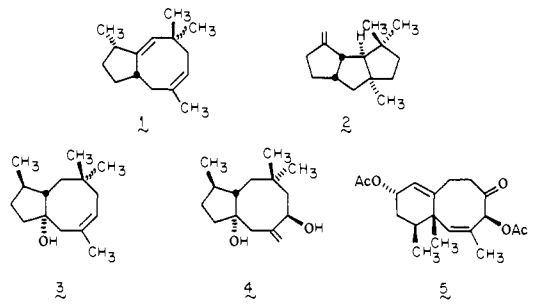
General Approach to Annulated 4-Cyclooctenones by Aliphatic Claisen Rearrangement. Stereospecific Total Synthesis of (±)-Precapnelladiene

William A. Kinney, Michael J. Coghlan, and Leo A. Paquette*

Contribution from Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received June 14, 1985*

Abstract: An 11-step total synthesis of (+)-precapnelladiene (**1**) has been achieved in 20% overall yield from 8α-methylbicyclo[3.3.0]octan-2-one. Central to the overall strategy is the Claisen rearrangement of 6-alkenyl-2-methylenetetrahydropyrans. The end result of this general procedure is a new approach to annulated 4-cyclooctenones. Some migration of the external methylene double bond to the endocyclic position occurs during thermolysis when the original α-carbonyl site is unsubstituted. However, the presence of a β-methyl group completely inhibits this competitive side reaction without inducing fragmentation of the pyran ring. By making recourse to lactone **54a**, the Claisen process was shown most likely to proceed via a chair transition state. The alternative reaction mode involving a boat transition state would have been forced to produce a *trans*-4-cyclooctenone initially. Final installation of the second double bond in the eight-membered ring of **1** was accomplished by carbenoid decomposition of tosylhydrazone **58**. Although a substantial amount of isomeric diene **59** is also produced in this step, its exposure to rhodium trichloride in refluxing ethanol resulted in controlled isomerization to precapnelladiene.

The unusual sesquiterpene precapnelladiene (**1**) was isolated in 1979 by Djerassi and co-workers from the nonpolar extracts of the soft coral *Capnella imbricata*.[1] The complete features of this novel bicyclic marine natural product were established through chemical and spectroscopic methods, in conjunction with the CONGER computer program to guarantee consideration of all possible structural alternatives. Djerassi proposed that the $C_{15}H_{24}$ hydrocarbon be called precapnelladiene because of its possible role as a biosynthetic precursor[2] to various tricyclo[6.3.0.$0^{2,6}$]-undecanes such as $\Delta^{9(12)}$-capnellene (**2**)[3,4] with which it cooccurs.



From the synthetic standpoint, the more notable features of **1** are its fused 5/8 ring system, the 1,5-cyclooctadiene arrangement of its double bonds, and the cis relationship of its two stereogenic centers. Related interesting structural characteristics have been recently uncovered in dactylol (**3**),[5] poitediol (**4**),[6,7] and neolemnanyl acetate (**5**),[8] as well as in sester- and diterpenoids of the ophiobolin,[9-11] ceroplastol,[12] and fusicoccin type.[13] Prior to the present investigation, only syntheses of epiprecapnelladiene[14] and poitediol[7] had been completed. The present study demonstrates a new application of the aliphatic Claisen rearrangement[15] as a prelude to an expedient preparation of racemic **1**.[16]

Results and Discussion

The Claisen Rearrangement Strategy. In planning our synthesis of precapnelladiene, the retrograde pathway exemplified by **1** → **6** → **7** was viewed with particular attraction. Although we have recently reported an efficient and general anionic oxy-Cope ap-

(1) Ayanoglu, E.; Gebreyesus, T.; Beechan, C. M.; Djerassi, C. *Tetrahedron* **1979**, *35*, 1035.

(2) This original hypothesis has since received substantial indirect support. Consult, for example: Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, 3851. And ref 14.

(3) Isolation: Ayanoglu, E.; Begreyesus, T.; Beechan, C. M.; Djerassi, C.; Kaisin, M. *Tetrahedron Lett.* **1978**, 1671.

(4) Synthesis: (a) Stevens, K. E.; Paquette, L. A. *Tetrahedron Lett.* **1981**, 4393. Paquette, L. A.; Stevens, K. E. *Can. J. Chem.* **1984**, *62*, 2415. (b) Little, R. D.; Carroll, G. L.; Petersen, J. L. *J. Am. Chem. Soc.* **1983**, *105*, 928. (c) Oppolzer, W.; Battig, K. *Tetrahedron Lett.* **1982**, 4669. (d) Huguet, J.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 2413. (e) Mehta, G.; Reddy, D. S.; Murty, A. N. *J. Chem. Soc., Chem. Commun.* **1983**, 824. (f) Piers, E.; Karumaratne, V. *Can. J. Chem.* **1984**, *62*, 629. (g) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500.

(5) (a) Isolation: Schmitz, F. J.; Hollenbeak, K. H.; Vanderah, D. J. *Tetrahedron* **1978**, *34*, 2719. (b) Synthesis: Gadwood, R. C. *J. Chem. Soc., Chem. Commun.* **1985**, 123. Hayasaka, K.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1985**, 873. Paquette, L. A.; Ham, W. H.; Dime, D. S. *Ibid.* **1985**, 4983.

(6) Isolation: Fenical, W.; Schulte, G. R.; Finer, J.; Clardy, J. *J. Org. Chem.* **1978**, *43*, 3628.

(7) Synthesis: Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 3869.

(8) Izac, R. R.; Fenical, W.; Tagle, B.; Clardy, J. *Tetrahedron* **1981**, *37*, 2569.

(9) Review: Cordell, G. A. *Phytochemistry* **1974**, *13*, 2343.

(10) Isolation: (a) Ophiobolins B and C: Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1966**, 2211. Canonica, L.; Fiecchi, A.; Kienle, M. G.; Scala, A. *Ibid.* **1966**, 1329. Ishibashi, K. *J. Antibiot.* **1962**, *A15*, 88. (b) Ophiobolin D: Itai, A.; Nozoe, S.; Tsuda, K.; Okuda, S.; Iitaka, Y.; Nakayama, Y. *Tetrahedron Lett.* **1967**, 4111. Nozoe, S. et al. *Ibid.* **1967**, 4113. (c) Ophiobolin F: Nozoe, S.; Morisaki, M.; Fukushima, K.; Okuda, S. *Ibid.* **1968**, 4457. Nozoe, S.; Morisaki, M. *J. Chem. Soc. D* **1969**, 1319.

(11) Synthetic efforts: (a) Das, T. K.; Gupta, A. D.; Ghosal, P. K.; Dutta, P. C. *Indian J. Chem., Sect. B* **1976**, *14B*, 238. (b) Das, T. K.; Dutta, P. C. *Synth. Commun.* **1976**, *6*, 253. (c) Boeckman, R. K., Jr., Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1976**, *41*, 6062. (d) Dauben, W. G.; Hart, D. J. *Ibid.* **1977**, *42*, 922. (e) Baker, W. R.; Senter, P. D.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1011. Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org.* Chem. **1982**, *47*, 3597. (f) Paquette, L. A.; Andrews, D. R.; Springer, J. P. *Ibid.* **1983**, *48*, 1148. Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *Ibid.* **1985**, *50*, 201. (g) Grayson, D. H.; Wilson, D. H. R. *J. Chem. Soc., Chem. Commun.* **1984**, 1695.

(12) (a) Ceroplastol I and ceroplasteric acid: Iitake, Y.; Watanabe, I.; Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1968**, *90*, 1092. (b) Ceroplastol II: Rios, T.; Quijano, L. *Tetrahedron Lett.* **1969**, 1317. (c) Albolic acid: Rios, T.; Gomez, F. *Ibid.* **1969**, 2929.

(13) (a) Fusicoccin A: Hough, E.; Hursthouse, M. B.; Neidle, S.; Rodgers, D. *J. Chem. Soc., Chem. Commun.* **1968**, 1197. Ballio, A.; Brufani, M.; Casinori, C. G.; Cerrini, S.; Fedeli, W.; Pellicciari, R.; Santurbano, B.; Vaiaga, A. *Experientia* **1968**, *24*, 631. Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Thomas, R. *J. Chem. Soc. C* **1971**, 1265. (b) Fusicoccin H: Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Sharma, R. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 159. (c) Fusicoccin J: Barrow, K. D.; Barton, D. H. R.; Chain, R.; Bageend-Kasujja, D.; Mellows, G. *Ibid.* **1975**, 877. (d) Cotylenol: Sassa, T. *Agric. Biol. Chem.* **1972**, *36*, 2037; **1975**, *39*, 1729.

(14) Birch, A. M.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1980**, 1195; *J. Chem. Soc., Perkin Trans. 1* **1983**, 1913.

(15) (a) Rhoads, S. J.; Raulins, *N. R. Org. React. (N.Y.)* **1975**, *22*, 1. (b) Ziegler, R. E. *Acc. Chem. Res.* **1977**, *10*, 227.

(16) (a) Preliminary communication: Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868. (b) An alternative total synthesis of racemic precapnelladiene has since been reported: Mehta, G.; Narayana Murty, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1058.

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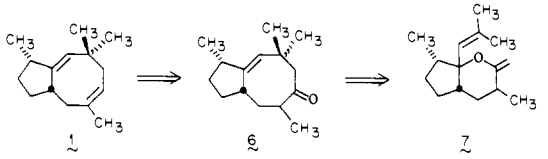
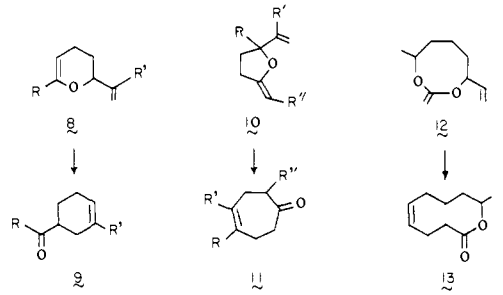
proach to 4-cyclooctenones,[11f] a more suitable permutation of [3,3]-sigmatropic bond reorganization manifold appeared, for the present purposes, to reside in the thermal rearrangement of **7**. The



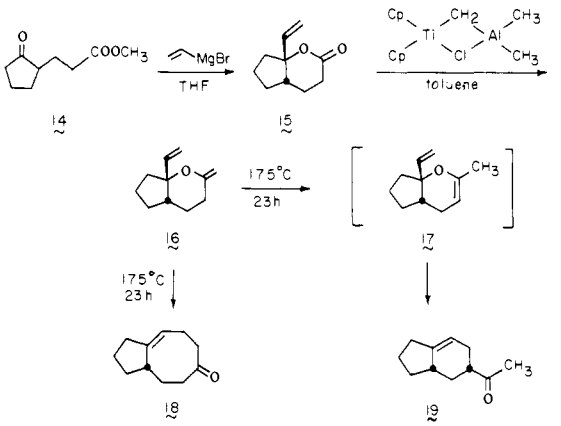
Claisen process holds considerable versatility for application to organic synthesis, much of which has been surfacing during the last 2 decades. Several of the permutations most relevant to the present work include the 3,4-dihydro-2*H*-pyranylethylene to 3-acylcyclohexene isomerization (**8** → **9**) studied by Büchi and Powell,[17] the conversion of 2-vinyl-5-methylenetetrahydrofurans to 4-cycloheptenones (**10** → **11**) investigated by Rhoads and Watson,[18] and Petrzilka's macrolide lactone synthesis (**12** → **13**).[19]



The scope for applicability of the Claisen rearrangement in synthesis has in principle[20] been substantially widened by the recent discovery of Tebbe and co-workers that [bis(cyclopentadienyl)-titanium](μ-chloro)(μ-methylidene)dimethylaluminum is a particularly effective reagent for converting esters and lactones into vinyl ethers.[21] This intrinsically high "Wittig-like" reactivity level was expected to guarantee access to **7** from a lactone precursor.

For the approach described above to be viable, it was first necessary to establish that 2-methylenetetrahydropyrans such as **7** possess the intrinsic stability needed to undergo the desired Claisen rearrangement. Several thermodynamic and spectral studies have been disclosed showing vinyl ethers of this type to be highly unstable relative to their endocyclic isomers, quite unlike **10**.[22,23] Consequently, several model systems were initially elaborated and subjected to thermal activation.

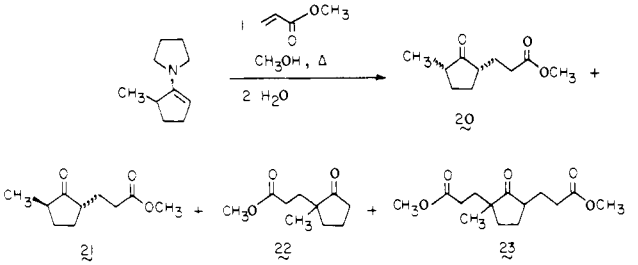
Nucleophilic addition of vinylmagnesium bromide to the readily available keto ester **14**[24] occurs trans to the α substituent to deliver lactone **15** in isomerically pure form. Olefination of **15** was efficiently accomplished with the Tebbe reagent to yield **16**. Direct transfer of **16** in toluene solution to potassium hydroxide-coated soft glass tubes was followed by heating at 175 °C for 23 h. After



chromatographic separation, the major product (42% overall from **15**) was identified as **18** on the basis of its ^{1}H NMR spectrum and the downfield position of its carbonyl ^{13}C chemical shift (214.39 ppm). The less prevalent isomeric ketone proved to be **19** (28%), the obvious end product of competitive 1,3-hydrogen migration within **16** to give **17** and Claisen rearrangement of the latter.

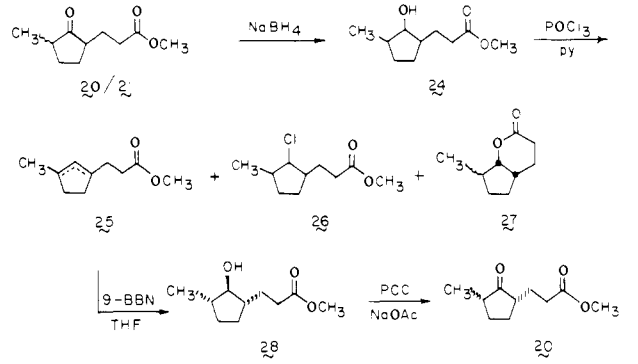
Despite the demonstrated favorable percentage of **18** in the aforementioned thermolysate, it remained to clarify the impact that added methyl substitution might exert on the product distribution. Effort was therefore next expended on introducing cis stereochemistry and testing a system containing the desired *gem*-dimethyl functionality.

Incorporation of Relative Stereochemistry and the Quaternary Carbon. Although keto ester **20** was easily obtained by condensation of the pyrrolidine enamine of 2-methylcyclopentanone with methyl acrylate, isomeric compounds **22** (15%) and **23** (11%) had to be removed chromatographically, and **20** was only difficulty separable from the trans isomer **21** (combined yield 47%). The



methyl doublets for **20** and **21** were clearly distinguished at 300 MHz; individual stereochemical assignments were based on the synthesis that follows. Since equilibration of the **20**/**21** mixture with acid or base did not alter their relative proportion (1:2), thermodynamic equilibration had evidently already taken place.

A four-step sequence was devised to convert the **20**/**21** mixture in stereocontrolled fashion to authentic **20**. While reduction with sodium borohydride proceeded uneventfully, the subsequent dehydration of **24** with phosphorus oxychloride and pyridine was less satisfactory in that byproducts **26** (19%) and **27** (22%) were formed in addition to **25** (46%). Other dehydrating agents were



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(18) (a) Rhoads, S. J.; Brandenburg, C. F. *J. Am. Chem. Soc.* **1971**, *93*, 5805. (b) Rhoads, S. J.; Watson, J. M. *Ibid.* **1971**, *93*, 5813. (c) See also: Demole, E.; Enggist, P. *J. Chem. Soc., Chem. Commun.* **1969**, 264.
(19) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 3075.
(20) Some translation into practical experiment has already been reported. Consult, for example: Stevenson, J. W. S.; Bryson, T. A. *Tetrahedron Lett.* **1982**, 3143.
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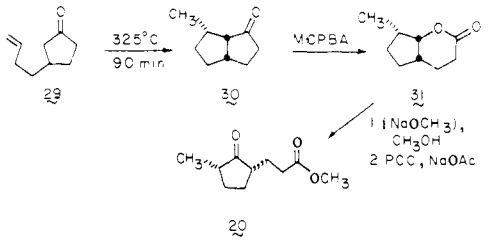
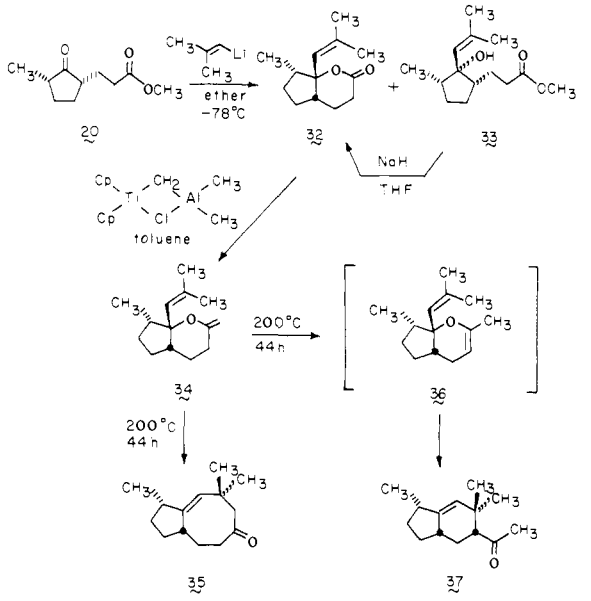
(22) Taskinen, E. *Acta Chem. Scand., Ser. B* **1974**, *B28*, 1234. (b) Taskinen, R. *Tetrahedron* **1978**, *34*, 433.
(23) (a) Ireland, R. E.; Habich, D. *Tetrahedron Lett.* **1980**, 1389. (b) Ireland, R. E.; Habich, D. *Chem. Ber.* **1981**, *115*, 1418.
(24) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

briefly examined, but the just cited conditions gave the best results. Hydroboration of **25** with 9-BBN[25] and oxidation with pyridinium chlorochromate (PCC)[26] afforded **20** in greater than 95% purity (300-MHz ^{1}H NMR analysis). Although this scheme was suitably cis stereoselective, it hardly qualified as efficient, and consequently an alternative synthetic entry was sought.

Conia and co-workers had previously shown that **29** undergoes thermal ene cyclization with exclusive formation of **30**.[27] Subsequent Baeyer–Villiger oxidation of **30** proceeded with full regioselectivity to form **31** whose ring opening with catalytic quantities of methoxide ion in methanol and oxidation with buffered PCC occurred without loss of stereochemistry to deliver epimerically pure **20** in highly acceptable overall yield.



With the availability of **20** in quantity, its treatment with 2-methyl-1-propenyllithium was carried out at −78 °C. Under these conditions, a mixture of **32** and **33** resulted. At this point, we capitalized on the fact that cyclization of **33** to **32** occurs rapidly in the presence of sodium hydride. As expected, methylenation of **32** with the Tebbe reagent led efficiently to **34**. Since untoward steric factors not present in **16** were anticipated for **34**,[28] its Claisen rearrangement was conducted at 200 °C for 44 h.



Smooth bond reorganization was observed to give **35** (38%) and **37** (32%) following chromatographic separation. Once again, the carbonyl carbon of **35** (213.82 ppm) was shifted to lower field relative to that in **37** (209.64 ppm). Distinction was also possible on the basis of the respective infrared carbonyl absorptions (1700 vs. 1710 cm^{-1}) and the presence of an acetyl methyl singlet in the ^{1}H NMR spectrum of **37**.

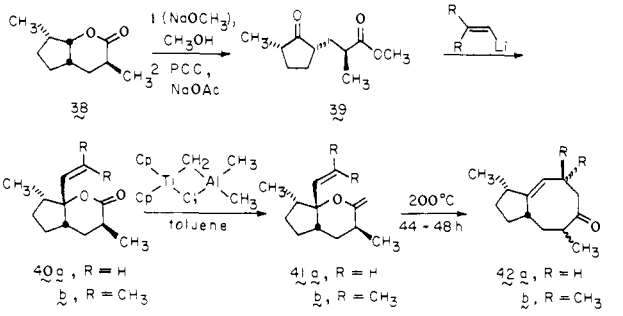
Model system **34** is therefore capable of delivering a product, i.e., **35**, having a carbocyclic framework closely comparable to that found in precapnelladiene (**1**). The approach undertaken so far is responsible to the question of stereochemistry and nicely installs the quaternary carbon. However, loss of product by competitive formation of **36** (and ultimately **37**) remained an unattractive feature that demanded further attention.

Arresting the Competitive Double Bond Migration. Because of the lability of 2-methylenetetrahydropyrans such as **16** and **34** to acid, our handling of these substances was intentionally limited to rapid filtration through activity III basic alumina prior to thermolysis. Accordingly, the possibility exists that the competing [1,3] hydrogen migration is catalyzed by residual Ti- or Al-containing byproducts from the Tebbe reaction, although a purely thermal process cannot, of course, be ruled out at this time. Notwithstanding the mechanistic origins of the isomerization, Dreiding models revealed that two chair conformations of roughly comparable energy are available to the pyran ring. In the first of these, the β-allylic proton is properly aligned for removal. In the other, the α-allylic proton enjoys suitable stereoalignment, although steric crowding in its immediate vicinity because of 1,3-diaxial relationship to the cyclopentane ring is unmistakable. Consequently, a solution to the demonstrated complication suggested itself.

Since methylation of the enolate anion of **30** occurs only from the convex face of the molecule to give **38**, it becomes an easy task to replace the β-hydrogen atom potentially capable of involvement in the undesired side reaction. [1,3] Migration of the α proton might well be kinetically retarded and perhaps not compete at all, since its location within the structural cavity should render it relatively inaccessible. Within the context of the projected precapnelladiene synthesis, the preparation of **38** achieves introduction of the last methyl group of the sesquiterpene.

From a different vantage point, primary allyl ethers are known to be rapidly isomerized to the corresponding *trans*-propenyl ethers with very high selectivity and in excellent yield by a variety of transition-metal catalysts.[29,30] Secondary ethers do not react, this reactivity difference lending itself to the selective transformation of allylic groups. Comparable steric factors should prove advantageous following arrival at **41a** and **41b** and presumably allow for exclusive operation of the desired Claisen rearrangement.

In order to ascertain the level of control that could be anticipated, lactone **38** was transformed as before to keto ester **39** without evidence for disruption of its three stereogenic centers (^{1}H and ^{13}C NMR analysis). Treatment of **39** with vinyllithium



at −78 °C followed by brief warming to room temperature afforded **40a**. Replacing the carbonyl oxygen by CH_2 and thermal activation was smoothly effected, and cyclooctenone **42a** was isolated in 91% overall yield. This high efficiency is in keeping with the location of the interactive groups on the open convex face of **41a**. Although stereochemical integrity has been preserved at the two key centers in **42a**, epimerization occurs at the third presumably because of enolate formation under the strongly basic thermolysis conditions. However, this event is of no consequence in arriving at **1** because a ring double bond must ultimately be positioned at this site.

(25) Brener, L.; Brown, H. C. *J. Org.* Chem. **1977**, *42*, 2702.
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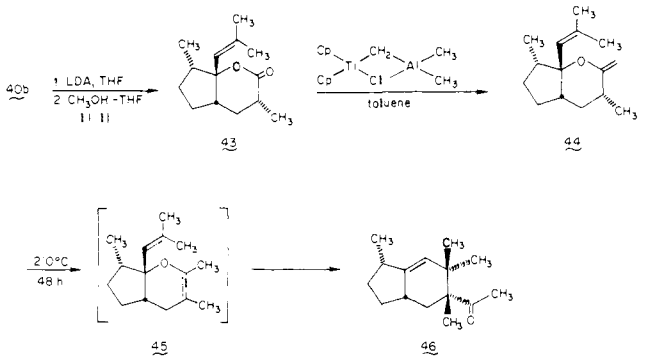
(28) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983.
(29) Baudry, D.; Ephritikhine, M.; Felkin, H. *J. Chem. Soc., Chem. Commun.* **1978**, 694.
(30) (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224; *Tetrahedron Lett.* **1975**, 3775. (b) Salomon, R. G.; Reuter, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 4372. (c) Hirai, K.; Suzuki, H.; Kashiwagi, H.; Moro-Oka, Y.; Ikawa, T. *Chem. Lett.* **1982**, 23. (d) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1977**, *42*, 3360. (e) Carless, H. A. J.; Haywood, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 980.

When the same two-step sequence was performed with **40b**, the pivotal 4-cyclooctenone **42b** was likewise formed exclusively and in high yield (87% overall).

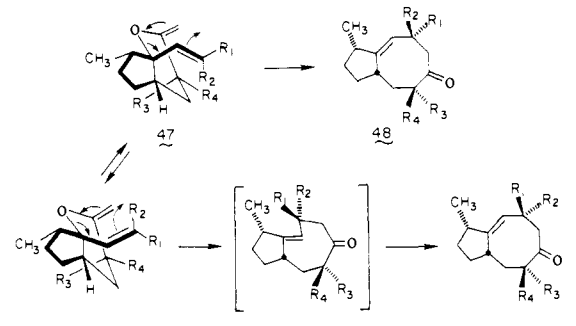
Although the predescribed results suited the overall synthetic plan perfectly, our assumptions concerning the unreactivity of the α-endo hydrogen toward [1,3] migration had not been completely evaluated. To this end, **40b** was deprotonated and its enolate solution quenched with a 1:1 mixture of methanol and tetrahydrofuran at 0 °C. Under these conditions, a 2.5:1 mixture of



43 and **40b** was produced. These epimers were readily separated by chromatography on silica gel. Thus, **43** was made available for conversion to **44**. When this allyl vinyl ether was thermally activated in the predescribed manner, no cyclooctenone product was observed. Instead, **46** was alone formed, indicating of course that Claisen rearrangement had proceeded only after **44** had been isomerized to **45**.

Given this fact, we are left with the two mechanistic options. The first is that **41** exhibits no tendency for thermal *exo–endo*-olefin isomerization, in line with our original assessment of steric inhibition to α-proton abstraction. Alternatively, the less likely possibility that **45** is capable of facile equilibration with both **44** and **41b** cannot strictly be ruled out. Should this be true, however, one is forced to accept the conclusion that the rate of Claisen rearrangement via *endo*-olefin **45** is much faster than that associated with **44** but much slower than that for **41b**. This is improbable since the transition state for bond reorganization within **45** is more sterically congested than those associated with either exocyclic olefin. The emergence of vicinal quaternary centers is **46** concisely addresses the steric issue.

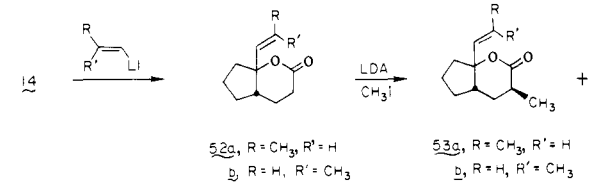
The Question of Transition-State Geometry. Studies on the mechanism of the aliphatic Claisen rearrangement have shown a chairlike transition state to be favored over a boatlike transition state.[15,31] This phenomenon has been the subject of theoretical

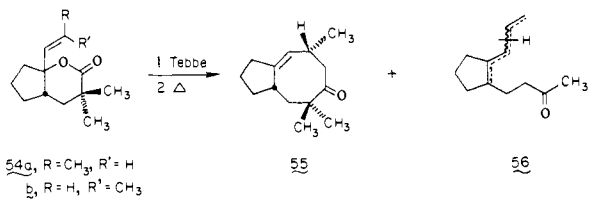


scrutiny.[32] However, many Claisen rearrangements forced to proceed via boatlike transition states do so readily.[15,33] In the present study, the relevant options are given by **47** and **49**. Since all the examples described above have $R_1 = R_2$, no distinction between the two mechanistic options is possible nor was it relevant to the synthetic strategem. However, the potential relevancy of this question in other contexts has led us to examine the rearrangement in more detail.

It is to be specifically noted that adoption of one or the other transition state in substrates wherein R_1 and R_2 are not alike leads ultimately to stereochemically distinctive products, viz., **48** and **51**. The latter pathway is further distinguished by a requirement for kinetic formation of a *trans*-cyclooctenone (**50**), subsequent isomerization of which delivers **51**. Although the latter possibility was viewed less likely, we sought to clarify this question as well. In this phase of our study, recourse has been made to α,α-dimethyl substitution in order to obviate complications arising from epimerization α to the carbonyl group in the 4-cyclooctenone products.

After lithiation of a 1:1 mixture of *cis*- and *trans*-1-bromopropene with *tert*-butyllithium and condensation with keto ester **14**, there was produced the isomeric lactones **52a** and **52b**. Their chromatographic separation could be accomplished readily. With





the pure substances in hand, individual methylation with LDA and CH_3I at −40 °C[34] led to **54a** and **54b** accompanied by larger amounts of their monomethyl counterparts. The latter could be reprocessed, in 70–80% yield, thereby enhancing the overall efficiency of the gem-dimethylation step. Although **54a** was found to be indefinitely stable, the *cis*-propenyl isomer **54b** proved exceptionally sensitive to light, was rapidly equilibrated with **54a** when handled without precaution under ordinary laboratory conditions, and could not be obtained free of its geometric isomer in sufficient quantity for independent study. Since no equilibration was noted during gas chromatography, thermal lability appeared not to be a contributing factor.

Under the predescribed Tebbe conditions, conversion of **54a** to the *exo*-methylene derivative was rapid. Subsequent thermal activation led to **55** (40%) and products of ring fission (**56**, 20%). When a 1:1 mixture of **54a** and **54b** was subjected to the same two-step treatment, *an identical product distribution was seen.* In analyzing the latter observation, one must remain mindful of the capability of transition metals (in trace quantities) to promote *cis*/*trans*-olefin equilibration.

The critical stereochemical assignment to **55** rests upon detailed NMR examination of the ketone. Identification of H-2 (see **57**) as the multiplet centered at δ 2.95 was achieved by irradiation of the secondary methyl doublet (J = 6.5 Hz) at δ 1.08. Considerable simplification of the absorption pattern resulted. The complementary double resonance experiment involving H-2 resulted in collapse of the methyl doublet. Additionally, an NOE difference experiment[35] revealed the existence of nuclear Overhauser enhancements between $CH_{3(c)}$ and H-2 as well as between

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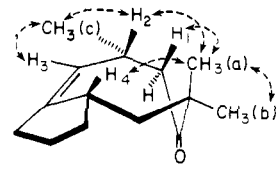

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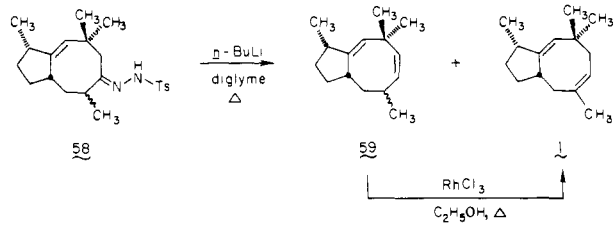
$CH_{3(c)}$ and H-3. When $CH_{3(a)}$ was similarly examined, strong through-space interactions with H-1, H-2, H-4, and $CH_{3(b)}$ were detected. In contrast, $CH_{3(b)}$ was characterized by the lone NOE interaction with $CH_{3(a)}$. Significantly $CH_{3(c)}$ gave no evidence of an NOE effect with either germinal methyl group. On this basis, we assign to **55** the conformation shown in **57**, upon which the observed NOE effects are overlaid.

With elucidation of the stereochemistry of **55** comes strong, though not fully conclusive, evidence that its precursor allyl vinyl ether enters into Claisen rearrangement via chair transition-state **47**. Presumably, this conclusion can be generalized to include the related molecules studied herein. Evidently, the heightened level of steric congestion that develops in **47** when R_2, R_3, and R_4 are methyl groups is sufficient to permit competitive fragmentation. The possibility that a catalyzed[20] "charge-accelerated" mechanism[36] operates as the predominant reaction mode warrants consideration.

Precapnelladiene Synthesis. The final stages of the synthesis demand the regiocontrolled conversion of the carbonyl group in ketone **42b** to a double bond. This overall transformation was anticipated to be difficult if mediated by a derived alcohol. The recognized high propensity of 4-cyclooctenyl cations for transannular cyclization[37] was expected to dominate all attempts at dehydration. When preliminary experiments on the sodium borohydride reduction product of **42b** showed our suspicions to be justified, tosylhydrazone **58** was prepared. Application of the



58 59 1

Shapiro reaction to **58** was expected to proceed exclusively or nearly so along that reaction channel, leading to the less-substituted olefin **59**.[38] However, a mixture of at least five hydrocarbons was obtained, of which **1** was a minor component. Conversely, when the decomposition of **58** was conducted under carbenoid conditions,[39] the mixture of **59** and **1** that resulted proved chromatographically separable on silica gel impregnated with 2% silver nitrate. Subsequent rhodium trichloride-promoted isomerization of **59**, which has precedent in the work of Rinehart and Lasky,[40] allowed for substantially enhanced throughput of precapnelladiene, whose infrared, ^1H NMR, and mass spectra proved identical with those of the natural product as furnished by Prof. Djerassi.[41] Relevantly, epiprecapnelladiene possesses spectral properties distinctively different from those of **1**.

Thus, the total synthesis of precapnelladiene (**1**) has been achieved in 11 steps from 8α-methylbicyclo[3.3.0]octan-2-one (**30**) with an overall yield of 20%. Central to the overall strategy is the Claisen rearrangement of 6-alkenyl-2-methylenetetrahydropyrans, a process particularly germane to the efficient elaboration of 4-cyclooctenones.

Experimental Section

***cis*-7a-Ethenyl-3,4,4a,5,6,7-hexahydrocyclopenta[*b*]pyran-2(3*H*)-one (15).** Vinyl bromide was added dropwise to magnesium turnings (490 mg, 20 mg-atom) in tetrahydrofuran (5 mL) until all the magnesium was consumed (initiation with 1,2-dibromoethane). After dilution with additional solvent (13 mL), the mixture was cooled to −78 °C, and **14** (1.70 g, 10 mmol) in tetrahydrofuran (5 mL) was added dropwise over 10 min and stirred at −78 °C for 3 h. The solution was allowed to warm for 20 min, quenched with saturated ammonium chloride solution, poured into water (50 mL), and acidified with acetic acid. The product was extracted into ether (3 × 50 mL), and the combined organic layers were washed with saturated sodium bicarbonate solution, dried, and evaporated. The residue was chromatographed on silica gel (MPLC, elution with 10% ethyl acetate in petroleum ether), affording 415 mg (25%) of **15**: IR (neat, cm^{-1}) 3000–2840, 1740, 1255, 1170, 1100, 1000, 925; ^1H NMR ($CDCl_3$) δ 6.0–5.0 (m, 3 H), 2.5–1.4 (series of m, 11 H); ^{13}C NMR ($CDCl_3$) δ 172.29, 140.68, 113.79, 93.07, 40.58, 40.36, 29.59, 26.48, 21.50; MS, *m/z* calcd (M^+) 166.0994, obs 166.0978.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.12; H, 8.55.

[Bis(cyclopentadienyl)titanium](μ-chloro)(μ-methylidene)dimethylaluminum. A solution of titanocene dichloride (6.00 g, 24.1 mmol) and 2 M trimethylaluminum (26 mL, 52 mmol) in toluene was prepared under argon.[21] After 48 h, all volatiles were removed under high vacuum, and the residue was dissolved in dry deoxygenated toluene (30 mL). The molarity of the reagent was determined by combining 1 mL of the stock solution with methyl benzoate (0.10 mL, 0.80 mmol) and pyridine (2 drops) in an NMR tube under argon. After 12 h, the ratio of methyl singlets in the ^1H NMR spectrum of this mixture indicated 74% conversion to product. Therefore, the concentration of reagent was approximately 0.59 M.

***cis*-7a-Ethenyl-3,4,4a,5,6,7-hexahydro-2-methylenecyclopenta[*b*]pyran (16).** A solution of **15** (101 mg, 0.61 mmol), pyridine (1 drop), tetrahydrofuran (0.5 mL), and toluene (1.5 mL) was prepared under argon. The mixture was cooled to 0 °C and 0.55 M Tebbe reagent (1.3 mL, 0.71 mmol) in toluene was added dropwise. After being stirred for 90 min at 25 °C, the solution was again cooled to 0 °C and quenched with 15% sodium hydroxide solution (0.30 mL). After gas evolution had ceased, ether was added and the mixture was dried, filtered, and evaporated. The residue was passed through a short column (6 × 3 cm) of basic alumina (activity III, elution with petroleum ether) to provide 92 mg (92%) of **16**; IR (neat, cm^{-1}) 3000–2820, 1650, 1450, 1270, 1110, 1015, 915; ^1H NMR (CCl_4) δ 6.1–4.9 (m, 3 H), 4.13 (br s, 1 H), 3.85 (br s, 1 H), 2.3–1.2 (series of m, 11 H); MS, *m/z* calcd (M^+) 164.1201, obsd 164.1204.

Thermal Isomerization of 16. A solution of **16** (57 mg) in toluene (1 mL) was sealed under vacuum in a potassium hydroxide-coated soft glass tube (7-mm o.d.) and heated at 175 °C for 23 h. The resulting pale-yellow solution was evaporated, and the residue was purified on silica gel (MPLC, elution with 10% ethyl acetate in petroleum ether). There was isolated 16 mg (28%) of **19**, followed by 24 mg (42%) of **18**.

For **18**: IR (neat, cm^{-1}) 3000–2800, 1710, 1440, 1335; ^1H NMR ($CDCl_3$) δ 5.44 (br t, 1 H), 2.8–2.1 (series of m, 9 H), 1.9–1.3 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 214.39, 149.74, 119.66, 47.66, 41.21, 40.12, 34.50, 33.48, 32.01, 24.34, 23.83; MS, *m/z* (M^+) calcd 164.1202, obsd 164.1192.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.04; H, 9.82.

For **19**: IR (neat, cm^{-1}) 3000–2800, 1710, 1435, 1355, 1160; ^1H NMR ($CDCl_3$) δ 5.35 (m, 1 H), 2.6–2.1 (m, 6 H), 2.14 (s, 3 H), 2.0–1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 211.83, 144.91, 115.26, 48.30, 33.07, 31.03, 29.69, 27.91, 27.53, 23.31; MS, *m/z* calcd (M^+) 164.1202, obsd 164.1191.

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(37) See, for example: (a) Kell, D. R.; McQuillin, F. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2096. (b) Souma, Y.; Sano, H.; Iyoda, J. *J. Org. Chem.* **1973**, *38*, 2016. (c) Norell, J. R. *Ibid.* **1972**, *37*, 1971. (d) Tabushi, I.; Fujita, K.; Oda, R. *Tetrahedron Lett.* **1967**, 3755, 3815. (e) Cantrell, T. S.; Strasser, B. S. *J. Org. Chem.* **1971**, *36*, 670. (f) Henry, P. M.; Davies, M.; Ferguson, G.; Philips, S.; Restivo, R. *J. Chem. Soc., Chem. Commun.* **1974**, 112. (g) Yamada, Y.; Shibata, A.; Iguchi, K.; Sanjoh, H. *Tetrahedron Lett.* **1977**, 2407. (h) Whitesell, J. K.; Matthews, R. S.; Solomon, P. A. *Ibid.* **1976**, 1549. (i) Haufe, G.; Kleinpeter, E.; Muhlstadt, M.; Graffe, J. *Monatsch. Chem.* **1978**, *109*, 575. (j) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555.
(38) (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405. (b) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734. (c) Kaufman, G.; Cook, F.; Shechter, H.; Bayless, J.; Friedman, L. *Ibid.* **1967**, *89*, 5736. (d) Stemke, J. E.; Bond, F. T. *Tetrahedron Lett.* **1975**, 1815. (e) Stemke, J. E.; Chamberlin, A. R.; Bond, F. T. *Ibid.* **1976**, 2947. (f) Traas, P. C.; Boelens, H.; Takken, H. J. *Ibid.* **1976**, 2887. (g) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017.
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(41) The olefinic out-of-plane deformation of **1** appears at 849 cm^{-1} and not at 899 cm^{-1} as originally reported (typographical error).

Methyl 3-Methyl-2-oxocyclopentanepropanoate (20/21). The pyrrolidine enamine of 2-methylcyclopentanone (1.0 g, 6.6 mmol) was dissolved in 9 mL of dry methanol, treated with 0.60 mL (6.7 mmol) of methyl acrylate, and heated at reflux for 3 h. Following addition of 1 mL of water, heating was continued for an additional hour. The methanol was removed in vacuo, and the residue was taken up into 75 mL of ether. The organic layer was washed with 5% hydrochloric acid (2 × 25 mL) and brine (25 mL) prior to drying. Concentration in vacuo afforded a mixture of four products which were separated into three fractions and purified by MPLC (silica gel, elution with 12% ethyl acetate in petroleum ether) to yield 570 mg (47%) of **20/21**, 180 mg (15%) of **22**, and 200 mg (11%) of dicondensation product **23**.

For **20/21**: IR (neat, cm^{-1}) 3000–2800, 1740, 1440, 1370, 1250, 1170; ^1H NMR ($CDCl_3$) δ 3.65 (s, 3 H), 2.4–2.3 (m, 2 H), 2.2–2.0 (m, 6 H), 1.7–1.6 (m, 2 H), 1.08 (d, J = 7 Hz, 2 H), 1.04 (d, J = 7 Hz, 1 H).

For **22**: IR (neat, cm^{-1}) 3000–2800, 1740, 1450, 1370, 1200, 1070; ^1H NMR ($CDCl_3$) δ 3.67 (s, 3 H), 2.5–1.5 (series of m, 10 H), 1.01 (s, 3 H).

For **23**: IR (neat, cm^{-1}) 3000–2800, 1740, 1440, 1370, 1200; ^1H NMR ($CDCl_3$) δ 3.68 (s, 6 H), 2.5–1.5 (series of m, 13 H), 1.01 (s, 1.5 H), 0.94 (s, 1.5 H); MS, m/z calcd (M^+) 270.1467, obsd 270.1453.

Methyl 2-Hydroxy-3-methylcyclopentanepropanoate (24). Reduction of **20/21** (27.4 g, 149 mmol) was achieved by treatment with 4.40 g (117 mmol) of sodium borohydride at 0 °C in 350 mL of anhydrous methanol. The mixture was stirred for 30-min intervals at 0 and 25 °C, quenched with 5% hydrochloric acid (100 mL), concentrated in vacuo, and diluted with water (100 mL). The aqueous layer was extracted with ether (3 × 130 mL), and the combined ethereal layers were washed with 75 mL of saturated sodium bicarbonate solution and 75 mL of brine, dried, and evaporated to yield 23.50 g (85%) of **24**: IR (neat, cm^{-1}) 3450, 3000–2800, 1740, 1445, 1250, 1170; ^1H NMR ($CDCl_3$) δ 3.7 (br s, 1 H), 3.66 (s, 3 H), 2.5–1.2 (series of m, 10 H), 1.2–0.9 (m, 3 H); MS, m/z calcd (M^+) 186.1256, obsd 186.1289.

Dehydration of 24. Dehydration of 364 mg (1.96 mmol) of **24** with 0.35 mL (3.83 mmol) of phosphorus oxychloride in 10 mL of dry pyridine was performed at 60 °C over 17 h. The reaction mixture was quenched with 50 mL of water and extracted with ether (2 × 50 mL). The combined organic layers were washed with 2 × 25 mL of 10% hydrochloric acid and with 25 mL of saturated sodium bicarbonate solution prior to drying. Chromatography of the residue on silica gel (MPLC, elution with 5% ethyl acetate in petroleum ether) afforded 153 mg (46%) of **25**, 78 mg (19%) of **26**, and upon increasing the polarity of eluent (27% ethyl acetate in petroleum ether) 66 mg (22%) of **27**.

For **25**: IR (neat, cm^{-1}) 3000–2800, 1745, 1440, 1250, 1170; ^1H NMR ($CDCl_3$) δ 5.25 (br s, 1 H), 3.67 (s, 3 H), 2.8–1.2 (series of m, >9 H), 0.96 (d, J = 7 Hz, <3 H); MS, m/z calcd (M^+) 168.1150, obsd 168.1188.

For **26**: ^1H NMR ($CDCl_3$) δ 4.3–3.9 (m, 1 H), 3.78 (s, 3 H), 2.6–1.3 (series of m, 10 H), 1.2–1.0 (series of d, J = 7 Hz, 3 H).

For **27**: IR (neat, cm^{-1}) 3000–2800, 1745, 1460, 1250, 1180, 1065, 1020; ^1H NMR ($CDCl_3$) δ 4.52–4.27 (m, 1 H), 2.7–1.2 (series of m, 10 H), 1.09 (d, J = 7 Hz, 3 H).

Methyl (1α,2β,3α)-2-Hydroxy-3-methylcyclopentanepropanoate (28). Hydroboration of **25** (1.18 g, 7.03 mmol) was accomplished with 860 mg (7.04 mmol) of 9-BBN in 10 mL of dry tetrahydrofuran for 24 h at reflux under argon. This solution was cooled to 0 °C and treated simultaneously with 3 mL of 3 M sodium hydroxide and 3 mL of 30% hydrogen peroxide. Following warming to room temperature, ether (75 mL) was added and the aqueous layer was removed. The organic phase was washed with 20 mL of 1% sodium carbonate solution, 20 mL of saturated sodium sulfite solution, and 20 mL of brine prior to drying. MPLC purification of the residue (silica gel, elution with 30% ethyl acetate in petroleum ether) afforded 391 mg of recovered **25** and 609 mg (47%, 70% based on recovered **25**) of **28**: IR (neat, cm^{-1}) 3450, 3000–2800, 1750, 1450, 1175, 1060; ^1H NMR ($CDCl_3$) δ 3.65 (s, 3 H), 3.2–3.0 (m, 1 H), 2.6–2.2 (m, 3 H), 2.0–1.1 (series of m, 8 H), 1.02 (d, J = 6 Hz, 3 H); ^{13}C NMR (C_6D_6) δ 173.89, 85.24, 51.04, 46.61, 42.35, 32.74, 29.67, 29.56, 27.40, 18.07; MS, m/z calcd (M^+) 186.1256, obsd 186.1281.

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.52; H, 9.78.

Methyl *cis*-3-Methyl-2-oxocyclopentanepropanoate (20). A suspension of pyridinium chlorochromate (104 mg, 0.48 mmol), sodium acetate (8 mg, 0.10 mmol), and Celite (300 mg) in 3 mL of dry dichloromethane was prepared under nitrogen. Alcohol **28** (79 mg, 0.42 mmol) in 3 mL of dichloromethane was introduced and the reaction mixture was stirred overnight (18 h). The slurry was filtered through Celite (subsequently rinsed with 50 mL of ether), and the filtrate was washed with 5% hydrochloric acid (20 mL) and 5% sodium bicarbonate solution (20 mL), dried, and evaporated. The residue was purified on silica gel (MPLC, elution with 20% ethyl acetate in petroleum ether) to give 73 mg (94%) of 96% isomerically pure **20** (determined by 300 MHz ^1H NMR integration); IR (neat, cm^{-1}) 3000–2800, 1740, 1440, 1165; ^1H NMR ($CDCl_3$) δ 3.65 (s, 3 H), 2.41 (t, J = 8 Hz, 2 H), 2.2–1.9 (m, 6 H), 1.6–1.5 (m, 2 H), 1.05 (d, J = 7 Hz, 3 H); MS, m/z calcd (M^+) 184.1100, obsd 184.1110.

(4aα,7α,7aα)-3,4,4a,5,6,7-Hexahydro-7-methylcyclopenta[*b*]pyran-2(*H*)-one (31). Baeyer–Villiger oxidation of **30** (1.52 g, 11.0 mmol) in 30 mL of dichloromethane was realized with 80% *m*-chloroperoxybenzoic acid (3.1 g, 14 mmol) during 48 h. The solution was diluted with 30 mL of solvent, washed with 30 mL of saturated sodium bicarbonate solution and brine, and dried. The residue was chromatographed on silica gel (MPLC, elution with 22% ethyl acetate in petroleum ether) to provide 1.29 g (76%) of **31**; IR (neat, cm^{-1}) 3000–2840, 1745, 1465, 1260, 1190, 1150–1000; ^1H NMR ($CDCl_3$) δ 4.45 (t, J = 5 Hz, 1 H), 2.46–1.41 (series of m, 10 H), 1.09 (d, J = 7 Hz, 3 H); MS, m/z (M^+) calcd 154.0994, obsd 154.1023.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.01; H, 9.20.

Conversion of 31 to 20. Catalytic sodium methoxide (14 mg) was added to a solution of **31** (115 mg, 0.74 mmol) in dry methanol (11 mL). After overnight standing, the methanol was removed in vacuo and the residue was dissolved in ether, washed with brine, dried, and concentrated. The resulting hydroxy ester in dichloromethane (5 mL) was immediately combined with a slurry of pyridinium chlorochromate (243 mg, 1.13 mmol), Celite (300 mg), and sodium acetate (18 mg, 0.22 mmol) in dichloromethane (5 mL) under argon. After 5 h, the usual workup and MPLC on silica gel (elution with 20% ethyl acetate in petroleum ether) afforded 86 mg (63%, 74% based on recovered **31**) of **20** and 18 mg of **31**. The 300-MHz ^1H NMR spectrum of **20** was identical with that prepared by the previous route.

(4aα,7α,7aα)-3,4,4a,5,6,7-Hexahydro-7-methyl-7a-(2-methyl-1-propenyl)cyclopenta[*b*]pyran-2(3*H*)-one (32). A solution of 2-methylpropen-1-yllithium in ether (20 mL) was prepared by dissolving 0.84 mL (8.0 mmol) of 1-bromo-2-methylpropene in ether and injecting 4.2 mL (8.0 mmol) of 1.9 M *tert*-butyllithium in pentane at −78 °C under argon. After being stirred at 0 °C for 30 min, the reagent was cooled to −78 °C, and a solution of **20** (509 mg, 2.76 mmol) in 4 mL of cold (−78 °C) ether was introduced via cannula. After 20 min, acetic acid (0.48 mL, 8.4 mmol) was added, and the reaction mixture was warmed to 25 °C, poured into saturated sodium bicarbonate solution (25 mL), and extracted with ether (3 × 25 mL) prior to drying. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) yielded 194 mg (29%) of **33**, 143 mg (25%) of **32**, and 158 mg (31%) of recovered **20** as a mixture of cis and trans isomers.

Conversion from **33** to **32** was accomplished by adding **33** (190 mg, 0.79 mmol) dropwise in anhydrous tetrahydrofuran (6 mL) to a cold (−78 °C) slurry of sodium hydride (60 mg of 50%, 1.25 mmol) in tetrahydrofuran (6 mL). The cooling bath was removed and the reaction mixture allowed to warm to room temperature over 1 h. Saturated ammonium chloride solution was added and the solution was poured into brine (25 mL). Extracting with ether (3 × 30 mL), drying, and purificating the residue by MPLC (silica gel, elution with 10% ethyl acetate in petroleum ether) afforded 119 mg (72%) of **32**.

For **33**: IR (neat, cm^{-1}) 3550, 3000–2800, 1740, 1440, 1370, 1270–1150; ^1H NMR ($CDCl_3$) δ 4.96 (m, 1 H), 3.65 (s, 3 H), 2.4–2.2 (m, 2 H), 1.9–1.3 (series of m, 8 H), 1.86 (d, J = 1 Hz, 3 H), 1.71 (d, J = 1 Hz, 3 H), 0.91 (d, J = 6 Hz, 3 H); ^{13}C NMR (C_6D_6 δ 174.03, 134.34, 129.31, 83.77, 50.97 (2 C), 45.77, 32.98, 29.92, 28.17, 27.90, 24.83, 18.98, 12.97; MS, m/z calcd (M^+) 240.1726, obsd 240.1701.

For **32**: IR (neat, cm^{-1}) 3000–2820, 1740, 1460, 1260, 1180, 1045, 1000; ^1H NMR ($CDCl_3$) δ 5.01 (m, 1 H), 2.39 (t, J = 7 Hz, 2 H), 2.2–1.4 (series of m, 8 H), 1.74 (d, J = 1 Hz, 3 H), 1.69 (d, J = 1 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.78, 135.98, 125.81, 94.05, 46.27, 42.60, 30.57, 27.79 (2 C), 26.47, 21.83, 19.04, 12.15; MS, m/z calcd (M^+) 208.1464, obsd 208.1436.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.86; H, 9.65.

Claisen Rearrangement of 34. Olefination of **32** (80 mg, 0.38 mmol) was achieved with pyridine (1 drop), tetrahydrofuran (0.5 mL), toluene (1 mL), and 0.56 M Tebbe reagent (0.68 mL, 0.38 mmol) during 20 min at −40 °C and 15 min at 25 °C. The reaction mixture was quenched at −20 °C, diluted with petroleum ether, dried, and evaporated. The residual oil was filtered through basic alumina (activity III, elution with petroleum ether), concentrated in vacuo, transferred with 0.75 mL of toluene to a potassium hydroxide-coated soft glass tube, sealed, and heated (200 °C, 44 h). The resulting pale-yellow solution was purified on silica gel (MPLC, elution with 3% ethyl acetate in petroleum ether), affording 25 mg (32%) of **37** and 30 mg (38%) of **35**.

For **35**: IR (neat, cm^{-1}) 3000–2800, 1700, 1450, 1365, 1300, 1210; ^1H NMR ($CDCl_3$) δ 5.28 (br s, 1 H), 3.12 (m, 1 H), 2.90 (d, J = 15 Hz, 1 H), 2.64 (td, J = 13 and 6 Hz, 1 H), 2.5–2.2 (m, 2 H), 2.31 (d, J = 15 Hz, 1 H), 1.9–1.1 (series of m, 6 H), 1.09 (d, J = 7 Hz, 3 H), 1.08 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.82, 145.56, 129.93, 56.02, 41.08, 40.65, 38.63, 35.90, 33.20, 31.71, 31.35, 30.87, 29.85, 20.89; MS, m/z calcd (M^+) 206.1657, obsd 206.1625.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.47; H, 10.90.

For **37**: IR (neat, cm^{-1}) 3000–2800, 1710, 1455, 1360, 1195; ^1H NMR ($CDCl_3$) δ 4.94 (m, 1 H), 2.6–2.2 (m, 3 H), 2.18 (s, 3 H), 1.9–1.2 (series of m, 6 H), 1.17 (s, 3 H), 0.99 (d, J = 7 Hz, 3 H), 0.88 (s, 3 H); ^{13}C NMR (C_6D_6) δ 209.64, 147.29, 127.30, 58.44, 41.44, 35.76, 35.25, 32.95, 31.03, 30.46, 30.20 (2 C), 25.47, 19.15; MS, m/z calcd (M^+) 206.1671, obsd 206.1625.

(3β,4aα,7α,7aα)-3,4,4a,5,6,7-Hexahydro-3,7-dimethylcyclopenta[*b*]pyran-2(3*H*)-one (38). To a cold (0 °C) solution of diisopropylamine (0.87 mL, 6.2 mmol) in tetrahydrofuran (14 mL) under argon was added 3.9 mL (6.0 mmol) of 1.55 M *n*-butyllithium in hexane. The reagent was cooled to −78 °C and lactone **31** (920 mg, 5.96 mmol) in tetrahydrofuran (6 mL) was added dropwise over 10 min. After an additional 20 min, the enolate was quenched with methyl iodide (0.39 mL, 6.3 mmol), and stirring was continued for 30 min. After the cooling bath was removed for 10 min, saturated ammonium chloride solution was added and the reaction mixture was poured into brine and extracted with ether. The organic layer was dried and evaporated. Chromatography of the resulting oil on silica gel (elution with 12% ethyl acetate in petroleum ether) yielded 870 mg (87%) of **38**: IR (neat, cm^{-1}) 3000–2840, 1730, 1460, 1385, 1260, 1185, 1130, 1075, 995; ^1H NMR ($CDCl_3$) δ 4.58 (t, J = 5 Hz, 1 H), 2.60–2.43 (m, 2 H), 2.08–1.33 (series of m, 7 H), 1.25 (d, J = 7 Hz, 3 H), 1.08 (d, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.98, 87.33, 41.27, 35.91, 31.56 (2C), 31.31, 28.56, 16.55, 13.36; MS, m/z calcd (M^+) 168.1150, obsd 168.1197.

Cleavage Oxidation of 38. A solution of 487 mg (2.89 mmol) of **38** and 24 mg of sodium methoxide in 15 mL of dry methanol was stirred for 5 h, treated with 0.5 mL of saturated ammonium chloride solution, and freed of methanol in vacuo. The residue was dissolved in ether, dried, concentrated, and added in 5 mL of dry dichloromethane to 950 mg (4.41 mmol) of pyridinium chlorochromate, 1.3 g of Celite, 70 mg (0.85 mmol) of sodium acetate, and 10 mL of dichloromethane. Workup and chromatography on silica gel (MPLC, elution with 8% ethyl acetate in petroleum ether) after 3 h afforded 406 mg (71%, 89% based on recovered **38**) of **39** and 100 mg of **38**: IR (neat, cm^{-1}) 3000–2840, 1740, 1460, 1380, 1180; ^1H NMR (C_6D_6) δ 3.34 (s, 3 H), 2.58 (m, 1 H), 1.96–1.03 (m, 8 H), 1.00 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H); ^{13}C NMR (C_6D_6) ppm 219.73, 176.23, 51.02, 45.98, 42.21, 38.06, 34.74, 28.80, 26.94, 17.30, 15.25; MS, m/z calcd (M^+) 198.1256, obsd 198.1230.

(3β,4aα,7α,7aα)-7a-Ethenyl-3,4,4a,5,6,7-hexahydro-3,7-dimethylcyclopenta[*b*]pyran-2(3*H*)-one (40a). A solution of vinyllithium in ether was prepared by adding excess vinyl bromide (0.40 mL, 5.7 mmol) via a cold syringe to cold (−78 °C) ether (10 mL) under argon and then by adding 2.0 M *tert*-butyllithium (0.80 mL, 1.6 mmol) in pentane. After 30 min, a cold (−78 °C) solution of **39** (141 mg, 0.71 mmol) in ether (5 mL) was injected via cannula. The reaction mixture was maintained at −78 °C for 20 min and allowed to warm to 25 °C over 20 min before being quenched with saturated ammonium chloride solution. The usual workup and purification on silica gel (MPLC, elution with 4% ethyl acetate in petroleum ether) afforded 86 mg (62%) of **40a**: IR (neat, cm^{-1}) 3000–2840, 1735, 1460, 1385, 1340, 1235, 1195, 1135, 1075, 985, 930; ^1H NMR ($CDCl_3$) δ 5.71–5.62 (m, 1 H), 5.30–5.22 (m, 2 H), 2.58–2.54 (m, 1 H), 2.26 (br s, 1 H), 1.96–1.43 (series of m, 7 H), 1.24 (d, J = 6 Hz, 3 H), 0.96 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.75, 139.76, 116.25, 94.60, 45.28, 41.18, 31.34, 30.36, 28.94, 26.20, 17.13, 11.66; MS, m/z calcd (M^+) 194.1307, obsd 194.1294.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.32; H, 9.47.

(1α,3aα)-1,2,3,3a,4,5,7,8-Octahydro-1,5-dimethyl-6*H*-cyclopentacycloocten-6-one (42a). Tebbe reagent (1.10 mL of 0.56 M, 0.62 mmol) was added dropwise to a cold (−40 °C) solution of **40a** (112 mg, 0.58 mmol), pyridine (1 drop), toluene (1 mL), and tetrahydrofuran (0.5 mL). After 20 min, the reaction mixture was warmed to room temperature for 10 min, recooled to −20 °C, and quenched. Workup as usual and filtration through basic alumina delivered a colorless oil, which was transferred with 0.55 mL of toluene to a base-coated soft glass tube. The carefully annealed tube was heated in a tube furnace (200 °C, 48 h), and the solution was concentrated and chromatographed on silica gel (MPLC, 3% ethyl acetate in petroleum ether). There was isolated 27 mg (24%) of one epimer of **42a** and 75 mg (67%) of the second.

For the less polar epimer: IR (neat, cm^{-1}) 3000–2800, 1710, 1450, 1375, 1210, 1155, 1095; ^1H NMR ($CDCl_3$) δ 5.60 (br t, J = 7 Hz, 1 H), 2.8–2.1 (series of m, 7 H), 1.9–1.1 (series of m, 6 H), 1.10 (d, J = 7 Hz, 3 H), 1.03 (d, J = 7 Hz, 3 H); MS, m/z calcd (M^+) 192.1515, obsd 192.1499.

For the more polar epimer: IR (neat, cm^{-1}) 3000–2800, 1710, 1455, 1380, 1195, 910, 840; ^1H NMR ($CDCl_3$) δ 5.40 (br t, J = 8 Hz, 1 H), 3.0–2.1 (series of m, 7 H), 1.8–1.2 (series of m, 6 H), 0.99 (d, J = 7 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H); ^{13}C NMR (C_6D_6) δ 213.41, 153.87, 119.89, 46.87, 42.66, 41.95, 41.83, 39.91, 33.59, 33.01, 23.62, 21.06, 19.40; MS, m/z calcd (M^+) 192.1515, obsd 192.1495.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.11; H, 10.54.

(3β,4aα,7α,7aα)-3,4,4a,5,6,7-Hexahydro-3,7-dimethyl-7a-(2-methyl-1-propenyl)cyclopenta[*b*]pyran-2(3*H*)-one (40b). A solution of 2-methylpropen-1-yllithium (1.85 mmol) in ether (25 mL) was prepared as before and cooled to −78 °C under argon. Keto ester **39** (336 mg, 1.69 mmol) in cold (−78 °C) ether (8 mL) was injected via cannula and reacted for 30 min before being warmed to 25 °C over 10 min. The quenched reaction mixture was worked up as usual and purified on silica gel (MPLC, elution with 5% ethyl acetate in petroleum ether), affording 220 mg (58%) of **40b**: IR (neat, cm^{-1}) 3000–2800, 1720, 1450, 1375, 1330, 1225, 1180, 1115, 1060, 975; ^1H NMR ($CDCl_3$) 4.99 (br s, 1 H), 2.8–1.4 (series of m, 9 H), 1.80 (d, J = 1 Hz, 3 H), 1.75 (d, J = 1 Hz, 3 H), 1.25 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.48, 135.98, 125.50, 94.98, 45.99, 42.64, 30.75, 30.12, 29.20, 27.84, 25.61, 18.78, 17.19, 11.98; MS, m/z calcd (M^+) 222.1620, obsd 222.1580.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.84; H, 10.05.

(1α,3aα)-1,2,3,3a,4,5,7,8-Octahydro-1,5,8,8-tetramethyl-6*H*-cyclopentacycloocten-6-one (42b). Lactone **40b** (112 mg, 0.40 mmol) was reacted with Tebbe reagent (0.98 mL of 0.59 M, 0.58 mmol) in the predescribed manner. The colorless oil, isolated upon purification, was transferred with toluene (0.75 mL) to a base-coated soft glass tube. Thermolysis (200 °C, 44 h) and purification on silica gel (MPLC, elution with 1.5% ethyl acetate in petroleum ether) cleanly afforded 22 mg (20%) of epimer A and 74 mg (67%) of epimer B of **42b**.

For epimer A: IR (neat, cm^{-1}) 3000–2800, 1710, 1450, 1370, 1320; ^1H NMR ($CDCl_3$) δ 5.10 (br s, 1 H), 3.09 (d, J = 13 Hz, 1 H), 3.09 (m, 1 H), 2.72 (m, 1 H), 2.34 (m, 1 H), 2.12 (d, J = 13 Hz, 1 H), 1.8–1.9 (series of m, 6 H), 1.24 (s, 3 H), 1.06 (s, 3 H), 1.02 (d, J = 7 Hz, 3 H), 0.92 (d, J = 6 Hz, 3 H); MS, m/z (M^+) calcd 220.1827, obsd 220.1830.

For epimer B: IR (neat, cm^{-1}) 3000–2800, 1700, 1450, 1370; ^1H NMR ($CDCl_3$) δ 5.26 (br s, 1 H), 3.1–2.3 (series of m, 3 H), 2.75 (d, J = 15 Hz, 1 H), 2.38 (d, J = 15 Hz, 1 H), 1.8–1.1 (series of m, 6 H), 1.08 (d, J = 7 Hz, 3 H), 1.04 (s, 3 H), 1.02 (s, 3 H), 0.97 (d, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.46, 146.38, 129.54, 56.16, 42.54, 40.65, 39.39, 38.44, 35.65, 32.81, 31.70, 31.15, 31.06, 20.91, 15.81; MS, m/z (M^+) calcd 220.1827, obsd 220.1784.

(3α,4aα,7α,7aα)-3,4,4a,5,6,7-Hexahydro-3,7-dimethyl-7a-(2-methyl-1-propenyl)-cyclopenta[*b*]pyran-2(3*H*)-one (43). A solution of lithium diisopropylamide was prepared at 0 °C by addition of 2.30 mL of 1.55 M *n*-butyllithium (in hexane) to a magnetically stirred solution of diisopropylamine (0.50 mL, 3.58 mmol) in anhydrous tetrahydrofuran (40 mL). After 15 min, this solution was cooled to −78 °C, and **40b** (615 mg, 2.77 mmol) in the same solvent (10 mL) was added dropwise. After 30 min, the enolate was transferred via cannula into 40 mL of cold (0 °C) methanol–tetrahydrofuran (1:1). The reaction mixture was concentrated, diluted with ether (50 mL), and washed with water (25 mL) and brine (25 mL). Drying and solvent removal afforded 617 mg of crude product, which was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether). There was isolated 400 mg of **40b** and 150 mg (70% based on recovered startlng material) of **43**: IR (neat, cm^{-1}) 2840, 2780, 1740, 1450, 1380, 1260, 1165, 1150; ^1H NMR ($CDCl_3$) δ 5.12 (m, 1 H), 2.55 (dq, J = 6.8, 13.0 Hz, 1 H), 2.49–2.10 (m, 2 H), 1.99–1.85 (m, 2 H), 1.75 (d, J = 2.1 Hz, 3 H), 1.72 (d, J = 1.4 Hz, 3 H), 1.65–1.11 (series of m, 4 H), 1.13 (d, J = 6.8 Hz, 3 H), 1.04 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.3, 134.7, 126.9, 92.3, 46.8, 44.2, 34.0, 32.8, 31.8, 30.7, 27.6, 19.1, 15.9, 12.1; MS, m/z calcd (M^+) 222.1620, obsd 222.1641.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.80; H, 10.06.

Thermal Rearrangement of 44. To a cold (−40 °C), magnetically stirred mixture of **43** (51.4 mg, 0.231 mmol), toluene (1 mL), tetrahydrofuran (0.5 mL), and pyridine (1 drop) was added dropwise 0.50 mL of 0.51 M Tebbe reagent. The resulting burgundy solution was kept at −40 °C for 30 min before being warmed to 0 °C where it was stirred for another 30 min. Sodium hydroxide solution (0.50 mL of 15%) was

added. When foaming had subsided, the reaction mixture was diluted with petroleum ether, dried, and concentrated in vacuo. The yellow solution of **44** was filtered through a short pad of activity III basic alumina using petroleum ether as eluant. The solvent was again removed in vacuo, and 2 mL of toluene was used to transfer the enol ether to a base-coated glass tube which was subsequently sealed for thermolysis. This tube was heated in a copper furnace at 210 °C for 48 h. The cooled reaction mixture was concentrated, and the residue was subjected to MPLC purification (silica gel, elution with 2% ethyl acetate in petroleum ether). Only one product was observed and identified as **46** (30 mg, 60%): IR (neat, cm^{-1}) 2975, 2880, 1700, 1460, 1375, 1350, 1260, 1100; ^1H NMR ($CDCl_3$) δ 4.83 (t, J = 2.2 Hz, 1 H), 2.47–2.20 (m, 2 H), 2.19 (s, 3 H), 1.92–1.55 (series of m, 4 H), 1.34–0.88 (series of m, 2 H), 1.14 (s, 3 H), 1.05 (s, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 0.89 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 214.6, 145.4, 126.1, 52.5, 37.7, 37.5, 36.2, 35.0, 32.6, 30.6, 29.0, 28.1, 24.6, 19.4, 19.0; MS, m/z calcd (M^+) 220.1821, obsd 220.1824.

7a-(1-Propenyl)-3,4,4a,5,6,7-hexahydrocyclopenta[*b*]pyran-2(3*H*)-one (52a and 52b). A solution of 1-bromopropene [3.30 mL (39.0 mmol) of 1:1 cis/trans mixture] in anhydrous ether (80 mL) was cooled to −78 °C and stirred as 52 mL of 1.50 M *tert*-butyllithium was added dropwise via syringe. After 1 h, a cold (−78 °C) solution of **14** (4.7 g, 27.6 mmol) in anhydrous ether (20 mL) was introduced via cannula, and the resulting creamy reaction mixture was stirred at −78 °C for 2 h. After warming to 25 °C during 1 h, saturated ammonium chloride solution (10 mL) was added, and the separated aqueous phase was extracted with ether. The combined organic layers were washed with water and brine, dried, and evaporated. The residue was chromatographed on a Waters Prep 500 instrument to afford 1.8 g of recovered **14** and 3.03 g (98%) of lactones **52a** and **52b**. These isomers wee separated by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether). There was isolated approximately 1 g of each lactone.

For **52a**: IR (neat, cm^{-1}) 2990, 2890, 1740, 1460, 1330, 1250, 1220, 1130, 1060; ^1H NMR ($CDCl_3$) δ 5.66 (dq, J = 6.3, 14.0 Hz, 1 H), 5.50 (dq, J = 1.6, 14.0 Hz, 1 H), 2.49–2.30 (m, 2 H), 2.25–1.50 (series of m, 9 H), 1.70 (dd, J = 1.6, 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.7, 133.7, 125.2, 93.1, 40.8, 40.5, 29.6, 26.6, 22.4, 21.6, 17.7; MS, m/z calcd (M^+) 180.1150, obsd 180.1155.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.60; H, 9.14.

For **52b**: IR (neat, cm^{-1}) 2925, 2840, 1740, 1460, 1350, 1260, 1165, 1120, 1090, 1020, 975, 930; ^1H NMR ($CDCl_3$) δ 5.56 (dq, J = 7.2, 11.8 Hz, 1 H), 5.45 (dq, J = 1.4, 11.8 Hz, 1 H), 2.48–2.30 (m, 2 H), 2.28–2.18 (m, 2 H), 2.12 (quintet, J = 5.8 Hz, 1 H), 1.97–1.65 (m, 6 H), 1.80 (dd, J = 1.5, 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.8, 132.7, 128.5, 92.8, 42.8, 40.4, 30.1, 27.0, 22.7, 21.9, 14.4; MS, m/z calcd (M^+) 180.1150, obsd 180.1157.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.86; H, 9.17.

Methylation of 52a. A solution of lithium diisopropylamide was prepared by addition of *n*-butyllithium (2.2 mL of 1.6 M in hexane) to a cold (0 °C) solution of diisopropylamine (0.50 mL, 3.58 mmol) in dry tetrahydrofuran (5 mL). After 15 min, the reaction mixture was cooled to −78 °C and a solution of **52a** (245 mg, 1.36 mmol) in the same solvent (4 mL) was added dropwise. Following 30 min at −78 °C, methyl iodide (0.5 mL, 23 mmol) was introduced, and the reaction temperature was allowed to rise to −40 °C. After 3 h, saturated ammonium chloride solution (10 mL) was added in one portion, and the separated aqueous layer was extracted with ether. The combined organic phases were washed with water and brine, dried, and evaporated. The residual oil (220 mg) was purified by MPLC on silica gel (elution with 10% ethyl acetaie in petroleum ether) to give 65 mg (23%) of **54a** and 130 mg (50%) of **53a**.

For **53a**: IR (neat, cm^{-1}) 2980, 2900, 1740, 1460, 1390, 1340, 1230, 1210, 1160, 1125, 1060, 970; ^1H NMR ($CDCl_3$) δ 5.65 (dq, J = 6.4, 14.3 Hz, 1 H), 5.45 (dq, J = 1.4, 14.7 Hz, 1 H), 2.54 (dq, J = 6.9, 8.8 Hz, 1 H), 2.14 (m, 1 H), 2.0–1.6 (series of m, 8 H), 1.70 (dd, J = 1.5, 6.4 Hz, 3 H), 1.24 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.9, 133.3, 125.6, 93.8, 40.9, 40.3, 30.2, 28.7, 27.9, 22.5, 17.7, 17.0; MS, m/z calcd (M^+) 194.1307, obsd 194.1307.

For **54a**: IR (neat, cm^{-1}) 2950, 1740, 1480, 1460, 1390, 1320, 1300, 1150; H NMR (C_6D_6) δ 5.30 (dq, J = 7.1, 14.7 Hz, 1 H), 5.20 (dq, J = 1.4, 14.7 Hz, 1 H), 2.05 (m, 1 H), 1.83 (dd, J = 1.3, 7.0 Hz, 3 H), 1.80–1.64 (br m, 2 H), 1.33–1.00 (series of m, 6 H), 1.20 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR (C_6D_6) δ 176.2, 135.6, 126.6, 91.4, 42.1, 41.5, 39.4, 36.8, 31.8, 28.7, 25.4, 22.6, 14.6; MS, m/z calcd (M^+) 208.1463, obsd 208.1458.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.49; H, 9.69.

Methylation of 52b. In a similar fashion, **52a** (173 mg, 0.96 mmol) was allowed to react with 3.96 mmol of LDA. Following exposure to methyl iodide (0.5 mL, 23 mmol) at −40 °C for 3 h and workup as before, there was obtained 180 mg of crude product. MPLC on silica gel furnished 72 mg (39%) of **54b** and 115 mg (61%) of **53b** as a 1:1 mixture of isomers which were not further characterized.

For **54b**: IR (neat, cm^{-1}) 2980, 2940, 1740, 1480, 1460, 1390, 1300, 1150, 1040, 970; ^1H NMR (C_6D_6) δ 5.30 (dq, J = 7.1, 10.6 Hz, 1 H), 5.20 (dq, J = 1.6, 10.6 Hz, 1 H), 2.05 (m, 1 H), 1.85 (dd, J = 1.5, 7.0 Hz, 3 H), 1.9–1.1 (series of m, 8 H), 1.21 (s, 3 H), 1.07 (s, 3 H); MS, m/z calcd (M^+) 208.1463, obsd 208.1464.

(3α,8β)-1,2,3,3a,4,5,7,8-Octahydro-5,5,8-trimethyl-6*H*-cyclopentacycloocten-6-one (55). A solution of **54a** (100 mg, 0.48 mmol), pyridine (6 drops), dry tetrahydrofuran (1 mL), and toluene (2 mL) was magnetically stirred at −40 °C as 1 mL of 0.51 M Tebbe reagent was added dropwise via syringe. After 1 h at −40 °C, the reaction mixture was warmed to 0 °C and stirred for an additional hour prior to quenching with 1 mL of 15% sodium hydroxide solution. Workup as before afforded 80 mg of crude enol ether which was dissolved in toluene (2 mL) and heated at 220 °C for 48 h in a base-coated sealed glass tube. The customary workup was followed by MPLC purification on silica gel (elution with 3% ethyl acetate in petroleum ether). There was isolated 40 mg (40%) of **55** and 20 mg (20%) of a two-component mixture identified as **56**: GC/MS, m/z calcd (M^+) 206, obsd (for each component) 206.

For **55**: IR (neat, cm^{-1}) 2950, 1705, 1460, 1440, 1395, 1375, 1320, 1240, 1120; ^1H NMR ($CDCl_3$) δ 5.16 (br d, J = 6.0 Hz, 1 H), 2.95 (dd with additional fine splitting, J = 6.0, 6.5 Hz, 1 H), 2.85 (dd, J = 5.4, 11.8 Hz, 1 H), 2.72 (m, 1 H), 2.23 (dt, J = 6.0, 7.0 Hz, 1 H), 2.17–2.0 (m, 2 H), 1.90 (dq, J = 7.8, 13.0 Hz, 1 H), 1.64 (m, 1 H), 1.5–1.0 (series of m, 4 H), 1.42 (s, 3 H), 1.08 (d, J = 6.5 Hz, 3 H), 1.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.9, 147.8, 125.8, 53.1, 47.7, 46.7, 37.6, 35.2, 32.6, 30.6, 29.5, 24.0, 22.8, 22.0; MS, m/z calcd (M^+) 206.1670, obsd 206.1689.

A 1:1 mixture of **54a** and **54b** (110 mg) was treated with the Tebbe reagent and thermally activated in entirely comparable fashion. A comparable quantity (41 mg, 37%) of **55** was produced along with a four-component mixture of acetyl byproducts.

Tosylhydrazone 58. A solution of the more polar epimer of **42b** (94 mg, 0.427 mmol) and tosylhydrazine (120 mg, 0.644 mmol) in methanol (3 mL) containing 1 drop of concentrated hydrochloric acid was stirred at −20 °C for 40 h. The precipitated tosylhydrazone was separated by filtration and recrystallized from methanol to afford 160 mg (96%) of **58** as colorless crystals: mp 148.5–149.5 °C dec; IR ($CDCl_3$, cm^{-1}) 3160, 2960, 1800, 1610, 1470, 1385, 1170, 1090; ^1H NMR ($CDCl_3$) δ 7.82 (d, J = 6 Hz, 2 H), 7.33 (d, J = 6 Hz, 2 H), 5.15 (br s, 1 H), 2.59–2.04 (m, 5 H), 2.42 (s, 3 H), 1.73 (m, 1 H), 1.52 (m, 1 H), 1.31–1.07 (m, 5 H), 1.03 (d, J = 7.0 Hz, 3 H), 1.01 (s, 6 H), 0.98 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.1, 143.9, 135.5, 130.0, 129.3 (2 C), 128.9, 128.3 (2C), 42.3, 42.1, 40.6, 38.8, 36.8, 36.2, 32.4, 31.7 (2C), 31.5, 21.6, 21.0, 18.1.

Anal. Calcd for $C_{22}H_{32}N_2O_2S$: C, 68.01; H, 8.30. Found: C, 67.66; H, 8.36.

Carbenoid Decomposition of 58. Precapnelladiene (1). A solution of **58** (145 mg, 0.373 mmol) in dry diglyme (3 mL) was stirred at 25 °C as 0.35 mL of 1.42 M *n*-butyllithium in hexane was introduced dropwise via syringe. After 10 min, the reaction mixture was heated to reflux for 30 min, cooled, and poured into 50 mL of purified petroleum ether. The organic solution was washed with water (6 × 20 mL), dried, and carefully evaporated. Capillary GC/MS analysis indicated the ratio of **59** to **1** to be 3:1. Flash chromatography of the mixture (107 mg) on silica gel impregnated with 2% silver nitrate (elution with purified hexane) afforded 47 mg (62%) of **59** and 24 mg (32%) of **1** both as colorless oils.

For **59**: ^1H NMR ($CDCl_3$) δ 5.43 (d, J = 11.4 Hz, 1 H), 5.18 (d, J = 1.6 Hz, 1 H), 4.91 (dd, J = 11.4, 9.2 Hz, 1 H), 3.06 (dt, J = 11.8, 6.8 Hz, 1 H), 2.73 (m, 1 H), 2.34 (m, 1 H), 1.78 (m, 1 H), 1.60 (m, 1 H), 1.44 (dd, J = 13, 6.5 Hz, 1 H), 1.30–1.10 (m, 3 H), 1.11 (s, 3 H), 1.06 (d, J = 7.4 Hz, 3 H), 1.05 (s, 3 H), 0.95 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.2, 137.7, 133.1, 130.8, 40.2, 38.9, 38.6, 38.4, 33.0, 32.3, 32.2, 31.6, 29.8, 21.3, 20.8; MS, m/z calcd (M^+) 204.1878, obsd 204.1855.

For **1**: ^1H NMR ($CDCl_3$) δ 5.33 (t, J = 8.3 Hz, 1 H), 5.02 (d, J = 1.5 Hz, 1 H), 3.51 (dt, J = 13.0, 6.0 Hz, 1 H), 2.90 (dd, J = 13.0, 9.3 Hz, 1 H), 2.38 (m, 2 H), 1.8–1.5 (br m, 4 H), 1.63 (br s, 3 H), 1.42 (m, 1 H), 1.25 (m, 1 H), 1.04 (d, J = 6.8 Hz, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.5, 136.2, 130.3, 121.8, 42.4, 40.5, 39.6, 38.9, 38.7, 33.7, 31.5, 31.3, 29.8, 26.7, 22.0.

Isomerization of 59 to Precapnelladiene. A magnetically stirred solution of **59** (60 mg, 0.294 mmol) and rhodium(III) chloride trihydrate (107 mg, 0.410 mmol) in absolute ethanol (20 mL) was heated at reflux for 30 h. At this point, an additional 105 mg of catalyst was introduced and heating was resumed for 42 h. The cooled mixture was filtered, a fresh 95 mg of $RhCl_3$ was added to the filtrate, and heating was resumed for a final 48 h (total reaction time of 5 days). Capillary GC analysis indicated the **59**:**1** ratio to be 1:10. The reaction mixture was poured in 15% potassium cyanide solution and extracted with purified petroleum ether (4 × 10 mL). The combined organic extracts were dried and carefully evaporated. Chromatography in the aforementioned manner provided 27 mg (45%) of pure precapnelladiene.

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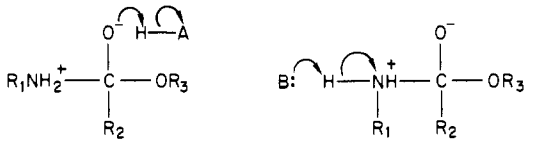
Transition-State Structures for Ester Aminolysis with and without Rate-Limiting Proton Transfer[1]

Ildiko M. Kovach, Michael Belz, Mark Larson, Steven Rousy, and Richard L. Schowen*

Contribution from the Department of Chemistry, University of Kansas, Lawrence, Kansas 66045-2112. *Received June 17, 1985*

Abstract: The reaction of phenyl acetate ($CH_3CO_2C_6H_5$ and $CD_3CO_2C_6H_5$) with methoxyamine at 25 °C in water exhibits β-secondary deuterium isotope effects k_{3H}/k_{3D} of 0.857 ± 0.024 (general-acid catalysis by $CH_3O_2CCH_2CH(CO_2CH_3)NH_3^+$, k_{HOH}/k_{DOD} = 3.9 ± 0.8) and 0.867 ± 0.009 (general-acid catalysis by $CH_3ONH_3^+$, k_{HOH}/k_{DOD} = 1.75 ± 0.06). These values are consistent with rate-limiting proton transfer from general acid to a zwitterionic tetrahedral adduct and rate-limiting solvent reorganization in a complex of general acid and zwitterionic adduct (Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 572-580). The reaction of hydrazine with phenyl acetate, with general-base catalysis by hydrazine, exhibits k_{3H}/k_{3D} = 0.972 ± 0.002 (H_2O solvent) and 0.970 ± 0.009 (D_2O solvent) and k_{HOH}/k_{DOD} = 1.44 ± 0.02. This is not consistent with proton transfer from a tetrahedral adduct but rather suggests a near-trigonal structure at carbonyl in the transition state. Possibly leaving-group expulsion in a cyclic process with external stabilization by a base catalyst is rate-determining. The uncatalyzed reaction of semicarbazide with 2,4-dinitrophenyl acetate has k_{3H}/k_{3D} = 0.975 ± 0.009, also consistent with a near-trigonal transition state.

The general acid–base catalyzed aminolysis of esters (and by implication its reverse, the general catalyzed alcoholysis of amides, the reaction catalyzed by serine–hydrolase enzymes) is thought, on the basis of an analysis of structure–reactivity relationships and kinetic isotope effects by Jencks and his co-workers,[2] to involve for certain structures and conditions rate-limiting proton transfers between general catalyst and the zwitterionic tetrahedral intermediates (**1** and **2**). Such processes follow special mechanisms in order for the actual proton-switch itself to become kinetically significant, as opposed to the slower diffusional steps which precede and succeed proton transfer. Examples of these special mechanisms include generation of tetrahedral adducts within a solvent cage already containing the general acid or base, perhaps hydrogen bonded to one of the reaction partners (pre-association), or the occurrence of a further chemical reaction, after proton transfer, more rapidly than diffusion apart of the proton-transfer products (spectator catalysis). Other general-catalyzed reactions which do not meet such criteria may have the diffusional steps of the proton-transfer sequence rate-limiting, or there may be, in the rate-limiting transition state, one form or another of coupling between the proton transfer and the formation or fission of heavy-atom bonds.



1 **2**

Table I. Observed First-Order Rate Constants k_0^{3L} for Reaction of Phenyl Acetate ($C_6H_5OCOCL_3$, L = H, D) with Methoxyamine (0.055 M) and Methoxyammonium Ion (0.045 M) in the Presence of Aspartic Acid Dimethyl Ester Conjugate Acid (HA,DA) in H_2O and D_2O Solvents, μ = 1.0 (KCl), 25.00 ± 0.05 °C

[HA] or [DA], M	$10^6k_0^{3H}$, s^{-1}	$10^6k_0^{3D}$, s^{-1}	k_0^{3H}/k_0^{3D}
	Solvent H_2O, pH 4.80[a]		
0.08	2.95, 2.97	3.22, 3.38	0.895
0.16	3.28, 3.22	3.76, 3.78	0.861
0.32	3.57, 3.66	4.34, 4.23	0.849
0.48	3.92, 4.07	4.74, 4.63	0.853
0.64	4.44, 4.45	5.11, 5.21	0.862
0.80	4.89, 4.94	5.60, 5.64	0.874
	Solvent D_2O, pD 5.30[b]		
0.08	1.49 ± 0.10		
0.16	1.76 ± 0.03		
0.32	1.84 ± 0.06		
0.48	1.86 ± 0.01		
0.64	1.87[c]		
0.80	2.09 ± 0.08		

[a] Reactions of protiated and deuterated substrates measured in alternation with the same solutions. [b] Except as indicated, rate constants are the mean of four measurements. [c] Single measurement.

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