), 3.59 (dd, J = 7, 10 Hz, 1H), 3.66−3.72 (m, 1H), 3.88 (dd, J = 5, 14 Hz, 1H), 4.35 (dd, J 6, 9 Hz, 1H), 4.46 (t, J = 9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 23.7, 43.9, 55.2, 58.4, 59.2, 65.8, 74.8, 158.9; HRMS (CI) *m*/*z* 200.0925 (calcd for $C_9H_{14}NO_4$: 200.0923).

(1a*R*,8a*R*,9*R*,9a*R*)-9-(Benzyloxy)octahydro[1,3]oxazolo-[3,4-*a*]oxireno[2,3-*d*]azocin-6-one (28). A mixture of **27** (3.0 mg, 0.015 mmol), benzyl bromide (20 mL, 0.168 mmol), and tetra-*n*-butylammonium iodide (1 mg) in THF (2 mL) was stirred for 4 h at ambient temperature. A saturated solution of NH_4Cl was added, and the product was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (3 g of silica gel, EtOAc−hexane, 1:1) produced 4.3 mg (98%) of **28** as colorless prisms: mp 78−80 °C; $[\alpha]_D^{23}$ +64.2 (*c* 0.24, $CHCl_3$); IR (neat) 2911, 2842, 1763, 1454, 1426, 1377, 1259, 1147, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20−1.31 (m, 1H), 1.61−1.70 (m, 2H), 2.05−2.23 (m, 2H), 2.96−3.05 (m, 2H), 3.36 (dd, J = 7, 10 Hz, 1H), 3.69−3.75 (m, 1H), 3.88 (dd, J = 5, 14 Hz, 1H), 4.15 (dd, J = 6, 9 Hz, 1H), 4.43 (t, J = 9 Hz, 1H), 4.61 (d, J = 11 Hz, 1H), 4.90 (d, J = 11 Hz, 1H), 7.31−7.53 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 23.7, 44.1, 53.0, 57.1, 58.7, 66.2, 71.9, 80.6, 127.9, 128.4, 128.5, 128.8, 137.2, 158.8; HRMS (CI) *m*/*z* 290.1389 (calcd for $C_{16}H_{20}NO_2$: 290.1391).

(1*R*,2*R*,3*R*,7a*S*)-Benzyloxy-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2-diol (29). To a solution of **28** (2.5 mg, 8.6 mmol) in a EtOH−H_2O mixture (0.5 mL) was added LiOH (3.6 mg, 0.086 mmol), and the solution was stirred for 24 h at 96 °C. The mixture was concentrated under reduced pressure and was extracted with $CHCl_3$ (5 × 0.5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 2.2 mg (92%) of **29** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.80−1.89 (m, 1H), 1.91−2.07 (m, 3H), 2.84−2.94 (m, 1H), 3.01 (q, J = 8 Hz, 1H), 3.24 (br s, 1H), 3.55−3.67 (m, 1H), 3.73 (dd, J = 6, 12 Hz, 1H), 3.89 (dd, J = 3, 12 Hz, 1H), 3.95−3.96 (m, 1H), 4.08−4.09 (m, 1H), 4.61 (d, J = 12 Hz, 1H), 4.66 (d, J = 12 Hz, 1H), 7.28−7.37 (m, 5H); HRMS (CI) *m*/*z* 280.1548 (calcd for $C_{15}H_{22}NO_3$: 280.1548).

2-[(4*S*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]acetic Acid (31). To a solution of (*S*)-malic acid (**30**, 300 mg, 2.24 mmol) in 2,2-dimethoxypropane (20 mL) was added camphorsulfonic acid (10 mg), and the mixture was stirred for 18 h at room temperature. Sodium acetate was added to the mixture, and stirring was continued for a further 1 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. Crystallization of the residue from a $CHCl_3$−hexane mixture afforded 331 mg (85%) of **31** as a colorless oil: $[\alpha]_D^{23}$ +4.0 (2.82 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.63 (s, 3H), 2.86 (dd, J = 7, 18 Hz, 1H), 3.00 (dd, J = 4, 21 Hz, 1H), 4.72 (dd, J = 4, 7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 27.0, 36.2, 70.6, 111.6, 172.0, 174.9; MS (CI) *m*/*z* 175 (M^+ + 1), 157, 147, 131, 117, 103, 89; HRMS (CI) *m*/*z* 175.0606 (calcd for $C_7H_{11}O_5$: 175.0606).

(3*S*)-3-Hydroxydihydro-2(3*H*)-furanone (32). To a solution of **31** (2.00 g, 11.5 mmol) in THF (150 mL) maintained at 0 °C was added a 1 M solution of BH_3 in THF (14.0 mL, 14.0 mmol) dropwise over 45 min. The mixture was stirred for 2 h at 0 °C and for 18 h at room temperature, MeOH (30 mL) was added, and the mixture was stirred for a further 1 h at room temperature. Volatiles were removed under reduced pressure, the residue was dissolved in $CHCl_3$ (40 mL), and camphorsolfonic acid (1 g) was added. The mixture was stirred for 10 h at room temperature and filtered, and the filtrate was concentrated under reduced pressure. Chromatogaphy of the residue (80 g of silica gel, EtOAc−hexane, 2:1) gave 0.840 g (72%) of **32** as a colorless oil: $[\alpha]_D^{23}$ −69.7 (*c* 0.93, $CHCl_3$); IR (neat) 3413, 2916, 1773, 1231, 1181, 1132, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.22−2.39 (m, 1H), 2.56−2.66 (m, 1H), 4.19−4.28 (m, 1H), 4.40−4.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.0, 65.4, 67.6, 178.3; MS (CI) *m*/*z* 103 (M^+ + 1), 91, 85, 75, 71; HRMS (CI) *m*/*z* 103.0396 (calcd for $C_4H_7O_3$: 103.0395).

(3*S*)-3-(Methoxy)dihydro-2(3*H*)-furanone (33). To a solution of **32** (120 mg, 1.17 mmol) and dimethoxymethane (1.00 mL, 11.3 mmol) in $CHCl_3$ (5 mL) was added P_2O_5 (ca. 50 mg), and the mixture was stirred for 5 h at room temperature. The organic phase was separated, neutralized with with solid $NaHCO_3$, and filtered. The filtrate was concentrated under reduced presure, and the residue was chromatographed (15 g of silica gel, EtOAc−hexane, 1:3) to furnish 165 mg (96%) of **33** as a colorless oil: $[\alpha]_D^{23}$ −122.4 (*c* 2.59, $CHCl_3$); IR (neat) 2935, 1792, 1460, 1391, 1240, 1157, 1064, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23−2.36 (m, 1H), 2.53−2.63 (m, 1H), 3.43 (s, 3H), 4.20−4.28 (m, 1H), 4.40−4.47 (m, 2H), 4.72 (d, J = 7 Hz, 1H), 4.96 (d, J = 7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 56.1, 65.3, 70.4, 96.1, 175.1; MS (CI) *m*/*z* 147 (M^+ + 1), 130, 117, 115, 87, 71; HRMS (CI) *m*/*z* 147.0657 (calcd for $C_6H_{11}O_4$: 147.0657).

(3*S*)-3-(Methoxymethoxy)tetrahydro-2-furanol (34). To a solution of **33** (0.880 g, 5.47 mmol) in dry CH_2Cl_2 (30 mL) maintained at −78 °C was added a 1.5 M solution of DIBALH in toluene (4.0 mL, 6 mmol), and the mixture was stirred for 30 min at −78 °C. Solid NH_4Cl (0.4 g) and MeOH (1 drop) were added, and the mixture was filtered through a short column of silica gel which was subsequently rinsed with a EtOAc−MeOH (5%) mixture. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (20 g of silica gel, EtOAc−hexane, 1:1) to afford 0.621 g (76%) of **34** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.91−2.30

(m, 4H), 3.38 (s, 3H), 3.41 (s, 3H), 3.80−3.88 (m, 1H), 4.01−4.17 (m, 5H), 4.66 (s, 2), 4.68−4.74 (m, 2H), 5.31 (d, J = 4 Hz, 1H), 5.40 (s, 1H). This material was used immediately for the conversion to **35**.

(3*S*)-3-(Methoxymethoxy)-4-penten-1-ol (35). To a suspension of methyltriphenylphosphonium bromide (222 mg, 0.62 mmol) in THF (40 mL) maintained at 0 °C under an argon atmosphere was added a 0.5 M solution of KHMDS in toluene (1.86 mL, 0.93 mmol), and the mixture was stirred for 30 min at 0 °C. The mixture was then cooled to −78 °C, and a solution of **34** (85.2 mg, 0.380 mmol) in THF (0.5 mL) was added. The mixture was stirred for 10 h at room temperature, and the reaction was quenched with a saturated solution of NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (4 g of silica gel, EtOAc−hexane, 1:3) gave 142.4 mg (65%) of **35** as a colorless oil: $[\alpha]_D^{23}$ −120.5 (*c* 1.25, $CHCl_3$); IR (neat) 3424, 2955, 2891, 1650, 1474, 1162, 1108, 1040, 927 cm^{-1}; ^1H NMR((300 MHz, $CDCl_3$) δ 1.84 (q, J = 6 Hz, 2H), 2.01 (br s, 1H), 3.41 (s, 3H), 3.72−3.87 (m, 2H), 4.27 (q, J = 6 Hz, 1H), 4.57 (d, J = 7 Hz, 1H), 4.72 (d, J = 7 Hz, 1H), 5.20−5.29 (m, 2H), 5.68−5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9, 55.8, 60.2, 76.5, 94.2, 117.6, 137.8; HRMS (CI) *m*/*z* 146.0941 (calcd for $C_7H_{14}O_3$: 146.0942);

(3*S*)-3-(Methoxymethoxy)-4-pentenyl 4-Methylbenzenesulfonate (36). A solution of **35** (151 mg, 1.03 mmol), *p*-toluenesulfonyl chloride (0.197 g, 1.03 mmol), DMAP (10 mg), and triethylamine (0.216 mL, 1.54 mmol) in dry CH_2Cl_2 (20 mL) was stirred for 3 h at ambient temperature. An aqueous solution of HCl (2%, 15 mL) was added, and the organic phase was separated, washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (20 g of silica gel, EtOAc−hexane, 1:3) afforded 284 mg (92%) of **36** as a colorless oil: $[\alpha]_D^{23}$ −51.6 (*c* 1.29, $CHCl_3$); IR (neat) 2950, 2876, 1596, 1357, 1192, 1040, 922, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79−2.01 (m, 2H), 2.46 (s, 3H), 3.30 (s, 3H), 4.06−4.25 (m, 3H), 4.47 (d, J = 7 Hz, 1H), 4.63 (d, J = 7 Hz, 1H), 5.15−5.21 (m, 2H), 5.55−5.67 (m, 1H), 7.35 (d, J = 8 Hz, 2H), 7.80 (d, J = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 34.9, 55.8, 67.2, 73.6, 94.1, 118.5, 128.1, 130.0, 133.3, 137.2, 145.0; MS (CI) *m*/*z* 301 (M^+ + 1), 239, 215, 201, 173, 155, 99, 68; HRMS (CI) *m*/*z* 301.1109 (calcd for $C_{14}H_{21}O_5S$: 301.1109).

(4*R*)-3-[(3*S*)-3-(Methoxymethoxy)-4-pentenyl]-4-[(1*S*)-1-(methoxymethoxy)-2-propenyl]-1,3-oxazolidin-2-one (37). To a solution of **20** (5.0 mg, 0.027 mmol) in benzene (0.5 mL) were added NaH (50 wt % dispersion in mineral oil, 6.4 mg, 0.133 mmol), tetra-*n*-butylammonium bromide (ca. 1 mg), and a solution of **36** (12.7 mg, 0.035 mmol) in benzene (0.1 mL). The resulting mixture was refluxed for 10 h, after which the volatiles were removed under reduced pressure, and the residue was chromatographed (4 g of silica gel, EtOAc−hexane, 1:5) to yield 7.1 mg (84%) of **37** as a colorless oil: $[\alpha]_D^{23}$ +39.9 (*c* 3.03, $CHCl_3$); IR (neat) 2920, 1758, 1426, 1235, 1152, 1108, 1030, 927 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.84−1.93 (q, J = 8 Hz, 2H), 3.17−3.32 (m, 1H), 3.36 (s, 3H), 3.39 (s, 3H), 3.67−3.79 (m, 1H), 3.86−3.97 (m, 1H), 4.21−4.32 (m, 3H), 4.57 (d, J = 7 Hz, 2H), 4.70 (d, J = 7 Hz, 2H), 5.21−5.33 (m, 2H), 5.37−5.48 (m, 2H), 5.60−5.79 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.9, 38.9, 55.8, 56.1, 58.0, 62.9, 75.1, 75.6, 94.2, 94.4, 118.1, 120.7, 132.9, 137.5, 158.5; MS (CI) *m*/*z* 316 (M^+ + 1), 284, 254, 240, 210, 184, 170, 156, 130, 100; HRMS (CI) *m*/*z* 316.1760 (calcd for $C_{15}H_{26}NO_6$: 316.1760).

(4*R*)-3-[(3*S*)-3-Hydroxy-4-pentenyl]-4-[(1*S*)-1-hydroxy-2-propenyl]-1,3-oxazolidin-2-one (38). To a solution of **37** (36 mg, 0.114 mmol) in CH_3CN (3 mL) was added an aqueous solution of HBr (48%, 3 drops), and the mixture was stirred for 1 h at ambient temperature. Solid $NaHCO_3$ (20 mg) was added, and stirring was continued for 30 min. The mixture was filtered through a short column of silica gel, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (5 g of silica gel, EtOAc−hexane, 5:1) gave 16 mg (93%) of **38** as a colorless oil: $[\alpha]_D^{23}$ +11.4 (*c* 1.63, $CHCl_3$); IR (neat) 3420, 2956, 1730, 1432, 1273, 1155, 1026, 934 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17−1.81 (m, 1H), 1.85−1.93 (m, 1H), 3.03 (br s, 2H), 3.47 (t, J = 7 Hz, 1H), 3.87−3.91 (m, 1H), 4.18−4.27 (m, 3H), 4.45−4.46 (m, 1H), 5.12 (d, J = 10 Hz, 1H), 5.25−5.32 (m, 2H), 5.47 (dd, J = 1, 18 Hz, 1H), 5.72−5.80 (m, 1H), 5.87−5.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.0, 40.0, 60.2, 69.9, 70.7, 115.0, 118.3, 135.0, 140.4, 159.8; MS(CI) *m*/*z* 228 (M^+ + 1), 210, 170, 156, 144, 116, 112, 88, 71. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.90; H, 7.59; N, 6.42.

(3*S*)-3-[(4-Methoxybenzyl)oxy]dihydro-2(3*H*)-furanone (39). To a solution of **32** (59.2 mg, 0.405 mmol) and *p*-methoxybenzyl 2,2,2-trichloroacetimidate (228 mg, 0.810 mmol) in dry CH_2Cl_2 (10 mL) was added a 1 M solution of trifluoromethanesulfonic acid in CH_2Cl_2 (12 μL, 0.0120 mmol), and the mixture was stirred for 4 h at ambient temperature. The reaction was neutralized with solid $NaHCO_3$ (10 mg), the mixture was filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (12 g of silica gel, EtOAc−hexane, 1:3) gave 83 mg (92%) of **39** as a colorless oil: $[\alpha]_D^{23}$ −56.3 (*c* 4.73 $CHCl_3$); IR (neat) 2925, 1772, 1733, 1611, 1513, 1259, 1176, 1137, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.20−2.32 (m, 1H), 2.38−2.49 (m, 1H), 3.81 (s, 3H), 4.13−4.25 (m, 2H), 4.41 (dt, J = 4, 8 Hz, 1H), 4.67 (d, J = 11 Hz, 1H), 4.87 (d, J = 11 Hz, 1H), 6.89−6.92 (m, 2H), 7.30−7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 55.5, 65.7, 72.0, 72.2, 113.9, 114.1, 129.1, 130.1, 159.7, 175.3; MS (CI) *m*/*z* 222 (M^+ + 1), 162, 137, 126, 121, 98; HRMS (CI) *m*/*z* 222.0891 (calcd for $C_{12}H_{14}O_4$: 222.0892).

(3*S*)-3-[4-Methoxybenzyl)oxy]tetrahydro-2-furanol (40). To a solution of **39** (93.6 mg, 0.412 mmol) in CH_2Cl_2 (15 mL) maintained at −78 °C was added a 1 M solution of DIBALH in hexanes (0.50 mL, 0.50 mmol), and the mixture was stirred for 30 min at −78 °C. Solid NH_4Cl and MeOH (1 drop) were added, and the mixture was filtered through a short column of silica gel, which was subsequently rinsed with a EtOAc−MeOH (5%) mixture. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (10 g of silica gel, EtOAc−hexane, 1:1) to afford 57.3 mg (60%) of **40** as a colorless oil: IR (neat) 3404, 2890, 16116, 1518, 1255, 1127, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92−2.25 (m, 4H), 3.79 (s, 3H), 3.80 (s, 3H), 3.97−4.09 (m, 4H), 4.48−4.56 (m, 4H), 5.30 (d, J = 4 Hz, 1H), 5.41 (s, 1H), 6.85−6.91 (m, 2H), 7.25−7.28 (m, 2H). This material was used immediately for the conversion to **41**.

(3*S*)-3-[(4-Methoxybenzyl)oxy]-4-penten-1-ol (41). To a stirred suspension of methyltriphenylphosphonium bromide (271 mg, 0.760 mmol) in THF (20 mL) cooled to 0 °C was added a 0.5 M solution of KHMDS in toluene (2.3 mL, 1.13 mmol), and the mixture was stirred for 30 min at 0 °C. The solution was then cooled to −78 °C, and a solution of **40** (85.2 mg, 0.380 mmol) in THF (0.5 mL) was added. The mixture was allowed to warm to ambient temperature, was stirred for 18 h, and then was quenched with a saturated solution of NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 × 8 mL), and the combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (4 g of silica gel, EtOAc−hexane, 1:3) gave 180.0 mg (67%) of **41** as a colorless oil: $[\alpha]_D^{23}$ −56.0 (*c* 1.42, $CHCl_3$); IR (neat) 3412, 2929, 1624, 1513, 1248, 1039, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74−1.92 (m, 2H), 2.15 (br s, 1H), 3.69−3.78 (m, 2H), 3.81 (s, 3H), 3.97−4.05 (m, 1H), 4.30 (d, J = 11 Hz, 1H), 4.57 (d, J = 11 Hz, 1H), 5.25 (s, 1H), 5.29−5.30 (m, 1H), 5.74−5.86 (m, 1H), 8.87−6.90 (m, 2H), 7.24−7.27 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9, 55.5, 60.9, 70.1, 79.8, 114.1, 117.6, 129.6, 130.1, 130.4, 138.4, 159.4; MS (CI) *m*/*z* 222 (M^+ + 1), 203, 175, 149, 137, 121, 109, 85; HRMS (CI) *m*/*z* 222.1256 (calcd for $C_{13}H_{18}O_3$: 222.1256).

***tert*-Butyl (4*R*)-4-{(1*S*)-1-[(*tert*-Butoxycarbonyl)oxy]-2-propenyl}-2-oxo-1,3-oxazolidine-3-carboxylate (43).** To a solution of **19** (8.2 mg, 0.057 mmol) in CH_2Cl_2 (0.5 mL) were added triethylamine (18 mL, 0.129 mmol), di-*tert*-butyl carbon-

ate (41.2 mL, 0.183 mmol), and DMAP (2 mg), and the mixture was stirred for 1 h at room temperature. The solution was concentrated under reduced pressure, and the residue was chromatographed (1 g of silica gel, EtOAc−hexane, 1:8) to give 18.4 mg (93%) of **43** as a colorless oil: $[\alpha]_D^{23}$ +47.7 (*c* 1.36, $CHCl_3$); IR (neat) 2979, 2935, 1826, 1796, 1752, 1371, 1279, 1254, 1162, 1132, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.57 (s, 9H), 4.24 (d, J = 9 Hz, 1H), 4.33 (d, J = 9 Hz, 1H), 4.34 (d, J = 9 Hz, 1H), 4.37−4.42 (m, 1H), 5.37 (d, J = 10 Hz, 1H), 5.41−5.49 (m, 1H), 5.72−5.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 28.1, 56.9, 61.7, 74.0, 83.5, 84.5, 119.6, 131.2, 149.2, 151.9, 152.8; MS (CI) *m*/*z* 344 (M^+ + 1), 321, 232, 216, 188, 170, 144, 126, 86; HRMS (CI) *m*/*z* 344.1707 (calcd for $C_{16}H_{26}NO_7$: 344.1709).

***tert*-Butyl (1*R*,2*S*)-2-Hydroxy-1-(hydroxymethyl)-3-butenylcarbamate (44).** To a solution of **43** (13.6 mg, 0.039 mmol) in dry EtOH (1 mL) was added a 2 M solution of NaOEt in EtOH (60 μL, 0.120 mmol), and the mixture was stirred for 7 h at ambient temperature. The reaction was quenched with solid NH_4Cl (40 mg), the mixture was filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (1.5 g of silica gel, EtOAc−hexane, 2:1) yielded 6.2 mg (72%) of **44** as a colorless oil: $[\alpha]_D^{23}$ −5.4 (*c* 1.10, $CHCl_3$); IR (neat) 3389, 2972, 2928, 1703, 1512, 1368, 1262, 1162, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.08 (br s, 2H), 3.63 (s br, 1H), 3.68−3.71 (m, 1H), 3.92 (dd, J = 4, 11 Hz, 1H), 4.36 (br s, 1H), 5.24−5.27 (m, 1H), 5.36−5.41 (m, 1H), 5.42 (br s, 1H), 5.88−5.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 55.0, 62.3, 74.7, 116.5, 137.4, 156.2; MS (CI) *m*/*z* 218 (M^+ + 1), 202, 188, 172, 162, 144, 118, 114, 104, 100; HRMS (CI) *m*/*z* 218.1391 (calcd for $C_{10}H_{20}NO_4$: 218.1392).

***tert*-Butyl (2*R*,4*S*,5*R*)-2-Phenyl-4-vinyl-1,3-dioxan-5-ylcarbamate (45).** A solution of **44** (19.0 mg, 0.087 mmol), benzaldehyde dimethylacetal (26.2 μL, 0.1.75 mmol), and camphorsulfonic acid (2 mg) in CH_2Cl_2 (1 mL) was stirred for 6 h at ambient temperature. $NaHCO_3$ (10 mg) was added, and the mixture was stirred for a further 1 h and was filtered. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (2 g of silica gel, EtOAc−hexane, 1:10) to afford 24.2 mg (96%) of **45** as a colorless oil: $[\alpha]_D^{23}$ −29.6 (*c* 1.55, $CHCl_3$); IR (neat) 3360, 2979, 1694, 1528, 1308, 1235, 1171, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 3.58−3.65 (m, 1H), 3.73 (br s, 1H), 4.31 (d, J = 8 Hz, 1H), 4.38 (dd, J = 5, 10 Hz, 1H), 5.31 (dd, J = 1, 10 Hz, 1H), 5.43 (d, J = 17 Hz, 1H), 5.23 (s, 1H), 5.92−6.09 (m, 1H), 7.32−7.41 (m, 3H), 7.50−7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 47.9, 70.1, 82.3, 101.2, 119.2, 126.4, 128.5, 129.2, 134.7, 137.8; MS (CI) *m*/*z* 250, 172, 151, 144, 107, 83, 69; HRMS (CI) *m*/*z* 306.1703 (calcd for $C_{17}H_{24}dNO_4$: 306.1705).

***tert*-Butyl (3*S*)-3-[(4-Methoxybenzyl)oxy]-4-pentenyl-[(4*S*,5*R*)-2-phenyl-4-vinyl-1,3-dioxolan-5-yl]carbamate (46).** To a solution of **41** (10 mg, 0.045 mmol) in triethylamine (31 mL, 0.225 mmol) and CH_2Cl_2 (1 mL) was added trifluoromethanesulfonic anhydride (9.8 mL, 0.058 mmol), and the mixture was stirred for 1 h at 0 °C. An aqueous solution of HCl (5%, 1 mL) was added, and the organic phase was separated, washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford 15.3 mg of **42** which was not further purified.

To a solution of **45** (3.8 mg, 0.013 mmol) in THF (0.5 mL) was added NaH (50 wt % dispersion in mineral oil, 6.2 mg, 0.14 mmol), and the mixture was stirred at room temperature for 1 h. The solution was cooled to −78 °C, and a solution of **42** (5.1 mg, 0.019 mmol) in THF (0.2 mL) was added. The mixture was warmed to room temperature, stirred for a further 10 h, and then was quenched with a saturated solution of NH_4Cl (0.5 mL). The mixture was extracted with CH_2Cl_2 (3 × 1 mL), and the combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (1 g of silica gel, hexanes−EtOAc, 10:1) gave 5.4 mg (82%) of **46** as a colorless oil: IR (neat) 2962, 2926, 1694, 1509, 1365, 1247, 1139, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48−1.57 (m, 9H), 1.64−1.82 (m, 2H), 2.01−2.13 (m, 2H), 2.99−3.32 (m, 2H), 3.62−3.73 (br s, 1H), 3.79 (s, 3H), 4.13 (br s, 1H), 4.24 (d, J = 11 Hz, 1H), 4.52 (d, J = 11 Hz, 1H), 5.25 (d, J = 10 Hz, 1H), 5.33 (d, J = 15 Hz, 1H), 5.36 (d, J = 15 Hz, 1H), 5.50−5.69 (m, 2H), 5.84−5.95 (m, 1H), 6.88 (d, J = 8 Hz, 2H), 7.26 (d, J = 8 Hz, 2H), 7.35−7.37 (m, 3H), 7.49−7.51 (m, 2H); HRMS (CI) *m*/*z* 494.2909 (calcd for $C_{30}H_{40}NO_5$: 494.2906).

(4*S*,5*R*)-5-[4*S*)-3-Benzyl-2-oxo-1,3-oxazolidin-4-yl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (47). To a solution of oxalyl chloride (22.0 mL, 0.252 mmol) in CH_2Cl_2 (0.5 mL) maintained at −78 °C was added a solution of DMSO (32.8 mL, 0.462 mmol) in CH_2Cl_2 (0.5 mL), followed after 2 min by a solution of **15** (64.5 mg, 0.210 mmol) in CH_2Cl_2 (0.1 mL). The mixture was stirred for 30 min at −78 °C, and triethylamine (0.146, 0.0105 mmol) was added. Stirring was continued for 2 h at −78 °C, and the mixture was concentrated under reduced pressure. The residue was taken up into EtOAc (15 mL), and the solution was filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (12 g of silica gel, EtOAc−hexane, 1:1) to afford 47.4 mg (74%) of **47** as a colorless oil: $[\alpha]_D^{23}$ −27.0 (*c* 2.52, $CHCl_3$); IR (neat) 2988, 2935, 1752, 1435, 1264, 1220., 1103, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.61 (s, 3H), 3.94−3.98 (m, 1H), 4.06 (d, J = 6 Hz, 1H), 4.28−4.36 (m, 4H), 4.90 (d, J = 15 Hz, 1H), 7.31−7.50 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.4, 47.1, 54.8, 62.6, 76.1, 80.6, 111.9, 128.1, 128.9, 129.1, 135.7, 158.7, 202.3; MS (CI) *m*/*z* 306 (M^+ + 1), 304, 248, 178, 176, 95, 91, 89, 83, 73; HRMS (CI) *m*/*z* 306.1343 (calcd for $C_{16}H_{20}NO_5N$: 306.1341).

(4*S*)-3-Benzyl-4-[(4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one (48). To a suspension of methyltriphenylphosphonium bromide (83.6 mg, 0.178 mmol) in THF (15 mL) was added a 1.6 M solution of *n*-BuLi in hexanes (0.11 mL, 0.18 mmol), and the resulting solution was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C, and a solution of **47** (27.2 mg, 0.089 mmol) in THF (0.1 mL) was added. The mixture was gradually warmed to 60 °C, stirred for a further 18 h, and then diluted with EtOAc (20 mL) and filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (5 g of silica gel, EtOAc−hexane, 1:7) to give 17.2 mg (64%) of **48** as a colorless oil: $[\alpha]_D^{23}$ −22.7 (*c* 2.37, $CHCl_3$); IR (neat) 2979, 1762, 1430, 1235, 1083, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.46 (s, 3H), 3.77−3.82 (m, 1H), 3.90 (dd, J = 2, 8 Hz, 1H), 4.01 (t, J = 8 Hz, 1H), 4.20−4.31 (m, 3H), 4.84 (d, J = 15 Hz, 1H), 5.27 (d, J = 16 Hz, 1H), 5.31 (d, J = 23 Hz, 1H), 5.69−5.80 (m, 1H), 7.29−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 27.0, 47.0, 53.6, 62.5, 78.4, 78.5, 110.0, 120.2, 128.2, 128.4, 130.0, 134.7, 135.9, 158.5; MS (CI) *m*/*z* 304 (M^+ + 1), 246, 176, 127, 61; HRMS (CI) *m*/*z* 304.1549 (calcd for $C_{17}H_{22}NO_4$: 304.1549).

(4*R*)-4-[(1*S*,2*E*)-1-Hydroxy-2-butenyl]-1,3-oxazolidin-2-one (49). Anhydrous ammonia (7 mL) was condensed into a 25 mL two-necked flask containing a solution of **48** (44.0 mg, 0.145 mmol) in THF (0.5 mL) maintained at −78 °C. Sodium metal was added to the solution until a blue color persisted, and the solution was stirred for 2 h at −78 °C. The reaction was quenched with solid NH_4Cl, the ammonia was evaporated, and the residue was extracted with a EtOAc−MeOH (5%) mixture (3 × 5 mL). The combined extracts were filtered through a short column of silica gel, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (2 g of silica gel, EtOAc−hexane, 1:1) yielded 15.1 mg (66%) of **49** as a colorless oil: $[\alpha]_D^{23}$ +0.1 (*c* 0.90, $CHCl_3$); IR (neat) 3326, 2925, 1748, 1421, 1250, 1157, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, 3H), 3.14 (br s, 1H), 3.84−3.90 (m, 1H), 4.12 (br s, 1H), 4.31−4.44 (m, 2H), 5.40 (ddd, J = 2, 7, 8 Hz, 1H), 5.79−5.91 (m, 1H), 6.23 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 56.5, 66.6, 73.3, 128.1, 131.2, 160.7; MS (CI) *m*/*z* 158 (M^+ + 1), 140, 128, 114, 96, 86, 71; HRMS (CI) *m*/*z* 158.0817 (calcd for $C_7H_{12}NO_3$: 158.0817).

{(2*S*,3*R*)-3-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]oxiranyl}methyl 3-Butenylcarbamate (50). To a solution of 4-pentenoic acid (1.03 mL, 10.0 mmol) in benzene (20 mL) were

added diphenylphosphoryl azide (1.85 mL, 8.6 mmol) and triethylamine (2.4 mL, 17.2 mmol), and the mixture was stirred for 2 h at ambient temperature. The mixture was filtered through a short column of silica gel (6 g) which was subsequently rinsed with dry benzene (20 mL). The filtrate was warmed to 90 °C and stirred for 1.5 h. The temperature of the mixture was then lowered to 60 °C, and **9** (0.50 g, 2.87 mmol) was added followed by triethylamine (1 mL). The mixture was stirred for 18 h at 60 °C and was concentrated under reduced pressure. Chromatography of the residue (40 g of silica gel, EtOAc−hexane, 1:1) furnished 0.72 g (92%) of **50** as a colorless oil: $[\alpha]_D^{23}$ −20.3 (*c* 0.69, $CHCl_3$); IR (neat) 3345, 2989, 1723, 1548, 1377, 1255, 1230, 1152, 1065 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.40 (s, 3H), 2.21−2.28 (m, 2H), 2.94−2.96 (m, 1H), 3.16−3.18 (m, 1H), 3.21−3.27 (m, 2H), 3.79−3.86 (m, 1H), 3.96 (dd, J = 6, 12 Hz, 1H), 4.02−4.11 (m, 2H), 4.35 (dd, J = 3, 12 Hz, 1H), 4.90 (br s, 1H), 5.06−5.12 (m, 2H), 5.66−5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 26.4, 34.2, 40.2, 53.0, 55.9, 64.2, 66.1, 75.1, 110.2, 117.2, 135.1, 156.0; MS (CI) *m*/*z* 272 (M^+ + 1), 256, 230, 214, 154, 117, 112, 99, 83; HRMS (CI) *m*/*z* 272.1497 (calcd for $C_{13}H_{22}NO_5$: 272.1498).

(4*R*)-3-(3-Butenyl)-4-[(2*R*)-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl](hydroxy)methyl]-1,3-oxazolidin-2-one (51). To a solution of **50** (0.72 g, 2.65 mmol) in dry THF (100 mL) was added a 1 M solution of potassium *tert*-butoxide in *tert*-BuOH (4.23 mL, 0.42 mmol), and the mixture was stirred for 2 h at −10 °C. The reaction was quenched with a saturated NH_4Cl solution (10 mL), and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (40 g of silica gel, EtOAc−hexane, 2:1) afforded 0.45 g (63%) of **51** as a pale yellow solid: mp 69−75 °C; $[\alpha]_D^{23}$ +10.1 (*c* 1.12, $CHCl_3$); IR (neat) 3399, 2984, 2930, 1738, 1445, 1377, 1264, 1226, 1167, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.45 (s, 3H), 2.29−2.42 (m, 2H), 2.72 (d, J = 6 Hz, 1H), 3.11−3.23 (m, 1H), 3.54−3.64 (m, 1H), 3.76−3.86 (m, 2H), 3.93−4.03 (m, 1H), 4.05−4.13 (m, 2H), 4.27 (t, J = 9 Hz, 1H), 4.49 (dd, J = 6, 9 Hz, 1H), 5.09 (dd, J = 1, 6 Hz, 1H), 5.14 (dd, J = 1, 6 Hz, 1H), 5.72−5.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 26.3, 32.0, 41.7, 58.6, 63.3, 66.5, 67.8, 75.8, 110.3, 117.8, 135.0, 159.0; MS (CI) *m*/*z* 272 (M^+ + 1), 242, 230, 214, 199, 153, 139, 127; HRMS (CI) *m*/*z* 272.1997 (calcd for $C_{13}H_{22}O_5$: 272.1999).

(4*R*)-3-(3-Butenyl)-4-[(4*R*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one (52). To a solution of **51** (230 mg, 0.85 mmol) in dry acetone (25 mL) was added Amberlyst 15 resin (ca. 20 mg), and the mixture was stirred for 18 h at room temperature. The mixture was filtered, and the filtrate was treated with solid $NaHCO_3$ (50 mg) and stirred for 1 h. The solution was filtered, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (40 g of silica gel, EtOAc−hexane, 1:1) gave 143 mg (62%) of **52** as a colorless solid: mp 76−80 °C; $[\alpha]_D^{23}$ +10.1 (*c* 1.12, $CHCl_3$); IR (neat) 3428, 2994, 1738, 1450, 1377, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.43 (s, 3H), 2.28−2.44 (m, 2H), 3.19−3.28 (m, 1H), 3.57−3.83 (m, 4H), 4.05 (t, J = 8 Hz, 1H), 4.21 (d, J = 8 Hz, 1H), 4.29 (d, J = 7 Hz, 2H), 5.06−5.15 (m, 2H), 5.72−5.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 27.2, 31.9, 41.9, 55.1, 62.5, 62.7, 75.7, 77.0, 110.0, 117.6, 134.9, 158.4; MS (CI) *m*/*z* 272 (M^+ + 1), 230, 214, 167, 149, 137, 113, 95, 89; HRMS (CI) *m*/*z* 272.1497 (calcd for $C_{13}H_{22}NO_5$: 272.1498).

(4*R*,5*R*)-5-[(4*R*)-3-(3-Butenyl)-2-oxo-1,3-oxazolidin-4-yl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (53). To a solution of oxalyl chloride (0.10 mL, 1.15 mmol) in CH_2Cl_2 (3.0 mL) maintained at −78 °C was added a mixture of DMSO (0.15 mL, 2.11 mmol) and CH_2Cl_2 (0.75 mL), followed after 3 min by a solution **52** (216 mg, 0.80 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 30 min at −78 °C, and triethylamine (0.15 mL, 0.010 mmol) was added. Stirring was continued for 2 h at −78 °C, and the mixture was concentrated under reduced pressure. The residue was taken up into dry EtOAc (15 mL), and the solution was filtered through a short column of silica gel. The filtrate was concentrated under reduced pressure, and the residue was chromatographed (20 g of silica gel, EtOAc−hexane, 1:1) to give 47.4 mg (59%) of **53** as a colorless oil: $[\alpha]_D^{23}$ −15.7 (*c* 1.15, $CHCl_3$); IR (neat) 2979, 2925, 1748, 1435, 1367, 1264, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.,54 (s, 3H), 2.29−2.46 (m, 2H), 3.20−3.29 (m, 1H), 3.62−3.71 (m, 1H), 4.06 (d, J = 6 Hz, 1H), 4.10−4.16 (m, 1H), 4.16−4.36 (m, 4H), 5.07−5.17 (m, 2H), 5.73−5.82 (m, 1H), 9.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.3, 31.7, 42.2, 55.3, 62.5, 76.4, 80.4, 111.9, 117.7, 134.7, 158.5, 202.7; MS (CI) *m*/*z* 270 (M^+ + 1), 228, 21, 170, 140, 129, 100; HRMS (CI) *m*/*z* 270.1340 (calcd for $C_{13}H_{20}NO_5$: 270.1341).

(4*R*)-3-(3-Butenyl)-4-[(4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]1,3-oxazolidin-2-one (54). To a suspension of methyltriphenylphosphonium bromide (443 mg, 1.24 mmol) in dry THF (5 mL) was added a 0.5 M solution of KHMDS in toluene (2.34 mL, 1.17 mmol), and the mixture was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C, and a solution of **53** (0.167 g, 0.620 mmol) in THF (1 mL) was added. The reaction was allowed to gradually warm to room temperature and was stirred for an additional 18 h. EtOAc (30 mL) was added, the solution was filtered through a short column of silica gel, and the filtrate was concentrated under reduced pressure. Chromatography of the residue (5 g of silica gel, EtOAc−hexane, 1:1) yielded 323 mg (74%) of **54** as a colorless oil: $[\alpha]_D^{23}$ +2.4 (*c* 1.51, $CHCl_3$); IR (neat) 2981, 1748, 1425, 1370, 1221, 1082, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.44 (s, 3H), 2.27−2.46 (m, 2H), 3.20−3.29 (m, 1H), 3.59−3.69 (m, 1H), 3.93 (dd, J = 2, 8 Hz, 1H), 3.98−4.09 (m, 2H), 4.20−4.31 (m, 2H), 5.06−5.14 (m, 2H), 5.34 (d, J = 21 Hz, 1H), 5.39 (d, J = 28 Hz, 1H), 5.73−5.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 26.7, 31.6, 41.8, 53.9, 62.3, 78.2, 78.8, 109.7, 117.3, 120.2, 134.6, 158.0; MS (CI) *m*/*z* 268 (M^+ + 1), 226. 210, 168, 140, 127, 97, 86, 69; HRMS (CI) *m*/*z* 268.1550 (calcd for $C_{14}H_{22}NO_4$: 268.1549).

(3a*R*,11a*R*,11b*R*)-2,2-Dimethyl-3a,6,7,11,11a,11b-hexahydro[1,3]dioxolo[4,5-*c*][1,3]oxazolo[3,4-*a*]azocin-9-one (55). To a stirred solution of **54** (6.0 mg, 0.022 mmol) in CH_2Cl_2 (4.5 mL) under an argon atmosphere was added Grubbs's catalyst (**24**, 4.6 mg, 5.6 mmol), and the mixture was stirred at room temperature for 5 h. The mixture was concentrated under reduced pressure, and the residue was chromatographed (1 g of silical gel, EtOAc−hexane, 1:2) to give 5.1 mg (90%) of **55** as a colorless oil: $[\alpha]_D^{23}$ −7.1 (*c* 1.47, $CHCl_3$); IR (neat) 2984, 1763, 1421, 1372, 1220, 1079, 874 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.43 (s, 3H), 2.36−2.56 (m, 2H), 3.15−3.24 (m, 1H), 3.57 (t, J = 9 Hz, 1H), 3.67−3.74 (m, 1H), 4.34−4.44 (m, 2H), 4.68−4.73 (m, 1H), 5.57−5.68 (m, 1H), 5.76 (dd, J = 5, 12 Hz, 1H); ^{13}C NMR (75 MHz, d_6-acetone) δ 27.0, 27.3, 29.1, 44.3, 58.0, 67.3, 77.7, 83.3, 109.8, 128.2, 130.6, 159.2; MS (CI) *m*/*z* 240.1235 (calcd for $C_{12}H_{18}NO_4$: 240.1236).

(3a*R*,3b*S*,4a*S*,10a*R*,10b*R*)-2,2-Dimethyloctahydro[1,3]dioxolo[4,5-*c*][1,3]oxazolo[3,4-*a*]oxireno[2,3-*e*]azocin-8-one (56). A solution of **55** (12.5 mg, 0.052 mmol) and *m*-chloroperoxybenzoic acid (50 wt %, 54.0 mg, 0.157 mol) in CH_2Cl_2 (0.7 mL) was stirred for 18 h at room temperature. The mixture was treated with methyl sulfide (50 μL) and a saturated solution of Na_2CO_3 (0.5 mL), and stirring was continued for 30 min. The organic phase was separated, the aqueous solution was extracted with dichloromethane (4 × 1 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed (1 g of silica gel, EtOAc−hexane, 1:1) to give 6.2 mg (64%) of **56** as colorless needles: mp 156−159 °C; $[\alpha]_D^{23}$ +2.1 (*c* 0.62, $CHCl_3$); IR (neat) 2984, 2926, 1767, 1377, 1250, 1216, 1079, 863 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.46 (s, 3H), 1.64−1.80 (m, 2H), 2.41−2.49 (m, 1H), 3.09−3.17 (m, 3H), 3.60−3.66 (m, 1H), 1.64−1.80 (m, 2H), 2.41−2.49 (m, 1H), 3.09−3.17 (m, 3H), 3.60−3.66 (m, 1H), 3.73−3.81 (m, 2H), 3.93−4.03 (m, 1H), 4.37 (dd, J = 8, 9 Hz, 1H), 4.46 (dd, J = 3, 9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 27.0, 27.6, 41.4, 52.1, 55.9, 57.2, 67.0,

78.5, 79.9, 110.6, 159.0; MS (CI) *m/z* 256 ($M^+ + 1$), 240, 198, 182, 123, 85, 83, 68; HRMS (CI) *m/z* 256.1184 (calcd for $C_{12}H_{18}NO_5$: 256.1185).

(9*R*,10*R*,10a*R*)-9,10-Dihydroxy-1,5,6,9,10,10a-hexahydro-[1,3]oxazolo[3,4-*a*]azocin-3-one (57). To a solution of **55** (170 mg, 0.797 mmol) in CH_3CN (20 mL) was added an aqueous solution of HBr (48%, 1 mL), and the mixture was stirred for 1 h at ambient temperature. Volatiles were removed under reduced pressure, and the residue was taken up into acetonitrile (20 mL). To the solution was added solid $NaHCO_3$, and the mixture was stirred for 30 min at ambient temperature and then was filtered through a short pad of silica gel which was subsequently rinsed with a EtOAc−MeOH (5%) mixture. The filtrate was concentrated under reduced pressure to leave 140 mg (99%) of **57** as a colorless oil which was not further purified: $[\alpha]_D^{23}$ +4.2 (*c* 0.67, CH_3CN); IR (neat) 3412, 2936, 1736, 1435, 1222, 1080 cm^{-1}; ^1H NMR (400 MHz, d_6-acetone) δ 2.29−2.38 (m, 2H), 3.13−3.22 (m, 2H), 3.48−3.58 (m, 3H), 3.81 (d, J = 1 Hz, 1H), 4.22−4.25 (m, 1H), 4.30 (dd, J = 8, 8 Hz, 1H), 4.41 (dd, J = 2, 8 Hz, 1H), 5.54−5.62 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 27.6, 45.1, 59.5, 69.2, 71.6, 126.9, 136.1, 161.2; MS (CI) *m/z* 200 ($M^+ + 1$), 182, 166, 149, 138, 93, 69; HRMS (CI) *m/z* 200.0923 (calcd for $C_9H_{14}O_4N$: 200.0928).

(1a*S*,7a*R*,8*R*,9*S*,9a*R*)-8,9-Dihydroxyoctahydro[1,3]-oxazolo[3,4-*a*]oxireno[2,3-*e*]azocin-5-one (58). To a solution of **57** (4.1 mg, 0.021 mmol) in THF (1 mL) was added *m*-chloroperoxybenzoic acid (50 wt %, 14 mg, 0.041 mmol), and the mixture was stirred for 7 h at ambient temperature. The mixture was treated with methyl sulfide (10 mL) and solid Na_2CO_3 (15 mg), and stirring was continued for 1 h. The suspension was filtered through a short column of silica gel, which was subsequently rinsed with a EtOAc−MeOH (5%) mixture, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (1 g of silica gel, EtOAc−MeOH, 10:1) to give 2.7 mg (62%) of **58** as colorless prisms: mp 92−96 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32−1.52 (m, 1H), 2.18−2.26 (m, 1H), 2.78 (dd, J = 4,7 Hz, 1H), 2.91−2.98 (m, 1H), 3.10 (m, 1H), 3.22−3.40 (m, 3H), 3.91 (dt, J = 5, 14 Hz, 1H), 4.19−4.26 (m, 1H), 3.45 (d, J = 14 Hz, 1H) HRMS *m/z* 216.0871 (calcd for $C_9H_{14}NO_5$: 216.0872).

[(3a*R*,4*R*,9a*R*)-2,2-Dimethyl-3a,4,5,6,7,9a-hexahydro-[1,3]dioxolo[4,5-*c*]azocin-4-yl]methanol (59). To a solution of **55** (12 mg, 0.050 mmol) in EtOAc (10 mL) was added a 0.5 M solution of sodium ethoxide in EtOH (1 mL), and the mixture was stirred for 18 h at 70 °C. The mixture was concentrated under reduced pressure, and the residue was treated with a saturated solution of NH_4Cl (2 mL). The mixture was extracted with $CHCl_3$ (4 × 5 mL), and the combined organic extracts were washed with a saturated solution of NaCl and dried over anhydrous Na_2SO_4. Volatiles were removed under reduced pressure to afford 11 mg (100% of virtually pure **59** as a colorless oil: $[\alpha]_D^{23}$ −14.4 (*c* 0.50, $CHCl_3$); IR (neat) 3370, 2920, 1738, 1465, 1372, 1235, 1142, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.42 (s, 3H), 2.06−2.30 (m, 1H), 2.35−2.42 (m, 1H), 2.68−2.73 (m, 1H), 2.89 (ddd, J = 4, 12, 12, 1H), 2.99 (ddd, J = 1, 6, 8 Hz, 1H), 3.20 (d, J = 9 Hz, 1H), 3.27 (dd, J = 8, 10 Hz, 1H), 3.78 (dd, J = 5, 10 Hz, 1H), 4.54 (t, J = 7 Hz, 1H), 5.60−5.67 (m, 1H), 5.90−5.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 27.2, 28.7, 47.0, 58.2, 64.4, 78.5, 82.7, 109.5, 127.4, 130.9; MS (CI) *m/z* 214 ($M^+ + 1$), 182, 162, 156, 138, 124, 119, 95, 91; HRMS (CI) *m/z* 214.1443 (calcd for $C_{11}H_{20}NO_3$: 214.1443).

(9*R*,10*R*,10a*R*)-9,10-Bis(benzyloxy)-1,5,6,9,10,10a-hexahydro[1,3]oxazolo[3,4-*a*]azocin-3-one (60). To a solution of **56** (100 mg, 0.502 mmol) in dry THF (10 mL) were added KH (50 wt % suspension in mineral oil, 220 mg, 4.50 mmol) and tetra-*n*-butylammonium iodide (10 mg), and the mixture was stirred for 30 min at ambient temperature. Benzyl bromide (200 mL, 1.68 mmol) was added, and the mixture was warmed to 50 °C and stirred for 2 h. The mixture was treated with a saturated solution of NH_4Cl (3 mL) and extracted with $CHCl_3$ (4 × 4 mL), and the combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed (15 g of silica gel, EtOAc−hexane, 1:2) to give 160 mg (84%) of **60** as a colorless oil: $[\alpha]_D^{23}$ +22.8 (*c* 1.33, $CHCl_3$); IR (neat) 3023, 2920, 2861, 1753, 1460, 1421, 1215, 1079, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26−2.37 (m, 1H), 2.39−2.44 (m, 1H), 3.10−3.16 (m, 1H), 3.43−3.52 (m, 1H), 3.76 (dd, J = 5, 13, 1H), 4.17 (dd, J = 1, 8 Hz, 1H), 4.18−4.33 (m, 3H), 4.51 (d, J = 12 Hz, 1H), 4.58 (d, J = 11 Hz, 1H), 4.73 (d, J = 11 Hz, 1H), 5.14 (d, J = 11 Hz, 1H), 5.71−5.82 (m, 2H), 7.28−7.39 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 44.0, 58.8, 68.6, 71.3, 76.0, 78.9, 81.6, 127.8, 128.2, 128.5, 128.6, 128.7, 133.2, 138.0, 138.2, 159.9;MS (CI) *m/z* 380 ($M^+ + 1$), 279, 272, 182, 149, 107, 91; HRMS (CI) *m/z* 380.1862 (calcd for $C_{23}H_{26}NO_4$: 380.1862).

(1a*S*,7a*R*,8*R*,9S,9a*S*)-8,9-Bis(benzyloxy)octahydro[1,3]-oxazolo[3,4-*a*]oxireno[2,3-*e*]azocin-5-one (61). A solution of **60** (160 mg, 0.422 mmol) and *m*-chloroperoxybenzoic acid (50 wt %) (0.58 g, 1.68 mmol) in CH_2Cl_2 (5 mL) was stirred for 6 h at ambient temperature and then was treated with Me_2S (100 μL). Stirring was continued for 15 min, and the solution was washed with a saturated solution of Na_2CO_3 and a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue (10 g of silica gel, EtOAc−hexane, 1:2) afforded 125 mg (75%) of **61** as colorless needles: mp 127−129 °C; $[\alpha]_D^{23}$ + 48.6 (*c* 0.72, $CHCl_3$); IR (neat) 2911, 2847, 1758, 1465, 1420, 1215, 1137, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39−1.50 (m, 2H), 2.37−2.40 (m, 1H), 3.08−3.19 (m, 3H), 3.44 (t, J = 7 Hz, 1H), 3.52−3.59 (m, 2H), 4.04 (dt, J = 5, 14 Hz, 1H), 4.24 (dd, J = 1, 9 Hz, 1H), 4.32 (dd, J = 7, 9 Hz, 1H), 4.59 (d, J = 11 Hz, 1H), 4.72 (d, J = 11 Hz, 1H), 4.97 (d, J = 11 Hz, 1H), 5.16 (d, J = 11 Hz, 1H), 7.19−7.43 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 42.7, 51.9, 57.2, 58.4, 68.8, 73.1, 76.7, 79.3, 81.8, 128.0, 128.2, 128.3, 128.6, 128.8, 137.7, 138.2, 160.4; MS (CI) *m/z* 396 ($M^+ + 1$), 380, 306, 184, 165, 113, 107, 91, 79. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 70.02; H, 6.39; N, 3.60.

(1*S*,5*R*,6*R*,7*R*,7a*R*)-6,7-Bis(benzyloxy)-5-(hydroxyethyl)-hexahydro-1*H*-pyrrolizin-1-ol (1,2-Di-(*O*-benzyl)australine, 62). To a solution of **61** (50 mg, 0.126 mmol) in EtOH−H_2O (1:1, 20 mL) was added LiOH−H_2O (53 mg, 1.26 mmol), and the mixture was stirred for 18 h at 94 °C. The mixture was extracted with $CHCl_3$ (3 × 5 mL), and the combined organic extracts were washed with a saturated solution of NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 47 mg (100%) of pure **62** as a colorless oil: $[\alpha]_D^{23}$ +13.2 (*c* 0.94, $CHCl_3$); IR (neat) 3389, 2876, 1465, 1142, 1074, 1040, 747, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.93−1.99 (m, 2H), 2.74 (q, J = 8 Hz, 1H), 2.98−3.01 (m, 1H), 3.14−3.19 (m, 1H), 3.52 (dd, J = 5, 5 Hz, 1H), 4.59 (d, J = 2 Hz, 2H), 4.64 (d, J = 4, 7 Hz, 1H), 4.13−4.19 (m, 2H), 4.33 (dd, J = 5, 5 Hz, 1H), 4.59 (d, J = 2 Hz, 2H), 4.64 (d, J = 11 Hz, 1H), 4.75 (d, J = 11 Hz, 1H), 7.28−7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.0, 51.9, 60.8, 71.3, 71.7, 72.5, 72.9, 73,0.1, 81.4, 85.2, 128.0, 128.1, 128.7, 138.0, 138.3; MS(CI) *m/z* 370($M^+ + 1$), 338, 262, 229, 207, 135, 107, 91, 79, 69; HRMS (CI) *m/z* 370.2018 (calcd for $C_{22}H_{28}NO_4$: 370.2018).

(1*R*,2*R*,3*R*,7*S*,7a*R*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizidine-1,2,7-triol. Australine (3). A suspension of **62** (26 mg, 0.07 mmol) and $Pd(OH)_2/C$ (20%, 10 mg) in MeOH (2 mL) was stirred for 24 h under a hydrogen atmosphere. The mixture was filtered through a short column of silica gel, and the filtrate was concentrated under reduced pressure to furnish 13.4 mg (100%) of **3** as a colorless oil: $[\alpha]_D^{23}$ +16.6 (*c* 1.37, MeOH); IR (neat) 3331, 2915, 1621, 1426, 1118, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92−2.01 (m, 1H), 2.02−2.06 (m, 1H), 2.72−2.78 (m, 2H), 3.15−3.22 (m, 2H), 3.63 (dd, J 6, 12 Hz, 1H), 3.81 (dd, J = 3, 12 Hz,1H), 3.91 (t, J = 9 Hz, 1H), 4.25 (t. J = 8 Hz, 1H), 4.39 (s, 1H); ^{13}C NMR (100 MHz, D_2O) δ 35.4, 52.1, 62.9, 69.8, 70.8, 71.0, 73.4, 79.1; MS (CI) *m/z* 190 ($M^+ + 1$), 184, 172, 158, 152, 140, 112, 99; HRMS (CI) *m/z* 190.1079 (calcd for $C_8H_{16}NO_4$: 190.1079).

Acknowledgment. We are grateful to Professor Alexandre Yokochi of this Department for X-ray crystal structures of **56** and **61**; to Professor George Fleet of Oxford University, Dr. Robert Nash of The Institute of Grassland and Environmental Research Aberystwyth, Wales, and Dr. Russell J. Molyneux, USDA, Albany, California, for samples and spectra of natural australine; and to Professor Scott Denmark, University of Illinois, and Professor William H. Pearson, University of Michigan, for helpful correspondence. Financial support was provided by the National Institutes of Health (GM58889).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **7**−**20**, **22**, **23**, **25**−**29**, **31**−**41**, **43**−**63**, australine (**3**), X-ray crystallographic data for **28**, **56**, and **61**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0012748