^{1}H NMR Spectrum of Nap-*S*-Val-NH^{t}Bu (2d) (C_6D_6): δ 14.96 (s, 1 H, OH), 8.70 (s, 1 H, CH=N), 7.65 (d, J = 8.5 Hz, 1 H, ArH), 7.42–7.45 (m, 1 H, ArH), 7.38 (d, J = 9.4 Hz, 1 H, ArH), 7.22–7.26 (m, 1 H, ArH), 7.09–7.20 (shielded with the solvent, 2 H, ArH), 5.81 (s, 1 H, NH), 3.53 (d, J = 4.3 Hz, 1 H, CαH), 2.47–2.59 (m, 1 H, CαCH), 1.25 (s, 9 H, *tert*-butyl CH_3), 1.01 (d, J = 6.8 Hz, 3 H, isopropyl CH_3), 0.75 (d, J = 6.8 Hz, 3 H, isopropyl CH_3).

^{1}H NMR Spectrum of the Mixture of Nap-*S*-Val-NH^{t}Bu (2d) and Me_3Al (5) (C_6D_6). δ 8.70 (s, 1 H, CH=N), 7.83 (d, J = 8.1 Hz, 1 H, ArH), 7.35–7.41 (m, 2 H, ArH), 7.28–7.32 (m, 1 H, ArH), 7.16 (d, J = 9.0 Hz, 1 H, ArH), 7.07–7.12 (m, 1 H, ArH), 5.65 (s, 1 H, NH), 3.16 (d, J = 6.0 Hz, 1 H, CαH), 1.84–1.97 (m, 1 H, CαCH), 1.19 (s, 9 H, *tert*-butyl CH_3), 0.76 (d, J = 6.8 Hz, 3 H, isopropyl CH_3), 0.71 (d, J = 6.8 Hz, 3 H, isopropyl CH_3), 0.09 (s, 3 H, $AlCH_3$), –0.25 (s, 3 H, $AlCH_3$).

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Supplementary Material Available: ^{1}H NMR spectra for compounds **2d**, **3b**, and the mixture of **2a** or **2d** and Me_3Al (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of (±)-γ-Lycorane by the Intramolecular Cycloaddition of an Azide with an ω-Chloroalkene

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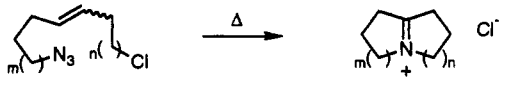
Cyclization of 1-[2-(chloromethyl)-4,5-(methylenedioxy)phenyl]-3-(2-azidoethyl)cyclohex-1-ene (**16**) in benzene at 140 °C caused the following sequence of events: (1) intramolecular 1,3-dipolar cycloaddition of the azide onto the alkene; (2) formation of an imine by loss of nitrogen from the triazoline intermediate with concomitant hydrogen migration; and (3) intramolecular N-alkylation of the imine nitrogen with the benzylic chloride. Without isolation, the resultant iminium ion was reduced with sodium borohydride to give (±)-γ-lycorane (**3**). The cyclization precursor **16** was prepared using a novel allylic substitution reaction, where the allylic alcohol **10** or the allylic acetate **11** was treated with 1-ethoxy-1-[(*tert*-butyldimethylsilyl)oxy]ethene and lithium perchlorate in ether to produce the γ,δ-unsaturated ester **12**. An alternative synthesis of (±)-γ-lycorane (**3**) was accomplished using a similar 1,3-dipolar cycloaddition approach, except that the benzylic chloride functionality was absent (i.e., **26** → **27**). Reduction of the resultant imine followed by a Bischler–Napieralski cyclization gave the known lactam **31**, which had previously been converted to (±)-γ-lycorane.

We have recently described a method for the generation of bicyclic iminium ions **2** in one operation from azides **1** (eq 1).[1,2] The reaction proceeds by an intramolecular 1,3-dipolar cycloaddition of an azide onto an alkene, producing an intermediate triazoline. Fragmentation of the triazoline and rearrangement to a monocyclic imine occurs, which is internally N-alkylated by the pendant alkyl chloride, delivering the iminium ion **2**. We now report the use of this methodology for the synthesis of (±)-γ-lycorane (**3**).



1 **2**

γ-Lycorane (**3**) is a representative of the lycorine class of Amaryllidaceae alkaloids.[3] While most of these alkaloids have a trans-B,C ring juncture (e.g., lycorine, **4**), compounds with a cis-B,C ring juncture such as that found in γ-lycorane have recently appeared, including fortucine (**5**)[4] and siculinine (**6**).[5] The biological activity of lycorine and related compounds includes antitumor activity, plant growth inhibition, and the inhibition of protein synthesis,[3] thus eliciting a considerable amount of interest in the synthesis of these alkaloids.[3,6,7] Most of the synthetic

(1) Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett.* **1990**, *31*, 7571–7574.

(2) For related double cyclizations of azides where the second ring is formed by an intramolecular alkylation or acylation, see: (a) Bennett, R. B., III; Choi, J.-R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580–2582. (b) Bennett, R. B., III; Cha, J. K. *Tetrahedron Lett.* **1990**, *31*, 5437–5440. (c) Heidt, P. C.; Bergmeier, S. C.; Pearson, W. H. *Tetrahedron Lett* **1990**, *31*, 5441–5444. (d) Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem* **1991**, *56*, 1976–1978. (e) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513–5516. (f) Choi, J.-R.; Han, S.; Cha, J. K. *Tetrahedron Lett.* **1991**, *32*, 6469–6472. (g) Pearson, W. H.; Bergmeier, S. C.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977–3987.

(3) Review of the Amaryllidaceae alkaloids: Martin, S. F. In *The Alkaloids*; Brossi, A. Ed.; Academic Press: New York, 1987; Vol. 30, pp 251–376.

(4) Tokhtabaeva, G. M.; Sheichenko, V. I.; Yartseva, I. V.; Talkachev, O. N. *Khim. Prir. Soedin.* **1987**, 872–875; *Chem. Abstr.* **1988**, *109*, 89687u.

(5) Richomme, P.; Pabuçcuoglu, V.; Gözler, T.; Freyer, A. J.; Shamma, M. *J. Nat. Prod.* **1989**, *52*, 1150–1152.

(6) For a survey of synthetic efforts directed toward lycorine and its derivatives, see: (a) Martin, S. F.; Tu, C.-Y.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634–3643. See also: (b) Wang, C.-L.; Ripka, W. C.; Confalone, P. N. *Tetrahedron Lett.* **1984**, *25*, 4613–4616. (c) Boeckman, R. K., Jr.; Sabatucci, J. P.; Goldstein, S. W. *J. Org. Chem.* **1986**, *51*, 3740–3742. (d) Boeckman, R. K., Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250–8252. (e) Bäckvall, J.-E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988–2993. (f) Pérez, D.; Guitián, E.; Castedo, L. *Tetrahedron Lett.* **1992**, *33*, 2407–2408.

(7) For syntheses of γ-lycorane specifically, see ref 6e and the following: (a) Kotera, K. *Tetrahedron* **1961**, *12*, 248–261. (b) Ueda, N.; Tokuyama, T.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2012–2014. (c) Irie, H.; Nishitani, Y.; Sugita, M.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1313–1314. (d) Ganem, B. *Tetrahedron Lett.* **1971**, 4105–4108. (e) Hara, H.; Hoshino, O.; Umezawa, B. *Tetrahedron Lett.* **1972**, 5031–5034. (f) Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2502–2506. (g) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sato, S.; Numao, N. *J. Org. Chem.* **1977**, *42*, 4272–4275. (h) Iida, H.; Yaasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1074–1080. (i) Higashiyama, H.; Honda, T.; Otomasu, H.; Kametani, T. *Planta Med.* **1983**, *48*, 268–271. (j) Sugiyama, N.; Narima, M.; Iida, H.; Kikuchi, T. *J. Heterocycl. Chem.* **1988**, *25*, 1455–1457.

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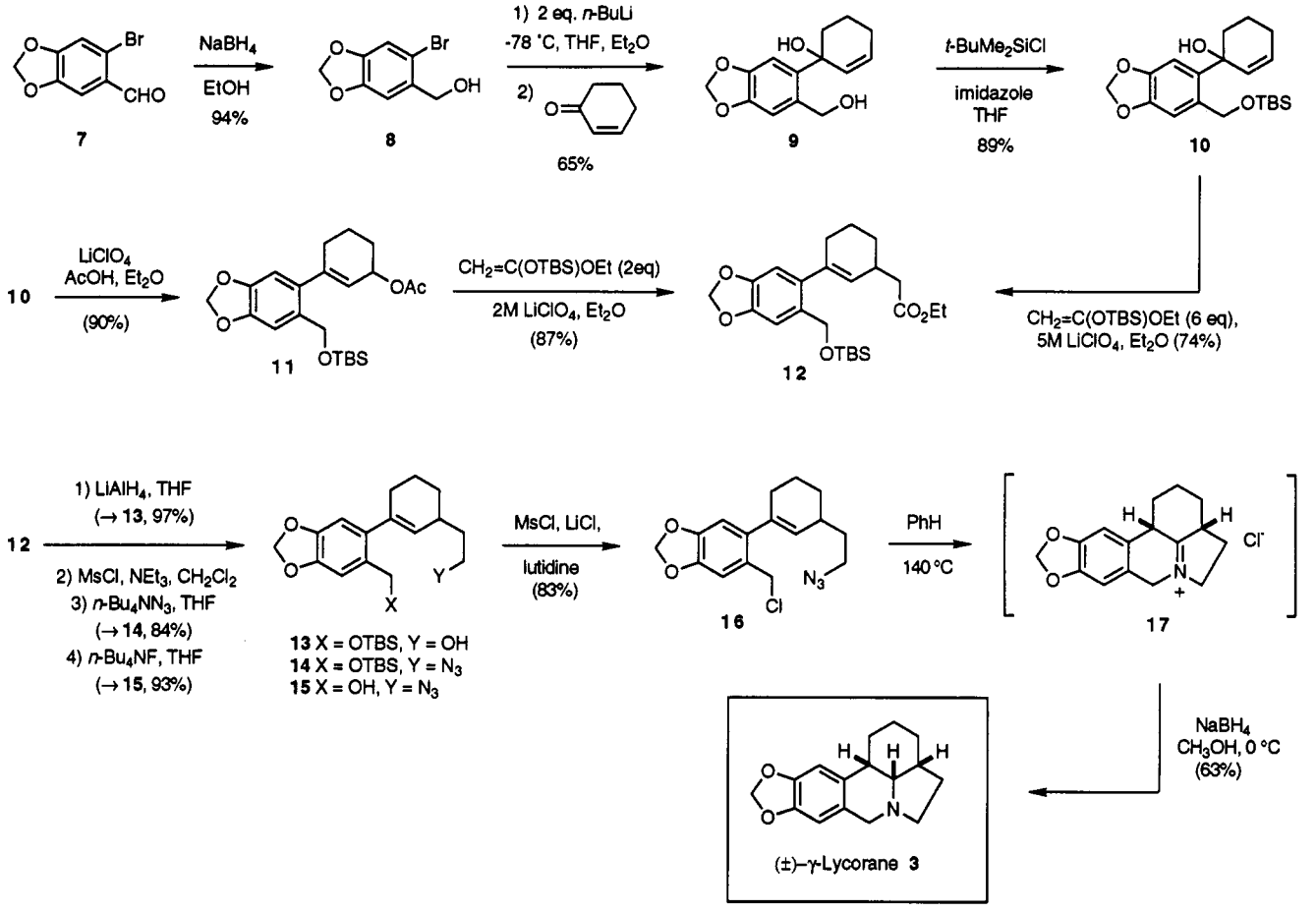
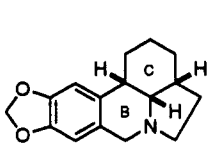
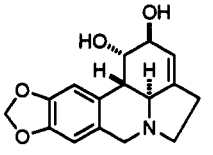
Scheme I. Synthesis of (±)-Lycorane (3)



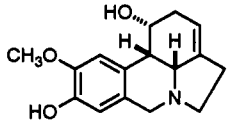
effort has been focused on those compounds with the trans-B,C ring juncture. The synthesis of γ-lycorane reported below illustrates a synthetic strategy that may be useful for the synthesis of more complex alkaloids having the cis-B,C ring juncture (e.g., **5** and **6**).



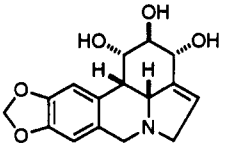
γ-Lycorane **3**



Lycorine **4**



Fortucine **5**



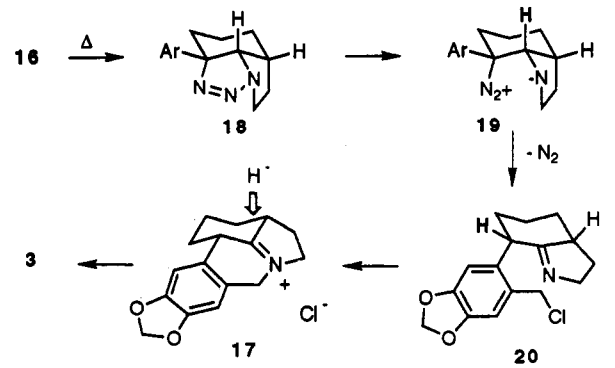
Siculinine **6**

The synthesis of the appropriate cyclization precursor **16** and its transformation to γ-lycorane in one pot is shown in Scheme I. Reduction of bromopiperonal **7**[8] afforded the alcohol **8**,[9] which was converted to a dianion with *n*-BuLi and quenched with 2-cyclohexen-1-one. The resultant diol **9** was selectively silylated at the primary position to provide **10**. At this stage, we had planned to convert **10** to **12** by either a Claisen rearrangement or palladium-catalyzed alkylation of an appropriate carbon nucleophile.[10] Unfortunately, both methods proceeded in poor yield. Inspired by the work of Grieco,[11] we reasoned that the ionization of **10** to an allylic carbocation in the presence of a soft carbon nucleophile might serve to accomplish this transformation. Indeed, lithium perchlorate promoted substitution of **10** with a silyl ketene acetal proceeded smoothly, providing **12** in good yield. Other examples of this method for allylic substitution have recently appeared.[12,13] An alternative method for the conversion of **10** to **12** was also developed which produced **10** in slightly higher yield using less ketene acetal. Hence, lithium perchlorate assisted solvolysis of **10** in acetic acid gave the rearranged allylic acetate **11**, which was subjected to the substitution reaction using only 2 equiv of ketene acetal rather than 6. In addition, the substitution of **11** could be carried out with a lower concentration of lithium perchlorate. Reduction of **12**, mesylation of the resultant alcohol, and displacement with azide ion gave **14**. Desilylation followed by conversion of the benzylic alcohol to a chloride[14] gave the desired chloro azide **16**.

Heating **16** in benzene at 140 °C in a sealed tube gave the iminium ion **17**, which was reduced with sodium borohydride to provide (±)-γ-lycorane (**3**) in 63% yield as

(8) Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586–591.
(9) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535–556.
(10) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 585–661.
(11) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488–5489.
(12) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 2986–2987.
(13) Grieco, P. A.; Collins, J. L.; Henry, K. J., Jr. *Tetrahedron Lett.* **1992**, *33*, 4735–4738.
(14) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044–3045.

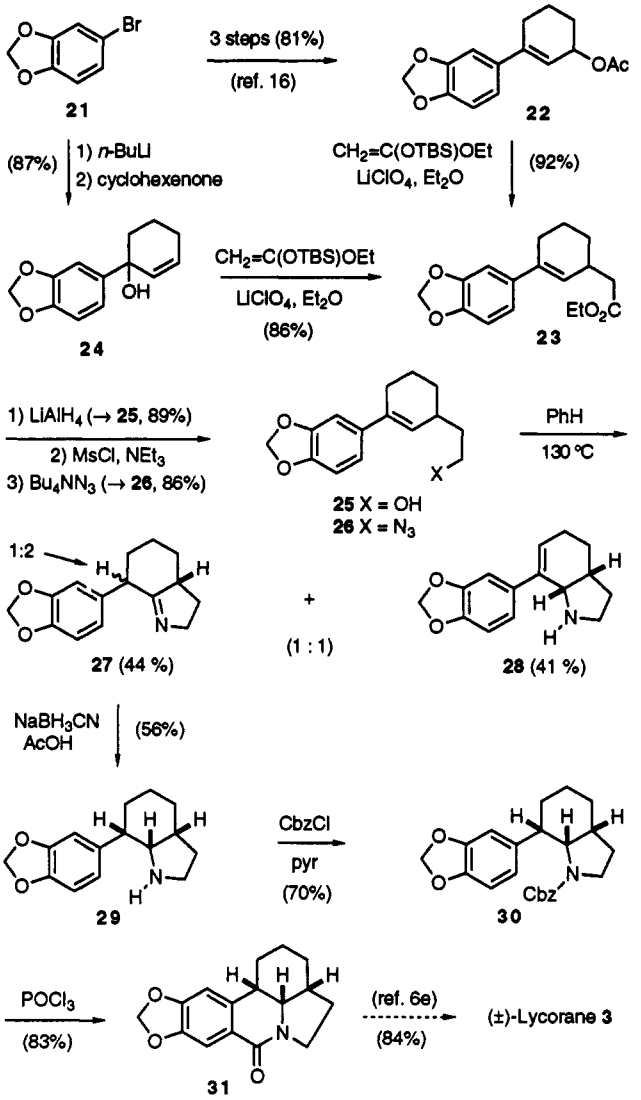
Scheme II. Mechanism for the Formation of γ-Lycorane (3) from 16



a single diastereomer.[15] A rationale for the stereochemical outcome of this tandem cyclization is presented in Scheme II. Intramolecular 1,3-dipolar cycloaddition of **16** should produce the triazoline **18**, with the all-cis fusion of the three rings. Fragmentation of the triazoline may produce the zwitterion **19**, which may then rearrange by migration of the emboldened hydrogen, which is properly oriented for backside displacement of the dinitrogen leaving group. The resultant imine **20** is then internally alkylated to give the iminium ion **17**. It is also likely that **17** is simply the most stable stereoisomer, since epimerization at the benzylic position (via the enamine) is probably facile. Reduction of **17** from the least crowded face then provides (±)-γ-lycorane.

The tandem cyclization route was compared to a more stepwise route to γ-lycorane (Scheme III), where the last ring was formed by a Bischler–Napieralski cyclization. The known acetate **22**, available in three steps from **21**,[16] was converted to **23** using the lithium perchlorate method. Alternatively, **21** could be converted to **23** in only two steps by conversion to the tertiary allylic alcohol **24** followed by substitution with allylic inversion using lithium perchlorate and a ketene acetal. Ester **23** was then converted into the azide **26** by standard chemistry. Thermal cyclization gave the desired imine **27** as a 1:2 mixture of diastereomers in 44% isolated yield (stereochemistry not assigned), accompanied by a 41% yield of **28**, the product of double bond migration. Both of these compounds were easily air oxidized. The diastereomers of **27** could not be separated, possibly due to an equilibrium between the imine and conjugated enamine forms.[17] The formation of **28** is proposed to be a result of elimination during the fragmentation of the triazoline intermediate. Reduction of **27** with acidic sodium cyanoborohydride gave the amine **29** as a single diastereomer. This amine was found to be air-sensitive, producing the hydroxylamine derivative upon standing. The isolation of a single diastereomer of **29** from the reduction of a 1:2 mixture of diastereomeric imines may be explained by rapid epimerization of the N-protonated form of **27** on the time scale of the reduction combined with a larger rate constant for the reduction of the *cis*-iminium ion. It is also possible that only one of the two diastereomeric imines is reduced, accounting for both the stereoselectivity and the moderate yield. However, examination of the crude reaction mixture showed only **29**, with no remaining imine. Acylation of **29** gave

Scheme III. Second Synthesis of (±)-Lycorane



30, which was cyclized to **31**. The reduction of **31** to γ-lycorane is known,[6e] therefore concluding a formal total synthesis of this alkaloid.

While the cyclization of **26** in Scheme III is efficient, the complications associated with the formation of the byproduct **28** combined with the modest yield of the reduction of **27** make this route less efficient than the tandem cyclization route in Scheme I. The immediate capture of the imine **20** by the pendant alkyl chloride is probably responsible for the more predictable outcome of the latter route.

The method used in Scheme I for the synthesis of γ-lycorane should be useful for the preparation of more complex alkaloids such as **5** and **6**, where the C-ring functionality will necessitate the use of a more complex cyclohexenone as a starting material. Efforts along these lines are underway.

Experimental Section

General. Reagents and starting materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and ether were distilled from sodium/benzophenone ketyl. Methylene chloride and triethylamine were distilled from calcium hydride. Dimethylformamide was distilled from barium oxide at reduced pressure. All reactions were conducted under an atmosphere of dry nitrogen. Chromatography refers to flash column chromatography on silica gel (230–400 mesh) unless otherwise noted. Combustion analyses were performed

(15) The spectral data for **3** were consistent with those reported in ref 6e.

(16) Keck, G. E.; Webb, R. R., III. *J. Am. Chem. Soc.* **1981**, *103*, 3173–3177.

(17) Imine–enamine tautomerization is especially facile when the enamine form is conjugated with an aromatic ring. See: Burchalter, J. H.; Short, J. H. *J. Org. Chem.* **1958**, *23*, 1278–1281.

by Spang Microanalytical Laboratories (Eagle Harbor, MI) or by the microanalytical facility operated by the University of Michigan. J-Modulated spin echo Fourier transform (JMOD) ^{13}C NMR experiments are reported as (+) (for CH_3 and CH) or (–) (for CH_2 and C) and are used as an alternative to off resonance decoupling experiments.

1-[2-(Hydroxymethyl)-4,5-(methylenedioxy)phenyl]-2-cyclohexen-1-ol (9). To a cold (–78 °C) solution of alcohol 8 (0.50 g, 2.16 mmol) in ether (4 mL) and THF (2 mL) was added *n*-BuLi (2.16 mL, 2.0 M in hexane) dropwise via syringe. After 5 min, metalation was complete as determined by GC, and 2-cyclohexen-1-one (0.23 g, 2.38 mmol) was added dropwise via syringe. After the solution was allowed to warm to 23 °C over 2 h and stirred an additional 8 h, H_2O (25 mL) was added and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with H_2O (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (35% EtOAc/hex) gave 0.348 g (65%) of **9** as a white foam, R_f = 0.12 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.84 (s, 1 H), 6.82 (s, 1 H), 6.02 (dt, J = 3.5, 10.0 Hz, 1 H), 5.92 (s, 2 H), 5.80 (d, J = 10.0 Hz, 1 H), 4.95 (d, J = 11.8 Hz, 1 H), 4.35 (d, J = 11.8 Hz, 1 H), 3.70–2.80 (br m, 2 H), 2.10–1.45 (series of multiplets, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.48, 146.19, 138.65, 133.18, 132.62, 130.48, 102.03, 108.68, 101.10, 74.68, 64.39, 38.95, 24.74, 19.16; IR (neat) 3389 (s), 1504 (s), 1241 (s), 1039 (s), 878 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 248 (M^+, 15.6), 230 (22.1), 202 (63.2), 201 (26.9), 173 (16.2), 144 (12.4), 115 (21.7), 86 (33.5), 84 (49.5), 77 (21.1), 49 (100.0), 39 (26.8); HRMS calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1041. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.71; H, 6.50. Found: C, 67.59; H, 6.39.

1-[2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4,5-(methylenedioxy)phenyl]-2-cyclohexen-1-ol (10). To a cool (0 °C) solution of diol **9** (0.82 g, 3.3 mmol) and imidazole (0.34 g, 4.9 mmol) in dry THF (10 mL) was added *tert*-butyldimethylsilyl chloride (0.60 g, 3.96 mmol). After the mixture was stirred for 8 h at 23 °C, water (25 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with H_2O (2 × 50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. Chromatography (10% EtOAc/hex) gave 1.06 g (89%) of **10** as white crystals, mp 108–109.5 °C, R_f = 0.70 (35% EtOAc/hex): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.98 (s, 1 H), 6.94 (s, 1 H), 5.98 (dt, J = 3.2, 10.0 Hz, 1 H), 5.93 (s, 2 H), 5.77 (d, J = 10 Hz, 1 H), 4.90, 4.79 (AB q, J_{AB} = 12.6 Hz, 2 H), 3.27 (s, 1 H), 1.95 (m, 5 H), 1.60 (m, 1 H), 0.93 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 146.23, 146.12, 136.65, 133.58, 131.78, 129.54, 109.64, 108.33, 101.02, 73.36, 64.00, 38.36, 25.96, 24.86, 19.18, 18.34, 5.82, –5.13; IR (KBr) 3650 (m), 3553 (m), 1496 (m), 1479 (s), 1244 (s), 1079 (s), 1039 (m), 852 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 362 (M^+, 2.9), 344 (9.9), 213 (100.0), 183 (18.4), 155 (16.2), 75 (16.5); HRMS calcd for $C_{20}H_{30}O_4Si$ 362.1913, found 362.1923. Anal. Calcd for $C_{20}H_{30}O_4Si$: C, 66.26; H, 8.35. Found: C, 66.30; H, 8.30.

1-[2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4,5-(methylenedioxy)phenyl]-3-acetoxycyclohex-1-ene (11). To a solution of **10** (1.0 g, 2.75 mmol) in ether (10 mL) was added acetic acid (0.50 g, 8.30 mmol). No reaction had occurred after 45 min by TLC. The mixture was cooled at 0 °C, and $LiClO_4$ (2.12 g, 20.0 mmol) was added. After stirring for 5 min, water (50 mL) was added and the mixture was extracted with ether (3 × 25 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography (2.5% EtOAc/hex) gave 1.0 g (90%) of the **11** as a clear, colorless oil, R_f = 0.32 (10% EtOAc/hexanes): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.96 (s, 1 H), 6.56 (s, 1 H), 5.92 (s, 2 H), 5.55 (m, 1 H), 5.38 (m, 1 H), 4.56 (s, 2 H), 2.21 (m, 2 H), 2.05 (s, 3 H), 1.80 (m, 4 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 170.63, 146.62, 146.14, 142.74, 134.60, 131.61, 124.79, 107.91, 107.67, 100.83, 68.19, 62.39, 30.56, 27.83, 25.89, 21.28, 19.33, 18.32, –5.35; IR (neat) 1731 (s), 1504 (m), 1484 (s), 1371 (m), 1239 (s), 1192 (m), 1091 (s), 1040 (s), 838 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 404 (M^+, 0.28), 214 (17.4), 213 (100.0), 183 (23.2), 155 (22.0), 117 (11.3), 75 (20.6), 43 (41); HRMS calcd for $C_{22}H_{32}O_5Si$ 404.2019, found 404.2014. Anal. Calcd for $C_{22}H_{32}O_5Si$: C, 65.31; H, 7.97. Found: C, 65.35; H, 7.87.

1-[2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4,5-(methylenedioxy)phenyl]-3-[(ethoxycarbonyl)methyl]cyclohex-1-ene (12). Method A. To a solution of **11** (0.86 g, 2.13 mmol) in ether (10 mL) was added 1-[(*tert*-butyldimethylsilyl)oxy]-1-ethoxyethene (0.86 g, 4.25 mmol). The mixture was cooled to 0 °C, and $LiClO_4$ (2.12 g, 20.0 mmol) was added. After the mixture was stirred for 1 h, water (50 mL) was added, and the resulting mixture was extracted with ether (3 × 25 mL). The organic phases were combined, washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography (2.5% EtOAc/hex) gave 0.79 g (87%) of the ester **12** as a clear, colorless oil, R_f = 0.38 (10% EtOAc/hexanes): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1 H), 6.55 (s, 1 H), 5.91 (s, 2 H), 5.38 (m, 1 H), 4.57 (s, 2 H), 4.13 (q, J = 7.1 Hz, 2 H), 2.71 (m, 1 H), 2.33 (m, 2 H), 2.13 (m, 2 H), 1.85 (m, 2 H), 1.65 (m, 1 H), 1.31 (m, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 0.93 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.47, 146.60, 146.30, 138.55, 135.99, 132.06, 129.67, 108.24, 107.83, 100.83, 62.63, 60.21, 41.04, 32.77, 30.77, 28.52, 26.04, 21.66, 18.43, 14.29, –5.22; IR (neat) 1731 (s), 1618 (w), 1503 (s), 1483 (s), 1250 (s), 1175 (s), 1094 (s), 1040 (s), 938 (s), 837 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 432 (M^+, 6.3), 375 (17.7), 214 (12.9), 213 (63.4), 202 (23.7), 86 (53.9), 84 (82.7), 51 (34.4), 49 (100.0); HRMS calcd for $C_{24}H_{36}O_5Si$ 432.2332, found 432.2324. Anal. Calcd for $C_{24}H_{36}O_5Si$: C, 66.63; H, 8.39. Found: C, 66.40; H, 8.55.

Method B. To a solution of the alcohol **10** (0.25 g, 0.69 mmol) in ether (3 mL) was added 1-[(*tert*-butyldimethylsilyl)oxy]-1-ethoxyethene (0.70 g, 3.45 mmol). The mixture was cooled to 0 °C, and $LiClO_4$ (1.59 g, 15.0 mmol) was added. After the mixture was stirred for 24 h at 23 °C, it was worked up as reported above to give 0.22 g (74%) of ester **12** after chromatography.

1-[2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4,5-(methylenedioxy)phenyl]-3-(2-hydroxyethyl)cyclohex-1-ene (13). To a cold (0 °C) solution of ester **12** (0.20 g, 0.46 mmol) in THF (2 mL) was added $LiAlH_4$ (18.0 mg, 0.46 mmol). After the mixture was stirred for 1 h, water (10 mL) was added, and the resulting mixture was extracted with ether (3 × 15 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to give 175 mg (97%) of the alcohol **13** as a clear, colorless oil, R_f = 0.25 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1 H), 6.55 (s, 1 H), 5.92 (s, 2 H), 5.42 (m, 1 H), 4.58 (s, 2 H), 3.75 (t, J = 6.9 Hz, 2 H), 2.40–1.20 (series of multiplets, 10 H), 0.94 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 146.24, 145.99, 137.32, 136.05, 131.74, 130.80, 108.10, 107.60, 100.74, 62.49, 60.76, 39.20, 32.10, 30.77, 28.50, 25.96, 21.86, 18.40, –5.26; IR (neat) 3362 (m), 1618 (w), 1503 (m), 1482 (s), 1250 (s), 1090 (s), 1041 (s), 837 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 390 (M^+, 2.23), 259 (10.7), 258 (37.9), 241 (19.9), 213 (100.0), 185 (31.0), 173 (24.5), 155 (13.1), 135 (27.4), 115 (16.7), 81 (18.9), 41 (22.3); HRMS calcd for $C_{22}H_{34}O_4Si$ 390.2226, found 390.2196. Anal. Calcd for $C_{22}H_{34}O_4Si$: C, 67.65; H, 8.78. Found: C, 68.02; H, 9.07. When the reaction was performed on a 900-mg scale following the procedure above, the alcohol **13** was obtained in 96% yield.

1-[2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-4,5-(methylenedioxy)phenyl]-3-(2-azidoethyl)cyclohex-1-ene (14). To a cold (–50 °C) solution of alcohol **13** (0.80 mg, 2.05 mmol) and triethylamine (0.46 g, 0.63 mL, 4.51 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise methanesulfonyl chloride (0.47 g, 0.42 mL, 4.09 mmol). The reaction was monitored by TLC (25% EtOAc/hex, R_f of mesylate = 0.31) and was found to be complete in 1 h. Water was added at –50 °C, and the solution was allowed to warm to 23 °C. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated. The resulting oil was dissolved in THF (3 mL), and Bu_4NN_3 (1.46 g, 5.12 mmol) was added. After the mixture was stirred for 2 h, water (25 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography (2.5% EtOAc/hex) gave 0.70 g (84%) of the azide **14**, R_f = 0.30 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.98 (s, 1 H), 6.56 (s, 1 H), 5.92 (s, 2 H), 5.40 (s, 1 H), 4.57 (s, 2 H), 3.37 (t, J = 6.1 Hz, 2 H), 2.40–1.20 (series of mult, 9 H), 0.91 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 146.34, 146.06, 138.00, 135.87, 131.70, 129.80, 108.06, 107.72, 100.79, 62.51, 49.17, 35.10, 32.86, 30.74, 28.24, 25.96, 21.76, 18.42, –5.25; IR (neat) 2096 (s), 1619 (w), 1503 (m), 1482 (s), 1382 (m), 1251 (s), 1090 (s), 836 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 387 (M^+ – 28, 0.41), 344 (5.27), 256 (38.2), 255 (25.7), 254 (100.0), 242 (13.1), 226 (23.1),

213 (36.0), 183 (19.1), 155 (25.4), 115 (22.1), 82 (10.94), 43 (36.9); HRMS (CI, NH_3) calcd for $C_{22}H_{33}N_3O_3SiNH_4$ 433.2635, found 433.2620.

1-[2-(Hydroxymethyl)-4,5-(methylenedioxy)phenyl]-3-(2-azidoethyl)cyclohex-1-ene (15). To a cold (0 °C) solution of azide **14** (0.70 g, 1.68 mmol) in THF (1 mL) was added Bu_4NF (3.37 mL, 1.0 M, in THF, 3.37 mmol). After the mixture was stirred for 2 h, H_2O (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Chromatography (SiO_2, 10–25% EtOAc/hex gradient) gave 0.47 g (93%) of the alcohol **15** as a white solid, mp 40–42 °C, R_f = 0.22 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.92 (s, 1 H), 6.58 (s, 1 H), 5.93 (s, 2 H), 5.45 (m, 1 H), 4.53 (s, 2 H), 3.36 (t, J = 7.2 Hz, 2 H), 2.50–1.10 (series of mult, 10 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 146.67, 146.45, 138.18, 137.22, 131.18, 130.13, 108.50, 100.92, 62.86, 49.18, 35.04, 32.90, 31.08, 28.14, 21.72; IR (neat) 3361 (s), 2096 (s), 1616 (w), 1558 (w), 1486 (s), 1372 (m), 1242 (s), 1079 (m), 1039 (s), 934 (s) cm^{-1}; MS (CI with NH_3) m/z (rel int) 433 ($M^+ + NH_4$, 0.20), 388 (5.0), 284 (100.0), 272 (34.3), 258 (29.9), 256 (40.3), 249 (64.6), 213 (31.9), 136 (31.8), 94 (2.7). Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 64.12; H, 6.21; N, 13.53.

1-[2-(Chloromethyl)-4,5-(methylenedioxy)phenyl]-3-(2-azidoethyl)cyclohex-1-ene (16). To a cool (0 °C) solution of alcohol **15** (57 mg, 0.19 mmol), lutidine (41 mg, 44 μL, 0.38 mmol), and LiCl (16 mg, 0.38 mmol) in dry DMF (0.3 mL) was added in a dropwise fashion methanesulfonyl chloride (43 mg, 38 μL, 0.38 mmol). After the mixture was stirred for 1 h, water was added, and the resulting mixture was extracted with ether (3 × 5 mL). The combined organic phases were washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Chromatography (2.5–5% EtOAc/hex gradient) gave 50 mg (83%) of the azide **16**, R_f = 0.47 (10% EtOAc/hex): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.87 (s, 1 H), 6.59 (s, 1 H), 5.95 (s, 2 H), 5.56 (m, 1 H), 4.53 (s, 2 H), 3.39 (t, J = 7.2 Hz, 2 H), 2.40–1.20 (series of mult, 9 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 147.65, 138.57, 137.41, 130.61, 127.60, 109.88, 108.51, 101.28, 49.19, 44.93, 35.06, 32.89, 30.99, 28.20, 21.72; IR (neat) 2096 (s), 1616 (w), 1504 (s), 1485 (s), 1372 (m), 1251 (m), 1211 (m), 1038 (m), 938 (w) cm^{-1}; MS (CI with NH_3) m/z (rel int) 284 (M^+ – Cl, 100.0), 258 (10.1), 256 (27.4), 136 (71.34); HRMS calcd for $C_{16}H_{18}ClN_3O_2$ – Cl 284.1399, found 284.1392. Anal. Calcd for $C_{16}H_{18}ClN_3O_2$: C, 60.17; H, 5.68; N, 13.16. Found: C, 60.22; H, 5.82; N, 12.81.

(±)-γ-Lycorane (3). A degassed solution of the azide **16** (40 mg, 0.13 mmol) in benzene (3 mL) was heated to 140 °C in a sealed glass tube. After 32 h, the solution was cooled and the benzene was decanted from the precipitate. The precipitate was dissolved in methanol (1 mL), cooled to 0 °C, and treated with $NaBH_4$ (5.6 mg, 0.15 mmol). After 2 h, the methanol was removed in vacuo, and the residue was partitioned between H_2O and EtOAc. The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (SiO_2, 70–230 mesh, 2:70:30 Et_3N/hex/EtOAc) gave 24 mg (63%) of (±)-γ-lycorane (**3**), R_f = 0.33 (2:70:30 Et_3N/hex/EtOAc): mp 99–100 °C (lit.[7j] mp 101–103 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.61 (s, 1 H), 6.49 (s, 1 H), 5.89, 5.88 (AB q, J_{AB} = 1.5 Hz, 2 H), 4.01 (d, J = 14.3 Hz, 1 H), 3.38 (dt, J = 3.8, 9.1 Hz, 1 H), 3.21 (d, J = 14.3 Hz, 1 H), 2.75 (dt, J = 4.8, 11.6 Hz, 1 H), 2.36 (t, J = 4.8 Hz, 1 H), 2.25–1.90 (m, 3 H), 1.80–1.00 (m, 3 H), 1.55–1.20 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.23, 145.86, 133.36, 108.39, 106.28, 100.66, 63.01, 57.12, 53.69, 39.85, 37.68, 31.78, 30.41, 29.48, 25.36; IR (CCl_4) 2929 (s), 1505 (s), 1483 (s), 1448 (m), 1376 (m), 1340 (w), 1318 (s), 1230 (s), 1154 (m), 1138 (m), 1043 (s), 943 (s), 867 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 257 (M^+, 32.6), 256 (M^+ – 1, 100.0), 226 (2.24), 214 (2.53), 212 (1.81), 188 (1.51), 163 (2.1), 130 (2.16), 107 (8.02), 94, (4.76), 77 (9.73), 41 (8.20); HRMS (CI with NH_3) calcd for $C_{16}H_{19}NO_2H^+$ 258.1494, found 258.1478. These data matched the literature data.[6e]

1-[3,4-(Methylenedioxy)phenyl]-2-cyclohexen-1-ol (24). To a cold (–78 °C) solution of **21** (10.0 g, 49.7 mmol) in ether (100 mL) and THF (50 mL) was added *n*-BuLi (26.1 mL of a 2.0 M solution in hexane, 52.2 mmol) dropwise so the temperature (internal thermometer) did not rise above –70 °C (ca. 15 min). The solution was stirred for 20 min at –78 °C, and 2-cyclohexen-1-one (5.25 g, 54.7 mmol) in ether (10 mL) was added. The solution was slowly warmed to 23 °C (4 h), and saturated aqueous $NaHCO_3$ (100 mL) was added. The mixture was extracted with ether (3 × 75 mL), and the combined organic phases were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated to give a yellow oil. Chromatography (10% EtOAc/hex) gave 9.40 g (87%) of **24** as a white solid, mp 54.5–55.5 °C, R_f = 0.35 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.00 (d, J = 1.9 Hz, 1 H), 6.92, (dd, J = 1.9, 8.1 Hz, 1 H), 6.75 (d, J = 8.1 Hz, 1 H), 5.99 (dt, J = 3.4, 10.0 Hz, 1 H), 5.93 (s, 2 H), 5.74 (d, J = 10.0 Hz, 1 H), 2.20–1.53 (m, 7 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 147.40 (–), 146.25 (–), 142.16 (–), 132.32 (+), 130.30 (+), 107.50 (+), 106.50 (+), 100.80 (–), 72.04 (–), 39.54 (–), 24.88 (–), 19.15 (–); IR (melt) 3404 (s), 1645 (w), 1609 (w), 1484 (s), 1433 (s), 1349 (m), 1239 (s), 1039 (s), 935 (s), 811 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 218 (M^+, 49.9), 190 (41.0), 189 (31.3), 160 (40.9), 149 (26.2), 135 (100.0), 132 (25.4), 122 (23.2), 121 (23.5), 91 (10.9), 77 (15.6), 55 (14.4); HRMS calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0940. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.53; H, 6.47. Found: C, 71.57; H, 6.41.

1-[3,4-(Methylenedioxy)phenyl]-3-[(ethoxycarbonyl)methyl]cyclohex-1-ene (23). Method A. To a solution of **22** (139 mg, 0.534 mmol) in ether (2 mL) was added 1-[(*tert*-butyldimethylsilyl)oxy]-1-ethoxyethene (324 mg, 1.60 mmol). The mixture was cooled to 0 °C, and $LiClO_4$ (636 mg, 6.00 mmol) was added. After the mixture was stirred for 1 h, water (10 mL) was added, and the resulting mixture was extracted with ether (3 × 25 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography (5% EtOAc/hex) gave 140 mg (92%) of **23** as a clear, colorless oil, R_f = 0.47 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.88 (s, 1 H), 6.84 (d, J = 8.1 Hz, 1 H), 6.74 (d, J = 8.1 Hz, 1 H), 5.93 (s, 2 H), 5.84 (s, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 2.75 (m, 1 H), 2.35 (m, 4 H), 1.88 (m, 2 H), 1.69 (m, 1 H), 1.31 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 172.85 (–), 147.61 (–), 137.12 (–), 136.68 (–), 126.52 (+), 118.43 (+), 107.87 (+), 105.86 (+), 100.85 (–), 60.23 (–), 40.95 (–), 32.99 (+), 28.44 (–), 27.70 (–), 21.57 (–), 14.29 (+); IR (neat) 1731 (s), 1606 (w), 1504 (s), 1487 (s), 1444 (m), 1371 (s), 1278 (s), 1244 (m), 1219 (m), 1176 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 288 (M^+, 17.9), 214 (14.6), 201 (100.0), 135 (43.4) 115 (11.2), 79 (18.4); HRMS calcd for $C_{17}H_{20}O_4$ 288.1362, found 288.1369. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.88; H, 6.91.

Method B. The alcohol **24** (6.44 g, 0.030 mol), 1-[(*tert*-butyldimethylsilyl)oxy]-1-ethoxyethene (11.87 g, 0.060 mol), and lithium perchlorate (19.0 g, 0.179 mol) were combined for 1.5 h as in method A above to yield 7.31 g (86%) of **23** after chromatography.

1-[3,4-(Methylenedioxy)phenyl]-3-(2-hydroxyethyl)cyclohex-1-ene (25). To a cool (0 °C) suspension of $LiAlH_4$ (0.96 g, 25.4 mmol) in dry THF (25 mL) was added dropwise a solution of **23** (7.31 g, 25.4 mmol) in 15 mL of THF. After the mixture stirred for 1 h, water (25 mL) and then 10% HCl (25 mL) were added, and the mixture was extracted with EtOAc (3 × 75 mL). The combined organic phases were washed with H_2O (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. Chromatography (25% EtOAc/hex) gives 5.53 g (89%) of **25** as a clear oil, R_f = 0.17 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.89 (d, J = 1.7 Hz, 1 H), 6.85 (dd, J = 1.7, 8.1 Hz, 1 H), 6.75 (d, J = 8.1 Hz, 1 H), 5.93 (s, 2 H), 5.88 (s, 1 H), 3.78 (dt, J = 2.1, 6.6 Hz, 2 H), 2.40 (m, 3 H), 1.88 (m, 2 H), 1.65 (m, 3 H), 1.40 (bs, 1 H), 1.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 147.69 (–), 146.46 (–), 137.11 (–), 136.48 (–), 128.02 (+), 118.43 (+), 107.93 (+), 105.84 (+), 100.87 (–), 60.82 (–), 39.30 (–), 32.66 (+), 28.60 (–), 27.90 (–), 21.88 (–); IR (neat) 3390 (m), 1675 (w), 1500 (s), 1497 (s), 1460 (m), 1230 (s), 1086 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 247 (M^+ + 1, 10.3), 246 (M^+, 53.6), 201 (100.0), 135 (19.3), 128 (8.9), 79 (5.72). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.20; H, 7.37. Found: C, 73.02; H, 7.57.

1-[3,4-(Methylenedioxy)phenyl]-3-(2-azidoethyl)cyclohex-1-ene (26). To a cold (–50 °C) solution of **25** (4.00 g, 16.2 mmol) and triethylamine (1.81 g, 2.50 mL, 17.9 mmol) in dry CH_2Cl_2 (20 mL) was added in a dropwise fashion methanesulfonyl chloride (2.05 g, 1.38 mL, 17.91 mmol). The reaction was monitored by TLC (eluting twice with 25% EtOAc/hex, R_f (mesylate) = 0.35) and was found to be complete in 1 h. Water was added

at −50 °C, and the solution was allowed to warm to 23 °C. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were washed with H_2O (50 mL), dried ($MgSO_4$), and concentrated. The resulting oil was dissolved in THF (20 mL), and Bu_4NN_3 (9.24 g, 32.5 mmol) was added. After the 9 h, water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography (100% hex to 5% EtOAc/hex gradient) gave 3.80 g 86%) of azide **26** as a pale yellow oil, R_f = 0.60 (25% EtOAc/hex): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.89 (d, J = 1.8 Hz, 1 H), 6.85 (dd, J = 1.8, 8.1 Hz, 1 H), 6.76 (d, J = 8.1 Hz, 1 H), 5.94 (s, 2 H), 5.84 (s, 1 H), 3.39 (dt, J = 1.9, 7.3 Hz, 2 H), 2.37 (m, 3 H), 1.89 (m, 2 H), 1.70 (m, 3 H), 1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 147.73 (−), 146.60 (−), 137.12 (−), 136.87 (−), 126.96 (+), 118.49 (+), 107.98 (+), 105.84 (+), 100.94 (−), 49.3 (−), 35.18 (−), 33.34 (+), 28.30 (−), 27.87 (−), 21.78 (−); IR (neat) 2098 (s), 1605 (w), 1504 (s), 1487 (s), 1443 (s), 1343 (m), 1248 (s), 1218 (s), 1040 (s), 936 (s), 805 (s) cm^{-1}; MS (CI with NH_3) m/z (rel int) 289 [$(M + NH_4)^+$, 4.4], 265 (8.5), 244 (82.2), 240 (100.0), 223 (8.9), 136 (32.8); HRMS (CI, NH_3) calcd for $C_{15}H_{17}N_3O_2NH_4$ 289.1665, found 289.1668.

7-[3,4-(Methylenedioxy)phenyl]-3,3a,4,5,6,7-hexahydro-2*H*-indole (27) and (3a*R,7*S**)-7-[3,4-(Methylenedioxy)-phenyl]-2,3,3a,4,5,7a-hexahydro-1*H*-indole (28).** A degassed (three freeze–thaw cycles) solution of azide **26** (622 mg, 2.29 mmol) in benzene was heated to 130 °C in a sealed glass tube. After 29 h the solution was cooled and the benzene was removed in vacuo to give a pale oil which consisted of three compounds (two diastereomers of **27** plus **28**) by ^1H NMR. Changing the solvent to $CDCl_3$, pyridine-d_5, or DMSO-d_6 had little effect on the ratio of products formed. Purification was accomplished using deactivated flash silica gel[18] (10–30% THF/hex gradient). The first component to elute was 247 mg of an inseparable 2:1 mixture of imines **27** (44%, contaminated with ca. 5% of an oxidation product) as an easily oxidized oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.78 (m, 3.5 H), 6.65 (d, J = 8.0 Hz, 1 H), 5.89 (s, 1 H), 5.79, 5.73 (AB q, J_{AB} = 15 Hz, 2 H), 3.97 (d, J = 6.1 Hz, 0.5 H), 3.86 (m, 1.5 H), 3.72 (m, 0.5 H), 3.50 (m, 1 H), 3.38 (m, 1 H), 2.69 (m, 1.5 H), 2.40 (d, J = 13.5 Hz, 0.5 H), 2.12 (m, 4 H), 1.87 (m, 1.5 H), 1.65 (m, 3 H), 1.43 (m, 1.5 H), 1.20 (m, 1.5 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 180.15 (−), 179.84 (−), 147.91 (−), 147.44 (−), 146.16 (−), 145.93 (−), 135.37 (−), 134.08 (−), 121.31 (+), 120.10 (+), 109.05 (+), 108.02 (+), 107.88 (+), 107.47 (+), 100.75 (−), 100.60 (−), 59.43 (−), 58.98 (−), 49.02 (+), 48.88 (+), 45.41 (+), 43.85 (+), 35.36 (−), 34.79 (−), 34.65 (−), 30.48 (−), 29.59 (−), 29.53 (−), 25.60 (−), 20.89 (−); IR (neat) 2931 (s), 1650 (m), 1644 (m), 1609 (w), 1504 (s), 1487 (s), 1441 (s), 1238 (s), 1189 (m), 1038 (s), 935 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 243 (M^+, 100.0), 242 ($M^+ - 1$, 50.5), 214 (9.30), 200 (6.0), 161 (7.9), 145 (7.2), 131 (15.4), 122 (20.9), 115 (10.0), 103 (11.8), 77 (19.0). This compound was easily air oxidized to an unknown material and was best used without further manipulation. For the unknown oxidized material: MS (EI, 70 eV), m/z (rel int) 260 ($M^+ + 1$, 2.7), 259 (M^+, 14.30), 149 (17.6), 121 (9.1), 110 (100.0), 82 (7.3), 65 (9.0), 55 (7.0).

The second component to elute from the column was 230 mg of the amine **28** (41%, contaminated with ca. 5% of an oxidation product): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (s, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 6.73 (d, J = 8.2 Hz, 1 H), 6.02 (t, J = 4.1 Hz, 1 H), 5.90, 5.89 (AB q, J_{AB} = 2.1 Hz, 2 H), 3.75 (d, J = 5.8 Hz, 1 H), 3.00 (m, 1 H), 2.82 (m, 1 H), 2.15 (m, 3 H), 2.04 (m, 1 H), 1.60 (m, 2 H), 1.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz, JMOD) δ 147.73 (−), 146.57 (−), 137.92 (−), 135.69 (−), 126.14 (+), 119.49 (+), 108.00 (+), 106.72 (+), 100.76 (−), 58.23 (+), 44.90 (−), 37.09 (+), 31.46 (−), 25.04 (−); IR (neat) 3334 (w), 1656 (w), 1605 (w), 1504 (s), 1487 (s), 1440 (s), 1337 (w), 1246 (s), 1039 (s), 935 (m), 861 (m), 809 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 243 (M^+, 16.5), 242 ($M^+ - 1$, 12.3), 226 (20.3), 214 (31.8), 198 (8.4), 115 (12.8), 82 (91.4), 77 (11.0), 68 (15.8), 63 (7.4), 45 (100.0); HRMS calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1261. This compound was also easily air oxidized.

(3a*R,7*S**,7a*S**)-7-[3,4-(Methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydro-1*H*-indole (29) and (3a*R**,7*S**,7a*S**)-1-Hydroxy-7-[3,4-(methylenedioxy)-phenyl]-2,3,3a,4,5,6,7,7a-octahydro-1*H*-indole.** To a cool (0 °C) solution of **27** (200 mg, 0.82 mmol) in glacial acetic acid (4 mL) and THF (6 mL) was added $NaCNBH_3$ (160 mg, 2.47 mmol). After 1 h, 1 N NaOH was added until the solution was neutral. The mixture was then extracted with EtOAc (3 × 25 mL), and the combined organic phases were washed with H_2O (2 × 15 mL) and brine (25 mL), dried (Na_2SO_4), and concentrated. Chromatography (deactivated silica gel,[18] 20–30% THF/hex gradient) gave 112 mg (56%) of amine **29**, R_f = 0.06 (silica, EtOAc): ^1H NMR ($CDCl_3$, 360 MHz) δ 6.78 (s, 1 H), 6.72 (m, 2 H), 5.89 (s, 2 H), 3.18 (app t, J = 4.1 Hz, 1 H), 3.00 (m, 1 H), 2.82 (m, 2 H), 2.03 (m, 1 H), 1.80 (m, 3 H), 1.50 (m, 3 H), 1.25 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.57, 145.73, 139.13, 120.17, 108.05, 100.67, 63.18, 44.86, 43.34, 38.82, 31.58, 27.70, 25.93, 25.07; IR (neat) 3362 (w), 1504 (s), 1487 (s), 1441 (s), 1395 (m), 1247 (s), 1188 (m), 1144 (m), 1097 (m), 1040 (s), 937 (s), 809 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 246 ($M^+ + 1$, 2.8), 245 (M^+, 15.9), 244 ($M^+ - 1$, 1.1), 1.48 (2.4), 147 (3.0), 135 (3.8), 109 (3.6), 89 (3.0), 82 (100.0), 69 (11.7), 68 (17.8), 41 (3.8); HRMS calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1406. Further elution gave 12 mg (6%) of (3a*R**,7*S**,7a*S**)-1-hydroxy-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydro-1*H*-indole: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (s, 1 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.72 (d, J = 8.1 Hz, 1 H), 5.89 (s, 2 H), 3.44 (d, J = 8.6 Hz, 1 H), 3.09 (dd, J = 6.2, 8.6 Hz, 1 H), 2.87 (m, 1 H), 2.23 (m, 2 H), 1.75 (m, 8 H), 1.38 (m, 1 H), ^{13}C NMR ($CDCl_3$, 90 MHz) δ 147.30, 145.64, 144.67, 118.25, 107.49, 106.34, 100.80, 72.30, 62.30, 45.60, 37.98, 37.15, 30.82, 25.98, 16.74; IR ($CDCl_3$) 3393 (w), 1504 (s), 1485 (s), 1239 (s), 1042 (s), 930 (m), 914 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 262 ($M^+ + 1$, 3.0), 261 (M^+, 15.8), 164 (5.6), 149 (17.1), 112 (26.8), 95 (29.9), 82 (100.0), 69 (42.5), 68 (47.7), 43 (19.0).

(3a*R,7*S**,7a*S**)-1-(Benzyloxycarbonyl)-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydro-1*H*-indole (30).** To a solution of amine **29** (70 mg, 0.28 mmol) in dry CH_2Cl_2 (1 mL) was added pyridine (0.45 g, 0.046 mL, 0.57 mmol). The mixture was cooled to 0 °C, and benzyl chloroformate (97 mg, 0.57 mmol) was added. After the mixture was stirred for 1 h, water (15 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with H_2O (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. Chromatography (5–25% EtOAc/hex gradient) gave 76 mg (70%) of carbamate **30** as a clear oil. R_f = 0.77 (EtOAc): ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 5 H), 6.78 (s, 1 H), 6.65 (d, J = 8.1 Hz, 1 H), 6.59 (d, J = 8.1 Hz, 1 H), 5.89, 5.89 (AB q, J_{AB} = 1.5 Hz, 2 H), 5.11 (d, J = 12.3 Hz, 1 H), 4.81 (br d, J = 12.3 Hz, 1 H), 4.20 (app t, J = 7.2 Hz, 1 H), 3.44 (m, 1 H), 3.19 (m, 1 H), 2.97 (m, 1 H), 2.40 (m, 1 H), 2.10–1.50 (m, 8 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.52, 147.30, 145.64, 138.14, 137.32, 128.37, 127.92, 127.76, 121.84, 109.22, 107.68, 100.62, 66.57, 59.10, 46.41, 40.82, 37.43, 29.18, 26.45, 25.03, 18.89; IR ($CDCl_3$) 1701 (s), 1504 (s), 1489 (s), 1442 (m), 1416 (s), 1359 (m), 1336 (m), 1234 (s), 1214 (m), 1096 (m), 1044 (s), 810 (s), 805 (s), 800 (m), 748 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 379 (M^+, 2.8), 244 (4.7), 227 (2.3), 172 (27.6), 135 (16.4), 92 (8.1), 91 (100.0), 65 (5.6), 41 (4.8).

(3a*R,11b*S**,11c*S**)-1,2,3,3a,4,5,11b,11c-Octahydro-9,10-(methylenedioxy)pyrrolo[3,2,1-*de*]phenanthridin-7-one (31).**[6e] A solution of carbamate **30** (32 mg, 0.084 mmol) in distilled $POCl_3$ (1 mL) was heated to 70 °C for 24 h and to 80 °C for another 24 h. The resulting yellow solution was cooled to 0 °C, and 1 N NaOH was added *carefully* until the solution was basic (pH ca. 9). The mixture was extracted with EtOAc (3 × 25 mL), and the combined organic phases were washed with water (until neutral) and brine (25 mL), dried ($MgSO_4$), and concentrated. Chromatography (50–75% EtOAc/hex gradient) gave 19 mg (83%) of **31**, R_f = 0.28 (75% EtOAc/hex): ^1H NMR ($CDCl_3$, 360 MHz) δ 7.53 (s, 1 H), 6.62 (s, 1 H), 5.98, 5.96 (AB q, J_{AB} = 1.1 Hz, 2 H), 3.85 (app t, J = 4.6 Hz, H), 3.74 (dd, J = 10, 12 Hz, 1 H), 3.62 (dt, J = 7.6, 11.5 Hz, 1 H), 2.79 (dt, J = 5.0, 12.0 Hz, 1 H), 2.27 (sextet, J = 5.6 Hz, 1 H), 1.95 (m, 1 H), 1.70 (m, 4 H), 1.20 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz, JMOD) δ 162.84 (−), 150.24 (−), 146.73

(18) Deactivated silica gel was prepared by adding 20% by weight of hexamethyldisilazane to a suspension of silica gel in hexane. After allowing to cool, the resulting mixture was used to wet-pack a chromatography column. The column was then washed successively with ethyl acetate, 50% ethyl acetate/hexane, and finally with the desired elution solvent before loading the sample.

(-), 138.50 (-), 123.00 (-), 107.65 (+), 106.99 (+), 101.40 (+), 57.99 (+), 42.74 (-), 39.16 (+), 38.14 (+), 29.96 (-), 28.99 (-), 26.27 (-), 23.77 (-); IR (CCl_4) 2935 (s), 1650 (s), 1613 (s), 1504 (s), 1478 (s), 1461 (s), 1411 (s), 1392 (m), 1355 (s), 1320 (m), 1282 (m), 1248 (s), 1042 (s), 943 (m), 804 (s), 797 (s) cm^{-1}, MS (EI, 70 eV) m/z (rel int) 271 (M^+, 2.5), 270 ($M^+ - 1$, 2.4), 242 (0.4), 228 (1.0), 203 (1.0), 189 (1.1), 123 (3.4), 121 (32.2), 119 (97.3), 117 (100.0), 86 (2.7), 84 (16.6), 82 (25.1), 49 (11.0), 47 (34.0); HRMS calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1196. These data matched the literature data.[6e]

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Supplementary Material Available: Improved experimental procedures for the preparation of **8** and **32** and ^1H NMR and ^{13}C NMR spectra of the compounds which had no elemental analysis: **3** (γ-lycorane), **14**, **26–31**, and *N*-hydroxy **29** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Asymmetric Synthesis of Alkane- and Arenesulfinates of Diacetone-D-glucose (DAG): An Improved and General Route to Both Enantiomerically Pure Sulfoxides

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Diacetone-D-glucose (DAG), a commercially available, sugar-derived secondary alcohol, was found to react with alkane- and arenesulfinyl chlorides in the presence of a tertiary amine in a very useful manner. When *i*-Pr_2NEt is used as the base, (-)-(*S*)-alkane- and arenesulfinates are obtained in 50–90% yield with 89–≥95% de. Simply changing the base from *i*-Pr_2NEt to Py affords (+)-(*R*)-alkane- and arenesulfinates in 56–87% yield with 70–≥95% de. The de's were determined by ^1H NMR. Optically pure alkane- and arenesulfinates are obtained either by recrystallization or by column chromatography. These sulfinates were transformed into various enantiomerically pure sulfoxides (alkyl alkyl and alkyl aryl) by reaction with different Grignard reagents. This new methodology is cheap, quick, and very convenient when both enantiomers of a given sulfoxide are needed enantiomerically pure. The influence of the solvent, as well as the effect of other types of bases, on the stereochemical course of the reaction has been evaluated, and a possible origin of the diastereoselectivity is discussed. Other optically pure secondary alcohols are used in the same reaction, and the comparison of their behavior with that of DAG is also reported.

Introduction

Optically active sulfoxides have proven themselves to be powerful auxiliaries in highly efficient asymmetric syntheses.[1-8] Additionally, molecules bearing a sulfinyl function (such as sparsomycin[9] and oxisurane[10] and their analogs,[11] carpetomycin A,[12] RP49356,[13] and several methyl vinyl sulfoxides[14]) are of great biological interest. For these reasons, the preparation of sulfoxides with high enantiomeric purity has received considerable attention over the years.

Nowadays, practically all types of optically pure sulfoxides can be prepared by combining the different methods described in the literature. Nevertheless, a simple and general protocol that permits quick access to the desired sulfoxide is still greatly needed. Up to now, there have been two basic approaches to the synthesis of optically pure (op) sulfoxides: (i) the asymmetric oxidation of prochiral sulfides[15] and (ii) the nucleophilic addition of alkyl or aryl ligands to an electrophilic sulfur with established chirality and the subsequent displacement of the sulfoxide. Because of the limited generality of the former

(1) Solladié, G. *Synthesis* **1981**, 185.
(2) Mikolaczyk, M.; Drabowicz, J. *Top. Stereochem.* **1982**, *13*, 333.
(3) Solladié, G. *Chimia* **1984**, *38*, 233.
(4) Barbachyn, M. R.; Johnson, C. R. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984, Vol. 4, p 227.
(5) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72.
(6) Andersen, K. K. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappaport, Z., Stirling, C., Eds.; Wiley and Sons: New York, 1988; Chapter 3. Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. *Ibid.* Chapter 8. Posner, G. M. *Ibid.* Chapter 16.
(7) Davis, F.; Kern, J. R.; Kurtz, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873.
(8) Hua, D. H.; Bharathi, S. N.; Takusagawa, F.; Tsujimoto, A.; Panagadan, J. A. K.; Hung, M.; Bravo, A.; Erpelding, A. M. *J. Org. Chem.* **1989**, *54*, 5659.
(9) (a) Chandrakumar, N. S.; Hajdu, J. *J. Org. Chem.* **1983**, *48*, 1197. (b) Ottenheijm, H. C. J.; v. d. Broek, L. A. G.; Ballesta, J. P. G.; Zylicz, Z. *Prog. Med. Chem.* **1986**, *23*, 219.
(10) (a) Kazmer, J. S.; Daddona, P. E.; Dalke, A. P.; Kelley, W. N. *Biochem. Pharmacol.* **1983**, *32*, 805. (b) Briziarelli, G.; Abrutyn, D.; Tornaben, J. A.; Schwartz, E. *Toxicol. Appl. Pharmacol.* **1976**, *36*, 49.
(11) (a) Alcudia, F.; Fernández, I.; Trujillo, M.; Zorrilla, F.; Marhuenda, E. *Tetrahedron* **1989**, *45*, 1491. (b) Marhuenda, E.; López, J. A.; Toro, M. V.; Trujillo, M. *Rev. Farmacol. Clin. Exp.* **1990**, *7*, 145. (c) Toro, M. V.; Marhuenda, E.; López, J. A.; Fernández, I. *Ann. Pharmaceutiques Françaises* **1991**, *49*, 92.
(12) Iimori, T.; Takahashi, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 1965.
(13) Robertson, D. W.; Steimberg, M. I. *Annual Reports in Medicinal Chemistry*; Allen, R. C., Ed.; Academic Press: San Diego, 1989; pp 24–91.
(14) Madesclaire, M.; Roche, D.; Carpy, A.; Boucherle, A. *Arch. Pharm. (Weinheim)* **1982**, *315*, 741.
(15) (a) Holland, H. *Chem. Rev.* **1988**, *88*, 473. (b) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188. (c) Pitchen, P.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 1049. (d) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis* **1984**, 325. (e) Kagan, H. B.; Dunach, E.; Pitchen, P.; Samuel, O. *Pure Appl. Chem.* **1985**, *57*, 1911. (f) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135. (g) Davis, F. A.; Jenkins, R. H., Jr.; Awad, S. B.; Stinger, O. D.; Watson, W. H.; Galloy, J. *J. Am. Chem. Soc.* **1983**, *104*, 5412.

0022-3263/92/1957-6789$03.00/0