

Only one other 19-hydroxylated sterol has been isolated² from natural sources to the best of our knowledge.

Sterol 1 was found to be slightly cytotoxic, ED₅₀ in PS, 4.9 μg/mL.⁸

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer 298 spectrophotometer. NMR spectra were taken on Varian XL-100 and Nicolet 270 MHz instruments in the solvent specified; signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were taken on CEC 110 (Du Pont) and Hewlett-Packard 5985B spectrometers. A Perkin-Elmer 141 polarimeter was used for obtaining optical rotations. The chromatographic adsorbent used was Brinkmann silica gel 60 (230-400 mesh). An Altex 5- μ m 10 mm \times 25 cm preparative silica gel (LiChrosorb 60) column was used for HPLC separations.

Isolation of 1a. Specimens of the sponge *Dysidea sp.* were collected at ~10-15 M around Guam Is. and transported frozen to Oklahoma. Freshly thawed material (wet weight 177.4 g) was extracted at room temperature first with chloroform-methanol (1:1) for 2 days and then with methanol for 1 week. Evaporation of the extracts in vacuo afforded residues weighing 1.64 and 0.36 g, respectively. Chromatography of 1.5 g of the combined extracts on 100 g of silica gel using chloroform followed by chloroform with increasing amounts of methanol afforded 18 fractions. Crystallization of fraction 13 (34 mg, eluted with chloroform-methanol (98:2)) from 4 mL of chloroform-hexane (1:2) overnight in a refrigerator yielded 6 mg of white crystals. This crystalline material was purified further by high-pressure liquid chromatography using a reverse-phase C₁₈ column with a mobile phase of methanol-water (90:10). Crystallization of the major HPLC fraction from chloroform-hexane (1:2) yielded 4.2 mg of white crystals: mp 229-230 °C; [α]_D²⁰ +42.6° (c 0.07, CHCl₃); IR(CHCl₃) 3585, 3650-3250 (brd), 1736, 1665 (vs), 1468, 1375, 1240 cm⁻¹; 270-MHz ¹H NMR (CDCl₃) (number of protons, multiplicity, *J* in Hz, assignment) δ 0.60 (3, s, H-18), 0.86 (6, d, *J* = 7 Hz, H-26, 27), 0.92 (3, d, *J* = 7 Hz, H-21), 2.07 (1, dd, *J* = 14.2, 5.2 Hz, 4 α -H), 2.15 (3, s, OAc), 2.18 (1, dd, *J* = 15.0, 6.3 Hz, 12 β -H), 2.36 (1, m, 14 α -H), 3.40 (1, d, *J* = 4.7 Hz, 11 β -H), 3.80 (1, dd, *J* = 12, 4.35 Hz, H-19 coupled also with OH), 6-H), (1, dd, *J* = 12, 4.35 Hz, H-19 coupled also with OH), 4.06 (1, m, 3 α -H), 5.22 (1, dd, *J* = 3.5, 1.0 Hz, H-7), 5.32 (1, dd, *J* = 3.5, 0.8 Hz, 6 α -H); mass spectrum (12 eV, low resolution), *m/e* (relative intensity) 490 (M⁺ C₂₉H₄₆O₆, 3), 473 (5), 472 (17), 455 (2), 431 (15), 430 (42), 413 (34), 412 (100), 402 (10), 401 (18), 400 (20), 399 (16), 397 (10), 395 (14), 394 (35), 385 (12), 384 (21), 365 (24), 326 (21), 304 (63), 292 (29), 289 (24), 245 (43), 237 (46), 191 (22), 152 (21); high-resolution mass spectrum, observed *m/e* (composition, interpretation, calculated millimass) 472.31624 (C₂₉H₄₄O₅, M⁺ - H₂O, 472.31887), 454.31132 (C₂₉H₄₂O₄, M⁺ - 2H₂O, 454.30831), 430.30507 (C₂₇H₄₂O₄, M⁺ - AcOH, 430.30831), 412.29752 (C₂₇H₄₀O₃, M⁺ - H₂O - AcOH, 412.29774), 400.29395 (C₂₆H₄₀O₃, M⁺ - AcOH - CH₂O, 400.29774); 394.28593 (C₂₇H₃₈O₂, M⁺ - AcOH - 2H₂O), 382.28795 (C₂₆H₃₈O₂, M⁺ - AcOH - H₂O - CH₂O, 382.28718), 299.16488 (C₁₉H₂₃O₃, M⁺ - H₂O - AcOH - C₈H₁₇, 299.16472), 281.15433 (C₁₉H₂₁O₂, M⁺ - 2H₂O - AcOH - C₈H₁₇, 281.15415), 245.11806 (C₁₅H₁₇O₃, M⁺ - AcOH - CH₂O - C₁₁H₂₃, 245.11777), 227.10701 (C₁₅H₁₅O₂, M⁺ - H₂O - AcOH - CH₂O - C₁₁H₂₃, 227.10720), 155.08575 (C₁₁H₂₃); 300-MHz ¹H NMR (pyridine-*d*₅) δ 0.82 (3, s, H-18), 0.87 (9, d, *J* = 7 Hz, H-21, -26, -27), 1.50 (m, H-20, H-25), 1.94 (1, d, *J* = 15.0 Hz, 12 α -H), 2.01 (3, s, OAc), 2.29 (1, dd, *J* = 15.0, 4.7 Hz, 12 β -H), 2.62 (1, m, H-14), 2.77 (1, dd, *J* = 14.2, 5.2 Hz, 4 α -H), 3.92 (1, d, *J* = 4.7 Hz, 11 β -H), 4.21 (1, dd, *J* = 12.6, 5 Hz, H-19 coupled also with OH), 4.50 (1, dd, *J* = 12.6, 5 Hz, H-19 coupled also with OH), 4.75 (1, m, 3 α -H), 5.67 (1, br s, 6 α -H), 5.82 (1, s, 5-OH), 5.86 (1, br s, H-7), 6.21 (1, d, 3-OH), 6.55 (1, t, 4, C-19-OH).

Acetylation of 1a. Sterol 1a (1 mg) was reacted with 1 mL of acetic anhydride-pyridine (1:19) at room temperature overnight.

Purification of the product by HPLC using silica gel with petroleum ether-chloroform (1:2) afforded 1b which showed the following spectral properties: IR (neat) 3600 (w), 3500 (s), 1742, 1470, 1370, 1240 cm⁻¹; 100-MHz ¹H NMR (CDCl₃) δ 0.51 (3, s, H-18), 0.88 (6, d, *J* = 7 Hz, H-26, -27), 0.90 (3, d, H-21), 2.01, 2.08, 2.17 (3 each, s, OAc), 3.33 (1, d, 5.0, 11 β -H), 4.10 (1, d, *J* = 11.5 Hz, H-19), 4.55 (1, d, *J* = 11.5 Hz, H-19), 5.16 (1, m, 3 α -H), 5.31 (2, m, H-6, -7); mass spectrum (70 eV, low resolution), *m/e* (relative intensity) 514 (3% M⁺ - CH₃COOH), 486 (0.9), 472 (0.7), 471 (1.2), 455 (1.3), 412 (2), 395 (13), 394 (32), 281 (5), 253 (8), 248 (16), 232 (21), 149 (19), 129 (11), 106 (46), 83 (100).

Hydrolysis of 1a. 1a (1.5 mg) was heated with 5% KOH in 95% ethanol (5 mL) under reflux for 30 min, and the reaction mixture was cooled to room temperature, acidified, diluted with water, and then extracted with methylene chloride. The organic phase was dried over MgSO₄, the solvent evaporated in vacuo, and the residue purified by HPLC using a silica gel column and CHCl₃-MeOH (98:2) as eluant to yield pure 1c: IR (neat) 3435 (sh), 3340, 1575, 1482, 1375 cm⁻¹; 270-MHz ¹H NMR (pyridine-*d*₅) δ 0.86 (6, d, *J* = 7 Hz, H-26, -27), 0.88 (3, s, H-18), 0.97 (3, d, *J* = 7 Hz, H-21), 3.04 (1, dd, *J* = 13.1, 2.7 Hz, 4 α -H), 3.90 (1, d, *J* = 8.7 Hz, H-19), 4.16 (1, d, *J* = 8.7, H-19), 4.48 (2, m, H-11 and COH), 4.52 (1, m, 3 α -H), 5.72 (1, s, H-7); low-resolution mass spectrum (70 eV), *m/e* (relative intensity) 448 (C₂₇H₄₄O₅, 2%), 431 (5), 430 (13), 415 (1), 413 (3), 412 (8), 401 (4), 383 (6), 317 (11), 305 (12), 299 (10), 430 (13), 227 (13), 213 (12), 211 (12), 209 (12), 205 (17), 193 (22), 182 (20), 167 (24), 163 (29), 161 (24), 159 (26), 149 (49), 147 (43), 137 (55), 121 (76), 109 (90), 95 (86), 81 (100).

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Registry No. 1a, 84473-32-5; 1b, 84473-33-6; 1c, 84473-34-7.

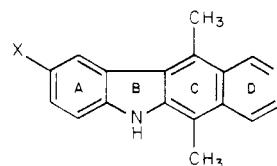
Total Synthesis of Ellipticine and 9-Methoxyellipticine via Benzotriazole Intermediates

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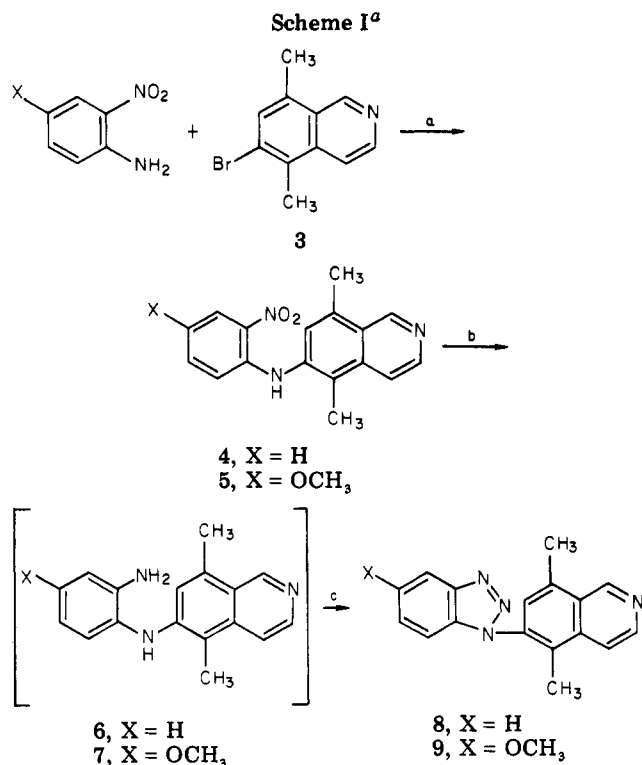
Ellipticine (1) and 9-methoxyellipticine (2), members of



1, X = H
2, X = OCH₃

the 6H-pyrido[4,3-b]carbazole class of alkaloids, have been shown to possess significant anticancer activity.¹ As a

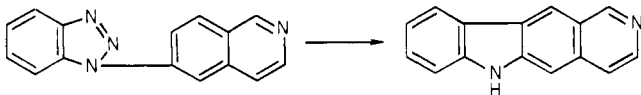
(8) Gueran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3*, 1972, 3, 1-103. Effective doses (ED₅₀) in the tissue culture tests are expressed as concentrations in μg/mL of test material in the growth medium that cause 50% inhibition of cell growth. "Active" materials display in ED₅₀ ≤ 20 μg/mL. PS refers to in vitro lymphocytic leukemia.



^a (a) Copper bronze, K₂CO₃, I₂(catalyst); (b) H₂NNH₂, Raney Ni (catalyst), 95% EtOH; (c) HOAc, aqueous NaNO₂.

result, many synthetic approaches to these alkaloids have been developed,² including a general synthesis of ellipticine recently reported from our laboratories.³ In this latter synthesis the last step was formation of ring B by a palladium-induced carbon-carbon bond-forming reaction. Although the synthesis proved to be competitive with other synthetic approaches and is of a general nature, problems of poor conversion and inability to make the palladium reaction catalytic caused us to look for an alternative method for formation of ring B. A solution to this problem using benzotriazole intermediates is described in this paper.

As in our earlier work, in order to maximize versatility it was decided that ring A and the isoquinoline portion (rings C and D) should be kept separate until just prior to ring B formation. By analogy to work of Bisagni et al.⁴ it was thought that an appropriate benzotriazole would provide a route for ring B formation:



It was found that the desired benzotriazoles could readily be prepared in a three-step sequence (see Scheme I). Goldberg coupling of *o*-nitroaniline or 4-methoxy-2-nitroaniline with 6-bromo-5,8-dimethylisoquinoline³ (3) in the presence of copper bronze gave the diarylamines 4

(54% yield)^{5,6} and 5 (53% yield), respectively. The nitro group in these diarylamines was reduced quantitatively by using hydrazine hydrate and a catalytic amount of Raney nickel. The resulting diamines 6 and 7 without purification were diazotized with aqueous sodium nitrite in acetic acid, giving the desired benzotriazoles 8 (97% yield)^{5,7} and 9 (94% yield).

A variety of methods to induce triazole decomposition were studied. First, following a modified procedure by Kermack and Storey,⁸ benzotriazole 8 was heated (220 °C) in polyphosphoric acid to give ellipticine (1) in 16% yield. Next, benzotriazole 8 was photolyzed (methanol solution containing acetone and triethylamine in a quartz tube) to give ellipticine (1) in 33% yield (26% conversion). Finally, benzotriazole 8 was pyrolyzed at 500 °C in a simple hot-tube flow system (see Experimental Section) to give ellipticine (1) in 69% yield. When this latter procedure was applied to methoxybenzotriazole 9, 9-methoxyellipticine (2) was obtained in 62% yield.

The above sequence represents a new four-step synthesis of ellipticine and 9-methoxyellipticine from the readily available 6-bromo-5,8-dimethylisoquinoline in an overall yield of 30–35%.

Experimental Section

For reactions depicted in Scheme I only a representative description for X = OMe is given. Identical conditions were employed for the series X = H, and melting points and spectral data are given in footnotes.

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance (¹H NMR) spectra were recorded on a Varian EM-390 instrument. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane (Me₄Si). Combustion analyses were performed by the University of California, Berkeley, analytical laboratories. High-resolution mass spectra were obtained with a Du Pont 492 spectrometer through the Facility for Advanced Instrumentation, University of California, Davis. All reactions were carried out under a nitrogen atmosphere. Anhydrous sodium sulfate was used as the drying agent.

6-(4-Methoxy-2-nitroanilino)-5,8-dimethylisoquinoline (5).

A mixture of 6-bromo-5,8-dimethylisoquinoline (2.00 g, 8.47 mmol, 1.00 equiv), 4-methoxy-2-nitroaniline (Aldrich; 7.12 g, 42.3 mmol, 5.00 equiv), freshly activated copper bronze⁹ (540 mg, 8.50 mmol, 1.00 equiv), anhydrous potassium carbonate (1.17 g, 8.47 mmol, 1.00 equiv), and a catalytic amount of iodine was heated in a 120 °C oil bath for 24 h. At the end of this time, the excess 4-methoxy-2-nitroaniline was removed by steam distillation. The residue from the distillation was extracted with dichloromethane, and the combined extracts were washed with water followed by brine, dried, and evaporated to afford a dark blood-red solid. Chromatography on silica gel (eluting with 4:1 dichloromethane/fat extraction ether) gave a blood-red solid (1.44 g, 53% yield). An analytical sample was prepared by silica gel preparative thin-layer chromatography: mp 173–174.5 °C; ¹H NMR (CDCl₃) δ 2.48 (s, 6 H), 3.79 (s, 3 H), 6.85 (unsymmetrical d, J = 10 Hz, 1 H), 7.05 (unsymmetrical dd, J = 3, 10 Hz, 1 H), 7.60 (s, 1 H), 7.66 (d, J = 3 Hz, 1 H), 7.78 (d, J = 6 Hz, 1 H), 8.60 (d, J = 6 Hz, 1 H), 9.29 (br s, 1 H), 9.39 (s, 1 H); IR (KBr) 3380, 2940, 1610, 1570, 1505, 1230, 1035, 815 cm⁻¹. Anal. Calcd for C₁₈H₁₇N₃O₃: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.57; H, 5.36; N, 12.81.

6-(2-Amino-4-methoxyanilino)-5,8-dimethylisoquinoline (7). By use of a modified procedure of Fletch and Namkung,¹⁰

(5) Satisfactory analytical data and an IR spectrum were obtained for this compound.

(6) Mp 146–147 °C; ¹H NMR (CDCl₃) δ 2.47 (s, 3 H), 2.70 (s, 3 H), 6.66–6.93 (m, 2 H), 7.19–7.73 (m, 2 H), 8.14 (d, J = 6 Hz, 1 H), 8.23 (d, J = 7 Hz, 1 H), 8.58 (d, J = 6 Hz, 1 H), 9.41 (br s, 1 H), 9.47 (s, 1 H).

(7) Mp 195–196 °C; ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.70 (s, 3 H), 7.25–7.67 (m, 4 H), 7.98 (d, J = 6 Hz, 1 H), 8.14–8.33 (m, 1 H), 8.80 (d, J = 6 Hz, 1 H), 9.04 (s, 1 H).

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a solution of 6-(4-methoxy-2-nitroanilino)-5,8-dimethylisoquinoline (1.00 g, 3.10 mmol, 1.00 equiv), hydrazine hydrate (98%; 929 mg, 900 μ L, 18.6 mmol, 6.00 equiv), and a catalytic amount of Raney nickel, all in 95% ethanol (10 mL), was heated to reflux on a steam bath for 1 h. At the end of this time, the solvent was removed at atmospheric pressure until the vapors were no longer alkaline. The resulting mixture was taken up in dichloromethane, filtered, washed with brine, dried, and evaporated to yield a brown solid (974 mg) which was used without further purification: $^1\text{H NMR}$ (CDCl_3) δ 2.42 (s, 3H), 2.54 (s, 3 H), 3.80 (broadened s, 5 H), 5.59 (br s, 1 H), 6.13-7.13 (m, 4 H), 7.98 (d, $J = 6$ Hz, 1 H), 8.37 (d, $J = 6$ Hz, 1 H), 9.12 (s, 1 H); IR (KBr) 3360, 3275, 3100, 1595, 1265, 1025, 820, 750 cm^{-1} .

5-Methoxy-1-(5,8-dimethylisoquinolin-6-yl)-1H-benzotriazole (9). By use of a modified procedure of Bisagni et al.¹¹ the crude 6-(2-amino-4-methoxyanilino)-5,8-dimethylisoquinoline (7, 974 mg) obtained above was dissolved in glacial acetic acid (5 mL) and water (0.5 mL) and diazotized with a solution of sodium nitrite (280 mg, 4.07 mmol, 1.10 equiv) in water (1 mL) while at 0 $^\circ\text{C}$. The resulting solution was stirred for 2 h while warming to ambient temperature. At the end of this time, ice (25 g) was added, and the mixture was neutralized with concentrated aqueous ammonia and then extracted with dichloromethane. The combined extracts were washed with water followed by brine, dried, and evaporated to give a tan solid (885 mg, 94% yield) after chromatography on silica gel (eluting with 9:1 dichloromethane/fat extraction ether): mp 175-176 $^\circ\text{C}$; $^1\text{H NMR}$ (CDCl_3) δ 2.39 (s, 3 H), 2.82 (s, 3 H), 3.92 (s, 3 H), 7.19 (s, 1 H), 7.20 (s, 1 H), 7.40 (s, 1 H), 7.49 (t, $J = 2$ Hz, 1 H), 7.92 (d, $J = 6$ Hz, 1 H), 8.74 (d, $J = 6$ Hz, 1 H), 9.59 (s, 1 H); IR (KBr) 3080, 2960, 1610, 1490, 1295, 1200, 1020, 865, 815, 800 cm^{-1} ; high-resolution mass spectrum, calcd for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}$ m/e 304.1324, found m/e 304.1292.

Ellipticine (1). A solution of 1-(5,8-dimethylisoquinolin-6-yl)-1H-benzotriazole (8; 20.0 mg, 72.9 μ mol), acetone (1 mL), and methanol (14 mL) was injected via a motor-driven syringe at a rate of 0.382 mL/min into a 30-cm Vigreux column filled with quartz chips and heated to 500 $^\circ\text{C}$ under a flow of nitrogen (5 mL/s). The resulting yellow solution was evaporated to afford a yellow solid (14.8 mg) which was purified by preparative thin-layer chromatography on silica gel (eluting with 9:1 fat extraction ether/methanol) to yield ellipticine: 12.4 mg (69% yield); mp 308-311 $^\circ\text{C}$ dec (lit.¹² 309-313 $^\circ\text{C}$); $^1\text{H NMR}$ (10% methanol- d_4 in CDCl_3) δ 2.73 (s, 3 H), 3.22 (s, 3 H), 7.38-7.73 (m, 6 H, CHCl_3 present), 7.90-8.16 (m, 2 H), 8.35-8.63 (m, 3 H), 9.73 (br s, 1 H).

9-Methoxyellipticine (2). A solution of 5-methoxy-1-(5,8-dimethylisoquinolin-6-yl)-1H-benzotriazole (9; 20.0 mg, 65.7 μ mol), acetone (1 mL), and methanol (14 mL) was injected by means of a motor-driven syringe at a rate of 0.382 mL/min into a 30-cm Vigreux column filled with quartz chips and heated to 500 $^\circ\text{C}$ under a flow of nitrogen (5 mL/s). The resulting light brown solution was evaporated to yield a yellow-brown solid (20.1 mg). Purification by preparative thin-layer chromatography on silica gel (eluting with 9:1 fat extraction ether/methanol) gave an amber solid: 11.3 mg (62% yield); mp 291-295 $^\circ\text{C}$ dec (lit.¹³ mp 293-295 $^\circ\text{C}$); $^1\text{H NMR}$ (10% methanol- d_4 in CDCl_3) δ 2.70 (s, 3 H), 3.18 (s, 3 H), 3.73 (s, 3 H), 7.10-7.63 (m, 2 H), 7.63-8.07 (m, 2 H), 8.30-8.53 (m, 2 H), 9.53-9.70 (m, 1 H).

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Registry No. 1, 519-23-3; 2, 10371-86-5; 3, 76372-29-7; 4, 84537-53-1; 5, 84537-54-2; 7, 84537-55-3; 8, 84537-56-4; 9, 84537-57-5; 4-methoxy-2-nitroaniline, 96-96-8; *o*-nitroaniline, 88-74-4.

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Epoxidation of Alkenes with Trichloroacetonitrile/Hydrogen Peroxide in a Neutral Biphasic Solvent System

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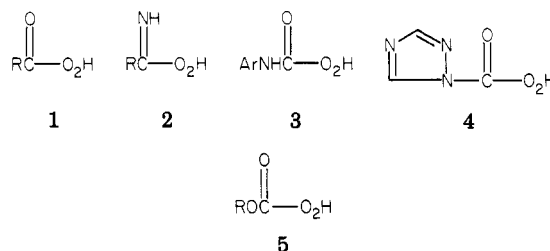
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An epoxide is a highly reactive functional group that can serve as a versatile synthetic intermediate. Epoxides are typically prepared from alkenes on a laboratory scale by the action of organic peroxides and metal catalysts¹ or by a variety of peroxy acids.² In general, the rate of epoxidation is enhanced by increased alkyl substitution on the double bond of the alkene which results in elevating the energy of the π bond (HOMO). Electron-withdrawing groups that have the capacity to lower the energy of the σ^* level of the O-O bond (NLUMO) of the peracid will also facilitate oxygen transfer.

Trifluoroacetic acid³ is one of the most reactive peroxy acids, but it suffers the disadvantage of having to be prepared in situ by the action of trifluoroacetic anhydride and 90% hydrogen peroxide. The resulting solution is highly acidic and can have deleterious effects upon the yield of epoxide. Attempts to utilize a carboxylic acid-peracid exchange with H_2O_2 also requires a strong acid catalyst. Consequently, *m*-chloroperbenzoic acid (MCPBA)⁴ is one of the most commonly used commercially available oxidants in the epoxidation of simple alkenes.

Two research objectives in the area of oxirane chemistry that have recently received attention include the development of chiral metal catalysts for use in asymmetric epoxidation⁵ and the utilization of hydrogen peroxide as the primary oxidant.⁶ Since hydrogen peroxide is not sufficiently electrophilic to directly epoxidize a nonconjugated carbon-carbon double bond, its reactivity must be enhanced by placing the OOH moiety in conjugation with a multiple bond as exemplified in structures 1-5.



One of the earliest and most useful adaptations of this principle was accomplished by Payne.⁷ He successfully activated the O-O bond by the in situ formation of a peroxyimidic acid (2) resulting from the base-catalyzed addition of H_2O_2 to a nitrile. Both aceto- and benzonitrile

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