(M^+, 2/3, 7), 231/229 (OCH_3, 2/3, 9), 203/201 (2/3, 2), 175/173 (2/3, base), 147/143 (2/3, 25), 109 (17); HRMS, $C_{11}H_{10}Cl_2O_3$ requires *m/e* 260.0003, found 259.9980.

25: ^1H NMR ($CDCl_3$) δ 7.95 (2 H, d, J = 9 Hz, aromatic), 6.93 (2 H, d, J = 9 Hz, aromatic), 4.18 (2 H, t, J = 6 Hz, CO_2CH_2), 3.86 (3 H, s, OCH_3), 3.77 (2 H, t, J = 6 Hz, CH_2OH), 3.26 (2 H, t, J = 6 Hz, $COCH_2CH_2CO_2$), 2.73 (2 H, t, J = 6 Hz, $COCH_2CH_2CO_2$), 2.2 (1 H, br s, OH), 1.87 (2 H, p, J = 6 Hz, $OCH_2CH_2CH_2O$); IR ($CHCl_3$) ν_{max} 3500 (OH), 1720 (C=O), 1675, 1580, 1508, 1260, 1170, 1035 cm^{-1}; EIMS *m/e* (rel intensity) 266 (M^+, 2), 236 (1), 209 (4), 191 (10), 163 (2) 135 (base, 100); HRMS, $C_{14}H_{18}O_5$ requires *m/e* 266.1153, found 266.1148.

General Procedure for the Preparation of Butenolides: Reaction of *p*-Nitroacetophenone with Cyclopropenone Ketal 1. Method C. Preparation of 20. *p*-Nitroacetophenone (103 mg, 0.625 mmol) and cyclopropenone ketal **1** (140 mg, 1.25 mmol, 2 equiv) were combined in heptane (5 mL), and the resulting suspension was warmed at reflux (12 h). The crude product was concentrated in vacuo and treated with acetic acid–tetrahydrofuran–water (1:3:1) at 25 °C (72 h). Chromatography (SiO_2, ethyl acetate–hexane gradient) afforded 42 mg (137 mg theoretical, 31%) of **20** as a white solid: mp 69 °C; ^1H NMR ($CDCl_3$) δ 8.24 (2 H, d, J = 9 Hz, ArC2–H, ArC6–H), 7.65 (1 H, d, J = 6 Hz, CCH=$CHCO_2$), 7.58 (2 H, d, J = 9 Hz, ArC3–H, ArC5–H), 6.13 (1 H, d, J = 6 Hz, CCH=$CHCO_2$), 1.86 (3 H, s, CH_3); IR ($CHCl_3$) ν_{max} 1780 cm^{-1}; EIMS, *m/e* (rel intensity) 219 (M^+, 5), 204 (CH_3, 100), 177 (61), 176 (83), 160 (16), 158 (19), 150 (18), 146 (23), 130 (33), 102 (32), 76 (53); HRMS, $C_{11}H_9NO_4$ requires *m/e* 219.0531, found 219.0527.

24: ^1H NMR ($CDCl_3$) δ 7.72 (1 H, d, J = 1 Hz, ArC3–H), 7.49 (2 H, m, ArC5–H, ArC6–H), 5.84 (1 H, t, J = 3 Hz, C=CH), 3.46 (2 H, d, J = 3 Hz, C=$CHCH_2$); IR ($CHCl_3$) ν_{max} 3050, 1800 (C=O), 1480, 1395, 1305, 1140, 1005, 1000, 920 cm^{-1}; EIMS, *m/e* (rel intensity) 230/228 (M^+, 2/3, 61), 193 (34), 175/173 (base, 2/3, 100), 165 (72), 149 (15), 147 (28), 145 (31), 109 (31); HRMS, $C_{10}H_6Cl_2O_2$ requires *m/e* 227.9744, found 227.9757.

Acknowledgment. This work was assisted financially by the Searle Scholars Fund and the National Institutes of Health (CA 00898/01134, CA 33668/42056). We thank Prof. G. I. Georg for her contribution to this work (Table II) and for stimulating discussions. We thank Profs. G. E. Keck, D. A. Hart, A. R. Chamberlin, T. A. Engler, A. W. Burgstahler, and R. S. Givens for valuable discussions and suggestions on aspects of this work.

Registry No. 1, 60935-21-9; **2**, 23529-83-1; *cis*-**3a**, 94922-97-1; *trans*-**3a**, 94922-98-2; *cis*-**3b**, 77462-53-4; *trans*-**3b**, 77462-54-5; *cis*-**3c**, 94922-99-3; *trans*-**3c**, 94923-00-9; *cis*-**3d**, 103384-75-4; *trans*-**3d**, 94923-06-5; *cis*-**3e**, 103384-76-5; *trans*-**3e**, 94923-02-1; *cis*-**3f**, 94923-03-2; *trans*-**3f**, 94923-04-3; *cis*-**3g**, 103384-77-6; *trans*-**3g**, 103384-88-9; **3h**, 103384-78-7; **3i**, 103384-79-8; **3j**, 103384-80-1; **4a**, 88442-07-3; **4b**, 88442-08-4; **4c**, 88442-09-5; **4d**, 88442-10-8; **4e**, 88442-11-9; **4f**, 88442-12-0; **4g**, 103422-00-0; *cis*-**4h**, 103384-81-2; *trans*-4h, 103384-89-0; 4i, 88442-05-1; **4j**, 103384-82-3; **4k**, 103384-84-5; **5c**, 103384-86-7; **7a**, 103384-83-4; **7b**, 103384-85-6; **10**, 103384-87-8; **12**, 60935-26-4; **14**, 103384-92-5; **16**, 95652-68-9; **17**, 95652-70-3; **18**, 95652-71-4; **19**, 95652-69-0; **20**, 95652-72-5; **21**, 95652-73-6; **22**, 95652-74-7; **23**, 95652-75-8; **24**, 95609-49-7; **25**, 103384-90-3; **26**, 53774-21-3; **27**, 103384-91-4; CH_2=$CHS(O)Ph$, 20451-53-0; $PhSC(CO_2Et)$=CH_2, 56685-62-2; $PhCH$=$C(CO_2Et)_2$, 5292-53-5; $PhCH$=$C(CO_2Me)_2$, 6626-84-2; CH_3CH=$C(CO_2Et)_2$, 1462-12-0; $PhCH$=$C(CN)_2$, 2700-22-3; $(CH_3)_2C$=$C(CO_2Et)_2$, 6802-75-1; Ph_2C=$C(CO_2Et)_2$, 24824-36-0; $PhS(O)C(CO_2CH_3)$=CH_2, 85908-47-0; CH_2=$C(OCH_3)_2$, 922-69-0; $CH_3(CH_2)_2C$≡CCO_2CH_3, 18937-79-6; CH_3O_2CC≡CCO_2CH_3, 762-42-5; CH_2=$CHCO_2CH_3$, 96-33-3; CH_2=$CHCN$, 107-13-1; $CH_3C(CO_2CH_3)$=CH_2, 80-62-6; CH_2=$C(CN)CH_3$, 126-98-7; $PhC(CO_2Et)$=CH_2, 22286-82-4; (*E*)-CH_3O_2CCH=$CHCO_2CH_3$, 624-49-7; $CH_3O_2CC(CO_2CH_3)$=$CHOCH_3$, 22398-14-7; CH≡CCO_2CH_3, 922-67-8; *p*-$NO_2C_6H_4CHO$, 555-16-8; *p*-$NO_2C_6H_4COCH_3$, 100-19-6; 3,4-$Cl_2C_6H_3CHO$, 6287-38-3; *p*-$CH_3OC_6H_4CHO$, 123-11-5; $PhCOCH_3$, 98-86-2; $EtOCOCOCO_2Et$, 609-09-6; $HO(CH_2)_3OH$, 504-63-2; 2-cyclopenten-1-one, 930-30-3; 1-nitrocyclohexene, 2562-37-0; 2-pyrone, 504-31-4; 6,6-dimethyl-3-carbethoxy-3-norpinen-2-one, 88442-04-0; diethyl cyclohexylidenemalonate, 41589-43-9; cyclohexene, 110-83-8; 3,4-dihydro-2*H*-pyran, 110-87-2; 1-(cyclohexenylmethylene)malonitrile, 103384-73-2; methyl 3-(1-cyclohexenyl)-2-cyano-2-propanoate, 103384-74-3; 5,6,7,8-tetrahydro-3-methoxycarbonyl-2*H*-benzopyran-2-one, 85531-80-2; 3-methoxycarbonyl-2*H*-pyran-2-one, 25991-27-9; 3-methoxycarbonyl-7,10-dimethoxy-9-bromo-2*H*-naphtho[1,2*b*]pyran-2-one, 88442-03-9; 5-methoxycarbonyl-2*H*-pyran-2-one, 6018-41-3; 2-(bromomethyl)-2-(chloromethyl)-1,3-dioxane, 60935-30-0; 1-bromo-3-chloro-2,2-dimethoxypropane, 22089-54-9.

Supplementary Material Available: Figures showing atom numbering and views of **5c**, tables of fractional coordinates, thermal parameters, and bond distances and angles, and a listing of structure factor analysis (16 pages). Ordering information is given on any current masthead page.

Thermal Reactions of Cyclopropenone Ketals. Application of the Cycloaddition Reactions of Delocalized Singlet Vinylcarbenes: Three-Carbon 1,1-/1,3-Dipoles. An Alternative Synthesis of Deacetamidocolchiceine: Formal Total Synthesis of Colchicine

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Abstract: An alternative preparation of deacetamidocolchiceine, constituting a formal total synthesis of colchicine, is detailed and is based on the thermal [3 + 4] cycloaddition of Eschenmoser's α-pyrone with cyclopropenone 1,3-propanediyl ketal in a process which proceeds via the reversible, thermal generation of a delocalized singlet vinylcarbene, a three-carbon 1,1-/1,3-dipole, and its subsequent $_\pi2_s$ participation in a $[_\pi4_s + _\pi2_s]$ cycloaddition.

Colchicine (**1**), a potent mitotic inhibitor which exhibits a characteristic and specific binding with tubulin preventing microtubule assembly, spindle formation, and consequently cell division, has been the focus of initial extensive and subsequent

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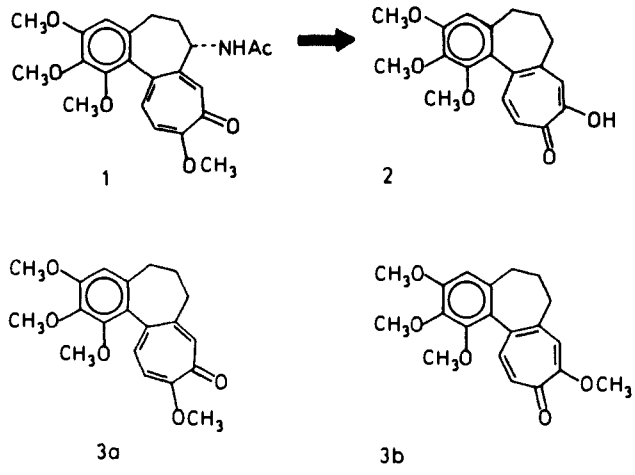
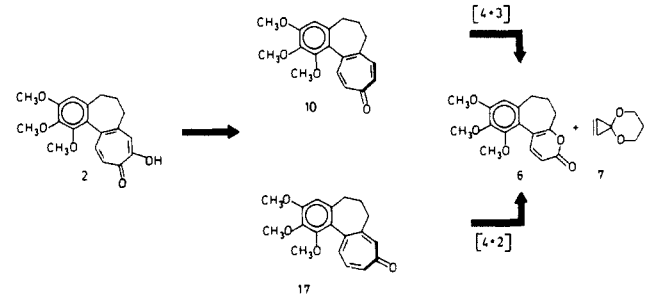
periodic synthetic efforts[2] which have complemented the continuous biochemical investigations.[3] Most recent efforts have focused



on defining the complete spectrum of colchicine's biological properties and include efforts to clearly define its mechanism of cytotoxic and antimitotic action[3,4] as well as continued efforts on the complete exploration of the structural features which affect potency, tubulin binding, or toxicity.[3,5] Despite the interest in such studies, most investigations have been limited to those employing colchicine or derivatives readily prepared from naturally occurring colchicine because of the relative difficulty expectantly encountered in the total syntheses of structurally related tropolones.

Scheme I



In all but three notable instances,[2d,f,k] deacetamidocolchiceine (**2**) or deacetamidoisocolchicine (**3b**) have served as the key intermediates enroute to colchicine. Consequently, most synthetic efforts[2] have relied on the initial work of Eschenmoser[2b] and van Tamelen[2c] for formal completion of a total synthesis of colchicine. The final introduction of the 7-acetamido group required in the conversion of deacetamidocolchiceine (**2**) to colchicine (**1**),[2a,b,6] which requires the intermediacy of deacetamidoisocolchicine (**3b**), has offered the recognized advantage of providing synthetic intermediates including deacetamidocolchicine (**3a**) possessing structures of comparable or more significant interest than that of colchicine itself.[7]

In preceding work[8] designed to investigate and develop the potential utilization of the cycloaddition reactions of cyclopropenone ketals for the preparation of cycloheptatrienones suitable for application in the total synthesis of tropoloalkaloids,[9] we have detailed three approaches to tropolone introduction based on complementary cycloaddition reactions of cyclopropenone ketals with selected electron-deficient dienes: room temperature [4 + 2] cycloaddition with $_{\pi}2_s$ participation of the strained olefin in a $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition or thermal [3 + 4] cycloaddition with $_{\pi}2_s$ participation of an apparent delocalized singlet vinylcarbene in a $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition,[8,10] eq 1.

Herein we provide full details[10] of a simple, alternative preparation of deacetamidocolchiceine (**2**), constituting a formal total

(1) (a) Searle Scholar Recipient, 1981–1985. National Institutes of Health research career development award recipient, 1983–1988 (CA00898). Alfred P. Sloan research fellow, 1985–1989. Correspondence regarding this work should be addressed to this author at: Department of Chemistry, Purdue University, West Lafayette, IN 47907. (b) National Institutes of Health predoctoral fellow, 1981–1984 (GM 07775).

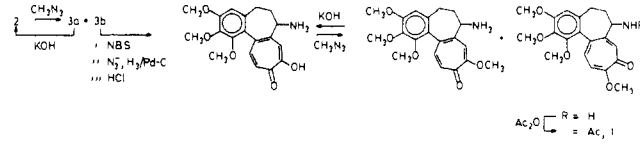
(2) Structure determination: (a) Dewar, M. J. S. *Nature (London)* **1955**, *155*, 141. Total synthesis: (b) Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Threlfall, T.; Eschenmoser, A. *Helv. Chim. Acta* **1961**, *44*, 540. (c) van Tamelen, E. E.; Spencer, T. A.; Allen, D. S.; Orvis, R. L. *Tetrahedron* **1961**, *14*, 8. (d) Sunagawa, G.; Nakamura, T.; Nakazawa, J. *Chem. Pharm. Bull.* **1962**, *10*, 291. Nakamura, T. *Chem. Pharm. Bull.* **1962**, *10*, 299. (e) Scott, A. I.; McCapra, F.; Buchanan, R. L.; Day, A. C.; Young, D. W. *Tetrahedron* **1965**, *21*, 3605. Scott, A. I.; McCapra, E.; Nabney, J.; Young, D. W.; Day, A. C.; Baker, A. J.; Davidson, T. A. *J. Am. Chem. Soc.* **1963**, *85*, 3040. (f) Woodward, R. B. *Harvey Lect.* **1963**, 31. (g) Martel, J.; Toromanoff, E.; Huynh, C. *J. Org. Chem.* **1965**, *30*, 1752. (h) Matsui, M.; Yamashita, K.; Mori, K.; Kaneko, S. *Agric. Biol. Chem.* **1967**, *31*, 675. Kaneko, S.; Matsui, M. *Agric. Biol. Chem.* **1968**, *32*, 995. (i) Kato, M.; Kido, F.; Wu, M. D.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1516. (j) Kotani, E.; Miyazaki, F.; Tobinaga, S. *J. Chem. Soc., Chem. Commun.* **1974**, 300. Tobinaga, S. *Bioorg. Chem.* **1975**, *4*, 110. (k) Evans, D. A.; Hart, D. J.; Koelsch, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 4593. Evans, D. A.; Tanis, S. P.; Hart, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 5813. (l) For resolution methods in the conversion of deacetamidocolchiceine (**2b**) to colchicine with resolution of deacetylcolchiceine: Corrodi, H.; Hardegger, E. *Helv. Chim. Acta* **1957**, *40*, 193.

(3) For a recent review, see: Capraro, H.-G.; Brossi, A. *The Alkaloids*; Brossi, A., Ed.; Academic: Orlando, FL, 1984; Vol. 23, pp 1–70.

(4) For recent work, see: (a) Ito, S. In *Natural Products Chemistry*; Nakanishi, K. et al., Eds.; Academic: New York, 1975; Vol. 2, p 255. (b) Olmsted, J. B.; Borisy, G. G. *Annu. Rev. Biochem.* **1973**, *42*, 507. Zweig, M. H.; Chignell, C. F. *Biochem. Pharmacol.* **1973**, *22*, 2141. (c) Naidus, R. M.; Rodvein, R.; Mielke, H. *Arch. Intern. Med.* **1977**, *137*, 394. (d) Dustin, P. *Microtubules*; Springer-Verlag: New York, 1978. Garland, D. L. *Biochemistry* **1978**, *17*, 4266. Schiff, P. B.; Horwitz, S. B. *Biochemistry* **1981**, *20*, 3247. Detrich, H. W., III; Williams, R. C., Jr.; Wilson, L. *Biochemistry* **1982**, *21*, 2392. Pantaloni, D.; Carlier, M. F.; Simon, C.; Batelier, G. *Biochemistry* **1981**, *20*, 4709. Banerjee, A.; Banerjee, A. C.; Bhattacharyya, B. *FEBS Lett.* **1981**, *124*, 285. Roberts, K.; Hyams, J. S. *Microtubules*, Academic: New York, 1979. Sternlicht, H.; Ringel, I.; Szasz, J. *Biophys. J.* **1983**, *42*, 255.

(5) Quinn, F. R.; Beisler, J. A. *J. Med. Chem.* **1981**, *24*, 251. Schindler, R. *J. Pharmacol. Exp. Theor.* **1965**, *149*, 409. Lettre, H.; Fitzgerald, T. J.; Siebs, W. *Naturwissenschaften* **1966**, *53*, 132. Fitzgerald, T. J.; Williams, B.; Uyeki, E. M. *Pharmacology* **1971**, 265. Fitzgerald, T. J.; Williams, B.; Uyeki, E. M. *Proc. Soc. Exp. Biol. Med.* **1971**, 115. Fitzgerald, T. J. *Biochem. Pharmacol.* **1976**, *25*, 1383. Ray, K.; Bhattacharyya, B.; Biswas, B. B. *J. Biol. Chem.* **1981**, *256*, 6241. Cortese, F.; Bhattacharyya, B.; Wolff, J. *J. Biol. Chem.* **1977**, *252*, 1134. Choudhury, G. G.; Banerjee, A.; Bhattacharyya, B.; Biswas, B. B. *FEBS Lett.* **1983**, *161*, 55.

(6) The conversion of deacetamidocolchiceine (**2**) to (±)-colchicine (**1**) as detailed by Eschenmoser[2b] and van Tamelen[2c] is summarized below.

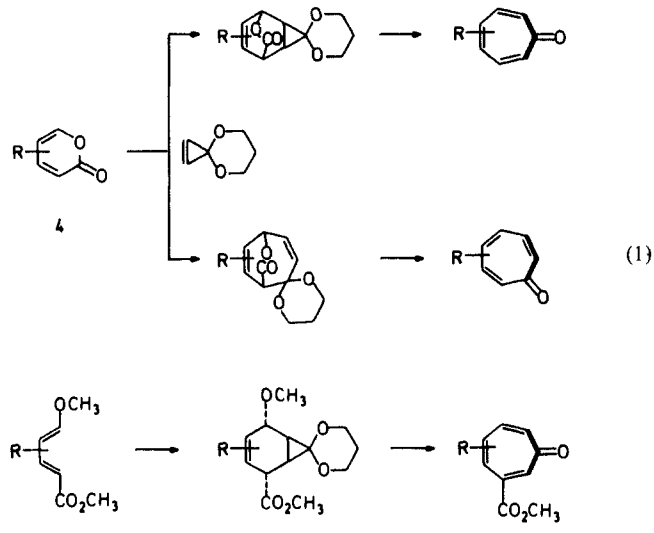


(7) Among the derivatives prepared to date, deacetamidocolchicine (**3a**) and colchicide have proven especially interesting. Deacetamidocolchicine (**3a**) has been shown to be approximately 10 times as potent as colchicine in vitro against P-815-X2 mast cell tumors (cf.: Schindler, R. *Nature (London)* **1962**, *196*, 73) though its efficacy in vivo is less pronounced than that of colchicine. Colchicide (10-demethoxycolchicine), which lacks the methoxy group once thought essential for activity, has proven to be slightly less active in vivo than colchicine (P388 T/C = 140 at 9.2 μmol/kg vs. 0.4 μmol/kg), exhibits essentially equal or comparable specific binding to tubulin as colchicine, and is substantially less toxic than colchicine (LD_{50} = 169 μmol/kg vs. 3 μmol/kg). For this and related information, see ref 3 and 5 and work cited therein.

(8) (a) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.*, preceding paper in this issue. (b) Boger, D. L.; Brotherton, C. E., unpublished observations. (c) Boger, D. L.; Brotherton, C. E. *Tetrahedron* **1986**, *42*, 2777. For related work, see: (d) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805. (e) Boger, D. L.; Brotherton, C. E. *Tetrahedron Lett.* **1984**, *25*, 5611. (f) Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Tetrahedron Lett.* **1984**, *25*, 5615. (g) For the preparation of cyclopropenone 1,3-propanediyl ketal **7**, see: Butler, G. B.; Herring, K. H.; Lewis, P. L.; Sharpe, V. V.; Veazey, R. L. *J. Org. Chem.* **1977**, *42*, 679. Boger, D. L.; Brotherton, C. E.; Georg, G. I. *Org. Synth.*, in press.

(9) Tropoloalkaloids include (a) colchicine and its related congeners (Capraro, H. G. *The Alkaloids*; Academic: Orlando, FL, 1984; Vol. 23, pp 1–70), (b) imerubrine and grandirubrine (Buck, K. T. *The Alkaloids*; Academic: Orlando, FL, 1984; Vol. 23, pp 301–325), and (c) rubrolone (Palleroni, N. J.; Reichelt, K. E.; Mueller, D.; Epps, R.; Tabenkin, B.; Bull, D. N.; Schuep, W.; Berger, J. *J. Antibiot.* **1978**, *31*, 1218. Schuep, W.; Blount, J. F.; Williams, T. H.; Stempe, A. *J. Antibiot.* **1978**, *31*, 1226).

(10) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.* **1985**, *50*, 3425.

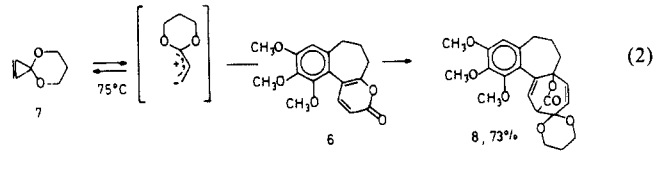


synthesis of colchicine, which is based on the implementation of the three-carbon plus four-carbon cycloaddition of the cyclopropenone ketal **7** with Eschenmoser's α-pyrone **6** in a process proceeding via the reversible, thermal generation and subsequent $_{\pi}2_s$ participation of a delocalized singlet vinylcarbene, a three-carbon 1,1-/1,3-dipole, in a $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition. The deliberate decision to utilize deacetamidocolchiceine (**2**) enroute to colchicine in initial studies was based on the potential opportunities that this strategy presents for the preparation of recognized, e.g., deacetamidocolchicine (**3a**), as well as potential, new agents of biological significance, e.g., deacetamidoisocolchicide.[3,7]

Additional efforts on the development of a complementary approach to the preparation of deacetamidocolchiceine (**2**) based on the implementation of a room-temperature, pressure-promoted [4 + 2] Diels–Alder cycloaddition[8b,c] of Eschenmoser's α-pyrone **6** with the cyclopropenone ketal **7** with $_{\pi}2_s$ participation of the strained olefin in a $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition are detailed, Scheme I.

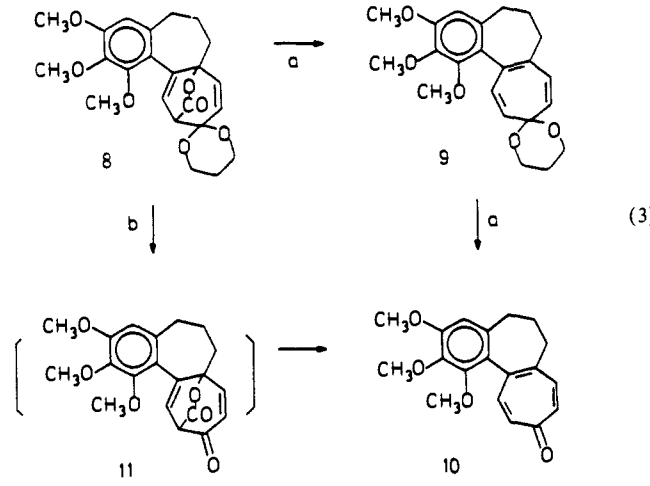
Results and Discussion

Thermal [3 + 4] Cycloaddition of Eschenmoser's α-Pyrone 6 with Cyclopropenone Ketal 7. $[_{\pi}4_s + _{\pi}2_s]$ Cycloaddition with $_{\pi}2_s$ Participation of a Delocalized Singlet Vinylcarbene. Preparation of Deacetamidocolchiceine (Formal Total Synthesis of Colchicine). Treatment of Eschenmoser's α-pyrone **6**[2b] with the cyclopropenone ketal **7**[8g] (2–3 equiv, 75 °C, 21–36 h, benzene) afforded the expected bicyclolactone **8** (73%) as the only significant reaction product[11] and thus represents an effective trap of the apparent, transient delocalized singlet vinylcarbene, eq 2. The basis for



the expectant observation of [3 + 4] cycloadduct **8** in the thermal reaction of α-pyrone **6** with **7** rests with the preliminary observation that the delocalized singlet vinylcarbene derived from cyclopropenone ketal **7** effectively participates as the $_{\pi}2_s$ component of a thermal $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition with α-pyrone.[8a,b] As with α-pyrone, the potential participation of the cyclopropenone ketal **7** in a competing [4 + 2] Diels–Alder reaction with the α-pyrone **6** is decelerated by unfavorable steric interactions which hinder the preferred exo as well as the potential endo transition state required of the [4 + 2]-cycloaddition reaction.[8a–c] This deceleration of the [4 + 2] cycloaddition allows for the observed and effective participation of the α-pyrone **6** in a thermal [3 + 4] cycloaddition with the cyciopropenone ketal 7 which proceeds via the reversible, thermal generation and subsequent $_{\pi}2_s$ participation of a delocalized singlet vinylcarbene in a $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition.[8a]

Expectant efforts to promote the decarboxylation of **8** to provide the cycloheptatrienone ketal **9** were successful although the decarboxylation reaction required selected conditions[12] for isolation and confirmation of the labile ketal, eq 3. Hydrolysis of **9**, which



(a) 210 °C, neat, 2–3 min (**8** to **9**); HOAc–THF–H_2O, 25 °C, 5 min, 60% overall.
(b) HOAc–THF–H_2O (6:5:2), 100 °C, 3.5 h, 70%.

occurred upon attempted chromatographic purification of **9** or upon mild aqueous acid treatment, provided **10** (60% from **8**). Alternatively and more conveniently, warm aqueous acid treatment of **8**, which proceeds with initial ketal hydrolysis and is followed by a subsequent thermal decarboxylation, provided the tropone **10**, deacetamidoisocolchicide, in an excellent direct conversion (70%). The expected intermediacy of the bicyclolactone **11** was anticipated on the basis of the related observations made in initial investigations[8a] and was demonstrated unambiguously by the isolation of **11** and its subsequent thermal conversion to tropone **10**.[13]

Introduction of the additional ring C hydroxyl group required for the conversion of tropone **10** to deacetamidocolchiceine (**2**) was accomplished via deacetamidoisocolchiceinamide (**12a**), employing existing protocols.[14] Treatment of **10** with hydrazine (EtOH, 0–25 °C) afforded deacetamidoisocolchiceinamide (**12a**, 53–54%)[14d] and the isomeric 11-aminotropone (**12b**, 37–46%),[14d] which were readily separated and independently characterized,[15] eq 4. Independent, basic hydrolysis of **12a** and **12b** provided exclusively deacetamidocolchiceine (**2**) and the isomeric tropolone

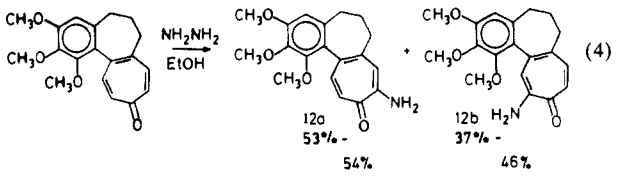
(11) Trace amounts (>5%) of the Diels–Alder [4 + 2] cycloadduct *exo*-**14** could be isolated in the thermal reaction of cyclopropenone ketal **7** with α-pyrone 6.

(12) Efforts to promote the thermal decarboxylation of **8** in solution were unsuccessful.

(13) The selective ketal hydrolysis of **8** under mildly acidic conditions without hydrolysis of the lactone and the ease with which **11** undergoes decarboxylation (110 °C, 1.5 h) as compared to **8** (210 °C) were anticipated on the basis of the analogous results previously detailed[8a] with the [3 + 4] cycloadduct derived from α-pyrone and cyclopropenone ketal **7**.

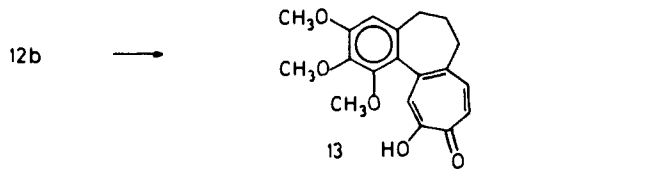
(14) (a) Takaya, H.; Hayakawa, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1778. (b) For the original preparation of α-aminotropones from tropones, see: Nozoe, T.; Seto, H.; Mukai, T.; Kitahara, Y. Japan Patent 5924, 1957; *Chem. Abstr.* **1958**, *52*, P11944d. (c) For similar transformations of isocolchiceinamide to colchiceine, see: Zeisel, S. *Monatsh. Chem.* **1888**, *9*, 1. Horowitz, R. M.; Ullyot, G. E. *J. Am. Chem. Soc.* **1952**, *74*, 587. (d) The reaction of tropone **10** with hydrazine under a range of conditions provided a 3:2 mixture of deacetamidoisocolchiceinamide (**12a**)–11-aminotropone **12b**.

(15) (a) Deacetamidocolchiceine (**2**) displays physical (mp[2b]) and spectroscopic [IR (published),[2b] UV[2b,2c]] properties identical with those previously reported. 11-Hydroxytropone **13** and deacetamidoisocolchiceinamide (**12a**) display spectroscopic [IR (published),[2b] UV[2b]] properties identical with those previously reported. (b) For the X-ray crystal structure of deacetamidocolchiceine, see: Rius, J.; Molins, E.; Miravitlles, C.; Blade-Font, A. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1984**, *C40*, 839.

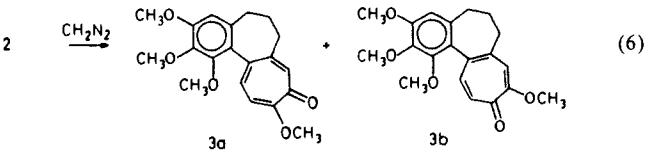


(4)

13, respectively, uncontaminated with isomeric hydrolysis products, eq 5.[2b] The conversion of 11-hydroxytropone **13** to deacetamidocolchiceine (**2**) via deacetamidoisocolchiceinamide (**12a**) as employed in Eschenmoser's total synthesis of colchicine allows the effective conversion of tropone **10** to deacetamidocolchiceine (**2**) from either **12a** or **12b**. Diazomethane methylation of deacetamidocolchiceine (**2**) provided deacetamidocolchicine (**3a**) and deacetamidoisocolchicine (**3b**) as previously described, eq 6.[2b] Deacetamidocolchiceine (**2**), deacetamidoisocolchiceinamide (**12a**), 11-hydroxytropone **13**, deacetamidoisocolchicine (**3b**), and deacetamidocolchicine (**3a**) displayed physical and spectroscopic properties identical in all respects with those previously disclosed.[2b,15]

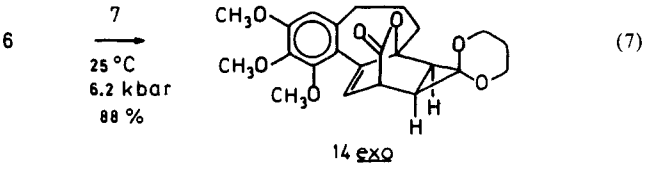


(5)



(6)

Pressure-Promoted, Room-Temperature [4 + 2] Cycloaddition of α-Pyrone 6 with Cyclopropenone Ketal. Attempted Preparation of Deacetamidocolchicide. Efforts to develop a complementary preparation of deacetamidocolchiceine from Eschenmoser's α-pyrone **6** by an expectantly straightforward process which proceeds with [4 + 2] cycloaddition of the cyclopropenone ketal **7** with the electron-deficient diene **6** followed by loss of carbon dioxide and subsequent electrocyclic rearrangement of the resultant norcaradiene providing deacetamidocolchicide 1,3-propanediyl ketal (**16**) proved more difficult than anticipated, Scheme II. Diels–Alder [4 + 2] cycloaddition of the cyclopropenone ketal **7** with the α-pyrone **6** was successfully conducted under modest pressure-promoted Diels–Alder conditions (6.2 kbar, 25 °C) and provided exclusively the exo cycloadduct, *exo*-**14** (88%), eq 7.



(7)

Table I summarizes representative results of a study of this [4 + 2] cycloaddition which proved ineffective at atmospheric pressure (25 °C). The [4 + 2] cycloaddition of α-pyrones with the cyclopropenone ketal **7** is decelerated by unfavorable steric interactions necessarily present in the preferred exo or potential endo transition state of the Diels–Alder reaction. The use of pressure-promoted Diels–Alder reaction conditions[16] (6.2 kbar, 25 °C) provided the necessary acceleration for observable and useful [4 + 2] cycloaddition and represents potentially an exclusive method for promoting the reaction.[17]

Scheme II

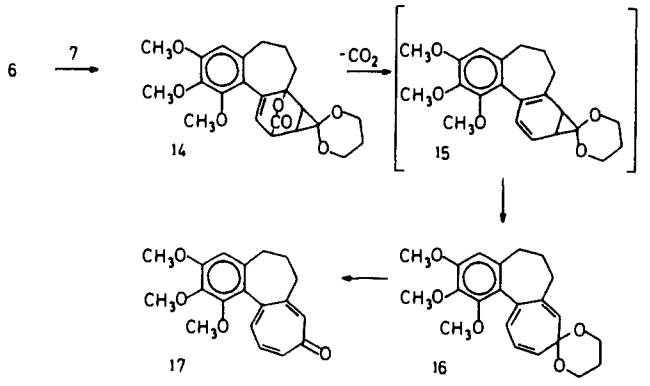


Table I. Diels–Alder Reaction of Eschenmoser's α-Pyrone 6 with Cyclopropenone 1,3-Propanediyl Ketal 7

conditions[a]	yield[b] of *exo*-14
96 h, neat, 25 °C (1 atm)	0%
240 h, neat, 25 °C (1 atm)	5%
24 h, neat, 25 °C (6.2 kbar)	33%
65 h, neat, 25 °C (6.2 kbar)	56%
108 h, neat, 25 °C (6.2 kbar)	88%

[a] All reactions were conducted as described in the Experimental Section employing 2.0 equiv of cyclopropenone ketal **7**. [b] All yields are based on isolated product purified by chromatography (SiO_2).

The [4 + 2] cycloadduct *exo*-**14** proved unexpectantly resistant to decarboxylation, and initial efforts to promote the conversion of *exo*-**14** to the desired deacetamidocolchicide (**17**) via the cycloheptatrienone ketal **16** have been unsuccessful. Attempts to promote the thermal decarboxylation of *exo*-**14** at modest temepratures (80–160 °C) provided recovered unchanged starting material, and this result is consistent with our prior observations on the thermal stability of the exo [4 + 2] cycloadducts derived from the cyclopropenone ketal **7** and α-pyrones.[8c,18] Under more vigorous thermal conditions (200–220 °C), the [4 + 2] cycloadduct *exo*-**14** provided the allocolchicine derivative **18**[19] possessing an unsubstituted benzenoid C ring indicating that decarboxylation could be thermally effected but without the detection or isolation of the desired cycloheptatrienone ketal **16** or its hydrolysis product deacetamidocolchicide (**17**), eq 8 (Chart I). The thermal conditions necessary to promote decarboxylation of *exo*-**14** proved sufficient to further promote the apparent expulsion of the stabilized singlet carbene i from the norcaradiene intermediate **15**, providing **18** competitive with the thermal generation of **15**.[19]

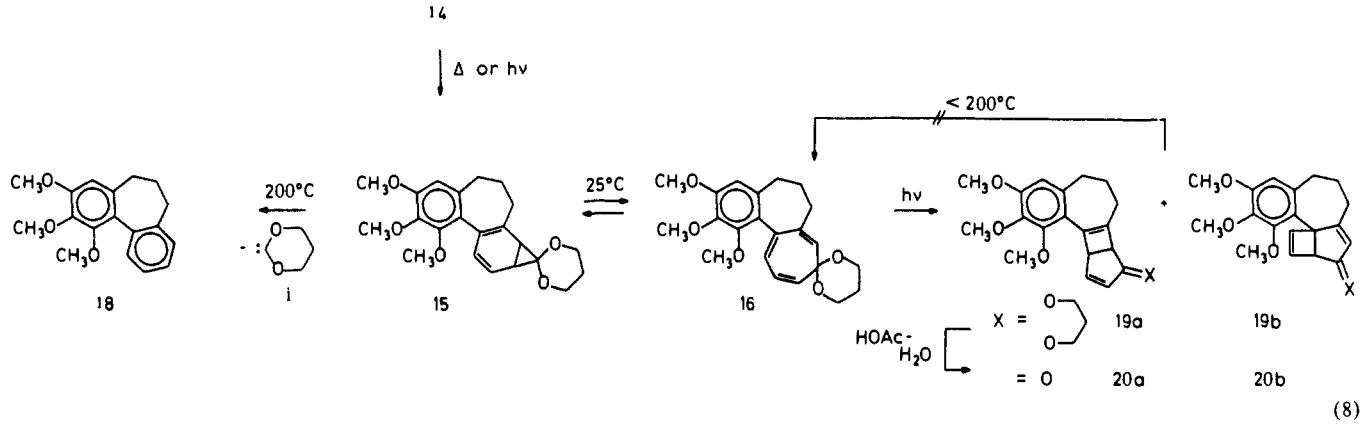
(16) For recent reviews, see: Asano, T.; le Noble, W. J. *Chem. Rev.* **1978**, *78*, 407. le Noble, W. J.; Kelm, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 841. Matsumoto, K. *Heterocycles* **1981**, *16*, 1367. Isaacs, N. S. *Liquid Phase High Pressure Chemistry*; Wiley-Interscience: New York, 1981. Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1. The pressure-promoted Diels–Alder reactions were carried out in a AGP-10002 pressure generator manufactured by Leco Corp., Tem-Press Division, Bellefonte, PA 16823. The unit has been described: DeShong, P.; Dicken, C. M.; Perez, J. J.; Shoff, R. M. *Org. Prep. Proced. Int.* **1982**, *14*, 369.

(17) Efforts to promote or accelerate the [4 + 2]-cycloaddition reactions of the cyclopropenone ketal **7** with the addition of conventional Lewis acids or radical cation catalysts have not been successful,[8c] and the thermal reaction of **7** with Eschenmoser's α-pyrone **6** provides the [3 + 4] cycloadduct. Thus, the use of pressure-promoted Diels–Alder conditions for accelerating the rate of [4 + 2] cycloaddition of **7** with **6** may represent an exclusive solution. Efforts to induce cyclopropenone to participate in a [4 + 2] cycloaddition with Eschenmoser's α-pyrone **6** (25 °C, 6.2 kbar, 60 h, CH_2Cl_2) provided recovered unchanged starting materials.

(18) Thermolysis of *exo*-**14** under mild conditions failed to promote decarboxylation [80 °C (2 h); 120 °C (2 h), toluene; 150 °C (4 h), mesitylene; recovered starting *exo*-**14** and provided **18** (200 °C, mesitylene, 50 min, 47%) without the detection of **16**/**17**.

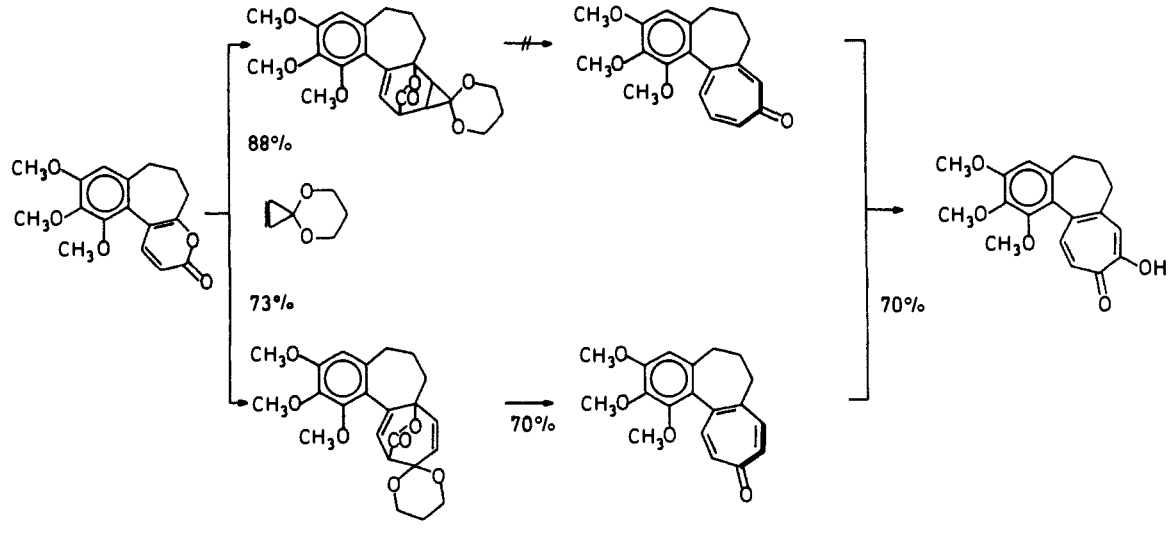
(19) Thermolysis of *exo*-**14** (200 °C, mesitylene, 50 min) provided **18** without the detection of **16**/**17**.

Chart I



(8)

Chart II



(9)

In attempts to avoid the problematic thermal decarboxylation, a photochemical-promoted decarboxylation[20] was investigated and proved similarly unsuccessful at providing the desired cycloheptatrienone ketal **16**. Irradiation (310 nm, 25 °C, 2–12 h, 25 °C) of *exo*-**14** provided the photoproducts **19a** and **19b** (6–9:1)[21] without the detection of the apparent desired intermediate cycloheptatrienone ketal **16**, eq 8. Again, decarboxylation of *exo*-**14** was proceeding under conditions in which the desired cycloheptatrienone ketal **16** was further participating in a well-precedented photochemical electrocyclic reaction[22] which proved competitive with the photochemical generation of the cycloheptatrienone ketal **16** itself. Subsequent efforts to thermally reverse the photochemical electrocyclic ring closure by subjecting the photoproduct **19a** or the corresponding parent ketone **20a**[23] to modest thermolysis conditions (80–200 °C) provided recovered starting materials. Since more vigorous thermal conditions apparently required for effecting the electrocyclic conversion of **19**/**20** to the cycloheptatriene **16**/**17** would prove sufficient to promote the thermal expulsion of the stabilized singlet carbene i from the equilibrating norcaradiene **15**, these efforts were discontinued.

Additional efforts to promote the decarboxylation of *exo*-**14** with the aid of acid catalysis, Lewis acid catalysis, or radical cation catalysis proved similarly unsuccessful.[24]

Conclusion

The successful alternative preparation of deacetamidocolchiceine (**2**), constituting a formal total synthesis of colchicine, based on the implementation of a thermal [3 + 4] cycloaddition of Eschenmoser's α-pyrone with the delocalized singlet vinylcarbene, a three-carbon 1,1-/1,3-dipole, thermally derived from cyclopropenone 1,3-propanediyl ketal (eq 9, Chart II), effectively illustrates the synthetic potential of such processes. Additional studies on the scope and application of the thermal reactions of delocalized singlet vinylcarbenes are in progress.

Experimental Section[25]

6,7-Dihydro-9,10,11-trimethoxybenzo[3,4]cyclohepta[1,2-*b*]pyran-3-(5*H*)-one (6). α-Pyrone 6[2b]: white solid, mp 110–112 °C [lit.[26] mp 112 °C, yellow solid]; ^{1}H NMR ($CDCl_3$) δ 7.55 (1 H, d, J = 10 Hz, *CH*=$CHCO_2$), 6.59 (1 H, s, aromatic), 6.24 (1 H, d, J = 10 Hz, CH=*CH*CO_2), 3.88 (6 H, s, two OCH_3), 3.75 (3 H, s, OCH_3), 2.46 (6 H, m, $CH_2CH_2CH_2$); IR ($CHCl_3$) ν_{max} 3013, 2941, 1718 (C=O), 1598, 1542, 1493, 1465, 1459, 1405, 1347, 1305, 1246, 1124, 1079 cm^{-1}.

(20) For a recent review on the photoextrusion of small molecules, see: Givens, R. S. *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1981; Vol. 5, p 227.

(21) For early explorations of the colchicine tropolone/cycloheptatriene photochemical electrocyclic reactions, see: Grewe, R. *Naturwissenschaften* **1946**, *33*, 187. Grewe, R.; Wulf, W. *Chem. Ber.* **1951**, *84*, 621. Santavy, F. *Collect. Czech. Chem. Commun.* **1951**, *16*, 655. Schenck, G. O.; Kuhn, H. J.; Neumuller, O. A. *Tetrahedron Lett.* **1961**, 12. Forbes, E. J. *J. Chem. Soc.* **1955**, 3864. Gardner, P. D.; Brandon, R. L.; Haynes, G. R. *J. Am. Chem. Soc.* **1957**, *79*, 6334. Chapman, O. L.; Smith, G. H.; King, R. W. *J. Am. Chem. Soc.* **1963**, *85*, 803, 806; **1961**, *83*, 3914. For isocolchicine, see: Dauben, W. G.; Cox, D. A. *J. Am. Chem. Soc.* **1963**, *85*, 2130. Chapman, O. L.; Smith, H. G.; Barks, P. A. *J. Am. Chem. Soc.* **1963**, *85*, 3171.

(22) Singh, S. P.; Stenberg, V. I.; Parmar, S. S. *Chem. Rev.* **1980**, *80*, 269 and references cited therein.

(23) Otterbacher, E. W.; Gajewski, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 5862.

(24) Unsuccessful efforts include the treatment of *exo*-**14** with $(BrC_6H_4)_3NSbCl_6$ (−78–25 °C, 1 h; 25 °C, 2 h, CH_2Cl_2, 0%), BF_3OEt_2 (−78–25 °C, CH_2Cl_2, 1 h, 0%), and $Cu(BF_4)_2$ (25 °C, 2 h; 60 °C, 48 h, THF, no reaction). For the utilization of $(BrC_6H_4)_3NSbCl_6$ as a catalyst in Diels–Alder reactions, see: Bellville, D. J.; Wirth, D. D.; Bauld, N. L. *J. Am. Chem. Soc.* **1981**, *103*, 718.

(25) General descriptions of experimental procedures, techniques, reagents, and instrumentation have been provided in the preceding paper in this issue.

Table II. Direct Conversion of **8** to Tropone **10**

conditions[a]	recovered **8**	tropone **10**
60 °C (15 h)	95–100%	trace
80 °C (19 h)	29%	40%
100 °C (2 h)	trace	68%
100 °C (3.5 h)	0%	70%

[a] The reaction was conducted in THF–HOAc–H_2O (5:6:2) as described above.

Thermal [3 + 4]-Cycloaddition Reaction of α-Pyrone 6 with 7. Preparation of 6′,7′-Dihydro-13′-oxo-1′,2′,3′-trimethoxyspiro[1,3-dioxane-2,10′(5′*H*)-[7a,11](epoxymethano)benzo[*a*]heptalene] (8). α-Pyrone **6** (63 mg, 0.209 mmol) in dry benzene (1 mL) under argon was treated with cyclopropenone ketal **7** (90 mg, 0.80 mmol, 3.8 equiv), and the resulting solution was warmed at 75 °C for 36 h. Chromatography (SiO_2, 50% ethyl acetate–hexane eluant) afforded 63.5 mg (73%) of pure **8** as a white, crystalline solid: mp 207–208 °C (with loss of CO_2); ^{1}H NMR ($CDCl_3$) δ 6.50 (1 H, s, aromatic), 6.02 (1 H, d, J = 7 Hz, CC*H*CH), 5.92 (1 H, d, J = 11 Hz, *CH*=CHC$(OCH_2)_2$), 5.75 (1 H, dd, $J_{8,9}$ = 11, $J_{9,11}$ = 2 Hz, CH=*CH*C$(OCH_2)_2$), 4.25 (5 H, m, *CH*CO_2 and O*CH*$_2$CH$_2$*CH*$_2$O), 3.85 (6 H, s, two OCH_3), 3.70 (3 H, s, OCH_3), 2.50 (2 H, m, $ArCH_2$), 1.80 (6 H, m, $OCH_2CH_2CH_2O$ and $ArCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 170.8 (s, C=O), 153.3, 151.1, and 145.6 (three s, three aromatic *C*OCH_3), 141.0 (s, aromatic C), 137.1 (d, *C*H=CHC$(OCH_2)_2$), 134.3 (s, aromatic C), 128.7 (d, CH=*C*HC-$(OCH_2)_2$), 123.4 (d, C=*C*HCH), 122.3 (s, *C*=CHCH), 107.8 (d, aromatic *C*H), 91.7 (s, OCO), 79.8 (s, CH_2COC=O), 62.2 (q, OCH_3), 61.0 (q, OCH_3), 60.4 and 59.7 (two t, O*CH*$_2$CH$_2$*CH*$_2$O), 56.0 (q, OCH_3), 48.9 (d, *C*HCO_2), 33.0 and 30.6 (two t, Ar*CH*$_2$CH$_2$*CH*$_2$), 24.8 (t, $OCH_2CH_2CH_2O$), 19.6 (t, $ArCH_2CH_2$); IR ($CHCl_3$) ν_{max} 3013, 2959, 2940, 1738 (C=O), 1597, 1485, 1466, 1410, 1331, 1316, 1244, 1138, 1105 cm^{-1}; EIMS, *m/e* (rel intensity) 414 (M^+, 20), 386 (27), 383 (11), 370 (11), 355 (19), 312 (34), 243 (26), 165 (47), 140 (83), 112 (74); HRMS, $C_{23}H_{26}O_7$ requires *m/e* 414.1677, found 414.1689. Anal. Calcd for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.51; H, 6.30.

6,7-Dihydro-1,2,3-trimethoxybenzo[*a*]heptalen-10(5*H*)-one (10). Direct Conversion of 8 to Tropone 10 (Table II). A solution of the [3 + 4] cycloadduct **8** (72.2 mg, 0.174 mmol) in dry tetrahydrofuran (5 mL) was treated with 3:1 acetic acid–water (8 mL), and the resulting solution was warmed at 100 °C under nitrogen for 3.5 h. After cooling to 25 °C, the reaction mixture was diluted with methylene chloride, neutralized with 10% aqueous sodium bicarbonate, and extracted with methylene chloride (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 1.5 × 20 cm, 75% ethyl acetate–hexane eluant) afforded 37.8 mg (70%) of pure **10** as a white solid: mp 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 and 7.16 (two d, J = 12 Hz, 1 H each, C8–H and C12–H), 7.02 (1 H, dd, $J_{11,12}$ = 12, $J_{11,9}$ = 3 Hz, C_{11}–H), 6.92 (1 H, dd, $J_{8,9}$ = 12, $J_{9,11}$ = 3 Hz, C9–H), 6.56 (1 H, s, C4–H), 3.91, 3.90, and 3.71 (three s, 3 H each, OCH_3), 2.25 (m, 6 H, C5–H_2, C6–H_2, and C7–H_2); ^{13}C NMR ($CDCl_3$) δ 187.1 (s, C10), 153.7 (s, C3), 150.6 (s, C1), 145.8 (s, C7a), 142.3 (s, C2), 141.6 (d, C12), 140.9 (s, C12a), 140.6 (d, C8), 140.2 (d, C9), 137.7 (d, C11), 135.6 (s, C4a), 126.7 (s, C1a), 107.4 (d, C4), 61.1, 61.0, and 56.0 (three q, C1–OCH_3, C2–OCH_3, and C3-OCH_3), 35.9, 33.3, and 30.9 (three t, C5, C6, and C7); UV (EtOH) λ_{max} 232 (ε 28 600), 321 (ε 13 850) nm; IR (film) ν_{max} 2935, 2855, 1734 and 1624 (C=O), 1594, 1570, 1493, 1456, 1403, 1349, 1320, 1240, 1195, 1133, 1097, 1030 cm^{-1}; EIMS, *m/e* (rel intensity) 312 (M^+, 61), 285 (15), 284 (—CO, 100), 269 (26), 253 (11), 241 (17), 238 (36), 223 (18), 222 (21), 211 (25), 210 (20), 209 (34), 195 (28), 194 (36), 181 (31), 179 (21), 178 (27), 168 (21), 166 (34), 165 (69), 155 (54), 153 (61), 152 (74), 139 (42), 129 (35), 128 (38), 127 (45), 115 (73), 76 (79); HRMS, $C_{19}H_{20}O_4$ requires *m/e* 312.1360, found 312.1356.

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.80; H, 6.51.

Treatment of **8** with mild aqueous acid [5% aqueous H_2SO_4–dioxane (1:1), 25 °C, 15 h] provided a mixture of recovered **8** (90%) and **11** (10%) with no detectable **10**. **11**: ^{1}H NMR ($CDCl_3$) δ 6.75 (1 H, d, J = 11 Hz, *CH*=CCHC=O), 6.50 (1 H, s, aromatic), 6.25 (1 H, d, J = 7 Hz, C=*CH*CH), 5.70 (1 H, rough d, J = 11 Hz, CH=*CH*C=O), 4.55 (1 H, rough d, J = 7 Hz, O=CCHC=O), 3.90, 3.87, and 3.72 (three s, 3 H each, three OCH_3), 2.60 (2 H, J = 7 Hz, $ArCH_2$), 2.0 (4 H, m, CH_2CH_2). Thermolysis of **11** (toluene, 110 °C, 1.5 h) provided decarboxylation with complete conversion to tropone **10** identical in all respects with the material described above.

6′,7′-Dihydro-1′,2′,3′-trimethoxyspiro[1,3-dioxane-2,10′(5′*H*)-benzo-[*a*]heptalene] (9). Thermal Decarboxylation of 8 and Two-Step Conversion of 8 to Tropone 10. A solid sample of the [3 + 4] cycloadduct **8** (10 mg, 0.024 mmol) was warmed at 200 °C under argon until carbon dioxide elimination had ceased (2 min), affording cycloheptatrienone ketal **9**: ^{1}H NMR ($CDCl_3$) δ 6.55 (1 H, s, C4–H), 6.52 (1 H, d, J = 11 Hz, C12–H), 6.40 (1 H, d, J = 11 Hz, C8–H), 5.85 (1 H, rough d, J = 11 Hz, C11–H), 5.75 (1 H, rough d, J = 11 Hz, C9–H), 4.0 (4 H, m, O*CH*$_2$CH$_2$*CH*$_2$O), 3.90 (6 H, s, two OCH_3), 3.65 (3 H, s, OCH_3), 2.25 (8 H, m, $OCH_2CH_2CH_2O$, $CH_2CH_2CH_2$). The crude cycloheptatrienone ketal **9** was dissolved in dry tetrahydrofuran (0.2 mL) and was treated with 3:1 acetic acid–water (0.2 mL). The resulting solution was stirred at 25 °C for 5 min before dilution with methylene chloride, neutralization with 10% aqueous sodium bicarbonate, and extraction with methylene chloride (3×). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 75% ethyl acetate–hexane eluant) afforded 4.5 mg (60%) of pure **10** as a white solid, identical in all respects with that described above.

Efforts to promote the thermal decarboxylation of **8** in solution (120 °C, toluene, 15 h, recovered **8**; 150–160 °C, mesitylene, recovered **8** and unidentified products) were unsuccessful.

9-Amino-6,7-dihydro-1,2,3-trimethoxybenzo[*a*]heptalen-10(5*H*)-one (12a, Deacetamidoisocolchiceinamide) and 11-Amino-6,7-dihydro-1,2,3-trimethoxybenzo[*a*]heptalen-10(5*H*)-one (12b). A solution of tropone **10** (26.6 mg, 0.085 mmol) in 95% ethanol (6 mL) was treated with hydrazine hydrate (10 drops) at 0 °C. The stirred solution was allowed to warm to 25 °C (10 min) and was maintained at that temperature for an additional 4.5 h. The solvent was removed under a stream of nitrogen, and the resulting oil was concentrated in vacuo. Chromatography (SiO_2, 1 × 35 cm, 75–90% ethyl acetate–hexane with 2% triethylamine eluant) afforded 15 mg (54%) of pure deacetamidoisocolchiceinamide (**12a**) identical in all respects with that previously described[2b] and 12.8 mg (46%) of pure **12b**.

12a: yellow solid, mp 224–225 °C (methylene chloride/ether) [lit.[2b] mp 221–223 °C]; ^{1}H NMR ($CDCl_3$) δ 7.40 (1 H, d, J = 12 Hz, C12–H), 7.09 (1 H, d, J = 12 Hz, C11–H), 6.89 (1 H, s, C8–H), 6.53 (1 H, s, C4–H), 5.80 (2 H, br s, NH_2), 3.90 (6 H, s, two OCH_3), 3.61 (3 H, s, OCH_3), 2.25 (6 H, m, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 175.5 (s, C10), 154.9 (s, C9), 152.7 (s, C3), 150.5 (s, C1), 148.1 (s, C7a), 141.0 (d, C12), 140.9 (s, C2), 135.2 (s, C4a), 132.1 (s, C12a), 128.2 (d, C11), 127.8 (s, C1a), 115.6 (d, C8), 107.2 (d, C4), 61.2, 60.7, and 56.0 (three q, three OCH_3), 37.4 (t, C7), 32.7 and 30.8 (two t, C6 and C5); IR ($CHCl_3$) ν_{max} 3510, 3367, 1599, 1528, 1491, 1432 cm^{-1};[15] UV (EtOH) λ_{max} 402 (ε 7480), 372 (ε 13 040), 354 (ε 15 130), 247 (ε 24 890) nm;[15] EIMS, *m/e* (rel intensity) 327 (M^+, 100), 299 (CO, 23), 284 (4), 253 (15), 164 (9); HRMS, $C_{19}H_{21}NO_4$ requires *m/e* 327.1469, found 327.1469.

Isomeric 11-Aminotropone 12b: mp 224–225 °C (toluene); ^{1}H NMR ($CDCl_3$) δ 7.29 (1 H, d, J = 12 Hz, C8–H), 7.09 (1 H, d, J = 12 Hz, C9–H), 7.05 (1 H, s, C12–H), 6.54 (1 H, s, C4–H), 5.65 (2 H, br s, NH_2), 3.91 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 3.59 (3 H, s, OCH_3), 2.25 (6 H, m, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 175.6 (s, C10), 153.7 (s, C11), 153.2 (s, C3), 150.4 (s, C1), 144.0 (s, C7a), 140.9 (s, C2), 139.1 (d, C8), 135.9 (s, C4a), 135.4 (s, C12a), 130.2 (d, C12), 128.2 (s, C1a), 117.9 (d, C9), 107.2 (d, C4), 61.2, 60.9, and 55.9 (three q, three OCH_3), 35.2 (t, C7), 32.7 and 30.8 (two t, C6 and C5); IR ($CHCl_3$) ν_{max} 3512, 3367, 3006, 2941, 1595, 1527, 1489, 1474, 1432 cm^{-1}; UV (EtOH) λ_{max} 412 (ε 10 790), 348 (sh, ε 10 470), 308 (ε 18 380), 248 (ε 18 450) nm; EIMS, *m/e* (rel intensity) 327 (M^+, 100), 299 (CO, 9), 284 (7), 253 (6), 164 (5), 149 (7); HRMS, $C_{19}H_{21}NO_4$ requires *m/e* 327.1469, found 327.1468.

9-Hydroxy-6,7-dihydro-1,2,3-trimethoxybenzo[*a*]heptalen-10(5*H*)-one (2, Deacetamidocolchiceine). Deacetamidoisocolchiceinamide (**12a**) was converted to deacetamidocolchiceine (**2**) following the procedure described by Eschenmoser et al.:[2b] A solution of **12a** (7.5 mg, 0.023 mmol) in 1:1 ethanol–2 N aqueous potassium hydroxide (2 mL) was warmed at 100–110 °C under argon for 21 h. After cooling to 25 °C, the crude reaction mixture was diluted with methylene chloride, acidified with 10% aqueous hydrochloric acid, and extracted with methylene chloride (3×). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo, affording quantitative yield of **2**. Trituration (methylene chloride–ether) afforded 6.5 mg (87%) of pure **2** as a white solid: mp 164–165 °C [lit.[2b] mp 166–167 °C]; ^{1}H NMR ($CDCl_3$, 10 mg/mL) δ 7.60 (1 H, d, J = 12 Hz, C12–H), 7.52 (1 H, s, C8–H), 7.37 (1 H, d, J = 12 Hz, C11–H), 6.52 (1 H, s, C4–H), 3.90 (6 H, s, two OCH_3), 3.62 (3 H, s, OCH_3), 2.3 (6 H, m, $CH_2CH_2CH_2$); ^{1}H NMR ($CDCl_3$, 3 mg/mL) δ 7.55 (1 H, d, J = 12 Hz, C12–H), 7.40 (1 H, s, C8–H), 7.26 (1 H, d, J = 12 Hz, C11–H), 6.52 (1 H, s, C4–H), 3.90 (6 H, s, two OCH_3), 3.62 (3 H, s, OCH_3), 2.3 (6 H, m, $CH_2CH_2CH_2$); IR ($CHCl_3$) ν_{max} 3008, 2941, 2859, 1616, 1597, 1488, 1480, 1460, 1447, 1350, 1275, 1139, 1098 cm^{-1};[15] UV (EtOH) λ_{max} 353, 243, 232 (sh) nm;[15] EIMS, *m/e* (rel intensity) 329 (16), 328 (M^+, 61), 300 (40), 385 (14), 257 (16), 254 (46), 242 (25), 226 (29), 225 (34), 213 (21), 211 (23), 210 (24), 199 (30), 197 (28), 195 (17), 181 (37), 171 (85), 169 (28), 165 (47), 153

(49), 152 (67), 141 (46), 139 (42), 128 (80), 127 (59), 115 (base, 100); HRMS, $C_{19}H_{20}O_5$ requires *m/e* 328.1310, found 328.1321.

11-Hydroxy-6,7-dihydro-1,2,3-trimethoxybenzo[*a*]heptalen-10(5*H*)-one (13). 11-Aminotropone **12b** was converted to the corresponding 11-hydroxytropone by utilizing the procedure described above. **12b** (3.6 mg, 0.011 mmol) afforded 3 mg (84%) of **13**: ^{1}H NMR ($CDCl_3$) δ 7.45 (1 H, s, C12–H), 7.38 (1 H, d, J = 13 Hz, C8–H), 7.25 (1 H, d, J = 13 Hz, C9–H), 6.50 (1 H, s, C4–H), 3.90 (6 H, s, two OCH_3), 3.67 (3 H, s, OCH_3), 2.60–1.50 (6 H, m, C5–H_2, C6–H_2, C7–H_2); IR ($CHCl_3$) ν_{max} 3007, 2942, 2861, 1618, 1595, 1549, 1476, 1464, 1404, 1353, 1320 cm^{-1};[15] UV (EtOH + 1% 0.1 N HCl v/v) λ_{max} 382, 368, 324 (sh), 310, 241 nm;[15] UV (EtOH + 1% 0.1 N NaOH v/v) λ_{max} 412, 345, 300 (sh), 288, 244 nm;[15] EIMS, *m/e* (rel intensity) 328 (M^+, 27), 237 (13), 300 (20), 254 (19), 241 (11), 238 (14), 226 (14), 225 (24), 211 (17), 210 (20), 181 (39), 171 (43), 165 (53), 153 (48), 152 (65), 145 (30), 141 (43), 139 (38), 128 (74), 127 (50), 115 (base, 100); HRMS, $C_{19}H_{20}O_5$ requires *m/e* 328.1310, found 328.1322.

***exo*-1′,1a′,1b′,2′,3′,4′,10a′,10′-Octahydro-11′-oxo-6′,7′,8′-trimethoxyspiro[1,3-dioxane-2,1′-[1b,10](epoxymethano)benzo[*a*]cyclopropa[3,4]benzo[1,2-*c*]cycloheptene] (*exo*-14). Pressure-Promoted Diels–Alder Reaction of α-Pyrone 6 with 7.** α-Pyrone **6** (35 mg, 0.116 mmol) and cyclopropenone ketal **7** (40 mg, 0.36 mmol, 3 equiv) were combined in a Teflon tube. The tube was sealed and placed under pressure (6.2 kbar) for 5 days (25 °C). Chromatography (SiO_2, 50% ethyl acetate–hexane eluant) afforded 42 mg (88%) of pure ***exo*-14** as a white solid: mp 177–178 °C; ^{1}H NMR ($CDCl_3$) δ 6.55 (1 H, d, J = 6 Hz, C=CH), 6.47 (s, aromatic CH), 4.15–3.50 (5 H, m, O*C*H_2CH_2*C*H_2O, C*H*CO_2), 3.86 (6 H, s, two OCH_3), 3.65 (3 H, s, OCH_3), 2.85–1.25 (10 H, m, *C*H_2CH_2*C*H_2, OCH_2*C*H_2CH_2O, cyclopropyl CH's); ^{13}C NMR ($CDCl_3$) δ 172.9 (s, C=O), 153.2, 150.8, and 145.8 (three s, three aromatic *C*OCH$_3$), 140.8 and 135.5 (two s, two aromatic C), 130.0 (d, C=*C*H), 121.5 (s, *C*=CH), 108.1 (d, aromatic CH), 99.9 (s, OCO), 80.4 (s, *C*OC=O), 67.2 and 66.0 (two t, O*C*H_2CH_2*C*H_2O), 61.2, 61.0, and 55.9 (three q, three ArO*C*H_3), 41.7 (d, *C*HCO_2), 36.5 and 32.4 (two d, cyclopropyl CH's), 31.4 and 30.8 (two t, Ar*C*H_2CH_2*C*H_2), 25.4 (t, OCH_2*C*H_2CH_2O), 21.8 (t, ArCH_2*C*H_2CH_2); IR ($CHCl_3$) ν_{max} 1755 (C=O), 1138, 1115 cm^{-1}; UV (CH_3CN) λ_{max} 270 (ϵ 9200), 229 (ϵ 12910) nm; EIMS, *m/e* (rel intensity) 414 (M^+, 4), 386 (13), 371 (5), 370 (21), 369 (13), 355 (16), 339 (26), 312 (24), 311 (12), 287 (12), 285 (14), 284 (65), 269 (29), 253 (10), 241 (12), 238 (20), 165 (30), 155 (22), 153 (23), 152 (31), 115 (26); HRMS, $C_{23}H_{26}O_7$ requires *m/e* 414.1677, found 414.1671.

Thermal Decarboxylation of *exo*-14: Preparation of Deacetamidoallocolchicine (18). A solution of the [4 + 2] cycloadduct ***exo*-14** (11 mg, 0.0266 mmol) in dry mesitylene (0.2 mL) was flushed with argon for 15 min and then warmed in a sealed tube at 200 °C for 50 min. After the solution cooled, chromatography afforded 3.5 mg (7.5 mg theoretical, 45%) of pure **18**: ^{1}H NMR ($CDCl_3$) δ 7.25 (4 H, m, C8–H, C9–H, C10–H, C11–H), 6.53 (1 H, s, C4–H), 3.88 (6 H, s, two OCH_3), 3.56 (3 H, s, OCH_3), 2.70–1.75 (6 H, m, C5–H_2, C6–H_2, C7–H_2); IR (film) ν_{max} 2936, 1605, 1494, 1460, 1409, 1353, 1329, 1250, 1198, 1150, 1116, 1092 cm^{-1}; EIMS, *m/e* (rel intensity) 284 (M^+, 100), 269 (OCH_3, 29), 238 (19), 210 (11), 209 (15), 195 (11), 194 (15), 165 (27), 155 (21), 153 (21), 152 (22), 115 (17).

Photochemical-Promoted Decarboxylation of *exo*-14. The [4 + 2] cycloadduct **14** (11.2 mg, 0.027 mmol) in dry benzene (6 mL) was placed in a Pyrex tube, and the resulting solution was degassed under a stream of argon (10 min). The tube was irradiated at 310 nm for 2.5 h, and the crude reaction mixture was concentrated in vacuo. Chromatography afforded 4.2 mg (10 mg theoretical, 42%) of **19a**, 0.7 mg (7%) of **19b**, and 2.7 mg (24%) of recovered starting ***exo*-14**.

19a: ^{1}H NMR ($CDCl_3$) δ 6.52 (1 H, dd, J = 6, 2 Hz, CH*C*H=CH-C), 6.39 (1 H, s, aromatic CH), 6.08 (1 H, dd, J = 6, 1 Hz, CHCH=*C*HC), 4.03, 3.97, 3.90 (5 H, two overlapping t and overlapping m, respectively, J = 6 Hz, O*C*H_2CH_2*C*H_2O, bis allylic CH), 3.84 (3 H, s, OCH_3), 3.80 (6 H, s, two OCH_3), 3.40 (1 H, br s, CHC=C*C*HC), 2.80–2.20 (4 H, m, Ar*C*H_2CH_2*C*H_2), 2.15–1.50 (4 H, m, ArCH_2*C*H_2CH_2, OCH_2*C*H_2CH_2O); ^{13}C NMR ($CDCl_3$) δ 151.7, 151.5, and 145.3 (three Ar*C*OCH_3), 144.6 and 140.3 (two aromatic C), 141.9 (CHCH=*C*HC), 140.2 (Ar*C*CCH), 138.7 (ArC=*C*CH), 128.5 (CH*C*H=CHC), 108.9 (aromatic CH), 108.4 (OCO), 62.8 and 61.1 (O*C*H_2CH_2*C*H_2O), 60.7 (two OCH_3), 55.9 (OCH_3), 52.2 (bis allylic CH), 50.5 (C=C*C*H-CO_2), 36.8 (ArCH_2CH_2*C*H_2), 33.6 (Ar*C*H_2CH_2CH_2), 25.7 and 25.5 (OCH_2*C*H_2CH_2O, ArCH_2*C*H_2CH_2); IR (film) ν_{max} 2934, 2863, 1491, 1453, 1401, 1356, 1318, 1244, 1198, 1146, 1096, 1046, 994 cm^{-1}; UV (CH_3CN) λ_{max} 279, 227, 220 nm; EIMS, *m/e* (rel intensity) 370 (M^+, 100), 355 (7), 342 (38), 339 (13), 327 (23), 313 (11), 312 (25), 311 (29), 298 (40), 270 (94), 165 (88), 152 (70), 141 (48), 139 (41), 129 (34), 128 (55), 127 (61), 115 (62).

19b: ^{1}H NMR ($CDCl_3$) δ 6.85 (1 H, d, J = 3 Hz, C*C*H=CHCH), 6.33 (1 H, s, aromatic CH), 6.27 (1 H, ddd, J = 7, 3, 1 Hz, CCH=*C*HCH), 5.42 (1 H, d, J = 1 Hz, C=*C*H), 4.25–3.6 (5 H, m, O*C*H_2CH_2CH_2O, CCH=CH*C*H), 3.80 (6 H, s, two OCH_3), 3.74 (3 H, s, OCH_3), 3.25–2.25 (4 H, m, Ar*C*H_2CH_2*C*H_2), 2.25–1.5 (4 H, m, ArCH_2*C*H_2CH_2, OCH_2*C*H_2CH_2O); IR (film) ν_{max} 2936, 2861, 1596, 1489, 1456, 1402, 1347, 1320, 1246, 1194, 1152, 1113, 1096, 1038, 999 cm^{-1}; EIMS, *m/e* (rel intensity) 370 (M^+, 22), 369 (13), 342 (9), 340 (9), 339 (29), 312 (9), 311 (12), 285 (23), 284 (base, 100), 269 (32), 253 (13), 238 (22), 223 (11), 209 (14), 195 (10), 181 (11), 165 (24), 155 (18), 153 (17), 152 (20), 141 (15), 139 (12), 129 (14), 128 (18), 127 (22), 115 (20).

Cyclopentenone ketal **19a** (2.4 mg, 0.0065 mmol) in dry tetrahydrofuran (0.1 mL) was treated with 3:1 acetic acid–water (0.1 mL), and the resulting solution was stirred at 25 °C for 3 h. The crude reaction mixture was diluted with methylene chloride, neutralized with 10% aqueous sodium bicarbonate, and extracted with methylene chloride (3 × 15 mL). The combined organic phases were dried (sodium sulfate) and concentrated in vacuo. Chromatography (SiO_2, 50% ethyl acetate–hexane eluant) afforded 2 mg (2.0 mg theoretical, 100%) of pure **20a**: ^{1}H NMR ($CDCl_3$) δ 7.91 (1 H, dd, J = 6, J = 3 Hz, C*H*=CHC=O), 6.44 (1 H, s, aromatic CH), 6.07 (1 H, dd, J = 6, J = 1 Hz, CH=*C*HC=O), 4.15 (1 H, m, bis allylic CH), 3.95, 3.86, and 3.85 (three s, 3 H each, three OCH_3), 3.40 (1 H, m, CC*H*C=O), 2.75–2.55 (2 H, m, Ar*C*H_2CH_2CH_2), 2.55–2.25 (2 H, m, ArCH_2CH_2*C*H_2), 2.25–1.80 (2 H, m, ArCH_2*C*H_2CH_2); IR (film) ν_{max} 2919, 2849, 1696 (C=O), 1593, 1568, 1493, 1455, 1402, 1347, 1320, 1242, 1196, 1142, 1125, 1096, 1040, 1003 cm^{-1}; EIMS, *m/e* (rel intensity) 312 (M^+, 82), 297 (6), 282 (23), 281 (OCH_3, 100), 269 (12), 266 (10), 265 (12), 253 (12), 238 (13), 237 (14), 181 (16), 165 (27), 155 (15), 153 (21), 152 (24), 141 (15), 128 (21), 127 (23), 115 (22).

Acknowledgment. This work was assisted financially by the Searle Scholars fund and the National Institutes of Health (CA 00898/01134, CA 33668/42056, and GM 07775). We thank Profs. A. W. Burgstahler and T. A. Engler for helpful discussions.

Registry No. 1, 477-27-0; **2**, 5320-47-8; 6, 3476-63-9; **7**, 60935-21-9; **8**, 97860-63-4; **9**, 97827-48-0; **10**, 97827-49-1; **11**, 103532-92-9; **12a**, 3660-48-8; **12b**, 97827-51-5; **13**, 3476-62-8; ***exo*-14**, 97860-64-5; **18**, 103532-93-0; **19a**, 103532-94-1; **19b**, 103532-95-2; **20a**, 103532-96-3.