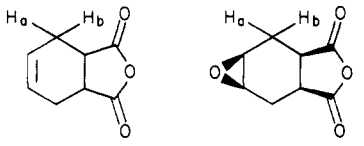
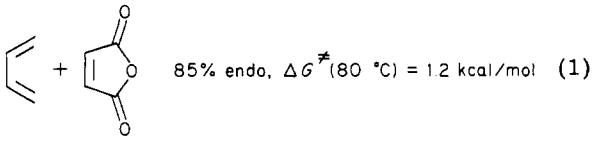
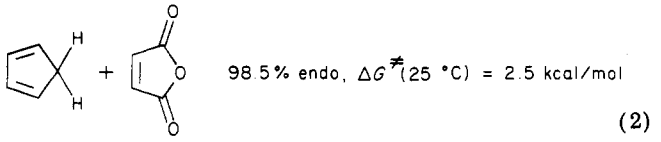


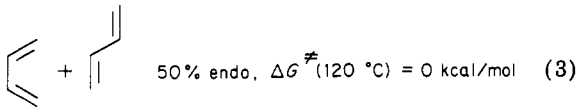
4 5

suggests that the low-field proton is cis to the anhydride. Since the low-field proton is also that which primarily remains undeuterated when 1 is employed, the major product is 3, as shown, and the predominant transition state is endo.

This experiment is in general agreement with other studies of this reaction.[10] Comparison of reactions 1 and 2 suggest that steric factors are important in forcing endo selectivity but are not an exclusive influence. Comparison of 1 and 3 also suggests that maleic anhydride is better disposed than is butadiene to take advantage of factors favoring endo selectivity.







The present result is particularly important in that it does not involve steric *destabilization* of exo transition states as a factor in endo selectivity. Indeed, in the case of butadiene plus maleic anhydride we would presume that steric repulsions in the endo transition state must be the larger. Thus the 1.2 kcal/mol favoring of endo must represent a *minimum* intrinsic energy advantage that one can associate with an electronic explanation of the Alder endo rule.

Acknowledgment. The work has been supported by the National Science Foundation Grant CHE-8012233.

(10) Most recently see Houk, K. N. *Tetrahedron Lett.* **1970**, 2621. By comparing cyclopentene to cyclopentadiene as dienophiles, Houk concludes that the second double bond stabilizes the endo transition state by 2.5–5.0 kcal/mol. This was ascribed to a secondary orbital interaction.

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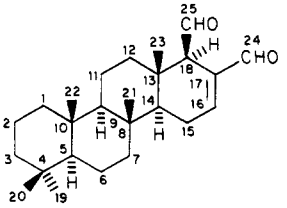
Biogenetic-Type Synthesis of Scalaranes

Summary: The *E*- and *Z*-isoprenologues **2a** and **3a** of methyl *ent*-copalate undergo stereospecific cationic cyclization to tetracyclic substances belonging to the scalarane class of sesterterpenes.

Sir: Certain sponges of the order Dictyoceratidae contain tetra- or pentacyclic sesterterpenes exemplified by the scalaradials (1), which exhibit various biological activities.[1,2] No synthesis of a scalarane is on record and there is no information on their biosynthesis. It has been proposed that the scalaranes arise by a triterpene-like cyclization of a geranylfarnesol precursor initiated at the isopropylidene group.[3] However, it is also possible that, like copalol or *ent*-copalol pyrophosphate in the biogenesis of tri- and tetracyclic diterpenes,[4] the isoprenologue **2b** of *ent*-copalol pyrophosphate is a way station on the enzymic route to the scalaranes. In the present communication we report stereospecific cationic cyclizations that stimulate this process and also describe elaboration of functionalities present in some naturally occurring scalaranes.[5]



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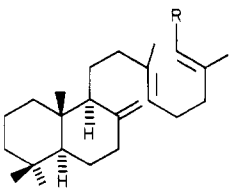
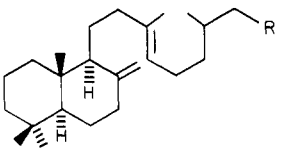


2a, R = CO_2Me
b, R = CH_2OPP
c, R = CH_2OH



3a, R = CO_2Me
b, R = CH_2OH

After failure of several other approaches, **2a** and **3a** were synthesized conveniently as follows. Combination of manool (4) and ethyl acetoacetate under Carroll reaction[6] conditions afforded 13*E* ketone **5** and its *Z* isomer (2:1, 70%), readily distinguished by ^{13}C NMR spectroscopy[7] and separated by HPLC. Condensation of **5** with trimethyl phosphonoacetate (NaH, Me_2SO)[8] then gave **2a** and **3a** (2:1, 75%), also easily distinguished by NMR spectroscopy[9] and separated by HPLC.

(1) (a) Cimino, G.; De Stefano, S.; Minale, L.; Trivellone, E. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1587 and references cited therein. (b) Cafieri, F.; De Napoli, L.; Fattorusso, E.; Santacroce, C.; Sica, D. *Tetrahedron Lett.* **1977**, 477. (c) *Experientia* **1977**, *33*, 994. (d) *Gazz. Chim. Ital.* **1977**, *107*, 71. (e) Kashman, Y.; Rudi, A. *Tetrahedron* **1977**, *33*, 2997. (f) Cafieri, F.; De Napoli, L.; Iengo, A.; Santacroce, C. *Experientia* **1978**, *34*, 300. (g) Cimino, G.; Cafieri, F.; De Napoli, L.; Fattorusso, E. *Tetrahedron Lett.* **1978**, 2041. (h) Cimino, G.; De Stefano, S.; Di Luccia, A. *Experientia* **1979**, *35*, 1277. (i) Kashman, Y.; Zviely, M. *Tetrahedron Lett.* **1979**, 3879. (i) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Daly, J. J. *Aust. J. Chem.* **1980**, *33*, 1783. (k) Walker, R. P.; Thompson, J. E.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4976; (l) Kikuchi, H.; Tsukitani, Y.; Shimizu, I.; Kobayashi, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1981**, *29*, 1492.

(2) Different authors have used different numbering systems for these compounds that are known as scalaranes. We use the one of ref 1j.

(3) Cordell, G. A. *Phytochemistry* **1974**, *14*, 2343.

(4) For references, see (a) Coates, R. M.; Cavender, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 6358. (b) Drengler, K. A.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 856.

(5) For biomimetic acid catalyzed cyclizations leading to other polycyclic systems, see (a) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. (b) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. (c) Van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *20*, 1259.

(6) Carroll, M. F. *J. Chem. Soc.* **1941**, 507.

(7) For the 13*E* isomer: C-12 δ 38.38 (t), 13-Me δ 15.92 (q); for the 13*Z* isomer, C-12 30.51 (t), 13-Me 23.28 (q). All new compounds gave satisfactory high-resolution mass spectra and were pure by ^1H and ^{13}C NMR criteria. ^1H NMR spectra were run at 270 MHz, ^{13}C NMR spectra at 67.89 MHz in $CDCl_3$ solution.

(8) Greenwald, R.; Chaykovsky, M.; Corey, E. *J. Org. Chem.* **1963**, *28*, 1128.

(9) For **2a**, 17-Me δ 2.18, 18.84 (q), C-15 41.00 (t); for **3a**, 17-Me δ 1.89, 25.53 (q), C-16 33.48 (t). $LiAlH_4$ reduction of **2a** or **3a** gave **2c** or **3b**.

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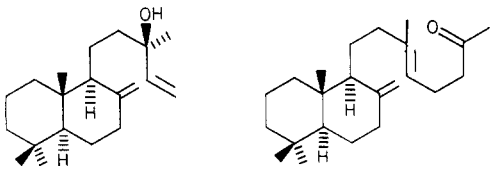

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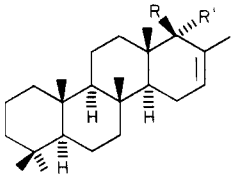
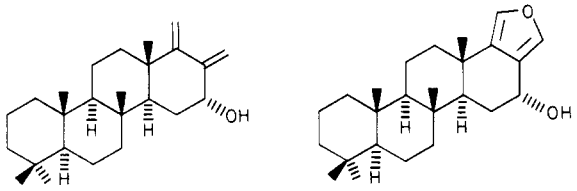


6a, R = CO_2Me; R′ = H
b, R = H; R′ = CO_2Me
c, R = CH_2OH; R′ = H
d, R = CH_2OTs; R′ = H
e, R = Me; R′ = H
f, R, R′ = $=CH_2$



7 8

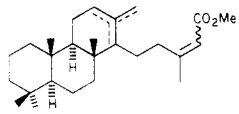
Cyclization of **2a** and **3a** separately ($SnCl_4$, C_6H_6, 1 h at room temperature)[10] gave **6a** (mp 165–169 °C, 25%) from **2a** and **6b** (gum, 18%) from **3a** after multiple TLC.[11] That cyclization to a tetracyclic ring system had taken place was deduced from the ^1H and ^{13}C NMR spectra[1,14] and the MS, which exhibited characteristic peaks for Δ^{16}-scalarane fragmentation.[1,15] As for stereochemistry, shifts and $W_{1/2}$ indicated that H-18 was pseudoaxial in **6a** and pseudoequatorial in **6b**[16] as in the cyclization of (*E*)-13- and (*Z*)-13-methyl anticopalate to *ent*-methyl isocopalate and *ent*-methyl 14-epiisocopalate;[17] hence by extrapolation the C-13 methyl group was axial and the C/D ring junction trans.[18] That addition of the 13,14 double bond to the cationic center at C-8 formed in the initial stage of the cyclization process occurred from the less hindered α face as it does in the cyclization of labda-8(17),13-dienes[17,19,20] to give an all-trans tetracyclic system was shown by the ^{13}C NMR spectrum of **6a** where C-21, C-22, and C-23 all appear at fields higher than δ 20.[21,22]

Conversion of **6a** to a compound closely related to a naturally occurring scalarane was achieved as follows. $LiAlH_4$ reduction (65%) to **6b** and treatment of tosylate **6b** (70%) with NaOEt–EtOH gave **6e** (77%). Photooxygenation ($^1O_2$),[23] followed by reduction [$P(OEt)_3$], afforded **7** (45%) with a pseudoaxial and α-oriented hydroxyl [H-14, δ 4.38 (t, J = 3 Hz)].[24] Further photooxygenation of **7** and exposure of the intermediate epidioxide to aqueous $FeSO_4$[23] gave **8** (12-deacetoxy-16-epiheteronemin).[25] Work to introduce the 12-hydroxyl group present in all sponge scalaranes is in progress.

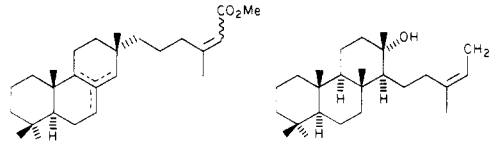
Our work has a bearing on the structure of one of the tricyclic and tetracyclic terpanes that are found in many crude oils and sediments.[26] On the basis of the MS it has been suggested that a tetracyclic hydrocarbon $C_{24}H_{42}$ in the lipid extracts of Georgia–South Carolina clays is derived by diagenesis of scalaranes and possesses structure **9b** or **9c**.[27a] As the origin of these clays is some importance, the presence of compounds so far linked only to marine organisms would be of considerable interest.

Catalytic reduction of **6e** from $LiAlH_4$ reduction of **6d** gave a mixture of C-17 epimers **9a** whose MS exhibited inter alia a very strong peak (95%) at m/z 259 due to ion A.[28] This peak is entirely missing from the MS of the $C_{24}H_{42}$ hydrocarbon,[29] which must therefore have a carbon

(10) Among many other reagents tried with **2a** only BF_3 gave some **6a**.
(11) The other product fraction from **2a** was a mixture of tricyclic E isomers ia and iia (NMR analysis), which we have so far not been able



ia, E isomers
b, Z isomers



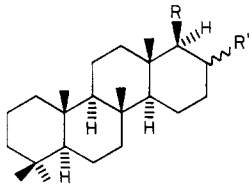
iia, E isomers
b, Z isomers

iii

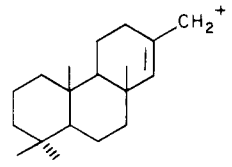
to separate. The other product fraction from **3a** was comprised of the *Z* isomers ib and iib. Esters ia,b possess the carbon skeleton of the fern sesterterpene cheilanthatriol iii,[12] which obviously represents an intermediate stage in the biogenesis of the scalaranes. The cyclization mode leading to ii is that of the tricyclic diterpenes;[13] sesterterpenes of this type seem to be unknown so far.

(12) (a) Kahn, J.; Zaman, A.; Chetty, G. L.; Gupta, A. S.; Dev, S. *Tetrahedron Lett.* **1971**, 4443. (b) Gupta, A. S.; Dev, S.; Sangare, M; Septe, B.; Lukacs, G. *Bull. Soc. Chim.* Fr. **1976**, 1879.
(13) (a) Hanson, J. R. *Fortschr. Chem. Org. Naturst.* **1971**, *29*, 395. (b) Coates, R. M. *Ibid.* **1976**, *33*, 73.
(14) ^1H NMR for **6a**: Me's at δ 0.80, 0.83, 0.84, 0.91, 0.94 (all s, the last H-23 solvent shifted to δ 1.17 in C_6D_6), 1.59 (br, H-24) allylically coupled to H-16 at δ 5.50 (br, $W_{1/2}$ = 10 Hz), 2.88 (br, H-18, $W_{1/2}$ = 9 Hz), 3.66 (OMe). ^1H NMR for **6b**: Me at δ 0.80, 0.84, 0.84, 0.90, 0.93 (all s, none solvent shifted in C_6D_6), 1.61 (br (H-24) allylically coupled to H-16 at δ 5.58 (m, $W_{1/2}$ = 10 Hz), 2.47 (br H-18, $W_{1/2}$ = 4 Hz), 3.69 (OMe); ^{13}C-NMR, requisite number of singlets, doublets, and triplets in the region δ 15–56; also for **6a** signals at δ 62.63 (d, C-18), 124.00 (d, C-16), 128.99 (s, C-17), 173.32 (s, C-25); for **6b** these signals occur at δ 61.92 (d), 124.63 (d), 128.48 (s), 174.70 (s).

(15) At m/z 260 for retro-Diels-Alder fragmentation, 205 (cleavage of 8,14 and 11,12 bonds), 191 (cleavage of 8,14 and 9,11 bonds), 137 (cleavage of 6,7 and 9,10 bonds) and 123 (cleavage of 5,6 and 9,10 bonds).
(16) Cf. shifts and $W_{1/2}$ of H-14 in *ent*-methyl isocopalate and *ent*-methyl 14-epiisocopalate.[17]
(17) Bory, S.; Do Khac Man, D.; Fetizon, M.; Kone, M.; Trong Anh, N. *Bull. Soc. Chim. Fr.* **1975**, 2347.
(18) See also the solvent shifts exhibited by the H-23 signal[14] that are in accordance with this deduction.
(19) Gonzalez, A. G.; Martin, J. D. *Tetrahedron Lett.* **1972**, 2259.
(20) Sundararaman, P.; Herz, W. *J. Org. Chem.* **1977**, *42*, 806. Herz, W.; Prasad, J. S.; Mohanraj, S. *J. Org. Chem.*, in press.
(21) (a) Balogh, B.; Wilson, D. N.; Burlingame, A. L. *Nature (London)* **1971**, *233*, 261. (b) Gouch, J. L.; Guthrie, J. P.; Stothers, J. B. *J. Chem. Soc., Chem. Commun.* **1972**, 979. (c) Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1974**, *52*, 870.
(22) In comparison with **6a**, **6b** exhibits an appreciable upfield shift for C-14 and an appreciable downfield shift for C-23; cf. **1b** with **1a**.[1b]
(23) (a) Turner, J. A.; Herz, W. *J. Org. Chem.* **1977**, *42*, 1900. (b) Mohanraj, S.; Herz, W. *Ibid.* **1981**, *46*, 1362.
(24) Compare chemical shifts of C-14 (δ 50.05) and C-16 (δ 72.79) with C-12 (δ 72.5) and C-9 (V 49.4) of 13(16),14-isocopaladien-12β-ol; de Miranda, D. S.; Brendolan, G.; Imamura, P. M.; Sierra, M. G.; Marsaioli, A. J.; Ruveda, E. *J. Org. Chem.* **1981**, *46*, 4851.
(25) For properties of heteronemin, see ref li and Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Tetrahedron Lett.* **1976**, 2631.
(26) (a) Aquino Neto, F. R.; Restle, A.; Connan, J., Albrecht, P.; Qurisson, G. *Tetrahedron Lett.* **1982**, *23*, 2027. (b) Ekweozor, C. M.; Strausz, O. P. *Ibid.* **1982**, *23*, 2711. (c) Trendel, J.-M.; Restle, A.; Connan, J.; Albrecht, P. *J. Chem. Soc., Chem. Commun.* **1982**, 304.
(27) (a) Scholefield, D.; Whitehurst, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 135. (b) We are indebted to Dr. Whitehurst for correspondence on this point.
(28) Significant peaks in the MS of **9a** were at m/z (composition, %) 344 (M^+, 30), 329 ($M^+ - CH_2$,21), 259 ($C_{19}H_{31}$, 95), 205 ($C_{15}H_{25}$, 10), 191 ($C_{14}H_{23}$,82), 177 ($C_{13}H_{21}$, 19), 163 ($C_{12}H_{19}$, 100), 137 ($C_{10}H_{17}$, 45), 123 (C_9H_{15}, 60), 109 (C_8H_{13}, 65), 95 (C_7H_{11}, 40), 81 (C_6H_9, 52), 69 (C_5H_9, 93), and 67 (C_5H_7, 54).



9a, R = R′ = Me
b, R = Me; R′ = H
c, R = H; R′ = Me



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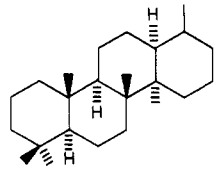

10

skeleton different from that attributed to it. The absence of peaks in the range between the M–CH_3 ion and m/z 206 is reminiscent of the mass spectral behavior of hopanes[27b] and, in fact, the MS of the $C_{24}H_{42}$ hydrocarbon is essentially identical with that of a C_{24} secohopane **10** recently synthesized by Albrecht and co-workers[26c] and shown to be the lowest member of a C_{24}–C_{27} series occurring in sediments and petroleums.

Acknowledgment. This study was supported in part by a National Science Foundation Grant (CHE-7801 191).

Supplementary Material Available: Experimental details on synthesis and ^1H NMR and mass spectra of all new compounds described in this work (11 pages). A table listing the ^{13}C NMR spectra of **2a,b**, **3a,b**, **5**, and (*Z*)-**5**, **6a,b,e,f** and **7** is included. Ordering information is given on any current masthead page.

(29) A copy of the computer-generated GC/MS of the $C_{24}H_{42}$ hydrocarbon kindly sent to us by Dr. Whitehurst had peaks at m/z (relative intensities approximate) 330 (10), 315 (10), 274 (1), 251 (1), 206 (12), 191 (68), 177 (38), 163 (8), 150 (23), 137 (25), 136 (28), 123 (42), 109 (78), 97 (100), 95 (59), 81 (49), 69 (21), and 67 (18). For the MS of **10**, see ref 26c.

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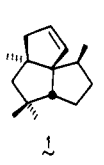
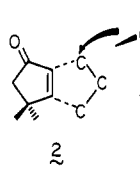
Total Synthesis of Racemic Silphinene

Summary: The tricyclic sesquiterpene silphinene (**1**) has been synthesized in fully stereocontrolled fashion from 4,4-dimethylcyclopentenone by a twofold five-ring annulation sequence in 15 steps and 10% overall yield.

Sir: Highly condensed polycyclopentanoid (polyquinane[2]) natural products have come to represent an increasingly important class of natural products. Considerable interest has been paid to the total synthesis of these substances because of their appealing and frequently intricate molecular architecture which has often mandated the development of new strategies. One of the more recent additions to this class is silphinene (**1**), a sesquiterpene hydrocarbon isolated in 1980 by Bohlmann and Jakupovic from *Silphium perfoliatum*.[3] The structural assignment



1



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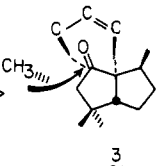

3

to **1** was based on its ^1H NMR spectrum and those of select oxidation products. Central to the derived formula is a tricyclo[6.3.0.$0^{4,8}$]undecene ring system possessing four logistically placed methyl groups. As such, silphinene is recognizable as a congener of isocomene[4,5] and pentalenene[6] whose directed syntheses we have completed earlier. Importantly, however, the unique stereodisposition of the double bond and pendant alkyl groups within **1** necessitates the implementation of an entirely different protocol. In this connection, we have now developed a short and notably efficient synthetic approach to **1** that fully confirms its assigned structure.

From the retrosynthetic perspective, we viewed **1** to be potentially accessible from 4,4-dimethylcyclopentenone (**2**).[7] Insertion of a three-carbon chain across the double bond was first to be implemented in a manner that would ultimately permit stereochemically clean introduction of a secondary β-methyl substituent. Judicious selection of functional groups was required, since the first cyclopentannulation was to be followed by a second to establish the tricyclic skeleton (see **3**). Because the latter ring-forming maneuver installs both an endocyclic olefinic center and angular α-methyl group, it appears to have different requirements from the first. Nevertheless, we anticipated the possibility of exploiting similar high-yielding aldol condensations in both contexts to achieve the needed stereo- and regiochemical control.

Central to the overall scheme is the ready availability of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane[8] and the efficiency with which this reactive intermediate undergoes CuBr·Me_2S-promoted conjugate addition to α,β-unsaturated enones.[9] Following admixture of these reagents with **2** in THF at −78 °C, the product was directly hydrolyzed (HCl, H_2O, THF) to give **4** (78%).[10] Since spontaneous dehydration is not encountered in β-hydroxy ketones of this type, conversion to **5** required formation of the mesylate and elimination with DBU in CH_2Cl_2 (76%; Scheme I).

Consideration was next given to the desirability of introducing the angular methyl group while simultaneously setting the stage for the second cyclopentannulation. To this end, **5** was treated with methyllithium and the tertiary allylic alcohol so formed was directly oxidized with PCC and Celite in CH_2Cl_2.[11] With the isolation of **6**, the feasibility of interring allylic rearrangement–oxidation was demonstrated for the first time.[12] Although the tertiary

(1) National Institutes of Health Postdoctoral Fellow, 1981–1982.
(2) Paquette, L. A. *Forschr. Chem. Forsch.* **1979**, *79*, 41.
(3) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.
(4) Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014; *J. Am. Chem. Soc.* **1981**, *103*, 1835.
(5) For additional isocomene syntheses, see: (a) Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493; *Tetrahedron*, **1981**, *37*, 4359. (b) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130; **1981**, *103*, 82. (c) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103.
(6) Annis, G. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 4504.
(7) Magnus, P. D.; Nobbs, M. S. *Synth. Commun.* **1980**, *10*, 273.
(8) Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560.
(9) For the earliest report of conjugate addition reactions of the related dioxolane, see Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 4217.
(10) (a) Each new compound exhibits infrared and ^1H NMR spectra (90, 200, or 300 MHz) fully compatible with its assignment. Analytical samples gave satisfactory C/H combustion analysis and/or appropriate high-resolution mass spectral parent ions. (b) All yields recorded herein are based upon isolated materials which exhibit one spot on TLC (>95% purity).
(11) Boeckman, R. K., Jr., personal communication.

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