Intramolecular 1,3-Dipolar Cycloaddition of Alkyl Azide Enones and Rearrangements of the Triazoline Intermediates. Formal Total Synthesis of (±)-Desamylperhydrohistrionicotoxin

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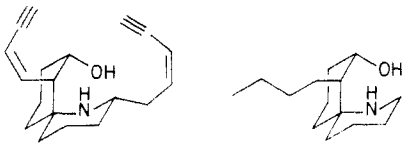
Received August 6, 1985

Azido enones **8**, **18**, **25**, **39**, and **45**, which were prepared by the treatment of the corresponding bromide **7**, methanesulfonate **17**, chloride **24**, bromide **38**, and toluenesulfonate **44** with sodium azide, were found to undergo intramolecular 1,3-dipolar cycloaddition reaction smoothly. Thermolysis of azido enone **8** gave products **15** and **16**. Thermolysis of azido enone **18** gave enaminone **22**. Thermolysis of azido enone **25** in aqueous methanol or toluene gave product **29** or **22**, respectively. 2-Substituted azido enones **39** and **45** afforded aziridinyl ketone **43** and **46** upon thermolysis. Compound **46** was reduced by chromous chloride to give spiro amino ketone **47**, which was alkylated with benzyl bromide to give the Godleski's intermediate **48** for the synthesis of (±)-desamylperhydrohistrionicotoxin (**2**).

The 1,3-dipolar cycloaddition reaction is one of the most useful synthetic methods for the construction of the five-membered ring heterocycles.[1,2] A large amount of the literature on the bimolecular 1,3-dipolar cycloaddition reaction between various 1,3-dipoles and double or triple bonds has appeared since the discovery of this reaction by Huisgen and his co-workers.[3-5] However, recently the intramolecular version of the 1,3-dipolar cycloaddition reaction started to receive more attention. The intramolecular 1,3-dipolar cycloaddition reaction of alkyl azides and olefins has been reviewed.[6] More recently Schultz investigated the intramolecular 1,3-dipolar cycloaddition of azido enones and azido quinones.[7] Hudlicky and Pearson reported the application of the intramolecular cycloaddition of dienic azide to the synthesis of pyrrolizidine alkaloids independently.[8] Herein, we report our study[9] of the intramolecular 1,3-dipolar cycloaddition of alkyl azides and enones and the application of this reaction to a formal total synthesis of (±)-desamylperhydrohistrionicotoxin (**2**).[10]

Results and Discussion

In our search for an efficient method for the synthesis of histrionicotoxin alkaloids (**1**)[11] and its structurally simplified analogues e.g., (±)-desamylperhydrohistrionicotoxin (**2**), we envisioned an approach for the construction of 1-azaspiro[5,5]undecane ring system e.g., **5**, by an intramolecular alkyl azide enone 1,3-dipolar cycloaddition re-



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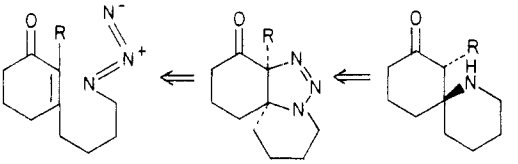
Scheme I



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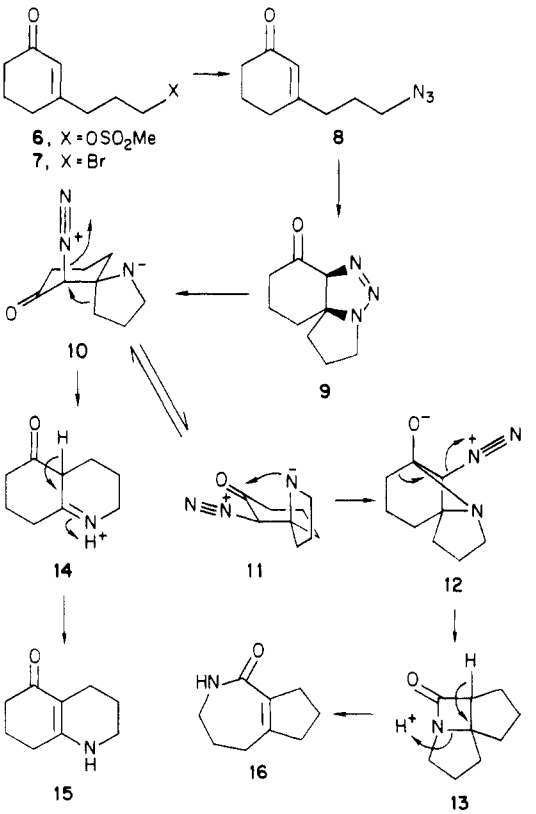
Scheme II



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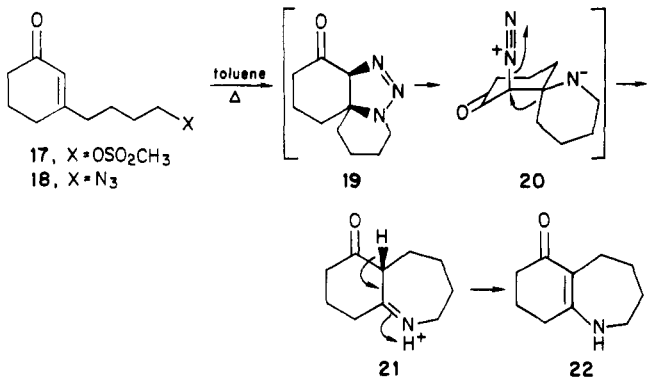
Scheme III



action as described in Scheme I.

We decided to explore this approach and to investigate the intramolecular 1,3-dipolar cycloaddition of alkyl azide enones systematically. We started with the study of the intramolecular cycloaddition reaction of azido enone **8**. The precursors, methanesulfonate **6** and bromide **7**, were prepared by the method of Becker.[12] When bromide **7** was treated with sodium azide in aqueous methanol at 80 °C, we obtained **15** and **16** in 24% and 67% yield, respectively. Alternatively, heating methanesulfonate **6** with sodium azide in dry dimethyformamide at 80 °C gave a similar result. The structure of the major product **16** was difficult to determine by spectroscopic data. A single-crystal X-ray analysis finally delineated the structure.[9] The unexpected structure of **16** resulted from an unusual rearrangement. A reasonable mechanism for the formation of **15** and **16** was proposed and is shown in Scheme II. Intramolecular 1,3-dipolar cycloaddition of **8** would give the triazoline **9**. The unstable triazoline **9** could decompose immediately to from the zwitterionic intermediate of conformation **10** or **11**. Conformation **11** has a nitrogen anion in the axial position, which could easily attack the carbonyl group to give **12**. Structure **12** could rearrange to give **16**, presumably via the intermediate **13**. On the other hand, conformation **10** could undergo a 1,2-alkyl shift and give the product **15** via **14**.

In order to understand the reaction mechanism, we prepared methanesulfonate **17**[13] with a longer side chain and treated **17** with sodium azide in dry dimethylformamide. We isolated azido enone **18** which is stable at room temperature. Heating **18** in refluxing toluene, enaminone **22** was obtained as the only product. Presumably, intramolecular 1,3-dipolar cycloaddition of **18** would give triazoline **19**, Scheme III. Decomposition of **19** followed by a 1,2-alkyl shift would afford enaminone **22** via **21**. Interestingly, the other rearrangement pathway as shown in Scheme II leading to **16** did not occur.

Furthermore, chloride **24** was prepared by the alkylation of lithiated **23** with 1-chloro-4-iodobutane,[14] followed by acid hydrolysis of the ketal group. Treatment of **24** with sodium azide in dry dimethylformamide at 60 °C gave azide **25**. Heating azide **25** in aqueous methanol or dry dimethylformamide gave **29** in low yield, while heating azide **25** in toluene, enaminone **22** was obtained as the major product, Scheme IV. Apparently, azide **25** underwent intramolecular cycloaddition reaction in two different modes.[15] In aqueous methanol or dimethylformamide, triazoline **26** was formed as an intermediate which could rearrange into product **29** via a 1,2-alkyl shift in the intermediate **27**. Alternatively, a 1,2-acyl shift[16] in **27** would give enaminone **31** via intermediate **30**. However, the spectroscopic data of the product have the following characteristics in favor of the structure **29**: UV (methanol) λ_{max} = 289 nm (35 000); ^{1}H NMR ($CDCl_3$) δ 4.6, broad singlet for NH proton of 2-amino enones;[17] ^{13}C NMR ($CDCl_3$) δ 139.0 (s), 142.1 (s) for vinyl carbon, 195.5 (s) for carbonyl in cyclohexenone moiety. The alternative structure **31** was predicted to have the following spectral data characteristics: UV λ_{max} (calculated) $\geq$ 320 nm; ^{1}H NMR NH proton of enaminones $\delta \geq 6$; ^{13}C NMR calculated for vinyl carbonyl $\delta \approx 100$ (s), 160 (s), for carbonyl in cyclopentenone $\delta \approx 210$ (s).[18] Therefore, **31** was ruled out as the product. On the other hand, in toluene a reversal of the regiochemistry of the cycloaddition afforded intermediate triazoline **32** which decomposed (**32** → **33** → **21**) to give product **22**.

At the same time, we also prepared enone **38**, with a methyl group at the C(2) carbon, by the method of Becker[12] starting from 3-ethoxy-2-methylcyclohex-2-en-1-one (**34**) (the detailed procedure is in the Experimental Section). To our surprise, treatment of enone **38** with sodium azide in dry dimethylformamide at 80 °C afforded the aziridine **43** as the product in 57% yield. Apparently no rearrangement similar to those in Scheme II and Scheme III had occurred. After examining the literature we rationalized that a triazoline such as **40**, might undergo a 1,3-dipolar cycloreversion reaction[19] via the intermediate **41** to give diazo imine **42**, Scheme V. Intramolecular carbenoid insertion reaction of **42** would give aziridine **43**. It is conceivable that the methyl group in intermediate **41** would occupy an equitorial position and force the anionic nitrogen atom into an equitorial position and prevent it from attacking the carbonyl group (arrow a). Furthermore, the 1,2-alkyl shift (arrow b) might also be retarded by the methyl group.

From the above study, we immediately recognized the usefulness of the transformation **38** → **43** for the synthesis of (±)-desamylperhydrohistrionicotoxin (**2**). To this end, tosylate **44** was prepared[14a] and reacted with sodium azide in dimethylformamide to give azide **45**. Heating azide **45** in refluxing xylene gave aziridine **46**. Chromous chloride reduction[20] of **46** gave amino ketone **47**. Benzylation of **47** afforded intermediate **48**, which has been converted into (±)-desamylperhydrohistrionicotoxin (**2**) by Godleski[10a] (Scheme VI).

In summary, the intramolecular 1,3-dipolar cycloaddition of alkyl azide enones could occur smoothly in the cases of proper regiochemical arrangement. In the process of the formation of triazoline **26**, however, the azido group and enone moiety were not in the proper regiochemical arrangement. Therefore, thermolysis of azide **25** in aqueous methanol or dry dimethylformamide gave **29** only in 10–20% yield. On the other hand, formation of aziridine **43** from azide **39** was an interesting discovery. At the temperature range of 80–110 °C, the rate of intramolecular 1,3-dipolar cycloadditions of alkyl azides to enones is usually much faster then the rate of the decompositions of azides to nitrenes. Thus, a direct nitrene enone addition

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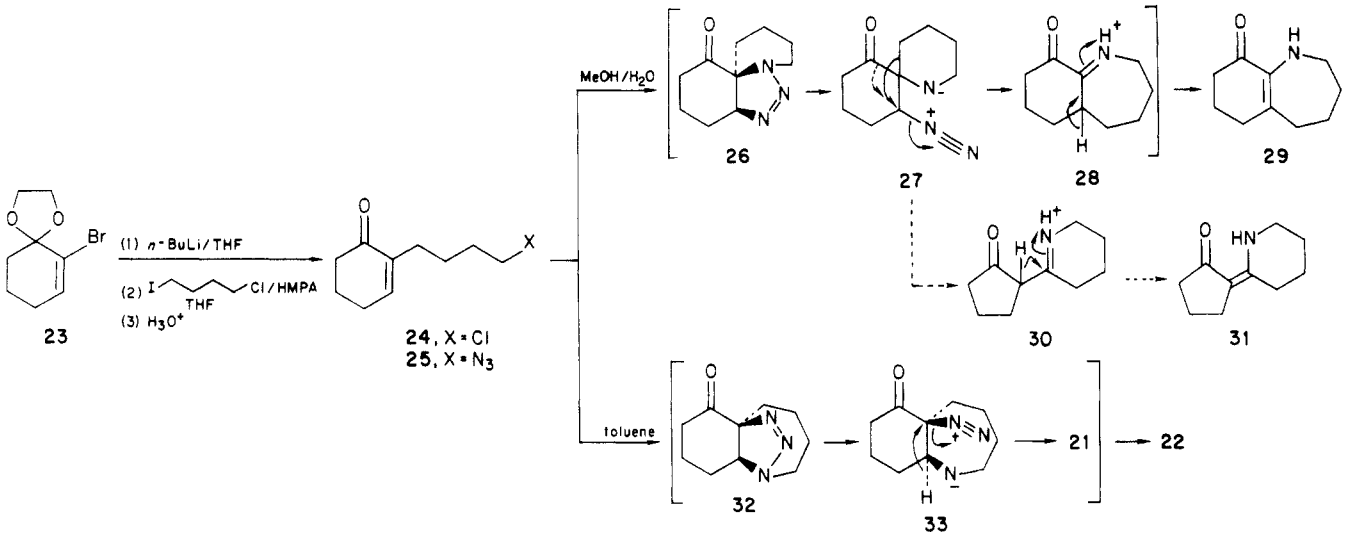
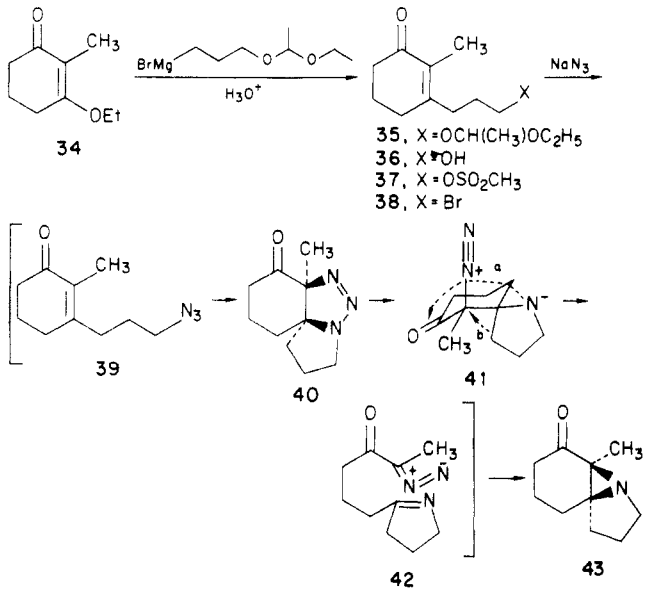
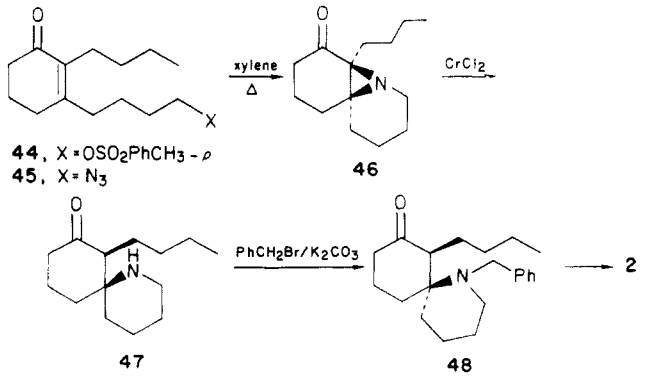
Scheme IV



Scheme V



Scheme VI



was not considered as a major reaction pathway. Only in the reaction of **45** → **46**, which was carried out in refluxing xylene, a direct nitrene enone addition could not be ruled out as an alternative reaction pathway. Finally, we successfully applied this reaction to a formal total synthesis of (±)-desamylperhydrohistrionicotoxin (**2**). Thus, reduction of aziridine **43** and **46** to cleave the aziridine ring also constitutes a new synthesis of the 1-azaspirobicyclic ring system.

Experimental Section

General Methods. ^1H NMR spectra were recorded at 100 MHz; data are reported in the following manner: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, and m = unsolved multiplet), coupling constant, and integration. ^{13}C NMR spectra were recorded at 25.02 MHz with data being reported as follows: $\{^1H\}$ ^{13}C, chemical shift and multiplicity as obtained from the coupled spectra (s = singlet, d = doublet, t = triplet, and q = quartet). Mass spectrum refers to the electron impact mass spectrum unless otherwise noted. Melting points are determined with a Fisher–Johns melting point block and are uncorrected. Chromatography was performed as follows: silica gel, Merck No. 7736 Kieselgel 60H, was placed in a sintered glass funnel packed dry. Solvent was flushed through the silica gel under a water aspirator vacuum. The compound was deposited with a minimal amount of solvent and then eluted with solvent by using the water aspirator as the vacuum source. Ether and tetrahydrofuran (THF) were distilled from potassium/sodium metal under a nitrogen atmosphere with benzophenone ketyl as the indicator. Dimethylformamide (DMF) was distilled at reduced pressure from calcium hydride prior to use. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere.

2,3,4,6,7,8-Hexahydro-5(1*H*)-quinolinone (15) and 3,4,5,6,7,8-Hexahydrocyclopent[*c*]azepin-1(2*H*)-one (16). To a solution of **7** (60 mg, 0.27 mmol) in methanol (2 mL) and water (1 mL) was added sodium azide (27 mg, 0.40 mmol). The reaction mixture was heated at 80 °C for 5 h. The solvent was removed on a rotary evaporator. The residue was taken up in a mixture of ether (2 mL) and dichloromethane (3 mL). The solution was extracted with water (5 mL) and brine (5 mL) and then concentrated. Silica gel chromatography (hexanes/ethyl acetate, 1:3) gave **15** (10 mg, 25%) and **16** (28 mg, 67%). Data for **15**: ^1H NMR ($CDCl_3$) δ 1.63–2.62 (m, 10 H), 3.52 (t, J = 7 Hz, 2 H), 9.15 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.2 (t), 21.3 (t), 27.1 (t), 31.0 (t), 38.4 (t), 47.3 (t), 98.6 (s), 161.5 (s), 202.1 (s); IR ($CHCl_3$ solution) 1645, 1553 cm^{-1}. UV (ethanol) λ_{max} 318 nm; ϵ 27 900; MS, (12 eV) m/e (relative intensity) 151 (M^+, 96), 123 (23), 95 (100). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.79; 8.74; N, 9.29. Data for **16**: ^1H NMR ($CDCl_3$) δ 1.48–2.08 (m, 4 H), 2.16–2.88 (m, 6 H), 3.22 (apparent q, J =4 Hz, 2 H), 6.30 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (t), 27.3 (t), 31.7 (t), 35.6 (t), 40.8 (t), 41.7 (t), 130.5 (s), 150.8 (s), 169.6 (s); IR ($CHCl_3$ solution) 3420, 1650, 1610 cm^{-1}; UV (ethanol) λ_{max} 222 nm; ϵ 34 000; MS, m/e (relative intensity) 151 (M^+, 100), 121 (30). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.26; H, 8.48; N, 9.02.

3-(4-((Methanesulfonyl)oxy)butyl)-2-cyclohexen-1-one (17). To a solution of 3-(4-hydroxybutyl)-2-cyclohexen-1-one[16] (1.565 g, 9.3 mmol) and triethylamine (1.669 g, 16.5 mmol) in tetrahydrofuran (15 mL) was added dropwise methanesulfonyl chloride (1.459 g, 12.7 mmol) at 0 °C. After stirring for 2 h, water

(15 mL) was added. The reaction mixture was concentrated to remove tetrahydrofuran. The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with cold 5% hydrochloric acid and saturated sodium bicarbonate solution and then dried with anhydrous magnesium sulfate. Concentration gave crude **17** (2.46 g), which was used for the next step without further purification. Data for crude **17**: ^{1}H NMR ($CDCl_3$) δ 1.40–2.60 (m, 12 H), 3.00 (s, 3 H), 4.25 (t, J = 6 Hz, 2 H), 5.90 (s, 1 H); IR (neat) 1670 cm^{-1}.

3-(4-Azidobutyl)-2-cyclohexen-1-one (18). To a solution of crude **17** (3.44 g, 14.0 mmol) in dimethylformamide (40 mL) was added sodium azide (2.73 g, 42.0 mmol). The reaction mixture was stirred at room temperature for 12 h. After the removal of the solvent by a rotary evaporator equipped with a vacuum pump, water (50 mL) was added. The aqueous mixture was then extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with brine and dried with anhydrous magnesium sulfate. Concentration and silica gel chromatography (hexanes/ethyl acetate, 1:3) gave compound **18** (2.38 g, 88%): ^{1}H NMR ($CDCl_3$) δ 5.82 (s, 1 H), 3.27 (t, J = 6 Hz, 2 H), 1.40–2.44 m (12 H); ^{13}C NMR ($CDCl_3$) δ 22.6 (t), 23.8 (t), 28.2 (t), 29.4 (t), 37.1 (t, 2 carbon singlet overlap), 50.8 (t), 125.4 (d), 165.0 (s), 199.0 (s); IR ($CHCl_3$ solution) 2100, 1665 cm^{-1}; MS, m/e (relative intensity) 165 (M^+ – 28, 100), 137 (64), 109 (73).

2,3,4,5,6,7,8,9-Octahydro-1*H*-1-benzazepin-6-one (22). Compound **18** (2.14 g, 11.1 mmol) was dissolved in toluene (50 mL). The reaction solution was heated at reflux for 24 h. Concentration and silica gel chromatography (hexanes/ethyl acetate, 1:1) afforded **22** (1.28 g, 70%). A sample for elemental analysis was obtained by recrystallization in hexanes (mp 76–78 °C): ^{1}H NMR ($CDCl_3$) δ 1.40–2.46 (m, 12 H), 3.27 (br s, 2 H), 10.53 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.3 (t), 20.3 (t), 22.1 (t), 26.6 (t), 26.8 (t), 38.6 (t), 41.1 (t), 100.4 (s), 158.7 (s), 200.2 (t). IR ($CDCl_3$ solution) 1615, 1565 cm^{-1}; MS, m/e (relative intensity) 165 (M^+, 100), 137 (23); UV (ethanol) λ_{max} 330 nm; ϵ 30900; Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.61; H, 9.29; N, 8.31.

2-(4-Chlorobutyl)-2-cyclohexen-1-one (24). To a solution of n-butyllithium (1.1 M in hexane, 22 mL, 24 mmol) and tetrahydrofuran (4 mL) was added 2-bromo-2-cyclohexene 1-ethylene ketal (2.872 g, 13 mmol, in 4 mL of tetrahydrofuran) dropwise under nitrogen at –78 °C. The mixture was stirred at this temperature for 3 h, then 4-chloro-1-iodobutane (9.15 g, 42 mmol) was added in 1 portion, and then hexamethylphosphoramide (6 mL) was added. The reaction mixture was stirred for 4.5 h at –78 °C. NaH_2PO_4 aqueous solution (20%, 10 mL) was added and extracted with ether. The organic layer was washed with brine and then concentrated. The crude product was hydrolyzed with 5% hydrochloric acid in methanol (10 mL) for 5 h. Methanol was then evaporated and aqueous solution was extracted with ether. The ether layer was washed with brine and dried over anhydrous magnesium sulfate and then concentrated. Silica gel chromatography (hexanes/ethyl acetate, 3:1) gave compound **24** (1.40 g, 57%): ^{1}H NMR ($CDCl_3$) δ 1.40–2.52 (m, 12 H), 3.50 (t, J = 7 Hz, 2 H), 6.70 (t, J = 4 Hz, 1 H); IR (neat) 1660 cm^{-1}; MS, m/e (relative intensity) 110 (31), 123 (23), 151 (100), 186 (M^+, 16), 188 (5).

2-(4-Azidobutyl)-2-cyclohexen-1-one (25). To a solution of **24** (0.523 g, 2.8 mmol in 10 mL of dimethylformamide) was added sodium azide (1.04 g, 16 mmol) and potassium iodide (20 mg). The mixture was heated at 60 °C under nitrogen for 24 h. Dimethylformamide was removed under vacuum. The residue was extracted with ether. The ether solution was washed with brine and dried over anhydrous magnesium sulfate and then concentrated to give product **25** (0.452 g, 84%): ^{1}H NMR ($CDCl_3$) δ 1.40–2.52 (m, 12 H), 3.27 (t, J = 7 Hz, 2 H), 6.73 (t, J = 4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 199.3 (s), 145.3 (s), 139.1 (s), 51.1 (t), 38.3 (t), 28.9 (t), 28.4 (t), 25.9 (t), 25.6 (t), 22.9 (t); IR (neat) 2935, 2865, 2090, 1670 cm^{-1}; MS, m/e 194 (M^+ + 1, 8), 165 (M^+ – 28, 33).

Thermolysis of 25 in Aqueous Methanol: 2,3,4,5,6,7,8,9-Octahydro-1*H*-1-benzazepin-9-one (29). Compound **25** (120 mg, 0.6 mmol) was dissolved in methanol (1 mL) and water (3 mL). The reaction solution was heated at reflux for 50 h. Methanol was removed, and the residue was extracted with ether. The ether layer was washed with brine, dried over anhydrous magnesium sulfate, and then concentrated. Silica gel chromatography (hexanes/ethyl acetate, 6:1) gave starting material **25** (35.2 mg) and compound **29** (15 mg, 20%): ^{1}H NMR ($CDCl_3$) δ 1.32–2.50 (m, 12 H), 2.8 (t, J = 5 Hz, 2 H), 4.6 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.4 (t), 24.8 (t), 31.4 (t), 32.7 (t), 35.7 (t), 36.6 (t), 47.6 (t), 139.0 (s), 142.1 (s), 195.5 (s); IR ($CHCl_3$ solution) 3350, 1660 cm^{-1}; UV (methanol) λ_{max} 289 nm; ϵ 35000; MS, m/e (relative intensity) 165 (M^+, 100), 150 (25), 136 (28), 137 (30), 109 (45).

Thermolysis of 25 in Toluene. Compound **25** (80 mg, 0.4 mmol) was dissolved in toluene (5 mL). The reaction solution was heated at reflux for 24 h. Concentration and silica gel chromatography (hexanes/ethyl acetate, 3:1) afforded compound **22** (27 mg, 39%).

3-[3-(1-Ethoxyethoxy)propyl]-2-methyl-2-cyclohexenone (35). To magnesium turnings (2.16 g, 90 mmol) in tetrahydrofuran (10 mL) was added a small portion (5 mL) of a solution of 1-bromo-3-(1-ethoxyethoxy)propane (6.3 g, 30 mmol) in tetrahydrofuran (20 mL). Dibromoethane (0.01 mL) was added to initiate the reaction. The rest of the solution was added slowly to keep the reaction temperature below 30 °C. After the addition, the reaction mixture was stirred at room temperature for 2 h. A solution of **34** (2.31 g, 15 mmol) in tetrahydrofuran (8 mL) was added dropwise to the reaction mixture at 5–10 °C. The reaction mixture was then warmed to room temperature and stirred for 15 h. The mixture was poured into ice (20 g). Dilute hydrochloric acid (5%) was added to adjust the pH to 5. The mixture was extracted with ether (3 × 20 mL). The combined organic layers were washed with brine and dried with anhydrous magnesium sulfate. Concentration and silica gel chromatography (hexanes/ethyl acetate, 3:1) gave **35** (2.52 g, 70%): ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.76 (br s, 3 H), 1.50–2.50 (m, 10 H), 3.20–3.75 (m, 4 H), 4.65 (q, J = 6 Hz, 1 H); IR (neat) 1665 cm^{-1}; MS, m/e 241 (M^+, 1.3), 168 (100).

3-(3-Hydroxypropyl)-2-methyl-2-cyclohexenone (36). To a solution of **35** (1.2 g, 5 mmol) in methanol (20 mL) was added oxalic acid (30 mg, 2.5 mmol). The reaction mixture was stirred at room temperature for 6 h. Sodium bicarbonate (1.6 g) was added. After removal of methanol, water (10 mL) was added. The aqueous solution was extracted with chloroform (3 × 10 mL). The organic phase was dried with anhydrous magnesium sulfate and concentrated to give crude product **36** (0.738 g): ^{1}H NMR ($CDCl_3$) δ 1.50–2.50 (m, 10 H), 1.78 (s, 3 H), 3.65 (t, J = 6 Hz); IR (neat) 3425, 1650 cm^{-1}; MS, m/e (relative intensity) 169 (M^+ + 1, 11), 124 (100).

3-(3-((Methanesulfonyl)oxy)propyl)-2-methyl-2-cyclohexenone (37). To a solution of crude **36** (738 mg, 4.39 mmol) in tetrahydrofuran (8 mL) was added triethylamine (1 mL). The reaction mixture was cooled to 0 °C. Methanesulfonyl chloride (0.41 mL, 5.19 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. Water (5 mL) was added, and the tetrahydrofuran was removed on a rotary evaporator. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic phase was washed with cold 5% hydrochloric acid (10 mL) and brine and then dried with anhydrous magnesium sulfate. Concentration gave crude product **37** (1.068 g): ^{1}H NMR ($CDCl_3$) δ 1.76 (br s, 3 H), 1.80–2.50 (m, 13 H), 4.22 (t, J = 6.5 Hz, 2 H); IR (neat) 1655, 1360 cm^{-1}. The crude product was not purified but was carried on to the next step.

3-(3-Bromopropyl)-2-methyl-2-cyclohexenone (38). To a solution of crude **37** in tetrahydrofuran (15 mL) was added anhydrous lithium bromide (982 mg, 11.4 mmol). The reaction mixture was stirred at room temperature for 15 h. Filtration and concentration gave the crude product, which was chromatographed on silica gel (hexanes/ethyl acetate, 1:1) to afford **38** (997 mg, overall yield from **33**, 78%): ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H), 1.65–2.50 (m, 10 H), 3.40 (t, J = 7 Hz, 2 H); IR (neat) 1650 cm^{-1}; MS, m/e (relative intensity) 230, 232 (M^+ and M^+ + 2, 5.3), 151 (100).

6-Methyl-5-azatricyclo[4.4.0.0^{1,5}]decan-7-one (43). To a solution of **38** (610 mg, 2.64 mmol) in dimethylformamide was added sodium azide (340 mg, 5.23 mmol). The reaction mixture was heated at 85 °C for 15 h. The solvent was removed on a rotary evaporator equipped with a mechanical vacuum pump. The residue was taken into a mixture of ether (15 mL) and dichloromethane (15 mL). The organic phase was washed with water (10 mL) and brine (10 mL) and then dried with anhydrous

magnesium sulfate. Concentration and silica gel chromatography (hexanes/ethyl acetate, 1:1) gave **43** (246 mg, 57%): ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3 H), 1.40–2.20 (m, 8 H), 2.30–3.45 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 6.8 (q), 20.7 (t), 27.8 (t), 27.9 (t), 31.1 (t), 36.2 (t), 49.9 (t), 50.7 (s), 61.1 (s), 207.9 (s); IR ($CHCl_3$ solution) 1700 cm^{-1}; MS, *m/e* (relative intensity) 165 (M^+, 77), 150 (32), 137 (50), 122 (100), 110 (82), 96 (11).

3-(4-Azidobutyl)-2-butylcyclohex-2-en-1-one (45). To a solution of **44**[14a] (290 mg, 0.77 mmol) in dimethylformamide (10 mL) was added sodium azide (280 mg, 4.3 mmol) and potassium iodide (20 mg). The mixture was stirred at room temperature for 12 h. After the solvent was removed under vacuum, the residue was taken up in ether (20 mL). The ether layer was washed with brine and dried over anhydrous magnesium sulfate. Concentration gave product **45** (148 mg, 78%): ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.0–2.5 (m, 18 H), 3.3 (t, 2 H); MS, *m/e* (relative intensity) 221 (M^+ - 28, 25), 178 (58), 85 (67), 83 (100).

7-*n*-Butyl-6-azatricyclo[4.5.0.0^{1,6}]undecan-8-one (46). A solution of comound **45** (214 mg, 0.86 mmol) in *m*-xylene (20 mL) was heated to reflux for 6 h. Concentration and silica gel chromatography (hexanes/ethyl acetate, 5:1) gave **46** (138 mg, 86%): ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.0–2.8 (m, 18 H), 3.0–3.4 (m, 2 H); ^{13}C NMR (C_6D_6) δ 14.9 (q), 18.8 (t), 19.1 (t), 23.2 (t), 24.1 (t), 24.3 (t), 25.9 (t), 29.1 (t), 33.0 (t), 38.8 (t), 42.1 (t), 43.4 (s), 52.0 (s), 206.8 (s); IR (neat) 2950, 1700 cm^{-1}. MS, *m/e* (relative intensity) 221 (M^+, 20). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.10; H, 10.48; N, 6.63.

(6*SR*,7*SR*)-7-*n*-Butyl-1-azaspiro[5.5]undecan-8-one (47). To a solution of **46** (180 mg, 0.81 mmol) in acetone (5 mL) was added a solution (4 mL) of freshly prepared chromous chloride.[20] The mixture was stirred at room temperature for 5 min, and acetone was removed. The aqueous layer was then basified with sodium carbonate. The aqueous solution was extracted with dichloromethane (3 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate. Concentration and silica gel chromatography (methanol/ethyl acetate, 1:2) gave **47** (134 mg, 74%): ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.0–2.8 (m, 22 H); MS, *m/e* (relative intensity) 223 (M^+, 80), 97 (100); IR (neat) 3350, 2950, 1710 cm^{-1}.

(6*SR*,7*SR*)-7-*n*-Butyl-*N*-benzyl-1-azaspiro[5.5]undecan-8-one (48). To a solution of **47** (66.7 mg, 0.3 mmol) and benzyl bromide (600 mg, 3.5 mmol) in tetrahydrofuran (15 mL) was added potassium carbonate (500 mg, 3.6 mmol). The reaction mixture was heated to reflux for 24 h and then poured into 5% hydrochloric acid (15 mL). The acidic solution was extracted with ether (10 mL) and then basified with sodium carbonate and extracted with dichloromethane (3 × 10 mL). Concentration and silica gel chromatography (hexanes/ethyl acetate, 3:1) gave **48** (79.7 mg, 85%): ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H), 1.1–1.8 (m, 16 H), 2.1–2.7 (m, 5 H), 3.50, 3.66 (AB q, 2 H), 7.1–7.4 (m, 5 H); IR (neat) 2910, 1705 cm^{-1}.

Acknowledgment. We thank the National Science Council of the Republic of China for the support of this work.

Registry No. (±)-**2**, 55228-77-8; **7**, 74056-07-8; **15**, 1006-51-5; **16**, 91891-64-4; **17**, 82026-14-0; **18**, 91891-61-1; **22**, 91891-66-6; **23**, 70156-98-8; **24**, 91891-62-2; **25**, 91891-63-3; **29**, 91891-67-7; **34**, 20643-20-3; (±)-**35**, 100466-69-1; **36**, 100466-70-4; **37**, 100466-71-5; **38**, 91891-59-7; (±)-**43**, 100466-72-6; **44**, 83562-30-5; **45**, 100466-73-7; (±)-**46**, 100466-74-8; (±)-**47**, 82260-14-8; (±)-**48**, 83562-34-9; I(CH_2)$_4$Cl, 10297-05-9; 3-(4-hydroxybutyl)-2-cyclohexen-1-one, 78877-14-2; 1-bromo-3-(1-ethoxyethoxy)propane, 34399-67-2.

Hypochlorite-Promoted Transformations of Trichothecenes. Verrucarol[1]

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Received October 2, 1985

Treatment of verrucarol in methanol with hypochlorite bleach containing added sodium hydroxide gave rise to two chlorine-containing rearrangement products **2a,b**. Their structures were established by ^{13}C and ^{1}H NMR spectroscopies and mass spectrometry. Both products possess an unusual pentacyclic ring system resulting from selective oxidation at C-4 followed by hemiketal formation and a haloform-like reaction in addition to rearrangement and are resistant to further oxidation.

Trichothecenes are an important class of mycotoxins produced in nature by a number of taxonomically unrelated genera of fungi and have attracted widespread interest because of their biological effects, most notably toxicity, in man and animals.[2] The skeleton of the tetracyclic sesquiterpenoid unit present in all trichothecenes, macrocyclic and nonmacrocyclic, was established by X-ray crystallography,[3] and chemical transformations of the simpler nonmacrocyclic trichothecenes have been extensively studied.[2a,4] The 12,13-epoxide, generally believed to be a crucial element for biological activity, was resistant to attack by a number of reagents including nucleophiles. Under acidic conditions, however, rearrangement to a tricyclic structure (termed apotrichothecene) readily occurred.[2a,5]

(1) Portions of this material were presented at the 189th American Chemical Society National Meeting, Miami Beach, FL, May 1985; ORGN 247.

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