Synthesis of Vicinal Amino Alcohols via a Tandem Acylnitrene Aziridination−Aziridine Ring Opening

Stephen C. Bergmeier* and Dionne M. Stanchina

Division of Medicinal Chemistry, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210

Received March 14, 1997[⊗]

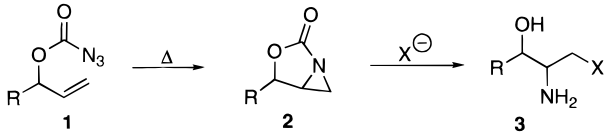
A facile synthesis of differently substituted vicinal amino alcohols is reported. We have demonstrated that these amino alcohols could be readily prepared from the oxazolidinones by treatment with aqueous base. We have synthesized a variety of substituted bicyclic aziridine precursors from the corresponding azidoformates using an intramolecular aziridination reaction. The nucleophilic ring opening of these bicyclic aziridines using carbon, oxygen, nitrogen, sulfur, and halogen-containing nucleophiles provided the oxazolidinones in good yield with high regioselectivity. In all cases, nucleophilic attack occurred exclusively at the least substituted carbon of the aziridine ring. Consequently, our approach allows for convenient and rapid access to the vicinal amino alcohol functionality, an important structural component of many natural products.

Introduction

The vicinal amino alcohol moiety is found in a wide variety of biologically active molecules. Examples include hydroxyamino acids such as bestatin,[1] sphingolipids,[2] and balanol.[3] A number of methods exist for the construction of this functionality:[4] hydride reduction of α-hydroxy oximino ethers;[4a] reaction of aldehydes with chiral organoboron reagents;[4b] cuprate, Michael, and cycloaddition reactions of γ-aminoolefins;[4c] and a variety of other methods[4d] have been used. In order to prepare a number of amino alcohols with varying substitution at either end of the molecule, one is often obliged to utilize a new substrate for the synthesis of each different amino alcohol. We had proposed that the formation of aziridines such as **2** via the intramolecular addition of an azidoformate to an olefin could allow one to prepare a single reactive intermediate and readily convert it to a variety of different amino alcohols.

Previously, only one intramolecular reaction between an azidoformate and an olefin has been reported.[5,6] In this earlier report, the thermolysis of an aryl azidoformate gave a bicyclic aziridine in good yield. An intramolecular dipolar cycloaddition of a carbamoyl azide has recently been reported.[7] This reaction did not yield an aziridine; instead, nucleophilic addition to a betaine intermediate provided an imidazolidinone. The thermal or photochemical intermolecular reactions of azidoformates with olefins to produce aziridines are well-known.[8] These types of reactions are somewhat limited as cyclic or strained olefins give the best yields. Furthermore, high molar ratios of azidoformate to olefin are required. Our plan was to cyclize an azidoformate (**1**) to the bicyclic aziridine **2** and then open the aziridine with a desired nucleophile (X) to produce **3** (Scheme 1).

Scheme 1



1 **2** **3**

Results and Discussion

The desired azidoformate **6** was readily prepared by reaction of cyclohexanecarboxaldehyde (**4**) with vinylmagnesium bromide to produce allylic alcohol **5**. The azidoformate can be synthesized by reaction of the alcohol with CDI followed by NaN_3.[9] A solution of **6** in 1,1,2,2-tetrachloroethane (TCE) was heated at reflux which smoothly converted **6** to a mixture of chlorides **7a** and **7b** in very good yield.[10] The ratio of **7a** (*trans*) to **7b** (*cis*) is 6.7:1 (Scheme 2). The isomeric identity was deter-

* Author to whom correspondence should be addressed. Telephone: 614-292-5499. E-mail: bergmeier.1@osu.edu.

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1997.

(1) (a) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiotics* **1976**, *29*, 97. (b) Abe, F.; Shibuya, K.; Ashizawa, J.; Takahashi, K.; Horinishi, H.; Matsuda, A.; Ishizuka, M.; Takeushi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 411. For some representative syntheses, see: (c) Fuji, K.; Kawabata, T.; Diryu, Y.; Sugiura, Y. *Heterocycles* **1996**, *42*, 701. (d) Palomo, C.; Aizpurua, J. M.; Cuevas, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1957. (e) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Chem. Lett.* **1990**, 723. (f) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235.

(2) (a) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354−363 and references therein. (b) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037−3040.

(3) For information on isolation and structure determination of balanol, see: (a) Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452−6453. Synthesis: (b) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402−8403. (c) Hughes, P. F.; Smith, S. H.; Olson, J. T. *J. Org. Chem.* **1994**, *59*, 5799−5802. (d) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147−5148. (e) Adams, C. P.; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2355−2362.

(4) (a) Williams, D. R.; Osterhout, M. H.; Reddy, J. P. *Tetrahedron Lett.* **1993**, *34*, 3271−3274. (b) Barrett, A. G. M.; Seefeld, M. A. *J. Chem. Soc., Chem. Commun.* **1993**, 339−341. (c) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164. (d) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30* (12), 1531−1750.

(5) (a) Rhouati, S.; Bernou, A. *J. Chem. Soc., Chem. Commun.* **1989**, 730−732.

(6) While the intramolecular cyclization of an azidoformate with an olefin is rare, the intermolecular insertion reaction between the nitrene and C-4 has been exploited to some advantage. See: (a) Lwowski, W.: Carbonylnitrenes In *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, 1970; pp 185−224. (b) Edwards, O. E. Acylnitrene Cyclizations. In *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, 1970; pp 225−304. (c) Lwowski, W.: Acyl Azides and Nitrene. In *Azides and Nitrenes*; Scriven, E., Ed.; Academic: Orlando, 1984; pp 205−246. (d) Lwowski, W. *Nitrenes. React. Intermed.* **1985**, *3*, 305−332.

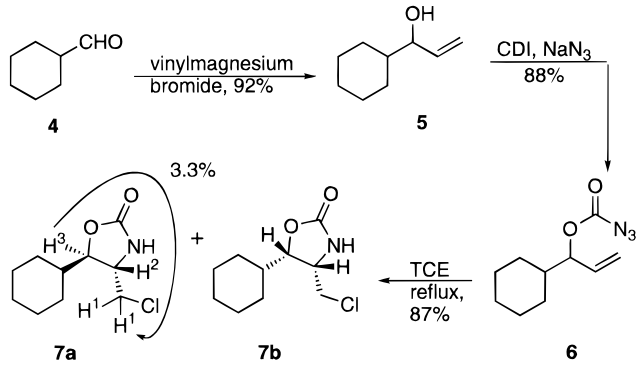
(7) Deroose, F. D.; De Clercq, P. J. *J. Org. Chem.* **1995**, *60*, 321−330.

(8) (a) Lwowski, W.; Mattingly, T. W., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1947−1958. (b) Lwowski, W. Acyl Azides and Nitrene. In *Azides and Nitrenes*; Scriven, E., Ed.; Academic: Orlando, 1984; pp 231−235.

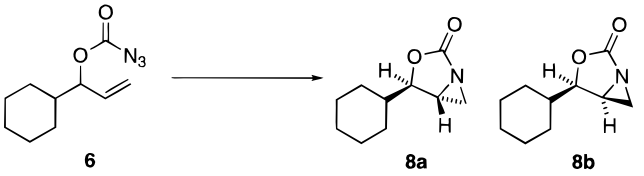
(9) Yuan, P.; Plourde, R.; Shoemaker, M. R.; Moore, C. L.; Hansen, D. E. *J. Org. Chem.* **1995**, *60*, 5360−5364.

S0022-3263(97)00473-8 CCC: $14.00

Scheme 2



Scheme 3



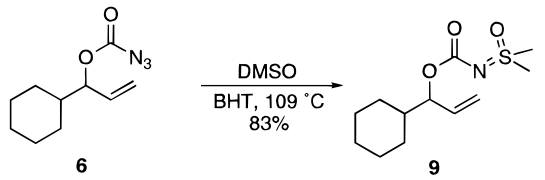
Entry	Solvent	Temp. (°C)	Time (h)	Products
1	CH_2Cl_2	140	4	**8** + polymeric material
2[a]	CH_2Cl_2	109	13	**8** (87%)
3[a]	CH_2Cl_2	95-90	22	**8** + polymeric material
4[a]	TCE	100	13	**7**[b] + **8**

[a]10 mol% of 2,6-Di-*tert*-butyl-4-methylphenol (BHT) was used. [b]A 1 : 12 ratio of **7** : **8** was obtained from ^{1}H NMR analysis of the crude reaction mixture.

mined via NMR experiments. For compound **7a**, irradiation of H3 produced a 3.3% NOE enhancement of the signal for H1. Additionally the coupling constant $J_{2,3}$ for **7a** (*trans*) was 3.23 Hz while the coupling constant $J_{2,3}$ for **7b** (*cis*) was 7.55 Hz. This is consistent with the observations that *trans*-oxazolidinones have smaller coupling constants than the corresponding *cis*-oxazolidinones.[11]

We speculated that the chloride might be coming from HCl generated at high temperatures in the presence of adventitious water. In an attempt to form only the bicyclic aziridine, we lowered the temperature of the reaction and included agents to remove water or acid from the solution.[12] These changes only lowered the yields of **7** or decreased the rate of the reaction. Upon changing the reaction solvent to methylene chloride (and carrying out the reaction in a sealed tube), a dramatic shift in product distribution was seen (Scheme 3). Now the major products seen in the crude ^{1}H NMR were the bicyclic aziridines **8a**/**8b** along with some polymeric products. Lowering the temperature further (109 °C) and including 10 mol % of 2,6-di-*tert*-butyl-4-methylphenol (BHT) gave the bicyclic aziridine as the sole product of

Scheme 4



the reaction. This also had the benefit of improving the ratio of *trans*:*cis* product from 6.7:1 to 10:1.[13] If the temperature was lowered even further, the reaction was slowed such that starting material and aziridine were the principle products observed.

The importance of the solvent in this cyclization is not yet clear. Carrying out the cyclization in TCE at 100 °C with 10 mol % BHT provides both the aziridine and the chloride. We speculate that upon heating TCE produces a considerable quantity of either HCl or Cl radical.

The bicyclic aziridine **8** proved to be impossible to purify. Attempts at purifying a relatively pure reaction product via column chromatography on silica or alumina did not give any products resembling the aziridine. We have thus taken to quantifying the product via NMR relative to an internal standard. This gives a yield for **8a**/**8b** of 87%.

As with any azide, two modes of aziridine formation are possible. Dipolar cyclization to form a triazoline intermediate with rearrangement to form the aziridine is well-known.[14] Equally well-known is the formation of the acylnitrene via thermolysis of azidoformates.[5] In an effort to determine which mode of aziridine formation may be operative in our system, we carried out the thermolysis of **6** in DMSO (Scheme 4). The only product obtained from this reaction was the sulfoximine **9** in 83% yield which is consistent with the product of a nitrene and DMSO.[15]

As our goal was to be able to prepare vicinal amino alcohols with a variety of groups on the alkyl chain, we next investigated the reaction of bicyclic aziridine **8a** with a series of nucleophilic reagents (Scheme 5). In all but one case, the opening of the aziridine **8a** provided the oxazolidinone **10** exclusively. The exceptional reactivity of this aziridine makes possible very mild conditions for nucleophilic ring opening. Oxygen nucleophiles such as water,[16] alcohols,[17] esters,[17d] ethers,[18] and carboxylic acids[16b,19] have been previously used to open aziridines. When water was used to open the aziridine **8a** to provide

(10) Bergmeier, S. C.; Stanchina, D. M. *Tetrahedron Lett.* **1995**, *36*, 4533−4536.

(11) Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101−1133.

(12) Powdered dry 4 Å molecular sieves, $CaSO_4$, $MgSO_4$, and acid scavengers such as poly(4-vinylpyridine) and 1,8-bis(dimethylamino)-naphthalene (Proton Sponge) were used to preclude the formation of HCl. We did not observe aziridine formation when any of these agents were used. Only oxazolidinones were obtained in low yield with the exception of the case of the Proton Sponge where only polymeric material was formed.

(13) The predominance of the *trans* isomer can be rationalized by a chair-like transition state as discussed in our earlier work. See ref 10.

(14) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, Chapter 12, pp 277−406.

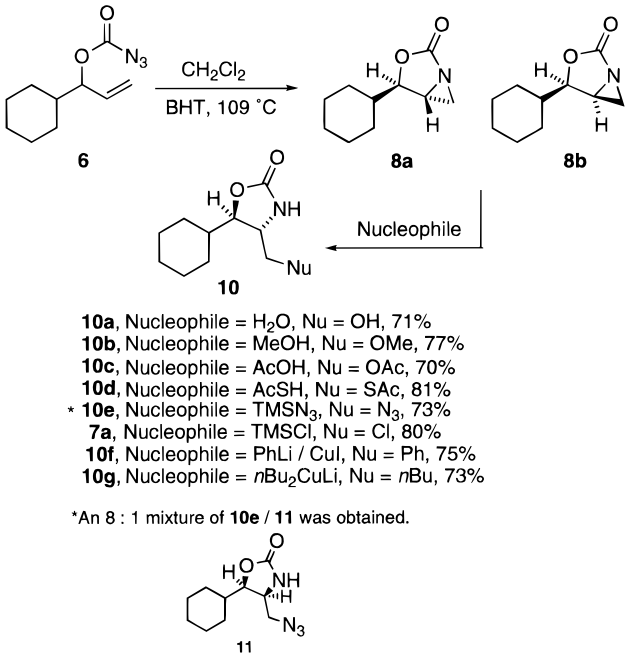
(15) Although the products are not as well characterized, heating in toluene or decane also gives only products consistent with nitrenes reacting with the solvent. (a) Anderson, D. J.; Horwell, D. C.; Stanton, E.; Gilchrist, T. L.; Rees, C.W. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1317−1320. (b) Colonna, S.; Stirling, C. J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2120−2122. (c) Atkinson, R. S. Azides and Nitrenes Attached to Elements Other than Carbon. In *Azides and Nitrenes*; Scriven, E., Ed.; Academic: Orlando, 1984; p 280. (d) Horner, L.; Christmann, A. *Chem. Ber.* **1963**, 388−398. (e) Jones, D. W.; Thornton-Pett, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 809−815.

(16) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (b) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243.

(17) (a) Kogami, Y.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2963. (b) Stamm, H.; Speth, D. *Arch. Pharm. (Weinheim, Ger.)* **1989**, *322*, 277. (c) Pirrung, M. C.; Nunn, D. S. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1489. (d) Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513.

(18) Dehmlow, H.; Mulzer, J.; Seilz, C.; Strecker, A. R.; Kohlmann, A. *Tetrahedron Lett.* **1992**, *33*, 3607.

Scheme 5



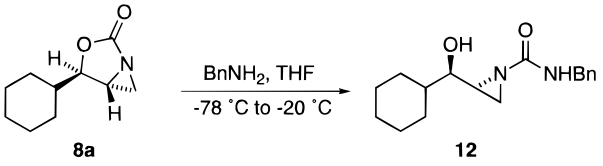
10a, a large excess of reagent as well as acid catalysis proved to be critical to success of the reaction. A number of acids were examined, and a catalytic amount of TFA proved optimal. When the reaction was carried out with 1−2 equiv of water or with a 1:1 mixture of water/solvent, a considerable quantity (30%) of another product which was inseparable from **10a** was obtained. On the basis of ^{1}H NMR decoupling experiments, it appeared to be the product resulting from attack at the internal carbon of the aziridine. A few examples of nucleophilic openings of bicyclic aziridines have been reported.[20] In several of these cases, nucleophilic attack occurred exclusively at the internal carbon of the bicyclic system.

Similarly, the reaction of **8a** with methanol required a large excess of reagent in addition to acid catalysis. However, it proved necessary to change the acid catalyst in order to achieve complete regioselectivity. Only mixtures of products resulting from attack at both the internal and terminal carbons of the aziridine were obtained when TFA was employed while a catalytic amount of sulfuric acid was required to provide **10b** exclusively.

Following a pattern analogous to the aforementioned oxygen nucleophiles, we found that a large excess of acetic acid was essential to the clean formation of the acetate **10c**. No additional reagents were required. Reaction of **8a** with nucleophiles such as NaOAc gave only polar materials, none of which resembled the oxazolidinone **10c**.

Ring-opening reactions of aziridines using sulfur-containing nucleophiles such as thiophenol have been well documented.[21,22c,23] However, upon treatment of **8a** with thiophenol under either acidic or basic conditions, we obtained mixtures of products in low yields. Thiolacetic acid proved to be the reagent of choice as a clean ring opening was achieved to provide **10d** in 81% yield. However, unlike the reaction with acetic acid where a large excess of reagent was required, only 1 equiv of thiolacetic acid was needed. No additional acid catalysis was necessary.

Scheme 6



Azides have also been used to open aziridine rings.[19d,21e,22,24a,c] Our best results have been obtained using $TMSN_3$. We obtained an 8:1 mixture of oxazolidinones **10e** and **11**, respectively, when $TMSN_3$ was used to open the aziridine. Reaction of **8a** with sodium azide under a variety of reaction conditions gave poor mixtures of products in only moderate yields. We have also attempted to introduce the nitrogen moiety by reaction of **8a** with benzylamine (Scheme 6). Although this was unsuccessful, some interesting results were obtained. Even though benzylamine appears to be a poor nucleophile for this particular reaction, it is worth noting that we do observe the opening of the oxazolidinone ring with benzylamine to provide the aziridine **12**, albeit in low yield. In a similar system, Dauban and co-workers[23] have also observed this kind of intermolecular ring opening when they attempted to open an aziridine using an alcohol in the presence of a Lewis acid.

Halogens have also been used as nucleophiles to open an aziridine ring.[21e,22c,24] Our attempts to open the aziridine **8a** with HCl gave only low yields of the chloride **7**. The use of TMSCl, on the other hand, readily provided **7a** in very good yield. As previously discussed in this report, **7** can also be formed directly from the azidoformate by refluxing **6** in TCE. However, milder reaction conditions and better selectivity result from first forming the aziridine **8a** and proceeding to open the ring with TMSCl.

We also wished to utilize organometallic reagents to the open the aziridine ring as this is a well-known

(19) (a) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 2* **1981**, 121. (b) Jones, D. S.; Srinivasan, A.; Kasina, S.; Fritzberg, A. R.; Wilkening, D. W. *J. Org. Chem.* **1989**, *54*, 1940. (c) Kim, N.-S.; Kang, C. H.; Cha, J. K. *Tetrahedron Lett.* **1994**, *35*, 3489. (d) Legters, J.; Willems, J. G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59.

(20) (a) De Kimpe, N.; Boelens, M.; Contreras, J. *Tetrahedron Lett.* **1996**, *37*, 3171−3174. (b) Kim, D.-K.; Kim, G.; Kim, Y. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 803−808. (c) Armstrong, R. W.; Moran, E. J. *J. Am. Chem. Soc.* **1992**, 371−372. (d) Hashimoto, M.; Matsumoto, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.* **1994**, *35*, 2207−2210.

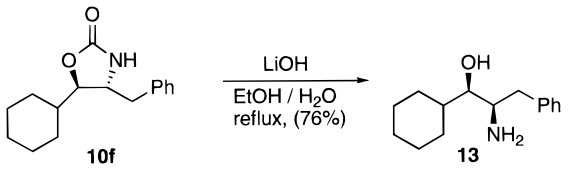
(21) (a) Lin, P.-Y.; Bellos, K.; Stamm, H.; Onistschemko, A. *Tetrahedron*, **1992**, *48*, 2359−2372. (b) Carreaux, F.; Dureault, A.; Depezey, J. C. *Synlett* **1992**, 527. (c) Voronkov, M. G.; Knutov, V. I.; Shevko, O. N. *J. Gen. Chem. USSR* **1992**, *5*, 704. (d) Hashimoto, H.; Shimada, K.; Horito, S. *Tetrahedron Lett.* **1993**, *34*, 4953 −4956. (e) Osborn, H. M. J.; Sweeney, J. B.; Howson, B. *Synlett* **1994**, 145. (f) Hashimoto, M.; Matsumoto, M.; Yamada, K.; Terashima, S. *Tetrahedron Lett.* **1994**, *35*, 2207−2210.

(22) (a) Gutherie, R. D.; Williams, G. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 801−804. (b) For a preparation of $TMSN_3$, see: Brandstrom, A.; Lamm, B.; Palmerlz, I. *Acta Chem. Scand. B* **1974**, *28*, 699−701. (c) Burgaud, B. G. M.; Horwell, D. C.; Padova, A.; Pritchard, M. C. *Tetrahedron* **1996**, *52*, 13035−13050. (d) Leung, W.-H.; Yu, M.-T.; Wu, M.-C.; Yeung, L.-L. *Tetrahedron Lett.* **1996**, *37*, 891−892.

(23) Dauban, P.; Chiaroni, A.; Riche, C.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2488−2496.

(24) For examples of opening activated aziridines with iodide, see: (a) Tanner, D.; Birgersson, C.; Dhaliwal, H. K. *Tetrahedron Lett.* **1990**, *31*, 1903−1906. (b) Nadir, U. K.; Basu, N. *Tetrahedron Lett.* **1992**, *33*, 7903−7906. For examples of opening of activated aziridines with bromide, see: (c) Dureault, A.; Tranchepain, I.; Depezay, J. C. *J. Org. Chem.* **1989**, *54*, 5324−5330. For examples of opening of aziridines with chloride, see: (d) Kyburz, E.; Els, H.; Majnoni, S.; Englert, G.; von Planta, C.; Furst, A.; Plattner, P. A. *Helv. Chim. Acta* **1966**, *49*, 359. (e) Gurjar, M. K.; Patil, V. J.; Yadav, J. S.; Rama Rao, A. V. *Carbohydr. Res.* **1984**, *129*, 267.

Scheme 7



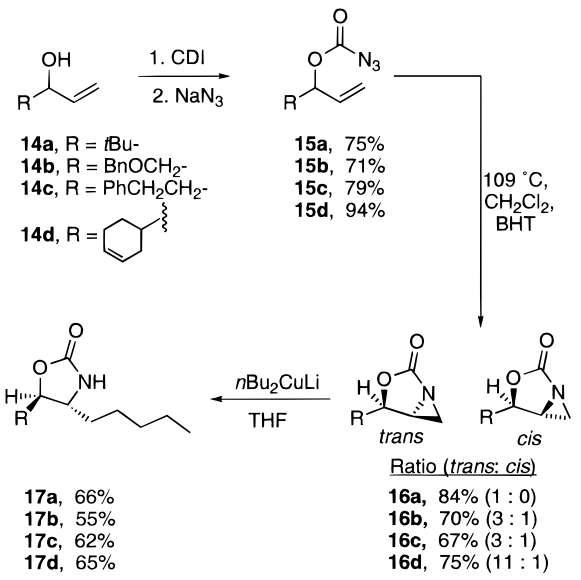
reaction of aziridines.[25] However, the reaction of **8a** with organolithium or Grignard reagents gave a poor mixture of products. A clean ring opening was effected by treating the intermediate aziridine with a cuprate. Both alkyl (n-Bu_2CuLi) and aryl (PhLi/CuI) cuprates were employed. While we did not encounter any problems with the more reactive alkyl cuprate, reaction of **8a** with Ph_2CuLi led to products resulting from opening of the aziridine with iodide. In order to circumvent this problem, it was necessary to use only a catalytic amount of copper iodide to provide **10f** exclusively.

Oxazolidinones are commonly used as protecting groups for amino alcohols.[26] They can be generated from the cyclocarbamation of 1,2- and 1,3-amino alcohols[27] and can be cleaved using a variety of methods.[26,28] In general, we have not converted the oxazolidinones to the free amino alcohols as these compounds are difficult to handle and purify. However, this transformation can be readily accomplished with aqueous base. For example, the conversion of **10f** to **13** proceeds in 76% yield with LiOH (Scheme 7).[29] The acetate derivative **10c** and the chloride derivative **7a** are incompatible with the basic conditions required to cleave these oxazolidinones and therefore cannot be converted to the free amino alcohol using these reaction conditions.

Aldehydes other than cyclohexanecarboxaldehyde (**4**) were utilized to prepare azidoformates that were subsequently cyclized to the corresponding aziridines. The allylic alcohols were prepared by addition of vinylmagnesium bromide to the corresponding aldehyde. Conversion of the allylic alcohol to the azidoformate utilizes the sequential reaction of the alcohol with CDI, followed by NaN_3 (Scheme 8). The azidoformates were then cyclized to the aziridines **16a**−**d** in generally good yield. For characterization, the aziridines were directly converted to the alkyl derivatives **17a**−**d** by reaction with n-butyl cuprate. Pivaldehyde was selected because we believed that the bulky *tert*-butyl moiety would enhance the stereoselectivity of the aziridination reaction. This was indeed the case as cyclization of the azidoformate **15a** gave the *trans* isomer **16a** exclusively.

We were concerned that other sites for nitrene reaction could be problematic. Thus, aromatic rings and Lewis

Scheme 8



basic groups were included in our selected set of aldehydes. 2-(Benzyloxy)acetaldehyde was chosen in order to determine whether the Lewis basic oxygen moiety would react with the nitrene. This did not appear to be the case as side products which could be formed from such a reaction were not evident in the crude ^{1}H NMR spectrum. In order to ascertain whether the presence of an aromatic ring would lead to products derived from nitrene insertion, hydrocinnamaldehyde was included as one of our chosen aldehydes. We did not observe the presence of any such products in the crude ^{1}H NMR spectrum and were able to obtain the aziridine **16c** in 67% yield. Similarly, 1,2,3,6-tetrahydrobenzaldehyde was selected because it contains an olefin which could potentially react with the nitrene. However, the presence of the olefin was of no consequence since the olefinic protons of the six-membered ring were still present in the crude ^{1}H NMR spectrum of the aziridine **16d**. Clearly, olefins or aromatic rings immediately adjacent to the azidoformate would produce mixtures of products. Unlike the more sterically hindered azidoformate **15a**, cyclization of azidoformates **15b**−**d** gave mixtures of both the *trans* and *cis* aziridines **16b**−**d**. In all of these cases, the *trans* isomer was the major isomer. Upon treatment of **16b**−**d** with n-butyl cuprate, followed by purification, only the *trans* oxazolidinones **17b**−**d** were isolated. Further investigation into the scope and selectivity of this reaction is currently underway in our laboratories.

We have also examined the use of nonterminal olefins. Starting with *trans*-2-hexen-1-ol, the azidoformate was prepared and cyclized to give a 43:1 mixture of bicyclic aziridines **20a** and **20b** (Scheme 9). We had anticipated that only the *trans* aziridine **20a** would be formed. Apparently, some fraction of the acylnitrene that is formed is in the triplet state which then adds nonstereospecifically in a stepwise fashion as described by Skell[30] allowing for the formation of **20b**. It is believed that for an intermolecular reaction of a thermolytically generated nitrene with an olefin, the amount of triplet nitrene which is produced is often on the order of 10%

(25) (a) Dureault, A.; Tranchepain, I.; Depezay, J-C. *J. Org. Chem.* **1989**, *54*, 5324−5330. (b) Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1852−1854. (c) Baldwin, J. E.; Farthing, C. N.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 3761−3764. (d) Aggarwal, V. K.; Vennall, G. P. *Tetrahedron Lett.* **1996**, *37*, 3745−3746. (e) Osowska-Pacewicka, K.; Zwierzak, A. *Synthesis*, **1996**, 333−335. (f) Chakraborty, T. K.; Gangakhedkar, K. *Tetrahedron Lett.* **1991**, *32*, 1897−1898.

(26) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185−4188.

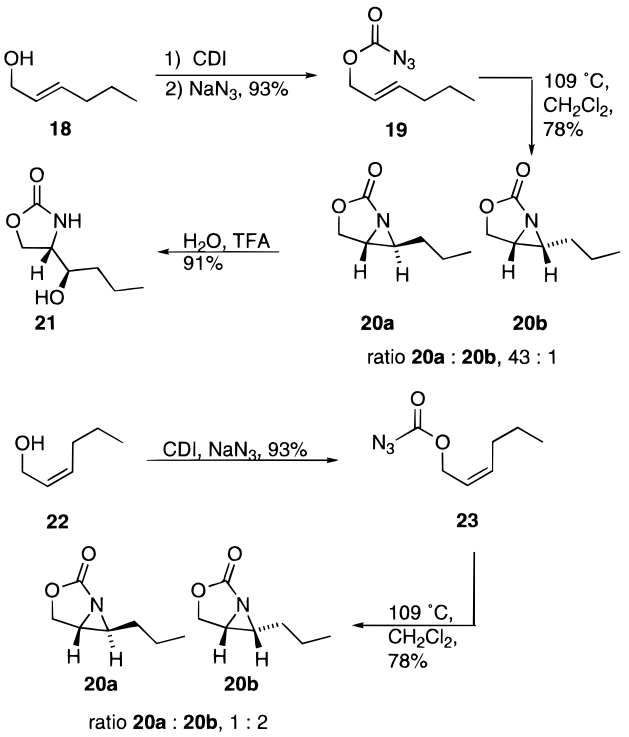
(27) (a) Yi, F.; Wang, T.; Izawa, S.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465−6466. (b) Hirama, M.; Nishizaki, I.; Shigemoto, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1986**, 393−394. (c) Bartlett, P. A.; Tauzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619−622.

(28) Dyen, M. E.; Swern, D. *Chem. Rev.* **1967**, *67*, 197.

(29) Kemp, S. J.; Jianming, B.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 7162−7167.

(30) (a) Skell, P. S.; Woodworth, R. C. *J. Am. Chem. Soc.* **1956**, *78*, 4496. (b) Woodworth, R. C.; Skell, P. S. *J. Am. Chem. Soc.* **1959**, *81*, 3384.

Scheme 9



and is dependent upon the concentration of the olefin.[8b] In general, as the concentration of olefin increases, the amount of nitrene in the triplet state decreases.[31] Since our system involves the intramolecular reaction of a nitrene and an olefin, we expected that the amount of **20b** that is formed should be significantly less than 10% due to the fact that the concentration of olefin is at its highest possible level. This appears to be the case since a 43:1 mixture of **20a** and **20b** is obtained. We anticipated then that the azidoformate resulting from *cis*-2-hexen-1-ol would cyclize to give primarily the *cis* product. Unfortunately, this was not the case and a 2:1 mixture of the *cis*:*trans* aziridines **20a** and **20b** was formed. The fact that the amount of *trans* aziridine formed was significantly greater than expected seems to indicate either that the conversion from the singlet state to the triplet state is faster than previously reported[31a,b] or that the lifetime for the nitrene is longer than might be anticipated.

The aziridine **20a** can also be readily opened to provide alcohol **21** in high yield. The alcohol **21** was subsequently acetylated in order to ascertain (by homonuclear proton decoupling experiments) whether nucleophilic ring opening had occurred at the internal carbon of the aziridine **20a** to form a six-membered ring or whether it had occurred at the external carbon to provide the five-membered oxazolidinone **21**. On the basis of these experiments, we found the latter to be the case since decoupling of the signal at 1.50 ppm corresponding to the protons on the alkyl chain resulted in the collapse of the signal for the proton on the carbon of the aceylated alcohol at 4.95 ppm. It is interesting to note that **20a** and **20b** can also be formed in refluxing TCE. Apparently, ring-opening reactions of these aziridines are not as facile as those of terminal aziridines. Furthermore, these aziridines can be purified, although the yield does drop upon chromatography.

In conclusion, we have developed a method for the preparation of differently substituted vicinal amino alcohols. This method utilizes a stereoselective intramolecular aziridination to form a bicyclic aziridine which is then reacted with the desired nucleophile to produce vicinal amino alcohols.

Experimental Section

General. Melting points were taken using a capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on precoated silica gel F_{254} aluminum foils. ^{1}H NMR spectra referenced to TMS were recorded at 250 MHz. Nuclear Overhauser enhancement (NOE) experiments were carried out at both 270 and 500 MHz. Mass spectra were recorded in the electron impact (EI) mode unless otherwise indicated. All reactions were carried out under a nitrogen atmosphere. Pyridine and NEt_3 were distilled from calcium hydride and stored over potassium hydroxide. Anhydrous DMS and anhydrous DMSO were used as received from Aldrich Chemical Co. DMF was distilled over barium oxide and stored over 4 Å molecular sieves. Acetic anhydride and oxalyl chloride were distilled under nitrogen immediately prior to use. Benzyl bromide was distilled at reduced pressure before use. THF was distilled from sodium/benzophenone ketyl prior to use. Benzene, CH_2Cl_2, and chlorotrimethylsilane were distilled from calcium hydride prior to use. 1,1′-Carbonyldiimidazole was recrystallized from dry THF immediately before use. Copper(I) iodide was purified prior to use.[32] All other reagents were used as purchased. Chromatography refers to flash chromatography on silica gel according to the method of Still.[33] **CAUTION: Azides are potentially explosive, especially upon heating. While we have observed no problems with stability or formation of the azidoformates, care should be exercised.**

Cyclohexaneallyl Alcohol (5). To a solution of vinylmagnesium bromide (60 mL of a 1.0 M solution in THF, 60 mmol) in THF (100 mL) at 0 °C was added cyclohexanecarboxaldehyde (5.60 g, 50 mmol). The reaction was stirred at 0 °C until it was complete by TLC (4 h). The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc (3 × 60 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed to afford 6.50 g of **5** (92%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.15 (m, 2H), 3.80 (m, 1H), 1.90−1.55 (m, 6H), 1.55−0.80 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 139.8, 115.2, 77.6, 77.5, 76.5, 43.5, 28.7, 28.3, 26.1, 26.1; HRMS calcd for $C_9H_{16}O$ 140.1202, found 140.1193.

1-[(Azidocarbonyl)oxy]-1-cyclohexyl-2-propene (6). To a solution of **5** (3.50 g, 25.0 mmol) in benzene (80 mL) and pyridine (5.93 g, 75.0 mmol) was added 1,1'-carbonyldiimidazole (8.11 g, 50.0 mmol). The reaction mixture was stirred at rt for 3.5 h. It was then diluted with EtOAc (100 mL), washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated. To this crude material was added DMF (117 mL) followed by NaN_3 (8.12 g, 125.0 mmol). The reaction mixture was then acidified to *ca*. pH 4 with concentrated HCl and stirred at rt for 18 h. It was then diluted with EtOAc (100 mL) and washed with brine (3 × 100 mL). The aqueous layers were then extracted with EtOAc (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by chromatography to afford 4.61g of **6** (88%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.70 (m, 1H), 5.25 (m, 2H), 4.90 (t, 1H), 1.85 −1.50 (m, 6H), 1.50−0.70 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 156.9, 133.8, 118.8, 84.0, 41.4, 28.4, 28.3, 28.2, 25.8, 25.7; IR (neat) 2100, 1750 cm^{-1}; HRMS calcd for $C_{10}H_{15}N_3O_2$ 209.1165, found 209.1173.

(4*S,5*R**)-4-(Chloromethyl)-5-cyclohexyl-1,3-oxazolidin-2-one (7a) and (4*R**,5*R**)-4-(Chloromethyl)-5-cyclohexyl-1,3-oxazolidin-2-one (7b).** A solution of **6** (2.10 g, 10 mmol) in TCE (200 mL) was heated to reflux for 4 h. The solvent

(31) (a) McConaghy, J. S., Jr.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 2357. (b) McConaghy, J. S., Jr.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 4450. (c) Mishra, A.; Rice, S. N.; Lwowski, W. *J. Org. Chem.* **1968**, *33*, 481.

(32) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1961**, *7*, 9−12.
(33) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *50*, 2923.

was then removed under vacuum. The crude oil was chromatographed to give 1.90 g (87%) of **7a**/**7b** as an off-white solid in a 6.7:1 mixture by ^{1}H NMR. Recrystallization from Et_2O/hexane gave 1.51 g of **7a** (70%) as a colorless solid: mp 93−96 °C; ^{1}H NMR ($CDCl_3$) δ 4.10 (dd, J = 4.4, 6.3 Hz, 1H), 3.83, (m, 1H), 3.51 (d, J = 5.52 Hz, 2H), 1.89−1.57 (m, 6H), 1.29−1.04 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 158.9, 83.9, 62.1, 46.2, 43.7, 41.9, 27.7, 27.2, 26.1, 25.5, 25.4; NOE experiment, irradiation of the multiplet at 4.10 ppm showed a 3.3% enhancement for the signal at 3.51 ppm; HRMS calcd for $C_{10}H_{16}ClNO_2$ 217.0871, found 217.0848.

Alternative Preparation of (4*S,5*R**)-4-(Chloromethyl)-5-cyclohexyl-1,3-oxazolidin-2-one (7a).** To a solution of freshly distilled chlorotrimethylsilane (72 mg, 0.66 mmol) in THF (1 mL) cooled to −30 °C was added a solution of **8** (100 mg, 0.55 mmol) in THF (1 mL). The reaction was stirred at −30 °C for 4 h and was then warmed to rt where stirring was continued for 19 h. The reaction mixture was then diluted with EtOAc (20 mL), washed with water (2 × 35 mL) and brine (1 × 40 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed (3.5:1 hexanes/EtOAc) to afford 95 mg of **7a** (80%) as a colorless solid identical to that prepared above.

(4*R,5*R**)-5-Cyclohexyl-1-oxa-3-azabicyclo[3.1.0]hexan-2-one (8a) and (4*S**,5*R**)-5-Cyclohexyl-1-oxa-3-azabicyclo-[3.1.0]hexan-2-one (8b).** A solution of **6** (400 mg, 1.91 mmol) and BHT (42 mg, 0.19 mmol) in CH_2Cl_2 (30 mL) was placed in an ACE Glass Model 8648B 100 mL capacity pressure tube. **CAUTION: Reactions conducted in pressure tubes are potentially explosive and should be carried out behind a protective shield. While we have observed no problems, care should be exercised.** The reaction vessel was cooled to −78 °C, evacuated, and sealed. The reaction mixture was then warmed to 109 °C in an oil bath for 13 h. It was then cooled to room temperature and concentrated to afford 300 mg (87%) of a mixture of **8a** and **8b** in 10:1 ratio, respectively. An ^{1}H NMR analysis of the crude material using the signal for the aromatic protons (6.85 ppm) of BHT as an internal standard was used to determine the yield of the reaction: ^{1}H NMR ($CDCl_3$) δ 4.30 (d, 1.1H), *3.05 (m, 0.1H), 2.95 (m, 0.9H), 2.50 (d, 0.9H), *2.45 (d, 0.1H), *2.20 (d, 0.1H), 2.10 (m, 1H), 1.75 (m, 6H), 1.20 (m, 5H) (* indicates minor isomer); NOE experiment ($CDCl_3$, 500 MHz), irradiation of peak at 4.30 ppm shows a 1.34% enhancement of the signal at 2.95 ppm and a 2.68% enhancement of the signal at 2.10 ppm; irradiation of peak at 2.95 ppm shows a 3.75% enhancement of the signal at 2.50 ppm.

***S,S*-Dimethyl-*N*-[((1-cyclohexyl-2-propenyl)oxy]carbonyl]sulfoximine (9).** A solution of **6** (200 mg, 0.96 mmol) in DMSO (30 mL) along with BHT (21 mg, 0.096 mmol) was placed in an Ace Glass Model 8648B 100 mL capacity pressure tube. The reaction vessel was cooled to −78 °C, evacuated, and sealed. The reaction mixture was then warmed to 100 °C in an oil bath for 13 h. It was then cooled to room temperature, concentrated, and chromatographed to give 103 mg of **9** (83%): ^{1}H NMR ($CDCl_3$) δ 5.70 (m, 1H), 5.15 (t, 2H), 4.85 (t, 1H), 3.25 (s, 6H), 1.65 (m, 6H), 1.05 (m, 5H); ^{13}C NMR ($CDCl_3$) 158.7, 135.3, 117.3, 80.9, 41.8, 41.7, 41.5, 28.5, 28,4, 26.2, 25.8, 25.8; IR (neat) 1758, 1663, 1020 cm^{-1}; HRMS calcd for $C_{12}H_{21}NO_3S$ 259.1243, found 259.1231.

(4*R,5*R**)-5-Cyclohexyl-4-(hydroxymethyl)-1,3-oxazolidin-2-one (10a).** To a solution of **8** (260 mg, 1.43 mmol) in water (3.1 mL) cooled to 5 °C was added trifluoroacetic acid (8.1 mg, 0.071 mmol). The ice bath was removed, and the reaction mixture was stirred at rt for 21 h. The reaction mixture was then diluted with EtOAc and separated. The organic layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed (6:1 EtOAc/hexanes) to afford 200 mg of **10a** (71%) as a colorless solid: mp 92−94 °C; ^{1}H NMR ($CDCl_3$) δ 4.10 (m, 1H), 3.65 (m, 2H), 3.50 (m, 1H), 1.65 (m, 6H), 1.15 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 160.2, 82.8, 64.1, 56.9, 41.7, 27.5, 27.3, 26.1, 25.5, 25.4. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.59; N, 7.03. Found: C, 60.36; H, 8.37; N, 7.01.

(4*R,5*R**)-5-Cyclohexyl-4-(methoxymethyl)-1,3-oxazolidin-2-one (10b).** To a solution of **8** (111 mg, 0.63 mmol) in MeOH (2.4 mL) cooled to 0 °C was added concentrated H_2SO_4 (6 mg, 0.063 mmol). The ice bath was removed and the reaction stirred at rt for 21.5 h. The reaction mixture was then quenched with saturated $NaHCO_3$, dried ($MgSO_4$), filtered, concentrated, and chromatographed to afford 100 mg of **10b** (77%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.95 (dd, 1H, J = 5.84 Hz (decoupled signal at 3.70 ppm)), 3.70 (m, 1H, J = 4.86 Hz (decoupled signal at 3.30 ppm)), 3.30 (m, 5H), 1.90−1.50 (m, 6H), 1.30−1.10 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 159.1, 82.9, 75.2, 70.6, 59.2, 54.6, 41.9, 27.7, 27.4, 26.6, 26.2, 25.7, 25.5. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.28; H, 8.74; N, 6.66.

(4*R,5*R**)-5-Cyclohexyl-4-(acetoxymethyl)-1,3-oxazolidin-2-one (10c).** To a solution of glacial acetic acid (2 mL) cooled to 10 °C was added a solution of **8** (200 mg, 1.10 mmol) in 1,4-dioxane (2 mL). The reaction mixture was stirred at 10 °C for 5 h and then allowed to warm to rt where it stirred for 20 h. The reaction mixture was then concentrated and chromatographed (95:5 Et_2O/MeOH) to afford 185 mg of **10c** (70%) as a colorless solid: mp 99−102 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (m, 3H, J = 6.94 Hz (decoupled signal at 3.75 Hz)), 3.75 (m, 1H, J = 5.02 Hz (decoupled signal at 3.95 Hz)), 2.00 (s, 3H), 1.65 (m, 6H), 1.10 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 170.5, 159.1, 82.6, 65.5, 53.7, 41.8, 27.3, 27.2, 25.9, 25.4, 25.3, 20.4. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.93; N, 5.80. Found: C, 59.67; H, 7.81; N, 5.79. ^{1}H−^{1}H COSY experiment (270 MHz, $CDCl_3$) showed a cross-peak at 6.85 ppm (NH) coupled with methine at 3.75 ppm.

(4*S,5*R**)-4-[(Acetylthio)methyl]-5-cyclohexyl-1,3-oxazolidin-2-one (10d).** To a solution of thiolacetic acid (0.097 g, 1.23 mmol) in THF (2 mL) cooled to −30 °C was added a solution of **8** (180 mg, 1.03 mmol) in THF (2 mL). The reaction mixture was stirred at −30 °C for 4 h and was warmed to rt where stirring continued overnight. The reaction mixture was then concentrated and chromatographed to afford 210 mg of **10d** (81%) as a colorless solid: mp 80−82 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (dd, 1H), 3.70 (m, 1H, J = 4.34 Hz (decoupled signal at 3.05 and 2.90 ppm); decoupled signal at 3.90 ppm lead to collapse of signal into a triplet), 3.05 (dd, 1H, (decoupled signal at 3.70 ppm lead to collapse of signal at 3.05 ppm)), 2.90 (dd, 1H, (decoupled signal at 3.70 ppm lead to collapse of signal at 2.90 ppm)), 2.30 (s, 3H), 1.70 (m, 6H), 1.15 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 194.8, 158.8, 85.1, 54.6, 41.8, 34.2, 30.5, 27.6, 27.3, 26.1, 25.6, 25.4. Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 56.35; H, 7.49; N, 5.42.

(4*R,5*R**)-4-(Azidomethyl)-5-cyclohexyl-1,3-oxazolidin-2-one (10e) and (4*R**,5*S**)-4-(Azidomethyl)-5-cyclohexyl-1,3-oxazolidin-2-one (11).** To a stirred suspension of NaN_3 (72 mg, 1.10 mmol) in DMF (1 mL) cooled to 0 °C was added chlorotrimethylsilane (130 mg, 1.20 mmol) dropwise over 5 min.[34] The reaction mixture was stirred for 30 min at 0 °C and 30 min at rt. A solution of **8** (180 mg, 1.00 mmol) in DMF (0.50 mL) was added at rt and stirring continued at rt for 5 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with water (3 × 50 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed to afford 160 mg of **2** (73%) as a colorless solid as an 8:1 mixture of **10e** (*trans*):**11** (*cis*): mp 89−92 °C; ^{1}H NMR ($CDCl_3$) δ *4.20 (m, 0.12H, J = 10.17 Hz (decoupled signal at *3.75 Hz)), 4.00 (m, 0.87H, J = 6.00 Hz (decoupled signal at 3.65 Hz)), *3.75 (m, 0.12H), 3.65 (m, 0.87H), 3.35 (m, 2H), 1.65 (m, 6H), 1.10 (m, 5H) (* indicates minor *cis* isomer); ^{13}C NMR ($CDCl_3$) 158.9, 83.5, 54.8, 54.4, 41.8, 27.6, 27.3, 26.1, 25.6, 25.4; IR (CCl_4) 2107, 1749 cm.$^{-1}$ HRMS calcd for $C_{10}H_{16}N_4O_2$ + H (M + H) 225.1275, found 225.1348.

(4*R,5*R**)-4-Benzyl-5-cyclohexyl-1,3-oxazolidin-2-one (10f).** To a suspension of CuI (98 mg, 0.51 mmol) in THF (1.6 mL) cooled to −78 °C was added PhLi (2.56 mL of a 2.0 M solution in cyclohexane/ether, 5.1 mmol). The reaction mixture was then warmed to −30 °C and stirred for 45 min. The mixture was then cooled to −78 °C, and a solution of **8** (93 mg, 0.51 mmol) in THF (1 mL) was added. The reaction stirred at −78 °C for 40 min and was subsequently warmed to rt by removing the ice bath. Stirring continued at rt for 28 h. After being quenched with saturated aqueous NH_4Cl, the

(34) Vorbruggen, H.; Krolikiewicz, K. *Collect. Czech. Chem. Commun.* **1979**, 35.

reaction mixture was extracted with EtOAc (2 × 30 mL). The organic layers were washed with water (2 × 35 mL) and brine (1 × 35 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed to afford 100 mg of **10f** (75%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 5H), 4.05 (dd, 1H, J = 5.88 Hz (decoupled signal at 3.75 ppm)), 3.75 (m, 1H, J = 4.65 Hz (decoupled signal at 2.80 ppm)), 2.80 (d, 2H), 1.80−1.40 (m, 6H), 1.10 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 158.7, 136.2, 129.1, 128.8, 127.1, 85.5, 56.4, 42.5, 41.8, 27.7, 27.4, 26.1, 25.6, 25.5; HRMS calcd for $C_{16}H_{21}NO_2$ 259.1573, found 259.1616.

(4*R,5*R**)-5-Cyclohexyl-4-pentyl-1,3-oxazolidin-2-one (10g).** To a suspension of CuI (192 mg, 1.01 mmol) in THF (3.5 mL) cooled to −78 °C was added *n*-BuLi (0.88 mL of a 2.3 M solution in hexanes, 2.02 mmol). The reaction mixture was then warmed to rt and stirred for 45 min. After the solution was cooled to −78 °C, **8** (175 mg, 0.965 mmol) in THF (1.3 mL) was added and stirring continued at −78 °C for 20 min. The reaction mixture was then warmed to rt by removing the ice bath and stirring was continued for 4 h. The reaction was quenched at this time with saturated aqueous NH_4Cl and extracted with EtOAc (2 × 35 mL). The organic layers were washed with water (1 × 35 mL) and brine (1 × 35 mL), dried ($MgSO_4$), filtered through Celite, concentrated, and chromatographed (5:1 hexanes/EtOAc) to afford 160 mg of **10g** (73%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.85 (dd, 1H, J = 5.1 Hz (decoupled signal at 1.50 ppm)), 3.50 (m, 1H, J = 4.99 Hz (decoupled signal at 1.50 ppm)), 1.90−0.70 (m, 22H); ^{13}C NMR ($CDCl_3$) δ 159.7, 86.3, 55.2, 41.9, 36.7, 36.2, 31.5, 31.4, 29.2, 29.1, 29.1, 27.9, 27.4, 26.2, 25.9, 25.5, 25.2, 24.7, 22.4, 22.3, 22.2, 13.7. Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.29; H, 10.60; N, 5.66.

(1*R,2*R**)-1-Cyclohexyl-2-amino-3-phenyl-1-propanol (13).** Oxazolidinone **10f** (100 mg, 0.39 mmol), LiOH (490 mg, 11.6 mmol), EtOH (7 mL), and water (3 mL) were heated at reflux for 17 h.[29] The reaction mixture was concentrated to 2 mL and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and chromatographed to give 68 mg of **13** (76%) as a colorless solid: mp 81−83 °C; ^{1}H NMR ($CDCl_3$ + D_2O) δ 7.20 (m, 5H), 4.70 (m, 2H), 3.00 (m, 1H), 2.55 (m, 1H), 1.75 (m, 6H), 1.25 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 139.3, 129.2, 128.6, 126.4, 29.9, 28.1, 26.5, 26.4, 26.2; HRMS calcd for $C_{15}H_{23}NO$ 233.1780, found 233.1743.

4,4-Dimethyl-1-penten-3-ol (14a). The allylic alcohol **14a** was prepared by the same method as **5** and was immediately used for the preparation of **15a**. Analytical data matched that reported for the known compound.[35]

1-(Benzyloxy)-3-buten-2-ol (14b). The allylic alcohol **14b** was prepared by the same method used for the preparation of **5** on an 8 mmol scale in 61% yield. Analytical data matched that reported for the known compound.[36]

1-Phenyl-4-penten-3-ol (14c). The allylic alcohol **14c** was prepared by the same method used for the preparation of **5** on a 1.86 mmol scale in 73% yield from commercially available hydrocinnamaldehyde: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.95 (m, 1H), 5.25 (m, 2H), 4.15 (m, 1H), 2.75 (m, 2H), 1.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 141.7, 140.9, 128.2, 128.1, 125.6, 114.4, 72.0, 38.3, 31.4; HRMS calcd for $C_{11}H_{14}O$ 162.1045, found 162.1046.

3-Cyclohexenylallyl Alcohol (14d). The allylic alcohol **14d** was prepared by the same method used for the preparation of **5** on a 18.2 mmol scale in 87% yield from commercially available 1,2,3,6-tetrahydrobenzaldehyde as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 5.85 (m, 1H), 5.65 (m, 2H), 5.20 (m, 2H), 3.90 (m, 1H), 1.85 (m, 6H), 1.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ *139.7, 139.6, 127.1, *126.9, 126.2, *126.1, 115.7, *115.5, 77.5, *77.1, 39.4, 27.6, *26.9, *25.0, 24.7, *24.2 (* indicates other isomer); HRMS calcd for $C_9H_{14}O$ 138.1045, found 138.1044.

4,4-Dimethyl-3-[(azidocarbonyl)oxy]-1-pentene (15a). The azidoformate **15a** was prepared by the same method used for the preparation of **6** on a 50 mmol scale in 75% yield as a colorless oil from **14a**: ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.30 (m, 2H), 4.85 (d, 1H), 0.90 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 156.9, 132.3, 119.7, 87.0, 34.3, 26.1, 25.5; IR (neat) 3025, 2138, 1735 cm^{-1}; HRMS calcd for $C_8H_{13}N_3O_2$ 183.1117, found 183.0984.

1-(Benzyloxy)-2-[(azidocarbonyl)oxy]-3-butene (15b). The azidoformate **15b** was prepared by the same method used for the preparation of **6** on a 4.9 mmol scale in 71% yield as a colorless oil from **14b**: ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.85 (m, 1H), 5.40 (m, 3H), 4.55 (m, 2H), 3.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 156.7, 137.6, 131.9, 128.3, 127.6, 127.5, 119.2, 77.9, 73.2, 70.8; IR (neat) 3020, 2187, 1731 cm^{-1}; HRMS calcd for $C_{12}H_{13}N_3O_3$ 247.0958, found 247.0951.

1-Phenyl-3-[(azidocarbonyl)oxy]-4-pentene (15c). The azidoformate **15c** was prepared by the same method used for the preparation of **6** on a 6.2 mmol scale in 79% yield from **14c**: ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 5H), 5.80 (m, 1H), 5.25 (m, 3H), 2.65, (m, 2H), 2.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 156.6, 140.6, 134.9, 128.4, 128.2, 126.4, 126.0, 118.2, 79.0, 35.4, 31.1; IR (neat) 3086, 2134, 1736 cm^{-1}; HRMS calcd for $C_{12}H_{13}N_3O_2$ 231.1008, found, 231.1009.

1-[(Azidocarbonyl)oxy]-1-(3-cyclohexenyl)-2-propene (15d). The azidoformate **15d** was prepared by the same method used for the preparation of **6** on a 9.4 mmol scale in 94% yield from **14d** as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 5.65 (m, 3H), 5.30 (m, 2H), 5.00 (m, 1H), 1.90 (m, 6H), 1.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 156.8, *156.7, 133.6, *133.5, 126.9, *126.7, *125.3, 125.1, *119.2, 118.9, *83.3, 83.0, *77.5, 77.0, 37.5, *37.2, 27.0, *26.8, 24.6, *24.2, 24.1 (* indicates other isomer); IR (neat) 2188, 2135, 1754, 1731 cm^{-1}; HRMS calcd for $C_{10}H_{13}N_3O_2$ 207.1009, found 207.1002.

(4*R,5*R**)-5-*tert*-Butyl-4-pentyl-1,3-oxazolidin-2-one (17a).** The aziridine **16a** was prepared by the same method used for the preparation of **8a** and **8b** on a 3.2 mmol scale in 84% yield from **15a** and was used immediately in the next reaction: ^{1}H NMR ($CDCl_3$) δ 4.10 (m, 1H), 2.90 (m, 1H, decoupled signal at 4.10 ppm leads to the collapse of the signal at 2.90 ppm), 2.40 (d, 1H), 2.00 (d, 1H), 0.90 (m, 9H). To a suspension of copper(I) iodide (500 mg, 2.64 mmol) in THF (9.6 mL) cooled to −78 °C was added *n*-BuLi (2.40 mL of a 2.3 M solution in hexanes, 5.53 mmol). The reaction mixture was warmed to −40 °C and stirred for 40 min. The solution was then cooled to −78 °C, and **16a** (410 mg, 2.64 mmol) in THF (3.42 mL) was added and stirring continued at −78 °C for 20 min. The reaction mixture was slowly warmed to rt by removing the ice bath. After 4 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl, extracted with EtOAc (3 × 50 mL), washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, concentrated, and chromatographed to afford 370 mg of **17a** (66%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.80 (d, 1H, J = 4.67 Hz (decoupled signal at 3.50 ppm leads to the collapse of the signal at 3.80 ppm)), 3.50 (m, 1H (decoupled signal at 3.80 ppm leads to the collapse of the signal at 3.50 ppm)), 1.40 (m, 8H), 0.90 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 159.9, 89.6, 53.3, 37.1, 34.1, 31.4, 24.8, 24.4, 22.3, 13.9. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.56. Found: C, 67.72; H, 11.15; N, 6.54. No NOE enhancements were observed.

(4*R,5*R**)-5-(Benzyloxy)-4-pentyl-1,3-oxazolidin-2-one (17b).** The aziridine **16b** was prepared by the same method used for the preparation of **8a** and **8b** on a 3.8 mmol scale in 70% yield as a 3:1 mixture of *trans*:*cis* isomers from **15b** and was used immediately in the next reaction: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), *4.85 (m, 0.33 H, J = 5.10 Hz (decoupled signal at 3.65 ppm; decoupled signal at 3.10 ppm leads to the collapse of the signal at *4.85 ppm)), 4.65 (m, 0.67H (decoupled signal at 3.65 and 3.10 ppm leads to the collapse of the signal at 4.65 ppm)), 4.50 (m, 2H), 3.65 (m, 2H (decoupled signal at 4.65 ppm leads to the collapse of the signal at 3.65 ppm), 3.10 (m, 1H, J = 3.41 Hz (decoupled signal at 2.50 ppm; decoupled signal at *4.85, 2.50, *2.40, 2.10 ppm leads to the collapse of the signal at 3.10 ppm)), 2.50 (d, 0.67 H) (decoupled signal at 3.10 ppm leads to the collapse of the signal at 2.50 ppm), *2.40 (d, 0.33H (decoupled signal at 3.10 ppm leads to the collapse of the signal at *2.40 ppm)), *2.35 (d, 0.33H (decoupled signal at 3.10 ppm leads to the collapse of the signal at *2.35 ppm)), 2.10 (d, 0.67H (decoupled signal

(35) Vittorelli, P.; Peter-Katalinic, J.; Mukherjee-Muller, G.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1379−1425.

(36) Takano, S.; Nishizawa, S.; Akiyama, M.; Ogasawara, K. *Heterocycles* **1984**, *22*, 1779−1788.

at 3.10 ppm leads to the collapse of the signal at 2.10 ppm)) (* indicates minor isomer). The oxazolidinone **17b** was prepared by the same method used for the preparation of **17a** on a 0.26 mmol scale in 82% yield as a 3:1 mixture of *trans*/*cis* isomers from **16b**: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.55 (s, 2H), 4.30 (m, 1H, J = 2.89 Hz (decoupled signal at 3.65 ppm)), 3.65 (m, 3H (decoupled signal at 4.30 ppm leads to the collapse of the signal at 3.65 ppm)), 1.55 (m, 2H), 1.25 (m, 6H), 0.85 (t, 3H); ^{13}C NMR ($CDCl_3$, *trans* isomer) δ 158.5, 137.6, 128.5, 127.9, 127.8, 127.7, 80.8, 73.7, 70.3, 54.6, 35.5, 31.5, 28.6, 24.9, 22.4, 13.8; HRMS calcd for $C_{16}H_{23}NO_3$ 277.1679, found 277.1689.

(4*R,5*R**)-4-Pentyl-5-phenethyl-1,3-oxazolidin-2-one (17c).** The aziridine **16c** was prepared by the same method used for the preparation of **8a** and **8b** on a 1.3 mmol scale in 67% yield as a 3:1 mixture of *trans*:*cis* isomers, respectively, from **15c** and was used immediately in the next reaction: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H), *4.65 (m, 0.33H, J = 4.81 Hz (decoupled signal at 2.00 ppm; decoupled signal at *3.05 ppm leads to collapse of signal at *4.65 ppm)), 4.55 (m, 0.67H (decoupled signal at 2.00 ppm leads to collapse of signal at 4.55 ppm)), *3.05 (m, 0.33H (decoupled signal at *4.65 ppm leads to collapse of signal at *3.05 ppm)), 2.75 (m, 2.67H), 2.50 (d, 1H), 2.40 (d, 1H), 2.00 (m, 2H) (* indicates minor isomer); NOE experiment ($CDCl_3$, 270 MHz), irradiation of the peak at *4.65 ppm shows a 5.18% enhancement of the signal at *3.05 ppm; irradiation of the peak at *3.05 ppm shows a 7.23% enhancement of the signal at *4.65 ppm. The oxazolidinone **17c** was prepared by the same method used for the preparation of **17a** on a 0.53 mmol scale in 93% yield as a 3:1 mixture of *trans*:*cis* isomers from **16c**: ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 5H), *4.55 (m, 0.33H), 4.15 (m, 0.67H), *3.70 (m, 0.33H, J = 7.48 Hz (decoupled signal at 1.35 ppm)), 3.40 (m, 0.67H, J = 5.33Hz (decoupled signal at 1.35 ppm)), 2.75 (m, 2H), 1.95 (m, 2H), 1.35 (m, 8H), 0.80 (t, 3H) (* indicates minor *cis* isomer); ^{13}C NMR ($CDCl_3$, *trans* isomer) δ 158.8, 128.6, 128.4, 126.2, 81.7, 77.5, 57.9, 36.6, 35.2, 31.6, 31.5, 31.2, 25.0, 22.7, 22.6, 22.4, 14.0, 13.8; HRMS calcd for $C_{16}H_{23}NO_2$ 261.1730, found 261.1713.

(4*R,5*R**)-5-(3-Cyclohexenyl)-4-pentyl-1,3-oxazolidin-2-one (17d).** The aziridine **16d** was prepared by the same method used for the preparation of **8a** and **8b** on a 3.2 mmol scale in 75% yield as an 11:1 mixture of *trans*:*cis* isomers, respectively, from **15d** and was used immediately in the next reaction: ^{1}H NMR ($CDCl_3$) δ 5.60 (m, 2H), 4.40 (m, 1.09H), *3.05 (m, 0.09H), 2.90 (m, 0.91H), 2.45 (d, 1H), 1.90 (m, 7H) (* indicates minor *cis* isomer); NOE experiment ($CDCl_3$, 270 MHz), irradiation of the peak at 4.40 ppm shows a 7.21% enhancement of the signal at *3.05 ppm. The oxazolidinone **17d** was prepared by the same method used for the preparation of **17a** on a 2.3 mmol scale in 71% yield as an 11:1 mixture of *trans*:*cis* isomers from **16d**: ^{1}H NMR ($CDCl_3$, *trans* isomer) δ 5.65 (m, 2H), 4.00 (m, 1H, J = 5.80 Hz (decoupled signal at 3.50 ppm)), 3.50 (m, 1H (decoupled signal at 4.00 ppm leads to the collapse of the signal at 3.50 ppm)), 2.00 (m, 6H), 1.30 (m, 9H), 0.85 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 159.4, 127.5, 128.7, 125.4, 124.8, 85.9, 85.3, 55.5, 55.4, 38.0, 36.4, 36.2, 31.5, 29.3, 26.7, 26.4, 24.9, 24.7, 24.6, 24.4, 23.9, 23.4, 22.4, 13.8. Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.96; H, 9.66; N, 5.60.

(2*E*)-1-[(Azidocarbonyl)oxy]hexene (19). The azidoformate **19** was prepared by the same method used for the preparation of **6** on a 6 mmol scale in 93% yield as a colorless oil from commercially available *trans*-2-hexen-1-ol (**18**); ^{1}H NMR ($CDCl_3$) δ 5.70 (m, 1H), 5.45 (m, 1H), 4.45 (d, 2H), 1.90 (m, 2H), 1.25 (m, 2H), 0.75 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 156.8, 137.5, 122.5, 68.6, 33.9, 21.6, 13.0; IR (neat) 2932, 2186, 1731 cm^{-1}; HRMS calcd for $C_7H_{11}N_3O_2$ 169.0852, found 169.0854.

Preparation of (4*R,6*S**)-6-Propyl-1-oxa-3-azabicyclo-[3.1.0]hexan-2-one (20a) and (4*R**,6*R**)-6-propyl-1-oxa-3-azabicyclo[3.1.0]hexan-2-one (20b) from 19.** The aziridines **20a** and **20b** were prepared by the same method used for the preparation of **8a** and **8b** on a 2.54 mmol scale in 78% yield from **19** as a 43:1 mixture of **20a** and **20b**, respectively: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.35 (m, 2H), *3.15 (m, 0.02H), 2.95 (m, 1H), *2.65 (m, 0.02H), 2.35 (m, 1H), 1.45 (m, 4H), 0.90 (m, 3H) (* indicates minor isomer); NOE experiment ($CDCl_3$, 500 MHz), irradiation of peak at *2.65 ppm shows 3.28% enhancement of signal at 3.15 ppm; irradiation of peak at *3.15 ppm shows a 3.89% enhancement of signal at *2.65 ppm and a 4.41% enhancement of signal at 4.35 ppm; irradiation of peak at 2.95 ppm shows 1.36% enhancement of signal at 2.35 ppm and a 3.88% enhancement of signal at 4.35 ppm; irradiation of peak at 2.35 ppm shows a 1.29% enhancement of signal at 2.95 ppm.

(4*S)-4-[(1*R**)-1-Hydroxybutyl]-1,3-oxazolidin-2-one (21).** To a solution of the aziridine **20** (120 mg, 0.83 mmol) in a 1:1 mixture of water/dioxane (0.5 mL:0.5 mL) cooled to 0 °C was added trifluoroacetic acid (9 mg, 0.083 mmol). The reaction mixture was stirred at 0 °C for 4.5 h. It was then concentrated and chromatographed (3:1 EtOAc/hexanes) to afford 120 mg of **21** (91%), a colorless oil, as a separable mixture of diastereomers in 43:1 *trans*/*cis* ratio: ^{1}H NMR ($CDCl_3$ + D_2O, *trans* isomer) δ 4.35 (m, 2H), 3.80 (m, 1H), 3.65 (m, 1H), 1.35 (m, 4H), 0.85 (t, 3H); ^{13}C NMR ($CDCl_3$) 160.9, 70.9, 65.8, 60.2, 56.9, 34.2, 18.7, 14.0, 13.7; FAB-MS m/z 160 (M + H). Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.88; H, 8.08; N, 8.71.

(2*Z*)-1-[(Azidocarbonyl)oxy]hexene (23). The azidoformate **23** was prepared by the same method used for the preparation of **6** on a 6 mmol scale in 93% yield as a colorless oil from commercially available *cis*-2-hexen-1-ol (**22**): ^{1}H NMR ($CDCl_3$) δ 5.55 (m, 1H), 5.50 (m,1H), 4.65 (d, 2H), 2.00 (m, 2H), 1.30 (m, 2H), 0.80 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 157.0, 136.2, 121.9, 63.7, 29.2, 22.2, 13.1; IR (neat) 3029, 2167, 1731 cm^{-1}; HRMS calcd for $C_7H_{11}N_3O_2$ 169.0852, found 169.0861.

Preparation of (4*R,6*S**)-6-Propyl-1-oxa-3-azabicyclo-[3.1.0]hexan-2-one (20a) and (4*R**,6*R**)-6-Propyl-1-oxa-3-azabicyclo[3.1.0]hexan-2-one (20b) from 23.** The aziridines **20a** and **20b** were prepared by the same method used for the preparation of **8a** and **8b** on a 2.54 mmol scale in 78% yield from **23** as a 1:2 mixture of **20a** and **20b**, respectively: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.35 (m, 2H), 3.15 (m, 1H), *2.95 (m, 0.5H), 2.65 (m, 1H, J = 4.81 Hz (decoupled signal at 1.45 ppm)), *2.35 (m, 0.5H, J = 3.68 Hz (decoupled signal at 1.45 ppm)), 1.45 (m, 4H), 0.90 (m, 3H) (* indicates minor isomer); NOE experiment ($CDCl_3$, 500 MHz), irradiation of peak at 3.15 ppm shows a 7.45% enhancement of signal at 2.65 ppm and a 6.60% enhancement of signal at 4.35 ppm; irradiation of peak at *2.95 ppm shows a 1.47% enhancement of signal at *2.35 ppm and a 2.91% enhancement of signal at 4.35 ppm; irradiation of peak at 2.65 ppm shows a 7.34% enhancement of signal at 3.15 ppm; irradiation of peak at *2.35 ppm shows a 0.97% enhancement of signal at *2.95 ppm.

Acknowledgment. This project was funded in part by the American Association of Colleges of Pharmacy Grant Program for New Investigators with funds from The Burroughs Wellcome Fund and the American Foundation for Pharmaceutical Education.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **5**−**9**, **10e**, **10f**, **11**, **13**, **14c**, **14d**, **15a**−**d**, **16a**−**d**, **17b**, **17c**, **19**, **20a**, **20b**, and **23** (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970473X