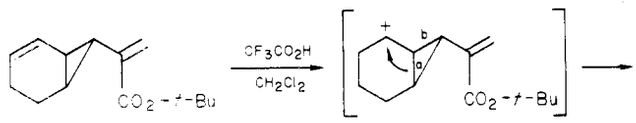
Communications

Ring Expansion Synthesis of Fused *trans*-α-Methylene γ-Lactones

Summary: A stereospecific ring-expansion synthesis of trans-fused α-methylene γ-lactones can be accomplished in excellent yield through the sequence of carbene addition of *tert*-butyl diazopyruvate to cyclic dienes, inverse Wittig condensation to give a *tert*-butyl ester substituted *trans*-divinylcyclopropane, and acid-catalyzed cleavage of the cyclopropane ring.

Sir: The construction of *trans*-α-methylene lactones[1] has significance because of the common occurrence of this association of functionality in many cytotoxic[2] and pharmacologically active natural products.[3] We wish to introduce a new strategy for the synthesis of this system based upon the cationic cleavage of cyclopropyl acrylates (**1** → **2** → **3**). In contrast to previous procedures, this



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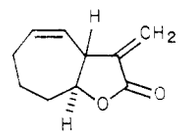

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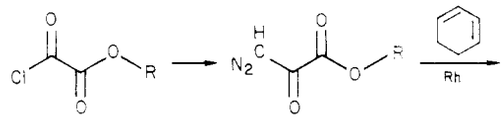
pathway combines the direct stereospecific formation of trans-fused α-methylene lactones with that of ring expansion.[4]

Treatment of *tert*-butyl 2-*exo*-(bicyclo[4.1.0]hept-2-enyl)propenoate (**1**) with 10% trifluoroacetic acid in methylene chloride at room temperature for 5 h results in an almost quantitative formation of *trans*-α-methylene γ-lactone **3** (mp 69–73 °C). Purification by chromatography gave an 84% yield of the lactone **3** (mp and mmp 74–75 °C), identical in all respects with authentic material.[5]

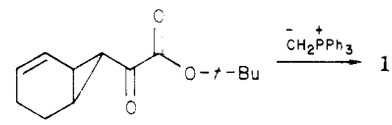
There is no observed formation of the alternate mode of cyclopropane ring cleavage (bond b) or of the cis-fused lactone. This new ring opening appears to be directed by the cross-conjugated, electron-withdrawing nature of the acrylate substituent and by the capture of the cyclopropyl carbinyl cation by the carboxylate function. If in the fragmentation bond b (**2**) were to break, positive charge would develop on an allylic carbon, a carbon which would then have a cross-conjugated resonance interaction with the electron-withdrawing ester group. This cross-conjugated interaction and perhaps inductive effects inhibit fragmentation at bond b.

The starting cyclopropyl acrylate derivative was prepared efficiently from *tert*-butyl diazopyruvate (**5**).[6]



4a, R = *t*-Bu
b, R = Me

5a, R = *t*-Bu
b, R = Me



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Rhodium(II) acetate[7] catalyzed addition of **5** to 1,3-cyclohexadiene followed by inverse treatment[8] of the intermediate *exo*-cyclopropyl glyoxalate (**6**; 67%, mp 40–42 °C) with methylenetriphenylphosphorane[9] yields cyclopropyl acrylate **1** [65%, oil; IR 1705, 1625, 1146 cm^{-1}; NMR δ 1.13–1.78 and 1.55 (12 H, m, s), 1.78–2.18 (4 H, m), 5.33 (2 H, s), 6.07 (2 H, s); *m/e* 220]. The required hydrocarbon soluble *tert*-butyl diazopyruvate (**5**) was prepared from oxalyl chloride by treatment with *tert*-butyl alcohol–pyridine in ether at −78 °C to give 64% acid chloride ester **4a** [bp 60–63 °C (23 mm); NMR δ 1.58], anilide mp 128–129 °C. Treatment of **4a** with diazomethane[10] afforded a 76% yield of yellow crystalline **5a** (mp 101–102 °C).

An alternate pathway involving the direct formation of cyclopropyl acrylates, though much less efficient and at this point of little preparative usefulness, nevertheless has considerable theoretical interest because of the cross-conjugated character of the reagent and the intermediate carbene generated. Methyl α-(diazomethyl)propenoate (**10**) has been prepared and caused to add to double bonds. Methyl β,β′-dibromoisobutyrate[11] reacts with potassium cyanate in methanol–dimethylformamide to yield 34%

(1) (a) P. A. Grieco, *Synthesis*, 67 (1975); (b) R. B. Gamill, C. A. Wilson, and T. A. Bryson, *Synth. Commun.*, **5**, 245 (1975); (c) S. S. Newaz, *Aldrichimca Acta*, **10** (4), 64 (1977).

(2) E. Rodriguez, G. H. N. Towers, and J. C. Mitchell, *Phytochemistry*, **15**, 1573 (1976).

(3) (a) T. K. Devon and A. J. Scott, "Handbook of Naturally Occurring Compounds", Vol. II, Academic Press, New York, 1972; (b) H. Yoshioka, T. J. Mabry, and B. N. Timmermann, "Sesquiterpene Lactones—Chemistry, NMR and Plant Distribution", University of Tokyo Press, Tokyo, 1973; (c) S. M. Kupchan, *Trans. N.Y. Acad. Sci.*, **32**, 85 (1970); (d) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); (e) J. L. Hartwell and B. J. Abbott, *Adv. Pharmacol. Chemother.*, **7**, 117 (1969); (f) K.-H. Lee, E.-S. Juang, C. Piantadosi, J. S. Pagano, and T. A. Geissman, *Cancer Res.*, **31**, 1649 (1971); (g) L. A. Mitscher in "Recent Advances in Phytochemistry", Vol. 9, V. C. Runeckles, Ed., Plenum Press, New York, 1975, pp 243–283; (h) P. M. Baker, C. C. Fortes, E. G. Fortes, G. Gassinelli, B. Gilbert, J. N. C. Lopes, J. Pellagrino, T. Tomassini, and W. Vichnewski, *J. Pharm. Pharmacol.*, **24**, 853 (1972); (i) W. Vichnewski, S. J. Sarti, B. Gilbertant, and W. Herz, *Phytochemistry*, **15**, 191 (1976).

(4) See, for example, (a) J. A. Marshall and R. H. Ellison, *J. Am. Chem. Soc.*, **98**, 4312 (1976); (b) J. A. Marshall and R. H. Ellison, *J. Org. Chem.*, **40**, 2070 (1975); (c) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. L. Studt, *Tetrahedron Lett.*, 2035 (1974); (d) P. F. Hudrlik, L. R. Rudnick, and S. H. Korzeniowski, *J. Am. Chem. Soc.*, **95**, 6848 (1973).

(5) Comparison spectra and an authentic sample of **3** were kindly provided by Professor J. P. Marino: J. P. Marino and J. S. Farina, *J. Org. Chem.*, **41**, 3213 (1976). Analytical data including IR, NMR, mass spectral, and elemental analyses were obtained for all new compounds.

(6) See for example P. Kolsaker, T. Jorgensen, and G. Larsen, *Tetrahedron*, **30**, 3393 (1974).

(7) S. Bien and Y. Segal, *J. Org. Chem.*, **42**, 1685 (1977).

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(9) Inverse addition was necessary. Ylide was generated from methyltriphenylphosphonium salt and lithium diisopropylamide.

(10) J. Ratusky and F. Sorin, *Chem. Listy*, **51**, 1091 (1957).

(11) A. F. Ferris, *J. Org. Chem.*, **20**, 780 (1955).

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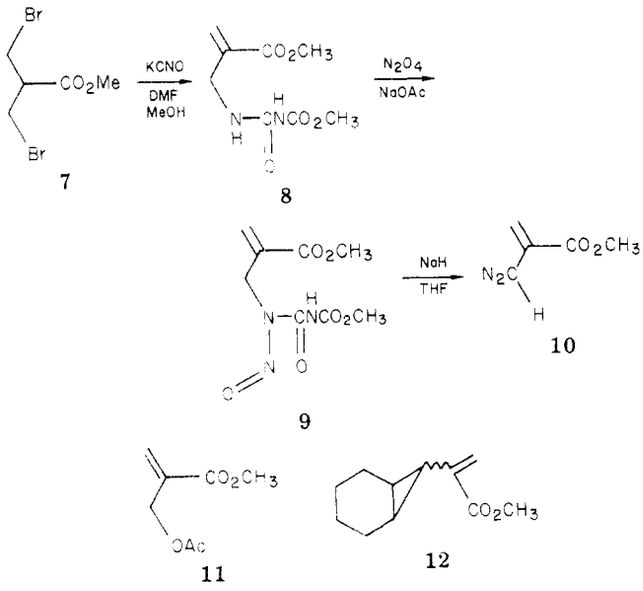

methyl 4-[2-(carbomethoxy)propen-3-yl]allophanate (**8**), mp 151–153 °C, and 47% 1,3,5-tris[2-(carbomethoxy)-propen-3-yl]-2,4,6-trioxo-5-triazine, mp 91–93 °C, which are easily separated by crystallization from benzene. Reaction of allophonate **8** with dinitrogen tetroxide in CCl_4 with NaOAc buffer at −15 °C afforded the 4-nitroso compound **9** in 98% yield (mp 81–83 °C). Treatment of this nitrosoallophanate **9** with sodium hydride in THF at 0 °C afforded orange-red solutions of **10** as evidenced by strong infrared bonds at 2075 (CHN_2), 1740, and 1660 cm^{-1} and by the observation that quenching portions of these solutions with acetic acid resulted in vigorous gas evolution and the formation of methyl 2-(acetoxymethyl)acrylate (**11**) (69%). Direct treatment of **9** with acetic acid yielded no **11**.

Copper trifluoroacetate catalyzed[12] decomposition of THF solutions of **10** in the presence of cyclohexene produced, among many other substances, a 2:1 ratio of the *exo*- and *endo*-methyl 2-(bicyclo[4.1.0]hepten-7-yl)-propenoates (*exo*-**12** and *endo*-**12**) (6% yield). Other components identified in the mixture were dimethyl terphthalate, dimethyl 1,3-cyclohexadiene-1,4-dicarboxylate,[13] and *cis*- and *trans*-1,3,5-cyclohexatriene-3,4-dicarboxylate;[14] these materials were apparently derived from the dimerization of **10** and electrocyclic closure. Compound *exo*-**12** was identified by synthesis of an authentic sample through Wittig condensation[9] with the cyclopropyl glyoxalate derived from methyl diazopyruvate (**5b**) and cyclohexene.[7] Studies of the addition of **10** to dienes and efforts to improve the yields of products such as **12** by this pathway are continuing.

The synthesis of the lower homologue, *tert*-butyl 2-(bicyclo[3.1.0]hex-6-enyl)propenoate, from cyclopentadiene and **5a** has also been accomplished and its rearrangement is under examination. Both the generation of cations (**2**) from alternative functional groups and the application of these procedures to the synthesis of natural products are being studied. We are particularly interested in using this approach for the synthesis of model structures necessary for the detailed study of the chemical interaction of *trans*-α-methylene γ-lactone functions with proteins.[15]

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Registry No. **1**, 71901-62-7; **3**, 60916-78-1; **4a**, 39061-59-1; **5a**, 71901-63-8; **6**, 71901-64-9; **7**, 22262-60-8; **8**, 71901-65-0; **9**, 71901-66-1; **10**, 71901-67-2; **11**, 30982-08-2; *exo*-**12**, 71901-68-3; *endo*-**12**, 71901-69-4; anilide, 71901-70-7; 1,3,5-tris[2-(carbomethoxy)propen-3-yl]-2,4,6-trioxo-5-triazine, 71901-71-8; *tert*-butyl *exo*-2-(bicyclo[3.1.0]-hex-6-enyl)propenoate, 71928-57-9; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4.

(12) R. G. Salomon, M. F. Salomon, and T. R. Heyne, *J. Org. Chem.*, **40**, 756 (1975).

(13) A sample of dimethyl 1,3-cyclohexadiene-1,4-dicarboxylate prepared according to a literature procedure was generously provided by Jeff Vanderbilt. See N. B. Chapman, S. Sotheeswaran, and K. J. Toyne, *J. Org. Chem.*, **35**, 917 (1970).

(14) Identified by mass spectral analysis only.

(15) S. Mitra and R. G. Lawton, *J. Am. Chem. Soc.*, **101**, 3097 (1979).

Larry G. Mueller, Richard G. Lawton*
Department of Chemistry and Interdepartmental Program in Medicinal Chemistry
The University of Michigan
Ann Arbor, Michigan 48109
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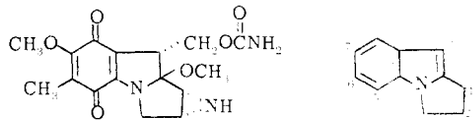
New Synthesis of Ethyl 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates via Apparent 1-Aza-1′-oxa [3,3]Sigmatropic Rearrangement

Summary: The reaction of *N*-arylhydroxylamines (**3a–f**) with ethyl 6-oxo-2-hexynoate (**4**) and sodium cyanoborohydride affords a series of tricyclic ethyl 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylates (**5a–g**) in 25–68% yield via apparent 1-aza-1′-oxa [3,3]sigmatropic rearrangements of *N*-aryl-*O*-vinylhydroxylamine intermediates (e.g., **7**).

Sir: The mitomycins (e.g., mitomycin A, **1**) constitute a small group of pyrroloindole quinones which are isolated from various *Streptomyces* cultures and exhibit both antibacterial and antitumor activities.[1] The novel structure and biological activities of these compounds have stimulated considerable interest in the synthesis of the parent 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles (**2**) as well as the



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natural products themselves.[2–4] Since we have developed

(1) For references on the earlier literature, see Sundberg, R. J. "The Chemistry of the Indoles"; Academic Press: New York, 1970; pp 431–434.

(2) References to research on the synthesis of pyrroloindoles and mitomycin analogues prior to spring, 1977, are given in the following: (a) Siuta, G. J.; Franck, R. W.; Kempton, R. J. *J. Org. Chem.* **1974**, *39*, 3739–3744. (b) Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835–4836.

(3) For recent total syntheses of the mitomycins, see Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8115–8116. Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295–4298.

(4) Other recent synthetic work in the mitomycin field includes the following: Rebek, J., Jr.; Gehret, J.-C. E. *Tetrahedron Lett.* **1977**, 3027–3028. Danishefsky, S.; Doehner, R. *Ibid.* **1977**, 3029–3030; *Ibid.* **1977**, 3031–3034. Akiba, M.; Kosugi, Y.; Takada, T. *J. Org. Chem.* **1978**, *43*, 4472–4475. Kametani, T.; Kigawa, Y.; Takahashi, K.; Nemoto, H.; Fukumoto, K. *Chem. Pharm. Bull.* **1978**, *26*, 1918–1922. Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 662–666. Parker, K. A.; Kang, S.-K. *J. Org. Chem.* **1979**, *44*, 1536–1540. For a review on the synthesis of pyrrolo[1,2-*a*]indoles, see Kametani, T.; Takahashi, K. *Heterocycles* **1978**, *9*, 293–351.

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