Ethyl 3,5-bis(trifluoromethyl)benzoate (1i): 66% yield; IR (neat) 1730 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.6 (t, 3), 4.5 (q, 2), 8.1 (s, 1), 8.5 (s, 2).

Anal. Calcd for $C_{11}H_8F_6O_2$: C, 46.15; H, 2.80; F, 39.38. Found: C, 46.62; H, 2.85; F, 39.64.

Products. Phenyl-*sec*-butylmethanol was prepared by the reduction of phenyl *sec*-butyl ketone with lithium aluminum hydride in ether. The ketone was added slowly to a slurry of the hydride in ether at room temperature. The mixture was stirred for 30 min and then quenced carefully with dilute sulfuric acid. Workup followed by distillation of the crude product gave the pure alcohol in high yield: bp 77–79 °C (0.82 mm); ^1H NMR ($CDCl_3$) δ 0.7–1.0 (m, 9), 1.8 (s, 1), 4.4 (m, 1), 7.3 (s, 5).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.49; H, 9.76. Found: C, 80.69; H, 9.59.

Phenyl di-*sec*-butylmethanol was prepared by the addition of ethyl benzoate (1 g, 6.7×10^{-3} mol) to 60 mL of 0.4 M *sec*-BuLi in cyclohexane under an argon atmosphere. The mixture was stirred for 5 min and then quenched with dilute sulfuric acid. The organic layer was washed with water and aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent and fractional distillation under vacuum gave the pure alcohol in ca. 62% yield: bp 92–94 °C (0.29 mm); ^1H NMR ($CDCl_3$) δ 0.9 (m, 18), 1.5 (s, 1), 7.5 (s, 5).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.82; H, 10.91. Found: C, 81.44; H, 10.62.

Product Analysis. Effluents from the stopped-flow instrument obtained from the reactions of excess *sec*-BuLi with several esters were quenched with water. Each mixture was neutralized with dilute sulfuric acid and extracted with several portions of ether. The organic layer was washed with aqueous sodium bicarbonate and water and dried over anhydrous magnesium sulfate. Removal of the solvent afforded the crude product mixture which was analyzed by NMR spectroscopy and gas chromatography. In all cases, the tertiary alcohol (addition product) was the predominant constituent (>70%) of the product mixture. The reduction and enolization side products (i.e., secondary alcohol and ketone) accounted for the remaining portion of the product mixture. For example, the stopped-flow effluent from the reaction of ethyl benzoate with *sec*-BuLi contained 80% phenyldi-*sec*-butylmethanol, 18% phenyl-*sec*-butylmethanol, and 2% phenyl *sec*-butyl ketone by GC (3 ft × 0.125-in. column of 15% Carbowax 20 M on Chromosorb P, 165 °C column temperature). Product identities were confirmed by comparison of retention times with those of authentic samples.

Registry No. 1 (X = 3-CF_3), 76783-59-0; **1a**, 93-89-0; **1b**, 31994-68-0; **1c**, 94-30-4; **1d**, 5406-57-5; **1e**, 7335-27-5; **1f**, 451-02-5; **1g**, 120-33-2; **1h**, 91085-56-2; **1i**, 96617-71-9; *sec*-BuLi, 598-30-1; BuLi, 109-72-8; *sec*-BuC(O)Ph, 938-87-4; PhCH(*sec*-Bu)OH, 3968-86-3; PhC(*sec*-Bu)$_2$OH, 92860-07-6; cyclopentyllithium, 23473-12-3.

Diels–Alder Reaction of 1-Azadienes. A Total Synthesis of Deoxynupharidine

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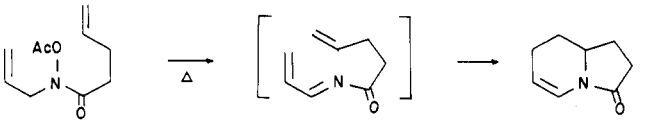
The Diels–Alder reaction of a *N*-acyl-1-azadiene was a key step in the total synthesis of the quinolizidine alkaloid (–)-deoxynupharidine.

Introduction

A six-membered ring containing a nitrogen atom is a common structural feature among the known alkaloids.[1] As a consequence, a central problem in alkaloid total synthesis has been concerned with the preparation and modification of piperidine derivatives. The Diels–Alder reaction of hetero dienes[2] and dienophiles[3] offers an important solution to this problem. The value of this reaction is that in one step two ring bonds are formed with potential control of stereochemistry at the new tetrahedral centers. Impressive demonstrations of this reaction have been provided by Weinreb and co-workers, who have applied the Diels–Alder reaction of imines to the efficient synthesis of a number of natural products.[4]

We have recently reported[5] that 1-azadienes, possessing an *N*-acyl substituent, will participate in the intramolecular version of the Diels–Alder reaction. The *N*-acylazadienes, prepared by the thermal elimination of acetic acid from hydroxamic acid derivatives **1**, are not isolated but readily react under the conditions of their formation to give the Diels–Alder adduct **3**.



1 2 3

An additional advantage of the Diels–Alder reaction of 1-azadienes is that the product is an endo-substituted enamine derivative.[6] Enamines are valuable intermediates in organic synthesis[7] as well as being important intermediates in alkaloid biosynthesis.[8] Thus, the Diels–Alder

(1) Glasby, J. S. "Encyclopedia of the Alkaloids"; Plenum Press: New York, 1975, Vol. 1–3.
(2) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
(3) (a) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949; (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
(4) (a) Bailey, T. R.; Barigipat, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240. (b) Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1984**, 261. (c) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065. (d) Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *Ibid.* **1981**, *103*, 7573. (e) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *Ibid.* **1981**, *103*, 6387. (f) Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T.-T. *Ibid.* **1982**, *104*, 536. (g) Basha, F. Z.; Hibino, S.; Kim, D.; Pye, W. E.; Wu, T.-T.; Weinreb, S. M. *Ibid.* **1980**, *102*, 3962. (h) Kim, D.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 121. (i) Schmitthenner, H. F.; Weinreb, S. M. *Ibid.* **1980**, *45*, 3372.
(5) (a) Cheng, Y.-S.; Fowler, F. W.; Lupo, Jr., A. T. *J. Am. Chem. Soc.* **1981**, *103*, 2090. (b) Cheng, Y.-S.; Lupo, Jr., A. T.; Fowler, F. W. *J. Am. Chem. Soc.* **1983**, *105*, 7696. For recent examples of the use of 1-azadienes in the Diels–Alder reaction see: (c) Ihara, M.; Kirihara, T.; Kawaguchi, A.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1984**, 4541. (d) Whitesell, M. A.; Kyba, E. P. *Tetrahedron Lett.* **1984**, 2119.
(6) (a) Stevens, R. V. *Acc. Chem. Res.* **1977**, 193. (b) Wenkert, E. *Ibid.* **1968**, *1*, 78.
(7) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975, 3363.
(8) Cordell, G. A. "Introduction to the Alkaloids: A Biosynthetic Approach"; Wiley-Interscience: New York, 1981.

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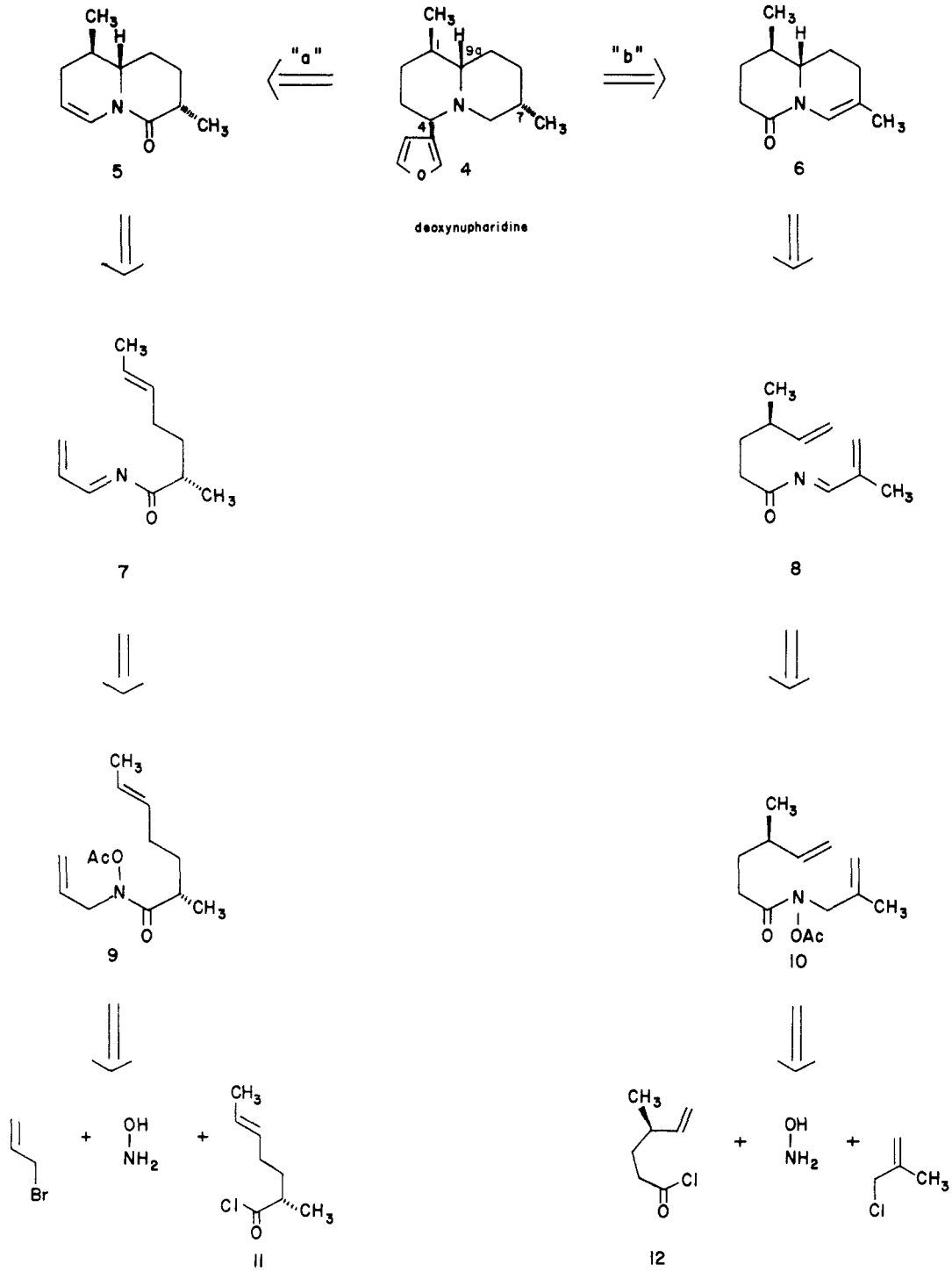
Scheme I



reaction of *N*-acyl-1-azadienes appears to offer an efficient solution to problems in alkaloid synthesis. Not only is a six membered nitrogen heterocycle formed, but the endocyclic enamine may be useful for further structural elaboration along biomimetic lines.

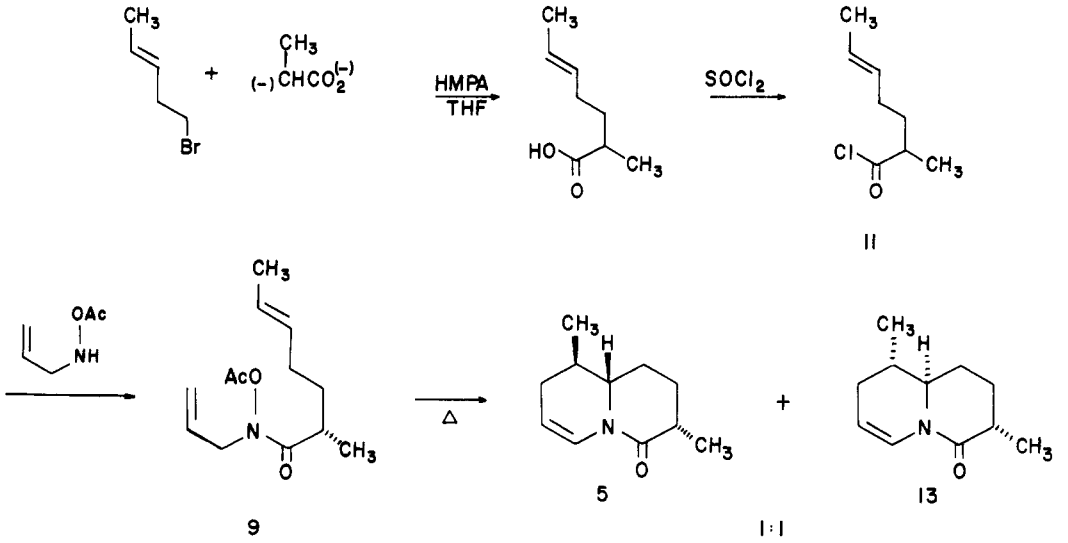
Deoxynupharidine (4) is an alkaloid that has been isolated from the rhizomes of *Nuphar luteum* and *Nuphar japonicum* and, more recently, from the scent gland of the Canadian beaver.[9] It is distinct from most alkaloids that occur in nature because the ring system, biosynthetically, is of terpene rather than of amino acid origin. Deoxynupharidine (4) is a suitable goal compound to evaluate the Diels–Alder reaction of 1-azadienes in directed synthesis. It is a reasonable complex heterocycle and has been the object of no less than five synthetic efforts.[10]

Since deoxynupharidine contains two piperidine rings, two retrosynthetic pathways using the Diels–Alder reaction can be envisioned (see Scheme I). Because of possible

(9) (a) Kotake, M.; Kawanaga, K.; Kubota, T.; Hagitani, A. *Proc. Imp. Acad. (Tokyo)* **1943**, *19*, 490. (b) Wong, C. F.; LaLonde, R. T. *Phytochemistry* **1970**, *9*, 2417. (c) Maurer, B.; Ohloff, G. *Helv. Chim. Acta* **1976**, *59*, 1169.

(10) (a) Kotake, M.; Kusumoto, I.; Okamoto, T.; Kusumoto, S.; Kaneko, T. *Justus Liebigs Ann. Chem.* **1960**, *636*, 158. (b) Arata, Y.; Nakanishi, T.; Asaoka, Y. *Chem. Pharm. Bull. Japan* **1962**, *10*, 675. (c) Jezo, I.; Karwas, M.f Tihlarik, K. *Chem. Zvesti.* **1961**, *15*, 283. (d) Wrpbel, J. T.; Dabrowski, Z. *Rocz. Chem.* **1965**, *39*, 1239. (e) Szychowski, J.; Lenewski, A.; Wrobel, J. T. *Chem. Ind. (London)* **1978**, 273. (f) Yasuda, S.; Hanaoka, M.; Arata, Y. *Chem. Pharm. Bull.* **1980**, *28*, 831.

Scheme II



complications during the Diels–Alder reaction, it was decided to attach the furan ring during the latter stages of the synthesis, and the Diels–Alder adducts **5** and **6** were considered to be reasonable intermediates for the synthesis of deoxynupharidine. Our previous studies suggest that the hydroxamic acid derivatives **9** and **10** should serve as suitable precursors for the Diels–Alder adducts **5** and **6**, and these hydroxamic acid derivatives should be readily prepared from hydroxylamine. In both schemes all of the reactants except the acyl halide are commercially available. Thus, these two syntheses of deoxynupharidine using the Diels–Alder reaction simply reduce to a preparation to the acyl chlorides **11** and **12**.

A concern in the evaluation of the relative merits of these pathways is the control of the stereochemistry at positions 1, 4, 7, and 9a. Path a has the advantage that the relative configuration of positions 1 and 9a can be controlled by taking advantage of the Diels–Alder cis principle. That is, the relative stereochemistry of substituents on the double bonds of the diene and the dienophile will be transfered to the product. Pathway b has the advantage that the stereochemistry of the methyl group at position 7 can be established by using catalytic hydrogenation. It is well-known in analogous systems that hydrogen will add to the β face of the quinolizidine.[10] Both of these schemes have the disadvantage that it is not known with certainty the relative configuration of chiral centers on the connecting chain (position 7 in path a and position 1 in path b) to new chiral centers that develop in the product of the Diels–Alder reaction.[11]

Results and Discussion

Since both of the retrosynthetic pathways appear reasonable and have interesting features, they were persued simultaneously. The first synthetic goals in these paths were the acid chlorides **11** and **12**.

The acid chloride **11** was prepared by alkylation of the propionic acid dianion[12] with 5-bromopent-2-ene[13] followed by treatment with thionyl chloride (see Scheme II).

Acylation of *N*-allyl-*O*-acetylhydroxylamine[5] using **11** provided the hydroxamic acid **9** in 95% yield. Evaporation of **9** through a hot tube produced a 1:1 mixture of the Diels–Alder adduct **5** and its diastereomer **13** in 70% yield.

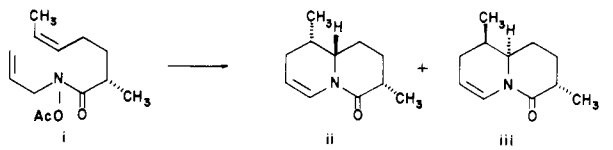
The acid chloride **12** was prepared from dihydromyrcene analogous to a previously reported scheme.[14] We found that the acid chloride **12** could be most efficiently obtained by first treating dihydromyrcene with *m*-chloroperbenzoic acid to form the epoxide derivative of the trisubstituted double bond. Hydrolysis of the epoxide to the diol followed by oxidative cleavage using a chromium trioxide–periodic acid mixture gave the acid. Conversion of the acid to the acid chloride was accomplished with thionyl chloride. An advantage of the use of acid chloride **12** in Scheme Ib is that dihydromyrcene starting material originates from the naturally occurring α- and β-pinenes.[15] The synthesis of the naturally occurring (−)-deoxynupharidine requires (*R*)-dihydromyrcene, which could be obtained from commercial sources in 86% optical purity.[16]

Acylation of *N*-methallyl-*O*-acetylhydroxylamine with acid chloride **12** provided the hydroxamic acid derivative **10** in 94% yield. Evaporation of **10** through a hot tube produced a 3:1 mixture of **6** and its diastereomer **14** in a 70% yield. Consistent with previous observations,[5] the *O*-methoxycarbonyl derivative of the hydroxamic acid proceeded in higher yield (Scheme III).

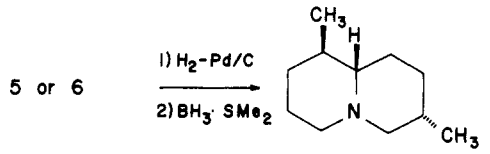
The structures of quinolizidinones **5** and **6** were correlated with each other by reduction to the same quinolizidine, **15**.

The analysis of the intramolecular Diels–Alder reaction for compounds that contain chiral centers on the connecting chain can be relatively complex.[18] For example,

(11) (a) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (b) Oppolzer, W. *Angew. Chem., Intern. Ed. Engl.* **1977**, *16*, 10. (c) Ciganek, E. *Org. React.* in press, 1984.
(12) Pfeffer, P. E.; Silbert, L. S.; Chirinko, Jr., J. M. *J. Org. Chem.* **1972**, *37*, 451.
(13) Biernacki, W.; Sobotka, W. *Rocz. Chem.* **1977**, *51*, 469.
(14) Mori, K.; Suguro, T.; Masuda, S. *Tetrahedron Lett.* **1978**, 3447.
(15) (a) Rienacker, R.; Ohloff, G. *Angew. Chem.* **1961**, *73*, 2400. (b) Pines, H.; Hoffman, N. E.; Ipatieff, V. I. *J. Am. Chem. Soc.* **1954**, *76*, 4412.
(16) We thank Dr. F. Naf at Firmenich Laboratories for his generous supply of (*R*)-dihydromyrcene.
(17) An unseparable mixture consisting of compound 9 and its cis



isomer i (in a ratio of 3.5:1, respectively) was evaporated through the reaction tube to give a reaction mixture consisting of 5, 13, ii, and iii in a ratio of 4:4:1:1, respectively.
(18) For an analysis of this problem see: Pyne, S. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719.

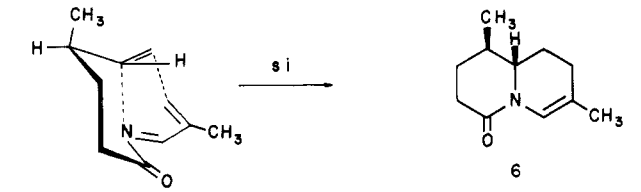


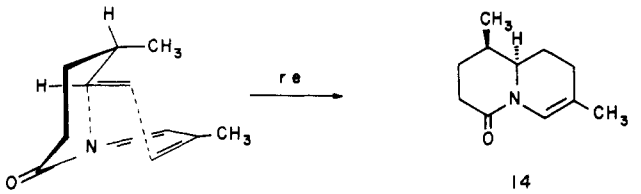
15

the stereoisomers **5** and **13**, produced in the Diels–Alder reaction of **9**, arise by attack of the diene on the *re* or *si* face of the dienophile. Since the diene can approach the dienophile with either an exo or endo orientation,[5b] there are four diastereomeric transition states possible leading to the two stereoisomers **5** and **13**. Within each of these configurationally different transition states there are additional conformational possibilities, such as the chair and boat, that must also be considered for a complete analysis of the intramolecular Diels–Alder reaction.

From previous work[5b] we believe the products of the intramolecular Diels–Alder reaction of 1-azadienes are under kinetic control and are a result of the reaction proceeding primarily, but not exclusively, through the exo transition state. Stereoisomers, that are the result of exo and endo pathways, show no tendency to interconvert when purified and subjected to the reaction conditions.[5b]

The two exo transition states leading to **6** and **14** are shown below. It can be seen that the major product, **6**,





is derived from the transition state that carries the methyl group on the connecting chain in an equatorial position with respect to the six membered ring. The minor isomer, **14**, carries this same methyl group in an axial position. A similar analysis of the endo transition state leads to the same conclusion, that the major product **6** is derived from the transition state where the methyl group occupies the equatorial position.

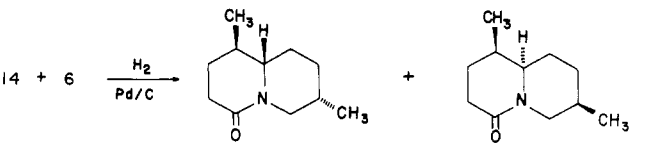
Because of the behavior of azadiene **8**, we do not believe that the 1:1 ratio of **5** to **13** obtained from the Diels–Alder reaction of azadiene **7** is simply reflecting nonstereospecific exo and endo. Rather, we believe the exo pathway, as described above, is proceeding primarily through the transition state where the methyl group occupies the equatorial position leading to **13**.

In contrast to the exo pathway we believe the endo pathway is proceeding through the boat conformation. There are two factors that favor the boat conformation for the endo transition state of azadiene **7**. First, a characteristic of all intramolecular Diels–Alder reactions for the formation of two fused six membered rings is that (*E*)-dienes occupy an axial position in the transition state when the connecting chain is in a chair conformation such as structure **16**. It is not surprising that boat conformations are believed to be important for the endo pathway of a number of intramolecular Diels–Alder reactions[19] (see Scheme IV).

A second factor that favors the boat over the chair conformation for the endo pathway is that it is only in the boat transition state that the interaction of the developing lone pair of electrons with the carbonyl group can occur to a significant degree. Since we believe the developing amide resonance energy is an important factor in facilitating all Diels–Alder reactions of *N*-acyl-1-azadienes, we believe this latter factor must be important in favoring the boat over the chain conformation in the endo transition state.

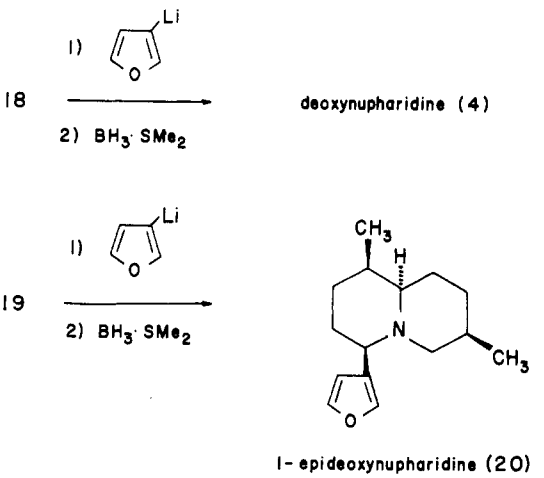
Therefore, the 1:1 ratio of **5** to **13** is most likely the result of unequal diastereoface selectivities of the exo and endo pathways being compensated by unequal fractions of the azadiene **7** proceeding through these pathways. In contrast to azadiene **7**, where different stereoisomers are believed to be the major products of the exo and endo pathways, the same stereoisomer is predicted to be favored in the Diels–Alder reactions of azadiene **8**. Molecular models clearly indicate that the lowest energy exo chair as well as endo boat transition state leads to stereoisomer **6**.

The synthesis of deoxynupharidine was completed by catalytic reduction of the product mixture formed in Scheme III followed by separation of the stereoisomers **18** and **19**. As anticipated, this reduction occurred stereo-



selectively from the β face. The other stereoisomers, resulting from reduction from the α face, could not be detected.

The introduction of the furan ring was accomplished by first treating **18** with 3-lithiofuran followed by reduction with borane–dimethyl sulfide complex. This reaction also

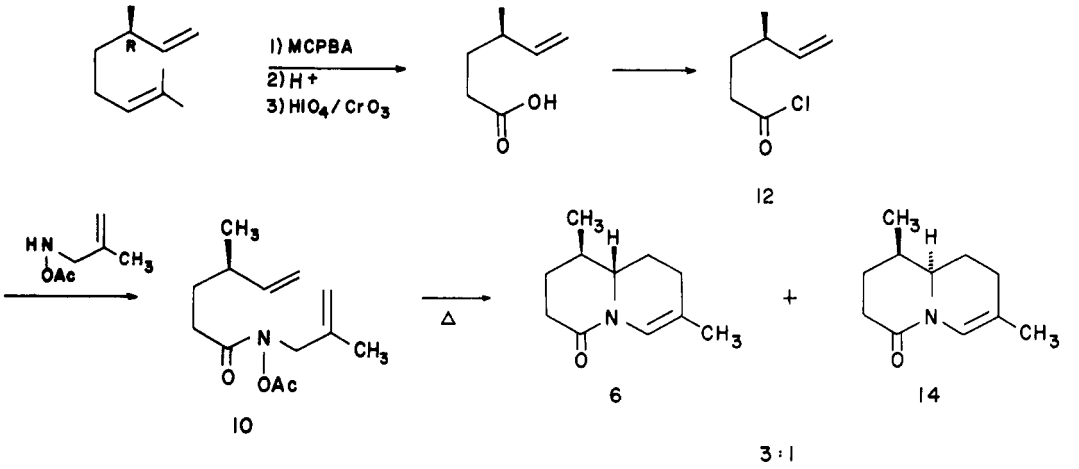


occurred with a high degree of stereoselectivity, producing deoxynupharidine and its C-4 isomer in a ratio of 18:1.

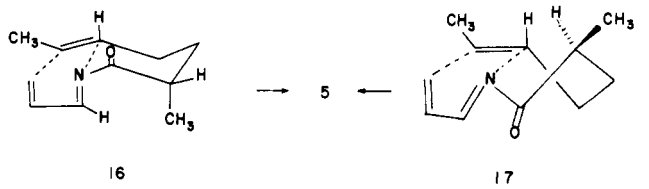
Deoxynupharidine, along with three of its stereoisomers, has been isolated from the scent gland of the Canadian Beaver (*Castor fiber L*).[9] The synthesis of one of these stereoisomers, 1-*epi*-deoxynupharidine, was readily accomplished from **19** by using the procedure described above. In summary, we have employed the intramolecular

(19) For example see and references cited therein: (a) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992. (b) Reference 4(a).

Scheme III



Scheme IV



Diels–Alder reaction of 1-azadienes as a key step in a synthesis of deoxynupharidine. Compared to the previously reported syntheses, this route is relatively efficient since the construction of both rings with stereochemical control of the substituents was achieved in one step. We believe this synthesis illustrates the potential of 1-azadienes to the solution of problems in heterocyclic synthesis. It should also be recognized that these pericyclic reactions are conceptually different from most reactions employed for the construction of heterocyclic compounds. In general, heterocyclic ring forming reactions explicitly employ the lone pair of electrons on nitrogen in the cyclization process whereas the lone pair of electrons does not play an active part in the pericyclic reaction.

Experimental Section

General Methods. Melting points were recorded on a Thomas-Hoover Unimelt melting point apparatus or on a Fisher-Johns melting point block and were uncorrected. Optical rotations were determined at 20 °C with a Perkin-Elmer Model 247 polarimeter equipped with a thermostat and are corrected with (+)-camphor. Infrared spectra were recorded on either a Perkin-Elmer 727 or a Perkin-Elmer 567 spectrometer as either thin films or KBr solid solutions. The absorption intensities are described as being strong (s), medium (m), or weak (w) and were referenced to either the 1601.4- or the 1944-cm^{-1} absorption of polystyrene. Proton NMR spectra were recorded on either a Varian HFT-80 or a Nicolet NT-300 spectrometer. Carbon-13 NMR spectra were recorded on a Nicolet NT-300 spectrometer. All chemical shifts were reported in ppm (units) from tetramethylsilane as an internal standard and described as being either singlet (s), doublet (d), triplet (t), quartet (q), quintet (q'), or multiplet (m). Low-resolution mass spectra (MS) were recorded on a Hewlett-Packard 5980A spectrometer. High-resolution mass spectra (HRMS) were recorded on an AEI MS-30 spectrometer. Analytical gas chromatography was determined on a Hewlett-Packard 5830 chromatograph equipped with a flame ionization detector. Preparative gas chromatography was carried out on a Varian 920 chromatograph equipped with a hot wire detector. Thin layer chromatography was carried out on Anatech silica gel HLF precoated thin layer chromatography plates. Flash column chromatography was carried out on 230–400 mesh silica gel 60 (E. Merck). Dry tetrahydrofuran (THF) and dry diethyl ether were freshly distilled over sodium benzophenone ketyl under a nitrogen atmosphere. Dry hexamethylphosphoramide (HMPA) was distilled over calcium hydride and stored over 4A molecular sieves under a nitrogen atmosphere.

2-Methylhept-5-enoyl Chloride (11). A solution of cyclopropyl methyl ketone (8.40 g, 0.10 mol; prepared from 2-acetylbutyrolactone in 80% overall yield according to a known procedure[20]) in anhydrous diethyl ether (22 mL) was added dropwise to a well-stirred mixture of lithium aluminum hydride (3.00 g, 0.08 mol) and anhydrous diethyl ether (67 mL). After the addition was completed, the mixture was refluxed for 20 min and then cooled to room temperature. A 20% NaOH aqueous solution (10 mL) was added dropwise to the mixture. The resulting mixture was filtered, and the filtrate was dried over anhydrous sodium sulfate and concentrated in vacuo to afford cyclopropylmethylcarbinol (6.51 g, 76%) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 0.1–1.07 (m, 5 H, cyclopropyl H), 1.28 (d, 3 H, J = 7.2 Hz, Me), 1.84 (s, 1 H, OH), 3.01 (m, 1 H, C*H*OH); IR (film) 3360 (s), 3090 (m), 3020 (s), 2985 (s), 2890 (m), 1450 (m), 1380 (m), 1100 (s), 1080 (s), 1020 (m), 950 (s) cm^{-1}.

To the cooled (10 °C) cyclopropylmethylcarbinol (4.30 g, 0.05 mol) was added 48% HBr (16.7 mL) within 2 min. The reaction mixture was stirred at 10 °C for 20 min and then at room temperature overnight. The resulting mixture was extracted with pentanes, and the pentane extracts were combined, washed with 10% sodium bicarbonate aqueous solution, dried over anhydrous sodium sulfate, concentrated in vacuo, and distilled to afford a mixture of *trans*- and *cis*-5-bromopent-2-ene as a colorless liquid (6.68 g, 89%), bp 125–126 °C. The ratio of trans to cis isomer was 3.5:1, respectively, according to ^{13}C NMR. (The chemical shifts of both trans and cis isomers were assigned by comparison with those of *trans*- and *cis*-hex-2-ene[21]): ^1H NMR ($CDCl_3$) δ 1.67 (m, 3 H, MeC=), 2.58 (m, 2 H, CH_2C=), 3.36 (t, 2 H, J = 7.3 Hz, CH_2Br), 5.49 (m, 2 H, CH=C*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) *trans*-5-bromopent-2-ene δ 17.8, 32.6, 36.0, 127.6, 128.1; *cis*-5-bromopent-2-ene δ 12.9, 30.5, 32.3, 126.7, 126.8; IR (film) 3030 (m), 2980 (s), 2940 (s), 2870 (m), 1670 (w), 1440 (s), 1380 (m), 1270 (s), 1210 (s), 1060 (w), 970 (s), 640 (w) cm^{-1}.

This mixture of trans and cis isomers was used without further purification. Freshly distilled dry THF (52 mL) and diisopropylamine (9.6 mL, 0.068 mol) were added to a dried flask purged with nitrogen gas and maintained under a nitrogen atmosphere. To this cooled (−78 °C) solution was added dropwise a solution of *n*-butyllithium in *n*-hexene (51 mL of 1.331 M, 0.068 mol). The resulting mixture was stirred at 0 °C for 20 min. To this cooled (0 °C) lithium diisopropylamide solution was added dropwise a solution of propionic acid (2.22 g, 0.03 mol) in dry THF (6 mL). A milky white solution formed that turned homogeneous after the addition of HMPA (6 mL, 0.034 mol). The reaction mixture was stirred at room temperature for 30 min and cooled to 0 °C. A 3.5:1 mixture of *trans*- and *cis*-5-bromopent-2-ene (4.46

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(21) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds"; Wiley: New York, 1981, p 263.

g, 0.03 mol) was rapidly added. After 1.5 h at room temperature the reaction was quenched by adding an ice-cold 10% HCl aqueous solution. The mixture was extracted with diethyl ether. The combined ether extracts were washed with 10% HCl, water, and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Pure product (3.62 g, 85%; a 3.5:1 mixture of *trans*- and *cis*-2-methylhept-5-enoic acid) was obtained by flash column chromatography (R_f 0.30 silica gel, diethyl ether:hexanes = 2:1): ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3 H, J = 7.2 Hz, Me), 2.21–1.34 (m, overlap with a dd of MeC= at 1.63, 7 H), 2.43 (m, 1 H, $CHCO_2$), 5.42 (m, 2 H, CH=CH), 10.1 (br s, 1 H, CO_2H); IR (film) 2500–3500 (s), 1710 (s), 1470 (m), 1380 (w), 1300 (m), 1250 (m), 970 (s) cm^{-1}; MS, m/z (relative intensity) 142 (M^+, 14), 124 (12), 74 (100), 69 (63), 55 (19); HRMS, m/e 142.0993 ($C_8H_{14}O_2$ requires 142.0994).

To the well-stirred mixture of trans and cis acids (1.09 g, 7.68 mmol) was added dropwise thionyl chloride (0.9 mL, 10.6 mmol). The reaction mixture was refluxed for 30 min and distilled under reduced pressure. Pure acid chloride (0.859 g, 70%; a 3.5:1 mixture of **11** and its cis isomer) was obtained as a colorless liquid, which showed a single spot on TLC (silica gel, diethyl ether:hexanes = 2:5): ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 7.2 Hz, Me), 2.21–1.37 (m, overlap with a dd of MeC= at 1.64, 7 H), 2.87 (m, 1 H, CHCO), 5.42 (m, 2 H, CH=CH); IR (film) 3030 (m), 2990 (s), 2955 (s), 2870 (m), 1800 (s), 1670 (w), 1470 (m), 1380 (w), 1300 (m), 1250 (m), 970 (s) cm^{-1}.

***O*-Acetyl-*N*-allyl-*N*-(2-methylhept-5-enoyl)hydroxylamine (9).** To a solution of *O*-acetyl-*N*-allylhydroxylamine[5] (98 mg, 0.85 mmol) and triethylamine (86 mg, 0.85 mmol) in carbon tetrachloride (3 mL) was added dropwise a solution of acyl chloride **11** and its cis isomer (143 mg, 0.89 mmol; a 3.5:1 mixture) in carbon tetrachloride (2 mL). The reaction mixture was stirred at room temperature for 1.5 h. Then the resulting mixture was washed with 5% sodium bicarbonate aqueous solution (5 mL). The organic layer was dried over anhydrous sodium carbonate and magnesium sulfate and concentrated in vacuo. Pure product (193 mg, 95%; a 3.5:1 mixture of **9** and its cis isomer, one single spot on TLC) was obtained by flash column chromatography (R_f 0.25 gel, diethyl ether:hexanes = 2:5) as a colorless liquid, which showed one single peak on GC (OV 1, 180 °C). Compound **9** does not show parent ion in the low-resolution mass spectrum. The highest mass absorption is M – 59 (loss of CH_3CO_2). Compound **9**: ^{1}H NMR ($CDCl_3$) δ 1.10 (d, 3 H, J = 6.6 Hz, Me), 1.42 (m, 2 H, CH_2), 1.63 (br d, 3 H, J = 6.0 Hz, MeC=), 1.97 (m, 2 H, CH_2C=), 2.17 (s, 3 H, MeCO), 2.51 (m, 1 H, CHCO), 4.3 (br d, 2 H, J = 6.4 Hz, CH_2N), 5.5–5.18 (m, 4 H, CH=CH and CH_2=C), 5.81 (m, 1 H, C*H*=CH_2); IR (film) 3100 (w), 2995 (s), 2955 (s), 2870 (m), 1796 (s), 1660 (s), 1440 (s), 1405 (s), 1380 (s), 1240 (m), 1180 (s), 990 (m), 974 (m), 920 (s), 740 (s) cm^{-1}; MS, m/z (relative intensity) 180 (M – 59, 4), 171 (34), 125 (24), 97 (100), 55 (66), 43 (30); HRMS, m/e 239.1532 ($C_{13}H_{21}NO_3$ requires 239.1521).

3,9-Dimethyl-1,2,3,8,9,9a-hexahydro-4*H*-quinolizin-4-one (5 and 13). With use of the standard thermolysis procedure described previously,[5] 47.8 mg (0.2 mmol) of the 3.5:1 mixture of **9** and its cis isomer was evaporated and passed through the thermolysis tube. After removal of the acetic acid (generated in this process) by potassium carbonate, 32 mg of crude product was obtained which consisted of four stereoisomers, **5**, **13**, and their C-9 epimers, in a ratio of 4:4:1:1, respectively (according to ^{1}H and ^{13}C NMR and GC analysis). Flash column chromatography (silica gel, ethyl acetate:hexanes = 1:4) of the crude mixture afforded two pairs of diastereoisomers. The first pair (12.0 mg, single spot on TLC, R_f 0.30) is the mixture of isomers **13** and its C-9 epimer in a ratio of 4:1, respectively. The second pair (12.3 mg, single spot on TLC, R_f 0.25) is the mixture of isomers **5** and its C-9 epimer in a ratio of 4:1, respectively (total 24.3 mg, 68%). The chemical shifts of both ^{1}H and ^{13}C NMR were assigned by comparison with those of the analogous compounds.[22]

^{1}H NMR ($CDCl_3$, 300 MHz): compound **5**, δ 1.01 (d, 3 H, J = 6.6 Hz, C_9Me), 1.27 (d, 3 H, J = 7.5 Hz, C_3Me), 1.52–2.15 (m, 7 H), 2.62 (dq′, 1 H, J = 7.5, 2.0 Hz, C_3H), 3.10 (dt, 1 H, J = 11.0, 5.0 Hz, C_{9a}H), 5.11 (m, 1 H, C_7H), 7.24 (br d, 1 H, J = 8.0 Hz, C_6H); compound **13**, δ 0.99 (d, 3 H, J = 6.6 Hz, C_9Me), 1.25 (d, 3 H, J = 7.2 Hz, C_3Me), 1.40–2.24 (m, 7 H), 2.35 (br q′, 1 H, C_3H), 3.11 (dt, 1 H, J = 11.0, 5.0 Hz, C_{9a}H), 5.10 (m, 1 H, C_7H), 7.25 (br d, 1 H, J = 8.0 Hz, C_6H); 9-*epi*-**5**, δ 0.89 (d, 3 H, J = 6.9 Hz, C_9Me), 1.29 (d, 3 H, J = 7.5 Hz, C_3Me), 1.50–2.20 (m, 7 H), 2.62 (m, 1 H, C_3H), 3.56 (m, 1 H, C_{9a}H), 5.02 (m, 1 H, C_7H), 7.19 (br d, 1 H, J = 8.0 Hz, C_6H); 9-*epi*-**13**, δ 0.87 (d, 3 H, J = 6.9 Hz, C_9Me), 1.25 (d, 3 H, J = 7.2 Hz, C_3Me), 1.40–2.40 (m, 8 H), 3.59 (m, 1 H, C_{9a}H), 4.99 (m, 1 H, C_7H), 7.19 (br d, 1 H, J = 8.0 Hz, C_6H).

^{13}C NMR ($CDCl_3$, 75 MHz): compound **5**; δ 17.9, 18.6, 23.3, 26.6, 31.4, 34.3, 35.4, 60.9, 108.6, 124.6, 171.4; compound **13**, δ 17.7, 27.1, 28.6, 31.4, 34.2, 37.0, 61.4, 109.2, 124.3, 171.3; 9-*epi*-**5**, δ 12.7, 19.0, 22.9, 30.8, 30.9, 36.0, 37.2, 58.2, 107.2, 124.1, 171.4; 9-*epi*-**13**, δ 12.6, 17.6, 27.0, 30.3, 30.8, 37.4, 58.7, 107.8, 124.8, 171.3.

IR (film): **5** and its C-9 epimer, 3070 (w), 2980 (s), 2945 (s), 2890 (m), 1650 (s), 1465 (m), 1410 (s), 1380 (m), 1345 (m), 1290 (s), 1275 (s), 1120 (m) cm^{-1}.

MS, m/z (relative intensity): compound **5**; 179 (M^+, 100), 164 (56), 150 (22), 136 (29), 112 (33), 108 (43), 96 (38), 94 (57); compound **13**, 179 (M^+, 100), 164 (65), 150 (22), 136 (29), 112 (45), 108 (42), 96 (42), 94 (60); 9-*epi*-**5**, 179 (M^+, 100), 164 (67), 150 (25), 136 (31), 112 (39), 108 (40), 96 (43), 94 (57); 9-*epi*-**13**, 179 (M^+, 100), 164 (58), 150 (27), 136 (27), 112 (47), 108 (40), 96 (38), 94 (51).

HRMS: compounds **5** and 9-*epi*-**5**, m/e 179.1308; compounds **13** and 9-*epi*-**13**, m/e 179.1311 ($C_{11}H_{17}NO$ requires 179.1310).

(4*R*)-4-Methylhex-5-enoyl Chloride (12). To a cooled (–10 °C) solution of (3*R*)-3,7-dimethyloct-1-ene-6,7-diol 12.06 g, 0.012 mol; prepared from *R*-dihydromyrcene (1.93 g, 0.014 mol; $[\alpha]^{20}_D$ –8.34°, neat[15]) in 86% overall yield according to a known procedure][23] in acetone (120 mL) was added dropwise a cooled (ice bath) solution of H_5IO_6 (3.56 g, 15.6 mmol) and CrO_3 (0.60 g, 6 mmol) in water (100 mL). The resulting mixture was stirred in an ice–NaCl bath for 4 h, and then saturated sodium bisulfate solution was added. The mixture turned blue-green upon stirring at room temperature for 30 min. After being concentrated to half of its original volume, the mixture was extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, and concentration in vacuo to afford the crude product. Pure (4*R*)-4-methylhex-5-enoic acid (1.30 g, 84%; $[\alpha]^{20}_D$ –12.86°, neat (lit.[14] $[\alpha]^{20.5}_D$ +14.72°, neat), for (4*S*)-4-methylhex-5-enoic acid) as obtained by a bulb-to-bulb distillation (0.05 torr, oven 50 °C). This acid was a single pure compound by GC (OV 101, 150 °C): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (d, 3 H, J = 7.5 Hz, Me), 1.64 (m, 2 H, CH_2), 2.17 (m, 1 H, CHC=), 2.35 (m, 2 H, CH_2CO), 4.99 (m, 2 H, CH_2=CH), 5.64 (m, 1 H, C*H*=CH_2), 10.33 (br s, 1 H, CO_2H); IR (film) 2500–3500 (s), 1709 (s), 1640 (w), 1456 (w), 1418 (m), 1374 (w), 990 (w), 915 (m) cm^{-1}.

Thionyl chloride (5.29 mL, 60 mmol) was added dropwise to the well-stirred (4*R*)-4-methylhex-5-enoic acid (5.12 g, 40 mmol). The reaction mixture was refluxed for 1 h and distilled under reduced pressure. Pure acyl chloride **12** (5.29 g, 90%) was obtained as a colorless liquid, which showed a single spot on TLC (silica gel, ether:hexanes = 1:3): ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 7.5 Hz, Me), 1.70 (m, 2 H, CH_2), 2.15 (m, 1 H, CHC=), 2.87 (t, 2 H, J = 7.5 Hz, CH_2CO), 5.00 (m, 2 H, CH_2=CH), 5.64 (m, 1 H, C*H*=CH_2); IR (film) 3130 (w), 3020 (s), 1800 (s), 1640 (w), 1450 (m), 1420 (m), 1378 (w), 1030 (m), 990 (m), 950 (m), 920 (m) cm^{-1}.

***O*-Acetyl-*N*-(2-methylprop-2-enyl)-*N*-[(4*R*)-4-methylhex-5-enoyl]hydroxylamine (10).** A mixture of 2-methylprop-2-enyl chloride (18.11 g, 0.2 mol), potassium iodide (49.8 g, 0.3 mol), and dimethylformamide (40 mL) was stirred at room temperature for 3 h. After filtration, to the filtrate (consisting of 91% of 2-methylprop-2-enyl iodide and 9% of the chloride according to GC: OV 1, 50 °C) was added *N*,*O*-diacetylhydroxylamine[5] (11.70 g, 0.1 mol) and potassium carbonate (13.82 g, 0.1 mol). The resulting mixture was stirred at room temperature for 24 h. The precipitate was filtered off and the filtrate was distilled under reduced pressure to afford pure *N*,*O*-diacetyl-*N*-(2-methylprop-2-enyl)hydroxylamine (9.23 g, 54%) as a colorless liquid: bp 26–27 °C (0.05 torr); ^{1}H NMR ($CDCl_3$) δ 1.75 (br s, 3 H, MeC=), 2.04 (s, 3 H, $MeCO_2$), 2.16 (s, 3 H, *Me*CON), 4.22

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(s, 2 H, CH_2N), 4.88 (br s, 2 H, CH_2=C); IR (film) 3120 (w), 2970 (m), 1790 (s), 1670 (s), 1420 (s), 1370 (s), 1172 (s), 1070 (w), 1000 (w), 900 (w), 850 (m) cm^{-1}; MS, *m/z* (relative intensity) 171 (M^+, 4), 129 (91), 112 (100), 111 (51), 87 (53), 72 (58), 70 (50), 43 (80); HRMS, *m/e* 171.0935 ($C_8H_{13}NO_3$ requires 171.0895).

Following the same procedure described previously,[5] the *N*,*O*-diacetyl-*N*-(2-methylprop-2-enyl)hydroxylamine (2.85 g, 16.6 mmol) was treated with 6 N HCl (16.5 mL), then with sodium carbonate (6.68 g, 63 mmol) to afford *O*-acetyl-*N*-(2-methylprop-2-enyl)hydroxylamine (1.29 g, 60%) as a colorless liquid after flash column chromatography (R_f 0.25 silica gel, diethyl ether:hexanes = 1:1). This compound is not stable and was used immediately after purification: ^1H NMR ($CDCl_3$) δ 1.81 (t, 3 H, *J* = 1.2 Hz, MeC=), 2.07 (s, 3 H, $MeCO_2$), 3.52 (br s, 2 H, CH_2N), 4.93 (m, 2 H, CH_2=C), 7.63 (br s, 1 H, NH); IR (film) 3160 (w), 2975 (m), 1725 (s), 1420 (s), 1370 (s), 1226 (s), 1000 (m), 900 (w), 850 (m) cm^{-1}.

Compound **10** was prepared from (4*R*)-4-methylhex-5-enoyl chloride (**12**) (0.50 g, 3.4 mmol) and *O*-acetyl-*N*-(2-methylprop-2-enyl)hydroxylamine (0.42 g, 3.3 mmol) by following the procedure described in the preparation of compound **9**. Compound **10** was obtained as a colorless liquid (0.727 g, 94%; one spot on TLC) after flash column chromatography (R_f 0.25 silica gel, diethyl ether:hexanes = 1:3). GC showed this product to be 98.7% pure (OV 1, 150 °C): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (d, 3 H, *J* = 7.2 Hz, Me), 1.62 (m, 2 H, CH_2), 1.75 (br s, 3 H, MeC=), 2.15 (s, 3 H, $MeCO_2$), 2.22 (m, 3 H, CHC= and CH_2COe), 4.24 (br s, 2 H, CH_2N), 4.94 (m, 4 H, CH_2=C and CH_2=CH), 5.63 (m, 1 H, CH=CH_2); IR (CCl_4) 3176 (w), 3006 (m), 1790 (s), 1678 (s), 1400 (m), 1172 (s), 990 (m), 905 (m) cm^{-1}; MS, *m/z* (relative intensity) 180 (M – 59, 49), 129 (36), 111 (55), 83 (35), 69 (43), 55 (100), 43 (54); HRMS, *m/e* 239.1531 ($C_{13}H_{21}NO_3$ requires 239.1521).

(1*R*,9a*S*)-1,7-Dimethyl-1,2,3,8,9,9a-hexahydro-4*H*-quinolizin-4-one (6). (a) With use of the standard thermolysis procedure described previously,[5] 51.2 mg (0.2 mmol) of compound **10** gave a mixture containing **6** and its C-9a epimer **14** in a ratio of 3:1, respectively (according to ^1H and ^{13}C NMR). Flash column chromatography (silica gel, diethyl ether:hexanes = 2:1) of the crude product afforded a mixture (R_f 0.25, 26.5 mg, 69%) of compounds **6** and **14** as a pale yellow liquid, which was 98.9% pure according to GC (OV 1, temperature program 140–180 °C). The chemical shifts of **6** and **14** were assigned by comparison with those of the analogous compounds.[22]

Compound **6**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (d, 3 H, *J* = 6.0 Hz, C_1Me), 1.73 (s, 3 H, C_7Me), 1.4–2.6 (m, 9 H), 2.98 (dt, 1 H, *J* = 10.5, 1.8 Hz, $C_{9a}H$), 7.02 (s, 1 H, C_6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.8, 20.9, 27.5, 27.8, 28.7, 32.1, 34.2, 61.1, 119.0, 119.3, 167.0.

Compound **14**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (d, 3 H, *J* = 7.5 Hz, C_1Me), 1.73 (s, 3 H, C_7Me), 1.4–2.6 (m, 9 H), 3.48 (td, 1 H, *J* = 10.5, 3.0 Hz, $C_{9a}H$), 7.10 (s, 1 H, C_6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.9, 18.9, 21.0, 26.7, 26.9, 27.9, 30.2, 57.5, 118.5, 119.2, 166.6.

Compounds **6** + **14**: IR (CCl_4) 3130 (w), 2960 (s), 1640 (s), 1460 (m), 1400 (ss), 1380 (m), 1300 (s), 1275 (s) cm^{-1}; MS, *m/z* (relative intensity) 179 (M^+, 85), 136 (20), 109 (38), 108 (23), 96 (100), 95 (56), 94 (38), 68 (20); HRMS, *m/e* 179.1319 ($C_{11}H_{17}NO$ requires 179.1310).

(b) Compound **6** was also prepared from the *O*-methoxycarboxycarbonyl derivative of the hydroxamic acid as following: A mixture of *tert*-butyl *N*-((methoxycarbonyl)oxy)carbamate (1.91 g, 10 mmol, prepared from hydroxylamine hydrochloride, *tert*-butyl azidoformate, and methyl chloroformate in 72% overall yield[24]), 2-methylprop-2-enyl chloride (0.91 g, 10 mmol), potassium iodide (1.66 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol), and dimethylformamide (6 mL) was stirred at room temperature for 24 h. After filtration the filtrate was distilled under reduced pressure to remove dimethylformamide. The residue was chromatographed (silica gel, diethyl ether:hexanes = 1:3) to afford pure *N*-*tert*-butyloxycarbonyl-*N*-(2-methylprop-2-enyl)-*O*-(methoxycarbonyl)hydroxylamine (R_f 0.30, 2.20 g, 90%) as a pale yellow liquid: ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H, *t*-Bu), 1.76 (br s, 3 H, MeC=), 3.26 (s, 3 H, CO_2Me), 4.13 (br s, 2 H, CH_2N), 4.91 (br s, 2 H, CH_2=C); MS, *m/z* (relative intensity) 189 (M – 56, 9), 172 (9), 145 (31), 69 (19), 57 (10), 41 (18).

To a solution of the above compound (0.974 g, 4 mmol) in methylene chloride (10 mLe) was added dropwise trifluoroacetic acid (3.05 g, 26 mmol). The resulting mixture was stirred at room temperature for 2 h and then washed with 5% sodium bicarbonate aqueous solution to remove the excess acid. The organic layer was dried over sodium carbonate and concentrated in vacuo to afford crude product which was then chromatographed (silica gel, diethyl ether:hexanes = 1:4) to give pure *N*-(2-methylprop-2-enyl)-*O*-(methoxycarbonyl)hydroxylamine (R_f 0.25, 0.404 g 70%) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 1.82 (br s, 3 H, MeC=), 3.60 (d, 2 H, *J* = 6.0 Hz, CH_2N), 3.83 (s, 3 H, CO_2Me), 4.95 (br s, 2 H, CH_2=C), 6.93 (t, 1 H, *J* = 6.0 Hz, NH).

Using the same procedure for the preparation of compound **10**, *O*-(methoxycarbonyl)-*N*-(2-methylprop-2-enyl)-*N*-[(4*R*)-4-methylhex-5-enoyl]hydroxylamine was obtained (87%, from acyl chloride **12** and the above hydroxamic acid derivative) as a colorless liquid after column chromatography (R_f 0.25, silica gel, diethyl ether:hexanes = 1:4): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (d, 3 H, *J* = 6.6 Hz, Me), 1.62 (m, 2 H, CH_2), 1.74 (br s, 3 H, MeC=), 2.17 (m, 1 H, CHC=), 2.31 (t, 2 H, *J* = 8.0 Hz, CH_2CO), 3.91 (s, 3 H, CO_2Me), 4.28 (s, 2 H, CH_2N), 4.95 (m, 4 H, CH_2=CH and CH_2=C), 5.63 (m, 1 H, CH=CH_2); MS, *m/z* (relative intensity) 180 (M – 75, 49), 129 (36), 111 (55), 83 (35), 69 (43), 55 (100), 43 (54); HRMS, *m/e* 255.1479 ($C_{13}H_{21}NO_4$ requires 255.1471).

Following the standard thermolysis mentioned previously, the above compound (52.7 mg, 0.21 mmol) was evaporated and passed through the thermolysis tube to give **6** and **14** (31.1 mg, 84%, purified) in a ratio of 3:1, respectively.

(1*R*,7*S*,9a*S*)-1,7-Dimethyloctahydro-4*H*-quinolizin-4-one (18). The mixture of **6** and **14** (3:1) (240 mg, 1.3 mmol) was hydrogenated (1 atm) in ethanol (10 mL) over 5% Pd–C (36.4 mg, 15 mmol) at room temperature for 24 h. The resulting mixture was passed through a short column of Celite and then concentrated in vacuo to afford crude product (238 mg, 98%) which consists of 74.4% of **18** and 24.6% of **19** according to GC and NMR. The crude mixture was chromatographed (silica gel, ethyl acetate:hexanes = 4:5) to afford pure **18** (174 mg, R_f 0.26; $[\alpha]^{20}_D$ +55.2°, c 5.0, MeOH) and pure **19** (56 mg, R_f 0.19) as a colorless liquid (total yield 95%). Compounds **18** and **19** had 100% and 98.3% of purity, respectively, according to GC (OV 1, 160 °C). The physical properties of **18** and **19** are also consistent with those reported by Bohlmann and Wrobel.[10]

Compound **18**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (d, 3 H, *J* = 7.2 Hz, C_7Me), 1.06 (d, 3 H, *J* = 6.3 Hz, C_1Me), 1.40–1.80 (m, 7 H), 1.99 (m, 1 H, C_7H), 2.34 (ddd, 1 H, *J* = 17.0, 11.6, 5.4 Hz, C_3H_{ax}), 2.46 (ddd, 1 H, *J* = 17.0, 5.4, 4.0 Hz, C_3H_{eq}), 2, 59 (dd, 1 H, *J* = 13.0, 3.0 Hz, C_6H_{ax}), 2.79 (ddd, 1 H, *J* = 11.0, 8.4, 2.7 Hz, $C_{9a}H$), 4.55 (td, 1 H, *J* = 13.0, 2.2 Hz, C_6H_{eq}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.8, 18.9, 27.2, 27.3, 27.7, 30.0, 31.9, 35.4, 47.2, 63.4, 169.8; IR (CH_2Cl_2) 2980 (m), 1625 (s), 1470 (m) cm^{-1}; MS, *m/z* (relative intensity) 181 (M^+, 58), 166 (93), 152 (32), 139 (38), 111 (100), 98 (36), 97 (53), 82 (22), 55 (25); HRMS, *m/e* 181.1460 ($C_{11}H_{19}NO$ requires 181.1466).

Compound **19**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (d, 3 H, *J* = 7.2 Hz, C_7Me), 0.96 (d, 3 H, *J* = 7.2 Hz, C_1Me), 1.42–1.75 (m, 6 H), 1.96 (m, 1 H, C_7H), 2.06 (m, 1 H, C_1H), 2.32 (ddd, 1 H, *J* = 17.7, 10.2, 7.5 Hz, C_3H_{ax}), 2.46 (ddd, 1 H, *J* = 17.7, 5.4, 3.6 Hz, C_3H_{eq}), 2.66 (dd, 1 H, *J* = 12.9, 2.1 Hz, C_6H_{ax}), 3.23 (ddd, 1 H, *J* = 11.0, 6.0, 3.0 Hz, $C_{9a}H$), 4.50 (td, 1 H, *J* = 12.9, 2.1 Hz, C_6H_{eq}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3, 16.7, 21.5, 25.5, 28.5, 30.8, 31.7, 32.1, 48.8, 61.4, 169.4; MS, *m/z* (relative intensity) 181 (M^+, 67), 166 (100), 152 (38), 139 (42), 111 (78), 98 (24), 97 (37), 82 (21), 55 (21); HRMS, *m/e* 181.1455.

(1*R*,7*S*,9a*S*)-1,7-Dimethyloctahydro-2*H*-quinolizine (15).[25] The 4:1 mixture of **5** and its C-9 epimer (42.8 mg, 0.24 mmol) was hydrogenated (1 atm) in ethanol (2 mL) over 5% Pd–C (6.5 mg, 0.003 mmol) at room temperature for 22 h (approximately 6 mL of hydrogen was absorbed). The resulting mixture was passed through a short column of Celite and then concentrated in vacuo

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to afford crude product (consisting of (3*S**,9*R**,9a*S**)-3,9-dimethyl-4*H*-quinolizin-4-one and its C-9 epimer). The crude product was chromatographed (silica gel, diethyl ether:hexanes = 4:1) to afford (3*S**,9*R**,9a*S**)-3,9-dimethyloctahydro-4*H*-quinolizin-4-one (R_f 0.25, 30.2 mg, 70%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (d, 3 H, J = 6.6 Hz, C_9Me), 1.23 (d, 3 H, J = 7.2 Hz, C_3Me), 1.15–1.96 (m, 9 H), 2.36 (m, 1 H, C_6H_{ax}), 2.45 (m, 1 H, C_3H), 2.88 (m, 1 H, $C_{9a}H$), 4.79 (m, 1 H, C_6H_{eq}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.0, 18.5, 23.5, 25.5, 25.9, 34.2, 36.4, 37.4, 43.3, 63.1, 172.6; IR (film) 2950 (s), 2880 (s), 1630 (s), 1470 (s), 1445 (s), 1370 (m), 1350 (m), 1280 (s), 1270 (s), 1120 (m) cm^{-1}; MS, m/z (relative intensity) 181 (M^+, 100), 166 (69), 126 (61), 125 (27), 111 (22), 98 (29); HRMS, m/e 181.1468 ($C_{11}H_{19}NO$ requires 181.1466).

To a refluxing solution of the above amide (26 mg, 0.14 mmol) in dry THF (1 mL) was added dropwise a solution of borane–dimethyl sulfide in THF (0.14 mL of 2 M solution, 0.28 mmol). Dimethyl sulfide was distilled off during 15 min. After removal of solvent by rotary evaporator, the residue was heated to 100 °C, and an aqueous solution of 0.2 N hydrochloric acid (0.9 mL) was added. The resulting mixture was heated at this temperature for 30 min. After cooling to room temperature, the mixture was basified with 5% sodium hydroxide aqueous solution. The resulting mixture was saturated with potassium carbonate and then extracted with diethyl ether. The ether extracts were combined, dried over potassium carbonate, and concentrated in vacuo to afford crude product (14 mg, 58%) as a yellow liquid. The ^{1}H and ^{13}C NMR of this compound matched perfectly with those of compound **15**, obtained by a borane–dimethyl sulfide reduction of **18** in 62% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (d, 3 H, J = 6.0 Hz, C_1Me), 1.09 (d, 3 H, J = 7.1 Hz, C_7Me), 1.26–1.75 (m, 10 H), 1.84 (m, 1 H, C_4H_{ax}), 1.96 (dt, 1 H, J = 11.0, 3.0 Hz, $C_{9a}H$), 2.14 (dd, 1 H, J = 11.3, 3.6 Hz, C_6H_{ax}), 2.54 (md, 1 H, J = 11.3 Hz, C_6H_{eq}), 2.68 (md, 1 H, J = 10.0 Hz, C_4H_{eq}); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 18.8, 24.9, 25.2, 28.6, 30.2, 34.4, 35.5, 57.2, 62.1, 69.5; IR (film) 2950 (s), 2815 (m), 2760 (m), 1470 (s), 1380 (m) cm^{-1}; MS, m/z (relative intensity) 167 (M^+, 66), 166 (100), 152 (55), 138 (37), 124 (59), 112 (48), 111 (68), 110 (51), 97 (89), 96 (480, 82 (59), 55 (38), 41 (41); HRMS, m/e 167.1647 ($C_{11}H_{21}N$ requires 167.1674). The data for **15** are also consistent with those previously reported for this compound.[10]

Deoxynupharidine (4). To a cooled (−78 °C) solution of *n*-butyllithium (0.66 mL of 1.38 M solution in *n*-hexane, 0.9 mmol) in dry diethyl ether (2 mL) was added a solution of 3-bromofuran (176 mg, 1.2 mmol) in dry diethyl ether (3 mL). The resulting mixture was stirred at −78 °C for 20 min, and then to it was added dropwise a solution of lactam **18** (54 mg, 0.3 mmol) in dry diethyl ether (2 mL). The resulting mixture was warmed to room temperature and stirred for 1.5 h. The intermediate carbinol amine derivative was reduced by borane–dimethyl sulfide complex (0.7 mL of 10 M) at room temperature for 30 min to afford the crude product[26] (65 mg) which consists of **4** and its C-4 epimer in a ratio of 18:1, respectively (according to GC). Flash column chromatography (silica gel, ethyl acetate:hexanes = 1:7) of the crude mixture afforded pure **4** (R_f 0.25, 55 mg, 79%; $[\alpha]^{20}_D$ −82.5° (*c* 1.94, methanol); lit.[9c] −90° (*c* 1.0) lit.[9b] −105° (*c* 2.5, methanol)) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, 3 H, J = 6.4 Hz, C_1Me), 0.99 (d, 3 H, J = 7.0 Hz, C_7Me), 1.12 (m, 1 H, C_8H_{ax}), 1.38–1.78 (m, 10 H), 1.81 (dd, 1 H, J = 11.5, 3.0 Hz, C_6H_{ax}), 2.65 (td, 1 H, J = 11.5, 2.0 Hz, C_6H_{eq}), 2.92 (dd, 1 H, J = 8.0, 6.0 Hz, C_4H_{ax}), 6.38 (m, 1 H, 4-furyl-H), 7.25 (m, 1 H, 2-furyl-H), 7.32 (m, 1 H, 5-furyl-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.6 (q), 19.1 (q), 25.7 (te, 28.6 (d), 30.5 (t), 33.9 (t), 34.9 (t), 35.7 (d), 58.1 (t), 60.1 (d), 69.5 (d), 109.6 (d), 129.9 (s), 139.2 (d), 142.7 (d); IR (film) 3140 (w), 2970 (s), 2940 (s), 2870 (s), 2805 (m), 2780 (m), 1600 (w), 1570 (w), 1500 (m), 1470 (m), 1450 (m), 1390 (s), 1380 (m), 1160 (s), 1035 (s), 880 (s), 790 (s), 770 (m) cm^{-1}; MS, m/z (relative intensity) 233 (M^+, 18), 232 (9), 204 (14), 190 (23), 162 (22), 148 (42), 136 (45), 98 (100), 94 (88), 55 (18); HRMS, m/e 233.1784 ($C_{15}H_{23}NO$ requires 233.1779).

1-Epideoxynupharidine (20). By use of the same method described for the preparation of **4**, lactam **19** (60 mg, 0.33 mmol) was treated with 3-furyllithium (0.9 mmol) and then borane–dimethyl sulfide complex (0.6 mL of 10 M) to afford crude product (65 mg). The crude mixture consists of 1-epideoxynupharidine and its C-4 epimer in a ratio of 6.3:1, respectively (according to GC). Flash column chromatography (silica gel, ethyl acetate:hexane = 1:1.7) of the crude product afforded pure 1-epideoxynupharidine (R_f 0.20, 51 mg, 66%; $[\alpha]^{20}_D$ +21.4° (*c* 0.23, methanol)) lit.[9c] −36° (*c* 0.5) for its enantiomer as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (d, 3 H, J = 7.2 Hz, C_7Me), 1.09 (d, 3 H, J = 6.9 Hz, C_1Me), 1.16 (md, 1 H, J = 12.5 Hz, C_9H_{eq}), 1.40–1.82 (m, 10 H), 1.96 (td, 1 H, J = 11.4, 2.7 Hz, $C_{9a}H$), 2.67 (td, 1 H, J = 10.9, 2.0 Hz, C_6H_{eq}), 2.78 (dd, 1 H, J = 11.4, 3.4 Hz, C_4H_{ax}), 6.38 (m, 1 H, 4-furyl-H), 7.24 (m, 1 H, 2-furyl-H), 7.32 (m, 1 H, 5-furyl-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 17.2, 25.8, 28.6, 30.6, 30.7, 32.3, 33.0, 59.3, 61.0, 65.9, 109.5, 120.5, 139.0, 142.6; IR (film) 2950 (s), 2870 (s), 2810 (m), 2780 (m), 1500 (m), 1470 (m), 1395 (m), 1380 (m), 1160 (s), 1030 (s), 880 (s), 790 (s) cm^{-1}; MS, m/z (relative intensity) 233 (M^+, 11), 190 (13), 162 (13), 148 (14), 136 (39), 98 (100), 94 (69); HRMS, m/e 233.1785 ($C_{15}H_{23}NO$ requires 233.1779). The physical data for deoxynupharidine and 1-epideoxynupharidine are consistent with those previously reported.[9,10]

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Registry No. **4**, 1143-54-0; (±)-**5**, 96791-39-8; (±)-9-*epi*-**5**, 96791-60-5; (±)-[5] (dihydro deriv), 96791-59-2; **6**, 96791-40-1; (±)-**9**, 96791-41-2; (±)-(*Z*)-**9**, 96791-48-9; **10**, 96791-42-3; **10** (*O*-(methoxycarbonyl) analogue), 96791-57-0; (±)-**11**, 96791-43-4; (±)-(*Z*)-**11**, 96791-47-8; (±)-**11** (acid), 96791-45-6; (±)-(*Z*)-**11** (acid), 96791-46-7; **12**, 96791-44-5; **12** (acid), 96791-49-0; (±)-**13**, 96807-21-5; (±)-9-*epi*-**13**, 96791-61-6; **14**, 96791-56-9; **15**, 96791-54-7; (±)-**15**, 96844-54-1; **18**, 96791-53-6; **19**, 96791-58-1; **20**, 96844-55-2; *trans*-$CH_3CH{=}CH(CH_2)_2Br$, 7515-62-0; *cis*-$CH_3CH{=}CH(CH_2)_2Br$, 50273-84-2; $CH_3CH_2CO_2H$, 79-09-4; $CH_2{=}CHCH_2NHOAc$, 87842-66-8; $CH_2{=}CHCH(CH_3)(CH_2)_2CH(OH)C(OH)(CH_3)_2$, 57714-93-9; $CH_2{=}C(CH_3)CH_2Cl$, 563-47-3; $CH_2{=}C(CH_3)CH_2I$, 3756-30-7; AcONHAc, 7340-09-2; $AcON(Ac)CH_2C(CH_3){=}CH_2$, 96791-50-3; $AcONHCH_2C(CH_3){=}CH_2$, 96791-55-8; *t*-$BuOCONHOCO_2CH_3$, 27920-29-2; *t*-$BuOCON(OCO_2CH_3)CH_2C(CH_3){=}CH_2$, 96791-51-4; $CH_3O_2CONHCH_2C(CH_3){=}CH_2$, 96791-52-5; cyclopropyl methyl ketone, 765-43-5; (±)-cyclopropylmethylcarbinol, 10367-79-0; 3-bromofuran, 22037-28-1.

(26) The workup procedure for borane–dimethyl sulfide complex reduction was the same as that described for the preparation of compound **15**; see also ref 25.