Acknowledgment. We are grateful to Drs. K. Nagahara and Y. Okamoto of Kitasato University for helpful discussions on ^{13}C NMR spectra. We also thank Dr. K. Saito and H. Yamanaka of this school for measurement of mass spectra. A part of this work was supported by a Grant-in-Aid from Tokyo Biochemical Foundation.

Registry No. **1a**, 60026-36-0; **1b**, 63069-55-6; **1c**, 41661-91-0; **1d**, 59776-20-4; **1e**, 96429-52-6; **1f**, 59776-21-5; **1g**, 62758-20-7; **7a**, 96429-53-7; **7b**, 96429-54-8; **7c**, 96429-55-9; **7d**, 96429-56-0; **7e**, 96429-57-1; **7f**, 96429-58-2; **8a**, 96429-59-3; **8b**, 96429-60-6; **8c**, 96429-61-7; **8d**, 96429-62-8; **8e**, 96429-63-9; **8f**, 96429-64-0; **9**, 96429-65-1; **10c**, 25696-85-9; **10d**, 30561-26-3; **10e**, 65358-01-2; **10f**, 25775-01-3; diethyl acetylenedicarboxylate, 762-21-0; ethyl phenylpropiolate, 2216-94-6.

Supplementary Material Available: Tables of atomic coordinates, anisotropic temperature factors, bond distances and angles, and least-square planes for **7a** and **7c** (10 pages). Ordering information is given on any current masthead page.

Stereocontrolled Synthesis of Tetrahydrofurans and Tetrahydropyrans Using Thallium(III)-Induced Cyclizations

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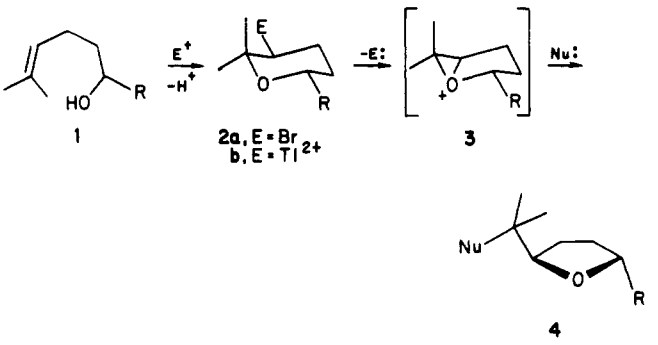
Various substituted 4-alkenols undergo electrophilic cyclization with thallium(III) salts in a regio- and stereoselective manner. The organothallium intermediate is not isolated but undergoes dethallation with concomitant 1,2-oxygen migration, leading to ring-expanded or -contracted products. The method constitutes a particularly efficient, one-step procedure for the synthesis of trans-2,5-disubstituted tetrahydrofurans (e.g., 1 → 4). In these cases stereochemical control in the attachment of nucleophiles to the side chain is also manifested. In general, the method is less effective for formation of tetrahydropyrans by the ring-expansion mechanism or when severe 1,3-diaxial interactions are developed during cyclizations to six-membered rings (e.g., with substrates 11 and 12). When *trans*-2-allylcyclohexanols are employed as substrates, 6,6- or 6,5-fused bicyclic ethers are formed with good stereochemical control and with a regiospecificity that can be manipulated in a Markovnikov fashion (e.g., 39 → 40 or 41).

In our continuing efforts[2] to devise stereochemically unambiguous syntheses of five- and six-membered cyclic ethers, common structural subunits in a wide variety of natural products,[3] we recently reported a two-step preparation of trans-2,5-disubstituted tetrahydrofurans 4.[2d] The sequence involved bromocyclization of 4-alkenols 1 to give the tetrahydropyrans **2a** and subsequent silver ion induced ring contraction, presumably by way of the bridged oxonium cations **3** (Scheme I). The stereochemistry is dictated from the outset by the equatorial preference of R in the chair-like transition state that leads to tetrahydropyran formation, and it is preserved in the subsequent ring contraction. Although highly stereoselective, the initial cyclization reaction produces varying amounts of the undesired tetrahydrofuran regioisomer, depending on the particular substitution pattern and polarization of the double bond.

We now report an improvement in this strategy which accomplishes the transformation of **1** to **4** regiospecifically and in a single step. The key to success lies in the use of thallium(III) salts as the electrophilic reagents. We reasoned that thallium, together with its accompanying counterions, should be much more sterically demanding than bromine and hence show a greater propensity for inducing cyclization to the tetrahydropyran regioisomer

Scheme I



2b. The greater sensitivity to the intramolecular participation of a hydroxyl group that electrophilic attack by thallium(III)[4a] shows in comparison to bromine[4b] should also favor stereocontrol as well as regiocontrol. Most importantly, the well-documented nucleofugality of thallium(III) should lead to the spontaneous decomposition of **2b**, the ring oxygen atom being ideally placed to assist in displacing the departing thallium(I) species and to stabilize the carbocation formally produced. As in our previous synthesis, bridged oxonium ions **3** are the putative intermediates, solvolysis of which produces the desired trans-2,5-disubstituted tetrahydrofurans **4**.

Examples of the oxythallation of alkenes with intramolecular nucleophilic participation are less common than might be expected,[5] especially when compared to the iso-

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Table I. Cyclizations of 1-Cyclohexyl-5-methylhex-4-en-1-ol (5a) with Thallium(III) Salts

entry	products (% yield)[a]	solv	conditns	products (% yield)[a]
1	TTA	CH_3CO_2H	room temp, 1 h	**6a** (72)
2	TTA	acetone/H_2O (4:1) + HBF_4	0 °C, 25 min	**6b** (73)
3	TTA	CH_3OH	0 °C, 30 min	**6a** (11); **6b** (5); **6c** (62)
4	TTN	CH_3OH	0 °C, 30 min	**6c** (34); **6d** (29)
5	TTN	CH_3OH/HC-$(OMe)_3$ (1:1)	0 °C, 45 min	**6c** (33); **6d** (28)
6	TTN	THF	0 °C, 30 min	**6b** (6); **6d** (56)
7	TTA	CH_3CN	reflux, 2 h	**6a** (28); **6b** (11); **6e** (40)

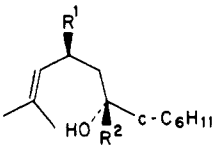
[a] Isolated yields of purified products.

electronic oxymercurations.[6] Furthermore, in many of these examples, it is only *after* intermolecular oxythallation of the alkene has occurred that the intramolecular nucleophile becomes involved, either by formally displacing thallium[7] or by capturing a carbocation generated by 1,2-shifts of carbon or hydrogen to the position vacated by thallium.[8] In the few reported 4-alkenol oxythallations that actually do involve OH participation in the addition step, reaction is generally completed by migration of carbon or hydrogen,[9] by elimination,[10] or by displacement of the thallium by solvent[11,12] or the counterion.[12] To our knowledge, only with an *o*-allylphenol has a two-stage participation/oxygen migration been reported.[13]

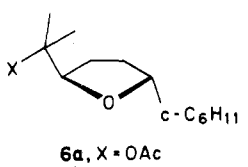
In the oxidative rearrangement of alkenes with thallium(III) reagents, 1,2-shifts of carbon and hydrogen are invariably encountered. By contrast, 1,2-shifts of oxygen are rare. In but a handful of cases[14] is there reasonable evidence for an oxygen shift, via cyclic oxonium ions, accompanying heterolysis of the C–Tl bond; epoxide isolation, however, is exceptional.[15] Oxiranyl intermediates have also been proposed in the thallium(III)-induced oxidation of ketones to 2-hydroxy ketones[16] and of chalcones to benzils.[17]

Results and Discussion

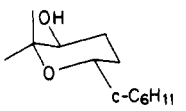
Stereospecific Tetrahydrofuran Synthesis. In order to establish appropriate conditions for the desired transformation, 1-cyclohexyl-5-methylhex-4-en-1-ol (**5a**) was chosen as the substrate[18] and its reactions with thallium triacetate sesquihydrate (TTA) or thallium trinitrate trihydrate (TTN) in a variety of solvents were surveyed (Table I). In all but one case (entry 7) reaction is complete within minutes at room temperature or 0 °C, affording the trans-2,5-disubstituted tetrahydrofurans **6** in yields between 60 and 80%. In the case of entry 2, analysis of the crude product mixture by capillary gas chromatography showed that the cis isomer of **6b** and the tetrahydropyranol regioisomer **7** between them constitute less than 4% of the organic products formed. The trans stereochemistry of



5a, $R^1 = R^2 = H$
b, $R^1 = Me$, $R^2 = H$
c, $R^1 = H$, $R^2 = Me$



6a, X = OAc
b, X = OH
c, X = OMe
d, X = ONO_2
e, X = NHAc



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the major products **6** was deduced by comparison of their ^1H and ^{13}C NMR spectra with those obtained for the related isopropyl derivatives **6b** and **6c** (isopropyl instead of cyclohexyl).[2d] Authentic samples of materials for comparison were obtained by treatment of **5a** with *m*-chloroperoxybenzoic acid followed by boron trifluoride. An approximately 1:1 mixture of cis and trans tetrahydrofurans **6b** (46%) and tetrahydropyranol **7** (13%) was isolated. In contrast to the favorable results obtained with thallium(III), reaction of **5a** with lead(IV) acetate in acetic acid required 25 h at room temperature for completion, and the isolated yield of **6a** was only 31%.[19]

As the table shows, preparatively useful incorporation of the nucleophiles acetic acid, water, and methanol into products **6** can be achieved. With water as solvent, it is necessary to maintain a low pH in order to keep the thallium(III) species in solution. In attempts to optimize the formation of the methoxy compound **6c**, we found significant incorporation of nitrate ion accompanying the use of TTN (entries 4, 5); this side reaction is suppressed by using TTA (entry 3). By using TTN in a nonnucleophilic solvent (entry 6), the nitrate ester **6d** can be obtained in fair yield. Finally, with acetonitrile as solvent, an unusually mild Ritter reaction gives the amide **6e** in modest yield and convenience over our previously reported two-step bromination/ring contraction sequence.[2d] Also by way of contrast, in the reported palladium(II)-induced cyclization of **1** (R = Ph) the palladated intermediate suffers

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(15) (a) Kruse, W.; Bednarski, T. M. *J. Org. Chem.* **1971**, *36*, 1154. (b) Lethbridge, A.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2763. (c) Dahlmann, J.; Klose, B. *Z. Chem.* **1979**, 371.
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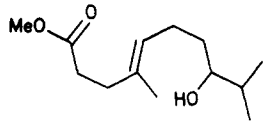
(17) McKillop, A.; Swann, B. P.; Ford, M. E.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3641.
(18) Substrates **1** (R = isopropyl), used in our bromination/rearrangement studies,[2d] also underwent the thallation reaction, but owing to product volatility, isolated yields were never satisfactory. Compound **4** (R = isopropyl, Nu = OH), prepared by the present route, was identical in all respects with the product previously reported.
(19) (a) Moriarty, R. M.; Kepadia, K. *Tetrahedron Lett.* **1964**, 1164. (b) Moriarty, R. M.; Walsh, H. G.; Gopal, H. *Ibid.* **1966**, 4363. (c) Corey, E. J.; Gross, A. W. *Ibid.* **1980**, *21*, 1819.

elimination to a dihydropyran rather than rearrangement to a tetrahydrofuran.[20]

We expected that nucleophilic interception of the bridged oxonium ion would be not only regioselective but also highly stereoselective: the nucleophile should cleave the oxiranium ring by rear-side attack, leading to controllable stereochemistry at a side-chain stereocenter in appropriate situations. We explored this possibility using the alkenol–ester **8**. With TTA in acetic acid followed by hydrolysis of the intermediate acetate and acid-induced lactonization, product **9** was obtained in 54% yield and better than 98% isomeric purity (capillary GC).[21] With TTA in acetone–water–tetrafluoroboric acid, **8** yielded **9** (49%) directly, along with a mixture of the isomers **10** (12%) in which the ester rather than the alcohol had participated in oxythallation.



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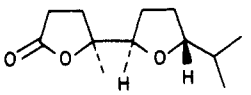

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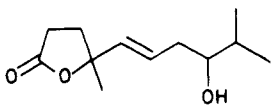
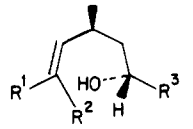
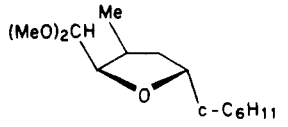


10

Cis-2,3-trans-2,5-trisubstituted tetrahydrofuran rings occur in several polyether antibiotics,[3] and we attempted to apply the thallium sequence to the synthesis of simple model systems containing this substitution pattern. With compound **5b**, no identifiable products could be isolated, presumably because of 1,3-diaxial interactions in the transition state for ring closure. The tertiary alcohol **5c** also gave ambiguous results, probably for the same reason.



11a, R^1 = MeO, R^2 = H, R^3 = c-C_6H_{11}
b, R^1 = H, R^2 = MeO, R^3 = c-C_6H_{11}
c, R^1 = H, R^2 = MeO, R^3 = *i*-Pr



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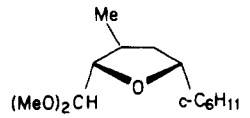

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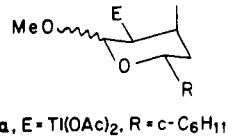


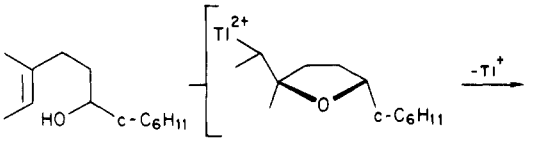
14a, E = Tl(OAc)$_2$, R = c-C_6H_{11}
b, E = Br, R = *i*-Pr

We attempted to transcend this steric pitfall by increasing the electrophilicity of the alkene. The reactions of the enol ethers **11a** and **11b** with TTA in methanol require more vigorous conditions (heating under reflux) for completion, the rapidly formed thallated intermediates apparently being rather stable. The trans enol ether **11a** affords tetrahydrofuran products in 50% yield; however, stereoisomeric products **12** and **13** are formed in a 3:2 ratio.[22] In this case, it is feasible that, owing to the strong stabilization afforded by the methoxy group, the initial thallium-induced cyclization produces both anomers of **14a**. This would parallel our findings on the course of bromination and ring contraction of a related trans-enol ether, in which the isopropyl analogues of **12** and **13** are produced via **14b**.[2d] In addition, a side product formed in 6% yield has been tentatively assigned the structure of the lactol **15**; this material apparently arises from nonconcerted loss of the thallium or from cyclization and rearrangement via the sequence shown in Scheme II.

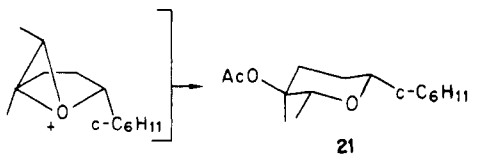
With the cis-enol ether **11b**, the tetrahydrofurans **12** and **13** are minor components of the product, isolated in 3.3% and 6.6% yield, respectively. The major products are the lactone **16** (20%), the related ester **17** (30%), and the dihydropyran **18** (10%). Similarly, the cis-enol ether **11c** gives lactone **16** (R = *i*-Pr, 42%) as the sole identifiable product. These products probably arise from an axial thallated intermediate formed by cyclization of the substrate **11b** via the alternative chair conformation, as shown in Scheme II as well. This cyclization behavior is again analogous to that observed in our earlier bromination study.[2d] Elimination rather than rearrangement, probably by a stepwise process, would explain the formation of **18**.[23]

Tetrahydropyran Formation. The relative stabilities of secondary vs. tertiary carbocationic centers effectively account for the regiochemical outcome of the thallation–ring contraction sequence with reactants like **5a**. For a substrate with the opposite double-bond polarization, cyclization to the tetrahydrofuran followed by ring expansion to the tetrahydropyran is expected.

Treatment of the trisubstituted olefin **19** (85:15 *E*/*Z*) with TTA/HOAc at room temperature affords predominantly tetrahydropyran **21** (50% yield), resulting from cyclization to the trans tetrahydrofuran **20** and subsequent ring expansion in the anticipated sense. We isolated a THF regioisomer **22** (6% yield), a stereoisomer of **21** (6% yield) and a trace of the dihydropyran **23** as minor products of this reaction. Cyclization of a mixture of olefins in which the *Z* isomer predominates (64:36) affords a completely different spectrum of products. Compound **21** is isolated in only 24% yield (reflecting the predominant product from the *E* component). The *Z* component gives rise to a number of products: an inseparable mixture of THF and THP products (3:2 ratio, 19% isolated yield, both different from **21** and **22**) and the dihydropyran **23** (18% yield).



19 **20**



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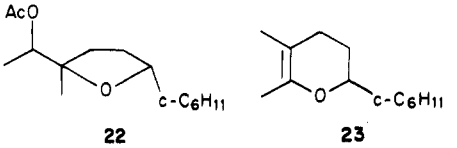


22 **23**

Compound **24**, in which the competition is between tertiary and primary electrophilic sites, also gives pre-

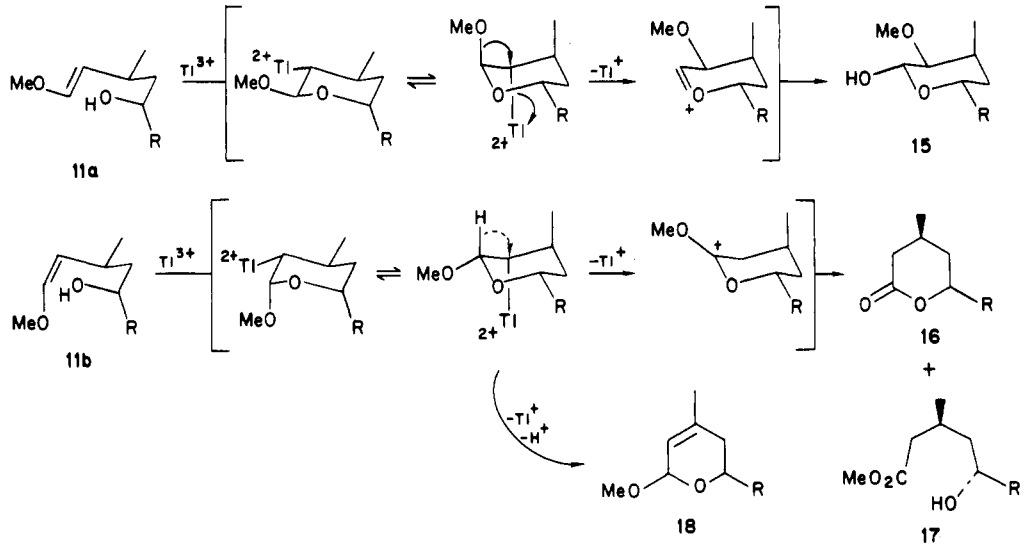
(20) Hosokawa, T.; Hirata, M.; Murahashi, S.-I.; Sonoda, A. *Tetrahedron Lett.* **1976**, 1821.

(21) The product was chromatographically and spectroscopically identical with material available from the bromination/rearrangement procedure.[2d]

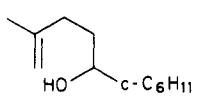
(22) Stereochemistry was assigned by ^1H and ^{13}C NMR spectroscopic comparison with the 5-isopropyl analogues.[2d]

(23) An alternative mechanism for the formation of **16** and **17** would simply be oxidative rearrangement of the enol ether **11b** to **17**, followed by partial lactonization.

Scheme II



dominantly tetrahydropyrans **25** (70% combined yield), although with some sacrifice of stereoselectivity (59:11 ratio of **25a–c**:**25d**). The relative stereochemistries of **25a** and **25d** were assigned from the proton chemical shifts of the methyl and acetoxy groups (1.58 and 1.97 ppm vs. 1.36 and 2.04 ppm), in accordance with the generally observed resonance at lower field of axial substituents.[26]



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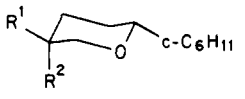
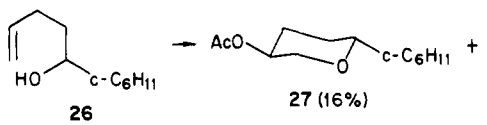
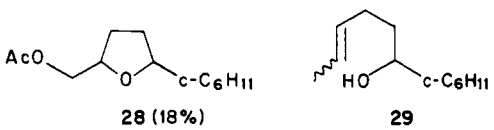


25a, R^1 = OAc, R^2 = Me
b, R^1 = Cl, R^2 = Me
c, R^1 = OH, R^2 = Me
d, R^1 = Me, R^2 = OAc

Substrates for which the thallium-induced cyclization did not provide useful results were the mono- and 1,2-disubstituted derivatives **26** and **29** (E/Z = 3:2). Monosubstituted olefin **26** gives only a low yield of cyclic product, as a mixture of stereo- and regioisomers; the only material we could characterize from reaction of **29** was 1-cyclohexyl-1-hydroxy-4-hexanone, the product of oxidative rearrangement of the alkene moiety. It is worth noting that with both **24** and **26**, that is, when the alkene is terminal, the rapidly formed thallated intermediates have a significant lifetime; in the latter case, elevated temperatures are needed to induce final product formation, and in the former, nucleophiles introduced during the workup procedure become incorporated into the tetrahydropyran products **25b** and **25c** when the reaction is run for the length of time sufficient for complete conversion of non-terminal alkenes. It is instructive to compare the results obtained using substrate **24** with those found by Semmelhack and Bodurow in their palladium(II)-induced cyclization/carbonylation of an alkenol having a similar substitution pattern: in that case the products arise from exclusive tetrahydrofuran formation during ring closure, but cis and trans diastereomers are formed in equal amounts.[25] They also reported the formation of mixtures of tetrahydrofurans and tetrahydropyrans from 4,5-disubstituted 4-alkenols.

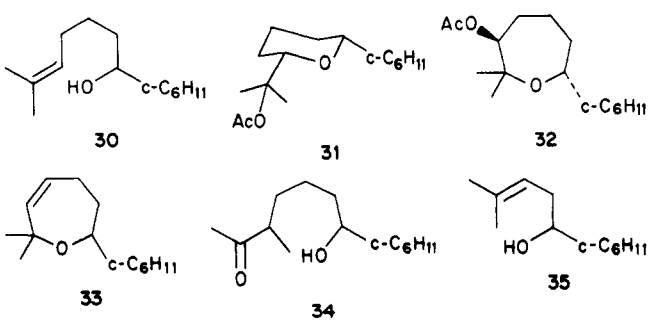


26 **27** (16%)



28 (18%) **29**

We also examined the reactions of **30** and **35**, the upper and lower homologues of our standard substrate **5a**, with TTA in acetic acid at room temperature. It was to be expected that the formation of a seven-membered ring on thallation of **30** would not be especially favorable, although the subsequent ring contraction should proceed rapidly. Its reaction is in fact slower (20 h) than the comparable reaction of **5a**, and it provides only a 33% yield of tetrahydropyran **31**, although that is the major product. Products **32** and **33** containing seven-membered rings make up 8% of the isolated products, and oxidative rearrangement gives ketone **34** (15%). From the reaction of **35**, the lower homologue of **5a**, we were unable to isolate any homogeneous products at all.



30 **31** **32**

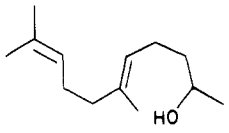
33 **34** **35**

Cyclization of 6,10-Dimethylundeca-5(*E*),9-dien-2-ol (36). Cation-initiated polyolefin cyclizations[26] often permit direct access to polycyclic fused-ring systems with spectacular stereochemical control. We were intrigued by the possibility of using thallium(III) to induce cyclization of a polyolefin system possessing an OH group as cyclization terminator. Precedents for neighbouring C=C bond participation during the thallation of alkenes are reason-

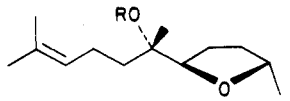
(24) "Stereochemistry: Fundamentals and Methods"; Kagan, H. B., Ed.; Georg Thieme Publishers: Stuttgart, 1977; Vol. 3, p 102.
(25) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496.
(26) Bartlett, P. A. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 5, pp 341–409.

able,[5] and in fact with *o*-prenylphenols, tri- and even tetracyclic products have been isolated.[27] We chose to investigate the oxythallation of **36**[28] because of its curiously different reactions with other "soft" electrophiles. Mercury(II) trifluoroacetate has been reported to react at the double bond farthest from the OH group, giving the bicyclic ether in rather poor yield.[29] However, phenylselenenyl chloride reacts exclusively at the internal double bond to give a mixture of tetrahydrofuran and tetrahydropyran products which rearrange to bicyclic ethers only on subsequent acid treatment.[28]

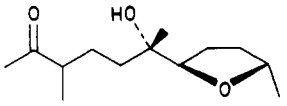
Upon treatment of **36** with TTA in acetic acid, the major isolable product is the tetrahydrofuran **37a** (61%); the



36



37a, R = Ac
b, R = H

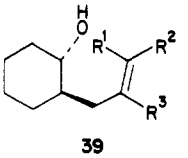


38

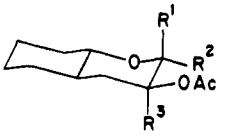
regioisomeric tetrahydropyran is formed to the extent of less than 2%, and no bicyclic product could be detected. The reaction thus conforms to our "standard" cyclization, with oxythallation taking place at the internal double bond. In accord with our findings in the cyclohexyl carbinol system, a high degree of stereocontrol is manifested with this substrate as well: no evidence for another diastereomer was seen by capillary gas chromatography or ^{13}C NMR.[30] Predictably, when the tertiary alcohol **37b** is treated with TTA in acetic acid, a second cyclization to a bis(tetrahydrofuranyl) product does not occur, presumably for steric reasons; simple oxidative rearrangement of the remaining double bond takes place instead, and a diastereomeric mixture of ketones **38** is isolated (54%).

Bicyclic Ether Formation. The degree of acyclic stereocontrol exerted by the substituent on the carbinol carbon atom in the above examples is noteworthy. Our final investigations were on a group of substrates in which conformational control over the course of the reaction is perhaps inescapable: *trans*-2-allylcyclohexanols. Both possible product types, cyclohexannulated tetrahydrofurans or tetrahydropyrans, are of intrinsic interest as constituents of various natural products.

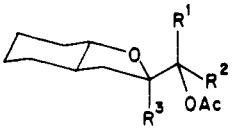
Intramolecular oxythallation/reductive dethallation of substrate **39a** proceeds as expected from the substitution pattern: initial cyclization to the tetrahydrofuran is followed by ring expansion to provide the 6,6-fused product **40a** in 50% isolated yield. In contrast, reaction of **39b**, which has the opposite Markovnikov bias, leads to the formation of a 9:2 mixture of the 6,5- and 6,6-fused bicyclic ethers **40b** and **41b**, respectively (70% yield).[31] In order to maintain selectivity for the 6,6-system while preserving the substitution pattern of substrate **39a**, we introduced an electron-withdrawing ester group to modify the polarization of the C=C bond yet again. Cyclization of allylic ester **39c** in fact favors the 6,6-bicycle **40c** over the 6,5-isomer **41c** (5:1 ratio); however, these compounds are isolated in only 43% combined yield. Finally, the symmetrically substituted *trans*-alkene **39d** also shows a preference for tetrahydropyran **40d** rather than tetrahydrofuran **41d** formation; however, in this instance simple oxidative rearrangement to ketone **42** is the major reaction pathway. The ratio of the three products is 4:1:6, respectively. Although these latter reactions have not been optimized, it is clear that appropriate manipulation of substituent effects provides a means for controlling the regiochemical outcome of the cyclizations.



39



40a, $R^1 = H$, $R^2 = R^3 = Me$
b, $R^1 = R^2 = Me$, $R^3 = H$
c, $R^1 = Me$, $R^2 = CH_2O_2C\text{-}2,4\text{-}Cl_2C_6H_4$, $R^3 = H$
d, $R^1 = R^3 = H$, $R^2 = Me$



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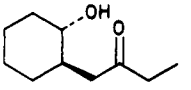

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Experimental Section[32]

Representative experimental procedures are given in this section; the remaining experimental details are available in the supplementary material.

General Method for the Reaction of Alkenols with Thallium(III) Acetate Sesquihydrate in Glacial Acetic Acid. Thallium(III) acetate sesquihydrate (1.0–1.3 molar equiv) is added in one portion at room temperature to a stirred solution of the substrate (100–300 mg) in glacial acetic acid (2–3 mL). TLC shows that the starting material is usually consumed within 30–60 min. Workup involves removal of the solvent at reduced pressure on a rotary evaporator, followed by the addition of brine solution (ca. 10 mL) and sufficient solid K_2CO_3 to neutralize the resulting solution. The inorganic precipitate thus produced is removed by filtration through Celite and washed with brine and then with CH_2Cl_2. The aqueous phase is extracted several times with CH_2Cl_2, and the combined organic phases are dried ($MgSO_4$) and evaporated to yield a crude product which is purified by chromatography.

(2*R,5*R**)-2-(1-Acetoxy-1-methylethyl)-5-cyclohexyltetrahydrofuran (6a).** The general procedure was followed by using thallium(III) acetate sesquihydrate (225 mg, 0.55 mmol),

(27) Yamada, Y.; Nakamura, S.; Iguchi, K.; Hosaka, K. *Tetrahedron Lett.* **1981**, *22*, 1355.
(28) Rouessac, A.; Rouessac, F. *Tetrahedron* **1981**, *37*, 4165.
(29) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461.
(30) The relative stereochemistry in the side chain of **37a** has been assigned only on the basis of mechanistic considerations.
(31) In this and subsequent experiments, product ratios were determined from the ^1H NMR spectra of the product mixtures.
(32) General procedures: IR spectra were recorded on a Perkin-Elmer Model 1420 instrument. Unless otherwise stated, spectra were measured on neat liquids as thin films between sodium chloride plates. ^1H NMR spectra were measured at 250 MHz in $CDCl_3$ solution and are reported on the δ scale relative to tetramethylsilane. ^1H NMR data are reported as follows: chemical shift (number of protons, multiplicity, coupling constants in hertz). ^{13}C NMR spectra were measured in $CDCl_3$ solution at 50.78 MHz. Chromatography refers to flash column chromatography on silica gel 230–400 mesh (particle size 0.040–0.063 mm) according to the method of Still.[33] Thin-layer chromatograms were run on Analtech silica gel GHLF plates (layer thickness 250 μm). Preparative HPLC purifications were performed on a Waters Prep LC/System 500A instrument using prepacked silica gel cartridges. Capillary gas chromatography (CGC) was performed on a Hewlett-Packard Model 5790A series gas chromatograph equipped with a cross-linked 5% phenylmethylsilicone Ultra No. 2 column (25 m × 0.20 mm internal diameter, 0.33-μm standard film) and using helium as carrier gas and a column pressure of ca. 1.12 kg/cm^2. Purification of samples for elemental analysis was generally by flash column chromatography of a small quantity of the material using mixtures of AR hexane and ether as eluant unless otherwise indicated. Tetrahydrofuran and toluene were distilled from sodium benzophenone prior to use.
(33) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 293.

1-cyclohexyl-5-methylhex-4-en-1-ol (**5a**; 108 mg, 0.55 mmol), glacial acetic acid (2.5 mL), and a reaction time of 1 h. Workup gave the crude product mixture as a colorless liquid (129 mg). Chromatography (4% ethyl acetate in hexane) yielded the ester **6a** (101 mg, 72%) as a colorless liquid in >97% isomeric purity as judged by CGC: R_f (10% EtOAc/hexane) 0.40; IR 3000, 2945, 2875, 1645, 1374, 1260, 1075 cm^{-1}; ^1H NMR δ 3.98 (1, dd, J = 8.5, 6.6 Hz), 3.61 (1, ddd, J = 9.0, 7.8, 5.2 Hz), 1.98 and 2.0–1.83 (5, s and m), 1.83–1.5 (5, m), 1.46 and 1.45 (6, 2 s), 1.45–0.85 (8, m); ^{13}C NMR δ 170.36, 84.73, 83.65, 83.60, 42.95, 30.07, 29.72, 28.58, 26.81, 26.49, 25.95, 25.82, 22.43, 22.05, 21.46. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.79; H, 10.14.

(2*R,5*R**)-2-Cyclohexyl-5-(1-hydroxy-1-methylethyl)-tetrahydrofuran (6b).** Thallium(III) acetate sesquihydrate (245 mg, 0.60 mmol) was added to a stirred solution of 1-cyclohexyl-5-methylhex-4-en-1-ol (**5a**; 104.5 mg, 0.53 mmol) in a mixture of acetone (2 mL), water (0.5 mL), and 48% aqueous HBF_4 (0.3 mL) at 0 °C. After 25 min, brine (5 mL) and a little solid K_2CO_3 were added. Further workup according to the general procedure gave the crude product as a colorless liquid (110 mg). Chromatography (7% ethyl acetate in hexane) yielded the alcohol **6b** (83 mg, 73%) as a colorless liquid in >99% isomeric purity as judged by CGC: R_f (10% EtOAc/hexane) 0.23; IR 3580 (shoulder), 3470 (br), 2985, 2935, 2865, 1453, 1383, 1140, 1079, 1062, 1048, 950 cm^{-1}; ^1H NMR δ 3.70 (1, dd, J = 9.3, 6.2 Hz), 3.61 (1, ddd, J = 9.0, 7.8, 5.4 Hz), 2.21 (1, br s), 2.0–1.5 (8, m) 1.45–1.15 and 1.22 (7, m and s), 1.11 and 1.05–0.8 (6, s and m); ^{13}C NMR δ 85.15, 84.73, 71.54, 43.36, 30.30, 30.02, 28.67, 27.25, 26.94, 26.52, 26.00, 25.85, 23.91. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.68; H, 11.08.

(5*R)-5-[(2*S**,5*S**)-5-(1-methylethyl)tetrahydrofuran-2-yl]dihydrofuran-2-one (9).** The general procedure was followed, using thallium(III) acetate sesquihydrate (306 mg, 0.75 mmol), methyl 4,9-dimethyl-8-hydroxy-4(*E*)-decenoate[2d] (**8**; 130 mg, 0.57 mmol), glacial acetic acid (2 mL), and a reaction time of 40 min. Workup gave a colorless liquid (159 mg). This product was dissolved in methanol (5 mL); anhydrous K_2CO_3 (450 mg, 3.26 mmol) was added, and the mixture was stirred at room temperature for 13 h. Concentrated HCl was added dropwise until the mixture was just acidic. After 30 min the methanol was evaporated and the residue was partitioned between water and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to yield a liquid (111 mg). Chromatography (hexane–ethyl acetate mixtures) yielded some impure starting material (11.5 mg, <9%) and the lactone **9** (65.5 mg, 54%) which showed identical spectroscopic and chromatographic behavior to a sample prepared by an alternative method.[2d] The compound was >98.5% isomerically pure, as demonstrated by CGC. A better resolved ^1H NMR spectrum than that previously reported[2d] was obtained: δ 4.03 (1, dd, J = 8.9, 6.3 Hz), 3.7–3.5 (1, m), 2.8–2.45 (2, m), 2.28 (1, ddd, J = 12.9, 10.2, 5.2 Hz), 2.1–1.95 (2, m), 1.87 (1, ddd, J = 13.0, 10.2, 8.4 Hz), 1.35 (3, s), 0.94 (3, d, J = 6.6 Hz), 0.84 (3, d, J = 6.8 Hz).

(2*R,3*S**,5*R**)-2-(Dimethoxymethyl)-3-methyl-2-cyclohexyltetrahydrofuran (12) and the (2*R**,3*R**,5*S**) Isomer 13. Oxythallation of (1*R**,3*S**)-1-Cyclohexyl-5-methoxy-3-methylpent-4(*E*)-en-1-ol (11a).** The general procedure was followed, using thallium(III) acetate sesquihydrate (360 mg, 0.88 mmol), the enol ether **11a** (158 mg, 0.75 mmol), and methanol (3 mL) as solvent. After 3 h the mixture was heated under reflux for another 3 h. Workup gave a liquid (165 mg) which was purified by chromatography (hexane–ethyl acetate mixtures). The major product (91 mg, 50%) consisted of a 3:2 mixture (by ^1H NMR spectroscopy) of the 2,3-cis-2,5-trans acetal **12** and the 2,3-trans-2,5-cis isomer **13**. By careful chromatography, pure samples of each isomer could be obtained for characterization.

The (2*R**,3*S**,5*R**) isomer **12** was obtained as a colorless liquid and was shown to be >88% isomerically pure by CGC: R_f (20% EtOAc/hexane) 0.63; IR 2935, 2865, 1748 (w), 1452, 1198, 1165, 1100, 1084, 1058, 1008, 965 cm^{-1}; ^1H NMR δ 4.31 (1, d, J = 7.5 Hz), 3.9–3.7 (2, m), 3.41 and 3.38 (6, 2 s), 2.4–2.35 (1, m), 2.0–1.85 (1, m), 1.85–1.5 (7, m), 1.5–1.3 (1, m), 1.3–1.1 (3, m), 1.1–0.8 and 1.03 (5, m and d, J = 7.4 Hz); ^{13}C NMR δ 103.37, 82.17, 79.30, 53.90, 52.67, 43.43, 37.40, 35.23, 29.76, 28.19, 26.56, 26.04, 25.97, 14.41. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.04; H, 10.75.

The (2*R**,3*R**,5*R**) isomer **13** was obtained as a colorless liquid and was shown to be isomerically pure by CGC: R_f (20% EtOAc/hexane) 0.69; IR 2935, 2860, 1450, 1194, 1100, 1067, 968 cm^{-1}; ^1H NMR δ 4.17 (1, d, J = 5.9 Hz), 3.65 (1, q, J = 7.2 Hz), 3.48 (1, t, J = 5.8 Hz), 3.43 and 3.42 (6, 2 × s), 2.25–2.05 (1, m), 2.0–1.85 (1, br d, J = 13 Hz), 1.85–1.45 (6, m), 1.45–1.1 (5, m), 1.06 (3, d, J = 6.9 Hz), 1.05–0.85 (2, m); ^{13}C NMR δ 106.53, 85.04, 83.03, 55.54, 54.16, 42.97, 37.24, 34.74, 29.89, 28.80, 26.56, 26.03, 25.98, 19.29. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.11; H, 10.81.

A further minor product (11 mg, 6.4%) was tentatively identified as **(2*R**,3*R**,4*R**,6*S**)-6-cyclohexyl-3-methoxy-4-methyltetrahydropyran-2-ol (15)**: R_f (20% EtOAc/hexane) 0.34; IR 3480 (br), 2860, 1740 (w), 1453, 1210, 1145, 1058 cm^{-1}; ^1H NMR δ 4.30 (1, d, J = 8.1 Hz), 3.52 (3, s), 3.45 (1, dd, J = 7.9, 5.7 Hz), 3.32 (1, ddd, J = 7.1, 6.0, 3.6 Hz), 2.4–2.25 (1, m), 2.25 (1, br s), 2.1–1.95 (1, br d, J = 12.5 Hz), 1.8–1.55 (9, m), 1.15–1.1 (4, m), 1.1–0.85 and 1.06 (5, m and d, J = 7.3 Hz).

Oxythallation of (1*R,3*S**)-1-Cyclohexyl-5-methoxy-3-methylpent-4(*Z*)-en-1-ol (11b).** The general procedure was followed, using thallium(III) acetate sesquihydrate (365 mg, 0.89 mmol), the enol ether **11b** (155 mg, 0.73 mmol), and methanol (3.5 mL) as solvent. After 15 min the mixture was heated under reflux for 6 h. Workup gave a liquid (165 mg) which was purified by chromatography (hexane–ethyl acetate mixtures). Two major products and three minor products were obtained. **Methyl (3*R**,5*S**)-5-cyclohexyl-5-hydroxy-3-methylpentanoate (17)** was obtained as a colorless liquid (50 mg, 30%) which was shown to be a single diastereomer by CGC: R_f (20% EtOAc/hexane) 0.29; IR 3450 (br), 2935, 2860, 1740, 1452, 1169 cm^{-1}; ^1H NMR δ 3.67 (3, s), 3.38 (1, q, J = 6.0 Hz), 2.45–2.3 (1, m), 2.3–2.1 (2, m), 2.08 (1, br s), 1.9–1.6 (5, m), 1.40 (1, t, J = 6.8 Hz), 1.35–0.95 and 1.00 (9, m and d, J = 6.5 Hz); ^{13}C NMR δ 174.07, 73.33, 51.44, 43.71, 41.21, 40.56, 29.19, 27.54, 26.95, 26.47, 26.27, 26.12, 21.16. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 67.99; H, 10.61. **(4*R**,6*S**)-6-Cyclohexyl-4-methyltetrahydropyran-2-one (16**; 28.5 mg, 20%) was obtained as a colorless solid and a single diastereomer by CGC: R_f (20% EtOAc/hexane) 0.33; mp 53–54 °C; IR 2940, 2865, 1732, 1456, 1289, 1260, 1090, 1070, 997 cm^{-1}; ^1H NMR δ 4.11 (1, ddd, J = 10.2, 6.4, 3.9 Hz), 2.55 (1, dd, J = 9.6, 9.3 Hz), 2.25–2.1 (2, m), 2.05–1.9 (1, br d, J = 12 Hz), 1.9–1.6 (5, m), 1.6–1.45 (2, m), 1.35–0.9 and 1.09 (8, m and d, J = 6.5 Hz); ^{13}C NMR δ 172.85, 81.06, 42.04, 37.31, 31.98, 28.34, 26.19, 26.11, 25.87, 25.74, 23.81, 21.34. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.63; H, 10.39. **(2*R**,3*S**,5*R**)-5-Cyclohexyl-2-(dimethoxymethyl)-3-methyltetrahydrofuran (12**; 6 mg, 3.3%) and **(2*R**,3*R**,5*S**)-5-cyclohexyl-2-(dimethoxymethyl)-3-methyltetrahydrofuran (13**; 12 mg, 6.6%) were isolated cleanly. Finally, a product tentatively identified as a stereoisomer of **6-cyclohexyl-2-methoxy-4-methyl-5,6(2*H*)-dihydropyran (18)** was obtained as a colorless liquid (15 mg, 9.8%): R_f (20% EtOAc/hexane) 0.73; IR 2925, 2855, 2825, 1683, 1452, 1393, 1188, 1164, 1149, 1134, 1063, 1024, 977, 956 cm^{-1}; ^1H NMR δ 5.46 (1, br s), 4.85 (1, br s), 3.58 (1, ddd, J = 10.9, 7.4, 3.6 Hz), 3.40 (3, s, s at δ 3.48 possibly indicates ca. 9% of the anomer is also present), 2.15–1.6 and 1.73 (9, m and s), 1.5–0.9 (7, m); ^{13}C NMR δ 137.75, 119.44, 96.24, 70.50, 54.86, 42.26, 32.98, 29.21, 28.69, 26.55, 26.08, 25.88, 25.78 (spurious?), 22.93. HRMS Calcd for $C_{13}H_{22}O_2$: 213.1620. Found: 210.1626.

(2*R,3*S**,6*R**)-3-Acetoxy-6-cyclohexyl-2,3-dimethyltetrahydropyran (21). Acetoxythallation of 1-Cyclohexyl-4-methylhex-4-en-1-ol (19).** The general procedure was followed, using thallium(III) acetate sesquihydrate (400 mg, 0.98 mmol), a sample of **19** in which the E/Z isomer ratio was 85:15 (164 mg, 0.84 mmol), glacial acetic acid (2.5 mL), and a reaction time of 45 min. Work-up gave the crude product as a liquid (185 mg). Chromatography (hexane–ethyl acetate mixtures) afforded one major product that was fully characterized, and several minor products tentatively identified on the basis of their ^1H NMR spectra. The tetrahydropyran **21** (107 mg, 50%) was obtained as a colorless liquid and was shown by CGC to be isomerically pure: R_f (10% EtOAc: hexane) 0.50; IR 2990, 2935, 2860, 1742, 1454, 1370, 1251, 1119, 1094, 1023 cm^{-1}; ^1H NMR δ 3.48 (1, q, J = 6.4 Hz), 3.08 (1, ddd, J = 11.4, 6.6, 2.3 Hz), 2.75–2.65 (1, m), 1.96 and 2.0–1.85 (4, s and m), 1.8–1.55 (6, m), 1.44 (3, s), 1.4–0.85 and 1.10 (10, m and d, J = 6.4 Hz); ^{13}C NMR δ 170.11, 82.46, 80.83,

77.58, 42.51, 35.00, 29.33, 28.49, 26.50 (2 superimposed signals?), 26.16, 26.06, 22.32, 16.42, 14.71. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.76; H, 10.20. Stereoisomer of **21** (14 mg, 6.6%; >87% of a single isomer, by CGC): R_f (10% EtOAc/hexane) 0.28; IR 2985, 2935, 2860, 1734, 1455, 1370, 1258, 1115 cm^{-1}; ^1H NMR δ 4.13 (1, q, J = 6.7 Hz), 3.35–3.25 (1, m), 2.3–2.15 (1, m), 2.02 (3, s), 2.0–1.5 (8, m), 1.40 (3, s), 1.45–1.1 and 1.1 (7, m and d, J = 6.4 Hz), 1.0–0.85 (2, m). **2-(1-Acetoxyethyl)-5-cyclohexyl-2-methyltetrahydrofuran (22**; 13.5 mg, 6.3%; >85% of a single isomer by CGC; possibly the (2*R**,5*R**,1′*S**) isomer, based on mechanistic considerations): R_f (10% EtOAc/hexane) 0.35; IR 2980, 2935, 2860, 1742, 1453, 1374, 1247, 1100, 1057 cm^{-1}; ^1H NMR δ 4.88 (1, q, J = 6.4 Hz), 3.7–3.55 (1, m), 2.04 (3, s), 1.95–1.8 (2, m), 1.8–1.55 (6, m), 1.45–1.1 with δ 1.20 and 1.15 (10, m with d, J = 6.4 Hz, and s), 1.05–0.8 (3, m). A fraction (13 mg, 6.1%) containing a mixture of various isomers of the above compounds (showing by CGC a ratio of 65:35 in favor of tetrahydrofuran isomers) was also obtained. **6-Cyclohexyl-2,3-dimethyl-4,5(6*H*)-dihydropyran (23**; 3 mg, <1.8%): see supplementary material for characterization.

Acetoxythallation of 1-Cyclohexyl-4-methylpent-4-en-1-ol (24). The general procedure was followed, using thallium(III) acetate sesquihydrate (350 mg, 0.86 mmol), the substrate **24** (144 mg, 0.79 mmol), glacial acetic acid (2.5 mL), and a reaction time of 30 min. Workup gave the crude product mixture (183 mg) which was purified by chromatography (hexane–ethyl acetate mixtures). Three major products were fully characterized, and two others were tentatively identified. **(2*R**,5*S**)-5-Acetoxy-2-cyclohexyl-5-methyltetrahydropyran (25a**; 67 mg, 35%) was obtained as a colorless liquid: R_f (10% EtOAc/hexane) 0.53; IR 2930, 2860, 1740, 1455, 1370, 1250, 1217, 1169, 1153, 1025, 859 cm^{-1}; ^1H NMR δ 3.92 (1, dd, J = 10.8, 2.6 Hz), 3.34 (1, d, J = 10.8 Hz), 3.02 (1, ddd, J = 10.9, 6.5, 2.4 Hz), 2.45–2.3 (1, m), 1.97 and 1.95–1.8 (4, s and m), 1.8–1.55 and 1.58 (9, m and s), 1.55–0.8 (7, m); ^{13}C NMR δ 170.04, 82.36, 78.30, 74.08, 42.32, 34.46, 29.09, 28.68, 26.48, 26.17, 26.04, 25.87, 22.15, 20.69. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.15; H, 10.09. **(2*R**,5*S**)-5-Chloro-2-cyclohexyl-5-methyltetrahydropyran (25b**; 32 mg, 19%) was obtained as a colorless liquid: R_f (10% EtOAc/hexane) 0.85; IR 2990, 2935, 2865, 1453, 1085 cm^{-1}; ^1H NMR δ 3.77 (1, dd, J = 10.9, 2.7 Hz), 3.53 (1, d, J = 10.9 Hz), 3.05 (1, ddd, J = 10.7, 6.5, 3.0 Hz), 2.2–1.8 (2, m), 1.8–1.45 and 1.65 (8, m and s), 1.45–0.85 (6, m); ^{13}C NMR δ 82.25, 77.46, 65.74, 42.43, 40.02, 29.04, 28.67, 27.15, 26.48, 26.37, 26.18, 26.05. Anal. Calcd for $C_{12}H_{21}ClO$: C, 66.50; H, 9.77; Cl, 16.36. Found: C, 66.56; H, 9.74; Cl, 16.50.

(2*R,5*S**)-2-Cyclohexyl-5-methyltetrahydropyran-5-ol (25c**; 8 mg, 5%), obtained as a colorless solid: mp 78–80 °C; its ^1H NMR spectrum was identical with that of a sample prepared by hydrolysis of acetate **25a** with potassium carbonate in methanol; R_f (10% EtOAc/hexane) 0.10; IR 3290 (br), 2930, 2855, 1451, 1130, 1094 cm^{-1}; ^1H NMR δ 3.58 (1, dd, J = 10.7, 2.6 Hz), 3.20 (1, d, J = 10.7 Hz), 2.99 (1, ddd, J = 10.3, 6.6, 2.3), 1.95–1.5 (7, m), 1.5–1.1 and 1.31 (9, m and s), 1.1–0.8 (3, m); HRMS: Calcd. for $C_{12}H_{22}O_2$: 198.1620. Found: 198.1623. **(2*R**,5*R**)-5-Acetoxy-2-cyclohexyl-5-methyltetrahydropyran (25d**; 21 mg, 11%) was obtained as a colorless liquid: R_f (10% EtOAc/hexane) 0.46; IR 2930, 2860, 1740, 1453, 1370, 1250, 1200, 1185, 1105, 1024 cm^{-1}; ^1H NMR δ 4.26 (1, dd, J = 12.3, 3.0 Hz), 3.15 (1, d, J = 12.3 Hz), 2.97 (1, dd, J = 12.8, 6.7 Hz with further fine coupling), 2.55–2.4 (1, m), 2.04 (3, s), 2.0–1.85 (1, m), 1.75–1.6 (4, m), 1.55–0.8 and 1.36 (12, m and s); ^{13}C NMR δ 170.70, 81.92, 77.75, 73.86, 42.64, 33.76, 29.22, 28.57, 26.55, 26.21, 26.05, 24.01, 22.35, 21.60. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.14; H, 9.99. **2-(Acetoxymethyl)-5-cyclohexyl-2-methyltetrahydrofuran** (55:45 mixture of diastereomers by CGC) (13.5 mg, 7%) was obtained as a colorless liquid: R_f (10% EtOAc/hexane) 0.42; IR 2980, 2935, 2865, 1748, 1455, 1375, 1240, 1046 cm^{-1}; ^1H NMR δ 3.98 and 3.97 (1.5, A of AB system, J = 11.1 Hz, superimposed on s), 3.87 (0.5, B of AB system, J = 11.0 Hz), 3.75–3.65 (1, m), 2.09 (<3, s), 1.95–1.8 (3, m), 1.8–1.6 (5, m), 1.55–1.1 and 1.24, 1.22 (8, m and 2 s), 1.1–0.8 (2, m); ^{13}C NMR δ 171.12, 171.05, 84.37, 83.82, 80.46, 80.39, 69.88, 69.58, 42.91, 42.84, 34.73, 34.44, 33.76, 29.87, 29.23, 28.84, 28.53, 28.48, 28.41, 26.58, 26.22, 26.05, 24.64, 24.11, 24.02, 20.99, 14.10. HRMS Calcd for $C_{14}H_{24}O_3$: 240.1725. Found: 240.1730.

(2*R,5*S**)-2-[(1*S**)-1-Acetoxy-1,5-dimethylhex-4-en-1-yl]-5-methyltetrahydrofuran (37a).** The general procedure was followed, using thallium(III) acetate sesquihydrate (280 mg, 0.69 mmol), 6,10-dimethylundeca-5(*E*),9-dien-2-ol[28] (128 mg, 0.65 mmol), glacial acetic acid (2 mL), and a reaction time of 1 h. After this time a further portion of the thallium salt (140 mg, 0.34 mmol) was added, and stirring was continued for another 30 min. Brine (5 mL) and water (3 mL) were added, followed by sufficient solid K_2CO_3 to neutralize the acetic acid. Further workup according to the general procedure gave the crude product mixture (152 mg). Chromatography (4% EtOAc/hexane) yielded some recovered starting material (12 mg, 9%), several impure and unidentified minor components (38.5 mg), the desired tetrahydrofuran **37a** (101.5 mg, 61%) as a colorless liquid, and a minor component tentatively identified as **(2*R**,3*S**,6*S**)-3-acetoxy-2,6-dimethyl-2-(4-methylpent-3-en-1-yl)tetrahydropyran** (3 mg, 1.8%). Tetrahydrofuran **37**: CGC showed the compound to be >99% isomerically pure; R_f (10% EtOAc/hexane) 0.41; IR 2980, 2935, 2850, 1735, 1450, 1370, 1256, 1090, 1023, 915, 738 cm^{-1}; ^1H NMR δ 5.10 (1, t, J = 6.9 Hz with further fine coupling), 4.40 (1, dd, J = 8.4, 6.9 Hz), 4.15–4.0 (1, m), 2.2–1.7 and 1.98 (11, m and s), 1.67 (3, d, J = 0.6 Hz), 1.60 (3, s), 1.42 (3, s), 1.21 (3, d, J = 6.0 Hz); ^{13}C NMR δ 170.10, 131.35, 124.01, 85.79, 81.27, 76.10, 35.29, 34.03, 27.03, 25.57, 22.19 (2 superimposed peaks?), 21.01, 19.37, 17.44. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.91; H, 10.22. Tetrahydropyran: R_f (10% EtOAc/hexane) 0.51; IR 2980, 2940, 2880, 1746, 1374, 1240 cm^{-1}; ^1H NMR δ 5.08 (1, t, J = 7.1 Hz with further fine coupling), 4.69 (1, dd, J = 11.1, 4.9 Hz), 3.75–3.6 (1, m), 2.2–1.8 and 2.03 (6, m and s), 1.75–1.6 with 1.66 and 1.59 (7, m and 2 s), 1.5–1.2 and 1.21 (7, m and s), 1.10 (3, d, J = 6.1 Hz); ^{13}C NMR δ 170.35, 131.22, 124.71, 74.54, 73.81, 65.57, 40.53, 32.84, 25.70, 24.95, 21.81, 21.30, 21.07, 17.62, 16.40. HRMS Calcd for $C_{15}H_{26}O_3$: 254.1882. Found: 254.1878.

(1*R,3*S**,4*R**,6*S**)-4-Acetoxy-3-[((2,4-dichlorobenzoyl)oxy)methyl]-3-methyl-2-oxabicyclo[4.4.0]decane (40c) and (1*R**,6*S**,8*S**)-8-[1-Acetoxy-2-((2,4-dichlorobenzoyl)oxy)-1-methylethyl]-7-oxabicyclo[4.3.0]nonane (41c). Acetoxythallation of 4-[(1*R**,2*S**)-2-Hydroxycyclohexyl]-2-methylbut-2(*E*)-enyl 2,4-Dichlorobenzoate (39c).** The general procedure was followed, using thallium(III) acetate sesquihydrate (265 mg, 0.65 mmol), the dichlorobenzoate **39c** (176 mg, 0.49 mmol), glacial acetic acid (2.5 mL), and a reaction time of 21.5 h. Workup gave the crude product mixture as a viscous oil (180 mg). Chromatography (hexane–ethyl acetate mixtures) yielded, as the major component, an inseparable mixture of the 6,6-bicyclic ether **40c** and the 6,5-isomer **41c** (89 mg, 43%; 82:18 mixture by ^1H NMR) as a colorless liquid; R_f (10% EtOAc/hexane) 0.54; IR 3010, 2870, 1732, 1588, 1377, 1294, 1247, 1132, 1108, 1054 cm^{-1}; ^1H NMR δ 7.86 (1, d, J = 8.4 Hz), 7.46 (1, d, J = 2.0 Hz), 7.31 (1, dd, J = 8.5, 1.7 Hz), 5.05 (0.82, dd, J = 11.0, 4.7 Hz), 4.79 and 4.75 (0.36, AB system, J = 11.8), 4.50 (0.18, dd, J = 9.3, 6.3 Hz), 4.22 (1.64, s), 3.3–3.1 (1, m), 2.1–1.9 and 2.01 (4, m and s), 1.9–1.75 (2, m), 1.75–1.6 (2, m), 1.55–0.9 and 1.32 (9, m and s); ^{13}C NMR, major isomer, δ 169.93, 164.47, 138.31, 134.88, 132.66, 130.80, 128.11, 14.10, minor isomer, δ 170.01, 164.17, 138.13, 134.78, 132.51, 130.91, 128.27, 126.89, 16.92, other peaks, δ 84.20, 83.35, 79.03, 76.14, 74.64, 74.34, 70.23, 69.22, 66.42, 45.49, 41.26, 32.11, 31.51, 30.95, 28.81, 25.66, 25.41, 25.25, 25.05, 24.82, 24.31, 24.15, 22.06, 21.10. Anal. Calcd for $C_{20}H_{24}Cl_2O_3$: C, 57.84; H, 5.82; Cl, 17.07. Found: C, 57.95; H, 6.08; Cl, 16.69.

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Registry No. 5a, 96481-91-3; **6a**, 96481-92-4; **6b**, 96481-93-5; **6c**, 96481-94-6; **6d**, 96481-95-7; **6e**, 96481-96-8; **8**, 89065-48-5; **9**, 89065-50-9; **10**, 96481-97-9; **11a**, 96481-98-0; **11b**, 96482-02-9; **12**, 96481-99-1; **13**, 96482-00-7; **15**, 96482-01-8; **16**, 96502-11-3; **17**, 96482-03-0; **18**, 96482-04-1; (*E*)-**19**, 96482-05-2; (*Z*)-**19**, 96482-19-8; **21**, 96482-06-3; **22**, 96482-07-4; **23**, 96482-08-5; **24**, 96482-09-6; **25a**, 96482-10-9; **25b**, 96482-11-0; **25c**, 96482-12-1; **25d**, 96482-13-2; **37a**, 96482-16-5; **39c**, 96502-30-6; **40c**, 96482-18-7; **41c**, 96502-31-7; $CH_3CH(OH)(CH_2)_2CH{=}C(CH_3)(CH_2)_2C{=}C(CH_3)_2$, 7733-91-7; $Tl(OAc)_3$, 2570-63-0; $Tl(NO_2)_3$, 13746-98-0; 2-(acetoxymethyl)-5-

cyclohexyl-2-methyltetrahydrofuran (isomer 1), 96482-14-3; 2-(acetoxymethyl)-5-cyclohexyl-2-methyltetrahydrofuran (isomer 2), 96482-15-4; (2*R**,3*S**,6*S**)-3-acetoxy-2,6-dimethyl-2-(4-methylpent-3-en-1-yl)tetrahydropyran, 96482-17-6.

Supplementary Material Available: Experimental procedures, spectral data, and characterization of compounds not described in the Experimental Section (33 pages). Ordering information is given on any current masthead page.

Iminium Ion Mediated Cyclizations of 4-Aryl-1,4-dihydropyridines. Bridging with Acetals, Carbonyls, and Thiocarbonyls

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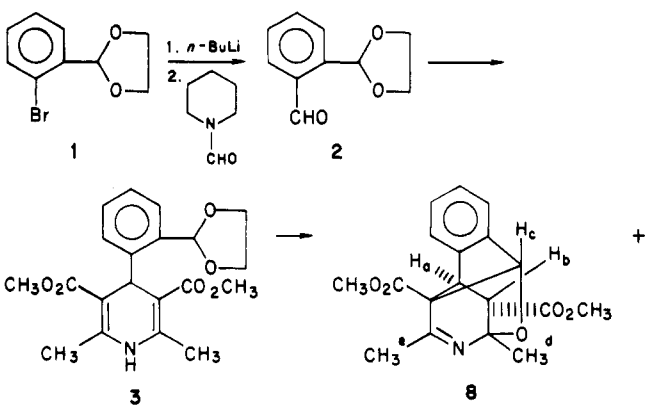
The preparation of new aldehyde and acetal derivatives of 4-aryl-1,4-dihydropyridines has been carried out. Treatment of these compounds under acid conditions affords novel caged molecules derived from sequential intramolecular addition reactions. This process involves initial nucleophilic attack by the dihydropyridine on the acetal function, followed by closure of the resultant hydroxy moiety on an electrophilic iminium species. These molecules represent novel, conformationally restricted analogues of calcium entry blocking agents.

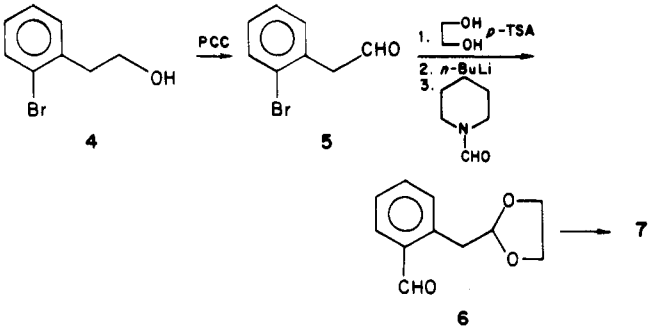
There is an abundant, fruitful literature relating to the chemistry of the dihydropyridines.[1,2] Members of this structural class have served as efficient intermediates in the synthesis of alkaloids such as yohimbine,[3,4] ajmaline,[5] sesbanine,[6] and morphine,[7] as well as in synthetic routes to substituted pyridines.[8,9]

The utility of 4-aryl-1,4-dihydropyridines as therapeutic agents in cardiovascular disorders[10,11] has also fostered interest in the chemistry[12-17] of these compounds. One intriguing question that remains to be answered for this potent class of calcium channel blockers[18] pertains to the geometrical requirements at the dihydropyridine receptor.[19-21] Only recently have compounds[22-24] appeared that, due to conformational restriction, will test these requirements. We wish to report the synthesis of novel, conformationally rigid dihydropyridine analogues prepared via sequential intramolecular acid-catalyzed addition processes.

Scheme I



Scheme II



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