A Stereoselective Organopalladium Route toward Perhydrohistrionicotoxin

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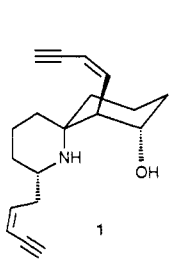
Received February 2, 1989

An efficient stereocontrolled route to the spirocyclic alkaloid perhydrohistrionicotoxin (**2**) is described. The readily available 2-substituted 1,3-cyclohexadiene **4** was converted regio- and stereoselectively to the chloro acetate **5** by using organopalladium methodology. Chemoselective S_N2' displacement of the chloride via a copper-catalyzed Grignard reaction furnished **6**, thus establishing the correct relative configuration at two adjacent centers. Further elaboration to the δ-amino alkene **10** was followed by a completely stereoselective iodocyclization reaction which yielded azaspirocycle **11**. This compound was transformed to depentylperhydrohistrionicotoxin (**3**) in essentially one operation, thus completing a formal total synthesis of the title alkaloid. The overall yield of **3** from **4** was 23% for nine operations. An alternative route to advanced intermediate **8** was also developed, the key step being the coupling of enol triflate **15** with the appropriate lithium organocuprate reagent.

Introduction

The "dart-poison" frogs of the Dendrobatid family found in South America have provided a variety of pharmacologically potent alkaloids, some of which function as noncompetitive acetylcholine antagonists.[1,2] For the organic chemist, perhaps the most fascinating of these is histrionicotoxin (**1**), which is an unusual azaspirocycle possessing cis enyne units in the side chains. The significance of histrionicotoxin as a neurophysiological tool,[3] its low natural abundance, and its intriguing structure have made this alkaloid and congeners such as **2** and **3** challenging and popular targets for total synthesis.[4] With the notable exception of the Kishi total synthesis of racemic histrionicotoxin itself,[5] the majority of synthetic efforts have been aimed at the perhydro- and depentylperhydrohistrionicotoxins (**2** and **3**, respectively) since these simpler materials display levels of biological activity quite similar to that of the parent alkaloid. The first total synthesis of **2**, which involved **3** as a key intermediate, was described by Corey[6] in 1975, and a wide range of approaches to these compounds have been reported to date.[4]



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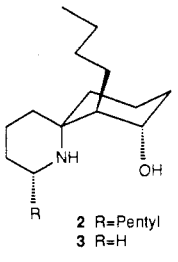
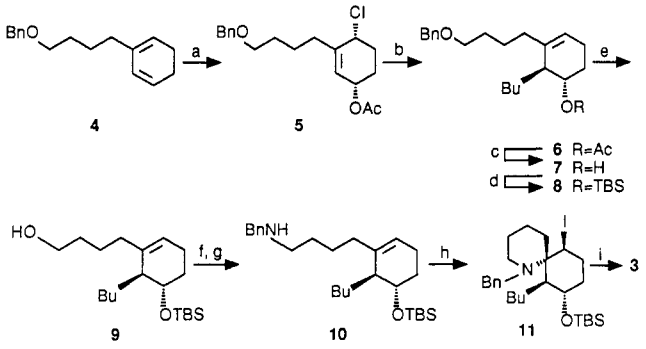


2 R=Pentyl
3 R=H

One of us[4d,7] has previously described a route to **3** which featured the efficient iodocyclization of a δ-amino olefin to form the azaspirocyclic skeleton, and in the present paper we present a novel and highly stereocontrolled synthesis of this alkaloid which employs the iodine-mediated reaction of amino alkene **10** (Scheme I) as the spirocyclization step. The butyl side chain and the hydroxyl group of the target molecule were introduced with the correct relative configuration at an early stage, complete regio- and stereocontrol being achieved by use of the versatile organopalladium[8] and organocopper[9] methodology developed by the Bäckvall group.

Scheme I[a]



[a] Bn = CH_2Ph, TBS = $SiMe_2{}^tBu$. Reagents and conditions: (a) $Pd(OAc)_2$, LiOAc, LiCl, benzoquinone, acetone/AcOH, 72%; (b) *n*-BuMgBr, CuCN, Et_2O, 0 °C, 89%; (c) K_2CO_3, MeOH/H_2O, 98%; (d) TBSCl, imidazole, DMF, 0 °C to room temperature, 92%; (e) Na, NH_3(l), -78 °C, 98%; (f) TsCl, pyridine, -20 to 0 °C, 98%; (g) $BnNH_2$, NaI, DMSO, room temperature, 87%; (h) I_2, $NaHCO_3$, CH_2Cl_2/H_2O, 68-74%; (i) H_2, $Pd(OH)_2/C$, MeOH; H^+/H_2O, 68%.

Results and Discussion

The present synthesis (Scheme I) started with the 2-substituted 1,3-cyclohexadiene **4**, which was readily prepared on a multigram scale as described in the Experimental Section. The chloroacetoxylation approach[8] allows introduction of two nucleophiles in the 1,4-, 1,2-, or 3,4-position of a diene, usually with full regio- and stereocontrol. In the present application it was desirable to add *n*-butyl and OH to the 3- and 4-positions, respectively, in a trans manner.

Regio- and stereoselective palladium-catalyzed 1,4-chloroacetoxylation[8] of **4** using a recently improved procedure[10] furnished **5**, and a subsequent copper-catalyzed S_N2' substitution of chloride by the butyl Grignard reagent[9] delivered **6** as the sole product in excellent yield. To ensure

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(2) Witkop, B.; Gössinger, E. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; pp 139-251.
(3) Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta* **1982**, *65*, 252.
(4) (a) Inubushi, Y.; Ibuka, T. *Heterocycles* **1982**, *17*, 507 (review). For more recent synthetic efforts, see: (b) Butlin, R. J.; Holmes, A. B.; McDonald, E. *Tetrahedron Lett.* **1988**, *29*, 2989. (c) Winkler, J. D.; Hershberger, P. M.; Springer, J. P. *Tetrahedron Lett.* **1986**, *27*, 5177. (d) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5657 and references therein. (e) Carruthers, W.; Cumming, S. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2383.
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(10) Bäckvall, J.-E.; Granberg, K.; Hopkins, R. B., to be published.

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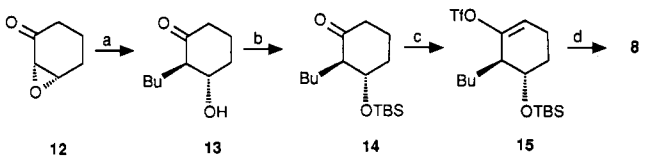
Scheme II[a]



[a] Reagents and conditions: (a) LDA, THF, −78 °C, 30 min, −78 °C; ^{n}BuLi, −20 °C, 12 h, 89%; (b) TBSCl, imidazole, DMF, 0 °C to room temperature, 90%; (c) LDA, THF, −78 °C, 1 h, $PhN(OTf)_2$, −20 °C, 87%; (d) $BnO(CH_2)_4Li$, CuI, THF, −78 °C, 12 h, −20 °C, 78%.

complete selectivity for S_N2' substitution in the copper-catalyzed reaction, the Grignard reagent was added slowly.[9a] This powerful combination of highly selective and catalytic organotransition-metal reactions thus secured the desired relative configuration at two of the three asymmetric centers of the target.

For tactical reasons, the acetate in **6** was replaced by the bulkier *tert*-butyldimethylsilyl group prior to removal of the benzyl moiety. Primary alcohol **9** was then transformed via the tosylate to the key spirocyclization precursor **10**. It was hoped that the iodocyclization[11] of **10** would yield predominantly **11** since the sterically demanding silyl ether in the homoallylic position was expected to direct formation of the presumed iodonium ion intermediate to the opposite face of the cyclohexene ring. In practice, our hopes were completely fulfilled since exposure of **10** to iodine under carefully controlled conditions (Experimental Section) smoothly produced the iodide **11** as a single diastereomer. That the correct relative configuration had indeed been obtained was immediately apparent from the 300-MHz ^{1}H NMR spectrum of the cyclization product, which showed, as expected, that the silyloxy, butyl, and iodo subsituents on the cyclohexane ring were all equatorially disposed. The proton geminal to the iodine appeared as a doublet of doublets at δ 4.44 (J_{aa} = 12.5 Hz, J_{ae} = 4.5 Hz) while the diastereotopic benzylic protons gave rise to an AB multiplet (J = 14 Hz) centered on δ 4.13.[4e]

Transformation of **11** to the target, **3**, was then performed in an essentially one pot operation. Thus, the benzyl and iodo groups were first removed by catalytic hydrogenation over the Pearlman catalyst[12] in methanol, the spent catalyst was removed by filtration, and finally the filtrate was treated with mineral acid to remove the silyl protecting group. This convenient sequence produced **3** in 68% yield based on **11**. The overall yield of **3** from **4** was thus 23% for nine operations, and the synthetic material proved to be identical with an authentic sample of **3**.

An alternative route to the advanced intermediate **8** was also developed, starting with the readily available[13] 2,3-epoxycyclohexanone (**12**, Scheme II). This compound was converted to **13** by the general procedure of Wender,[14] which involved formation of the lithium enolate (LDA, THF) followed by a completely regioselective ring-opening of the epoxide by butyllithium. The sensitive 3-hydroxy ketone was immediately protected as the silyl ether **14**, and the kinetic enolate of this ketone was then trapped[15a] as the enol triflate **15**. This material was relatively stable and could be stored for prolonged periods at low temperature. Exposure of **15** to the lithium organocuprate reagent[15b] derived from 4-(benzyloxy)-1-bromobutane smoothly delivered **8**, the material being in all respects identical with that prepared previously. The overall yield of **8** was 54% based on **12** (four operations).

Conclusions

The synthesis of alkaloids of the histrionicotoxin family described herein highlights the power and versatility of the palladium-catalyzed chloroacetoxylation technique and demonstrates its utility in the total synthesis of natural products. Although the large body of synthetic routes to the histrionicotoxin alkaloids is already replete with elegant (and often efficient) procedures, we feel that the high regio-, stereo-, and chemoselectivity of our organotransition-metal methodology in combination with the excellent stereoselectivity of the spirocyclization step makes the present approach both competitive and attractive.

Experimental Section

General Remarks. ^{1}H NMR spectra were obtained at 300 or 270 MHz by using $CDCl_3$ as solvent. ^{13}C NMR spectra were obtained at 75 MHz for $CDCl_3$ solutions. IR spectra were obtained for thin films, and only the strongest/structurally most important peaks (ν_{max}, cm^{-1}) are listed. When necessary, reaction solvents were dried and distilled under nitrogen by using standard procedures, while reaction flasks and syringes were oven-dried (120 °C) before use. Merck silica gel 60 (230–400 mesh) was used for flash chromatography. Compounds **11**, **13**, and **15** (for which satisfactory combustion analyses were not obtained) were judged to be ≥90% pure by ^{1}H NMR spectroscopy.

2-(4-(Phenylmethoxy)butyl)-1,3-cyclohexadiene (4). This material was prepared in four operations from 2-methoxybenzoic acid, as follows.

2-(4-(Phenylmethoxy)butyl)-2-cyclohexen-1-one. The general method of Taber[16] was used. A 1-L three-necked flask fitted with a mechanical stirrer and an acetone/dry ice condenser was charged with 2-methoxybenzoic acid (15.2 g, 100 mmol) and dry THF (100 mL). The stirred mixture was cooled to −78 °C, and ammonia (400 mL) was distilled into the reaction vessel to give a thick white slurry of the ammonium salt of the acid. To this mixture was added hexane-washed sodium in small pieces until a dark blue color persisted. A solution of 1-bromo-4-(phenylmethoxy)butane (36.3 g, 150 mmol) in THF (20 mL) was added in one portion. The cooling bath was removed and the ammonia allowed to evaporate. The residue was diluted with water (600 mL), acidified with concentrated HCl, and extracted with 1,2-dichloroethane (5 × 50 mL). The combined organic extracts were mixed with water (50 mL), concentrated HCl (50 mL), and hydroquinone (0.3 g) and refluxed under nitrogen for 1 h. The mixture was cooled, the layers were separated, and the organic phase was washed with 0.5 M aqueous sodium bicarbonate (50 mL). After drying over anhydrous potassium carbonate, the organic phase was concentrated and the residue purified by flash chromatography (hexane/EtOAc, 80:20). The ketone was obtained as a near-colorless oil (16.8 g, 65%): IR 1671 cm^{-1}; ^{1}H NMR 7.35–7.25 (m, 5 H, Ar), 6.70 (t, J = 4.5, 1 H, C=C*H*), 4.49 (s, 2 H, C*H*$_2$Ar), 3.46 (t, J = 6, 2 H, C*H*$_2$O), 2.42 (t, J = 6, 2 H), 2.34 (m, 2 H), 2.19 (m, 2 H), 1.97 (qn, J = 6, 2 H), 1.60 (m, 2 H), 1.49 (m, 2 H). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.01; H, 8.54.

2-(4-(Phenylmethoxy)butyl)-2-cyclohexen-1-ol. The procedure of Luche[17] was followed. A solution of the ketone from above (13.6 g, 52.7 mmol) in dry methanol (200 mL) was cooled with stirring to −78 °C. $CeCl_3 \cdot 7H_2O$ (19.6 g, 52.7 mmol) was added,

(11) For a recent review of this type of cyclization reaction, see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3 part B, pp 411–454.
(12) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.
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followed by $NaBH_4$ (2.99 g, 79 mmol). The reaction mixture was warmed slowly to 0 °C and stirred for 30 min. Aqueous NaOH (2 M) (130 mL) was added carefully and the mixture extracted thrice with ether. The combined extracts were dried over $MgSO_4$ and concentrated to yield the crude alcohol, which was sufficiently pure for the next step (13.15 g, 96%). The analytical sample was obtained by flash chromatography (hexane/EtOAc, 80:20): IR 3400 cm^{-1}; ^1H NMR 7.35 (m, 5 H, Ar), 5.45 (m, 1 H, C=C*H*), 4.40 (s, 2 H, CH_2Ar), 3.96 (brm, 1 H, *CH*OH), 3.39 (t, J = 6, 2 H, CH_2OH), 2.10 (m, 2 H), 1.90 (m, 4 H), 1.65–1.40 (m, 6 H), 1.32 (d, J = 6.5, 1 H, OH). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.31; H, 9.18.

2-(4-(Phenylmethoxy)butyl)-2-cyclohexen-1-yl Acetate. The alcohol from above (11.94 g, 45.9 mmol) was dissolved in dry pyridine (25 mL), and acetic anhydride (9.39 g, 92 mmol) was added. The solution was stored at room temperature for 12 h and then diluted with ether (100 mL). The resultant solution was washed with several portions of $CuSO_4$(aq) to remove the pyridine and then with water. The ethereal layer was dried over $MgSO_4$ and concentrated to give a residue, which was purified by flash chromatography (hexane/EtOAc, 95:5). There was obtained 13.58 g (98%) of the acetate as a colorless oil: IR 1735 cm^{-1}; ^1H NMR 7.35–7.20 (m, 5 H, Ar), 5.69 (m, 1 H, C=C*H*), 5.26 (t, J = 4.5, 1 H, *CH*OAc), 4.48 (s, 2 H, CH_2Ar), 3.45 (t, J = 6.5, 2 H, CH_2O), 2.04 (s, 3 H, OAc), 2.00–1.89 (m, 2 H), 1.85–1.35 (m, 10 H). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.08; H, 8.60.

The acetate was converted to **4** by the method of Trost.[18] The acetate (13.0 g, 43 mmol) was dissolved with stirring under nitrogen in anhydrous THF (90 mL). Triethylamine (4.79 g, 47.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.50 g, 1.3 mmol) were added, and the solution was refluxed for 24 h. The solution was cooled and then concentrated to give a dark residue, which was applied directly to a short column of silica gel. Elution with hexane and removal of solvent yielded **4** as a colorless oil (9.89 g, 95%). Spectral data for **4**: IR 3030, 2930, 2860, 1650, 1600, 1585, 1110, 735, 700 cm^{-1}; ^1H NMR δ 7.35–7.27 (m, 5 H, Ar), 5.84–5.79 (m, 2 H, C*H*=C*H*), 5.46 (m, 1 H, C*H*=C), 4.50 (s, 2 H, CH_2Ar), 3.47 (t, J = 6.5, 2 H, CH_2CH_2O), 2.09 (m, 4 H, =CCH_2C=), 2.05–2.00 (m, 2 H, $CH_2CH_2CH_2CH_2O$), 1.64–1.55 (m, 2 H, CH_2CH_2O), 1.52–1.43 (m, 2 H, $CH_2CH_2CH_2O$); ^{13}C NMR δ 138.64, 135.58, 128.32, 127.61, 127.45, 127.14, 126.65, 120.25, 72.84, 70.32, 35.29, 29.23, 24.88, 22.41, 22.33; MS, m/z 242 (M^+, 1), 131 (25), 91 (base peak). Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.86; H, 9.11.

***cis*-4-Chloro-3-(4-(phenylmethoxy)butyl)-2-cyclohexen-1-yl Acetate (5).** The diene **4** (5.14 g, 21.2 mmol) and LiCl (1.62 g, 38.2 mmol, dissolved in ~9 mL of HOAc) were added simultaneously via syringe-drive over 10 h to a stirred solution of $Pd(OAc)_2$ (0.247 g, 1.1 mmol), LiCl (0.18 g, 4.2 mmol), $LiOAc{\cdot}2H_2O$ (1.08 g, 10.6 mmol), and *p*-benzoquinone (4.59 g, 42.4 mmol) in a mixture of HOAc (6.5 mL) and acetone (60 mL). After complete addition, the reaction mixture was stirred for an additional 8 h. The solvents were removed in vacuo, and the residue was partitioned between water (40 mL), and ether/pentane (100 mL). The separated organics were washed with 2 M NaOH solution (3 × 25 mL) and then with water (15 mL). The organic phase was dried over $MgSO_4$ and concentrated to give a yellow oil, which was purified by flash chromatography (hexane/EtOAc, 80:20). There was obtained 5.14 g (72%) of the chloro acetate as a colorless oil: IR 2930, 2850, 1735, 1450, 1370, 1240, 1100, 1020, 735, 695 cm^{-1}; ^1H NMR δ 7.35–7.27 (m, 5 H, Ar), 5.52 (m, 1 H, C=C*H*), 5.35–5.27 (m, 1 H, *CH*OAc), 4.50 (s, 2 H, CH_2Ar), 4.45–4.41 (m, 1 H, *CH*Cl), 3.48 (t, J = 6.1, 2 H, CH_2O), 2.23–2.13 (m, 2 H, CH_2CHOAc), 2.10–2.03 (m, 2 H, $CH{=}OCH_2$), 2.07 (s, 3 H, *OAc*), 2.01–1.94 (m, 2 H, CH_2CHCl), 1.65–1.56 (m, 4 H, $CH_2CH_2CH_2O$); ^{13}C NMR δ 170.71, 144.59, 138.56, 128.29, 127.56, 127.46, 125.24, 72.86, 69.94, 69.43, 56.62, 33.85, 30.43, 29.28, 23.82, 23.34, 21.23; MS (CI), m/z 240 (M – HOAc and HCl). Anal. Calcd for $C_{19}H_{25}ClO_3$: C, 67.74; H, 7.48. Found: C, 67.72; H, 7.43.

***trans*-3-Butyl-2-(4-(phenylmethoxy)butyl)cyclohexen-4-yl Acetate (6).** To a stirred solution of chloro acetate **5** (6.52 g, 19.4 mmol) and CuCN (0.170 g, 1.9 mmol) in ether (20 mL) under N_2 at 0 °C was added an ethereal solution of butylmagnesium bromide (146 mL, 29.1 mmol) during 1.5 h a the syringe pump. After stirring for 4 h at 0 °C, the reaction was quenched with aqueous NH_4Cl. The mixture was extracted thrice with ether, and the combined organics were dried ($MgSO_4$) and concentrated to give an oil, which was purified by flash chromatography (5% ether/pentane). The acetate **6** (6.18 g, 89 %) was obtained as a colorless oil: IR 2930, 2860, 1730, 1450, 1370, 1240, 1100, 1020, 730, 695 cm^{-1}; ^1H NMR δ 7.35–7.27 (m, 5 H, Ar), 5.44–5.39 (m, 1 H, C*H*=C), 5.05–5.00 (m, 1 H, *CH*OAc), 4.50 (s, 2 H, CH_2Ar), 3.47 (t, J = 6.4, 2 H, CH_2O), 2.11–1.92 (m, 5 H, allylic protons), 2.02 (s, 3 H, OAc), 1.79–1.68 (m, 2 H, CH_2CHOAc), 1.67–1.45 (m, 4 H, $CH_2CH_2CH_2O$), 1.40–1.15 (m, 6 H, $CH_2CH_2CH_2CH_3$), 0.91–0.87 (m, 3 H, CH_3); ^{13}C NMR δ 170.98, 138.59, 137.83, 128.29, 127.55, 127.44, 121.00, 72.82, 71.86, 70.27, 41.25, 34.65, 30.94, 29.25, 28.94, 24.31, 23.23, 22.97, 21.39, 13.97; MS (CI), m/z 359 (M + 1). Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.64; H, 9.33.

***trans*-3-Butyl-2-(4-(phenylmethoxy)butyl)cyclohexen-4-ol (7).** The acetate **6** (6.157 g, 17.2 mmol) was dissolved with stirring in 5% aqueous MeOH (50 mL), and K_2CO_3 (11.86 g, 86 mmol) was added in portions. The resultant mixture was stirred at room temperature for 24 h and then diluted with water (50 mL). The mixture was extracted thrice with ether, and the combined organic layers were dried ($MgSO_4$) and concentrated to give an oil, which was purified by flash chromatography (20% EtOAc/hexane). The alcohol **7** (5.33 g, 98%) was obtained as a colorless oil: IR 3360, 2920, 2860, 1710, 1450, 1260, 1100, 1070, 1020, 735, 695 cm^{-1}; ^1H NMR δ 7.35–7.27 (m, 5 H, Ar), 5.42 (s, 1 H, C*H*=C), 4.50 (s, 2 H, CH_2Ar), 3.95–3.86 (m, 1 H, *CH*OH), 3.47 (t, J = 6.3, 2 H, CH_2O), 2.20–1.99 (m, 5 H, allylic protons), 1.81–1.48 (m, 6 H, CH_2CH_2-CH_2O and CH_2CHOH), 1.46–1.13 (m, 6 H, $CH_2CH_2CH_2CH_3$), 0.90 (distorted t, J = 6.7, 3 H, CH_3); ^{13}C NMR δ 138.52, 138.23, 128.26, 127.56, 127.41, 120.71, 72.81, 70.23, 68.13, 44.85, 34.95, 31.38, 29.41, 29.21, 25.66, 24.46, 22.98, 20.84, 13.99; MS (CI), m/z 317 (M + 1). Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.42; H, 10.04.

***trans*-3-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(phenylmethoxy)butyl)cyclohexene (8).** The alcohol **7** (5.451 g, 17.52 mmol) was dissolved with stirring under N_2 in dry DMF (20 mL) and the solution cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (3.165 g, 21 mmol) and imidazole (2.935 g, 43 mmol) were added, and the reaction mixture was allowed to reach room temperature over 3 h. The reaction mixture was then partitioned between ether and water. The dried organic phase was concentrated to give a viscous oil, which was purified by flash chromatography (hexane). The yield of silyl ether **8** (colorless oil) was 6.824 g (92%): IR 2920, 2860, 1460, 1355, 1250, 1080, 910, 835, 740 cm^{-1}; ^1H NMR δ 7.35–7.27 (m, 5 H, Ar), 5.38–5.32 (m, 1 H, C*H*=C), 4.50 (s, 2 H, CH_2Ar), 3.87–3.80 (m, 1 H, *CH*OSi), 3.49–3.41 (t, J = 6, 2 H, CH_2O), 2.18–1.80 (m, 5 H, allylic), 1.71–1.44 (m, 6 H, $CH_2CH_2CH_2O$ and CH_2CHOSi), 1.43–1.10 (m, 6 H, $(CH_2)_3CH_3$), 0.89 (distorted t, J = 7, CH_3), 0.87 (s, 9 H, ^{t}Bu), 0.05 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si); ^{13}C NMR δ 138.69, 138.13, 128.26, 127.37, 121.22, 72.83, 70.41, 69.16, 44.80, 34.87, 30.64, 29.25, 29.13, 27.27, 24.48, 23.15, 21.75, 18.00, 14.08; MS (CI), m/z 431 (M + 1). Anal. Calcd for $C_{27}H_{46}O_2Si$: C, 75.29; H, 10.76. Found: C, 75.14; H, 10.64.

4-(1-(*trans*-5-((*tert*-Butyldimethylsilyl)oxy)-6-butylcyclohexenyl))butanol (9). Benzyl ether **8** (6.33 g, 14.72 mmol) was dissolved in dry ether (50 mL) and the solution cooled with stirring to −78 °C. Ammonia (100 mL) was then distilled into the reaction vessel, and freshly cut sodium was added in small pieces until a dark blue color persisted. The resultant mixture was stirred for 1 h at −78 °C, and the reaction was quenched by addition of solid NH_4Cl. The cooling bath was removed, and the excess ammonia was allowed to evaporate. The residue was partitioned between ether and water, and the dried organic phase was concentrated to give an oil, which was purified by flash chromatography (20% EtOAc/hexane). There was obtained 4.90 g (98%) of alcohol **9** as a colorless oil: IR 3350, 2930, 2880, 1250, 1080 cm^{-1}; ^1H NMR 5.37 (m, 1 H, C*H*=C), 3.87–3.82 (m, 1 H, *CH*OSi), 3.66–3.58 (q, J = 6, 2 H, CH_2OH, coupled to OH), 2.19–1.89 (m, 5 H, allylic), 1.70–1.44 (m, 6 H, $CH_2CH_2CH_2O$ and CH_2CHOSi), 1.42–1.10 (m, 7 H, $(CH)_2CH_3$ and O*H*), 0.89 (distorted t, J = 7, 3 H, CH_3), 0.85 (s, 9 H, ^{t}Bu), 0.03 (s, 3 H, CH_3Si), 0.02 (s, 3 H, CH_3Si); ^{13}C NMR δ 138.08, 121.32, 69.14, 62.89, 44.79,

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34.76, 32.24, 30.68, 29.16, 27.17, 25.79, 23.89, 23.13, 21.69, 18.01, 14.07; MS (CI), m/z 341 (M + 1). Anal. Calcd for $C_{20}H_{40}O_2Si$: C, 70.52; H, 11.84. Found: C, 70.10; H, 11.73.

***trans*-3-Butyl-4-((*tert*-butyldimethylsilyl)oxy)-2-(4-(*N*-(phenylmethyl)amino)butyl)cyclohexene (10).** The alcohol **9** (4.61 g, 13.6 mmol) was dissolved with stirring under N_2 in dry pyridine (15 mL) and the solution cooled to −20 °C. Tosyl chloride (2.852 g, 14.96 mmol) was added in portions and the reaction mixture allowed to reach 0 °C over several hours. The mixture was diluted with ether (100 mL) and the precipitate filtered off. The filtrate was washed twice with $CuSO_4$(aq) to remove the pyridine and then with water. The dried organics were concentrated to yield the crude tosylate (6.587 g, 98%) as a viscous colorless oil. This material, which showed a single-spot TLC (5% EtOAc/hexane) and was ^{1}H NMR spectroscopically pure, was used immediately in the next step: IR 2920, 2870, 1590, 1460, 1360, 1250, 1190, 1170 cm^{-1}; ^{1}H NMR δ 7.79, 7.32 (AA′BB′, J_{AB} = 9, 4 H, Ar), 5.28 (m, 1 H, C*H*=C), 4.00 (t, J = 7, 2 H, CH_2OTs), 3.81 (m, 1 H, C*H*OSi), 2.42 (s, 3 H, tosyl Me), 2.17–1.74 (m, 5 H, allylic), 1.69–1.38 (m, 6 H, CH_2CH_2CH$_2$OTs and CH_2CHOSi), 1.35–1.02 (m, 6 H, (CH_2)$_3$CH$_3$), 0.89 (distorted t, J = 7, 3 H, CH_3), 0.83 (s, 9 H, ^{t}Bu), 0.02 (s, 3 H, CH_3Si), −0.01 (s, 3 H, CH_3Si), ^{13}C NMR δ 144.56, 137.39, 133.21, 129.77, 127.87, 121.77, 70.63, 68.97, 44.67, 34.18, 30.76, 29.20, 28.04, 26.97, 25.79, 23.43, 23.13, 21.70, 18.00, 14.08.

The crude tosylate (6.587 g, 13.33 mmol) was dissolved with stirring under N_2 in dry DMSO (35 mL). Sodium iodide (0.015 g) was added, followed by freshly distilled benzylamine (3.536 g, 33.3 mmol). The resultant solution was stirred for 12 h at room temperature and then poured into brine. The mixture was extracted thrice with EtOAc, and the combined organics were dried ($MgSO_4$). Removal of solvent gave a dark yellow oil, which was purified by flash chromatography (10% MeOH/EtOAc). The amine **10** (4.971 g, 87%) was obtained as a clear, near-colorless oil, which darkened upon standing. The material was stored under argon at −20 °C: IR 3300 (w, NH), 3050 (w), 2940–2850 (s), 1100 (s, OSi); ^{1}H NMR δ 7.40–7.20 (m, 5 H, Ar), 5.34 (m, 1 H, C=C*H*), 3.83 (m, 1 H, C*H*OSi), 3.78 (s, 2 H, CH_2Ar), 2.62 (t, J = 7, 2 H, CH_2N), 2.20–1.90 (m, 5 H, allylic), 1.71–1.10 (m, 12 H), 0.91 (t, J = 6.9, 3 H, CH$_2$CH_3), 0.89 (c, 9 H, ^{t}Bu), 0.04 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si); ^{13}C NMR δ 140.58, 138.21, 128.28, 128.05, 126.75, 121.12, 69.18, 54.11, 49.42, 44.85, 34.97, 30.56, 29.64, 29.06, 27.33, 25.79, 25.67, 23.13, 21.77, 17.99, 14.07; MS (CI), m/z 430 (M + 1). Anal. Calcd for $C_{27}H_{47}NOSi$: C, 75.46; H, 11.02; N, 3.26. Found: C, 75.57; H, 10.90; N, 3.30.

(6*S,7*S**,8*S**,11*S**)-7-Butyl-8-((*tert*-butyldimethylsilyl)oxy)-11-iodo-1-(phenylmethyl)-1-azaspiro[5.5]undecane (11).** The amine **10** (0.50 g, 1.17 mmol) was dissolved with rapid stirring under N_2 in a mixture of CH_2Cl_2 (15 mL) and 50% $NaHCO_3$(aq) (15 mL). A solution of iodine (1.19 g, 4.68 mmol) in CH_2Cl_2 was slowly added dropwise and the resultant two-phase system stirred for 3 h. A saturated aqueous solution of $Na_2S_2O_3$ was added dropwise until discoloration of the reaction mixture occurred. The layers were separated, and the aqueous phase was extracted with fresh CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated to yield the desired azaspirocycle **11** as a pale yellow oil. This material was extremely labile and decomposed upon attempted flash chromatography. The crude material was, however, sufficiently pure for the next step according to high-field ^{1}H NMR spectroscopic analysis, which showed the presence of a single diastereomer. Typical yields for this cyclization reaction lay in the range 68–74%, and the crude product was used as soon as possible in the final step: ^{1}H NMR δ 7.40–7.30 (m, 5 H, Ar), 4.44 (dd, J = 12.5, J = 4.5, 1 H, C*H*I), 4.21 (d, J = 14, 1 H, C*H*Ar), 4.07 (d, J = 14, 1 H, C*H*Ar), 3.85 (td, J = 10, 4.5, 1 H, C*H*OSi), 2.90 (m, 1 H, C*H*N), 2.35 (m, 1 H, C*H*N), 2.15–1.15 (m, 19 H), 0.90 (t, J = 7, 3 H, CH$_2$CH_3), 0.85 (s, 9 H, ^{t}Bu), 0.10 (s, 3 H, CH_3Si), 0.07 (s, 3 H, CH_3Si).

(±)-Dependylperhydrohistrionicotoxin (3). The crude iodide **11** (0.300 g, 0.54 mmol) was dissolved with stirring in methanol (5 mL), and the Pearlman catalyst[12] (0.045 g) was added. The reaction vessel was alternately evacuated and filled with argon several times, and the procedure was then repeated by using hydrogen gas. Finally, balloon pressure of hydrogen was applied and the mixture was stirred overnight. The spent catalyst was removed by filtration through a Celite pad, the filter cake was washed with fresh methanol (3 × 2 mL), and the combined filtrate and washings were acidified by addition of water (1 mL) and concentrated HCl (1 mL). The resultant solution was stirred at room temperature for 4 h, and then solid sodium bicarbonate was added to neutralize the acid. The mixture was filtered, the solvents were removed, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH, 84:15:1) to yield **3** as a colorless oil (0.083 g, 68% based on **11**). This material was identical (^{1}H and ^{13}C NMR, IR, MS, TLC) with an authentic sample provided by Dr. A. Brossi.

***trans*-2-Butyl-3-hydroxy-1-cyclohexanone (13).** Freshly dried and distilled diisopropylamine (4.70 mL) was dissolved with stirring under argon in dry THF (200 mL) and the solution cooled to 0 °C. *n*-Butyllithium (1.6 M, 20 mL, 32 mmol) was added dropwise and the solution stirred for 20 min at 0 °C before being cooled to −78 °C. A solution of 2,3-epoxycyclohexanone[13] (3.00 g, 27 mmol) in THF (10 mL) was added dropwise and the resultant solution stirred for 30 min at −78 °C before the addition of butyllithium (50 mL, 80 mmol). The reaction vessel was then sealed with a rubber septum and placed in the freezer (−20 °C) for 12 h. An aqueous solution of NH_4Cl was added, the layers were separated, and the aqueous phase was extracted with ether. The combined organics were stripped down to yield a pale yellow residue, which was purified by flash chromatography (70% ether/pentane) to give **13** as a colorless oil (4.085 g, 89%). This material was sensitive and was thus used directly: IR 3400 (br), 2950, 1700 cm^{-1}; ^{1}H NMR δ 3.80 (td, J = 9, 3, 1 H, C*H*OH), 2.35 (m, 3 H, α to carbonyl), 2.10 (m, 2 H), 1.80–1.60 (m, 4 H), 1.34 (m, 4 H), 0.90 (t, J = 7, 3 H, CH_3CH$_2$).

Further structural proof was obtained by the acid-catalyzed dehydration (toluenesulfonic acid, refluxing benzene, 90% yield) of **13** to give 2-butyl-2-cyclohexenone. The product was identical with an authentic sample prepared by the method of Taber.[16]

***trans*-2-Butyl-3-((*tert*-butyldimethylsilyl)oxy)cyclohexanone (14).** The alcohol **13** (4.085 g, 24 mmol) was converted to silyl ether **14** as described above for **8**. Flash chromatography (5% ether/pentane) yielded **14** as a colorless oil (6.134 g, 90%): IR 2950, 1710, 1100 cm^{-1}; ^{1}H NMR δ 3.82 (td, J = 8, 3, 1 H, C*H*OSi), 2.40–2.21 (m, 3 H, α to carbonyl), 2.05 (m, 2 H), 1.71–1.50 (m, 4 H), 1.30 (m, 4 H), 0.90 (t, J = 7, 3 H, CH_3CH$_2$, overlapping s, 9 H, ^{t}Bu), 0.02 (s, 6 H, SiMe_2). Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.23; H, 11.02.

***trans*-3-Butyl-4-((*tert*-butyldimethylsilyl)oxy)cyclohexen-2-yl Trifluoromethanesulfonate (15).** A solution of LDA in THF (40 mL) was prepared as described above for **13** from diisopropylamine (2.29 mL) and BuLi (10 mL of 1.6 M hexane solution). The solution was cooled with stirring under argon to −78 °C, and a solution of ketone **14** (3.768 g, 13.3 mmol) in THF (20 mL) was added dropwise. The resultant solution was stirred for 1 h at −78 °C before addition of a solution of *N*,*N*-bis[(trifluoromethyl)sulfonyl]phenylamine (Aldrich, 5.214 g, 14.6 mmol) in THF (20 mL). The reaction vessel was then sealed with a rubber septum and placed in the freezer for 12 h. The solvents were removed, and the residue was flash chromatographed (pentane, 1% ether/pentane) to yield the enol triflate **15** as a colorless oil (4.814 g, 87%): IR 2950, 1420, 1210, 1140, 1090 cm^{-1}; ^{1}H NMR δ 5.74 (dd, J = 6, 2, 1 H, vinylic), 3.98 (apparent q, J = 4, 1 H, C*H*OSi), 2.33 (m, 2 H, one allylic, one homoallylic), 2.09 (m, 1 H, allylic), 1.72–1.60 (m, 2 H, homoallylic, methine), 1.34 (m, 6 H), 0.91 (distorted t, J = 7, 3 H, CH_3CH$_2$, overlapping s, 9 H, ^{t}*Bu*), 0.08 (s, 6 H, SiMe_2).

Conversion of 15 to 8. A solution of 4-(phenylmethoxy)butyllithium in THF was prepared according to the literature[19] and stored under argon at −78 °C. Copper(I) iodide (0.977 g, 5.1 mmol) was slurried under argon in THF (20 mL) and cooled with stirring to −78 °C. The lithium reagent solution (10 mmol) was added via a cannula, and the resulant dark, turbid mixture was stirred for 30 min before addition of a solution of enol triflate **15** (0.541 g, 1.3 mmol) in THF (5 mL). The temperature was allowed to reach −20 °C and held there for 12 h. The reaction mixture was poured into a dropping funnel containing ether and an aqueous solution of NH_4Cl, and air was bubbled through the mixture for 10 min. The organics were separated, dried over $MgSO_4$, and

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stripped down to yield a pale yellow residue, which was flash chromatographed (hexane). There was obtained 0.436 g (78%) of 8 as an oil, which was chromatographically and spectroscopically identical with the sample prepared as described earlier.

Acknowledgment. We thank the Swedish Natural Science Research Council and Engineering Research Council of the Swedish National Board for Technical Development for financial support, and Dr. Arnold Brossi (NIH) for kindly providing an authentic sample of compound 3.

Registry No. (±)-3, 55228-77-8; 4, 120883-52-5; (±)-5, 120883-53-6; (±)-6, 120883-54-7; (±)-7, 120883-55-8; (±)-8, 120883-56-9; (±)-9, 120883-57-0; (±)-9 (tosylate), 120883-58-1; (±)-10, 120883-59-2; (±)-11, 120883-60-5; (±)-12, 98672-93-6; (±)-13, 120883-61-6; (±)-14, 120883-62-7; (±)-15, 120883-63-8; 2-$CH_3OC_6H_4CO_2H$, 579-75-9; $BnO(CH_2)_4Br$, 60789-54-0; $BnO(CH_2)_4Li$, 64740-31-4; 2-[4-(phenylmethoxy)butyl]-2-cyclohexen-1-one, 120883-49-0; (±)-2-[4-(phenylmethoxy)butyl]-2-cyclohexen-1-ol, 120883-50-3; (±)-2-[4-(phenylmethoxy)butyl]-2-cyclohexen-1-yl acetate, 120883-51-4; 2-butyl-2-cyclohexenone, 34737-39-8.

Chemistry of Singlet Oxygen. 52. Reaction with *trans*-Stilbene

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Received December 13, 1988

Substituted *trans*-stilbenes react with singlet oxygen to give substituted diendoperoxides along with corresponding epoxides, *cis*-stilbenes, and benzaldehydes. The diendoperoxides rearrange readily to keto compounds on treatment with base. In methyl alcohol, solvent adducts are isolated. Monoendoperoxides are the primary products isolated from the photooxygenation of mono- and dimethoxystilbenes. Structures of several products were confirmed by NMR and X-ray crystallography. The results suggest that endoperoxide formation occurs via a polar intermediate such as a perepoxide or zwitterion.

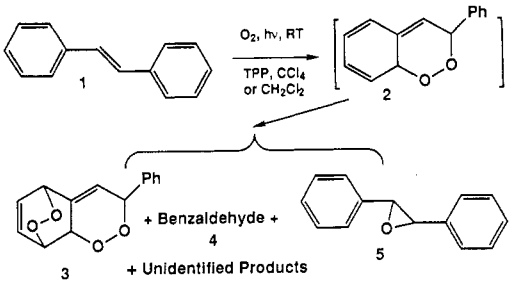
Introduction

Singlet oxygen usually reacts with conjugated dienes via [2 + 4] cycloaddition to give endoperoxides.[1] The reaction has been extensively studied since Schenck first used the term *endoperoxide* to describe bicyclic peroxides related to ascaridole[2] obtained by dye-sensitized photooxygenation of cyclohexa-1,3-dienes.[1]

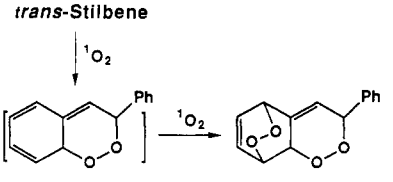
The mechanism of [2 + 4] cycloaddition of singlet oxygen to conjugated olefins has received relatively little attention because endoperoxidation resembles the well-known thermal Diels–Alder reaction. It is generally accepted that the cycloaddition of singlet oxygen to 1,3-dienes is concerted and proceeds through a six-membered transition state.[3] Recently, however, it has been suggested that polar intermediates (perepoxides or zwitterions) that rearrange to the endoperoxide are formed from acyclic dienes.[4] Zwitterionic intermediates have been proposed in the reactions of many dienes with electron-poor dienophiles; recent examples include hexadienes with singlet oxygen[5a] and triazolinediones.[5b-d]

Photosensitized oxygenation of vinyl aromatic compounds has been a recent area of investigation. Many groups have reported that stilbenes[6] and styrenes[7] react with singlet oxygen to give mono- or diendoperoxides. Singlet oxygen reacts initially at the β-position of the side chain and the ortho position of the aromatic ring to give a monoendoperoxide and, in some cases, goes on to form a diendoperoxide by further reaction with singlet oxygen.[6,7]

Scheme I



The photooxygenation of stilbene was first reported by Rio et al.[6a] to yield benzaldehyde as the final product. In 1977, Matsumoto et al.[6b] reinvestigated the photooxygenation of stilbenes and reported the formation of diendoperoxides. Foote and Boyd reported that the photooxygenation of stilbene depended on the reaction conditions.[6d] However, the structure of the initial monoendoperoxide and the mechanism of its formation are still unclear.



We report here a study of the photooxygenation of stilbenes in which careful characterization of products,

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