Cycloaddition Reactions of Aromatic Nitroso Compounds with Oxygenated Dienes. An Approach to the Synthesis of the FR-900482 Family of Antibiotics

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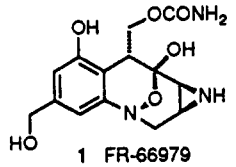
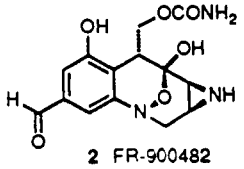
The clinically useful mitomycins have engendered a substantial amount of research in medicine, biology, and chemistry.[1] Two total syntheses of the mitomycins have been accomplished,[2,3] and considerable insight as to the mechanism of their bioactivation has been gathered.[4]

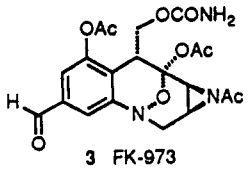
Recently two other naturally occurring aziridines, termed FR-66979 (1)[5] and FR-900482 (2),[6] have been described. While these compounds bear a superficial resemblance to mitomycins, the novelty of their structures and their interesting biological properties have already prompted synthetic explorations.[7-9]



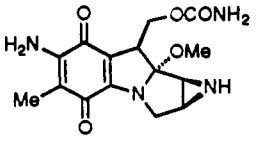
1 FR-66979



2 FR-900482

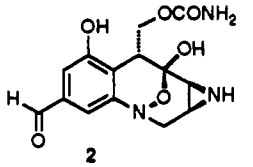


3 FK-973



mitomycin C

It has been claimed that the triacetyl derivative, FK-973 (3),[6] upon suitable bioactivation gives rise to an activated entity which causes interstrand DNA-DNA and DNA-protein cross links.[10,11] A reductive activation model has been proposed as an early phase of the bioactivation process.[8] The resultant product type 4 might cyclize to produce 5—a structure of significant similarity to the indoloid intermediates which have been implicated in mitomycin bioactivation.[4]



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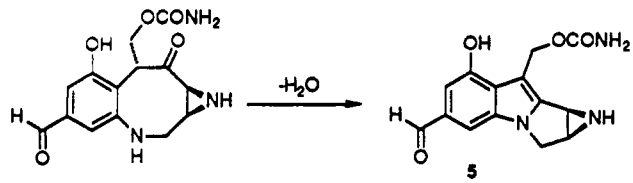


4 5

The study described below was initiated with a view toward assessing a strategy of the synthesis of antibiotics 1-3. At the same time we hoped to explore, albeit in a very preliminary fashion, the possibility of a chemical model for a solvolytic (of hydrolytic) as opposed to reductive activation cascade (vide infra).

Cycloaddition of an appropriate diene with a suitably functionalized arylnitroso compound could facilitate progress toward a synthesis of these targets. It would remain for trial and error to determine, in a precise way, the optimal components to be used in such a cycloaddition. Indeed the relative merits of intermolecular, or intramolecular, cycloaddition strategy must be carefully evaluated. However, before addressing issues of this level of sophistication, we deemed it necessary to answer an important question of feasibility. While the cycloaddition of arylnitroso compounds with dienes had been demonstrated,[13] the use of highly oxygenated dienes in this reaction was essentially unexplored. In earlier work in "all-carbon" Diels-Alder reactions, a massive polarity difference between the diene and dienophile was not always helpful.[14] In many cases electron transfer and simple addition could prevail over cycloaddition. Similarly, addition rather than cycloaddition is often encountered in Lewis acid catalyzed addition of such dienes to aldehydes.[15] Thus the program started with evaluation of the thermal cycloadditions of some representative arylnitroso compounds with oxygenated dienes.

Reaction of nitrosobenzene (7)[17] with (*E*)-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene[16] (8) occurs in methylene chloride at 0 °C. Evaporation of the volatiles and purification of the residue by column chromatography afforded a 95% yield of **9**. Similar reaction of **7**, with dienes 10[17] and 11,[18] affords **12** and **13** in 60 and 30% yields, respectively.[19] The former is converted to **14** by

(1) (a) Lipman, R.; Chawla, A. K.; Tomasz, M. *Structure and Expression DNA and its Drug Complexes*; Academic Press: New York, 1988; p 305. (b) Carter, S. K.; Crooke, S. T. *Mitomycin C. Current Status and New Developments*; Academic Press: New York, 1979.

(2) (a) Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115. (b) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295.

(3) (a) Yang, L.; Fukuyama, T. *J. Am. Chem. Soc.* **1987**, *109*, 7881. (b) Yang, L.; Fukuyama, T. *J. Am. Chem. Soc.* **1989**, *111*, 8303.

(4) (a) Iyer, V. N.; Szybalski, W. *Science* **1964**, *145*, 55. (b) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; Vol. 1 p 221 ff. (c) Franck, R. W.; Tomasz, M. *In the Chemistry of Antitumor Agents*; Wilman, D. F. V., Ed.; Blackie and Sons, Ltd.: Scotland, 1989. (d) Fisher, J. F.; Aristoff, P. A. *Prog. Drug Res.* **1988**, *32*, 411. (e) Tomasz, M.; Lipman, R.; Chowdary, D.; Pawlak, J.; Verdine, G.; Nakanishi, K. *Science* **1987**, *235*, 1204. (f) Teng, S. P.; Woodson, S. A.; Crothers, D. M. *Biochemistry* **1989**, *28*, 3901. (g) Cera, C.; Egbertson, M.; Teng, S. P.; Crothers, D. M.; Danishefsky, S. J. *Ibid.* **1989**, *28*, 5665. (h) Egbertson, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2204. (i) Hong, Y. P.; Kohn, H. *J. Am. Chem. Soc.* **1990**, *112*, 4596.

(5) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M. *J. Antibiot.* **1989**, *42*, 145.

(6) (a) Uchida, I.; Takase, S.; Kayakiri, S.; Hasimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 4108. (b) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589. (c) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okumura, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *Ibid.* **1987**, *40*, 594.

(7) Yasuda, N.; Williams, R. M. *Tetrahedron Lett.* **1989**, *30*, 3397.

(8) Goto, S.; Fukuyama, T. *Tetrahedron Lett.* **1989**, *30*, 6491.

(9) Jones, R. J.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 1144.

(10) Masuda, K.; Nakumura, T.; Mizota, T.; Mori, J.; Shimomura, K. *Cancer Res.* **1988**, *48*, 5172.

(11) Masuda, K.; Nakamura, T.; Shimomura, K.; Shibata, T.; Terano, H.; Kohsaka, M. *J. Antibiot.* **1988**, *41*, 1497.

(12) Egbertson, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 4648.

(13) (a) DeFoin, A.; Geffroy, G.; Le Nouen, D.; Streith, J. *Helv. Chim. Acta* **1989**, *72*, 1199. (b) For a review of arylnitroso Diels-Alder cycloadditions, see: Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, **1987**, p 71 ff. (c) For cycloadditions of the related acylnitroso compounds, see: Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1. Nickell, D. G.; Keck, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 3632.

(14) Cf: McKee, R.; Singh, R. K.; Danishefsky, S. J. *J. Org. Chem.* **1976**, *41*, 2934.

(15) Larson, E.; Askin, D.; Kato, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 1246.

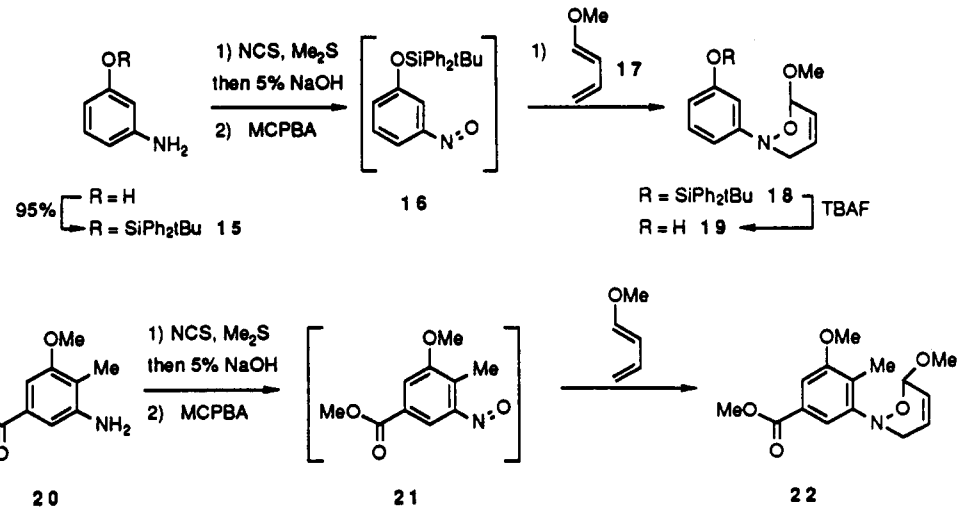
(16) Kitahara, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(17) Commercially available from Aldrich.

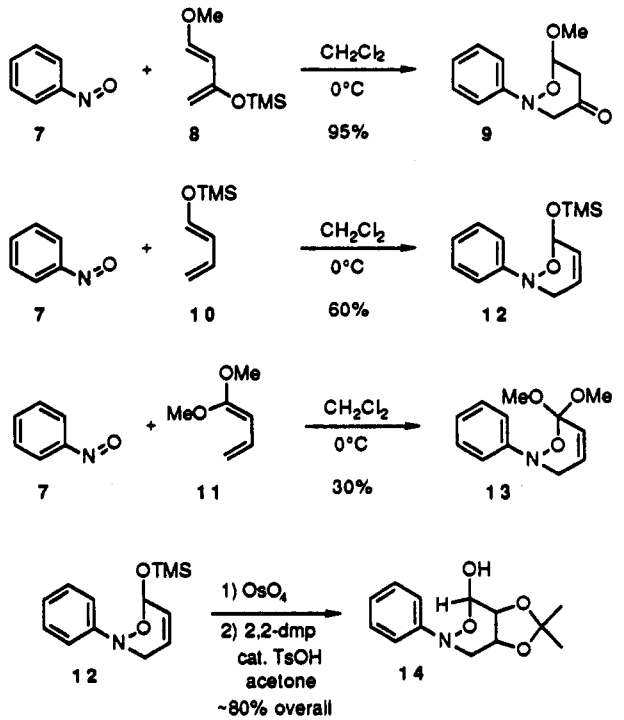
(18) Scheeren, J. W.; Marcelis, A. T. M.; Aben, R. W.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 196.

0022-3263/91/1956-0850$02.50/0

Scheme I



a sequence involving (i) oxidation with osmium tetraoxide, (ii) acetonization with 2,2-dimethoxypropane, and catalytic *p*-toluenesulfonic acid in acetone.[20]



Possibilities for incorporating additional aromatic functionality pertinent to the goals were explored. Silylation[21] of *m*-aminophenol afforded **15**. The conversion of the amino function to a nitroso group (cf. **16**) was accomplished by the sequence (i) *N*-chlorosuccinimide–dimethyl sulfide, (ii) 5% NaOH, (iii) *m*-chloroperoxybenzoic acid.[22] Compound **16** was treated directly with (*E*)-1-methoxybutadiene (**17**).[17] The resultant cycloadduct (**18**) was subjected to the action of TBAF to afford **19** (38% from **15**). In a more ambitious model, nitroso compound **21** was generated from **20**.[23] The compound thus produced in situ reacted with diene **17** to afford **22** (45% overall from **20**).

An alternative nonreductive nucleophilic activation of compound **2** shown in the sequence **2**–**6** was also examined using several of the adducts as primitive models (see Scheme II). If the nucleophile were a hydroxyl equivalent group, the resultant product would be particularly closely related to the key leucoaziridinomitosenes.[12] It was found that the reaction of **19** with methanol in the presence of BF_3 etherate gave a 20% yield[24] of **23**.[25]

Needless to say this observation can hardly be construed as evidence in favor of intervention of a hydrolytic (nonreductive) pathway in the actual bioprocessing of drugs **1**–**3**. It does however, suggest that novel chemistry can be anticipated from a more thorough examination of the aryloxazine systems now readily available through the Diels–Alder route described above. Further efforts directed to these issues and to the development of a workable synthetic route to systems of the type **1**–**3** are planned.

Experimental Section

General Experimental Procedure for Arylnitroso Diels–Alder Reactions. To a stirred solution of nitrosobenzene (0.52 g, 4.8 mmol) in 8 mL of dry CH_2Cl_2 was added 1.1 equiv of the diene at 0 °C under N_2 atmosphere. When the nitrosobenzene had been consumed, as indicated by TLC, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography to yield the pure Diels–Alder adduct.

6-Methoxy-*N*-phenyltetrahydro-2*H*-1,2-oxazin-4-one (9): 95% yield of tan solid; mp 88–89 °C; IR ($CHCl_3$) 1720 (s), 1480 (s), 1210 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.93 (d, 2 H, J = 5.6 Hz), 3.62 (s, 3 H), 3.80 (d, 1 H, J = 16.8 Hz), 4.08 (d, 1 H, J = 16.8 Hz), 5.14 (t, 1 H, J = 5.6 Hz), 7.0–7.14 (m, 3 H), 7.32–7.38 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 44.26, 56.18, 64.22, 100.41,

(19) Even at −78 °C, the formation of considerable quantities of unidentifiable side products accompanying **13** could not be avoided. Better yields have been carried with more substituted arylnitroso dienophiles.

(20) The regiochemistry of the acetonide formation was confirmed by acetylation of compound **17**, which leads to a downfield shift of this anomeric like methine resonance (5.34 ppm in **17**, 6.25 ppm in the corresponding acetate).

(21) Lavalee, P.; Hanessian, S. *Can. J. Chem.* **1977**, *55*, 562.

(22) McDaniel, K.; Skotnicki, J. S.; Taylor, E. C. *J. Org. Chem.* **1983**, *49*, 2500.

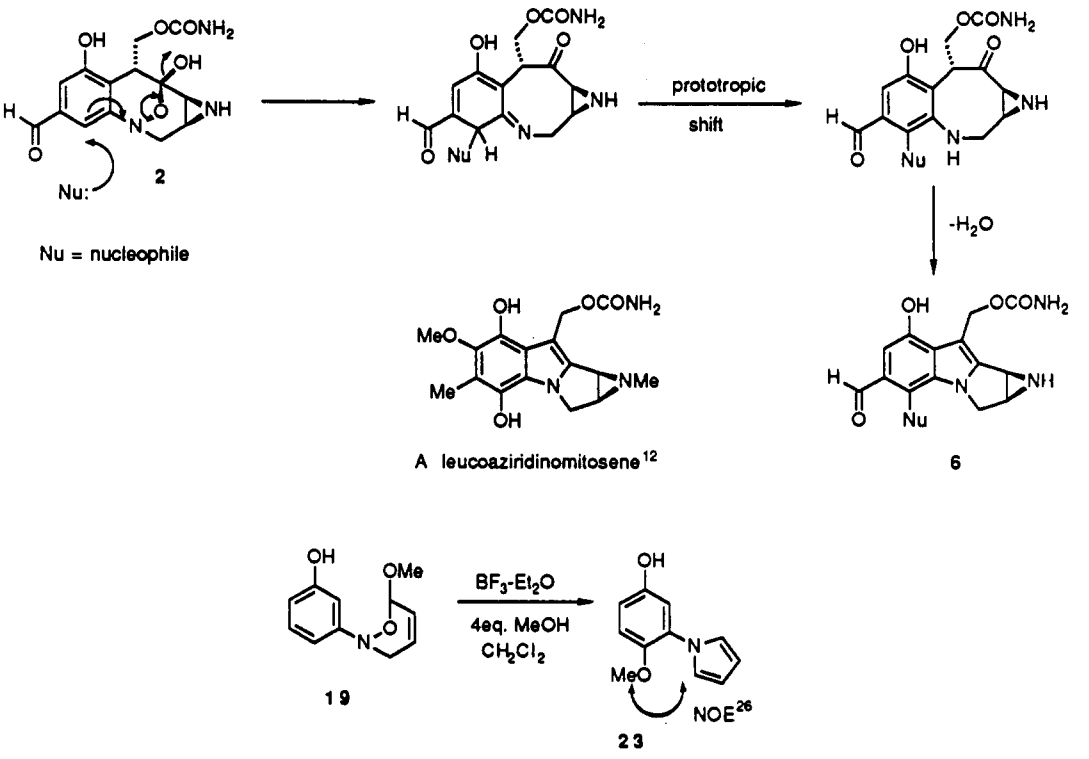
(23) Harris, C. M.; Kibby, J. J.; Fehlner, J. R.; Raabe, A. B.; Barber, T. A.; Harris, T. M. *J. Am. Chem. Soc.* **1979**, *101*, 437.

(24) The low yield is in part due to the tendency of the pyrrole product to undergo polymerization under the Lewis acidic reaction conditions.

(25) For a recent example of related Lewis acid mediated aromatic addition involving cleavage of a nitrogen oxygen bond, see: Shimada, M.; Kikugawa, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1440. For mechanistically related examples of ortho alkylation involving cleavage of a nitrogen oxygen bond in a [3,3]-sigmatropic rearrangement see: Hutchins, C. W.; Coates, R. M. *J. Org. Chem.* **1979**, *44*, 4742 and ref 13a. For relevant examples of ortho alkylation involving aryloxenium ions generated from oxygen nitrogen bond cleavage, see: Alverhne, G.; Inbasekarah, M. N.; Abramovitch, R. A. *Tetrahedron Lett.* **1977**, 1113. Alverhne, G.; Inbasekarah, M. N.; Abramovitch, R. A. *J. Chem. Soc., Chem. Commun.* **1978**, 149.

(26) Irradiation of the methyl ether protons at δ 3.92 gave a 9% enhancement of the downfield pyrrole protons at δ 7.00.

Scheme II



116.13, 124.00, 129.01, 148.97, 203.24; MS m/z (M^+) 207 (60), 122 (100), 105 (32), 100 (26), 85 (132). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 6.76; H, 63.32; N, 6.76. Found: C, 63.98; H, 6.21; N, 6.55.

3,6-Dihydro-2*H*-*N*-phenyl-6-(trimethylsiloxy)-1,2-oxazine (12): 60% yield of a yellow oil; IR ($CHCl_3$) 1610 (s), 1480 (s), 1250 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.22 (s, 9 H), 3.67 (dd, 1 H, J = 16.3, 1.8 Hz), 3.91 (dd, 1 H, J = 16.3, 4.6 Hz), 5.62 (br s, 1 H), 5.90 (ddd, 1 H, J = 10, 2.5, 1.8 Hz), 6.11 (br d, 1 H, J = 10 Hz), 7.01 (t, 1 H, J = 7.3 Hz), 7.14 (d, 2 H, J = 7.6 Hz), 7.30 (dd, 2 H, J = 7.6, 7.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 0.23, 52.30, 92.76, 116.19, 122.37, 126.13, 127.75, 128.58, 150.53; MS m/z (M^+) 249 (9), 142 (100), 73 (70). Anal. Calcd for $C_{13}H_{19}NO_2Si$: C, 62.62; H, 7.68; N, 5.61. Found: C, 62.65, H, 7.65, N, 5.55.

3,6-Dihydro-2*H*-6,6-dimethoxy-*N*-phenyl-1,2-oxazine (13): 30% yield of yellow oil; IR ($CHCl_3$) 1610 (s), 1500 (s), 1160 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.45 (s, 6 H), 3.83 (dd, 2 H, J = 3.5, 2.1 Hz), 5.93 (dt, 1 H, J = 10, 2.1 Hz), 6.29 (dt, 1 H, J = 10, 3.5 Hz), 7.03 (t, 1 H, J = 7 Hz), 7.19 (d, 2 H, J = 7.5 Hz), 7.31 (dd, 2 H, J = 7.5, 7 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 50.38, 52.07, 112.70, 115.86, 122.69, 125.26, 128.84, 129.33, 150.05; MS m/z (M^+) 221 (24), 158 (20), 130 (18), 114 (100), 99 (24). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.83; H, 6.90; N, 6.10.

6-Hydroxy-4,5-*O*-isopropylidene-*N*-phenyltetrahydro-2*H*-1,2-oxazine (14). To a stirred solution of NMO (1.34 g, 11.4 mmol) in ca. 15 mL of aqueous THF (enough water was added to completely dissolve the NMO) was added a solution of TMS-ether (12) (0.95 g, 3.81 mmol) in 3 mL of THF, followed by 1.2 mL (190 μmol) of a solution (0.157 M) of OsO_4 in THF at room temperature under a N_2 atmosphere. The resulting mixture was stirred for 10 h before diluting with Et_2O and quenching with saturated aqueous $NaHSO_3$. The aqueous layer was removed and extracted several times with Et_2O. The combined organic layer was washed with $NaHSO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in 20 mL of acetone, and excess 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid were added at room temperature. The resulting mixture was stirred for 3 h and concentrated, and the residue was purified by flash column chromatography using (1:1 Et_2O/hex) to give 790 mg (80%) of a colorless solid: mp 63–65 °C; IR ($CHCl_3$) 3580 (w), 3390 (m), 1600 (s), 1500 (s) 1390 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 (s, 3 H), 1.55 (s, 3 H), 3.45–3.68 (m, 3 H), 4.06 (t, 1 H, J = 4.4 Hz), 4.56 (g, 1 H, J = 5.1 Hz), 5.34 (t, 1 H, J = 4.4 Hz), 7.04 (td, 1 H, J= 7.2, 1.1 Hz), 7.14 (d, 2 H, J = 7.6 Hz), 7.26–7.34 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 25.99, 27.74, 55.08, 72.21, 75.40, 97.03, 109.88, 116.70, 123.02, 128.70, 149.53; MS m/z (M^+) 251 (70), 193 (100), 122 (88), 109 (40), 107 (68), 106 (97); high-resolution MS calcd for $C_{13}H_{17}NO_4$ m/e 251.1157, found 251.1174.

3-(*tert*-Butyldiphenylsiloxy)aniline (15): yellow oil; IR ($CHCl_3$) 1600 (m), 1540 (m), 1500 (m), 1220 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.08 (s, 9 H), 3.46 (br s, 2 H), 6.14–6.22 (m, 3 H), 6.84 (t, 1 H, J = 8.1 Hz), 7.31–7.41 (m, 6 H), 7.70–7.73 (m, 4 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.41, 26.54, 106.70, 108.26, 110.17, 127.64, 129.67, 129.72, 133.25, 135.47, 147.47, 156.57. Anal. Calcd for $C_{22}H_{25}NOSi$: C, 76.03; H, 7.25; N, 4.03. Found: C, 76.36; H, 7.28; N, 4.04.

3,6-Dihydro-2*H*-6-methoxy-*N*-[3-(*tert*-butyldiphenylsiloxy)phenyl]-1,2-oxazine (18). To a stirred solution of amine 15 (1.2 g, 4.12 mmol) in 5 mL of CH_2Cl_2 at −23 °C (CCl_4/CO_2) was added Me_2S (318 μL, 4.3 mmol) under a N_2 atmosphere. A solution of NCS (0.58 g, 4.3 mmol) in 30 mL of CH_2Cl_2 was then added dropwise via cannula over ca. 10 min. The reaction was stirred for an additional 40 min (−23 °C), after which 15 mL of 5% NaOH was added. The organic layer was then removed and washed with 15 mL of 5% NaOH and dried over Na_2SO_4. The crude dry filtrate was then poured into an ice-cold solution of 80–85% MCPBA (1.1 g, 5.2 mmol) in 20 mL of CH_2Cl_2. The resulting green solution was stirred for 30 min at 0 °C, poured into saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with Na_2CO_3, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C under a N_2 atmosphere. To this stirred solution was added 0.45 mL, (4.5 mmol) of diene 17. Stirring was discontinued, and the reaction mixture was placed in the refrigerator overnight. The reaction was then concentrated in vacuo, and the residue (~1.6 g) was purified by flash column chromatography (3:7 Et_2O/hex) to yield 700 mg (38%) of light yellow oil: IR ($CHCl_3$) 1600 (s), 1490 (s), 1320 (s), 1115 (s), 980 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (s, 9 H), 3.38 (s, 3 H), 3.46 (br d, 1 H, J = 16.5 Hz), 3.72 (dd, 1 H, J = 16.5, 5.2 Hz), 4.99 (br s, 1 H), 5.87 (br d, 1 H, J = 10 Hz), 6.08 (dd, 1 H, J = 10, 5.2 Hz), 6.44 (dd, 1 H, J = 2.2 Hz), 6.58 (br t, 1 H, J = 2.2 Hz), 6.66 (dd, 1 H, J = 8, 2 Hz), 7.03 (1 H, J = 8 Hz), 7.32–7.42 (m, 6 H), 7.69–7.73 (m, 4 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 19.48, 26.64, 51.20, 55.74, 98.88, 107.77, 108.67, 113.88, 124.97, 127.38, 127.70, 129.25, 129.78, 133.24, 135.55, 151.44, 156.19; MS m/z (M^+) 445 (64), 304 (100), 274 (21); high-resolution MS calcd for $C_{27}H_{31}NO_3Si$

m/e 445.2073, found 445.2099.

3,6-Dihydro-2*H*-6-methoxy-*N*-(3-hydroxyphenyl)-1,2-oxazine (19). To a stirred solution of **18** (314 mg, 0.7 mmol) in 2 mL of dry THF was added TBAF (0.74 mL, 0.74 mmol) as a 1 M solution in THF at 0 °C under a N_2 atmosphere. After being stirred for 5 min the brown reaction mixture was poured in saturated aqueous NH_4Cl and extracted several times with EtOAc, and the combined extracts were dried over $MgSO_4$. Concentration of the organic extracts and purification by flash column chromatography (7:3 Et_2O/hex) gave 140 mg of (95%) **22** as a colorless oil: IR ($CHCl_3$) 3350 (s), 1610 (s), 1500 (s), 1200 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.58 (s, 3 H), 3.61 (dd, 1 H, J = 12.7, 1.7 Hz), 3.89 (dd, 1 H, J = 12.7, 4.9 Hz), 5.12 (br s, 1 H), 5.51 (br s, 1 H), 5.94 (br d, 1 H, J = 10 Hz), 6.13 (ddd, 1 H, J = 10, 4.9, 1.7 Hz), 6.47 (dd, 1 H, J = 8.1, 1.5 Hz), 6.66–6.72 (m, 2 H), 7.14 (t, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 51.32, 55.75, 98.64, 103.19, 107.78, 109.72, 124.19, 127.73, 129.66, 151.52, 156.44; MS *m/z* (M^+) 207 (66), 84 (100); high-resolution MS calcd for $C_{11}H_{13}NO_3$ *m/e* 207.0895, found 207.0891.

4-Methoxy-5-(1*H*-pyrrol-1-yl)phenol (23). To a stirred solution of **19** (45 mg, 0.22 mmol) in MeOH (35 μL, 0.87 mmol) and 2 mL of dry CH_2Cl_2 was added BF_3-Et_2O (29 μL, 0.24 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was warmed to room temperature and stirred for an additional hour before diluting with CH_2Cl_2 and quenching with saturated aqueous $NaHCO_3$. The resulting mixture was decanted from the insoluble black polymeric material coating the reaction vessel and extracted with 2 × 6 mL of CH_2Cl_2. The extracts were washed with 1 × 6 mL of $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 20 mg of a brown oil. Purification by flash column chromatography (4:6 Et_2O/hex) gave 9 mg (20%) of **23** as a colorless foam: IR ($CHCl_3$) 3540 (m), 1520 (s), cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 5.72 (s, 1 H), 6.31 (t, 2 H), 6.87 (d, 2 H), 7.00 (m, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.25, 107.99, 109.89, 111.10, 112.05, 119.59, 135.18, 144.66, 146.25; MS *m/z* (M^+) 189 (100), 174 (36), 146 (28); high-resolution MS calcd for $C_{11}H_{11}NO_2$ *m/e* 189.0789, found 189.0801; NOE, irradiation of the methyl ether protons at δ 3.92 gave a 9% enhancement of the downfield pyrrole protons at δ 7.00.

3,6-Dihydro-2*H*-6-methoxy-*N*-(3-carbomethoxy-5-methoxy-6-methylphenyl)-1,2-oxazine (22). To a stirred solution of amine **20** (0.55 g, 2.83 mmol) in 8 mL of CH_2Cl_2 at −23 °C (CCl_4/CO_2) was added Me_2S (212 μL, 2.88 mmol) under a N_2 atmosphere. A solution of NCS (0.39 g, 2.90 mmol) in 22 mL of CH_2Cl_2 was then added dropwise via cannula over ca. 10 min. The reaction was stirred for an additional 40 min (−23 °C) after which 11 mL of 5% NaOH was added. The organic layer was then removed, washed with 11 mL of 5% NaOH, and dried over Na_2SO_4. The crude dry filtrate was then poured into an ice-cold solution of 80–85% MCPBA (0.74, 3.5 mmol) in 15 mL of CH_2Cl_2. The resulting green solution was stirred for 30 min at 0 °C, poured into saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with Na_2CO_3, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 15 mL of CH_2Cl_2 and cooled to 0 °C under a N_2 atmosphere. To this stirred solution was added (0.37 mL, 3.7 mmol) of diene **17**. Stirring was discontinued, and the reaction mixture was placed in the refrigerator overnight. The reaction was then concentrated in vacuo, and the residue (~1 g) was purified by flash column chromatography (25:75 Et_2O/hex) to yield 370 mg (45%) of light yellow solid: mp 103–105 °C; IR ($CHCl_3$) 1715 (s), 1585 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.27 (s, 2 H), 3.44 (s, 3 H), 3.57 (m, 2 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 5.12 (br s, 1 H), 5.91 (br d, 1 H, J = 10 Hz), 6.17 (br d, 1 H, J = 110 Hz), 7.40 (br s, 1 H), 7.84 (br s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 10.54, 51.74, 52.92, 55.42, 55.62, 99.08, 108.24, 113.96, 124.93, 126.84, 127.96, 128.52, 149.47, 157.90, 166.72; MS *m/e* (M^+) 293 (10), 235 (24), 84 (100); high-resolution MS calcd for $C_{15}H_{19}NO_5$ *m/e* 293.1263, found 293.1271. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.47; H, 6.54; N, 4.72.

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Metalation of Cyclopropane Rings: A Novel Trilithiation of a Biscyclopropyl Carbinol

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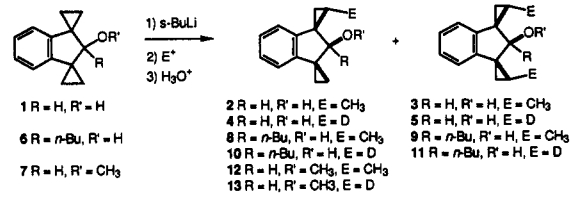
In conjunction with syntheses of systems for radical double clock experiments, we needed a number of ring-substituted biscyclopropylcarbinyl derivatives.[1] The thorough and elegant investigations by Klumpp and coworkers on directed lithiations of cyclopropylcarbinyl alcohols and ethers provides a basis for the efficient regio- and stereocontrolled syntheses of such systems.[2] Application of this approach to the substitution of dispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-2′-ol (**1**) is shown below. We expected the sequence of lithiation and methylation to provide the monomethylated product **2** but found that significant amounts of the dimethylated product **3** were also formed. We report here a brief study of this apparent polylithiation and the lithiations of the related alcohol **6** and the methyl ether **7**.



1 R = H, R' = H
6 R = *n*-Bu, R' = H
7 R = H, R' = CH_3

2 R = H, R' = H, E = CH_3
4 R = H, R' = H, E = D
8 R = *n*-Bu, R' = H, E = CH_3
10 R = *n*-Bu, R' = H, E = D
12 R = H, R' = CH_3, E = CH_3
13 R = H, R' = CH_3, E = D

3 R = H, R' = H, E = CH_3
5 R = H, R' = H, E = D
9 R = *n*-Bu, R' = H, E = CH_3
11 R = *n*-Bu, R' = H, E = D

The alcohol **1** was prepared in 90% yield by lithium aluminum hydride reduction of the known ketone.[3] Treatment of **1** with potassium hydride and methyl iodide provided the methyl ether **7** in 70% yield. The *n*-butyl alcohol **6** was synthesized in 95% yield by addition of *n*-butyllithium to the ketone.

Investigation of the lithiation of **1** provided conditions under which formation of either **2** or **3** could be favored. Treatment of **1** with 3.0 equiv of *sec*-butyllithium (*s*-BuLi) in ether at room temperature for 1 h, followed by addition of excess methyl iodide, provided 59% of the monomethylated product **2** and 15% of the dimethylated product **3**. Treatment of **1** with 6 equiv of *s*-BuLi for 50 h in ether at ~30 °C gave a heterogeneous reaction mixture, which, after reaction with methyl iodide for 12 h, provided 13% **2** and 46% **3**. The products have elemental analyses and ^1H and ^{13}C NMR, IR, and mass spectrometric data consistent with the assigned structures. Determination of the structure of **3** by X-ray diffraction confirms the assignment of the stereochemistry of both methyl groups to be anti to the phenyl ring and syn to the hydroxyl group. The geometry of the products is consistent with a lithium alkoxide directed metalation and retention of cyclopropyl anion configuration as observed in related systems.[2] The formation of disubstituted products tended to be quite variable, which we attribute to the heterogeneous conditions and the relatively slow reaction of methyl iodide.

(1) Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1990**, *55*, 5454.
(2) Klumpp, G. W. *Recl. Trav. Chim. Pay. Bas.* **1986**, *105*, 1 and references therein. For other directed lithiations of cyclopropyl rings, see: Eaton, P. E.; Daniels, R. G.; Cassucci, D.; Cunkle, G. T.; Engel, P. *J. Org. Chem.* **1987**, *52*, 2100 and references therein. For configurational stability of cyclopropyl anions, see: Applequist, D. E.; Peterson, A. H. *J. Am. Chem. Soc.* **1961**, *83*, 862. Motes, J. M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1970**, *92*, 2445.
(3) Klages, C. P.; Voss, J. *Chem. Ber.* **1980**, *113*, 2255.

0022-3263/91/1956-0853$02.50/0