Tetrahedron Vol 46, Nos 13/14, pp 4487-4502, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

STEREOSPECIFIC APPROACH TO 3-OXOCEN-7-ONES VIA ALIPHATIC CLAISEN REARRANGEMENT. SYNTHESIS OF (+)-(2*R*,8*S*)- AND (+)-(2*R*,8*R*)-LAUTHISAN†

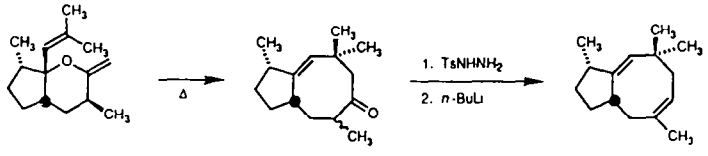
Leo A. Paquette* and Thomas J. Sweeney[1]

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

(*Received in UK 23 January* 1990)

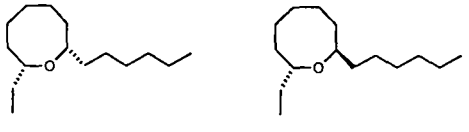
Abstract: A general synthetic strategy based upon thermally-induced Claisen ring expansion as the pivotal step allows for rapid elaboration of the lauthisans in enantiomerically pure condition and proper absolute configuration. The short sequence (nine steps) constitutes a new and versatile route to naturally occurring medium-ring ethers.

As a general reaction type, the Claisen rearrangement constitutes an exceptionally efficient bond reorganization process offering broad and versatile application to organic synthesis. Although such transformations have been widely studied,[2] only recently has its utility for the convenient elaboration of medium-ring carbocycles been demonstrated. Thus, Kinney, et al capitalized on the thermally induced conversion of 1 to 2 (87%) to accomplish a short, stereocontrolled synthesis of (±)-precapnelladiene (3).[3a] Kang's allied route to an epoxy basmenone is equally noteworthy.[3b] In addition to the valuable



1 2 3

features usually associated with Claisen technology (*viz.*, regiospecific allylic transposition, generation of specific olefin geometries, transfer of chirality, etc), this new application appeared to us to hold considerable added potential. The present study demonstrates these features within the context of concise, enantiocontrolled syntheses of *cis*-(4) and *trans*-lauthisan (5).[4]



4 5

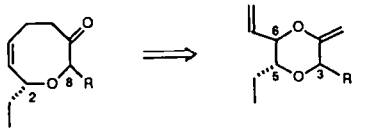
†Dedicated to Professor David Ollis, stereochemist extraordinaire, on the occasion of his 65th birthday.

The isolation of structurally unusual C_{15}-nonisoprenoid mesocyclic ethers from various *Laurencia* species as well as the opistobranch mollusks that consume these red algae has been reported with increasing frequency during the past two decades.[6] The varied biological activities of these oxygen heterocycles and their novel constitutional features have prompted them to become attractive synthetic targets.[7-16] While 4 is the skeleton of the marine natural product laurencin,[17] its acquisition has often served as the testing ground for efficient oxocane construction.[9a,11,14c]

From the outset, our expectations were that the Claisen-based strategy developed in this report would evolve as a highly flexible scheme with regard to stereochemistry and the incorporation of needed functional groups. These added advantages stem from initial reliance on the Sharpless epoxidation to set absolute configuration,[18] recourse to small, conveniently available building blocks to develop structural complexity as required, and the concomitant introduction of a double bond and carbonyl group following thermal activation.

Results and Discussion

The [3,3] sigmatropic model for mesocyclic ether construction leads one to envision the important C-C bond forming step in the context of ring expansion of a smaller heterocyclic ring.[14e] With 3-oxocen-7-ones as initial targets, the first synthetic task becomes one of gaining access to 1,4-dioxanes typified by 7. Critical to the serviceability of



6 7

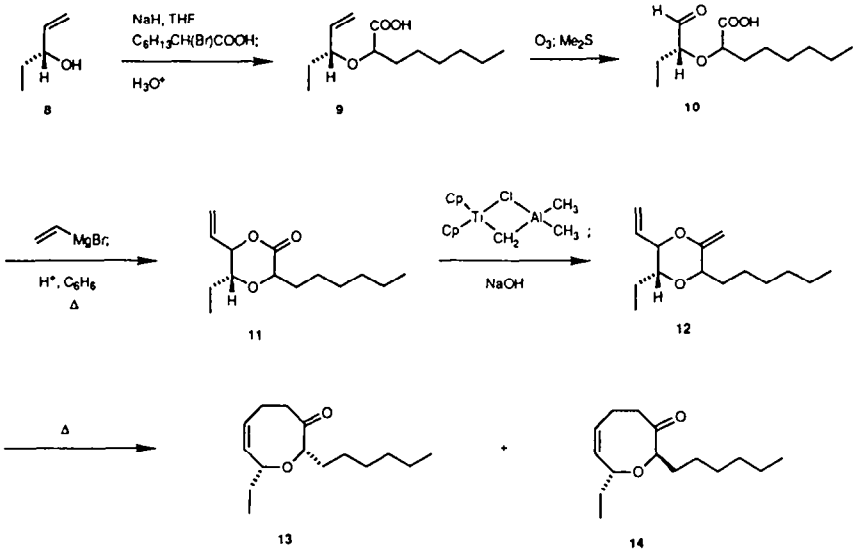
the 7 → 6 transposition was recognition that the stereochemistry at C-3 and C-6 in 7 is not of ultimate consequence. The topological and diastereofacial features associated with intramolecular capture of the 6-vinyl group by the exocyclic methylene was expected to be dominated overwhelmingly by installation of a cis double bond within the medium ring.[19] Beyond that, the stereochemistry at C-8 in 6 is ultimately subject to control by conventional epimerization. In contrast, definition of configuration at C-5 in 7 (or C-2 in 6) would be difficult to achieve by kinetic means or otherwise. Since the stereochemical features inherent to 6 can ultimately be related to that at C-2, the need exists for developing an approach in which this stereogenic center is defined early in an absolute sense.

This requirement is easily met. Thus, treatment of (±)-1-penten-3-ol with cumene

hydroperoxide and titanium isopropoxide in the presence of diisopropyl L-tartrate was performed such that epoxidation was allowed to proceed to approximately 70% completion. The unconsumed **8**, assumed to be the *R* enantiomer on the strength of Sharpless' mechanistic paradigm,[20] was shown to be of 100% ee purity by ^{19}F NMR analysis of its Mosher ester[21] and that of its racemate. A change to *D*-tartrate would have resulted in equally facile acquisition of the pure *S* enantiomer. Consequently, the opportunity for proceeding forward in either configurational series is established early and can in principle be applied to any allylic alcohol.

Heating of the sodium salt of **8** with commercially available (±)-2-bromooctanoic acid in tetrahydrofuran resulted in efficient conversion to **9** (90%, Scheme I). The presence of two diastereomers was reflected in the ^1H and ^{13}C NMR spectra of **9**. The configuration of the alkoxy carbon was not affected by these conditions and, as discussed above, that α to the carboxyl was not of long-term consequence. Accordingly, **9** was directly ozonolyzed and the resulting aldehyde **10** was condensed with vinylmagnesium bromide without undue delay. In this way, the possibility of unwanted enolization was greatly minimized. In fact, the $[\alpha]_D$ ultimately recorded for our synthetic sample of **4** showed that partial racemization was not operative during the formation and handling of aldehyde **10**.

Scheme I



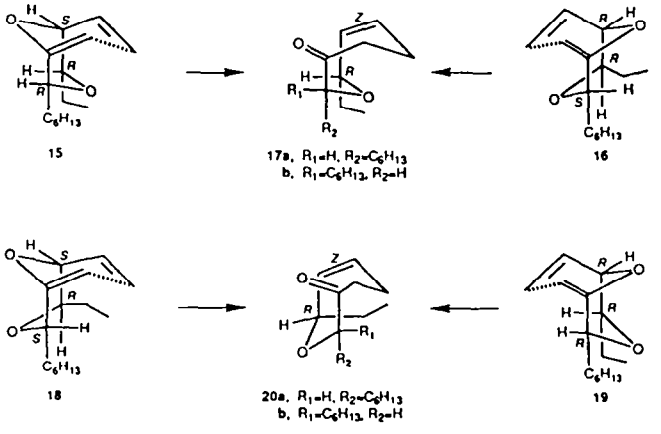
As a direct consequence of the presence of a chiral center α to the carbonyl group in **10**, 1,2-addition to this functional group operated with a certain amount of stereocontrol.[22] Acid-catalyzed cyclization of the hydroxy acids delivered **11** in 63% overall yield

from 9 in the form of two major and two minor diastereomers. Since neither of the two new stereochemical markers ultimately impact on the chiral integrity of the target molecules or the efficiency with which they are produced, no attempts were made to establish with certainty at this stage the prevailing configurational relationships.

The 1,4-dioxanone mixture was treated at room temperature with the Tebbe reagent[23] in a tetrahydrofuran-benzene solvent system containing a small amount of pyridine. The vinyl ether, isolated following a quench with 15% sodium hydroxide solution, required twofold chromatography on basic alumina to rid the sample completely of organometallic impurities. As will be discussed, failure to take this precaution eventuated in unwanted internalization of the vinyl ether double bond. Notwithstanding the need for this precaution, the yield of purified 12 was 65%. With the carbonyl oxygen replaced by CH_2, [3,3] sigmatropy could be performed smoothly in base-washed sealed tubes at 185 °C for 36 h. The oxocenones 13 and 14 were isolated with 86% efficiency in a ratio approximating 1:1.4.

Before proceeding to completion of the synthetic undertaking, it is appropriate to examine the various steric factors at play in the Claisen transition states (Scheme II). The assumption that a chair-like sigmatropic arrangement is adopted in all cases seems well grounded, since to do otherwise would necessitate that the double bond in the 3-oxocen-7-one products be trans. The added energy cost of approximately 10 kcal/mol[19] for introducing the alternative *E* geometry appears adequate to discourage involvement of any boat-like option. Another less likely possible interpretation is that all or part of the Claisen process proceeds by way of a boat-like spatial arrangement, with the *E* product subsequently isomerizing to the thermodynamically favored *Z* form under the reaction conditions.

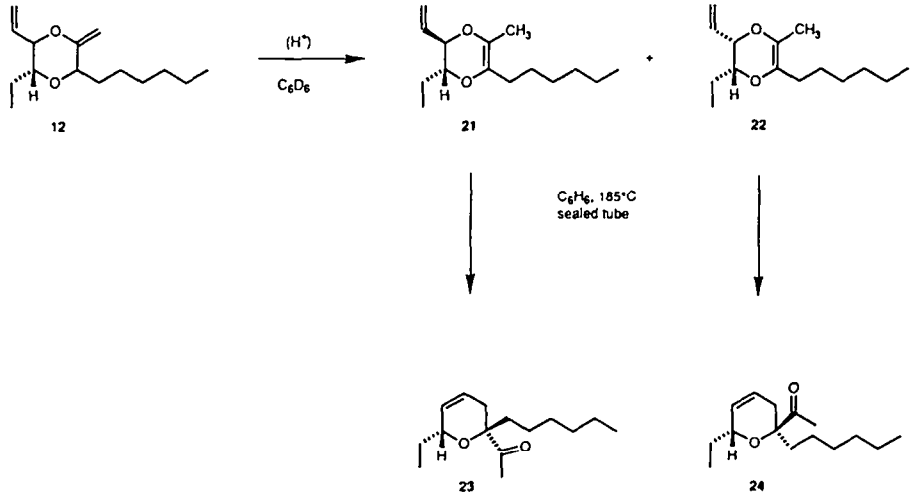
Scheme II



The data suggest further that the 2*R*,5*S*,6*R* and 2*S*,5*R*,6*R* stereoisomers **15** and **16** may be channeled through manifolds in which the 1,4-dioxane ring adopts chair-like features as well. The end result is initial production of the oxocenone in the non-extended geometry illustrated by **17**. In the two remaining diastereomers **18** and **19**, the likelihood exists that the dioxane ring may take on boat (or twist-boat) character in order to guarantee that the *n*-hexyl substituent become equatorially disposed. In **19**, the ethyl group is thereby also projected equatorially. The barrier to this conformational inversion in simpler 1,4-dioxanes is recognized to be low.[24] To the extent that these conformational tendencies are manifested in the latter transition states, the oxocenone will be initially formed with extended geometry as in **20**.

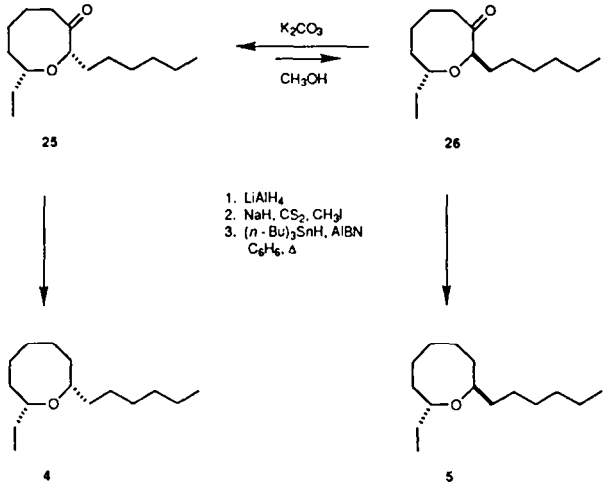
Divergence from the normal regiochemical course of these reactions was noted under certain circumstances and ultimately traced to the carry-through of organometallic residues from the Tebbe reaction. Although catalysis of Claisen rearrangements by Lewis acids is a well recognized phenomenon,[2e] such contaminants in the present context served to promote internalization of the double bond as in **21** and **22** prior to the sigmatropic shift. The acid lability of **12** allowed this proton transfer to be observed spectroscopically. Exposure of C_6D_6 solutions of **12** to head vapor from a concentrated hydrochloric acid container triggered complete isomerization to a 1.7:1 mixture of **21** and **22** during 12 h at room temperature (Scheme III). As expected,[3] these dioxenes underwent Claisen rearrangement efficiently in their own right. Dihydropyrans **23** and **24** derive from **21** and **22**, respectively, via chair-like transition states.

Scheme III



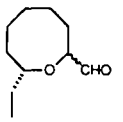
With arrival at ketones 13 and 14, it will be recognized that two highly functionalized medium-ring ethers are in hand. For our present purposes, saturation of their double bond would afford a clear route to the lauthisans. Consequently, the 13/14 mixture was hydrogenated over 5% palladium on carbon. In order to gain relevant information on the extent and direction of thermodynamic bias in these oxocanones, 25 and 26 were separated gas chromatographically and individually subjected to epimerization with potassium carbonate in methanol (Scheme IV). In light of the fact that the parent oxocane molecule prefers to adopt a ground state boat-chair conformation,[8b,25] cis isomer 25 should prove dominant because of its capacity for projecting both alkyl groups equatorially. This was indeed the case, the 25/26 equilibrium favoring 25 by a factor of 5.6:1 at 20 °C. This isomeric distribution is similar in magnitude to those determined earlier for 27 (cis/trans, 8:1)[14b] and 28 (cis/trans, 5:1).[14c]

Scheme IV

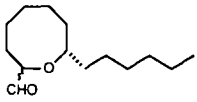


Removal of the carbonyl oxygen in 25 and 26 could be accomplished straightforwardly, although the proximity of the ether linkage had to be given proper consideration. For example, hetero atoms attached to α carbon atoms have long been recognized to be subject to reductive elimination under Clemmensen conditions.[26] Similar reactions occur with other reducing metals.[27] Furthermore, the popular Wolff-Kishner process could also eventuate in irreversible ring cleavage.[28] For these reasons, our attention turned to free radical methodology, since C-O bonds do *not* undergo homolytic cleavage when positioned β to an odd-electron site.[30-33]

Individual lithium aluminum hydride reduction of 25 and 26, conversion of each oxocanol to its xanthate, and subsequent heating with tri-*n*-butyltin hydride and AIBN in



27



28

benzene[34] gave 4 and 5, respectively, with comparable overall efficiencies of 82%. The specific rotations of 4, $[\alpha]_D^{22}$ +14.4° (*c* 0.09, $CHCl_3$), and of 5, $[\alpha]_D^{22}$ +13.7° (*c* 0.18, $CHCl_3$), are similar in magnitude and direction. Major contribution to the molar rotation by closely related conformations of the oxocane ring may be responsible. More relevantly, the $[\alpha]_D$ of our synthetic *cis*-lauthisan is virtually identical to the value recently reported by Katsuki, et al [+13.9° (*c* 0.15, $CHCl_3$)].[11] The identities of 4 and 5 were further confirmed by direct IR and ^1H NMR spectral comparison with those of samples prepared elsewhere by different routes.[9,14]

In summary, the fundamentally new approach outlined here significantly broadens the range of precursors potentially available for assembling chiral eight-membered cyclic ethers. More generally, the straightforward nature and brevity of the sequence provides for the ready acquisition of target medium-ring oxygen heterocycles in either enantiomeric series from simple allylic alcohol precursors. The various intermediates also offer considerable latitude with which to achieve chemical diversity, making inroads to more highly functionalized members of this class conveniently feasible. We hope to report on a number of developments in this field at a later date.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR spectra were recorded at 300 MHz, the ^1H NMR spectra at 75 MHz, and the ^{19}F NMR spectra at 250 MHz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter. Mass spectra were obtained at The Ohio State University Chemical Instrument Center through use of a Kratos MS-30 mass spectrometer. All solvents were reagent grade and were dried and distilled before use. All reactions were performed under argon unless otherwise indicated. TLC determinations were made on silica gel 60 F254 Merck plates (elution with 33% ether in hexanes); column chromatography was performed on silica gel 60 unless otherwise indicated. The preparative GC work made use of a Varian Series 2700 unit. The purity of all title compounds was judged to be ≥ 97% by TLC, GC, and $^1H/^{13}C$ NMR spectral determinations.

(-)-(*R*)-1-Penten-3-ol (8).[35] To an oven-dried 500 mL flask was added 2.5 g of 4 Å

molecular sieves, 190 mL of dichloromethane, 1.39 g (5.93 mmol) of diisopropyl *L*-tartrate, and 8.61 g (100 mmol) of 1-penten-3-ol. This mixture was cooled to -5 °C, treated with titanium isopropoxide (1.4 g, 4.0 mmol), and stirred for 30 min in order to "age" the catalyst. Cumene hydroperoxide (36 mL of 80%, 195 mmol), previously dried over 4 Å molecular sieves for 30 min, was slowly introduced over 30 min. The progress of reaction, monitored by GC (3 mm x 2.0 m 3% OV101 on 100/200 Gaschrom Q, 30 °C), was allowed to advance to the 70% level. Quenching was accomplished by adding the cold (-5 °C) mixture to an ice-cooled solution of ferrous sulfate heptahydrate (33 g, 0.12 mol) and citric acid monohydrate (11 g, 0.06 mol) in water (100 mL). After filtration and extraction with dichloromethane, the combined organic phases were concentrated and distilled (40-50 °C, 20 Torr) to give 3.0 g of an *ca* 1:1 mixture of cumene and 1-penten-3-ol (^{1}H NMR analysis). A pure sample of the alcohol obtained by preparative GC (11 ft x 0.25 in. 5% SE-30 on Chromosorb W, 70 °C) exhibited $[\alpha]_D^{25}$ -24° (*c* 0.45, $CHCl_3$). The Mosher ester of this alcohol prepared from the chloride of (*R*)-(+)-2-methoxy-2-(trifluoromethyl)phenylacetic acid consisted of a single observable diastereomer when analyzed by ^{19}F NMR (s at δ 72.59).

2-[(1-Ethyl-2-propenyl)oxy]octanoic Acid (9). To a mechanically stirred slurry of 6.90 g (162 mmol) of 60% sodium hydride dispersion (in oil) in dry tetrahydrofuran (40 mL) was added dropwise a solution of 1-penten-3-ol (4.00 g, 46 mmol) in tetrahydrofuran (40 mL). This mixture was heated at reflux for 12 h, then cooled to 0 °C. 2-Bromooctanoic acid (10.36 g, 46.4 mmol) was introduced dropwise as a solution in tetrahydrofuran over 20 min. The reaction mixture was refluxed for 48 h and cooled to 0 °C. The mixture was then slowly added to 200 mL of ice water. Following acidification to pH 4 with concentrated hydrochloric acid, the product was extracted into ether. The combined ether extracts were dried and concentrated. The residue was purified by silica gel chromatography (elution with 20-80% ether in hexanes). There was obtained 9.51 g (90%) of **9** as a pale yellow oil; IR (neat, cm^{-1}) 3080, 2960, 2920, 2870, 1718, 1460, 1420, 1380, 1235, 1130, 1100, 995, 930; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (br s, 1 H), 5.76-5.55 (m, 1 H), 5.26-5.14 (m, 2 H), 4.00-3.91 (m, 1 H), 3.70-3.62 (m, 1 H), 1.80-0.85 (series of m, 18 H); MS *m/z* (M^+) calcd 228.1725, obsd 228.1733.

A small sample of this acid was esterified with diazomethane and the ester was subjected to combustion analysis after preparative GC (1.5 m x 3 mm 5% SE-30 on Chromosorb W, 150 °C).

Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found. C, 69.65; H, 10.83.

When this reaction was repeated with (-)-(*R*)-1-penten-3-ol having 100% ee, the acid was produced in comparable yield.

6-Ethenyl-5-ethyl-3-hexyl-1,4-dioxan-2-one (11). Ozone was bubbled through a solution of 9 (5.92 g, 25.9 mmol) in 300 mL of chloroform until a blue color appeared. The reaction mixture was then flushed with oxygen to remove the excess ozone. Dimethyl sulfide (50 mL) was introduced and stirring was maintained overnight at room temperature. Following the addition of water (200 mL), the separated aqueous phase was extracted several times with dichloromethane. The combined organic layers were dried and concentrated to give 5.55 g (93%) of the aldehyde as a colorless oil, which was used directly without further purification.

A magnetically stirred solution of this aldehyde (2.68 g, 11.6 mmol) in dry tetrahydrofuran (60 mL) cooled to -78 °C was treated dropwise with a solution of vinylmagnesium bromide (11.6 mL of 1 M, 11.6 mmol) in tetrahydrofuran. After 30 min, an additional 23 mL (23 mmol) of Grignard reagent was added. The resulting cloudy mixture was stirred for 1.5 h at -78 °C prior to being acidified to pH 2 with 5% hydrochloric acid, allowed to warm to room temperature and agitated overnight. The reaction mixture was poured into water and the aqueous layer was extracted twice with ether. The combined extracts were concentrated and the resulting brown oil was taken up in benzene (60 mL), treated with camphorsulfonic acid (30 mg), and heated at reflux for 2 h under a Dean-Stark trap. After solvent evaporation, the residue was chromatographed (silica gel, elution with 8:1 hexanes-ether) to give 1.74 g (63%) of a pale yellow oil consisting of two major and two minor isomers; IR (neat, cm^{-1}) 3060, 2940, 2840, 1740, 1455, 1420, 1370, 1340, 1285, 1210, 1100, 1040, 1000, 980, 930; ^1H NMR (300 MHz, $CDCl_3$) (one major isomer) δ 6.03-5.69 (m, 1 H), 5.48-5.34 (m, 2 H), 4.65 (dd, J = 7.2, 8.2 Hz, 1 H), 4.36 (dd, J = 7.0, 12.9 Hz, 1 H), 3.50-3.44 (m, 1 H), 2.17-1.11 (series of m, 12 H), 1.04-0.95 (m, 3 H), 0.88 (t, J = 12.1 Hz, 3 H); (second major isomer) δ 6.03-5.69 (m, 1 H), 5.48-5.34 (m, 2 H), 4.73-4.69 (m, 1 H), 4.32-4.26 (m, 1 H), 3.83-3.67 (m, 1 H), 2.17-1.11 (series of m, 12 H), 1.04-0.95 (m, 3 H), 0.88 (t, J = 12.1 Hz, 3 H); MS *m/z* (M^+) calcd 240.1725, obsd 240.1718.

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 69.66; H, 10.25.

6-Ethenyl-5-ethyl-3-hexyl-2-methylidene-1,4-dioxane (12). The Tebbe reagent was prepared by adding titanocene dichloride (6.00 g, 24.1 mmol) to a solution of trimethylaluminum in toluene (26 mL of 2 M, 52 mmol) under argon. After 48 h, all volatiles were removed under high vacuum and the residue was dissolved in dry benzene (30 mL).

A solution of 11 (250 mg, 1.04 mmol), pyridine (3 drops), and dry tetrahydrofuran (1.5 mL) in benzene (3.5 mL) was prepared under argon. The magnetically stirred reaction mixture was cooled to 0 °C and Tebbe reagent (3 mL of 0.55 M, 1.65 mmol) was introduced

dropwise over 1 min. After 90 min of stirring at room temperature, the solution was cooled to 0 °C, quenched with 15% sodium hydroxide solution (0.6 mL), and diluted with ether (50 mL). The resulting slurry was filtered and concentrated to leave a residue that was chromatographed twice through basic alumina (activity II) using petroleum ether as eluant. There was obtained 160 mg (65%) of 12; IR (neat, cm^{-1}) 3070, 2950, 2920, 2860, 2840, 1655, 1645, 1460, 1420, 1375, 1320, 1270, 1120, 1090, 1060, 1020, 985, 925, 840; ^1H NMR (300 MHz, C_6D_6) δ 6.30-5.92 (m, 0.5 H), 5.71-5.59 (m, 0.5 H), 5.31-5.03 (m, 2 H), 4.71-4.62 (m, 1 H), 4.26-3.86 (m, 3 H), 3.70-3.65 (m, 0.21 H), 3.60-3.55 (m, 0.39 H), 3.52-3.45 (m, 0.23 H), 3.26-3.19 (m, 0.17 H), 1.97-0.74 (series of m, 18 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 159.69, 159.14, 157.92, 157.58, 134.91, 134.87, 133.89, 133.74, 118.97, 118.42 (2 C), 118.12, 91.70, 91.19, 90.73, 90.70, 83.00, 82.29, 80.44, 80.19, 80.02, 78.79, 75.46, 74.85, 72.70, 72.67, 72.42, 71.44, 32.97, 32.53, 32.36, 32.31, 32.25 (4 C), 29.69, 29.64, 29.53, 29.41, 26.00, 25.87, 25.68, 25.48, 24.95 (2 C), 24.53, 24.43, 23.05 (3 C), 22.60, 14.29 (4 C), 10.08, 9.97, 9.78 (2 C); MS *m/z* (M^+) calcd 238.1933, obsd 238.1937.

Thermal Isomerization of 12. A solution of 12 (602 mg, 2.53 mmol) in benzene (80 mL) was placed in a base-washed heavy-walled glass tube, sealed under vacuum, and heated at 185 °C for 36 h. The resulting yellow solution was concentrated and the residue was chromatographed on silica gel (elution with hexane-ether, 5:1) to give 515 mg (86%) of a 1:1.43 mixture of the cis 13 and trans 14 isomers. Preparative GC separation of this mixture (1.5 m x 3 mm 5% SE-30 on Chromosorb W, 175 °C) gave the individual isomers as colorless liquids.

For 13: IR ($CHCl_3$, cm^{-1}) 3000, 2960, 2930, 2870, 2860, 1700, 1460, 1420, 1400, 1380, 1330, 1220, 1125, 1115, 1090, 1000, 915; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78-5.68 (m, 1 H), 5.42-5.37 (m, 1 H), 3.86-3.81 (m, 1 H), 3.58 (dd, J = 3.0, 9.5 Hz, 1 H), 3.53-3.39 (m, 1 H), 2.93-2.74 (m, 1 H), 2.41-2.30 (m, 1 H), 2.04-1.94 (m, 1 H), 1.77-1.27 (series of m, 12 H), 0.98 (t, J = 14.7 Hz, 3 H), 0.89-0.83 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.40 131.54, 129.01, 88.30, 83.35, 40.00, 33.44, 31.65, 29.19, 28.91, 25.60, 22.56, 22.17, 14.04, 10.34; MS *m/z* (M^+) calcd 238.1933, obsd 238.1933.

For 14: IR ($CHCl_3$, cm^{-1}) 3000, 2960, 2930, 2880, 2860, 1700, 1460, 1420, 1395, 1380, 1350, 1330, 1220, 1160, 1125, 1110, 1075, 1000, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 5.99-5.71 (m, 1 H), 5.34 (dd, J = 3.8, 10.6 Hz, 1 H), 4.31-4.30 (m, 1 H), 3.80 (dd, J = 5.5, 7.8 Hz, 1 H), 2.99-2.82 (m, 2 H), 2.52-2.38 (m, 1 H), 2.35-2.24 (m, 1 H), 1.76-1.26 (series of m, 12 H), 0.95 (t, J = 14.7 Hz, 3 H), 0.86-0.73 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.20, 133.16, 130.92, 79.20, 75.90, 41.67, 32.27, 31.64, 29.14, 27.06, 25.52, 22.72, 22.55,

14.04, 10.26; MS *m/z* (M) calcd 238.1933, obsd 238.1933.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.57; H, 11.00.

When the analogous reaction was performed on enantiomerically pure material, the purified cis and trans ketones exhibited $[\alpha]_D^{25}$ values of +63° (*c* 0.46, $CHCl_3$) and -179° (*c* 0.38, $CHCl_3$), respectively.

Acid-Catalyzed Isomerization of 12. A solution of **12** (74.4 mg, 0.312 mmol) in benzene-d_6 (0.5 mL) was placed in an NMR tube into which a small amount of vapor from the air space inside a container of concentrated hydrochloric acid was introduced by means of a pipette. The isomerization to **21** and **22** was complete after 12 h at room temperature. The solution was filtered through a plug of activity III basic alumina and concentrated to give 74 mg (100%) of a 1.7:1 mixture of **21** and **22**; IR (neat, cm^{-1}) 3140, 3060, 2910, 2860, 2840, 1700, 1455, 1370, 1240, 1210, 1060, 980, 920; ^1H NMR (300 MHz, $CDCl_3$) (*trans*-**21**) δ 5.90-5.74 (m, 1 H), 5.41-5.23 (m, 2 H), 4.00-3.95 (t, J = 13.9 Hz, 1 H), 3.45-3.39 (m, 1 H), 2.08-2.00 (m, 2 H), 1.76 (s, 3 H), 1.73-1.28 (series of m, 10 H), 1.06-0.86 (series of m, 6 H); (*cis*-**22**) δ 5.90-5.74 (m, 1 H), 5.41-5.23 (m, 2 H), 4.34-4.31 (m, 1 H), 3.75-3.70 (m, 1 H), 2.08-2.00 (m, 2 H), 1.75 (s, 3 H), 1.73-0.86 (series of m, 16 H); MS *m/z* (M^+) calcd 238.1933, obsd 238.1923.

Claisen Rearrangement of 21/22. A solution of the **21/22** mixture (74.4 mg, 0.312 mmol) in benzene (15 mL) was placed in a heavy-walled glass tube, sealed under vacuum, and heated at 185 °C for 28 h. The resulting yellow solution was concentrated and the residue was chromatographed on silica gel (elution with ether-hexanes, 1:8) to give 59.1 mg (79%) of a 2:1 mixture of **23** and **24**. Careful rechromatography (silica gel, same eluant) resulted in clean separation of **23** from **24**.

For **23**: colorless oil; IR (neat, cm^{-1}) 3070, 2940, 2905, 2850, 2840, 1715, 1650, 1450, 1410, 1370, 1345, 1250, 1210, 1130, 1105, 1050, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 5.50-5.45 (m, 1 H), 5.36-5.32 (m, 1 H), 3.91-3.88 (m, 1 H), 2.16 (s, 3 H), 2.12-1.08 (series of m, 14 H), 0.96-0.91 (t, J = 14.7 Hz, 3 H), 0.88-0.47 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.74, 129.04, 122.50, 81.66, 69.95, 32.91, 31.65, 31.26, 29.62, 29.28, 25.96, 23.40, 22.54, 13.97, 9.37; MS *m/z* (M^+) calcd 238.1933, obsd 238.1978.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.52; H, 11.02.

For **24**: colorless oil; IR (neat, cm^{-1}) 3020, 2940, 2900, 2850, 2830, 1712, 1450, 1370; ^1H NMR (300 MHz, C_6D_6) δ 5.74-5.68 (m, 1 H), 5.41-5.36 (m, 1 H), 4.04-4.01 (m, 1 H), 2.82-2.73 (m, 1 H), 2.03 (s, 3 H), 1.94-1.84 (m, 2 H), 1.67-1.03 (series of m, 11 H), 1.02-0.97 (t, J = 19.7 Hz, 3 H), 0.96-0.35 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.51,

128.36, 123.62, 82.90, 72.55, 31.57, 29.65, 28.31, 24.09, 22.81, 22.64, 22.57, 21.00, 14.08, 9.00; MS *m/z* (M^+) calcd 238.1933, obsd 238.1971.

***cis*- and *trans*-Lauthisan-3-one (25 and 26).** A solution of the 13/14 mixture (57 mg, 0.239 mmol) in ethyl acetate (1 mL) containing 10 mg of 10% palladium on carbon was hydrogenated at atmosphereic pressure for 6 h. The reaction mixture was filtered through a Celite plug and concentrated to furnish 54.4 mg (95%) of the two saturated ketones. The pure individual isomers were obtained by preparative GC (same column as above, 160 °C).

For **25**: colorless oil; IR ($CHCl_3$, cm^{-1}) 2985, 2910, 2840, 1695, 1445, 1425, 1370, 1340, 1320, 1255, 1215, 1185, 1150, 1090, 1040, 990, 950, 905; ^1H NMR (300 MHz, $CDCl_3$) δ 3.44 (dd, J = 3.5, 9.4 Hz, 1 H), 3.34-3.28 (m, 1 H), 3.01-2.93 (m, 1 H), 2.11-2.05 (m, 1 H), 2.01-1.94 (m, 1 H), 1.77-1.18 (series of m, 17 H), 0.96 (t, J = 14.8 Hz, 3 H), 0.88 (t, J = 13.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.97, 86.06, 82.78, 37.60, 33.07, 31.63, 31.34, 29.33, 28.88, 27.70, 25.40, 22.53, 21.98, 14.00, 10.91; MS *m/z* (M^+) calcd 240.2089, obsd 240.2105.

For **26**: colorless oil; IR ($CHCl_3$, cm^{-1}) 2985, 2910, 2840, 1695, 1445, 1425, 1400, 1370, 1340, 1320, 1270, 1260, 1215, 1180, 1150, 1115, 1090, 1070, 905; ^1H NMR (300 MHz, $CDCl_3$) δ 3.70-3.64 (m, 2 H), 2.95-2.88 (m, 1 H), 2.11-1.98 (m, 2 H), 1.85-1.80 (m, 1 H), 1.67-1.03 (series of m, 16 H), 0.92-0.82 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 221.14, 82.03, 77.43, 37.86, 32.91, 31.74, 31.60, 29.88, 29.11, 26.53, 25.50, 25.24, 22.52, 13.98, 10.89; MS *m/z* (M^+) calcd 240.2089, obsd 240.2105.

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.09; H, 11.74.

When the analogous reaction was performed on enantiomerically pure material, the purified cis and trans isomers exhibited $[\alpha]_D^{25}$ values of +111° (*c* 0.14, $CHCl_3$) and -99° (*c* 0.51, $CHCl_3$), respectively.

***cis*- and *trans*-Lauthisan-3-ol.** A stirred slurry of lithium aluminum hydride (22 mg, 0.55 mmol) in dry tetrahydrofuran (1 mL) was treated dropwise with a solution of **25** (62.5 mg, 0.260 mmol) in the same solvent (1 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1.5 h prior to the slow addition of 1:1 ether/ethyl acetate (1 mL), 1 M sodium hydroxide solution (0.2 mL), and ether (10 mL). After filtration through Celite, the filtrate was dried and concentrated to give 57.3 mg (91%) of the stereoisomeric alcohols; IR (neat, cm^{-1}) 3400, 2940, 2910, 2840, 1455, 1370. 1110, 1080, 1060, 1020; ^1H NMR (300 MHz, C_6D_6) δ 3.55 (br s, 1 H), 3.41-3.34 (m, 1 H), 3.32-3.24 (m, 1 H), 3.23-3.12 (m, 1 H), 2.01-1.08 (series of m, 20 H), 0.98-0.85 (m, 6 H); ^{13}C NMR (75 MHz, C_6D_6) (major isomer) ppm 82.29, 80.90, 70.81, 34.35, 33.65, 32.32 (2 C), 30.03, 29.23, 26.58,

24.79, 23.06, 21.13, 14.33, 11.00; (minor isomer) 82.20, 81.73, 74.93, 35.41, 22.59, and overlapping signals at higher field; MS *m/z* (M^+) calcd 242.2246, obsd 242.2248.

Analogous reduction of **26** was equally efficient and gave a different pair of diastereomeric alcohols; IR (CCl_4, cm^{-1}) 3440, 2940, 2860, 2850, 1450, 1390, 1375, 1360, 1295, 1270, 1250, 1220, 1125, 1075, 1050, 1010, 995, 950, 910, 880, 835; ^1H NMR (300 MHz, C_6D_6) δ 3.68 (br s, 1 H), 3.53-3.41 (m, 3 H), 2.28-1.11 (series of m, 20 H), 1.04-0.99 (m, 6 H); ^{13}C NMR (75 MHz, C_6D_6) (major isomer) ppm 80.12, 72.16, 69.80, 34.33, 33.57, 32.32, 30.09, 29.01, 28.91, 27.62, 26.51, 23.06, 19.69, 14.34, 11.36; MS *m/z* (M^+) calcd 242.2246, obsd 242.2254.

***cis*- and *trans*-Lauthisan (4 and 5).** To a magnetically stirred suspension of 98% sodium hydride (20 mg, 0.83 mmol) in carbon disulfide (0.5 mL, freshly filtered throught basic alumina) was added a solution of the first epimeric alcohol pair (46.9 mg, 0.193 mmol) in the same solvent (1 mL) during 10 min. This mixture was stirred for 30 min, treated slowly with methyl iodide (0.6 mL) during 25 min, and agitated for 38 h. The reaction mixture was brought to 0 °C where it was quenched with saturated ammonium chloride solution and extracted with several portions of ether. The combined organic phases were dried and concentrated. The residue was purified by chromatography on silica gel (elution with 8:1 petroleum ether-ethyl acetate) to give 62.8 mg (98%) of the xanthate, which was used directly.

To a hot (80 °C) solution of xanthate (44.1 mg, 0.133 mmol) and AIBN (3 mg) in benzene (2.5 mL) was added neat *n*-butyltin hydride (0.15 mL, 0.536 mmol) via syringe. The reaction mixture was refluxed for 30 min, cooled, and concentrated. The residue was passed through a column of silica gel (elution with petroleum ether) to give 27.5 mg (92%) of **4**; colorless oil; IR ($CHCl_3$, cm^{-1}) 2920, 2840, 1455, 1440, 1375, 1350, 1340, 1105, 1085, 1060, 995, 945; ^1H NMR (300 MHz, C_6D_6) δ 3.35-3.30 (m, 1 H), 3.24-3.17 (m, 1 H), 1.83-1.29 (series of m, 22 H), 0.98 (t, J = 14.7 Hz, 3 H), 0.90 (t, J = 13.4 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 80.53, 79.21, 37.40, 33.82, 33.65, 32.37, 30.18, 30.01, 27.47, 26.70, 24.34 (2 C), 23.10, 14.26, 11.05; MS *m/z* (M^+) calcd 226.2297, obsd 226.2276.

Entirely comparable handling of the other diastereomeric alcohol pair gave **5** (90% for the two steps); colorless oil; IR ($CHCl_3$, cm^{-1}) 2960, 2930, 2880, 2860, 1455, 1445, 1380, 1360, 1260, 1200, 1160, 1130, 1080, 1000, 910; ^1H NMR (300 MHz, C_6D_6) δ 3.59-3.52 (m, 1 H), 3.48-3.41 (m, 1 H), 1.76-1.28 (series of m, 22 H), 0.98-0.88 (m, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 74.87, 74.17, 37.15, 32.80, 32.57, 32.32, 30.04, 29.95, 27.15, 26.52, 26.47, 26.25, 23.07, 14.34, 10.67; MS *m/z* (M^+) calcd 226.2297, obsd 226.2296.

Anal. Cal for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.33; H, 13.24.

When the analogous reaction was performed on enantiomerically pure material, the purified *cis*- and *trans*-lauthisans exhibited $[\alpha]_D^{25}$ values of +14.4° (*c* 0.09, $CHCl_3$) and +13.7° (*c* 0.18, $CHCl_3$), respectively.

Acknowledgment. This research was made possible by financial support provided by the National Institutes of Health (Grant GM 30827) and Eli Lilly Company. We thank Mr. Carl Engelman for his help in carrying out the ^{19}F NMR experiments. The courtesy extended by Andrew Holmes and K. C. Nicolaou in providing authentic spectra of *cis*-lauthisan is deeply appreciated.

References and Notes

(1) Medical Scientist Program Fellow.

(2) (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1. (c) Bennett, G. B. *Synthesis* **1977**, 589. (d) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 277. (e) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 105.

(3) (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868; **1985**, *107*, 7352. (b) Kang, H.-J.; Paquette, L. A. submitted for publication.

(4) Preliminary communication: Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703.

(5) (a) Paquette, L. A.; Begland, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3784. (b) Leonard, N. J.; Milligan, T. W.; Brown, T. L. *Ibid.* **1960**, *82*, 4075.

(6) For reviews see: (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed., Academic: New York, 1978; Vol. 1, Chapter 2. (b) Erickson, K. K. *Ibid.* 1983; Vol. 5, p 131. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251; **1986**, *5*, 613.

(7) (a) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127. (b) Masamune, T.; Murase, H.; Matsue, H.; Murai, A. *Ibid.* **1979**, *52*, 135. (c) Murao, A.; Murase, H.; Matsue, H.; Masamune, T. *Tetrahedron Lett.* **1977**, 2507. (d) Masamune, T.; Matsue, H. *Chem. Lett.* **1975**, 895.

(8) (a) Paquette, L. A.; Begland, R. W. *J. Org. Chem.* **1967**, *32*, 2723. (b) Paquette, L. A.; Begland, R. W. *J. Am. Chem. Soc.* **1968**, *90*, 5159. (c) Paquette, L. A.; Begland, R. W.; Storm, P. C. *Ibid.* **1970**, *92*, 1971.

(9) (a) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504. (b) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Reddy, K. B. *Tetrahedron Lett.* **1987**,*28*, 1501. (c) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Reddy, K. B.; Marron, B. E.; McGarry, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 6800. (d) Nicolaou, K. C.; Duggan, M. E.; Hwang, K.-C. *Ibid.* **1986**, *108*, 2468.

(10) (a) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248. (b) Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516. (c) Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303. (d) Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695.

(11) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153.

(12) (a) Schreiber, S. L.; Kelly, S. E.; Porco, J. A., Jr., Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210. (b) Schreiber, S. L.; Kelly, S. E. *Tetrahedron Lett.* **1984**, *25*, 1757.

(13) (a) Mortimore, M.; Cockerill, G. S.; Kocienski, P.; Treadgold, R. *Tetrahedron Lett.* **1987**, *28*, 3747. (b) Cockerill, G. S.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093. (c) Cockerill, G. S.; Kocienski, P. *J. Chem. Soc., Chem. Commun.* **1983**, 705.

(14) (a) Carling, R. W.; Curtis, N. R.; Holmes, A. B. *Tetrahedron Lett.* **1989**, *30*, 6081. (b) Clark, J. S.; Holmes, A. B. *Ibid.* **1988**, *29*, 4333. (c) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565. (d) Carling, R. W.; Holmes, A. B. *Tetrahedron Lett.* **1986**, *27*, 6133. (e) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 325.

(15) (a) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417. (b) Heslin, J. C.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1986**, *27*, 1403.

(16) (a) Pirrung, M. E.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060. (b) Pornet, J.; Damour, D.; Miginiac, L. *Tetrahedron* **1986**, *42*, 2017. (c) Davies, S. G.; Polywka, M. E. C.; Thomas, S. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1277. (d) Guyot, B.; Pornet, J.; Miginiac, L. *J. Organometal. Chem.* **1989**, *373*, 279.

(17) Blunt, J. W.; Lake, R. J.; Munro, M. H. G.; Yorke, S. C. *Aust. J. Chem.* **1981**, *34*, 2393.

(18) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(19) *cis*-Cyclooctene is recognized to be 9.7 kcal/mol more stable than its *trans* counterpart: Turner, R. B.; Meador, W. R. *J. Am. Chem. Soc.* **1957**, *79*, 4133. Cope, A. C.; Moore, W. R. *Ibid.* **1960**, *82*, 1744.

(20) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*, Morrison, J. D., Ed., Academic Press: New York, 1985; Vol. 5, Chapter 8.

(21) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732.

(22) (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4320. (b) Burke, S. D.; Armistead, D. M.; Fevig, J. M. *Tetrahedron Lett.* **1985**, *26*, 1163. (c)

Burke, S. D.; Schoenen, F. J.; Murtiashaw, C. W. *Ibid.* 1986, *27*, 449. (d) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* 1986, *42*, 2787.

(23) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* 1978, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *Ibid.* 1980, *102*, 3270. (c) Brown Wensley, K. A.; Buchwald, S. L.; Cannizzo, I.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; Grubbs, R. H. *Pure Appl. Chem.* 1983, *55*, 1733. (d) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* 1985, *50*, 1212. (e) For a zirconium alkylidene analogue, see: Clift, S. M.; Schwartz, J. *J. Am. Chem. Soc.* 1984, *106*, 8300.

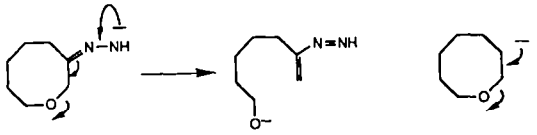
(24) (a) Hanack, M. *Conformation Theory*, Academic Press: New York, 1965; pp 310ff. (b) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, J. A. *Conformational Analysis*, John Wiley and Sons: New York, 1965, pp 248ff.

(25) Anet, F. A. L.; Degen, P. J. *J. Am. Chem. Soc.* 1972, *94*, 1390.

(26) Buchanan, J. G. St. C.; Woodgate, P. D. *Quart. Rev.* 1969, *23*, 522.

(27) House, H. O. *Modern Synthetic Reactions, Second Edition*, Benjamin/Cummings: Menlo Park, CA, 1972, Chapter 3.

(28) The following exemplifies this thinking:



I

Should **I** be produced along any reaction pathway, ring cleavage can be considered a real possibility since β-alkoxy carbanions are known to eject alkoxide readily with generation of olefinic centers.[29]

(29) (a) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* 1988, *53*, 1338. (b) Walling, C. *Tetrahedron* 1985, *41*, 3887. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *Tetrahedron Lett.* 1979, 2157.

(30) Paquette, L. A.; Maynard, G. D. *J. Org. Chem.* 1989, *54*, 5054.

(31) Beckwith, A. L. J.; Gloer, S. A. *Aust. J. Chem.* 1987, *40*, 157.

(32) Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, I.; Tamura, R.; Koji, A. *Tetrahedron* 1985, *41*, 4013.

(33) Migita, T.; Kosugi, M.; Takayama, K.; Nakagawa, Y. *Tetrahedron* 1973, *29*, 51.

(34) Reviews: (a) Hartwig, W. *Tetrahedron* 1983, *39*, 2609. (b) Crich, D.; Quintero, L. *Chem. Rev.* 1989, *89*, 1413.

(35) Compare Mori, K.; Seu, Y.-B. *Tetrahedron* 1985, *41*, 3429.