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Regio- and Stereoselectivity of Diethylaluminum Azide Opening of Trisubstituted Epoxides and Conversion of the 3° Azidohydrin Adducts to Isoprenoid Aziridines

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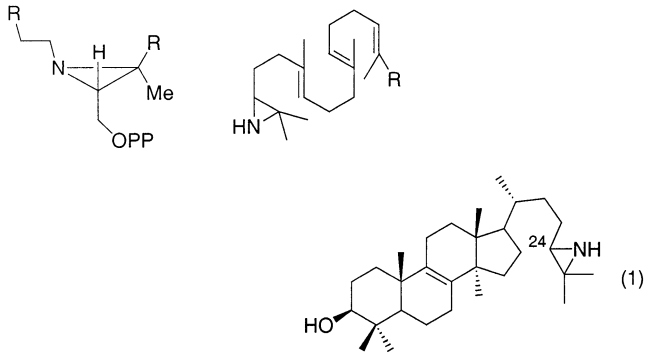
The regioisomer ratios (3°,2°/2°,3°), and in some cases the stereochemistry, of vicinal azidohydrins formed in reactions of 11 trisubstituted terpene epoxides with Et_2AlN_3 in toluene are reported. The more highly substituted azide usually predominated (3°,2°/2°,3° ratios ≥ 40:1 to 2.5−1) in accord with a Markovnikov orientation and an S_N1-like transition state. Reversed regioisomer ratios were observed with 6,7-epoxygeranyl acetate (1:2.5) and *cis*-1,2-epoxylimonene (1:3.3 to 1:10). The tertiary azido diols from 2,3-epoxygeraniol, 2,3-epoxyfarnesol, and 2,3-epoxynerol were formed as single isomers with inversion of configuration at C3 (≥ 35−40:1 for the C_{10} azido diols). The regioselectivity was affected by the presence and proximity of oxy functional groups on the epoxide substrate (OH, OAc, and OSi-tBuMe$_2$), the equivalents of Et_2AlN_3, and additives (EtOAc or EtOH). The results and trends are rationalized by consideration of the structural and stereoelectronic characteristics of proposed diethylaluminum epoxonium ion intermediates and transition states, together with the nucleophilicity of the azide donor. Six of the 3°,2° azidohydrins were converted to the corresponding aziridines by primary-selective silylations of four azido diols, mesylations, and reductive cyclizations with $LiAlH_4$.

Introduction

Aziridine analogues (eq 1) of presqualene pyrophosphate[1] and many polyene epoxides[2,3] in the protonated aziridinium forms are potential transition state inhibitors of enzymes associated with terpene and sterol biosynthesis.[4,5] However, in most cases the aziridines were prepared and assayed as racemic or diasteromeric mixtures. To understand and to characterize better the 3-dimensional interactions of these inhibitors with the respective enzyme active sites, we became interested in developing approaches for synthesis of these and related terpenyl aziridines as single enantiomers.

Although considerable research on enantioselective synthesis of aziridines is evident in the recent literature,[6] most methods are limited to, or investigated for, access to mono- and disubstituted types, and appear unsuitable for unactivated trisubstituted aziridines. The isoprenoid aziridine inhibitors have most commonly been obtained from the corresponding olefins by electrophilic addition of halo azide reagents followed by reductive cyclizations,[7]



(1)

or by epoxide formation, opening to the azidohydrin, and reductive cyclization of the azido sulfonate.[2,8] Since epoxides of trisubstituted olefins can be secured readily by asymmetric epoxidation,[9] or by asymmetric dihydroxylation,[10] and subsequent conversion to the epoxide,

(1) Koohang, A.; Coates, R. M.; Owen, D.; Poulter, C. D. *J. Org. Chem.* **1999**, *64*, 6.

(2) Corey, E. J.; Ortiz de Montellano, P. R.; Lin, K.; Dean, P. D. G. *J. Am. Chem. Soc.* **1967**, *89*, 2797.

(3) Jannssen, G. G.; Nes, W. D. *J. Biol. Chem.* **1992**, *267*, 25856.

(4) For reviews on oxidosqualene cyclase inhibitors, see: (a) Cattel, L.; Ceruti, M.; Viola, F.; Delprino, L.; Balliano, G.; Duriatti, A.; Bouvier-Nave, P. *Lipids* **1986**, *21*, 31. (b) Abe, I.; Rohmer, M.; Prestwich, G. D *Chem. Rev.* **1993**, *93*, 2189. (c) Abe, I.; Tomesch, J. C.; Wattanasin, S.; Prestwich, G. D *Nat. Prod. Rep.* **1994**, *11*, 279.

(5) For other examples and references for isoprenoid aziridine inhibitors, see: Koohang, A.; Stanchina, C. L.; Coates, R. M. *Tetrahedron* **1999**, *55*, 9669.

(6) (a) Coull, W. M. *Synthesis* **2000**, 1347. (b) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599. (c) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (d) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519. (e) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: Oxford, UK, 1996; p 1. (f) Rai, K. M.; Hassner, A. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Pergamon: Oxford, UK, 1996; p 61. (g) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559. Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.

(7) (a) Avruch, L.; Oehlschlager, A. C. *Synthesis* **1973**, 622. (b) Van Ende, D.; Krief, A. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 279. (c) Parrish, E. J.; Nes, W. D. *Synth. Commun.* **1988**, *18*, 221. (d) Nes, W. D.; Parrish, E. J. *Lipids* **1988**, *23*, 375.

(8) Corey, E. J.; Riddiford, L. M.; Ajami, A. M.; Yamamoto, H.; Anderson, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 1815.

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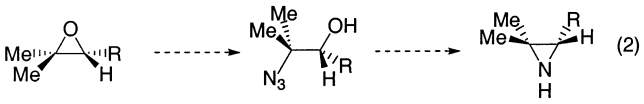
the latter approach appears quite attractive for this purpose. However, the methods for converting a chiral epoxide to the enantiomeric aziridine depend critically upon a Markovnikov orientation in the epoxide opening reaction with nitrogen nucleophiles such as azide to form the 3°,2° azido alcohol (eq 2) owing to the difficulty of activating the tertiary hydroxyl group in the regioisomeric 2°,3° azidohydrins. Unfortunately the low acidity of HN_3 together with the high nucleophilicity of azide ion and covalent azide donors usually favor the anti-Markovnikov adduct in reactions with trisubstituted epoxides.[11−13]



(2)

The use of oxyphilic organometallic azide reagents such as organoaluminum and organotitanium azides for Markovnikov opening of epoxides affords an appealing alternative. Thus the reaction of diethylaluminum azide (generated in solution from Et_3Al and HN_3) with 1-methylcyclohexene epoxide resulted in exclusive formation of the trans 3°,2° azidohydrin.[14] Similar electrophilic opening of 2,3-epoxy-3-methylbutenol with diethylaluminum azide (generated from Et_2AlCl and NaN_3) afforded a mixture of the Markovnikov adducts as azido- and chorohydrins.[15] Exclusive Markovnikov orienation was also observed in the reaction of 2,3-epoxygeraniol with $(iPrO)_2Ti(N_3)_2$,[16,17] although a substantial amount of the methylene diol arising from competing elimination was also formed.[16] In this paper we report the results of an investigation on the regio- and stereoselectivity of azide openings of representative trisubstituted isoprenoid epoxides with diethylaluminum azide and conversion of selected 3°,2° azidohydrins to the corresponding trisubstituted aziridines.

Epoxides, Diethylaluminum Azide Reagent, and Hydroazidation Procedure

A series of twelve trisubstituted epoxides with different electronic and structural environments was used in this study. 2,3-Epoxides of (*E*,*E*)-farnesol, geraniol, and nerol (**1**, **2**, and **5**) were chosen to establish the stereochemistry of azide addition and to prepare the way for synthesis of enantio pure aziridine inihibitors. Other epoxides selected were six 6,7-epoxygeranyl and 6,7-epoxycitronellyl derivatives (**7-OH**, **7-OAc**, **7-OTBS**, **9-OH**, **9-OAc**, and **9-OTBS**), *trans*- and *cis*-1,2-epoxylimonene isomers (**11** and **12**), and 24,25-epoxy lanosterol *tert*-butyldimethylsilyl ether (**15-OTBS**). The 2,3-epoxides were prepared by hydroxyl-directed epoxidations of (*E*,*E*)-farnesol, geraniol, and nerol ($VO(acac)_2$, *t*-BuOOH).[18] Most of the others were obtained by selective epoxidations of the precursor terpenols with *m*-$ClC_6H_4CO_3H$ followed by acetylation or silylation. Terminal epoxidation of geranyl acetate afforded **7-OAc**, saponification of which provided **7-OH**. A trans−cis mixture of limonene−1,2-epoxides is commercially available. The epoxides derived from citronellol and lanosterol were 1:1 mixtures of diastereomers.

Solutions of diethylaluminum azide in toluene were generated before use by reaction of sodium azide with commercial diethylaluminum chloride in toluene (room temperature, 6 h) according to a literature procedure.[15] Azide addition reactions were carried out by adding solutions of the epoxide in toluene to usually 2 molar equiv of Et_2AlN_3 in toluene at −78 °C, 0 °C, or room temperature for the times shown in Table 1. In some cases 1 equiv of ethyl acetate or ethanol was added to evaluate the effect of a polar coordinating carbonyl group or a proton donor. Reactions were stopped by dilution with ethyl acetate. Hydrolysis of the aluminoxide intermediates and isolation of the crude azidohydrin products were accomplished by adding solid NaF and water, and filtering through anhydrous Na_2SO_4.[15] Reaction progress was monitored by the disappearance of the epoxide starting material by TLC analysis of aliquots.

Ratios and Identification of Azidohydrin Adducts

The principal results of reactions of Et_2AlN_3 with the isoprenoid epoxide substrates are summarized in Table 1 and eqs 3−8. The tertiary azido diols **3**, **4**, and **6** from 2,3-epoxides of farnesol, geraniol, and nerol (**1**, **2**, and **5**) were formed as single isomers and obtained in 66, 54, and 63% yields, respectively, after purification by flash chromatography on silica gel (eqs 3 and 4). Integration ($C3-CH_3$ signals) of the proton NMR spectra of the crude products from **2** and **5** spiked with small amounts of **6** and **4** demonstrated that azide capture at C3 was essentially stereospecific (≥97%), i.e. isomer ratios ≥ 35−40:1. Furthermore no other isomers such as the regio-

(9) (a) Sharpless, K. B.; Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

(10) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, *248*.

(11) Anderson, R. J.; Henrick, C. A.; Siddall, J. B. *J. Org. Chem.* **1972**, *37*, 1266.

(12) For reviews see: (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (b) *The Chemistry of the Azide Group*; Patai, S., Ed.; Wiley: New York, 1971.

(13) For recent articles and leading references, see: (a) aq NaN_3 and polymeric phase transfer catalyst: Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* **2001**, *42*, 8721. (b) NaN_3 and metal salt catalysts: Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 5641. (c) Me_3SiN_3 and $Yb(OiPr)_3$ catalyst: Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1021. (d) aq NaN_3 and catalysts: Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **1999**, *64*, 6094. (e) Me_3SiN_3 and $Al(OiPr)_3$ or $Ti(OiPr)_4$ catalyst: Sutowardoyo, K. I.; Emziane, M.; Lhoste, P.; Sinou, D. *Tetrahedron* **1991**, *47*, 1435. (f) $NaN_3/PhB(OH)_2$ with 2,3-epoxy alcohols: Hayakawa, H.; Okada, N.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1999**, *40*, 4589. (g) Chiral Cr(III) complexes and meso epoxides: Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197. (h) N_3- or Me_3SiN_3 and transition metal catalysts: Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, L. E.; Pineschi, M. *Tetrahedron Lett.* **1996**, *37*, 1675. (i) NaN_3/NH_4Cl and 2,3-epoxyalcohols: Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696.

(14) Mereyala, H. B.; Frei, B. *Helv. Chim. Acta* **1986**, *69*, 415.

(15) Benedetti, F.; Berti, F.; Norbedo, S. *Tetrahedron Lett.* **1998**, *39*, 7971.

(16) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185.

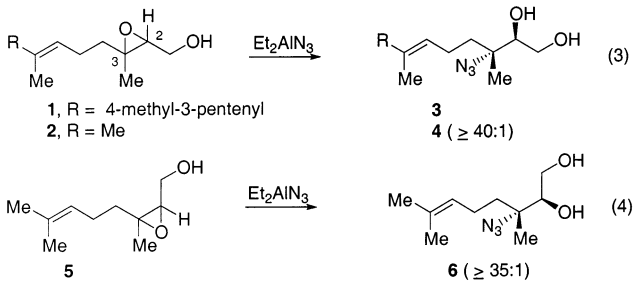
(17) (a)Aguilar, N.; Moyana, A.; Pericás, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 3560. (b) Reddy, K. S.; Solá, L.; Moyano, A.; Pericás, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969.

(18) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63. (c) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254.

TABLE 1. Regioisomer Ratios and Yields of Azidohydrins from Reaction of Et_2AlN_3 with Epoxides (eqs 3−8)

	epoxide		conditions[a]				azidohydrin product(s)		
entry	name	no.	variation[b]	temp (°C)	time (h)	conversion (%)[c]	no.	3°N_3/2°N_3[d]	yield (%)[e]
1	2,3-epoxy-farnesol	**1**		−78	1		**3**		66
				rt	16				
2	2,3-epoxy-geraniol	**2**					**4**	≥40:1	54
3	2,3-epoxy-nerol	**5**					**6**	≥35:1	63
4	6,7-epoxy-geraniol	**7-OH**		0	0.50		**8a,b-OH**	13:1	69
5	6,7-epoxy-geranyl acetate	**7-OAc**		−78	22	94	**8a,b-OAc**	1:2.5	81
6	6,7-epoxy-citronellol[f]	**9-OH**		0	0.50		**10,ab-OH**	11:1	72
7	6,7-epoxy-citronellyl acetate[f]	**9-OAc**		−78	22	70	**10a,b-OAc**	3:1	68
8				0	0.50			4.5:1	89
9			5 equiv[g]	0	0.50			5.9:1	78
10	6,7-epoxy-citronellyl silyl ether[f]	**9-OTBS**		−78	22	77	**10a,b-OTBS**	5.8:1	78
11				0	0.50			5:1	68
12			EtOAc[h]	0	0.50	75		2.5:1	75
13	1,2-epoxy limonenes[i]	**11** (trans)		0	0.17		**13**	5:1	89
		12 (cis)					**14a,b**	1:5	83
14				−78	0.17	96		>10:1	73
						62		1:6	14
15			EtOH[j]	0	0.25			≥5:1	69
								1:3.3	52
16			EtOAc[h]	0	0.25			≥10:1	83
								1:10	75
17			1 equiv[k]	rt	6			≥6:1	51
								1:4	31
18			EtOH[l]	−78	0.50	0			
19	24,25-epoxy lanosterol silyl ether[f]	**15-OTBS**		0	1		**16a,b-OTBS**	3:1	55

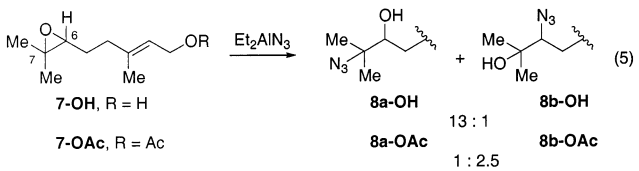
[a] 2 equiv of Et_2AlN_3 in toluene unless noted otherwise. rt = room temperature. [b] Equivalents of Et_2AlN_3 or ethyl acetate added or ethanol added. [c] Conversion based on the amount of recovered epoxide estimated by ^{1}H NMR analysis and/or isolated yield. Conversion was ∼100% unless specified otherwise. [d] Isomer ratio was determined by ^{1}H NMR analysis of crude product. The azidohydrins obtained from the citronellyl derivatives were ∼1:1 mixtures except **10b-OAc** was a ∼2:1 mixture of diastereomers. [e] Yields are based on the amount of unrecovered epoxides in incomplete reactions. [f] An approximate 1:1 mixture of diastereomers. [g] 5 equiv of Et_2AlN_3. [h] 1 equiv of ethyl acetate added. [i] A 1:1.3 mixture of trans and cis epoxides. [j] 1 equiv of ethanol added. [k] 1 equiv of Et_2AlN_3. [l] 2 equiv of ethanol added.



isomeric 2° azidohydrins could be detected although small amounts (5−6%) of the known 3-methylene-1,2-diol elimination byproduct[16,19] were isolated from reactions of the 2,3-epoxy monoterpene alcohols. Preliminary attempts to effect azide addition to 2,3-epoxyfarnesyl benzyl and *tert*-butyldimethylsilyl ethers with NaN_3,/NH_4Cl,[13i] Et_3Al/HN_3,[14] Et_2AlN_3,[15] and $Ti(OiPr)_2(N_3)_2$[16] were largely unsuccessful or proceeded slowly in low yields.

The racemic azidohydrin products were characterized by appropriate ^{1}H NMR, ^{13}C NMR, IR (N═N═N and O−H stretch), and mass spectral data. However the distinction of the two isomeric possibilities was somewhat subtle owing to the similarity of the chemical shifts for the C*H*OH and C*H*N_3 protons and the complex ABX spin systems for the C*H*XC*H*$_2$OH group. The tertiary azide and secondary hydroxyl structures shown were confirmed by conversion to the corresponding silyl azido mesylates (*t*-BuMe_2SiCl; MsCl) and reductive cyclizations ($LiAlH_4$) to the known 2,3-aziridino alcohols described in more detail below (eqs 9 and 10). The C2 C*H*OMs protons (δ_H 4.56−4.57) of the silyl azido mesylates intermediates are shifted downfield considerably by the methanesulfonyl substituent, thus verifying that the hydroxyl group had been secondary. Furthermore, it seems unlikely that the tertiary mesylates derived from the 2°,3° azido diols would have been stable on silica gel during chromatographic purifications.

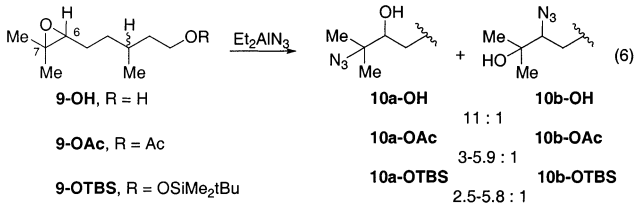
The reactions of the 6,7-epoxides of geraniol and citronellol and their OH derivatives with Et_2AlN_3 afforded mixtures of tertiary and secondary azidohydrins with ratios varying from 13:1 to 1:2.5 (eqs 5 and eq 6, and Table 1). Product ratios were estimated by ^{1}H NMR



analysis of the product mixtures prior to purification. High ratios favoring tertiary azido diols **8a-OH** (13:1) and **10a-OH** (11:1) were obtained from the epoxy alcohols whereas the acetates and silyl ethers gave considerably

(19) Morgans, D. J.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 462.

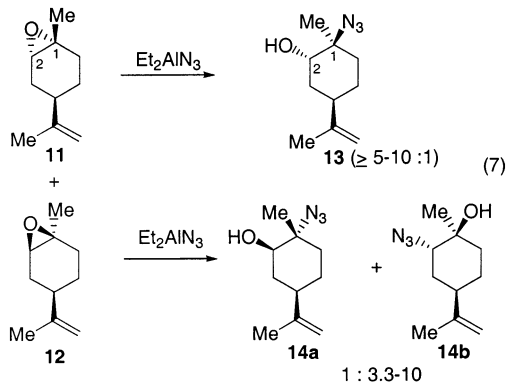
lower selectivities. Remarkably the product distribution for epoxy acetate **7-OAc** favored the opposite isomers (**8a-OAc**/**8b-OAc** 1:2.5) and the ratio for epoxy acetate **9-OAc** was markedly decreased (**10a-OAc**/**10b-OAc** 3:1) under comparable conditions (2 equiv of Et_2AlN_3, −78 °C). The selectivity in the latter case increased to 5.9:1 when 5 equiv of Et_2AlN_3 at 0 °C was used instead of 2. All of the citronellol azidohydrins were 1:1mixtures of distereomers with the exception of the secondary azidoacetate (**10b-OAc**) that was 2:1.



Although similar 3°/2° azide adducts (∼6.5:1) seemed to be formed in reactions of **7-OTBS**, full characterization of the products was not carried out in this case owing to the multicomponent product mixtures formed, extensive purification needed, and low recoveries obtained. However, the corresponding reactions of **9-OTBS** gave satisfactory yields and consistent ratios (−78 °C, 5.8:1, 78%; 0 °C, 5:1, 68%). The reactions of both **7-OAc** and **9-OTBS** were incomplete at −78 °C after 22 h (∼70−77% conversions). The presence of 1 equiv of ethyl acetate in the latter case resulted in a much slower rate (0 °C, 0.5 h, 75% conversion) and a lower regioisomer ratio (2.5:1).

The isomers were readily separated by flash chromatography owing to the increased polarity of the 2° azidohydrins (tertiary OH). The rather small chemical shift differences between the C6 protons in the ^{1}H NMR spectra of less polar isomers (C*H*OH δ_H 3.30) compared to those of the more polar isomers (C*H*N_3 δ_H 3.11) were insufficient for conclusive assignments. However, as in the case of the 2,3 azidohydrins above, the structures were confirmed by the downfield shifts for the C*H*OMs protons in the derived silyl azido mesylate (eq 11). The azidohydrin acetates **8b-OAc** and **10b-OAc** were correlated with the corresponding diols **8b-OH** and **10b-OH** by methanolysis of the esters, and tertiary azido diol **10a-OH** was interrelated with **10a-OTBS** by selective silylation of the primary hydroxyl group.

The reactions of Et_2AlN_3 with a 1:1.3 mixture of *trans*- and *cis*-limonene-1,2-epoxides (eq 7 and Table 1)

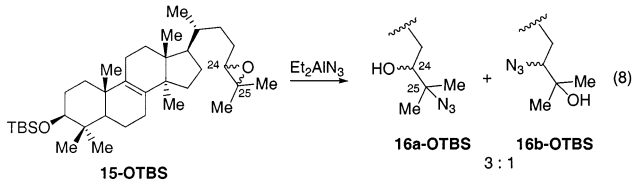


were investigated to evaluate the stereoelectronic effects in addition to these conformationally fixed trisubstituted oxiranes. Since each isomer gives a discrete set of readily identifiable azidohydrin products that could be analyzed by ^{1}H NMR analysis of the mixture, there seemed to be no compelling reason to study the pure isomers individually. As expected the reactions of the trans epoxide (**11**) afforded tertiary trans diaxial azidohydrin **13** as the only identified product with selectivities ≥ 5−10:1. In contrast the cis isomer **12** gave mixtures in which the secondary diaxial azidohydrin **14b** was the major product (**14a**/**14b** ratios 1:3.3−10). The higher reactivity of the trans epoxide was evident from the reaction at −78 °C, which resulted in 96% conversion of **11** to **13** (≥ 10:1 selectivity) as opposed to 62% conversion of **12**.

The product ratio from cis epoxide **12** proved to be dependent on the additives and the equivalents of Et_2AlN_3 reagent used. Lower anti-Markovnikov selectivity was observed in the presence of 1 equiv of EtOH (1:3.3) and when only 1 equiv of the aluminum reagent was employed. However, the anti-Markovnikov selectivity increased to 1:10 in the presence of 1 equiv of EtOAc. Although the EtOH additive appears to enhance the Markovnikov selectivity somewhat (1:3.3), the presence of the proton donor clearly depresses the rate of opening of the trans epoxide at −78 °C.

Pure samples of the azidohydrin products **13**, **14a**, and **14b** were isolated by flash chromatography. The stereochemistry of the axial 2-OH and 2-N_3 substituents in the major azidohydrins **13** and **14b** was evident from the lack of vicinal ^{1}H NMR couplings (**13**: δ_H 3.64, s; **14b**: δ_H 3.52, s), and the equatorial position of secondary OH in **14a** could be assigned in the same manner (δ_H 3.59, dd, J = 11.8, 4.5 Hz). The configurations of the tertiary azide substituents in **13** and **14a** were assumed to be trans to the adjacent secondary OH groups as a consequence of the expectation of trans openings. However, small amounts (≤ 5−10%) of other minor unidentified products isolated might have contained an azide functionality. The structure and trans stereochemistry of **13** were verified by conversion to the known *cis*-1,2-aziridino limonene by reductive cyclization of the corresponding mesylate (eq 12).[20]

Diethylaluminum azide-mediated opening of the 1:1 diastereomeric mixture of 24,25-epoxylanosterol *tert*-butyldimethylsilyl ethers **15-OTBS** by the usual procedure gave rise to a 3:1 mixture of tertiary and secondary azidohydrins **16a-OTBS** and **16b-OTBS** (eq 8) both of



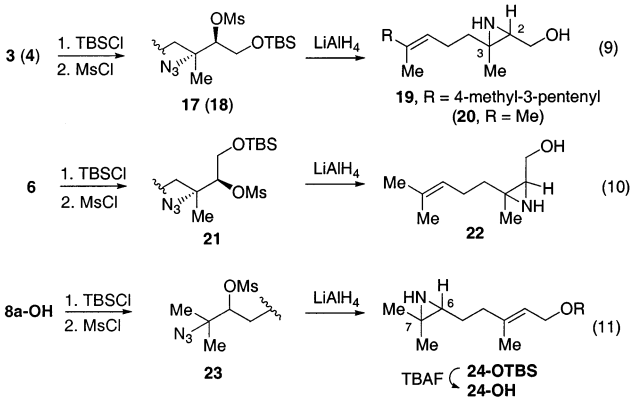
which were ∼1:1 mixtures of C-24 diastereomers, which could be separated by chromatography. The less polar isomer was determined to be the 3° isomer **16a-OTBS** based on the ^{1}H NMR shift upon conversion to the azido mesylate. Reactions of lanosterol 24,25-epoxide directly with Et_2AlN_3 afforded the azidohydrin adducts in much lower yield (24 and 32%) in two preliminary trials,

(20) Ferrero, L.; Geribaldi, S.; Rouillard, M.; Azzaro, M. *Can. J. Chem.* **1975**, *53*, 3227.

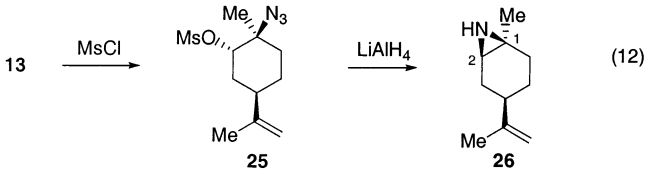
possibly owing to side products arising from hydrazoic acid generated by OH-Et_2Al exchange (see eq 14 below).

Conversion of Azidohydrins to Aziridines

Five of the monoterpene tertiary azidohydrins (eqs 9−12) and the diastereomeric lanosteryl azidohydrin mixture were converted to the corresponding aziridines. Azido diols **3**, **4**, **6**, and **8a-OH** were selectively silylated at the primary hydroxyl groups (*t*-$BuMe_2SiCl$, imidazole, DMAP, DMF, 0 °C).[21] The 1,2-diols afforded mixtures of primary (62−65%) and secondary isomers (14%) that were separated by flash chromatography. In contrast silylation of 1,6-diol **8a-OH** proceeded cleanly to the primary ether **8a-OTBS** (91%). The azidohydrin silyl ethers including **16a-OTBS** and limonene-derived azidohydrin **13** were converted to the corresponding azido mesylates with methanesulfonyl chloride (Et_3N, CH_2Cl_2, 0 °C).[22] The large downfield chemical shifts ($\Delta\delta_H$(CH→CHOMs) = 0.83−1.17) for the carbinyl protons (C*H*OMs)[23] confirmed the tertiary-secondary structures (**17**, **18**, **21**, **23**, **25**, and the diastereomeric mesylates of **16a-OTBS**).



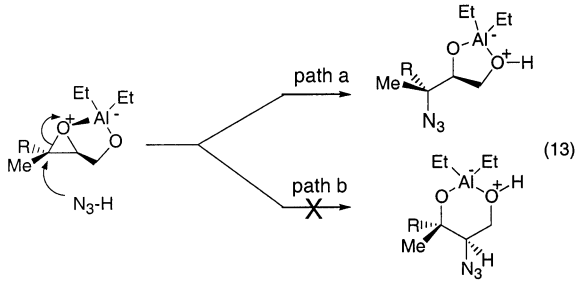
Reductive cyclizations of the azido mesylates **17**, **18**, and **21** proceeded with cleavage of the proximal silyl ethers to provide the known 2,3-aziridino farnesol, geraniol, and nerol (**19**, **20**, and **22**)[5] in moderate yields (43, 57, and 45% yields). The low yields are attributed to inefficient recovery of the potentially chelating azirdino alcohols from the aluminum salts formed in the hydrolysis step following the relatively small-scale $LiAlH_4$ reductions.[24] Reaction of azido mesylate **23** with $LiAlH_4$ gave aziridino ether **24-OTBS** (79%), which was desilated (Bu_4F, THF, 0 °C) to the known 6,7-aziridino geraniol (82%).[5,7b,c] Similar reductive cyclizations of limonene-derived azido mesylate **25** and the mesylate of **16a-OTBS** gave the known *cis*-1,2-aziridino limonene (50%)[20] and the silyl derivative of 24,25-aziridino lanosterol (75%), respectively.



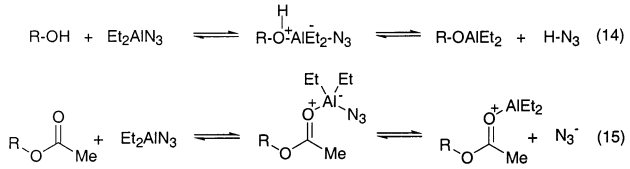
Discussion

The reactions of Et_2AlN_3 with the trisubstituted epoxides afforded the tertiary azido alcohols as the major product in most cases, consistent with an S_N1-like mechanism.[14,15] However, the isomer ratios varied considerably with the character of the substituents on the epoxide, functionality present, molar ratio, and absence or presence of a proton donor or ester additive.

The 2,3-epoxy isoprenoid alcohols underwent exclusive Markovnikov additions to form the tertiary azido diols **3**, **4**, and **6** with complete inversion of configuration at C3 (eq 13). The high regioselectivity is attributed to the



proximal hydroxyl group that either coordinates to the Et_2AlN_3 reagent or possibly exchanges proton for aluminum to form an aluminoxide intermediate and HN_3 (eq 14). Nucleophilic capture at C3 would be favored by displacement of an exocyclic leaving group (path a), as opposed to the endocyclic alternative (path b). Bias toward an S_N1-like mechanism with increased positive charge at carbon may also be caused by attack of a neutral azide nucleophile (HN_3 and/or excess Et_2AlN_3) upon the diethylaluminum epoxonium intermediate.



The significant effect of oxygen functionality present in the epoxide substrate on the regioselectivity is dramatically illustrated by comparison of the outcome of reactions with 6,7-epoxygeraniol (13:1 3° N_3/2° N_3 ratio) and the corresponding acetate (1:2.5 3° N_3/2° N_3 ratio). The tendency toward Markovnikov orientation with the epoxy alcohols may be a consequence of OH−$AlEt_2$ exchange (eq 14), proton catalysis, and a neutral, relatively weakly polarized HN_3 nucleophile. However, coordination of aluminum to the carbonyl group of the allylic acetate would presumably promote ionization (eq 15). The increased concentration of the highly nucleophilic azide anion would favor an S_N2-like transition state

(21) (a) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99. (b) Fujii, N.; Nakai, K.; Habashita, Y.; Hotta, Y.; Tamamura, H.; Otaka, A.; Ibuka, T. *Chem. Pharm. Bull.* **1994**, *42* (11), 2241.

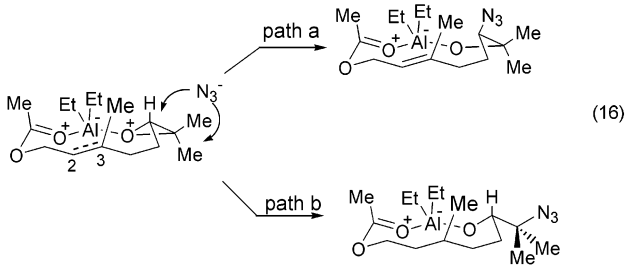
(22) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

(23) Pretsch, E.; Clerc, T.; Seibel, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin, Germany, 1989; p H145.

(24) Much higher yields (70 and 83%) were obtained in reductions of the enantiopure azido mesylates **18** conducted on gram scale (2.95 and 2.45 g): Bailey, J. L. MS Thesis, University of Illinois at Urbana−Champaign, 2000.

leading to the secondary azidohydrin. This inference is supported by the effect of the ethyl acetate additive, which resulted in decreased 3°/2° ratios (entries 12 and 16).

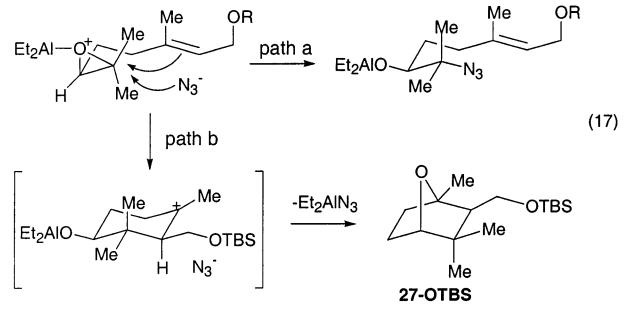
The regio-reversal between 6,7-epoxygeranyl acetate (1:2.5 3° N_3/2° N_3 ratio) and its 2,3-dihydro derivative 6,7-epoxycitronellyl acetate (3:1 3°/2° ratio) seems unlikely to be caused by a long-range electronic effect. The nonpolar medium and the tendency for the oxyphilic aluminum to become tetrahedral suggest the possibility of intramolecular coordination (eq 16). It seems plausible



(16)

that the different conformation(s) of the 11-membered dioxyaluminate rings from the rigid, planar 2,3-E double bond in the geranyl intermediate as opposed to the more flexible 2,3-ethano linkage of the citronellyl case would affect the regioselectivity of nucleophilic attack. Perhaps the 12-membered ring would better accommodate the E double bond, which would favor path a and formation of the 2°,3° adduct. On the other hand, the more conformationally mobile citronellyl moiety in the ring would permit azide capture at C7 and lead to Markovnikov orientation (path b). The deviation of the diastereomer ratio of citronellyl azidohydrin acetates **10b** (2:1 ratio by NMR analysis) from the expected 1:1 proportion may be explained by the influence of the C-3 configuration on the conformational properties of the distereomeric epoxonium-aluminate macrocyles.

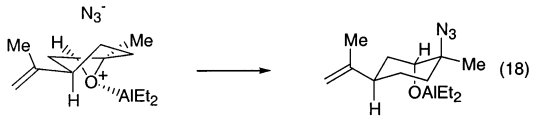
Several attempts to isolate the azido hydrin adducts from 6,7-epoxygeranyl *tert*-butyldimethylsilyl ether (**7-OTBS**) were frustrated by low yields and the presence of numerous side products. The bicyclic ether (**27-OTBS**, eq 17) was obtained in pure form (9%) and the spectral properties of the corresponding alcohol **27-OH** obtained by fluoride desilation correlate with literature data for this known product of Lewis acid-induced cyclizations of 6,7-epoxygeranyl acetate.[25] Evidently 2,3 double bond participation leading to cyclization onto the epoxonium ion (path b) competes with nucleophilic attack by an azide donor (eq 17). Nevertheless, the ratio of tertiary and



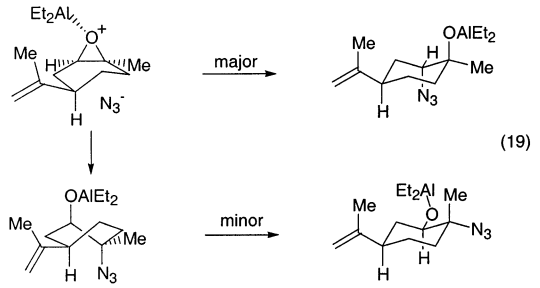
(17)

secondary azidohydrins **8a-OTBS** and **8b-OTBS** appeared to be similar to that of the related acetates **8a-OAc** and **8b-OAc**. The relative rate of π-cyclization must be somewhat depressed by the C1−OH (or C1−$OAlEt_2$) and C1−OAc substituents, which accounts for the higher yields of azide adducts in these cases.

The formation of a single trans azidohydrin from *trans*-1,2-epoxy limonene **11** is attributable to the reinforcing stereoelectronic and electronic effects (eq 18). Thus a Markovnikov orientation is favored by trans diaxial opening of the trans epoxonium ion through a chairlike transition state that gives rise to tertiary azido alcohol **13**. However, in the cis isomer the stereoelectronic and electronic effects are opposed to each other, and the major product was invariably the secondary azidohydrin **14b** arising from the opposite diaxial addition (eq 19). The minor tertiary azidohydrin **14a** is presumably formed through a strained twist boat intermediate that relaxes to the more stable trans diequatorial conformer.



(18)



(19)

In summary all but one of the trisubstituted epoxides underwent regioselective addition of the elements of HN_3 in the presence of Et_2AlN_3 to form azidohydrins bearing the tertiary azide as major products in accord with a Markovnikov orientation. The conversion of representative azidohydrins to the corresponding aziridines indicates enantiomerically or diasteromerically pure isoprenoid aziridines should be accessible from the corresponding epoxides by this means for evaluation of their inhibitory properties.

Experimental Section

A representative complete procedure for the epoxide opening reactions using Et_2AlN_3 in toluene is presented below in the case of 2,3-epoxyfarnesol (**1**). Amounts, conditions, and procedural variations for the epoxide reactions of 2,3-epoxygeraniol (**2**) and 2,3-epoxynerol (**3**) are given in the following abbreviated format: epoxide, reagents, temperature(s), time(s), crude product analysis. The procedures for synthesis of aziridines **19**, **20**, and **22** from the corresponding azidohydrins are detailed below. Other experimental procedures and data are presented in the Supporting Information.

(±)-(2*R,3*R**,6*E*)-3-Azido-3,7,11-trimethyl-6,10-dodecadien-1,2-diol (3).** The following procedure is based on that reported by Benedetti.[15] A suspension of NaN_3 (1.23 g, 18.9 mmol) in toluene (14 mL) was stirred and cooled at 0 °C as a solution of diethylaluminum chloride (9.44 mL, 17.1 mmol, 1.8 M in toluene) was added dropwise over 10 min via syringe. After 6 h at room temperature, the resulting suspension was

(25) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Palomino, P. L. *Tetrahedron* **1994**, *50*, 13239.

cooled to −78 °C under N_2, and a solution of (±)-2,3-epoxyfarnesol (**1**, 2.03 g, 8.53 mmol) in toluene (5.5 mL) was added dropwise over 10 min. The mixture was stirred for 1 h at −78 °C and for 16 h at room temperature, cooled to 0 °C, and diluted with EtOAc (40 mL). NaF (16.2 g) and H_2O (2.1 mL) were added sequentially, and the heterogeneous mixture was allowed to stir for 4 h at room temperature. Filtration through a pad of anhydrous Na_2SO_4 (ca. 100 g) to remove salts and water followed by solvent evaporation gave 1.83 g of a pale yellow oil. Purification by flash column chromatography (50% EtOAc/hexanes) afforded 1.58 g (66%) of azido diol **3** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.48 (ddd, J = 14.0, 10.8, 6.1 Hz, 1H), 1.60 (s, 3H), 1.62 (s, 3H), 1.64 (ddd, J = 14.1, 10.6, 5.9 Hz, 1H), 1.68 (s, 3H), 1.97 (3 peak m, 2H), 2.08 (br 8 peak m, 4H), 2.59 (s, 1H, exch with D_2O), 3.58 (br d, J = 7.0 Hz; AB*X* upon D_2O exch, J_{AX} = 3.2 Hz, J_{BX} = 7.7 Hz; 1H), 3.65 (br dd, J = 11.2, 7.7 Hz; A*B*X upon D_2O exch, J_{AB} = 11.2 Hz, J_{BX} = 7.7 Hz, 1H), 3.74 (br dd, J = 11.2, 3.0 Hz; *A*BX upon D_2O exch, J_{AB} = 11.2 Hz, J_{AX} = 3.2 Hz, 1H), 5.09 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.79, 17.47, 19.16, 22.02, 25.47, 26.39, 36.32, 39.42, 62.31, 65.4, 75.94, 122.82, 123.96, 131.32, 136.01; IR 3386 (OH), 2103 (N_3). Anal. Calcd for $C_{15}H_{27}N_3O_2$ (MW 281.39): C, 64.02; H, 9.67; N, 14.93. Found: C, 64.35; H, 9.52; N, 14.94.

(±)-(2*R,3*R**,6*E*)-3-Azido-3,7-dimethyl-6-octen-1,2-diol (4).** (±)-2,3-Epoxygeraniol (**2**, 1.00 g, 5.90 mmol), NaN_3 (0.85 g, 13.02 mmol), Et_2AlCl (6.6 mL, 11.83 mmol, 1.8 M in toluene), PhMe (10 mL); rt; 16 h; 1.05 g. Column purification of a 700-mg sample in the same manner as that described for **3** gave 0.436 g (54% based on recovered epoxide) of azido diol **4** as a pale yellow oil and 48 mg (6%) of the known enediol byproduct.[16] **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.47 (ddd, J = 13.9, 10.9, 5.8 Hz, 1H), 1.62 (s, 3H), 1.69 (d, J = 1.1 Hz, 3H), 1.65 (ddd, J = 14.1, 10.7, 4.7 Hz, 1H), 2.02−2.14 (10 peak m, 2H), 2.40−2.70 (br s, 2H, exch with D_2O), 3.57 (AB*X*, J_{AX} = 3.2 Hz, J_{BX} = 7.7 Hz, 1H), 3.66 (A*B*X, J_{AB} = 11.1 Hz, J_{BX} = 7.7 Hz, 1H), 3.75 (*AB*X, J_{AB} = 11.1 Hz, J_{AX} = 3.2 Hz, 1H), 5.08 (t sept, J = 7.1, 1.5 Hz, 1H); ^{13}C (126 MHz, $CDCl_3$) δ 17.42, 19.14, 22.11, 25.44, 36.32, 62.29, 65.41, 75.94, 122.96, 132.40; IR 3389 (OH), 2105 (N_3); MS (FI) *m*/*z* 214.2. Some peaks of the enediol (∼11%) were also present [δ 4.99 (s, 0.1H), 5.11 (s, 0.1H)] and the data correspond to the literature values.[16]

(±)-(2*S,3*R**,6*E*)-3-Azido-3,7-dimethyl-6-octen-1,2-diol (6).** (±)-2,3-Epoxynerol (**5**, 1.01 g, 5.95 mmol), NaN_3 (0.85 g, 13.03 mmol), Et_2AlCl (6.6 mL, 11.85 mmol, 1.8 M in PhMe), PhMe (10 mL); rt; 16 h; 0.97 g. Column purification of an 850-mg portion was carried out as described for **3** to give 0.690 g (63% based on recovered epoxide) of azido diol **6** as a pale yellow oil and 60 mg (5%) of the enediol. Data for azido diol **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.60 (ddd, J = 13.7, 10.9, 5.4 Hz, 1H, H4), 1.63 (s, 3H), 1.69 (d, J = 1.0 Hz, 3H), 1.73 (ddd, J = 13.9, 10.9, 5.8 Hz, 1H), 2.0−2.20 (br 10 peak m, 3H), 2.52−2.61 (br s, 1H, exch with D_2O), 3.63 (br 3 peak m, 2H), 3.74 (br 4 peak m, 1H), 5.10 (t sept, J = 7.1, 1.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 17.41, 18.85, 22.14, 25.44, 36.44, 62.29, 65.60, 75.81, 122.90, 132.36; IR 3389 (OH), 2111 (N_3); MS *m*/*z* 214.2; HRMS (CI+) *m*/*z* calcd for $C_{10}H_{19}N_3O_2$: 214.1809. Found: 214.1807. Some peaks of the enediol were also present (∼6%): δ 4.99 (s, 0.06H), 5.10 (s, 0.06H).

(±)-(2*R,3*R**,6*E*)-3-Azido-3,7,11-trimethyl-6,10-dodecadien-1,2-diol 1-*tert*-Butyldimethylsilyl Ether (3-OTBS).** The following procedure is based on that reported by Fujii and Ibuka.[21] A solution of the azido diol (**3**, 1.00 g, 3.57 mmol), imidazole (1.44 g, 21.2 mmol), and 4-DMAP (44 mg, 0.359 mmol) in DMF (5 mL) was stirred and cooled at 0 °C under N_2 as TBDMSCl (1.59 g, 10.6 mmol) in DMF (6 mL) was added dropwise over 5 min. The solution was warmed to room temperature and after 30 min ethanolamine (0.647 mL, 10.7 mmol) was added to scavenge excess TBDMSCl. After 2 h, H_2O (3 mL) was added, and the product was extracted with benzene (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to give 1.10 g of a colorless oil. Purification by flash column chromatography (5% EtOAc/hexanes) afforded 892 mg (65%) of the primary silyl ether and 198 mg (14%) of the secondary silyl ether in elution order. Data for primary silyl ether **3-OTBS**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.32 (s, 3H), 1.46 (ddd, J = 13.9, 10.2, 5.9 Hz, 1H), 1.60 (s, 3H), 1.62 (s, 3H), 1.63 (m, 1H), 1.68 (s, 3H), 1.98 (3 peak m, 2H), 2.08 (br 8 peak m, 4H), 2.78 (d, J = 2.93 Hz, 1H, exch with D_2O), 3.56 (AB*X* upon D_2O exch J_{AX} = 3.2 Hz, J_{BX} = 8.1 Hz, 1H), 3.61 (A*B*X upon D_2O exch, J_{AB} = 9.7 Hz, J_{BX} = 8.1 Hz, 1H), 3.74 (*AB*X upon D_2O exch, J_{AB} = 9.7 Hz, J_{AX} = 3.2 Hz, 1H), 5.10 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.62, 15.74, 17.46, 17.99, 18.93, 21.91, 25.47, 25.62, 26.42, 36.40, 39.44, 62.60, 64.69, 75.49, 123.12, 124.04, 131.23, 135.66; IR 3568 (OH), 2103 (N_3). Anal. Calcd for $C_{21}H_{41}N_3O_2Si$ (MW 395.65): C, 63.75; H, 10.44; N, 10.62. Found: C, 64.14; H, 10.49; N, 9.99. MS *m*/*z* 395.6. Data for secondary silyl ether: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 1.46 (ddd, J = 13.9, 10.2, 5.9 Hz, 1H), 1.58 (s, 3H), 1.60 (s, 3H), 1.62 (s, 3H), 1.62 (m, 1H), 1.68 (s, 3H), 1.98 (3 peak m, 2H), 2.08 (br 8 peak m, 4H), 3.55 (dd, J = 8.3, 3.2 Hz, 1H), 3.61 (dd, J = 9.4, 7.9 Hz, 1H), 3.75 (dd, J = 9.5, 3.3 Hz, 1H), 5.10 (m, 2H).

(±)-(2*R,3*R**,6*E*)-3-Azido-1-(*tert*-butyldimethylsilyloxy)-3,7,11-trimethyl-6,10-dodecadien-2-yl Methanesulfonate (17).** The following procedure is based on that reported by Crossland.[22] A solution of the primary silyl ether (**3-OTBS**, 0.366 g, 0.926 mmol) and Et_3N (0.291 g, 2.87 mmol) in CH_2Cl_2 (4 mL) was stirred and cooled at 0 °C under N_2 as neat methanesulfonyl chloride (0.402 g, 2.78 mmol) was added dropwise over 10 min. After 1 h, ice-cold H_2O (2 mL) was added, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with satd NaCl (2 × 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 400 mg of a yellow oil. Purification by flash column chromatography (5% EtOAc/hexanes) afforded 336 mg (78%) of the azido mesylate **17** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.40 (s, 3H), 1.58 (m, 1H), 1.60 (s, 3H), 1.62 (s, 3H), 1.64 (m, 1H), 1.68 (s, 3H), 1.97 (m, 2H), 2.10 (m, 4H), 3.15 (s, 3H), 3.86 (A*B*X, J_{AB} = 11.7 Hz, J_{BX} = 7.7 Hz, 1H), 3.94 (*AB*X, J_{AB} = 11.7 Hz, J_{AX} = 2.6 Hz, 1H), 4.57 (AB*X*, J_{AX} = 2.6 Hz, J_{BX} = 7.7 Hz, 1H), 5.08 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.66, 15.79, 17.46, 18.15, 19.53, 21.90, 25.47, 25.66, 26.37, 36.80, 38.84, 39.43, 62.34, 64.12, 87.68, 122.43, 123.96, 131.28, 136.17; IR 2109 (N_3).

(±)-*trans*-3-((*E*)-4,8-Dimethyl-3,7-nonadienyl)-3-methylaziridine-2-methanol (19). The following procedure is based on that reported by Guedj.[26] A suspension of $LiAlH_4$ (28 mg, 0.520 mmol) in Et_2O (2 mL) was stirred and cooled at 0 °C under N_2 as a solution of the azido mesylate (**17**, 100 mg, 0.210 mmol) in Et_2O (1 mL) was added dropwise over 2 min via syringe. After 4 h, the gray suspension was cooled to 0 °C and stirred as H_2O (28 μL), 15% NaOH (28 μL), and H_2O (84 μL) were added sequentially with occasional additions of Et_2O to maintain the volume at ca. 3 mL. After 2 h, the white solid was filtered and washed with EtOAc (4 × 3 mL). The filtrates were combined, dried ($MgSO_4$), and concentrated under reduced pressure to give 30 mg of a pale yellow oil. Purification by flash column chromatography (10% MeOH/CH_2Cl_2) afforded 22 mg (43%) of aziridine **19** as a colorless oil. The ^{1}H and ^{13}C NMR spectral data and assignments correspond to those reported in the literature.[1,5,27]

(±)-(2*R,3*R**,6*E*)-3-Azido-3,7-dimethyl-6-octen-1,2-diol 1-*tert*-Butyldimethylsilyl Ether (4-OTBS).** The silyl ether was prepared as described previously for **3** using azido diol **4** (478 mg, 2.24 mmol), imidazole (918 mg, 13.50 mmol),

(26) Forestier, M. A.; Ayi, A. Y.; Condom, R.; Boyode, B. P.; Conlin, J. N.; Selway, J.; Challand, R.; Guedj, R. *Nucleosides Nucleotides* **1993**, *12* (9), 915.

(27) Koohang, A., Ph.D. Thesis. University of Illinois at Urbana−Champaign, 1999.

4-DMAP (28 mg, 0.23 mmol), and TBDMSCl (1.016 g, 6.74 mmol) in DMF (7 mL). After 0.5 h, ethanolamine (4.30 g, 6.95 mmol) was added. Isolation of the crude product (925 mg) and purification in the same manner as that described for compound **3** gave 457 mg (62%) of the primary silyl ether and 105 mg (14%) of the secondary silyl ether. Data for primary silyl ether (**4-OTBS**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.32 (s, 3H), 1.45 (ddd, J = 14.1, 11.1, 5.8 Hz, 1H), 1.60 (m, 1H), 1.63 (s, 3H), 1.69 (d, J = 1.1 Hz, 3H), 2.04−2.12 (6 peak m, 2H), 2.79 (br s, 1H, exch with D_2O), 3.56 (AB*X*, J_{AX} = 3.4 Hz, J_{BX} = 8.2 Hz, 1H), 3.61 (A*B*X, J_{AB} = 9.4 Hz, J_{BX} = 8.2 Hz, 1H), 3.74 (*A*BX, J_{AB} = 9.4 Hz, J_{AX} = 3.4 Hz, 1H), 5.10 (t sept, J = 7.1, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.39, 19.17, 22.20, 25.68, 25.84, 36.61, 53.07, 62.78, 64.86, 75.65, 123.44, 123.49, 132.28; IR 3569 (OH), 2105 (N_3). Data for secondary silyl ether: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 3H), 0.16 (s, 3H), 0.95 (s, 9H), 1.49 (m, 1H), 1.57 (s, 3H), 1.64 (s, 3H), 1.64 (m, 1H), 1.70 (d, J = 1.2 Hz, 3H), 1.97 (dd, J = 6.9, 5.3 Hz, 1H), 2.08 (m, 2H), 3.60 (app t, J = 4.5 Hz, 1H), 3.70 (app dd, J = 9.5, 4.5 Hz, 1H), 3.79 (app dd, J = 9.4, 5.0 Hz, 1H), 5.09 (m, 1H).

(±)-(2*R,3*R**)-3-Azido-1-(*tert*-butyldimethylsilyloxy)-3,7-dimethyl-6-octen-2-yl Methanesulfonate (18).** The azido mesylate was prepared as described previously for **17** using primary silyl ether **4-OTBS** (425 mg, 1.30 mmol), Et_3N (421 mg, 4.16 mmol), and methanesulfonyl chloride (447 mg, 3.90 mmol) in CH_2Cl_2 (5 mL). Purification in the same manner as that described for compound **17** gave 383 mg (73%) of azido mesylate **18** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.39 (s, 3H), 1.56 (ddd, J = 14.2, 11.6, 5.6 Hz, 1H), 1.62 (s, 3H), 1.65 (m, 1H), 1.68 (d, J = 0.9 Hz, 3H), 2.02−2.17 (12 peak m, 2H), 3.15 (s, 3H), 3.86 (A*B*X, J_{AB} = 11.8 Hz, J_{BX} = 7.9 Hz, 1H), 3.94 (*A*BX, J_{AB} = 11.8 Hz, J_{AX} = 2.6 Hz, 1H), 4.57 (AB*X*, J_{AX} = 2.6 Hz, J_{BX} = 7.9 Hz, 1H), 5.07 (t sept., J = 7.1, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.51, 18.35, 19.64, 19.72, 22.19, 25.65, 25.93, 37.03, 39.09, 62.52, 64.27, 87.83, 122.72, 132.76; IR 2108 (N_3).

(±)-*trans*-3-(4-Methyl-3-pentenyl)-3-methylaziridine-2-methanol (20). The aziridine was prepared as described previously for (±)-2,3-aziridinofarnesol (**19**) using the azido mesylate (**18**, 355 mg, 0.876 mmol) and $LiAlH_4$ (94 mg, 2.46 mmol) in Et_2O (2 mL). After 5 h, H_2O (94 μL), 15% NaOH (94 μL), and H_2O (282 μL) were added dropwise in succession to give 100 mg of a colorless oil. Isolation and purification in the same manner as that described for compound **19** gave 85 mg (57%) of the aziridino alcohol **20** as a low-melting white solid. The aziridine was a clear oil at room temperature and a white solid at −20 °C. The ^{1}H NMR spectral data and assignments correspond to those reported in the literature.[5]

(±)-(2*S,3*R**)-3-Azido-3,7-dimethyl-6-octen-1, 2-diol 1-*tert*-Butyldimethylsilyl Ether (6-OTBS).** The silyl ether was prepared as described previously for **3-OTBS** using azido diol **6** (638 mg, 3.00 mmol), imidazole (1.23 g, 18.05 mmol), 4-DMAP (45 mg, 0.36 mmol), and TBDMSCl (1.36 g, 9.02 mmol) in DMF (10 mL). After 0.5 h, ethanolamine (0.607 g, 9.00 mmol) was added. Isolation of the crude product (963 mg) and purification in the same manner gave 646 mg (65%) of primary silyl ether **6-OTBS** and 137 mg (14%) of its secondary silyl ether isomer. Data for **6-OTBS**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.22 (s, 3H), 1.60 (m, 1H), 1.63 (s, 3H), 1.66 (m, 1H), 1.69 (s, 3H), 1.98−2.15 (12 peak m, 2H), 2.76 (d, J = 2.4 Hz, 1H, exch with D_2O), 3.60 (A*B*X, J_{AB} = 8.6 Hz, J_{BX} = 8.2 Hz, 1H), 3.62 (AB*X*, J_{AX} = 2.3 Hz, J_{BX} = 8.2 Hz, 1H), 3.73 (*A*BX, J_{AB} = 8.6 Hz, J_{AX} = 2.4 Hz, 1H), 5.11 (t sept, J = 5.8, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.63, 17.40, 18.01, 19.03, 22.12, 25.45, 25.61, 36.13, 62.74, 64.65, 76.13, 123.25, 132.07; IR 3571 (OH), 2105 (N_3); MS (CI+) *m*/*z* 328.3. Data for secondary silyl ether: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.18 (s, 3H), 0.96 (s, 9H), 1.28 (s, 3H), 1.60 (m, 1H), 1.64 (s, 3H), 1.70 (d, J = 1.0 Hz, 3H), 1.91 (br s, 1H), 2.08 (m, 2H), 3.59 (app dd, J = 8.6, 4.0 Hz, 1H), 3.65 (br dd, J = 11.2, 4.1 Hz, 1H), 3.73 (br dd, J = 11.3, 2.4 Hz, 1H), 5.10 (m, 1H).

(±)-(2*S,3*R**)-3-Azido-1-(*tert*-butyldimethylsilyloxy)-3,7-dimethyl-6-octen-2-yl Methanesulfonate (21).** The azido mesylate was prepared as described previously for **3-OTBS** using silyl ether **6-OTBS** (419 mg, 1.28 mmol), Et_3N (417 mg, 4.10 mmol), and methanesulfonyl chloride (444 mg, 3.84 mmol) in CH_2Cl_2 (5 mL). Purification in the same manner gave 318 mg (69%) of the azido mesylate **21** as a yellow oil and 50 mg (12%) of recovered starting material. Data for **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.38 (s, 3H), 1.57 (m, 1H), 1.63 (s, 3H), 1.65 (m, 1H), 1.69 (s, 3H), 2.01−2.18 (14 peak m, 2H), 3.15 (s, 3H), 3.83 (A*B*X, J_{AB} = 11.8 Hz, J_{BX} = 6.9 Hz, 1H), 3.94 (*A*BX, J_{AB} = 11.8 Hz, J_{AX} = 3.0 Hz, 1H), 4.56 (AB*X*, J_{AX} = 3.0 Hz, J_{BX} = 6.9 Hz, 1H), 5.07 (t sept., J = 7.1, 1.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −5.73, 17.45, 19.55, 21.91, 25.47, 36.10, 38.70, 52.86, 62.32, 64.24, 87.55, 122.62, 132.53; IR 2106 (N_3); MS *m*/*z* 406.2; HRMS (CI+) calcd for $C_{17}H_{35}N_3O_4SSi$ 406.2432, found 406.2434.

(±)-*cis*-3-(4-Methyl-3-pentenyl)-3-methylaziridine-2-methanol (22). The aziridine was prepared as described previously for (±)-2,3-aziridinofarnesol (**19**) using azido mesylate **21** (280 mg, 0.691 mmol) and $LiAlH_4$ (166 mg, 4.37 mmol) in Et_2O (2 mL). After 5 h, H_2O (166 μL), 15% NaOH (166 μL), and H_2O (498 μL) were added dropwise in succession to give 66 mg of a colorless oil. Isolation and purification in the same manner as that described previously gave 53 mg (45%) of the aziridino alcohol as a white solid. The melting point and ^{1}H NMR spectral data and assignments correspond to those reported in the literature.[5]

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Supporting Information Available: Procedural information and characterization data for all other substrates, general experimental details, and copies of ^{1}H NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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