Alkylaluminum-Catalyzed Claisen Expansion Reactions. Scope and Stereochemistry

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The triisobutylaluminum-catalyzed Claisen rearrangement of a series of bicyclic allyl vinyl ethers was examined in connection with a planned synthesis of the diterpene epoxydictymene. The exocyclic vinyl ethers studied undergo [3,3] sigmatropy via chairlike transition states to provide products having *Z* stereochemistry about the double bond of the eight-membered ring. Differences appear only in the extent of stereoselectivity in the ensuing carbonyl reduction step. Two companion endocyclic vinyl ethers were found to utilize boat transition states to deliver *Z* products exclusively. In all cases, the level of chirality transfer is excellent. An analysis is presented showing that the relative configurations of the newly generated stereogenic centers, established in several key examples by X-ray crystallography, follow directly from the boat-chair options, both of which have the latent ability to be influenced catalytically by $(i\text{-Bu})_3Al$.

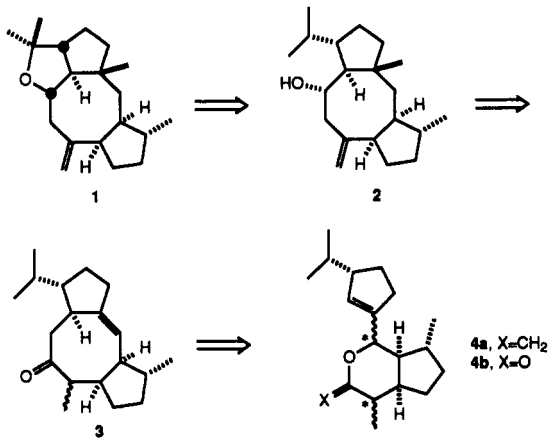
Epoxydictymene (1) is a tetracyclic diterpene that is produced by the brown algae *Dictyota dichotoma*.[2] The structure and stereochemistry of 1 were established by X-ray crystallography of a (*p*-bromophenyl)urethane derivative. An approach[3] to epoxydictymene in which the fusicoccin-like[4] carbon framework is assembled by a Claisen ring expansion reaction (**4a** to **3**, Scheme I) is currently being examined by this group. Despite the established synthetic potential of the alicyclic Claisen rearrangement,[5] only recently has attention been paid to the possible utilization of this [3,3] sigmatropic process for *ring expansion purposes*. Despite the many advantages offered by this methodology for the expedient construction of mesocyclic[6] natural products, recourse to this process has been made infrequently.[7-11]

The present effort has been directed toward charting the stereochemical course of the **4a** to **3** ring enlargement as it relates to the configuration of the pair of asterisked carbon atoms in the allyl vinyl ether. Elucidation of this fundamental issue has bee facilitated by ready access to all four possible isomers of a model system lacking the isopropyl group.[12] Recognition that the aliphatic Claisen rearrangement is subject to organoaluminum catalysis has been steadily growing,[13] although the extent of detailed scrutiny has been limited.[14,15] The potential benefit offered to stereoselection by the resultant substantive decrease in reaction temperature has been incorporated herein. The assimilation of all the features unique to **3** into the bicyclic lactone scaffold **4b** is shown to be feasible.

Results

Triisobutylaluminum-Catalyzed Claisen Ring Expansions. Stereochemical Consequences. Lactone **5** was first examined because the α-methyl substituent adjacent to its carbonyl was expected to deter internalization of the double bond[9] introduced following condensation with the Tebbe reagent.[16] Indeed, exposure of **5** to $Cp_2TiCH_2(Cl)AlMe_2$ and pyridine in CH_2Cl_2–THF (1:1) at −40 °C resulted in efficient conversion to **6** (Scheme II). The action of $(i\text{-Bu})_2AlH$ (Dibal-H) on **6** was expected to accelerate the Claisen process and effect conversion of the product to one or both of the cyclooctenols **7**. After 5 h at 25 °C in dry CH_2Cl_2, two products were formed in a 7:3 ratio. The major constituent, isolated in 42% yield, was shown to be the α-carbinol **7a**. The second substance was, however, not the epimer of **7a** but the unusual reduction product **8** (25%). The formation of **8** is partially suppressed by lowering the initial reaction temperature to −78

Scheme I



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(1) (a) Postdoctoral Fellow, Wigner-Stiftung der Technischen Universität Berlin (1989–1990) and the Deutsche Forschungsgemeinschaft (1990–1991). (b) Author to whom inquiries regarding the X-ray crystallographic analyses should be directed.

(2) Enoki, N.; Furusaki, A.; Suehiro, K.; Ishida, R.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 4341.

(3) An alternative strategy is being tested in the Schreiber laboratory: (a) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Abstracts of Papers*, 199th National Meeting of the American Chemical Society, Boston, MA, April 22–27, 1990; American Chemical Society: Washington, DC, 1990, paper ORGN 132.

(4) (a) Ballio, A.; Brufani, M.; Casinovi, C. G.; Cerrini, S.; Fedeli, W.; Pellicciari, R.; Santurbano, B.; Vaciago, A. *Experientia* **1968**, *24*, 631. (b) Barrow, K. D.; Barton, D. H. R.; Chain, E. B.; Ohnsorge, U. F. W.; Thomas, R. *Chem. Commun.* **1968**, 1198; *J. Chem. Soc. C* **1971**, 1265.

(5) (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*, 227.

(6) Leonard, N. J.; Milligan, T. W.; Brown, T. L. *J. Am. Chem. Soc.* **1960**, *82*, 4075, footnote 4.

(7) Demole, E.; Enggist, P.; Borer, C. *Helv. Chim. Acta* **1971**, *54*, 1845. See also ref 14c.

(8) (a) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2286, 3075. (b) Pitteloud, R.; Petrzilka, M. *Ibid.* **1979**, *62*, 1319.

(9) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868; **1985**, *107*, 7352.

(10) (a) Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252. (b) Paquette, L. A.; Kang, H.-J. Submitted for publication.

(11) (a) Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703; *Tetrahedron* **1990**, *46*, 4487. (b) Philippo, C. M. G.; Vo, N. H.; Paquette, L. A. *J. Am. Chem. Soc.*, in press. (c) Ezquerra, J.; He, W.; Paquette, L. A. *Tetrahedron Lett.* **1990**, *31*, 6979.

(12) Friedrich, D.; Paquette, L. A. *J. Org. Chem.*, preceding paper in this issue.

(13) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

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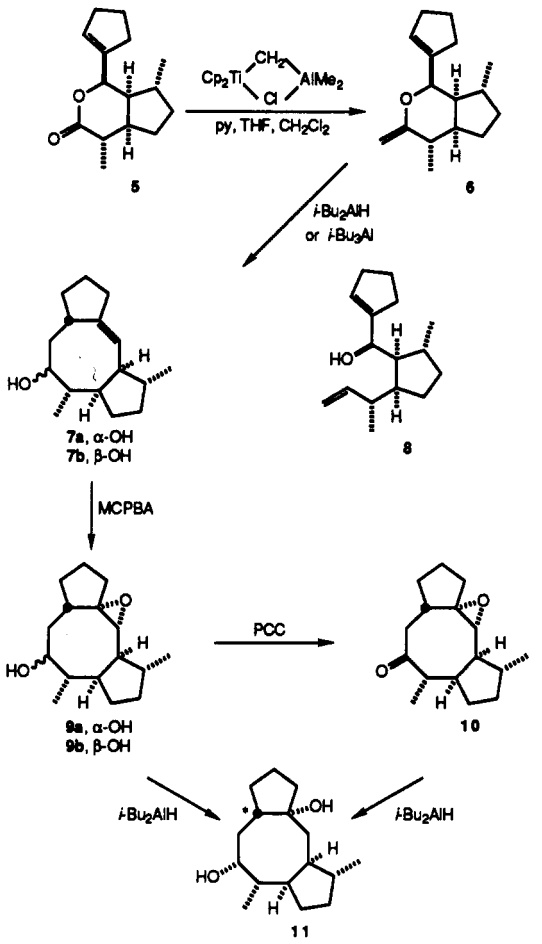
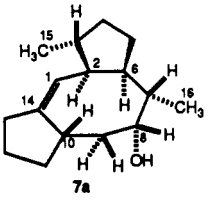
Scheme II



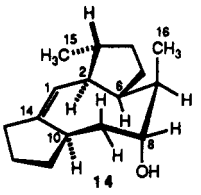
°C. The spectral features of 8 show it to be a single diastereomer.

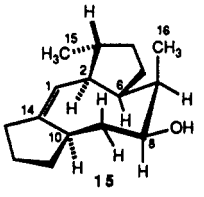
The alternate use of $(i\text{-Bu})_3Al$ (Tribal) as a catalyst for the rearrangement of **6** provides for conversion in high yield to a 5:1 mixture of **7a** and **7b**, with no evidence for the coproduction of **8**. Consequently, while both catalysts promote isomerization via the chair transition state (see Discussion), Dibal-H reduces the first-formed cyclooctenone stereoselectively, while Tribal does not. Since the hydridic reagent demonstrates a capacity for effecting undesirable C–O bond cleavage, its further use was discontinued.

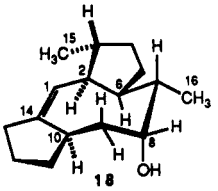
The relative stereochemistry of **7a** was initially suggested by a detailed analysis of coupling constants and NOE measurements (see supplementary material). Cyclooctenols **7a** and **7b** were stereoselectively transformed into epoxides **9a** and **9b** and oxidized to the identical epoxy ketone **10**, thereby requiring that they be epimeric solely at the carbinol center. When either pure **9a** or **10** was treated with Dibal-H, stereospecific conversion to diol **11** occurred. The relative configurations of the seven stereogenic centers in **11** were confirmed by X-ray analysis.



When the readily available α-cyclopentenyl isomer **12** was subjected to the Tebbe reaction as before and the vinyl ether product **13** was stirred overnight with Tribal, tricyclic alcohol **14** was isolated in 76% yield (Scheme III). Ketone **16**, the immediate Claisen product that can be independently prepared by pyridinium chlorochromate oxidation of **14**, was reduced stereoselectively under the reaction







conditions. The same exclusivity of β-attack operates when **16** is reduced with L-Selectride (Aldrich) or lithium aluminum hydride. Less optimal is Dibal-H, which acts on **16** to give a mixture of **14** and **15** in isolated yields of 68 and 19%, respectively.

Proton NMR studies showed the stereochemical status of β-alcohol **15** to be exceptionally well-defined because of its adoption of a rigid conformation (see supplementary material). The conformational situation within **14** is a more flexible one, with two spatial arrangements being largely preferred.

Ketone **16** was epimerized to **17** when heated with potassium *tert*-butoxide in tetrahydrofuran. The underlying driving force is provided by the attainment of equatorial status for the α-methyl group. Subsequent reduction of **17** with Dibal-H or $LiAlH_4$ proceeded with 100% stereoselectivity to generate the cis arrangement present in **18**. The axial nature of the newly generated hydroxyl group agreed well with both the measured coupling constants and observed NOE effects. With **14**, **15**, and **18** in hand, three of the possible stereoisomeric combinations involving these vicinal sites had been accessed. The fourth member of this group, **21**, is described in the following text.

The overwhelming preference shown by **6** and **13** to isomerize through a cyclic six-membered chairlike transition state continues to be the dominant feature during Claisen rearrangement of diastereomer **20**. However, this allyl ether, obtained efficiently (88%) by condensation of **19** with the Tebbe reagent, afforded a total of six products when exposed to Tribal under the usual conditions (Scheme IV). The major alcohol (72%) was easily identified as **18**. The companion cyclooctenol (5%) was shown to be **21** by tosylation[17] of **18** and exposure of the tosylate to potassium superoxide and 18-crown-6 in a DME–DMSO

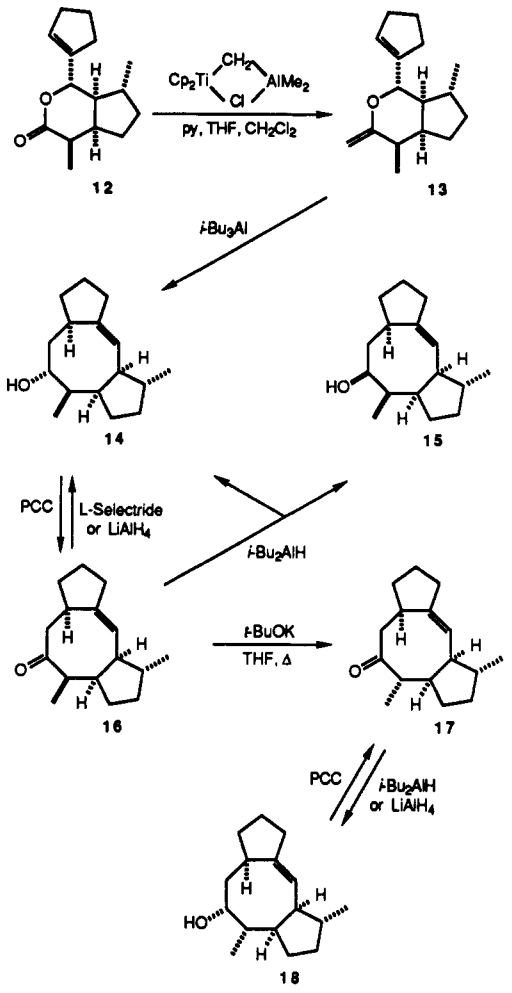
(14) (a) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985; *Idem. Bull. Chem. Soc. Jpn.* **1984**, *57*, 446. (b) Stevenson, J. W. S.; Bryson, T. A. *Ibid.* **1982**, *23*, 3143. (c) Mori, I.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron* **1984**, *40*, 4013.

(15) (a) Maruoka, K.; Nonoshita, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 7922. (b) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *Ibid.* **1990**.

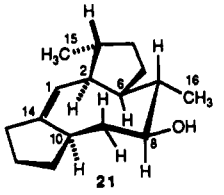
(16) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *Ibid.* **1980**, *102*, 3270. (c) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Straus, D.; 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.

(17) Field, L.; McFarland, J. W. *Organic Syntheses*; Wiley: New York, **1963**; *Collect. Vol. IV*, p 940.

Scheme III

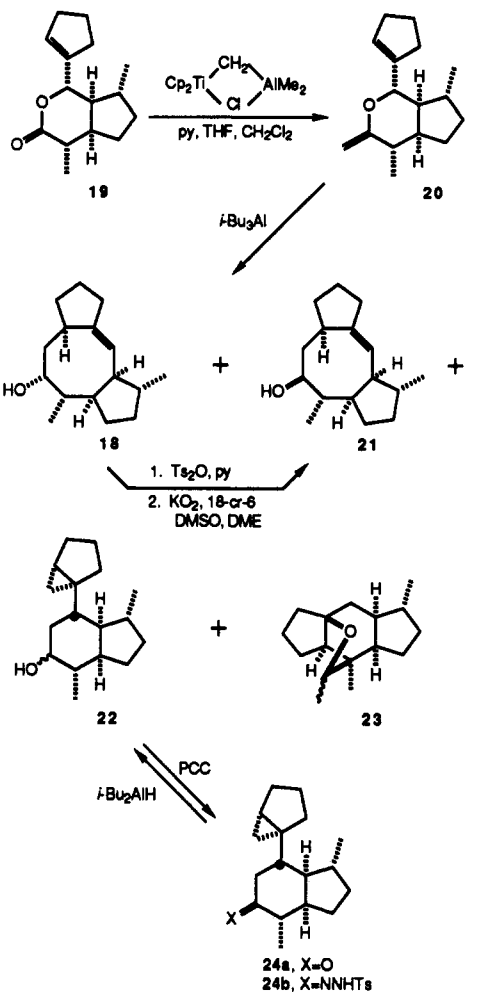


(1:2) solvent system,[18] resulting in smooth nucleophilic displacement with inversion of configuration.

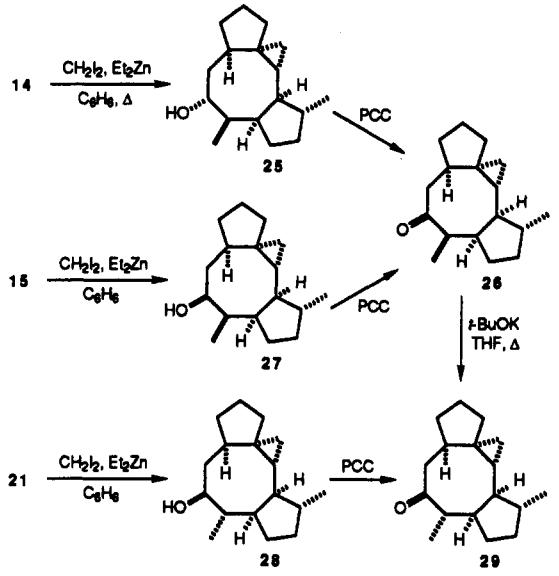


Also produced in the rearrangement of **20** were the alcohols **22** (7%) and ethers **23** (6%). To facilitate identification, **22** was oxidized to **24a**. NOE experiments and coupling constants were again helpful in establishing the ketone to possess a bicyclo[3.1.0]hexane partial structure, a conclusion that was corroborated by X-ray analysis of the derived tosylhydrazone **24b**. The structural features in evidence suggest the possibility that **20** experiences 1,3-alkyl oxygen-to-carbon migration and ultimately reduction and cyclopropanation. As will be discussed, **30** does not react under analogous conditions to produce **22**. The methylene carbenoid necessary for introduction of the three-membered ring is presumably generated in low concentration from the interaction of Tribal with CH_2Cl_2.[19] Since cyclopropanation of other Claisen products is not

Scheme IV



Scheme V



observed, a strong, chemospecific directing effect is likely operating in this specific example.[21]

As expected, the reduction of **24a** with Dibal-H produced both epimers of **22**. The ethers defined by **23** arise

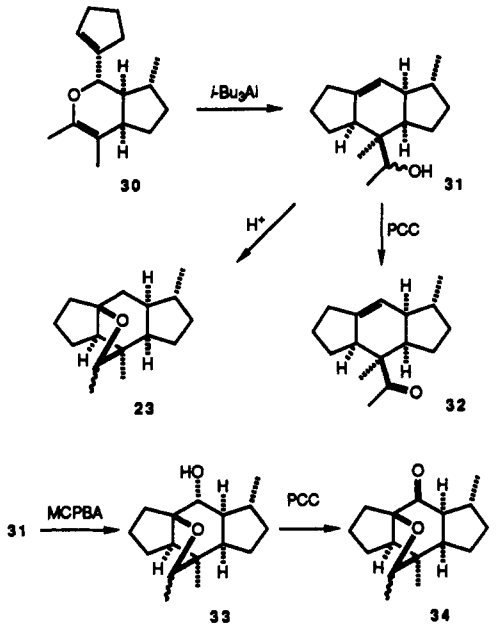
(18) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, 3183.

(19) Compare: Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 4412.

(20) (a) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647 and earlier references cited therein. (b) Sawada, S.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2669. (c) See also ref 21c.

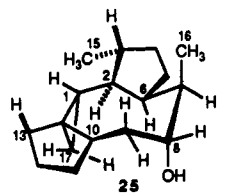
(21) (a) Poulter, C. D.; Friedrich, E. C.; Winstein, S. *J. Am. Chem. Soc.* **1969**, *91*, 6892 and earlier references cited therein. (b) Staroscik, J. A.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 738. (c) Kawabata, N.; Nakagawa, T.; Nakao, T.; Yamashita, S. *J. Org. Chem.* **1977**, *42*, 3031.

Scheme VI



from prior migration of the vinyl ether double bond to the adjacent site internal to the six-membered ring. The stereoselectivities of this Claisen rearrangement are examined later.

Cyclopropanation Studies Involving the Stereoisomeric Dicyclopenta[*a*,*d*]cyclooctenols. The studies detailed here were undertaken to gain knowledge about one-carbon homologations of the tricyclic alcohols described previously. Cyclic olefin **14** was relatively unreactive toward diethylzinc and diiodomethane in benzene.[20] After a total reaction time of 12 h, only a modest amount (34%) of **25** was isolated (Scheme V). The NMR spectral features of **25** indicated that cyclopropanation had

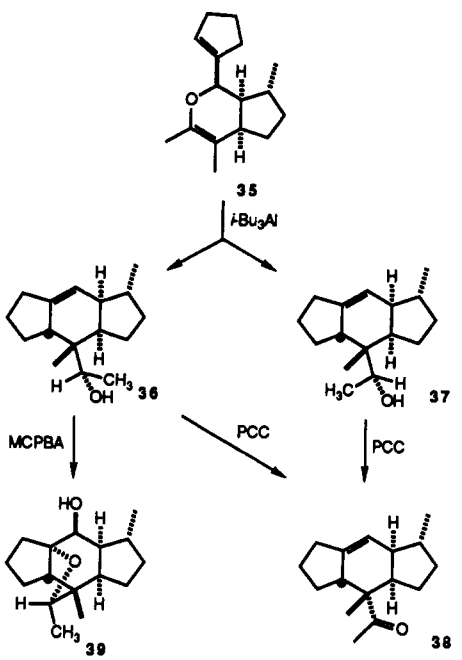


materialized as expected from the less sterically congested α-face of the π-bond. Ketone **26**, produced by chromate oxidation of **25**, proved to be identical with the substance formed comparably from **27**. This interrelationship reveals the hydroxyl group in **15** to be unable to guide the attacking carbenoid into syn addition.[21] The absence of a directing effect[22] must reflect a significant degree of steric crowding within the interior of the tublike conformation such that precomplexation is effectively deterred. Reaction efficiency is not a reliable indicator of this complication since **27** was isolated in 86% yield.

Partial relief of steric crowding by orienting the flanking methyl group α as in **21** does not result in cyclopropanation from the β-face. The oxidation of **28** delivered ketone **29**, identical with the product of epimerization of **26**.

Isomerization of the Vinyl Ether Double Bond. Stereocontrolled Route to Linearly Fused 5-6-5 Tricyclics. Prototropic isomerization of vinyl ether double

Scheme VII



bonds positioned exocyclic to six-membered rings is recognized to occur with reasonable facility.[9] The systems examined herein are not exempt from this thermodynamically driven olefinic migration. Thus, storage of **13** and **20** in benzene solution at room temperature for several days served as the method of choice for obtaining **30**. Both reactions are quantitative. Room-temperature Claisen rearrangement of **30** in the presence of excess Tribal proceeded efficiently to deliver alcohol **31** as an inseparable mixture of hydroxyl epimers (Scheme VI). The environment about the carbonyl group in **32** evidently is not effective in controlling facial selectivity during the ultimate hydride-transfer step. The stereochemical features assigned to **31** and **32a** follow on the basis of an assumed boat transition state for the sigmatropic event. This topography is dictated by the endocyclic location of the vinyl ether double bond. Oxidation of **31** led to stereochemically homogeneous **32**, thereby indicating the two alcohol isomers to be epimeric at the hydroxylic center. The spatial proximity of the functionalized sites in **31** allows for neighboring group participation as witnessed by its conversion to **23** and **33** when treated with acid or *m*-CPBA, respectively. These more conformationally rigid compounds, and ketone **34** as well, did not lend themselves to convenient diastereomer separation by chromatography.

The pair of alcohols resulting from catalyzed Claisen rearrangement of **35** were produced in widely disparate amounts (71% of **36** and 7% of **37**, Scheme VII). The independent conversion of both **36** and **37** to ketone **38** require that the five stereogenic centers in **38** be present in both precursor molecules. The epoxidation of **36** gave **39**, a crystalline alcohol whose assigned structure was corroborated by X-ray methods.

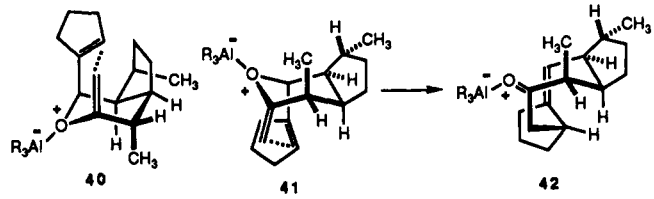
Discussion

Stereochemical Course of the Claisen Ring Expansion. The demonstration that Tribal appreciably accelerates the Claisen rearrangement of **6**, **13**, and **20** is in accord with earlier observations made by others,[14a,c] who also noted that the carbonyl products were reduced to alcohols under the mild conditions of the reaction. Since no information regarding chair/boat selectivity was derivable from the original examples, no comment regarding

(22) Effective use of this process was made, for example, by deMayo and co-workers in their synthesis of β-himachalene: (a) Challand, B. D.; Kornis, G.; Lange, G. L.; deMayo, P. *Chem. Commun.* **1967**, 704. (b) Challand, B. D.; Hikino, H.; Kornis, G.; Lange, G.; deMayo, P. *J. Org. Chem.* **1969**, *34*, 794.

mechanism was offered. While the present data shed some light on these issues, the extent of acceleration has not been specifically probed. Suffice it to say that isomerizations of the alicyclic Claisen type are clearly capable of being reliably performed at room temperature. Since charge acceleration is likely responsible for facilitating these reactions,[13] alkylaluminum-catalyzed Claisen rearrangements merit serious consideration as the cationic counterpart of the more well-established anionic oxy-Cope process.[23]

Ether **6** demonstrates by virtue of its Lewis acid catalyzed conversion to **7** that passage via chair transition state **40** is kinetically favored. Although Yamamoto proposed

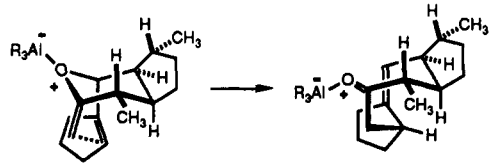


40 **41** **42**

an axial orientation for the complexation of bulky aluminum reagents to ether oxygen,[15] recent crystallographic and spectroscopic evidence suggests that the geometries of these complexes may be rather planar and we have adopted such formulations.

The structural features present in **13** presumably foster conformational alignment as in **41**. Given the current view that Claisen rearrangements have early transition states with advanced bond breaking,[25] this chairlike arrangement will transform itself into **42**. In situ reduction of this ketonic product gives cyclooctenol **14** exclusively. This stereoselectivity suggests that hydride transfer occurs only after **42** has undergone appreciable conformational realignment since the β-face of the carbonyl group in **42** is sterically inaccessible.

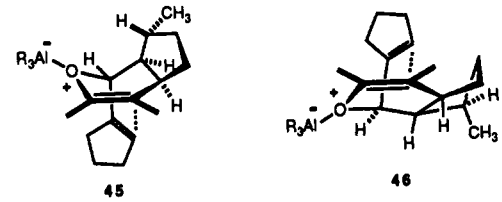
There exists equally clear indications that vinyl ether **20** makes exclusive use of chair alternatives **43** since **18** and **21** are the relevant products formed in this instance.



43 **44**

While the Claisen rearrangement of most vinyl ethers leads predominantly to products that possess *E* double-bond geometry,[5] this stereochemical tendency can be modified in a *Z*-selective direction under certain conditions by very bulky organoaluminum catalysts.[15] A general feature of the Claisen ring expansion is its *Z* selectivity, since the newly developing double bond is positioned within a ring.

Stereochemical Control in the Rearrangement of 30 and 35. As a result of the endocyclic position of the vinylic ether double bond in this isomer pair, no option exists for achieving adequate proximity of the π-bond termini in chairlike conformations. Only in the boatlike arrangements depicted in **45** and **46** can suitable bonding distances be realized. The structural elements in **46** are



45 **46**

more crowded than those seen in **45**. Consequently, **30** would be expected to enjoy a lower energy pathway to product. Notwithstanding, both substrates undergo complete Tribal-catalyzed rearrangement during overnight stirring at room temperature.

Summary

The transition states utilized by the exocyclic (**6, 13, 20**) and endocyclic ethers (**30, 35**) differ intrinsically in their geometry as a result of the change in locus of the vinyl double bond within an otherwise rigid structural framework. Both processes are completely *Z* selective in order to provide the less strained cis double-bond geometry in the respective products. To achieve this result, the endocyclic vinyl ethers must utilize boatlike transition states. The chairlike and boatlike alternatives both have the ability to be influenced catalytically by $(i\text{-Bu})_3$Al. Since this acceleration is expected to persist in still more sterically crowded situations, Claisen rearrangements should be capable of being performed routinely at room temperature or below. Current efforts in this laboratory are focused on the adaptation of this chemistry to a concise, highly stereoselective synthesis of enantiomerically pure **3**, and ultimately epoxydictymene (**1**).

Experimental Section

Melting points are uncorrected. IR and NMR spectra were recorded in CCl_4 and $CHCl_3$, respectively, unless noted. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75, 62.5, or 20 MHz. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All separations were carried out under flash chromatography conditions with Merck silica gel HF_{254}. The organic extracts were dried over anhydrous $MgSO_4$. Solvents were reagent grade and in many cases dried prior to use (PE is petroleum ether; E refers to ethyl ether; EA is ethyl acetate).

Tebbe Reaction on 5. A cold (−40 °C), magnetically stirred solution of **5** (30 mg, 0.128 mmol) and pyridine (10 mg) in dry CH_2Cl_2/THF (2 mL, 1:1) was treated with a solution of $Cp_2Ti(CH_2)ClAlMe_2$ in CH_2Cl_2 (0.25 mL of 0.72 M, 0.18 mmol). After 30 min at −40 °C, the reaction mixture was warmed to room temperature and maintained for 30 min prior to cooling in an ice–methanol bath. Following the addition of 20% NaOH solution (0.5 mL), the product was taken up in PE and washed with water and brine. After drying and solvent evaporation, the residue was passed through a 5-cm layer of activity III basic alumina (elution with PE). Concentration gave 28 mg (93%) of **6** as a colorless oil: IR (cm^{-1}) 1645; ^{1}H NMR (C_6D_6) δ 6.00 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 4.77 (s, 1 H), 4.52 (m, 1 H), 4.24 (d, J = 1 Hz, 1 H), 2.41–2.07 (m, 5 H), 2.06 (br dq, J = 7, 7 Hz, 1 H), 1.93–1.73 (m, 4 H), 1.66–1.39 (m, 3 H), 1.19–1.04 (m, 1 H), 1.07 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 165.2 (s), 143.5 (s), 124.3 (d), 90.2 (t), 77.1 (d), 48.6 (d), 46.2 (d), 35.6 (d), 33.8 (t), 33.5 (t), 32.6 (t), 32.3 (d), 30.7 (t), 23.4 (t), 21.7 (q), 19.1 (q); MS m/z (M^+) calcd 232.1827, obsd 232.1797.

Catalyzed Claisen Rearrangement of 6. A. Use of Dibal-H. After a solution of 0.35 mL (0.35 mmol) of $(i\text{-Bu})_2$AlH (1.0 M solution in hexanes) was added (2 min) to a cooled (below 0 °C), stirred solution of 28 mg (0.12 mmol) of **6** in 1.5 mL of anhydrous CH_2Cl_2 and the resultant solution was stirred for 5 h at ambient temperature, the mixture was partitioned between ether and water, and the separated organic phase was washed with 5% HCl, water, and brine, dried, and evaporated to leave 30 mg of a colorless oil, which after flash chromatography (PE–E (9:1, followed by 2:1)) afforded 12.0 mg (42%) of **7a** and 7.1 mg (25%) of **8**.

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(24) See, for example: (a) Galeffi, B.; Simard, M.; Wuest, J. D. *Inorg. Chem.* **1990**, *29*, 955. (b) Hunold, R.; Pilz, M.; Allwohn, J.; Stadler, M.; Massa, W.; Schleyer, P. v. R.; Berndt, A. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 781. (c) Wiberg, N.; Wagner, G.; Reber, G.; Reide, J.; Mueller, G. *J. Organometallics* **1987**, *6*, 35.

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For 7a: colorless oil; IR (cm^{-1}) 3630; ^1H NMR (C_6D_6) δ 5.05 (br dddd, J = 4, 2, 2, 2 Hz, 1 H), 3.54 (ddd, J = 10.5, 7.5, 1.5 Hz, 1 H), 2.94 (br m, 1 H), 2.50–2.35 (br m, 1 H), 2.23–2.10 (br m, 1 H), 2.22 (dddd, J = 11, 11, 7, 7 Hz, 1 H), 2.10 (ddd, J = 13.5, 11.5, 10.5 Hz, 1 H), 2.02–1.73 (m, 5 H), 1.77 (ddq, J = 7, 1.5, 7 Hz, 1 H), 1.71–1.39 (m, 3 H), 1.39–1.07 (m, 3 H), 1.11 (d, J = 7 Hz, 3 H), 1.04 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 146.2 (s), 124.8 (d), 77.6 (d), 45.9 (d), 43.9 (d), 41.8 (d, 2 C), 36.9 (d), 35.3 (t), 34.0 (t), 33.8 (t), 30.7 (t), 30.2 (t), 22.4 (q), 21.3 (t), 19.1 (q); MS m/z (M^+) calcd 234.1984, obsd 234.1991. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.93; H, 10.91.

For 8: colorless oil; IR (cm^{-1}) 3620; ^1H NMR δ 5.79 (ddd, J = 17, 10, 8 Hz, 1 H), 5.55 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 5.03 (ddd, J = 17, 2, 1 Hz, 1 H), 4.93 (ddd, J = 10, 2, 0.5 Hz, 1 H), 4.58 (m, 1 H), 2.42 (br ddq, J = 10, 8, 6.5 Hz, 1 H), 2.37–2.27 (m, 2 H), 2.25–2.08 (m, 2 H), 2.05 (dddq, J = 7, 7, 3.5, 7 Hz, 1 H), 1.98–1.77 (m, 4 H), 1.77–1.66 (m, 1 H), 1.67 (ddd, J = 8.5, 3.5, 2 Hz, 1 H), 1.45 (dddd, J = 12, 11.5, 11.5, 7.5 Hz, 1 H), 1.10–0.96 (m, 1 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.83 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 148.4 (s), 145.3 (d), 123.0 (d), 112.5 (t), 71.0 (d), 49.3 (d), 47.9 (d), 38.5 (d), 34.3 (t), 33.3 (t), 32.2 (t), 32.1 (d), 31.5 (t), 23.7 (t), 23.6 (q), 21.0 (q); MS m/z (M^+) calcd 239.1984, obsd 234.1954.

B. Use of Tribal. A cold (−78 °C), magnetically stirred solution of **6** (23 mg, 99 μmol) in dry CH_2Cl_2 (2 mL) was treated with $(i\text{-Bu})_3Al$ in toluene (0.30 mL of 1.0 M, 0.30 mmol) during 1 min. The reaction mixture was stirred at −78 °C for 10 min and at room temperature for 4 h. The predescribed workup gave an inseparable 5:1 mixture of **7a** and **7b** (^1H NMR analysis) as a colorless oil (19.5 mg, 84%).

For 7b: ^{13}C NMR (75 MHz) δ 147.0 (s), 124.0 (d), 76.2 (d), 47.5 (d), 46.4 (d), 44.0 (d), 39.8 (d), 38.7 (d), 35.5 (t), 34.1 (t), 33.6 (t), 30.8 (t), 30.7 (t), 22.0 (q), 21.3 (t), 17.5 (q).

Epoxidation of 7a. To a magnetically stirred solution of **7a** (23 mg, 98 μmol) in dry C_6H_6 (6 mL) was added m-CPBA (40 mg of 85%, 197 μmol). After 20 h at room temperature, the reaction mixture was diluted with ether and washed in turn with saturated $NaHSO_3$ solution, 5% KOH, water, and brine. The organic phase was dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (elution with PE–E (2:1)). There was isolated 19.2 mg (78%) of **9a** as a colorless oil: IR (cm^{-1}) 3620, 3550–3300; ^1H NMR (C_6D_6) δ 3.38 (ddd, J = 11, 8.5, 1 Hz, 1 H), 2.78 (d, J = 6 Hz, 1 H), 2.35–2.20 (m, 2 H), 2.07 (dddd, J = 11, 11, 6.5, 6.5 Hz, 1 H), 1.93–1.05 (series of m, 14 H), 1.08 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 76.9 (d), 71.0 (s), 64.0 (d), 50.2 (d), 41.5 (d), 41.1 (d), 39.3 (d), 36.6 (d), 33.8 (t), 32.2 (t), 31.4 (t), 30.4 (t), 30.3 (t), 23.0 (q), 20.1 (2C, d + t); MS m/z (M^+) calcd 250.1933, obsd 250.1927.

Epoxy Ketone 10. The 5:1 mixture of **7a** and **7b** produced earlier (32 mg, 137 μmol) in dry C_6H_6 (8 mL) was reacted with m-CPBA (55 mg of 85%, 271 μmol) in the predescribed manner to give the crude epoxy alcohols **9a** and **9b** (36.5 mg). This mixture and pyridine (50 mg) were dissolved in dry dichloromethane (3 mL) and treated at room temperature with NaOAc (300 mg) and pyridinium chlorochromate (100 mg, 464 μmol). After 2 h of stirring at room temperature, workup was undertaken by dilution with ether, filtration through a pad of Celite (ether wash), and solvent evaporation. The residue was taken up in ether and washed sequentially with 5% HCl, water, saturated $NaHCO_3$ solution, and brine. After drying and concentration, the residue was purified by flash chromatography (silica gel, elution with PE–E (2:1)) to give 26.1 mg (72%) of **10** as a colorless oil: IR (cm^{-1}) 1700; ^1H NMR (C_6D_6) δ 2.73 (d, J = 5.5 Hz, 1 H), 2.67 (dq, J = 10, 6.5 Hz, 1 H), 2.48 (dd, J = 18.5, 12 Hz, 1 H), 2.19 (dd, J = 18.5, 2 Hz, 1 H), 2.20–1.65 (series of m, 7 H), 1.55–1.25 (m, 5 H), 1.14–0.93 (m, 2 H), 1.14 (d, J = 6.5 Hz, 3 H), 0.78 (d, J = 7 Hz, 3 H); ^{13}C NMR (20 MHz, C_6D_6) δ 212.8 (s), 70.5 (s), 63.8 (d), 50.9 (d), 47.2 (d), 42.6 (d), 40.9 (t), 40.2 (d), 39.1 (d), 34.6 (t), 30.6 (t), 30.4 (t), 30.1 (t), 22.5 (q), 20.3 (t), 15.8 (q); MS m/z (M^+) calcd 248.1776, obsd 248.1809. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.33; H, 9.77.

Diol 11. A cold (−78 °C), magnetically stirred solution of **10** (24.2 mg, 0.97 mmol) in dry CH_2Cl_2 (2 mL) was treated during 5 min with $(i\text{-Bu})_2AlH$ (0.3 mL of 1.0 M in hexanes, 0.3 mmol). After being warmed to room temperature, the reaction mixture was stirred for 2 h, quenched at 0 °C with saturated NH_4Cl solution, and diluted with ether. The organic phase was washed with 5% HCl, water, and brine, and then dried and concentrated. The residue was subjected to flash chromatography on silica gel (elution with PE–E (1:6)) to give 14.5 mg (59%) of **11** as colorless needles (from ether–pentane): mp 145.5–146 °C; IR ($CHCl_3$, cm^{-1}) 3610; ^1H NMR (C_6D_6) δ 3.40 (ddd, J = 11, 6.5, 2.5 Hz, 1 H), 2.19–1.99 (m, 2 H), 1.82 (ddd, J = 14, 11, 7 Hz, 1 H), 1.80–1.25 (series of m, 14 H), 1.22–0.94 (m, 2 H), 1.08 (d, J = 7 Hz, 3 H), 1.06 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 79.0 (s), 76.3 (d), 46.4 (d), 43.4 (d), 42.9 (t), 42.3 (t), 41.9 (d), 39.1 (d), 35.1 (d), 33.2 (t), 32.9 (t), 32.7 (t), 32.2 (t), 20.8 (t), 20.2 (t), 18.8 (q); MS m/z (M^+) calcd 252.2089, obsd 252.2087. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.14. The same diol was obtained when **9a** was treated with Dibal-H as described previously.

Tebbe Reaction on 12. Lactone **12** (158 mg, 0.674 mmol) was treated with $Cp_2Ti(CH_2)ClAlMe_2$ (2.80 mL of 0.36 M in toluene, 1.01 mmol) and pyridine (5 drops) in THF/CH_2Cl_2 (12 mL of 1:1) as described previously, which afforded 133 mg (85%) of **13** as a pale yellowish oil: IR (cm^{-1}) 1655, 1615; ^1H NMR (C_6D_6) δ 5.60 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 4.78 (br d, J = 1.5 Hz, 1 H), 4.32 (m, 1 H), 4.14 (d, J = 1.5 Hz, 1 H), 2.83 (dddq, J = 5.5, 2, 1.5, 7 Hz, 1 H), 2.57–2.36 (m, 2 H), 2.34–2.24 (m, 2 H), 2.15 (br dddd, J = 11, 9, 7.5, 5.5 Hz, 1 H), 1.92–1.70 (m, 5 H), 1.61–1.39 (m, 2 H), 1.08–0.95 (m, 1 H), 0.96 (d, J = 7 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 163.2 (s), 146.2 (s), 125.8 (d), 87.6 (t), 76.5 (d), 48.4 (d), 41.1 (d), 38.1 (d), 34.1 (t), 32.9 (t), 32.8 (2C d + t), 26.3 (t), 23.6 (t), 20.0 (q), 15.7 (q); MS m/z (M^+) calcd 232.1827, obsd 232.1807.

Tribal-Catalyzed Claisen Rearrangement of 13. Ether **13** (77 mg, 0.331 mmol) was reacted with $(i\text{-Bu})_3Al$ (1.0 mL of 1.0 M in toluene, 1.0 mmol) in dry CH_2Cl_2 (10 mL) as described earlier, except that stirring at room temperature was maintained overnight. Similar workup and purification by flash chromatography (silica gel, elution with PE–E (2:1)) afforded pure **14** (59 mg, 76%) as a colorless oil: IR (cm^{-1}) 3550–3300; ^1H NMR (C_6D_6) δ 5.31 (dddd, J = 5.5, 2, 2, 1 Hz, 1 H), 3.73 (ddd, J = 7, 5.5, 3 Hz, 1 H), 3.00–2.89 (m, 1 H), 2.79 (dddd, J = 10, 10, 7.5, 3.5 Hz, 1 H), 2.43–2.33 (m, 1 H), 2.30–2.21 (m, 2 H), 1.99–1.42 (series of m, 10 H), 1.34 (dddd, J = 11.5, 7, 4, 3 Hz, 1 H), 1.19–1.08 (m, 1 H), 1.08 (d, J = 6.5 Hz, 3 H), 0.97 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (20 MHz) δ 147.0 (s), 124.5 (d), 75.0 (d), 48.6 (d), 44.3 (d), 42.6 (d), 42.5 (d), 41.4 (t), 35.6 (d), 35.1 (t), 33.5 (t), 31.8 (t), 31.0 (t), 23.5 (t), 20.9 (q), 14.4 (q); MS m/z (M^+) calcd 234.1984, obsd 234.1967.

Oxidation of 14. Alcohol **14** (96 mg, 0.41 mmol) was treated with pyridinium chlorochromate (320 mg, 1.48 mmol) and pyridine (0.2 mL) in CH_2Cl_2 (8 mL) at room temperature for 3 h. Workup by dilution with ether, filtration through Celite, and sequential washing with 5% HCl, water, dilute KOH solution, water, and brine, followed by flash chromatography (silica gel, elution with PE–E (4:1)) afforded pure **16** (82 mg, 86%) as a colorless oil: IR (cm^{-1}) 1710, 1690; ^1H NMR δ 5.12 (dddd, J = 6, 2, 2, 1.5 Hz, 1 H), 2.92 (br ddd, J = 9, 8, 7 Hz, 1 H), 2.78 (dd, J = 11.5, 7 Hz, 1 H), 2.63 (dq, J = 5, 7 Hz, 1 H), 2.49 (dddd, J = 10.5, 7.5, 7.5, 5 Hz, 1 H), 2.27 (dd, J = 11.5, 9 Hz, 1 H), 2.30–2.11 (m, 3 H), 1.95–1.62 (m, 5 H), 1.60–1.35 (m, 3 H), 1.18–1.04 (m, 1 H), 1.03 (d, J = 7 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (20 MHz) δ 214.3 (s), 147.3 (s), 125.0 (d), 49.1 (d), 48.4 (t), 46.8 (d), 45.2 (d), 41.5 (d), 37.4 (d), 33.9 (t), 32.3 (t), 32.1 (t), 27.1 (t), 23.4 (t), 21.3 (q), 14.5 (q); MS m/z (M^+) calcd 232.1827, obsd 232.1822. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.71; H, 10.42.

Reductions of 16. A. $LiAlH_4$ or L-Selectride. Reduction of **16** with lithium aluminum hydride in ether (−78 to 20 °C) or L-Selectride in THF (−78 to 20 °C) led to the production of **14** as the sole product, the absence of **15** being determined by ^1H NMR analysis of the crude residue.

B. $(i\text{-Bu})_2AlH$. Reduction of **16** (20 mg, 0.086 mmol) with Dibal-H (0.20 mL of 1.0 M in toluene, 0.2 mmol) in dry CH_2Cl_2 (4 mL) at −78 °C, followed by stirring overnight at room temperature and the usual workup, afforded 21.4 mg of a 77:23 mixture (^1H NMR analysis) of **14** and **15**. Separation by flash chromatography on silica gel (elution with PE–E (3:2)) afforded 13.7 mg (68%) of **14** and 3.9 mg (19%) of **15**.

For 15: colorless oil; IR (cm^{-1}) 3620, 3600–3350; ^1H NMR δ 5.15 (ddddd, J = 5, 1.5, 1.5, 1.5, 1.5 Hz, 1 H), 3.95 (ddd, J = 11,

3.5, 1.5 Hz, 1 H), 2.66 (br dd, J = 11, 9 Hz, 1 H), 2.34–2.14 (m, 4 H), 2.05 (dddq, J = 4.5, 1.5, 1, 7.5 Hz, 1 H), 1.98–1.34 (series of m, 9 H), 1.60 (dddd, J = 13, 3.5, 2.5, 1 Hz, 1 H), 1.14–1.00 (m, 1 H), 0.99 (d, J = 7 Hz, 3 H), 0.93 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (20 MHz) δ 146.5 (s), 125.5 (d), 77.2 (d), 48.1 (d), 46.8 (d), 42.8 (d), 42.1 (d), 42.0 (t), 37.8 (d), 35.1 (t), 33.1 (t), 32.3 (t), 30.7 (t), 23.9 (t), 21.8 (q), 9.9 (q); MS m/z (M^+) calcd 234.1984, obsd 234.1975.

Epimerization of 16. A solution of **16** (46.5 mg, 0.200 mmol) in dry THF (8 mL) was treated with potassium *tert*-butoxide (20 mg, 0.178 mmol) and heated at reflux for 10 h. The reaction mixture was diluted with ether and washed with 5% HCl, water, and brine. After drying and concentration, the residue was subjected to flash chromatography (silica gel, elution with PE–E (6:1)) to give 40.6 mg (87%) of **17** as a colorless oil: IR (cm^{-1}) 1705; ^{1}H NMR δ 5.16 (dddd, J = 8.5, 2, 2, 2, Hz, 1 H), 2.68–2.57 (m, 1 H), 2.52–2.37 (m, 2 H), 2.44 (dd, J = 12.5, 10 Hz, 1 H), 2.37–2.25 (m, 1 H), 2.30 (dd, J = 10, 3.5 Hz, 1 H), 2.06–1.90 (m, 4 H), 1.89–1.51 (m, 4 H), 1.45 (br ddd, J = 12, 6, 3.5 Hz, 1 H), 1.25–1.00 (m, 2 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 216.7 (s), 145.4 (s), 124.2 (d), 52.9 (t), 49.4 (d), 47.7 (d), 45.6 (d), 40.0 (d), 38.0 (d), 34.7 (t), 33.4 (t), 31.5 (t), 28.9 (t), 24.3 (t), 22.3 (q), 15.9 (q); MS m/z (M^+) calcd 232.1827, obsd 232.1840. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.90; H, 10.36.

Reduction of 17. A. $LiAlH_4$. A solution of **17** (40.6 mg, 0.175 mmol) in dry ether (2.5 mL) was added dropwise to a magnetically stirred suspension of $LiAlH_4$ (10 mg, 0.264 mmol) in ether (1 mL) at −78 °C. The mixture was allowed to warm to room temperature and stirred overnight. The usual workup afforded only **18** (37.8 mg, 92%) after flash chromatography (silica gel, elution with PE–E (2:1)).

B. Dibal-H. Treatment of **17** (36.5 mg, 0.157 mmol) with Dibal-H (0.4 mL of 1.0 M in hexanes, 0.4 mmol) in CH_2Cl_2 (4 mL) at −78 °C followed by warmup to room temperature overnight and the usual workup and purification by flash chromatography gave pure **18** (33.8 mg, 92%): IR (cm^{-1}) 3620; ^{1}H NMR (C_6D_6) δ 5.17 (dddd, J = 8, 2, 2, 2, Hz, 1 H), 3.64 (br dd, J = 6.5, 2.5 Hz, 1 H), 3.01–2.89 (br m, 1 H), 2.77 (br dd, J = 8, 6.5 Hz, 1 H), 2.41–2.23 (m, 2 H), 2.14 (dddd, J = 10.5, 10.5, 6.5, 6.5 Hz, 1 H), 2.08–1.93 (m, 2 H), 1.88–1.58 (m, 4 H), 1.73 (ddd, J = 13.5, 6.5, 3 Hz, 1 H), 1.56–1.42 (m, 1 H), 1.47 (ddd, J = 13.5, 11.5, 2.5 Hz, 1 H), 1.34–1.14 (m, 3 H), 1.10 (d, J = 7 Hz, 3 H), 1.04 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 146.6 (s), 123.6 (d), 76.9 (d), 49.3 (d), 45.8 (d), 42.9 (t), 40.6 (d), 38.7 (d), 35.8 (d), 34.2 (t), 32.7 (t), 31.4 (t), 30.6 (t), 24.1 (t), 22.4 (q), 21.0 (q); MS m/z (M^+) calcd 234.1984, obsd 234.1981.

Oxidation of 18. Alcohol **18** (44 mg, 0.188 mmol) was oxidized with pyridinium chlorochromate (150 mg, 0.696 mmol) and pyridine (5 drops) in dry CH_2Cl_2 (4 mL) at 20 °C for 3 h. The usual workup and purification by filtration through silica gel (elution with PE–E (2:1)) afforded pure **17** (39 mg, 89%).

Tebbe Reaction on 19. Lactone **19** (200 mg, 0.853 mmol) was treated with $Cp_2Ti(CH_2)ClAlMe_2$ (3.6 mL of 0.36 M in toluene, 1.30 mmol) and pyridine (3 drops) in THF/CH_2Cl_2 (12 mL of 1:1) as described previously. There was obtained 174 mg (88%) of **20** as a colorless oil: IR (cm^{-1}) 1660, 1620; ^{1}H NMR (C_6D_6) δ 5.61 (dddd, J = 2, 2, 2, 2 Hz, 1 H), 4.64 (br d, J = 1 Hz, 1 H), 4.38 (br d, J = 10 Hz, 1 H), 4.05 (br d, J = 1.5 Hz, 1 H), 2.79–2.65 (m, 1 H), 2.40–2.15 (m, 3 H), 2.08 (dddq, J = 10, 1.5, 1, 6.5 Hz, 1 H), 1.95–1.55 (m, 6 H), 1.45–1.30 (m, 2 H), 1.06–0.92 (m, 1 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (20 MHz, C_6D_6) δ 164.5 (s), 143.7 (s), 128.5 (d), 82.1 (t), 76.5 (d), 48.1 (d), 45.1 (d), 38.7 (d), 36.2 (d), 35.5 (t), 32.8 (t), 32.4 (t), 30.8 (t), 23.5 (t), 19.9 (q), 16.2 (q); MS m/z (M^+) calcd 232.1827, obsd 232.1846.

Tribal-Catalyzed Claisen Rearrangement of 20. Ether **20** (159 mg, 0.684 mmol) was treated with $(i\text{-}Bu)_3Al$ (2.0 mL of 1.0 M in toluene, 2.0 mmol) in dry CH_2Cl_2 (12 mL) as described for **13**. The usual workup including flash chromatography on silica gel (elution with PE–E (2:1)) afforded 10 mg (6%) of **23**, 115 mg (72%) of **18**, 8 mg (5%) of **21**, and 11 mg (7%) of **22**. All of these compounds (except **18**) were characterized by alternative synthesis as described in the following text.

Alcohol 21. A solution of **18** (37.8 mg, 0.161 mmol) in dry CH_2Cl_2 (3 mL) was treated with pyridine (0.60 mL, 7.45 mmol) and *p*-toluenesulfonic anhydride (120 mg, 0.368 mmol) at 20 °C. After overnight stirring, the reaction mixture was diluted with ether, washed sequentially with 5% HCl, water, and brine, and carried forward directly.

The tosylate in dry DME (2 mL) was added to a suspension of powdered potassium peroxide (120 mg, 1.69 mmol) and 18-crown-6 (200 mg, 0.76 mmol) in dry DMSO (4 mL), which was vigorously stirred under nitrogen while being cooled in ice. The reaction mixture was then stirred at room temperature for 3 h, diluted with ether, and carefully acidified with 5% HCl. The organic phase was washed with water and brine, dried, and evaporated. The residue was purified by flash chromatography (silica gel, elution with PE–E (3:2)) to give 26.8 mg (71%) of **2** as a colorless solid (from PE): mp 139.5–140.5 °C; IR ($CHCl_3$, cm^{-1}) 3610; ^{1}H NMR (C_6D_6) δ 5.09 (dddd, J = 8, 2, 2, 2, Hz, 1 H), 3.41 (ddd, J = 9.5, 6, 2.5 Hz, 1 H), 2.62–2.50 (br m, 1 H), 2.39–2.19 (m, 3 H), 2.08–1.55 (series of m, 7 H), 1.75 (ddd, J = 13, 3.5, 2.5 Hz, 1 H), 1.48–1.33 (m, 2 H), 1.46 (ddd, J = 13, 11, 9.5 Hz, 1 H), 1.23–1.05 (m, 2 H), 1.06 (d, J = 7 Hz, 3 H), 1.03 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 146.1 (s), 123.3 (d), 75.7 (d), 49.8 (d), 48.5 (d), 46.0 (t), 41.1 (d), 39.7 (d), 38.3 (d), 35.1 (t), 33.5 (t), 31.3 (t), 29.9 (t), 24.7 (t), 22.5 (q), 15.6 (q); MS m/z (M^+) calcd 234.1984, obsd 234.2009. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.11; H, 11.23.

Oxidation–Reduction of 22. An impure 20-mg sample of **22** was treated with PCC (80 mg) and pyridine (2 drops) in CH_2Cl_2 (3 mL) in the usual way. Isolation in the predescribed fashoin and flash chromatography on silica gel furnished 9.5 mg of **24a** as a pale yellow oil: IR (cm^{-1}) 1710; ^{1}H NMR δ 2.41 (dd, J = 17.5, 5 Hz, 1 H), 2.23 (dq, J = 10, 6.5 Hz, 1 H), 2.18 (dd, J = 17.5, 11 Hz, 1 H), 2.08–1.11 (series of m, 15 H), 1.06 (d, J = 6.5 Hz, 3 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.33 (dd, J = 5, 3.5 Hz, 1 H), 0.08 (br dd, J = 8, 5 Hz, 1 H); ^{13}C NMR (75 MHz) δ 215.4 (s), 48.1 (d), 46.3 (d), 45.8 (d), 43.8 (t), 42.9 (d), 38.8 (d), 34.2 (t), 32.3 (t), 31.2 (s), 27.6 (t), 27.0 (t), 24.7 (d), 20.8 (q), 20.5 (t), 13.1 (q), 11.6 (t); MS m/z (M^+) calcd 246.1984, obsd 246.2025.

A solution of **24a** (14.3 mg, 0.058 mmol) and tosyl hydrazide (12 mg, 0.064 mmol) in dry CH_3OH (0.2 mL) was stirred at room temperature for 2 h. The precipitated solid was isolated by removal of the liquid, washing with three small portions of methanol, and drying. There was obtained 18.6 mg (77%) of **24b** as colorless prisms (from methanol): mp 155–156 °C dec; IR (KBr, cm^{-1}) 3200; ^{1}H NMR δ 7.87 (d, J = 8 Hz, 2 H), 7.30 (br d, J = 8 Hz, 2 H), 7.05 (br s, 1 H), 2.42 (br s, 3 H), 2.21 (br dd, J = 17.5, 4 Hz, 1 H), 2.08 (br dq, J = 10.5, 6 Hz, 1 H), 2.02–1.42 (series of m, 10 H), 1.95 (br dd, J = 17.5, 12 Hz, 1 H), 1.29–1.05 (series of m, 5 H), 1.03 (d, J = 6 Hz, 3 H), 1.02 (d, J = 7 Hz, 3 H), 0.31 (dd, J = 4.5, 3.5 Hz, 1 H), −0.03 (br dd, J = 8, 4.5 Hz, 1 H); ^{13}C NMR (75 MHz) δ 143.8, 135.5, 129.3 (2 C), 128.3 (2 C), 47.5, 45.8, 41.9, 39.6, 39.3, 34.6, 32.5, 32.4, 30.9, 27.6, 26.3, 25.3, 21.6, 20.8, 20.5, 14.7, 11.7 (imino-C not observed); MS m/z ($M^+ - C_7H_7O_2$) calcd 259.2174, obsd 259.2240.

Dibal-H reduction of **24a** (CH_2Cl_2, −78 to 20 °C) afforded a 1:1 mixture of the epimeric alcohols **22** as a colorless oil in 80% yield. Isomer A: ^{1}H NMR δ 3.47 (ddd, J = 9.5, 9.5, 4.5 Hz, 1 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H), 0.35 (dd, J = 4.5, 4 Hz, 1 H), 0.19 (br dd, J = 8, 4.5 Hz, 1 H). Isomer B: ^{1}H NMR δ 3.89 (ddd, J = 10, 4.5, 4.5 Hz, 1 H), 0.98 (d, J = 7 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.28 (dd, J = 4.5, 4 Hz, 1 H), 0.02 (br dd, J = 8, 4.5 Hz, 1 H). Both isomers show a series of m at δ 2.40–0.80 (18 H each). For the mixture: ^{13}C NMR (75 MHz) δ 73.3 (d), 70.1 (d), 49.9 (d), 45.5 (d), 45.2 (d), 44.4 (d), 42.2 (d), 40.7 (d), 40.0 (d), 36.6 (d), 36.2 (t), 36.1 (d), 35.8 (d), 34.9 (t), 33.7 (s), 32.0 (t), 31.9 (t), 31.2 (s), 29.6 (t), 29.4 (t), 29.3 (t), 27.5 (t), 27.4 (t), 26.9 (t), 25.5 (d), 25.3 (d), 22.7 (q), 21.5 (t), 20.6 (t), 20.2 (q), 16.8 (q), 14.2 (q), 12.5 (t), 10.8 (t).

Simmons–Smith Cyclopropanation of 14. A solution of **14** (37 mg, 0.159 mmol) in dry C_6H_6 (1 mL) was treated with diethylzinc (1.0 mL of 1.1 M in toluene, 1.1 mmol) and CH_2I_2 (0.10 mL, 1.24 mmol). A white suspension formed exothermically after a short induction period. The reaction mixture was initially heated at reflux for 4 h. However, since only partial conversion materialized during this elapsed time (TLC analysis), heating was resumed with fresh reagents for an added 8 h. After dilution with ether, the organic phase was washed with 5% HCl, water, and brine, and then dried and concentrated. Flash chromatography on silica gel (elution with PE–E (2:1)) returned 9.1 mg (25%) of

unreacted **14**. In addition, 13.3 mg (34%) of **25** was obtained as a colorless oil: IR (cm^{-1}) 3620; ^1H NMR (C_6D_6) δ 3.95 (ddd, J = 7, 6, 2 Hz, 1 H), 2.36–2.21 (m, 2 H), 2.12–1.94 (m, 4 H), 1.91–1.58 (m, 3 H), 1.86 (br ddd, = 12, 6, 2 Hz, 1 H), 1.75 (ddd, J = 14, 12, 2 Hz, 1 H), 1.51 (br ddd, J = 12, 6, 6 Hz, 1 H), 1.37 (ddd, J = 12, 7.5, 3.5 Hz, 1 H), 1.33 (ddd, J = 14, 6, 2 Hz, 1 H), 1.21–1.08 (m, 2 H), 1.13 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 7.5 Hz, 3 H), 0.93 (ddd, J = 12, 8, 3.5 Hz, 1 H), 0.89 (br s, OH), 0.77 (ddd, J = 11, 8, 4.5 Hz, 1 H), 0.36 (dd, J = 8, 3 Hz, 1 H), –0.03 (ddd, J = 4.5, 3, 1 Hz, 1 H); ^{13}C NMR (75 MHz) δ 74.6 (d), 52.9 (d), 41.9 (d), 40.8 (d), 38.5 (d), 37.5 (d), 36.9 (t), 33.2 (t), 33.1 (t), 32.7 (t), 31.3 (s), 29.9 (t), 23.9 (t), 23.3 (q), 22.2 (t), 21.1 (t), 13.5 (q); MS m/z (M^+) calcd 248.2140, obsd 248.2136.

Simmons–Smith Cyclopropanation of 15. The condensation of **15** (14.4 mg, 0.061 mmol) with diethylzinc (0.50 mL of 1.1 M in toluene, 0.55 mmol) and CH_2I_2 (160 mg, 0.60 mmol) in dry C_6H_6 at room temperature for 18 h (two times with intermediate workup) furnished 13.1 mg (86%) of **27** as a colorless oil: IR (cm^{-1}) 3620, 3500–3250; ^1H NMR (C_6D_6) δ 3.59 (ddd, J = 8, 3, 1 Hz, 1 H), 2.18 (br dq, J = 6.5, 7.5 Hz, 1 H), 2.12–0.82 (series of m, 13 H), 1.86 (ddd, J = 13.5, 12.5, 11 Hz, 1 H), 1.21 (dddd, J = 13.5, 3, 2, 1 Hz, 1 H), 1.10 (d, J = 7.5 Hz, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.80 (br ddd, J = 11, 7, 2 Hz, 1 H), 0.72 (ddd, J = 11, 7.5, 4 Hz, 1 H), 0.28 (dd, J = 7.5, 3.5 Hz, 1 H), –0.15 (ddd, J = 4, 3.5, 1 Hz, 1 H); ^{13}C NMR (75 MHz) δ 76.9 (d), 52.7 (d), 45.7 (d), 42.2 (d), 41.3 (d), 41.1 (d), 39.2 (t), 33.3 (t), 32.9 (t), 32.7 (t), 31.4 (s), 29.8 (t), 23.7 (d), 23.6 (q), 21.7 (t), 21.1 (t), 9.9 (q); MS m/z (M^+) calcd 248.2140, obsd 248.2151.

Ketone 26. A. Oxidation of 25. PCC oxidation of a 5-mg sample of **25** under the usual conditions afforded ketone **26** as a colorless oil in 80% yield: IR (cm^{-1}) 1705, 1690; ^1H NMR δ 2.81 (dd, J = 11, 11 Hz, 1 H), 2.74 (ddq, J = 6.5, 1, 7.5 Hz, 1 H), 2.40–2.28 (m, 1 H), 2.14 (br ddd, J = 12.5, 8, 10 Hz, 1 H), 2.05 (ddd, J = 11, 4, 1 Hz, 1 H), 2.05–1.95 (m, 3 H), 1.87 (ddd, J = 12, 6.5, 4 Hz, 1 H), 1.81–1.69 (m, 2 H), 1.69–1.58 (m, 2 H), 1.51 (br ddd, J = 12, 7, 4 Hz, 1 H), 1.31 (d, J = 7.5 Hz, 3 H), 1.12–0.95 (m, 2 H), 0.95 (d, J = 7 Hz, 3 H), 0.95–0.82 (m, 2 H), 0.44 (br dd, J = 7.5, 3.5 Hz, 1 H), –0.01 (ddd, J = 4.5, 3.5, 1 Hz, 1 H); ^{13}C NMR (75 MHz) δ 218.9 (s), 52.8 (d), 46.8 (d), 45.6 (d), 44.3 (t), 42.0 (d), 41.0 (d), 33.9 (t), 32.7 (t), 32.2 (2C, t+s), 27.8 (t), 23.6 (d), 23.2 (q), 22.0 (t), 21.2 (t), 13.9 (q); MS m/z (M^+) calcd 246.1984, obsd 246.1999. Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.53; H, 10.56.

B. Oxidation of 27. PCC oxidation of **27** (11.4 mg, 0.046 mmol) in identical fashion furnished 10.3 mg (91%) of **26**, spectroscopically identical with the material described in A.

Simmons–Smith Cyclopropanation of 21. In a manner similar to that described for the preparation of **27**, alcohol **21** (10.1 mg, 0.043 mmol) was twice subjected to reaction with diethylzinc (2.0 mL of 1.1 M in toluene, 2.2 mmol) and CH_2I_2 (640 mg, 2.4 mmol) without added cosolvent for 18 h at room temperature. Flash chromatographic purification (silica gel, elution with PE–E (3:2)) furnished 7.3 mg (69%) of **28** as a colorless oil: IR (cm^{-1}) 3625; ^1H NMR δ 3.52–3.44 (m, 1 H), 2.12–0.95 (series of m, 17 H), 1.00 (d, J = 7 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 0.65 (ddd, J = 11.5, 8.5, 5 Hz, 1 H), 0.38 (dd, J = 8.5, 3.5 Hz, 1 H), –0.05 (br dd, J = 5, 3.5 Hz, 1 H); ^{13}C NMR (62.5 MHz) δ 75.8 (d), 52.3 (d), 49.3 (d), 43.2 (t), 41.9 (d), 41.2 (d), 39.7 (d), 33.7 (t), 33.4 (t), 31.5 (t), 30.8 (s), 29.3 (t), 23.4 (q), 23.0 (d), 21.6 (t), 21.1 (t), 15.3 (q); MS m/z (M^+) calcd 248.2140, obsd 248.2179.

Ketone 29. A. Oxidation of 28. Alcohol **28** (5.7 mg, 0.023 mmol) was oxidized with pyridinium chlorochromate (20 mg, 0.093 mmol) in dry CH_2Cl_2 (1 mL) containing pyridine (1 drop) for 3 h at 20 °C. The usual workup afforded **29** (4.5 mg, 80%) as a colorless oil: IR (cm^{-1}) 1700; ^1H NMR δ 2.77 (br dq, J = 10.5, 6.5 Hz, 1 H), 2.65 (dd, J = 12.5, 10.5 Hz, 1 H), 2.19 (br ddd, J = 12.5, 11, 7 Hz, 1 H), 2.10–1.00 (series of m, 13 H), 1.06 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H), 0.88 (br dd, J = 11.5, 6 Hz, 1 H), 0.77 (ddd, J = 11.5, 8, 5 Hz, 1 H), 0.45 (dd, J = 8, 3.5 Hz, 1 H), 0.00 (ddd, J = 5, 3.5, 1 Hz, 1 H); ^{13}C NMR (75 MHz) δ 219.4 (s), 52.8 (d), 48.2 (d), 48.1 (t), 46.9 (d), 42.1 (d), 40.1 (d), 33.2 (t), 32.9 (t), 31.6 (t), 31.2 (s), 28.5 (t), 23.1 (q), 22.7 (d), 20.8 (t), 20.5 (t), 16.2 (q); MS m/z (M^+) calcd 246.1984, obsd 246.2009.

B. Epimerization of 26. The same ketone was obtained exclusively (TLC, ^1H NMR) when a sample of **26** was heated at reflux with a solution of potassium *tert*-butoxide in *tert*-butyl alcohol overnight in that manner described earlier for **16**.

Double-Bond Isomerization in 13 and 20. A C_6D_6 solution of **13** or **20** was stored at room temperature for several days, during which time isomerization to **30** took place quantitatively. This process was strongly accelerated if a trace of hydrogen chloride gas was introduced into the tube.

For 30: colorless oil; IR (cm^{-1}) 1680; ^1H NMR (C_6D_6) δ 5.63 (dddd, J = 2, 2, 2, 2 Hz, 1 H), 4.01 (d, J = 10 Hz, 1 H), 2.67 (dddddd, J = 15, 9, 6.5, 2, 2, 2 Hz, 1 H), 2.48–2.25 (m, 3 H), 2.19 (dddqq, J = 11, 8, 7, 1.5, 1 Hz, 1 H), 1.99 (dddd, J = 11.5, 7, 6.5, 1.5 Hz, 1 H), 1.94–1.64 (m, 5 H), 1.87 (dq, J = 1.5, 1 Hz, 3 H), 1.66 (dq, J = 1, 1 Hz, 3 H), 1.22 (dddd, J = 11.5, 11.5, 11, 6.5 Hz, 1 H), 1.10–0.95 (m, 1 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 144.6 (s), 143.6 (d), 128.3 (d), 105.4 (s), 76.5 (d), 46.6 (d), 42.1 (d), 37.3 (d), 34.1 (t), 33.3 (t), 32.6 (t), 31.3 (t), 23.7 (t), 21.5 (q), 16.6 (q), 16.4 (q); MS m/z (M^+) calcd 232.1827, obsd 232.1834.

Claisen Rearrangement of 30. A sample of **20** (24.0 mg, 0.103 mmol) was isomerized to **30** in benzene solution as described previously and subjected to rearrangement by means of $(i\text{-Bu})_3Al$ catalysis (0.35 mL of 1.0 M, 0.35 mmol) in CH_2Cl_2 (2 mL) in the customary fashion. Flash chromatographic purification (silica gel, elution with PE–E (3:2)) afforded 20.9 mg (86%) of **31** (colorless oil) as an inseparable 1:1 mixture of epimeric alcohols: IR (cm^{-1}) 3630, 3550–3400; ^1H NMR δ (diastereomer A) 5.08 (br s, 1 H), 3.88 (q, J = 6 Hz, 1 H), 2.30–0.95 (series of m, 14 H), 1.23 (d, J = 6 Hz, 3 H), 1.01 (d, J = 7 Hz, 3 H), 0.94 (s, 3 H); (diastereomer B) 5.04 (br s, 1 H), 3.91 (q, J = 6 Hz, 1 H), 2.30–0.95 (series of m, 14 H), 1.18 (d, J = 6 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz) δ (diastereomer A) 141.8 (s), 121.2 (d), 70.9 (d), 47.7 (d), 45.6 (d), 44.3 (d), 40.1 (d), 39.1 (s), 32.7 (t), 29.1 (t), 27.8 (t), 25.3 (t), 22.3 (q), 22.2 (q), 21.7 (t), 18.9 (q); (diastereomer B) 142.4 (s), 120.4 (d), 71.2 (d), 47.8 (d), 45.8 (d), 45.5 (d), 39.5 (d), 39.2 (s), 32.5 (t), 29.2 (t), 28.1 (t), 24.7 (t), 22.3 (q), 22.1 (q), 21.5 (t), 17.9 (q); MS m/z (M^+) calcd 234.1984, obsd 234.1966.

Ketone 32. Alcohols **31** (135 mg, 0.576 mmol) were oxidized with pyridinium chlorochromate (450 mg, 2.09 mmol) and pyridine (0.2 mL) in CH_2Cl_2 (10 mL) at room temperature for 1.5 h. The customary workup and purification afforded 112 mg (84%) of **32** as a stereochemically homogeneous, colorless oil: IR (cm^{-1}) 1700, 1690; ^1H NMR δ 5.66 (dddd, J = 3, 2.5, 2.5, 1.5 Hz, 1 H), 2.48–2.35 (m, 1 H), 2.35–2.18 (m, 3 H), 2.05 (s, 3 H), 2.05–1.85 (m, 3 H), 1.85–1.66 (m, 3 H), 1.58–1.45 (m, 1 H), 1.30–1.05 (m, 3 H), 1.25 (s, 3 H), 1.01 (d, J = 6 Hz, 3 H); ^{13}C NMR (20 MHz) δ 212.9 (s), 141.4 (s), 119.2 (d), 52.4 (s), 50.6 (d), 48.9 (d), 48.6 (d), 39.3 (d), 35.3 (t), 31.7 (q), 31.2 (t), 28.2 (t), 26.8 (t), 26.2 (q), 24.6 (t), 18.6 (q); MS m/z (M^+) calcd 232.1827, obsd 232.1830. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.72; H, 10.35.

Acid-Promoted Cyclization of 31. A 1:1 mixture of alcohols **31** (10 mg) in THF (4 mL) was treated with concentrated HCl (50 mg) and left at room temperature overnight. The reaction mixture was diluted with ether, washed with saturated $NaHCO_3$ solution, dried, and evaporated. Flash chromatography of the residue (silica gel, elution with PE–E (9:1)) furnished 7.8 mg (78%) of **23** as a colorless oil: ^1H NMR δ (diastereomer A) 3.67 (br q, J = 7 Hz, 1 H), 2.27–0.90 (series of m, 16 H), 1.22 (d, J = 7 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.89 (s, 3 H); (diastereomer B) 3.99 (q, J = 7 Hz, 1 H), 2.27–0.90 (series of m, 16 H), 1.05 (d, J = 7 Hz, 3 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz) δ 91.2 (s), 90.7 (s), 80.4 (d), 76.6 (d), 59.3 (d), 57.8 (d), 52.8 (d), 51.5 (d), 48.8 (s), 46.9 (s), 45.2 (d), 44.9 (d), 40.3 (2 C, d), 37.6 (t), 36.9 (t), 36.2 (t), 36.0 (t), 34.7 (t), 33.9 (t), 26.0 (t), 25.2 (t), 24.7 (2 C, d), 24.1 (t), 24.0 (t), 19.4 (q), 18.5 (2 C, q), 17.5 (q), 17.2 (q), 15.0 (q); MS m/z (M^+) calcd 234.1984, obsd 234.2013.

Epoxidation of 31. A solution of **31** (18.7 mg, 0.080 mmol) in dry benzene (3 mL) was treated with purified *m*-chloroperbenzoic acid (25 mg, 0.145 mmol) at room temperature overnight. The predescribed workup was applied to give a crude product that was purified by flash chromatography on silica gel (elution with PE–E (1:1)). There was isolated 15.8 mg (79%) of **33** as a colorless oil consisting of a 1:1 mixture of stereoisomers: IR (cm^{-1}) 3625, 3550–3350; ^1H NMR δ (diastereomer A) 3.95 (q, J = 7 Hz, 1 H), 3.80 (br s, 1 H), 2.24 (ddd, J = 10, 9.5, 6 Hz, 1 H), 2.16–0.96 (series of m, 13 H), 1.10 (d, J = 7 Hz, 3 H), 1.01 (d, J = 6 Hz, 3 H), 0.93 (s, 3 H); (diastereomer B) 3.83 (br s, 1 H), 3.72 (dq,

J = 1, 7 Hz, 1 H), 2.34 (dddd, J = 10, 10, 6.5, 1 Hz, 1 H), 2.16–0.96 (series of m, 13 H), 1.24 (d, J = 7 Hz, 3 H), 1.03 (d, J = 6 Hz, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz) δ 93.9 (s), 92.8 (s), 80.1 (d), 76.7 (d), 72.4 (d), 72.1 (d), 56.7 (d), 56.6 (d), 53.7 (d), 52.1 (d), 50.9 (d), 49.4 (s), 49.3 (d), 47.3 (s), 39.9 (d), 39.4 (d), 34.7 (t), 34.0 (t), 33.5 (t), 32.7 (t), 26.2 (t), 25.4 (t), 25.2 (t), 25.1 (t), 24.5 (t), 24.4 (t), 19.4 (q), 18.8 (2 C, q), 17.6 (q), 17.3 (q), 15.1 (q): MS m/z (M^+) calcd 250.1933, obsd 250.1918.

Ketone 34. Alcohols **33** (13.4 mg, 0.057 mmol) were subjected to oxidation with pyridinium chlorochromate (50 mg, 0.232 mmol) in dry CH_2Cl_2 (3 mL) and pyridine (1 drop) at room temperature for 3 h. The usual workup and purification (elution with PE–E (4:1)) afforded 8.4 mg (63%) of **34** as a colorless oil: IR (cm^{-1}) 1715; ^{1}H NMR δ (diastereomer A) 4.20 (br q, J = 7 Hz, 1 H), 2.54–2.32 (m, 2 H), 2.20–1.15 (series of m, 12 H), 1.20 (d, J = 7 Hz, 3 H), 1.09 (d, J = 6 Hz, 3 H), 1.02 (s, 3 H); (diastereomer B) 3.95 (dq, J = 1, 7 Hz, 1 H), 2.54–2.32 (m, 1 H), 2.20–1.15 (series of m, 13 H), 1.35 (d, J = 7 Hz, 3 H), 1.08 (d, J = 6 Hz, 3 H), 1.01 (s, 3 H); ^{13}C NMR (75 MHz) δ 208.7 (s), 208.3 (s), 94.8 (s), 93.7 (s), 81.6 (d), 78.1 (d), 61.6 (d), 59.4 (2 C, d), 59.1 (d), 53.9 (d), 52.8 (d), 50.5 (s), 48.9 (s), 41.4 (d), 40.9 (d), 36.3 (t), 35.7 (t), 29.8 (t), 29.4 (t), 26.7 (t), 25.9 (t), 25.5 (t), 25.2 (t), 25.0 (t), 24.3 (t), 19.5 (q), 19.4 (q), 19.1 (q), 17.1 (q), 17.0 (q), 15.3 (q); MS m/z (M^+) calcd 248.1776, obsd 248.1804.

Double-Bond Isomerization in 6. A solution of **6** in C_6D_6 was allowed to stand at room temperature for 7 days when clean isomerization to **35** was complete. Solvent evaporation provided for the quantitative isolation of **35**, a pale yellowish oil: ^{1}H NMR (C_6D_6) δ 6.00 (ddddd, J = 2, 2, 2, 2, 2 Hz, 1 H), 4.39–4.34 (m, 1 H), 2.54 (brdd, J = 7.5, 6.5 Hz, 1 H), 2.45–2.14 (m, 5 H), 1.95–1.75 (m, 3 H), 1.85 (dq, J = 1.5, 1 Hz, 3 H), 1.82 (ddd, J = 7.5, 7.5, 2 Hz, 1 H), 1.75–1.50 (m, 2 H), 1.54 (dq, J = 1, 1 Hz, 3 H), 1.21–1.11 (m, 1 H), 0.98 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 146.3 (s), 143.9 (s), 124.0 (d), 104.9 (s), 75.5 (d), 51.0 (d), 44.1 (d), 33.3 (2 C, t), 32.6 (t), 31.2 (d), 28.7 (t), 23.7 (t), 22.8 (q), 16.8 (q), 15.3 (q); MS m/z (M^+) calcd 232.1827, obsd 232.1851.

Claisen Rearrangement of 35. Vinyl allyl ether **35** (48 mg, 0.207 mmol) in dry CH_2Cl_2 (5 mL) was subjected to the usual rearrangement conditions (–78 to 20 °C, overnight) in the presence of (i-Bu)$_3$Al (0.70 mL of 1.0 M in toluene, 0.70 mmol). Workup and purification as before furnished 34.5 mg (71%) of **36** and 3.2 mg (7%) of **37**.

For 36: colorless oil; IR (cm^{-1}) 3550; ^{1}H NMR δ 5.51 (br s, 1 H), 3.87 (dq, J = 2, 6.5 Hz, 1 H), 2.92 (br d, J = 2 Hz, OH), 2.41–2.14 (m, 5 H), 1.85–1.45 (m, 8 H), 1.34 (dddd, J = 12, 11.5, 10.5, 7 Hz, 1 H), 1.10–0.98 (m, 1 H), 1.10 (d, J = 6.5 Hz, 3 H), 1.06 (d, J = 6.5 Hz, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz) δ 142.6 (s), 123.4 (d), 73.9 (d), 46.7 (d), 46.6 (d), 41.4 (d), 40.9 (d), 40.1 (s), 32.5 (t), 30.2 (t), 28.5 (t), 26.1 (t), 24.8 (q), 23.8 (t), 21.5 (q), 17.6 (q); MS m/z (M^+) calcd 234.1984, obsd 234.1983.

For 37: colorless oil; ^{1}H NMR δ 5.31 (dddd, J = 2.5, 2.5, 2.5, 2.5 Hz, 1 H), 3.83 (q, J = 6.5 Hz, 1 H), 2.38–0.95 (series of m, 14 H), 1.15 (d, J = 6.5 Hz, 3 H), 1.00 (d, J = 6.5 Hz, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz) δ 139.8 (s), 121.5 (d), 70.4 (d), 46.8 (d), 45.8 (d), 45.0 (d), 41.0 (s), 40.5 (d), 32.1 (t), 30.7 (t), 28.8 (t), 27.6 (t), 24.3 (t), 21.7 (q), 19.5 (q), 18.8 (q); MS m/z (M^+) calcd 234.1984, obsd 234.1980.

Ketone 38. A. Oxidation of 36. A 14-mg (0.060 mmol) sample of **36** was oxidized in the usual manner with pyridinium chlorochromate (50 mg, 0.232 mmol) in dry CH_2Cl_2 (3 mL) containing pyridine (1 drop) at room temperature for 3 h. The usual workup and purification by filtration through silica gel (elution with PE–E (9:1)) afforded pure **38** (12.6 mg, 91%) as a colorless oil: IR (cm^{-1}) 1705; ^{1}H NMR δ 5.38–5.34 (m, 1 H), 2.36–2.23 (m, 3 H), 2.23–2.03 (m, 1 H), 2.08 (s, 3 H), 1.88–1.00 (series of m, 10 H), 1.20 (s, 3 H), 1.04 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 212.3 (s), 140.9 (s), 119.8 (d), 53.0 (s), 46.7 (d), 45.5 (d), 44.0 (d), 41.9 (d), 33.0 (t), 31.2 (t), 27.7 (t), 27.3 (q), 27.2 (t), 24.2 (t), 22.5 (q), 20.9 (q).

Ketone **38** was obtained by analogous oxidation of **37** as seen by appropriate TLC and high-field ^{1}H NMR comparisons.

Epoxidation of 36. A solution of **36** (24 mg, 0.102 mmol) in dry C_6H_6 (3 mL) was treated with purified m-CPBA (30 mg, 0.174 mmol) at 20 °C overnight. The usual workup and purification (elution with PE–E (3:2)) gave 18.4 mg (72%) of **39** as a colorless crystalline solid (from PE): mp 150–151 °C; IR (cm^{-1}) 3635, 3500–3350 ^{1}H NMR δ 3.90 (q, J = 6.5 Hz, 1 H), 3.82 (br d, J = 6 Hz, 1 H), 2.46 (br dd, J = 8.5, 8.5 Hz, 1 H), 2.30–2.15 (m, 1 H), 2.10–1.08 (series of m, 12 H), 1.15 (d, J = 6.5 Hz, 3 H), 1.02 (d, J = 7 Hz, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz) δ 94.2 (s), 81.4 (d), 71.8 (d), 48.0 (d), 45.4 (2C, d + s), 45.2 (d), 34.5 (t), 34.0 (t), 33.5 (t), 28.4 (t), 24.4 (t), 24.1 (t), 23.2 (q), 17.3 (q), 13.4 (q); MS m/z (M^+) calcd 250.1933, obsd 250.1975.

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Supplementary Material Available: Crystallographic details, crystallographic experimental, computer-generated drawings, tables of atomic positional and thermal parameters, bond distances and angles, and torsional angles (in selected compounds) for **11**, **24b**, and **39**; decoupling and NOE studies for **7a**, **14**, **15**, **18**, **21**, and **25**, and ^{1}H or ^{13}C spectra of those compounds for which elemental analyses are not available (56 pages). Ordering information is given on any current masthead page.

α-Amino Aldehyde Equivalents as Substrates for Rabbit Muscle Aldolase: Synthesis of 1,4-Dideoxy-D-arabinitol and 2(*R*),5(*R*)-Bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine

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This work examined the application of rabbit muscle aldolase (RAMA) to stereospecific carbon–carbon bond formation in the preparation of carbohydrates containing amino groups. Several α-amino aldehyde equivalents were evaluated as substrates for RAMA and for their synthetic utility in transformations following the aldol reaction. This methodology is illustrated by the syntheses of the pyrrolidine alkaloids 1,4-dideoxy-D-arabinitol and 2(*R*),5(*R*)-bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine. The kinetic resolution of racemic aldehydes by RAMA and mild methods for transforming the amino equivalents into the desired amines are discussed briefly.

Introduction

Polyhydroxylated amines have attracted attention for their activity as glycosidase inhibitors, with potential pharmaceutical applications as antibiotic and antitumor agents.[1] Pyrrolidines [e.g., swainsonine, 1,4-dideoxy-1,4-imino-D-arabinitol (1), and 2(*R*),5(*R*)-bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine (2)] inhibit several

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