(1975); G. L. Loper and E. K. C. Lee, *ibid.*, **63**, 264 (1975); J. Metcalf and E. K. C. Lee, *J. Am. Chem. Soc.*, **94**, 7 (1972); **95**, 1751 (1973).

(3) J. C. Dalton and J. J. Snyder, *J. Am. Chem. Soc.*, **97**, 5192 (1975); N. E. Schore and N. J. Turro, *ibid.*, **97**, 2482 (1975), N. J. Turro, J. C. Dalton, G. Farrington, M. Niemczyk, and D. M. Pond, *ibid.*, **92**, 6978 (1970).

(4) E. A. Abuin, M. V. Encina, E. A. Lissi, and J. C. Scaiano, *J. Chem. Soc., Faraday Trans. 1*, **71**, 1221 (1975); M. V. Encina, H. Soto, and E. A. Lissi, *J. Photochem.*, **3** 467 (1975).

(5) A. Weller and D. Rehm, *Isr. J. Chem.*, **8**, 259 (1970); H. Knibbe, D. Rehm, and A. Weller, *Z. Phys. Chem. (Frankfurt am Main)*, **56**, 95 (1967); H. Beens, H. Knibbe, and A. Weller, *J. Chem. Phys.*, **47**, 1183 (1967).

(6) Calculations were carried out using the GAUSSIAN 70 program.[7] For the ground state (S₀) the computations were carried out within the framework of Roothaan's Restricted Hartree-Fock formalism.[8] For the triplet state, computations were carried out within the framework of the Pople-Nesbet Unrestricted Hartree-Fock method.[9]

(7) W. J. Hehre, W. A. Latham, R. Ditchfield, M. D. Newton, and J. A. Pople, *Quantum Chemistry Program Exchange, University of Indiana, Bloomington, Indiana.*

(8) C. C. J. Roothan, *Rev. Mod. Phys.*, **23**, 69 (1951).

(9) J. A. Pople and R. K. Nesbet, *J. Chem. Phys.*, **22**, 571 (1954).

(10) L. Salem, *J. Am. Chem. Soc.*, **96**, 3486 (1974).

(11) G. W. Robinson and V. E. DiGiorgio. *Can. J. Chem.*, **36**, 31 (1958).

(12) Our investigation of the best triplet approach failed to show a minimum in the region of space associated with N–O bond distances 1.6–2.4 Å. Failure to find a minimum may be due to (a) our restricted basis set without configuration interaction, (b) an exciplex geometry far removed from our path of best approach, or (c) the absence of a stable exciplex formed between ammonia and triplet formaldehyde.

(13) We have learned that Morokuma and his co-workers have independently carried out similar calculations and have reached conclusions entirely consistent with what we report here. K. Morokuma, G. H. Neems and S. Yamabe, submitted for publication.

Utam Maharaj, Imre G. Czizmadia, Mitchell A. Winnik*

*Lash Miller Laboratories, Department of Chemistry
and Erindale College, University of Toronto
Toronto, Ontario, Canada M5S 1A1*

1

Scheme I

a, R = H
b, R = CH₃
c, R = CH₂CH₂CH₂CH₃

A Convergent Route to α-Substituted Acrylic Esters and Application to the Total Synthesis of (±)-Frullanolide[1]

Sir:

Esters of α-substituted acrylic acids are important substructures in a variety of cytotoxic and antineoplastic compounds.[2] As part of a project directed toward the synthesis of terpenoid antitumor agents, we have been examining new methods for the regio- and stereospecific introduction of intact or masked acrylic acid residues into suitable organic substrates. One particularly useful approach to this problem is a methylenic variant of the Claisen rearrangement (i → iii) or a formal equivalent thereof (e.g., ii → iii).[3] In this communication, we describe the first examples of this valuable new strategy for the synthesis of α-substituted acrylic esters, and application of the new method to the first total synthesis of the allergenic sesquiterpene frullanolide, 1.[4]

The approach we have been exploring is summarized by ii → iii. The feasibility of this methylenic Claisen rearrangement equivalent depends largely on the choice of the substituent X in ii. The required substituent would be one which would not be eliminated by an ester enolate or ketene acetal under the conditions of the Claisen rearrangement and yet subsequently could be eliminated under mild conditions to yield the sensitive acrylic ester iii.

We have examined a number of systems related to ii and have found that a particularly convenient pathway exists between an allylic alcohol and a rearranged acrylic ester like iii when X = NR₂. The sequence is outlined in Scheme I for several 2-cyclohexenol derivatives.

The intermediate β-pyrrolidinopropionates 3a–c (IR (neat) 1725, 1640 cm⁻¹) are readily prepared from the corresponding allylic alcohols by a simple one-flask procedure. An allylic alcohol is first treated with acryloyl chloride and ethyldiisopropylamine in methylene chloride (0 °C) and then excess
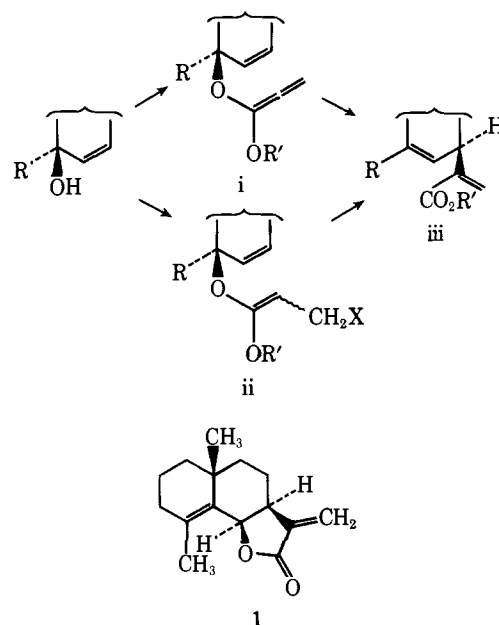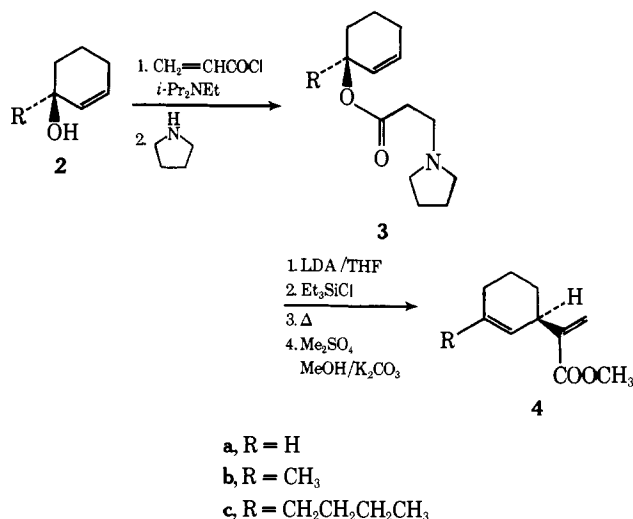
pyrrolidine is added to yield the Mannich base (e.g., 3) directly. Primary, secondary, and relatively unhindered tertiary alcohols are rapidly esterified under these conditions and yields of distilled, analytically pure β-pyrrolidinopropionates are routinely in excess of 90%.

We have found that allylic esters such as 3a–c are readily rearranged without elimination of pyrrolidine by a modified ester enolate Claisen procedure.[3b] First, the ester is converted to the corresponding silylketene acetal by treatment with lithium diisopropylamide and triethylchlorosilane[5] at −45 °C under argon. Next, Claisen rearrangement is effected by refluxing in THF or, in the case of relatively stable intermediates like that derived from 3a, by refluxing in toluene. Finally, conversion to the olefinic acrylate 4 is completed by removing the solvents in vacuo, refilling the reaction vessel with argon, and then stirring the residue with a mixture of dimethyl sulfate,[6] methanol, and potassium carbonate. Although a number of steps are involved in the transformation of 3 into 4, the entire operation may be conducted in a single flask. Thus acrylates 4a–c may be prepared by what is effectively a two-step procedure from the corresponding allylic alcohols in 65–75% overall yield. The products were identified[7] by their characteristic infrared (1720, 1620 cm⁻¹) and NMR spectra (=CH₂ δ 6.2, 5.5; =CCHC= δ 3.3) or, in the instance of 4a, by

comparison with authentic material prepared by another route.[8]

In principle, 4 could be prepared from allylic halides with the recently described α-carboethoxyvinylcuprate reagent.[8] However, the methylenic Claisen strategy offers complete regio- and stereospecificity and thus allows preparation of isomers which are not available by the cuprate procedure. For example, application of the methylenic Claisen sequence to 1-n-butyl-2-cyclohexenol (2c) gave the expected olefinic acrylate 4c (71% overall yield) while analogous reaction of the isomeric n-butylcyclohexenol 5 led to the isomeric acrylate 6 (57% yield, IR (neat) 1725, 1610 cm^{-1}; NMR (δ^{CCl_4}) 6.10 (1 H, d, J = 2 Hz), 5.85–5.50 (2H, m), 5.48 (1 H, d, J = 2 Hz), 3.68 (3 H, s)). Each product was isomerically pure by VPC and NMR.
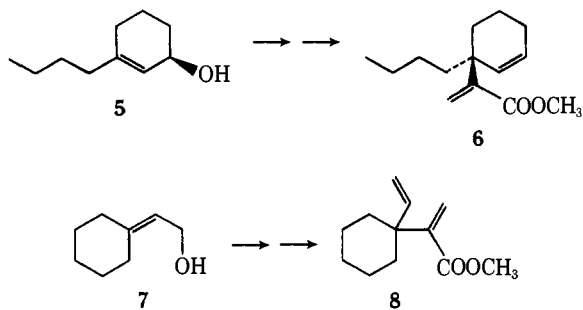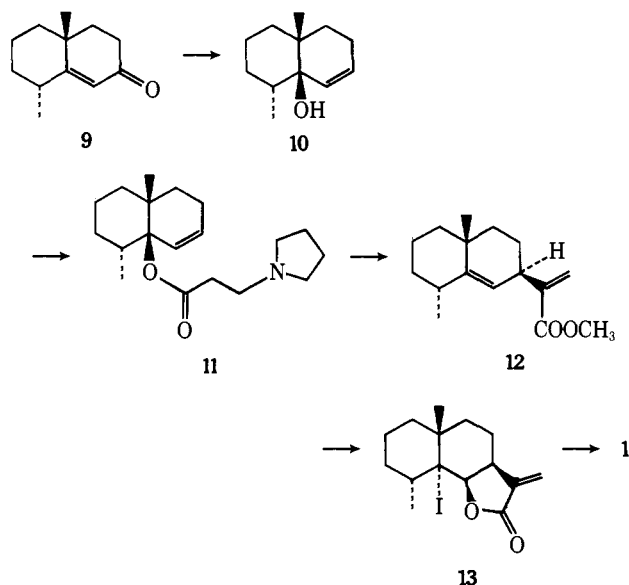

The reaction is, of course, not limited to 2-cyclohexenols. The hydroxyethylidene cyclohexane 7, for example, led via the usual β-pyrrolidinopropionate (96% yield; BP$_{0.05}$ 115 °C) to the interesting gem-disubstituted cyclohexane 8 (71% yield; IR (neat) 1725, 1625, 1610 cm^{-1}; NMR (δ^{CCl_4}) 6.05 (1 H, br s), 5.95 (1 H, dd, J = 11, 17 Hz), 5.55 (1 H, br s), 5.09–4.80 (2 H, m), 3.66 (3 H, s)).[9]

The Claisen route to α-substituted acrylic esters can offer efficient solutions to the synthesis of naturally occurring α-methylenelactones.[10] To illustrate this point, we describe its application to a concise, highly stereoselective synthesis of frullanolide 1[4] (Scheme II).

The prerequisite allylic alcohol (10) was first prepared from the readily available dimethyloctalone 9[11] by standard methods. Thus, 9 was treated with alkaline hydrogen peroxide (0 °C, 48 h) to give a 9:1 mixture of epimeric β (NMR, epoxide C–H, δ 3.03) and α (NMR, epoxide C–H, δ 3.12) epoxy ke-

tones.[12] The pure β-epoxide (mp 43–44 °C) was easily secured by low temperature crystallization in 87% yield. Wharton rearrangement (hydrazine hydrate, methanol) then gave 10 (71% yield; mp 43–44.5 °C; IR (Nujol) 3460, 1650 cm^{-1}; NMR (δ^{CCl_4}) 5.78 (2 H, br s), 0.99 (3 H, s), 0.96 (3 H, d, J = 7 Hz)).

Conversion of 10 to the corresponding β-pyrrolidinopropionate 11 could not be effected with acryloyl chloride and ethyldiisopropylamine. This problem is presumably due to the highly hindered nature of the hydroxyl group. We found, however, that treatment of the lithium salt of 10 in anhydrous THF with acryloyl chloride followed by the addition of excess pyrrolidine resulted in the formation of ester 11 in 80–85% yield (IR (neat) 1730 cm^{-1}). Crude 11 was converted to the corresponding triethylsilylketene acetal (LiNiPr$_2$/THF, Et$_3$SiCl, −45 °C), rearranged in refluxing toluene (20 min), and eliminated (Me$_2$SO$_4$, MeOH, K$_2$CO$_3$, 2 h) as described above. This one-flask procedure converted 11 to the desired acrylate 12 in 42% yield after column chromatography (silica gel G, 1.5% ether–pentane). The infrared of 12 showed bands characteristic of the α-substituted acrylic ester residue (1725, 1620 cm^{-1}) and the NMR showed the appropriate vinyl hydrogens at δ 6.12, 5.49 (α-methylene protons) and 5.12 (cyclohexenyl proton). The doubly allylic proton was displayed as a broad multiplet at δ 3.30. Saponification (KOH/MeOH–H$_2$O, 25 °C) and iodolactonization[8] (KI$_3$/NaHCO$_3$–H$_2$O, 25 °C) gave the crystalline iodolactone 13 (mp 80 °C dec; IR (Nujol) 1760, 1665 cm^{-1}). Dehydrohalogenation with DBU in THF (25 °C, 1.5 h) led smoothly to (±)-frullanolide, 1 (73% yield from 12), as the only product by TLC.

Synthetic 1 crystallized from pentane after preliminary purification by PLC to give fine needles, mp 92–92.5 °C (lit.,[3] prisms, mp 77 °C for optically active 1), and was completely indistinguishable from natural (+)-frullanolide by IR (CHCl$_3$), NMR, MS, and TLC.

Scheme II

References and Notes

(1) This work was presented in part at the 28th Southeastern Regional Meeting of the American Chemical Society, Oct 1976.
(2) S. M. Kupchan, Trans. N.Y. Acad. Sci., 32, 85 (1970); S. M. Kupchan, M. A. Eakin, and A. M. Thomas, J. Med. Chem., 14, 1147 (1971); K.-H. Lee, E.-S. Huang, C. Piantadosi, J. S. Pagano, and J. A. Geissman, Cancer Res., 31, 1649 (1971); K.-H. Lee, R. Meck, C. Piantadosi, and E.-S. Huang, J. Med. Chem., 16, 299 (1973).
(3) Claisen rearrangements: (a) W. S. Johnson, L. Wethermann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner, and M. R. Petersen, J. Am. Chem. Soc., 92, 741 (1970); (b) R. E. Ireland, R. H. Mueller, and A. K. Willard, ibid., 98, 2868 (1976).
(4) G. W. Perold, J.-C. Muller, and G. Ourisson, Tetrahedron, 28, 5797 (1972). A partial synthesis of (−)-frullanolide from α-santonin has been described: A. E. Green, J.-C. Muller, and G. Ourisson, Tetrahedron Lett., 2489 (1972).
(5) Triethylchlorosilane (Et$_3$SiCl) possesses a number of advantages over tert-butyldimethylchlorosilane (t-BuMe$_2$SiCl). Like t-BuMe$_2$SiCl, Et$_3$SiCl reacts with ester enolates to give largely O-silylation (cf. M. W. Rathke and D. F. Sullivan, Synth. Commun., 3, 67 (1973)). The reaction occurs within minutes at −45 °C in THF without added HMPA. In addition, Et$_3$SiCl is relatively inexpensive and will not freeze even when added directly to −78 °C reaction mixtures.
(6) Methyl iodide is less effective but may be used to prepare relatively unhindered acrylates like 4a–c.
(7) All new compounds gave satisfactory IR, NMR, and C, H analyses.
(8) J. P. Marino and D. M. Floyd, J. Am. Chem. Soc., 96, 7138 (1974). See also: I. Kuwajima and Y. Doi, Tetrahedron Lett., 1163 (1972); J. P. Marino and J. S. Farina, ibid., 3901 (1975); P. A. Grieco, C. J. Wang, and G. Majetich, J. Org. Chem., 41, 726 (1976).
(9) Cf. H. O. House, J. Lubinkowski, and J. J. Good, J. Org. Chem., 40, 86 (1975).
(10) α-Methylenelactone syntheses have been reviewed: P. A. Grieco, Synthesis,

67 (1975); R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synth. Commun.*, 5, 245 (1975).

(11) W. C. Still and F. L. VanMiddlesworth, *J. Org. Chem.*, in press.

(12) Cf., inter alia: (a) J. T. Edward and J.-M. Ferland, *Can. J. Chem.*, 44, 1317 (1966); (b) H. B. Henbest and W. R. Jackson, *J. Chem. Soc. C*, 2459 (1967); (c) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, 35, 161 (1970). See also: (d) B. M. Trost and T. N. Salzmann, *J. Chem. Soc., Chem. Commun.*, 571 (1975); (e) G. W. Schaffer, E. H. Eschinasi, K. L. Purzycki, and A. B. Doerr, *J. Org. Chem.*, 40, 2181 (1975).

W. Clark Still,* Marilyn J. Schneider

Department of Chemistry. Vanderbilt University
Nashville, Tennessee 37235

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## Overall Mechanism of Terpenoid Terminal Epoxide Polycyclizations[1]

Sir:

Past studies have revealed that in the nonenzymic generation of the AB[2] and ABC[3] ring systems of polycyclic terpenoids (including the lanosterol type) from polyene terminal epoxides (e.g., **1** → **2**), cyclizations do not proceed through partially


1   **2**
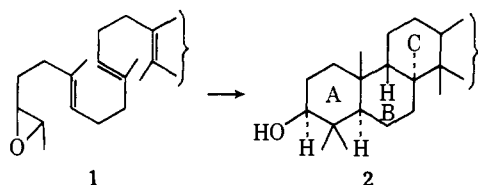
cyclized intermediates with newly formed π bonds requiring protonation for further reaction, or through equilibrating mono- and bicyclic carbonium ion conformers or other related species, but are more concerted, possibly involving intermediate "frozen" carbonium ions or ion pairs. We present herein a new body of results which, taken together with certain other considerations, (1) indicate that the A ring is formed with a high degree of neighboring π-bond participation during S_N2-like epoxide ring opening, and (2) suggest that the overall annulation process is not completely concerted, but involves a series of conformationally rigid carbocyclic cationic intermediates.[4] These conclusions are incorporated into an overall picture which represents the most detailed mechanistic interpretation to date of this fundamental cyclization process, a notable example of which is the biological conversion of squalene 2,3-oxide (**3**) to lanosterol (**4**) (Scheme I).

Anchimeric assistance in the epoxide ring opening process is revealed by comparison of the reaction rates of diene monoepoxides, e.g., **5a**[5] and **5b**, with saturated counterparts. For example, under conditions (8.65 × 10⁻⁴ M SnCl₄ in benzene at 5–7 °C) similar to those where under total polyene epoxide cyclization can be as high as 67%,[6] epoxide **6** is >90% recov-

5   **6**
a, R = CH₃; R' = R'' = H
b, R = H; R' = R'' = CH₃
c, R = R'' = CH₃; R' = H
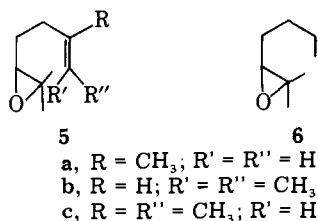
ered after 15 h, while the unsaturated epoxide **5b** reacts completely within 5 min[7] (competitive rates of disappearance of substances in the same vessel). In support of a concerted process, the 12,12,12-trideuterio-10,11-oxido-*trans,trans*-farnesyl acetate racemate, in which the 10-H and 11-CD₃ are cis (**7**),[8] cyclizes under conditions already described[6c] to a trideuteriohydroxydriminol (**8**) in which, as in the enzymic cycliza-

Scheme I
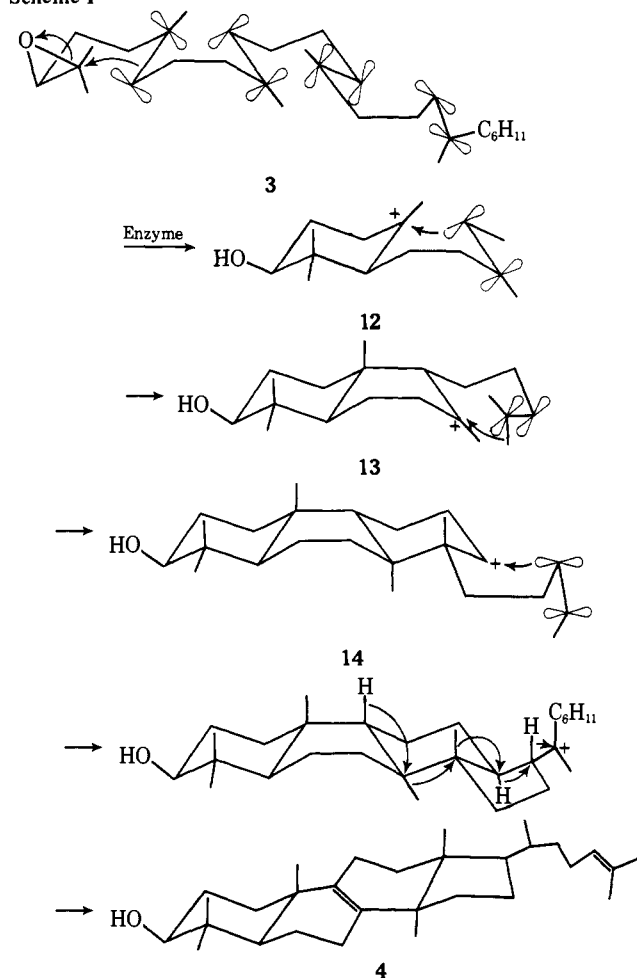
tion,[10] the isotopically labeled methyl group has maintained its stereochemical integrity and appears as an 4α-substituent, as revealed by the absence in **8** of the δ 0.98 (CDCl₃, 100 Hz) NMR signal assigned to the corresponding 4α-methyl in the undeuterated case.[9]

7   **8**
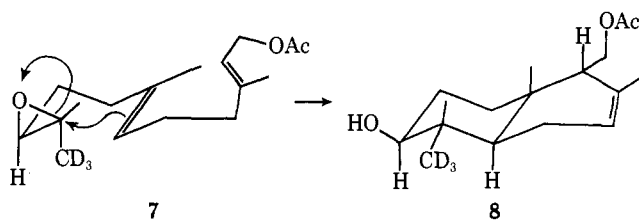
In an attempt to detect participation of additional π bonds in systems of the type where bicyclization and tricyclization can be extensive,[6] the rate of disappearance of diene monoepoxide **5c**[11] was compared (as in **5b/6** above) with that of triene monoepoxide **9**[11] and of tetraene monoepoxide **10**.[6b] Half-lives for **5c**, **9**, and **10** were ~75, 100, and 100 min, respectively, with rate ratios **5c/9** = 1.4 ± 0.1 and **5c/10** = 1.3 ± 0.2. Under these conditions, the total yield of cyclization product from, e.g., **10**, was ≥57% (>20% of previously described tricycles[6b] and 37% of 2,3,4-trimethylcyclohexanone(**11**), resulting from monocyclization and subsequent

9   **10**   **11**