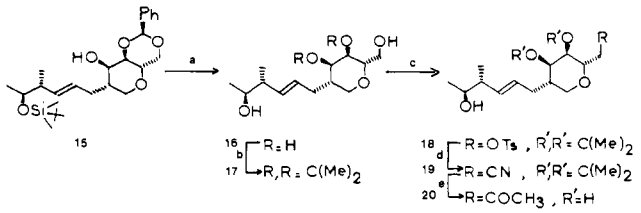
Scheme III[a]



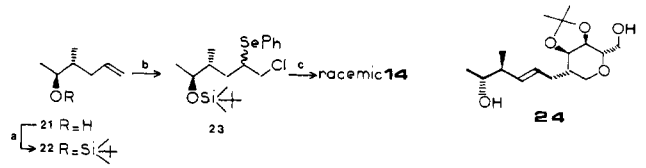
[a] Reagents: (a) 4:1 dioxane-1 N HCl, (v/v) room temperature, 6 h, 97%; (b) acetone, 0.5% H_2SO_4, molecular sieve 4 Å, room temperature, 20 min, 77%; (c) 1.1 equiv of TsCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 1.5 h, 96%; (d) KCN, HMPT, crown ether (18-crown-6), room temperature, 12 h, 94.5%; (e) $AlMe_3$, $Ni(acac)_2$, PhMe, 0 °C, 6 h, then (a), 84%.

afforded the expected product **15** in 43% yield. This reaction is characterized by the regiospecificity of the nucleophilic ring opening of the epoxide, the regiospecific formation, from the allylic Grignard reagent, of the "normal", i.e., "nonrearranged" addition product, and finally the formation of a *E* double bond,[12] these last two features being critical and far from obvious.[13] Acid hydrolysis of **15** gave the polyol **16**, which then converted into the acetonide derivative **17**[14] (Scheme III).

The use of the costly chiral chloride **14** can be averted by that of the racemic form, prepared in three steps from the easily available alcohol **21**,[13a,15] taking up an idea introduced by Raucher[16] (Scheme IV). Entry of the racemic chloride **14** into the previously described methodology finally gave two stereoisomers (ratio 1:1) separable on a silica gel column (3:1 toluene–acetone, v/v): **17**, fully identical with the compound previously prepared, and **24**.

Selective tosylation of **17** afforded **18**; treatment with potassium cyanide produced **19**. After extensive experimentation, the ketone **20** was obtained in 84% yield upon treatment of the cyanide **19** with trimethylaluminum in the presence of $Ni(acac)_2$,[17] followed by acid hydrolysis.[18] Elongation of the right side chain was essentially performed along lines already described.[4,19] Silylation of the ketone **20** (BSA,CH_3CN, room temperature, 12 h), reaction with the anion of ethyl diethylphosphonoacetate (dioxane, room

Scheme IV[a]



[a] Reagents: (a) TBDMSCl, imidazole, DMF, room temperature, 30 min, 96%; (b) PhSeCl, CCl_4, 0 °C, 15 min; (c) H_2O_2, pyridine, 0 °C, 20 min, then room temperature, 3 h, 72% from **22**.

temperature, 12 h), and desilylation (4:1 dioxane–1 NHCl, v/v, room temperature, 10 min) gave predominantly ethyl monate C (**1e**;[21] 82.4%), easily separated from the *Z* isomer (12.2% yield) on a silica gel column (13:1 CH_2Cl_2–MeOH, v/v). Saponification of the ester **1e** (aqueous 1 N NaOH, 30 equiv, room temperature, 1 h, then 65 °C, 5 min) and treatment of the isolated sodium salt with methyl 9-iodononanoate[22] (DMF, room temperature, 3 h) produced methyl pseudomonate C (**1d**), identical with the natural substance isolated by the Beecham group (TLC in various solvents, optical rotation, ^1H and ^{13}C NMR).

Since methyl pseudomonate C can be converted to pseudomonic acids A[23] and C,[5] the present work also constitutes formal total synthesis of pseudomonic acids A and C.

Acknowledgment. We thank the Centre National de la Recherche Scientifique for financial support (ERA 739), Dr. G. Lukacs and G. Berenger for ^{13}C NMR data, Nermag for GLC–MS, and Dr. N. H. Rogers for supplying various samples.

Supplementary Material Available: Spectral information and physical constants for key substances (6 pages). Ordering information is given on any current masthead page.

(12) Tiny amounts of *Z* isomer ($E/Z > 25$) were easily removed by silica gel chromatography in the subsequent steps.

(13) For discussions on these features, see: (a) Felkin, H.; Frajerman, C.; Roussi, G. *Bull. Soc. Chim. Fr.* **1970**, 3704. (b) Glaze, W. H.; Duncan, D. P.; Berry, D. J. *J. Org. Chem.* **1977**, *42*, 694. (c) Linstrumelle, G.; Lorne, R.; Dang, H. P. *Tetrahedron Lett.* **1978**, 4069. For a recent discussion on the η^1 structure ("σ compound") of allylic Grignard compounds, see: Schlosser, M.; Stähle, M. *Angew. Chem., Int. Ed. Engl.* **1980**, 487.

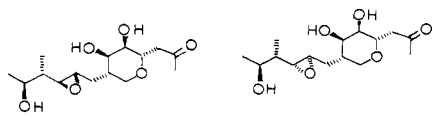
(14) The trans geometry of the C-10, C-11 double bond was clearly established[3] from the ^1H NMR spectrum of the ketal **17** in $CDCl_3$ after addition of 1 equiv of $Eu(fod)_3$, which induces a sufficient separation in the chemical shifts between H-10 and H-11 to enable measurement of the coupling constant, $J_{10,11} = 16$ Hz.

(15) cis-Epoxybutane was prepared according to Pasto and Lumbo: Pasto, D. J.; Lumbo, C. C. *J. Org. Chem.* **1965**, *30*, 1271.

(16) Raucher, S. *Tetrahedron Lett.* **1977**, 3909.

(17) Bagnell, L.; Jeffery, E. A.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1974**, *27*, 2577.

(18) Epoxidation of **20** with MCPBA (CH_2Cl_2, room temperature, 1.5 h) afforded a product (80% yield) that was chromatographically identical (TLC in various solvents) with the ketone obtained from pseudomonic acid A.[19] However, as shown by GLC, this was a mixture of i and ii in a ratio of about 2:3. This ratio was confirmed by ^{13}C NMR, where all the signals belonging to the synthetic sample i were fully identical with those of the sample derived from the natural antibiotic. After GLC (capillary column, CP SIL 5, 25 m × 0.25 mm, 210 °C) the mass spectra of both TMS synthetic and provided samples were identical. Epoxidation with TBHP–$VO(acac)_2$[20] did not significantly enhance production of the isomer i (1:1 ratio).



(19) Clayton, J. P.; Luk, K.; Rogers, N. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 308.

(20) Sharpless, K. P.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

(21) Identical with a sample provided by the Beecham group.

(22) Methyl 9-iodononanoate was prepared from the monomethyl ester of azelaic acid (a, $SOCl_2$; b, $NaBH_4$, dioxane; c, NIS, PPh_3, CH_2Cl_2).

(23) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *Tetrahedron Lett.* **1981**, *22*, 2059.

(24) Pougny, J.-R.; Sinaÿ, P. *J. Chem. Res., Miniprint* **1982**, 0186.

Vinylcyclopropene Triplet Rearrangement Mechanisms: Mechanistic and Exploratory Organic Photochemistry[1,2]

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In previous studies on vinylcyclopropene photochemistry considerable attention has been focused on the rearrangements deriving from the triplet excited state.[3-6] We now have evidence excluding two especially reasonable reaction mechanisms and establishing a mechanism previously thought to have only minor significance. This single mechanism accounts for all of the known triplet cyclopropene to cyclopentadiene rearrangements.

Thus, our earlier work[3,5,6] considered several triplet mechanisms outlined in Scheme I. Mechanism B involved a triplet three-ring opening to afford a carbene which then rearranged to cyclo-

(1) This is Paper 138 of our photochemical series.

(2) (a) For Paper 137 note: Zimmerman, H. E. *Chimia* **1982**, *36*, 423-428. (b) For Paper 136 see: Zimmerman, H. E. *Acc. Chem. Res.* **1982**, *15*, 312-317.

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(4) (a) Padwa, A.; Blacklock, T. J.; Getman, D.; Hatanake, N.; Loza, R. *J. Org. Chem.* **1978**, *43*, 1481-1492. (b) For a recent publication giving further references note: Padwa, A.; Blacklock, T. J.; Loza, R. *Ibid.* **1982**, *47*, 3712-3721.

(5) Zimmerman, H. E.; Hovey, M. C. *J. Org. Chem.* **1979**, *44*, 2331-2345.

(6) Zimmerman, H. E.; Kreil, D. J. *J. Org. Chem.* **1982**, *47*, 2060-2075.

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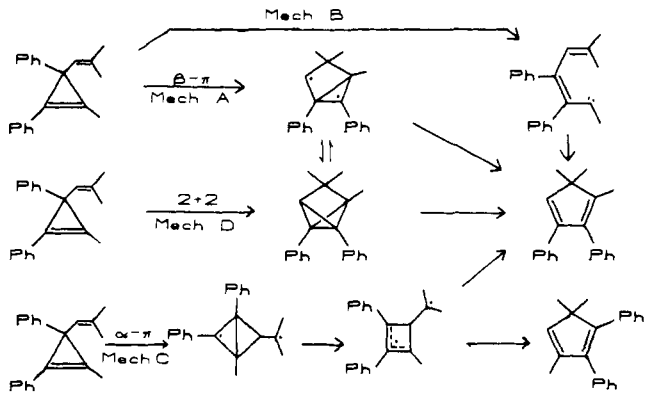
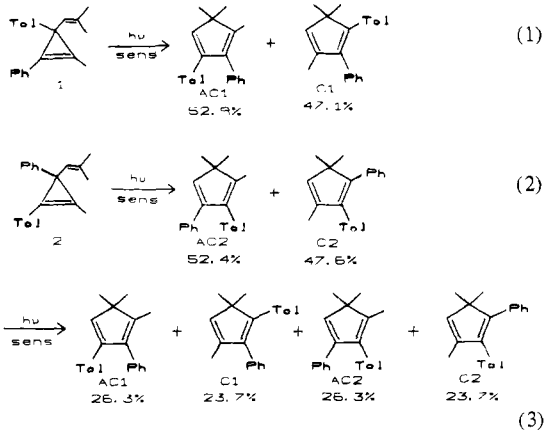
Scheme I. Mechanistic Alternatives for Triplet Cyclopropene Rearrangement



pentadiene product. This mechanism for the triplet[5,6] was excluded although it was considered possible for the singlet.[3-7] A preferred alternative, mechanism A, involved vinyl–vinyl bridging to afford a housane diradical and then product. Interestingly, mechanisms A and B are structurally equivalent.

The reversible closing of the housane diradical to afford a tricyclic intermediate seemed possible as well. Such a closing is tantamount to mechanism D, which involved an initial 2 + 2 cycloaddition with possible opening to the same diradical but, in any case, proceeding onward to cyclopentadiene product (note Scheme I).

A further mechanism, termed "C", appeared to intervene to some extent. This, too, is included in Scheme I. In our present study we investigated the triplet photochemistry of methyl-phenyl-p-tolyl-3-isobutenylcyclopropenes **1–3** (eq 1–3).



(1)

(2)

(3)

The first observation was that *p*-(dimethylamino)benzophenone-sensitized irradiation of the 3-tolylcyclopropene **1** led only to the 2-phenyl-3-*p*-tolylcyclopentadiene (**AC1**) and the 1-*p*-tolyl-2-phenylcyclopentadiene (**C1**) (note eq 1).[8]

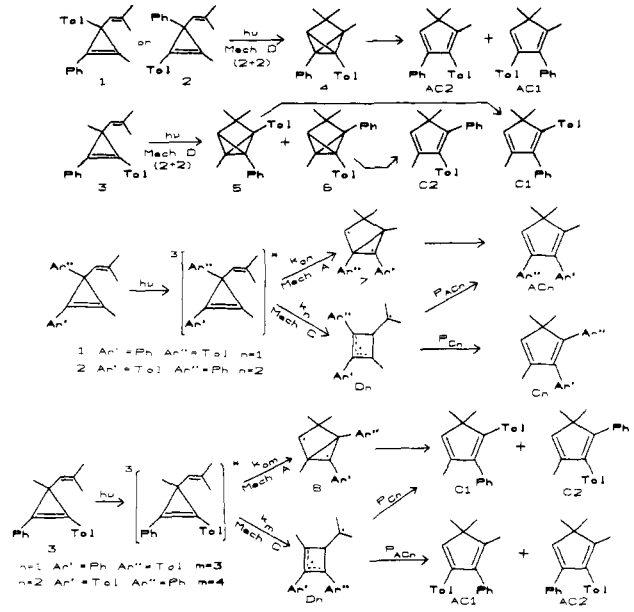
Similar sensitized irradiation of the 3-phenylcyclopropene **2** led, again, to just two products, 2-*p*-tolyl-3-phenylcyclopentadiene (**AC2**) and 1-phenyl-2-*p*-tolylcyclopentadiene (**C2**) as in eq 2.[8]

The designation **AC1** refers to a product that derives from either mechanism A or mechanism C starting with reactant **1**. **C1** is a product derived from reactant 1 only by mechanism C. Similarly **AC2** can be arrived at from cyclopropene **2** by mechanisms A and C while **C2** comes from **2** only via mechanism C.

Finally, sensitized photolysis of the 3-methylcyclopropene **3** led to all four photoproducts, **AC1**, **C1**, **AC2**, and **C2**.[8]

From these results a number of conclusions may be drawn. First, the triplet rearrangement cannot proceed via a tricyclic intermediate as **4** as in mechanism D or from touching of odd-electron centers of the mechanism A housane diradical. The

Scheme II. Mechanisms and Predicted Products



expected regioselectivity of cycloaddition of the 3-*p*-tolylcyclopropene **1** and the 3-phenylcyclopropene **2** would lead to the tricyclic intermediate **4**, and thus both **1** and **2** would give the same products, which is not the case (see Scheme II). The reverse regioselectivity in a 2 + 2 cycloaddition would lead to unobserved products.

Starting with the 3-methylcyclopropene **3** a 2 + 2 cycloaddition predicts the two observed products **C1** and **C2** but would not account for **AC1** and **AC2**, which are also formed.

The second conclusion is that mechanism A alone cannot be operative. From cyclopropenes **1** and **2** one cannot obtain **C1** or **C2**, the observed products (note Scheme II).

Our third conclusion is that mechanism C can account for all of the observed photoproducts. This is seen in Scheme II.

Our fourth point is that mechanism C must account for all of the rearrangement. This derives from consideration of the observed product ratios. Thus, in the reaction of the 3-tolylcyclopropene triplet ^{3}[**1***], k_1 is the rate of formation of diradical **D1**, P_{C1} and P_{AC1} are the respective probabilities of formation of **C1** and **AC1** via **D1**, and k_{o1} is the rate of formation of **AC1** by other routes such as mechanism A. Then eq 4 results. Similarly, eq 5 is obtained from consideration of the processes in eq 2.

$$(C1/AC1)_{run\,1} = (k_1P_{C1})/(k_1P_{AC1} + k_{o1}) \quad (4)$$

$$(C2/AC2)_{run\,2} = (k_2P_{C2})/(k_2P_{AC2} + k_{o2}) \quad (5)$$

$$(C1/AC1)_{run\,3} = (k_3P_{C1} + k_{o3})/(k_3P_{AC1}) \quad (6)$$

$$(C2/AC2)_{run\,3} = (k_4P_{C2} + k_{o4})/(k_4P_{AC2}) \quad (7)$$

Analogously, for the processes in eq 3 we can arrive at eq 6 and 7. This means that limits are set on the relative rates for processes (i.e., corresponding to the k_o's) other than mechanism C.

However, experimentally the ratio of **C1** to **AC1** was observed to be the same (0.89, 0.90) in runs starting with **1** and **3**. This means eq 4 and 6 require the k_o's to be zero. Similarly, the same ratio (0.90, 0.90) of **C2** to **AC2** was found in runs 2 and 3 so that eq 5 and 7 require the k_o's again to vanish. This means that only mechanism C is operating.[9]

Finally, we note that the type C diradical (e.g., **D1** or **D2**) with Hückel overlap,[10] the carbinyl orbital aiming inward and thus

(7) Zimmerman, H. E.; Bunce, R. A. *J. Org. Chem.* **1982**, *47*, 3377–3396.

(8) The percentages in eq 1–3 are normalized to 100%. Mass balances ranged 95–99%, and NMR analysis indicated absence of further products.

(9) Repetition of our previous study[5] reveals that adventitious oxygen quenching led to a product ratio reflecting triplet quenching and singlet reactivity. With rigorous exclusion of oxygen the diphenyl analogues of the present study give the same ratio from 2,3-diphenyl-1-methyl- and 1,2-diphenyl-3-methyl-3-isobutenylcyclopropenes.

being cyclobutadienoid, affords a bifunnel for decay[2b,11,12] to S_0 diradical. This should then adopt a crosswise p orbital orientation of a Möbius system which is ground-state preferred and leads onward to product.

Acknowledgment. Support of this research by NIH Grant GM07487 and the National Science Foundation is gratefully acknowledged. Mechanistic aspects were supported by NSF while exploration of the synthetic aspects were supported by NIH.

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Total Synthesis of Qinghaosu

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Since ancient times *Artemisia annua* L. has been used as a traditional Chinese herbal medicine known as Qinghao for treating fever. The effective constituent was isolated by Chinese investigators in 1972 and shown to be the sesquiterpene lactone **1**,[1] named qinghaosu (Chart I). It was found to be a potent plasmodicidal agent, and extensive clinical trials in China have revealed that **1** has considerable promise for the treatment of drug-resistant malaria.[2] The combination of an outstanding biological activity and an intriguing chemical structure having no precedent in the field of antimalarials incited us to develop a synthetic route toward this novel natural product.

(-)-Isopulegol (**2**) was converted into methoxymethyl ether **3**[3] ($ClCH_2OCH_3$, $PhN(CH_3)_2$, CH_2Cl_2, room temperature), which was hydroborated (B_2H_6, THF, 0 °C) to give after oxidative workup with alkaline hydrogen peroxide the 8*R* alcohol **4** in 80% yield along with 10% of the 8*S* epimer. This transformation was modeled after the stereoselective hydroboration of **2**.[4] After benzylation of the primary hydroxyl group ($PhCH_2Br$, KH, 4:1 THF:DMF, 0 °C) the methoxymethyl ether was cleaved (CH_3OH, HCl, 40 °C, 5 h) and the resulting alcohol **5** oxidized (PCC,[5] CH_2Cl_2, room temperature) to the (benzyloxy)menthone **6**. The overall yield for the conversion of (-)-isopulegol (**2**) into **6** was 58%.

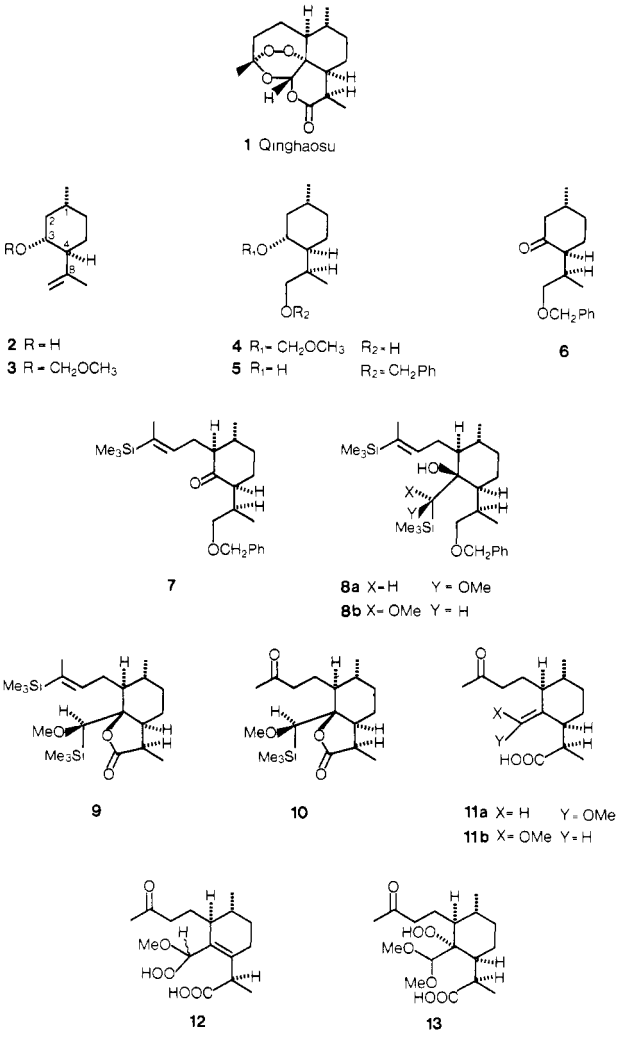
Kinetic deprotonation of **6** (LDA, THF, 0 °C) and treatment of the resulting enolate with (*E*)-(3-iodo-1-methyl-1-propenyl)-trimethylsilane[6] provided a 6:1 mixture of epimeric alkylation products from which the major isomer **7**[7] was isolated in 62% yield.

When ketone **7** was added to 1 equiv of lithium methoxy(trimethylsilyl)methylide[8] (THF, -78 °C), two diastereomeric alcohols, **8a** and **8b**, were obtained in a 1:1 ratio and almost quantitative yield. Since large nucleophiles are known to attack preferentially from the equatorial side of cyclohexanones,[9] both **8a** and **8b** must have the hydroxyl group in the axial position. By use of a 10-fold excess of the reagent the ratio of **8a** to **8b** was shifted to 8:1, and **8a** could be isolated in 89% yield. This stereoselectivity is the result of a kinetic resolution of the racemic organolithium reagent by the chiral ketone. At this point of the synthesis it was not possible to establish unambiguously the configuration of the newly formed exocyclic asymmetric center of **8a** and **8b**. However, the assignment of configuration **8a** to the major isomer followed from the result of the subsequent transformations.

Compound **8a** was debenzylated (Li, NH_3) and the resulting alcohol oxidized (excess PCC,[5] CH_2Cl_2, 15 h) to lactone **9** in 75% yield. Conversion of the vinylsilane group to a ketone[6] (*m*-CPBA, CH_2Cl_2; TFA, CH_2Cl_2, 0 °C, 3 min) was achieved in 72% yield. When the resulting ketone **10** was reacted with fluoride ion (*n*-Bu_4NF, THF, room temperature, 2 h), smooth desilylation occurred with simultaneous generation of the enol ether and carboxylic acid functions of **11a** in 95% yield. The same reaction sequence applied to isomer **8b** produced selectively enol ether **11b** with opposite configuration. The complementary formation of **11a** and **11b** is convincing evidence that the fluoride ion induced β elimination is stereospecific. A synchronous antiperiplanar process as in the acid-catalyzed E2 β elimination of β-(hydroxyalkyl)silanes[10] seems most likely.

When **11a** was reacted with $^1O_2$ (methylene blue, CH_2Cl_2, room temperature), an ene reaction led to hydroperoxide **12** isolated

Chart I



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(2) (a) Qinghaosu antimalarial coordinating research group, *Chinese Med. J.* **1979**, *92*, 811-816. (b) Bruce-Chwatt, L. J. *Brit. Med. J.* **1982**, *284*, 767-768.
(3) Reaction products were separated and purified by column chromatography; all compounds reported were homogeneous by TLC and showed ^1H NMR, IR, and mass spectra consistent with the assigned structures. Selected spectroscopic and physical data are provided as supplementary material.
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(6) (a) Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682-3684. (b) Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. Ibid. **1974**, *96*, 3684-3686. (c) Gauley, R. E. *Synthesis* **1976**, 792.
(7) The stereochemistry of **7**, was unambiguously established by ^1H NMR analysis of the alcohols obtained after $LiAlH_4$ reduction.
(8) Magnus, P. D.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822-823.
(9) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521-546.
(10) Hudrlik, P. F.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993-1996.

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