# Synthesis and Molecular Structure of Belted Spirocyclic Tetrahydrofurans, a New Class of Preorganized Hosts for Cations

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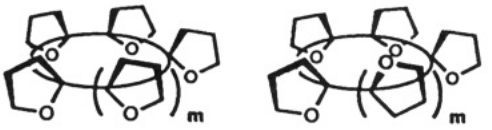
The preparation and binding properties of spirocyclic tetrahydrofurans **7–11** are described. The condensation of cyclopentanone with 5-lithio-2,3-dihydrofuran (**12**) provided an alcohol which readily rearranged to ketone **14** under acidic conditions. "Capping" of the carbonyl group in **14** so as to generate a second spiro tetrahydrofuran subunit gave rise to **7** and **8**. Starting with cyclobutanone, 2-fold ring expansion involving **12** provided the key reactions leading to **22** and **23**, which were "capped" as before. Crystal structure data are available for **9**, **11**, and **22**. In addition, the variable-temperature NMR behavior of **7** and **10** was quantified by means of 2-D measurements. A detailed analysis is presented that shows the gauche effect to be of major importance in dictating the major conformation adopted by these ionophores. The binding properties of **7–11** have been assayed. Considerable variation was found, the efficiency being critically dependent upon the number of oxygen atoms, the relative stereochemistry of the C–O bonds, and the relative ease of conformational readjustment necessary to achieve proper organization around the oxophilic metal ion.

Following recognition of the excellent cation-binding properties of coronands and cryptands,[2] considerable effort has been devoted to the design of nonmacrocyclic host molecules having ligating oxygens suitably preorganized for effective coordination. The conformational freedom routinely available to these linear analogues is usually antithetical to strong metal ion binding. However, through proper utilization of substitution and stereochemistry, it has been proven possible to reduce the populations of conformations unfavorable to chelation and produce those spatial arrangements that allow for efficient multipoint binding interactions. Interesting examples of structurally organized polyethers have recently been developed by Grubbs (helical tetrahydrofuran backbone)[3] and by Still (2,6-linked tetrahydropyran subunits).[4] Consequently, interest in molecules containing multiple combinations of these building blocks remains high.[5]

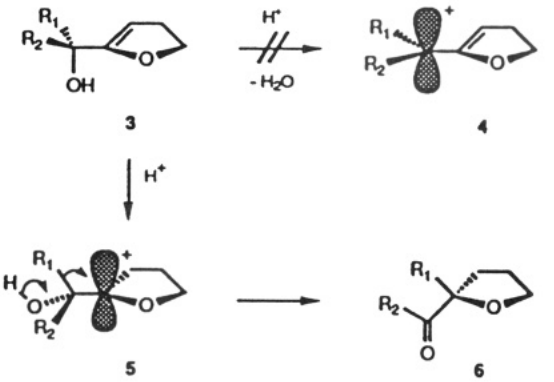
Notwithstanding, polyspirocyclic ionophores typified by structures **1** and **2** have not been accorded attention. The



**1** **2**

limiting conformational restrictions introduced by the central belt are likely to be linked directly to the energy required to cluster the oxygens properly about the guest ion during complexation. Effective binding capabilities could consequently be varied as a function of *m* for specific needs. Knowledge of the degree to which **2** and more extensively epimerized stereoisomeric arrays exhibit modulated levels of cation coordination would infuse valuable insight into several facets of rational synthetic design.

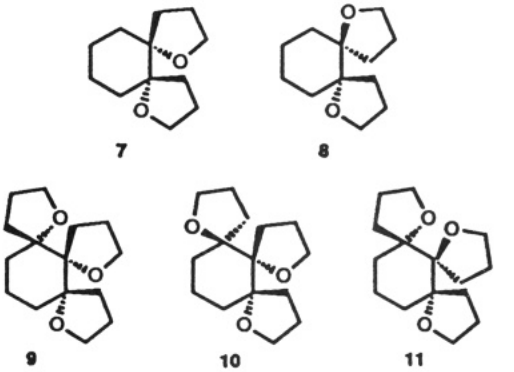
Our interest in a program aimed at developing a preparative route to molecules of this class stems from earlier work dealing with the response of alcohols of general formula **3** to acid catalysis. Although capable of direct $S_N1$ ionization to allylic cations **4**, such alcohols prefer to undergo kinetically controlled conversion to oxonium ions **5**.[6]



**3** **4** **5** **6**

A pinacol-like Wagner–Meerwein shift ensues to furnish ketones **6**. When $R_1$ and $R_2$ are mutually linked, the **3** → **6** process constitutes a net ring expansion with formation of spirocyclic tetrahydrofuranyl ketones.[6,7]

If **6** were condensed with 5-lithio-2,3-dihydrofuran and resubjected to acid-catalyzed rearrangement, a reiterative process would be available for the rapid construction of molecules having multiple ether binding sites. Herein we examine the effectiveness with which the ligand backbones defined by **7–11** can be elaborated in this fashion. Asso-



**7** **8** **9** **10** **11**

(1) Author to whom inquiries regarding the X-ray crystallographic analyses should be directed.

(2) Reviews: (a) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009. (b) Weber, E.; Vogtle, F. *Top. Curr. Chem.* **1981**, *98*, 1. (c) Vogtle, F. *Kem.-Kemi* **1989**, *16*, 796.

(3) Novak, B. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1988**, *110*, 960.

(4) (a) Iimori, T.; Still, W. C.; Rheingold, A. L.; Staley, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 3439. (b) Erickson, S. D.; Still, W. C. *Tetrahedron Lett.* **1990**, *31*, 4253.

(5) (a) Timko, J. M.; Moore, S. S.; Walba, D. M.; Hiberty, P. C.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 4207. (b) Kobuke, Y.; Hanji, K.; Horiguchi, K. L.; Asada, M.; Nakayama, Y.; Furukawa, J. *Ibid.* **1976**, *98*, 7414. (c) Schultz, W. J.; Etter, M. C.; Pocius, A. V.; Smith, S. *Ibid.* **1980**, *102*, 7981. (d) Gange, D.; Magnus, P.; Bass, L.; Arnold, E. V.; Clardy, J. *Ibid.* **1980**, *102*, 2134.

(6) Paquette, L. A.; Lawhorn, D. E.; Teleha, C. A. *Heterocycles* **1990**, *30*, 765.

(7) Preliminary communication: Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073.

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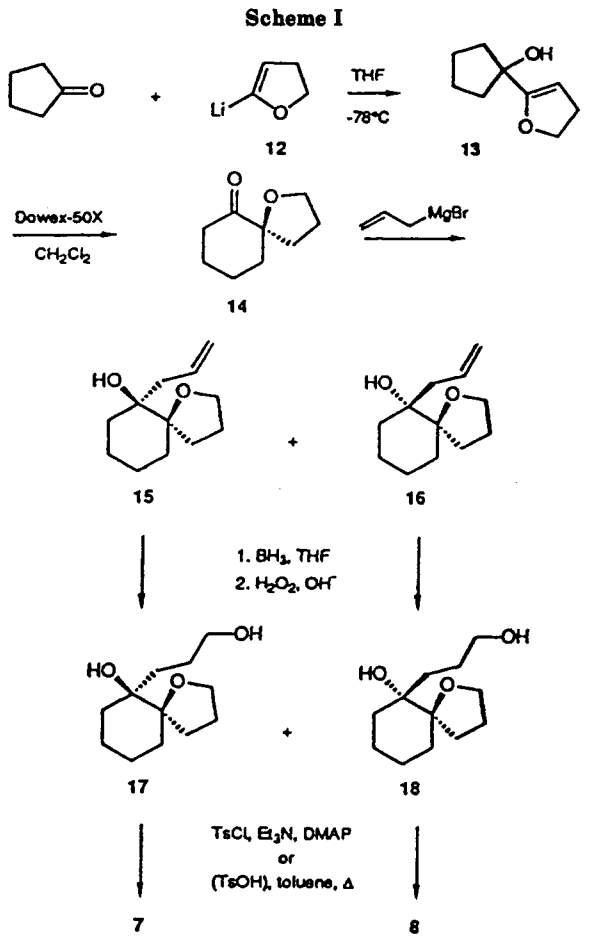
**Scheme I**




ciated stereochemical issues, migratory aptitudes, and limitations set by ring size are analyzed where possible. A capping process that conveniently transforms the carbonyl group in **6** into yet another spirotetrahydrofuranyl moiety has proven essential to the acquisition of **7–11**.

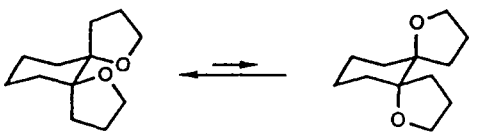
The solid-state conformational features of the crystalline members of this group have been determined by crystallographic methods. Additionally, the cation-binding properties of these preorganized ionophoric ethers have been assayed.

## Results

**The Dispiro Examples.** Alcohol **13** was available by 1,2-addition of **12**[8] to cyclopentanone according to precedent.[6] Stirring **13** with methanol-free[9] Dowex 50X resin in dichloromethane at room temperature resulted in efficient isomerization to **14** (96%). Addition of allylmagnesium bromide to **14** afforded the homoallylic alcohols **15** and **16** in a ratio of 5:1 (Scheme I). The major constituent was identified as the indicated axial diastereomer on the strength of its less polar nature[10,11] and ultimate conversion to the $C_s$ symmetric **7**. As a consequence, the α-alkoxy ketone is attacked stereoselectively from the equatorial direction in that conformer having the ether oxygen oriented equatorially. Although the axial preference for 2-methoxycyclohexanones is well established,[12,13] the need for oxygen to serve as a stereocontrol element by coordinating to magnesium(II)[14] could increase its relative steric bulk sufficiently to influence the conformational equilibrium. The ground-state structure of **24**, as determined crystallographically, has direct relevance to these considerations (see below).


Diols **17** and **18**, obtained by hydroboration–oxidation of **15** and **16**, respectively, are the penultimate intermediates for acquisition of dispiro ethers **7** and **8**. Two ring closure routes were employed. In the first, the primary monotosylates were prepared and stereospecifically cyclized in situ.[15,16] The second involved heating either isomer with a catalytic quantity of *p*-toluenesulfonic acid in toluene. These acidic conditions do not place the stereochemical relationships inherent to these diols in total jeopardy, since the inductive effect of the C–O bond adjacent to the tertiary carbinol acts to inhibit otherwise anticipated $S_N1$ ionization. As a consequence, the associative $S_N$ process[11] is kinetically dominant and high levels of stereocontrol are realized (15:1 for **17** and 16:1 for **18** in favor of retention).

The $C_2$-symmetric trans isomer **8** is characterized by a six-line carbon spectrum and a temperature-invariant $^1H$ NMR spectrum. This lack of dynamic conformational behavior is taken as a reflection of the significantly greater thermodynamic stability of conformer **A** relative to **B**. Evidently, the steric and electronic advantages associated with equatorial orientation of both C–O bonds are sufficient to maximize the effective concentration of **A** at the expense of **B**. The more stable conformer projects the



A B

strongly electronegative oxygen atoms into a gauche orientation. This arrangement, previously recognized to be favored in 1,2-disubstituted ethanes[17] and *trans*-1,2-dialkoxycyclohexanes,[18] so positions the nonbonded electron pairs that stabilizing attractive forces now operate.[19]

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(9) Failure to remove methanol from the resin results in conventional addition of methanol to the double bond of the enol ether.

(10) (a) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447. (b) Fort, Y.; Feghouli, A.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* **1990**, *55*, 5911.

(11) (a) Paquette, L. A.; Negri, J. T. *J. Am. Chem. Soc.* **1991**, *113*, 5072. (b) Negri, J. T.; Paquette, L. A. *J. Am. Chem. Soc.* In press.

(12) (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. Y.; Morrison, C. A. *Conformational Analysis*; Interscience: New York, 1965; pp 460–469. (b) Lambert, J. B. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P., Ed.; VCH: Weinheim, 1989; Chapter 2.

(13) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 3466 and relevant references cited therein.

(14) Review: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(15) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.

(16) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. I* **1988**, 1669.

(17) (a) Phillips, L.; Wray, V. *J. Chem. Soc., Chem. Commun.* **1973**, 90. (b) Wolfe, S.; Rauk, A.; Tel, L. M.; Csizmadia, I. G. *J. Chem. Soc. B* **1971**, 136. (c) Wolfe, S.; Tel, L. M.; Csizmadia, I. G. *Can. J. Chem.* **1973**, *51*, 2423. (d) Wolfe, S.; Tel, L. M.; Haines, W. J.; Robb, M. A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1973**, *95*, 4863. (e) Whangbo, M.-H.; Wolfe, S. *Can. J. Chem.* **1976**, *54*, 949, 963. (f) Van-Catledge, F. A. *J. Am. Chem. Soc.* **1974**, *96*, 5693.

(18) (a) Zefirov, N. S.; Gurvich, L. G.; Shashkov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211. (b) Zefirov, S. N.; Samoshin, V. V.; Subbotin, O. A.; Baranenkov, V. I.; Wolfe, S. *Ibid.* **1978**, *34*, 2953. (c) Zefirov, N. S.; Samoshin, V. V.; Palyulin, V. A. *Zh. Org. Khim.* **1983**, *19*, 1888.

(19) Reviews: (a) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102. (b) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 3193.

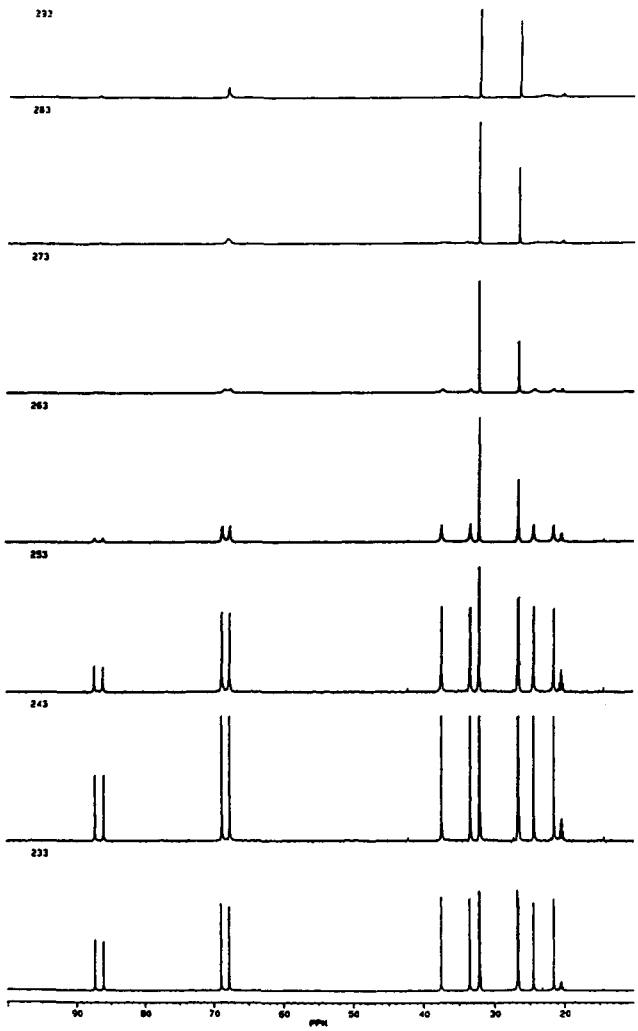


**Figure 1.** Variable-temperature 125-MHz $^{13}C$ NMR spectra of 7 in toluene-$d_8$ solution.

At the other extreme, cis isomer 7 is subject to ready conformational equilibration. The temperature dependence of its $^{13}C$ NMR spectrum in toluene-$d_8$ solution over the temperature range 233–303 K (Figure 1) clearly illustrates this dynamic behavior. Noteworthily, the pair of quaternary carbons that appear in the 85–90-ppm region are uniquely different. The sufficiently slow rates of their mutual exchange from 228 to 248 K conveniently permitted the acquisition of kinetic data (Figure 2).[20] An Eyring plot derived from measurements made at eight temperatures within these limits defined $\Delta G^{\ddagger}_{298}$, $\Delta H^{\ddagger}_{298}$, and $\Delta S^{\ddagger}$ to be 13.45 (±0.11) kcal mol$^{-1}$, 13.63 (±0.5) kcal mol$^{-1}$, and 0.8 (±2.0) eu, respectively. The rather large error limits on the entropy value stem from the relatively narrow temperature range available.[21]

The occurrence of the two sharp sets of signals under slow exchange conditions below 253 K is indicative of the fact that both conformers are equally populated at these lower temperatures. More rapid interconversion between C and D symmetrizes 7 and six lines are clearly apparent.

**The Trispiro Triad.** As shown in Scheme II, the synthesis of 9–11 began with the reaction of cyclobutanone with 12. Carbinol 19 then underwent smooth acid-catalyzed ring expansion to furnish 20 in 95% yield. Repetition

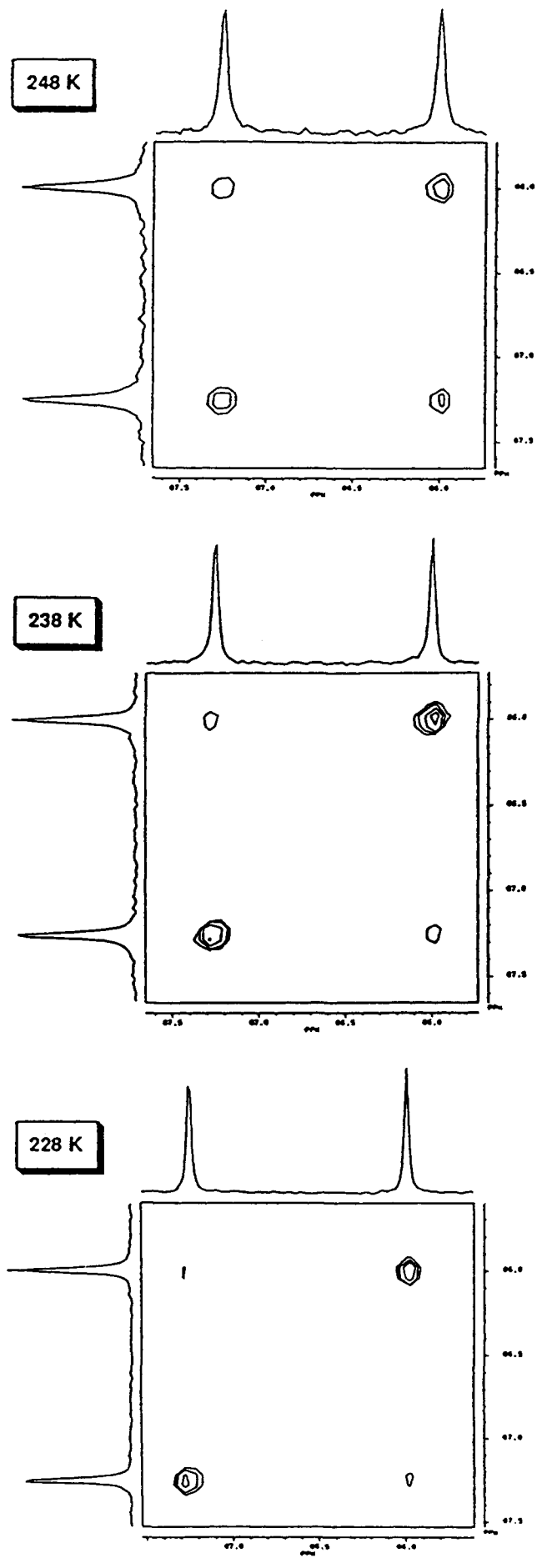
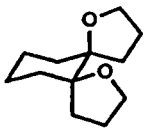


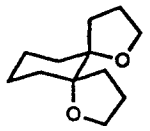

**Figure 2.** Contour plots of the 2-D EXSY spectra of 7 recorded in toluene-$d_8$ solution at the three temperatures indicated.

(20) For an earlier adoption of this technique, see: Paquette, L. A.; Wang, T.-Z.; Luo, J.; Cottrell, C. E.; Clough, A. E.; Anderson, L. B. *J. Am. Chem. Soc.* **1990**, *112*, 239.

(21) Wiberg, K. B. *Physical Organic Chemistry*; John Wiley and Sons: New York, 1964; p 379.



C

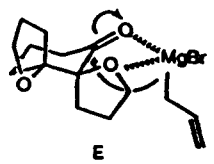


D

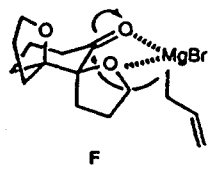
of the two-step sequence on **20** gave rise to the desired ketones **22** and **23** in equal amounts. The intermediate alcohol **21** was formed as a 1:1 mixture of diastereomers ($^1$H NMR analysis), despite the presence of a customarily powerful stereocontrol element for directing the reaction course.[22] This lack of stereochemical discrimination is presumably due to the less effective chelating abilities of $Li^+$ relative to $Mg^{2+}$ in such circumstances.[14] Since the individual isomers of **21** proved too sensitive for chromatography, it was not possible to effect their separation for the purpose of assessing ring enlargement stereoselectivity. Nonetheless, it is clear that both diastereomers undergo this transformation with exclusive migration of the more highly substituted $\alpha$-carbon.

Following the efficient separation of ketone **22** from **23**, the more polar, crystalline isomer **22** was identified by X-ray crystallography. The ORTEP diagram (Figure 3) reveals several interesting conformational features of this molecule. Although the cyclohexanone ring adopts a well-defined chairlike arrangement (see side view), the C–O bond flanking the carbonyl group is projected equatorially. This orientational preference does not conform to expectations based on the minimization of electrostatic interactions involving the carbonyl functionality and adjacent polar bond.[12,13] It should be recognized, however, that the axial conformer of 2-methoxycyclohexanone is favored only to the extent of 63%.[23] In **22**, this small effect is clearly overridden. The top-view projection of **22** provides for an unobstructed perspective of the extent to which the pair of C–O bonds to the quaternary carbons adopt a gauche relationship. The benefits of this vicinal interaction outweigh as well the normal preference of 1-oxaspiro[4.5]decanes to preferentially adopt that conformation having the oxygen disposed axially.[24] To all appearances then,[25] the relative importance of the "gauche effect"[19] should not be underestimated.

With **22** and **23** in hand, it proved an easy matter to "cap" their carbonyl groups as previously accomplished with **14**. The need to involve allylmagnesium bromide in the first step provided an opportunity to compare the chelation-controlled response of these diastereomers to the 1,2-addition. The 6:1 preference for nucleophilic attack on **23** as in **E** compares favorably to the product distribution earlier observed for **14**. A more equitable (3:2) ratio

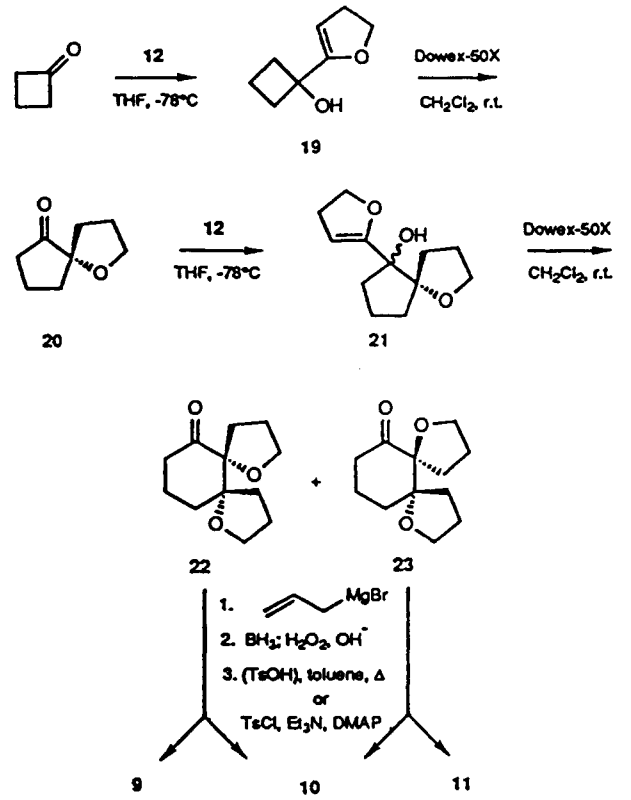



E




F

Scheme II




of epimers was seen with ketone **22**. Since the arrangement in **F** does not appear to be disadvantaged relative to **E**, it is clear that additional factors not explicitly considered here impact on the product composition. Precoordination to the more remote axial oxygen in **F** could be responsible for the heightened levels of syn-allylation observed.

The diol precursors to **9**–**11** were also subjected to acid-catalyzed cyclization in refluxing toluene as before. The intramolecular $S_N2$ mechanism was heavily dominant in all four examples, retention of stereochemistry being manifested in excess of 95% in every instance.

Ionophores **9** and **11** proved to be nicely crystalline compounds amenable to X-ray analysis. The solid-state structural information so obtained has proven to be highly informative. As seen in Figure 4, the three sequential C–O bonds in **9** adopt an equatorial–axial–equatorial arrangement. In **11**, the alignment is all-equatorial (Figure 5). The notable feature of these structures is that both species unambiguously take on that conformation possessing the maximum number of gauche interactions between the adjacent polar bonds. Since neither **9** nor **11** shows dynamic NMR behavior over a substantial temperature range, it is reasonable to conclude that the same geometrical features are equally dominant in solution.

The oily trispiro isomer **10** strands in contrast to its two diastereomers in being a conformationally fluxional molecule. Variable-temperature $^{13}$C NMR (125 MHz) studies, performed on toluene-$d_8$ solutions at 238–258 K, were particularly diagnostic. 2-D correlation experiments identified signals corresponding to the same carbon in each of two "frozen" conformers, whose distribution was approximately 80:20 at the lowest temperature examined. Use of this technique (Figure 6) has made possible quantitative determination of the rates of interconversion between the major and minor conformers at various temperatures. The kinetic analysis was fitted to the following equilibrium, with $k_1$ being the faster rate constant:

(22) (a) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) Still, W. C.; Schneider, J. A. *Ibid.* **1980**, *21*, 1035. (c) Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 6129. (d) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130.

(23) Consult ref 12b, page 56.

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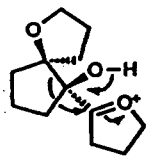
(25) Crystal packing forces could play a role in determining the preferred conformation of **22** in the solid state. However, because the factor that is universally shared in common by **9**, **11**, and **22** is strict adaptation to gauche C–O bond relationships, it seems reasonable to ascribe singular importance to this effect.

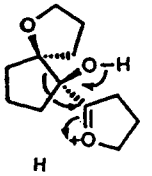
$$\text{10 (minor)} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{10 (major)}$$

The relevant $\Delta G^{\ddagger}_{298}$ values for the forward (14.48 ± 0.22 kcal mol$^{-1}$) and reverse reactions (15.01 ± 0.23 kcal mol$^{-1}$) were obtained from a standard Eyring plot.

**Ring Expansion Stereoselectivity.** Associated with the acid-catalyzed ring expansion of **21** and related carbinols are two stereochemical concerns. Does migration of the quaternary carbon occur with retention of stereochemistry or does formation of the second oxonium ion develop to such a pronounced level that "memory" is lost? In addition, since the protonated dihydrofuran moiety is $\sigma$-bonded to the carbinol carbon, the possibility for free rotation about this interconnective bond exists. The situation is illustrated in structures **G** and **H**. Is a kinetic preference to be expected? If so, in which direction and for what reason(s)?



G



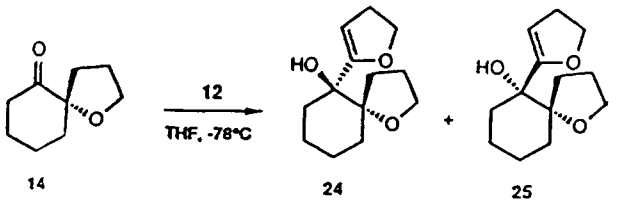
H

Since the diastereomeric alcohols **21** were not amenable to separation, an extension of this process was briefly examined. Addition of **12** to **14** resulted in formation of a 1.5:1 mixture of **24** and **25** (Scheme III). On standing, high quality crystals of **24** slowly deposited from the colorless oily mixture. X-ray analysis established the relative configurations of the stereogenic centers to be as depicted. Unfortunately, **24** did not undergo the intended ring expansion under a variety of conditions. Evidently, the formation of a seven-membered ring is not thermodynamically advantaged. Our observation agrees with a suggestion advanced by Trost in a related study[26] that an oxonium ion is too stabilized to drive bond migration in systems where ring strain increases.

Consequently, the stereochemical questions posed above need to be answered with molecular arrays more thermodynamically suited to the task. The ensuing paper[27] addresses one of these issues.

**Complexation Studies.** The binding properties of **7** and **9–11** were determined relative to lithium, sodium, and potassium picrate in water–deuteriochloroform mixtures by means of Cram's extraction method.[28a] The data obtained were quantified in terms of the extraction equilibrium constant ($K_{ex}$, M$^{-2}$),[28b] with values corrected for the slight water solubility of the hosts. Analogous measurements performed on 15-crown-5 and 12-crown-4 are included in Table I to allow for direct comparison.[29] The

**Scheme III**




14 24 25

**Table I. Extraction Equilibrium Constant $K_{ex}$ (M$^{-2}$ in $CDCl_3$ at 20 °C)[a]**

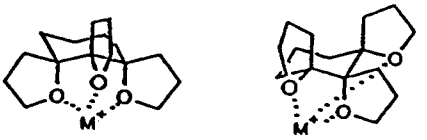
$$[M^+]_{eq} + [Pic^-]_{eq} + [host]_{org} \overset{K_{ex}}{\rightleftharpoons} [M^+\,Pic^-\,host]_{org}$$

| | log $K_{ex}$ | | |
|---|---|---|---|
| compd | $Li^+$ | $Na^+$ | $K^+$ |
| 15-crown-5 | 2.29 | 4.03 | 3.49 |
| | 2.34 | 3.98 | 3.46 |
| 12-crown-4 | 2.11 | 2.20 | 2.33 |
| | 2.14 | 2.27 | 2.33 |
| **9** | 2.04 | 2.01 | 2.17 |
| | 2.08 | 1.94 | 1.96 |
| **11** | 1.91 | 1.94 | 2.04 |
| | 1.93 | 1.91 | 1.97 |
| **10** | 1.45 | 1.53 | 2.16 |
| | 1.20 | 1.53 | 1.96 |
| **7** | 1.08 | 1.25 | 1.71 |
| | 1.02 | 1.20 | 1.75 |

[a] In the absence of more definitive information, the stoichiometry of complexation is assumed to be 1:1. To the extent that deviations from this ratio are occurring, the validity of these data is diminished.

$K_{ex}$ values realized, although modest in an absolute sense, are seen to be quite respectable for the limited number of oxygen atoms available for complexation to these systems.

As expected, the greatest coordinative ability resides in the syn-syn triether **9**, whose array of heteroatoms are notably well-disposed for the lithium ion. The relevant $K_{ex}$ closely approaches that for 12-crown-4 versus $K^+$, despite a 25% reduction in the number of potential binding sites. It is not known, however, whether the 1,3-diaxial (**I**) or 1,3-diequatorial conformation (**J**) is favored.



I J

Comparison of the data for **10** and **11** reveals that inversion of C–O bond stereochemistry is less detrimental to ion coordination ability when effected centrally rather than peripherally. This test indicates binding by a syn-1,3 oxygen array to be more efficacious than that by a syn-1,2 combination.

The chelating capacity of **7** is markedly lower than that of **10**. This finding suggests that the anti oxygen atom in **10** exerts a positive coordinative influence. The possibility is left open that the host:guest ratio in these systems may very well be greater than unity.

## Discussion

In the course of the present study, several considerations have been identified that bear on the feasibility of preparing cationic hosts and on their potential utility. Firstly,

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(28) (a) Koenig, K. E.; Lein, G. M.; Struckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553. (b) Inoue, Y.; Amano, F.; Okada, N.; Inada, H.; Ouchi, M.; Tai, A.; Hakushi, T.; Lin, Y.; Tong, L.-H. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1239.
(29) $K_{eq}$ values for 15-crown-5 have been reported previously.[28b] So far as 12-crown-4 is concerned, Still's values for the association constant[30] ($K_a$, M$^{-1}$; $K_a = K_{ex}/K_d$ (M$^+$ picrate, $CHCl_3/H_2O$))[28a] do not agree with those reported by others[31] who employed a slightly different technique. This is because the measurements involved are highly sensitive to small variations in many factors (solvent, temperature, concentration, method of mixing, etc.).
(30) Erickson, S. D.; Still, W. C. *Tetrahedron Lett.* **1990**, *30*, 4253.
(31) (a) Ouchi, M.; Inoue, Y.; Kanzaki, T.; Hakushi, T. *J. Org. Chem.* **1984**, *49*, 1408. (b) Lui, Y.; Inoue, Y.; Hakushi, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3044. In these publications, the % *E* values (extractabilities) are quoted as the percent of picrate extracted into the organic layer ($CH_2Cl_2$).

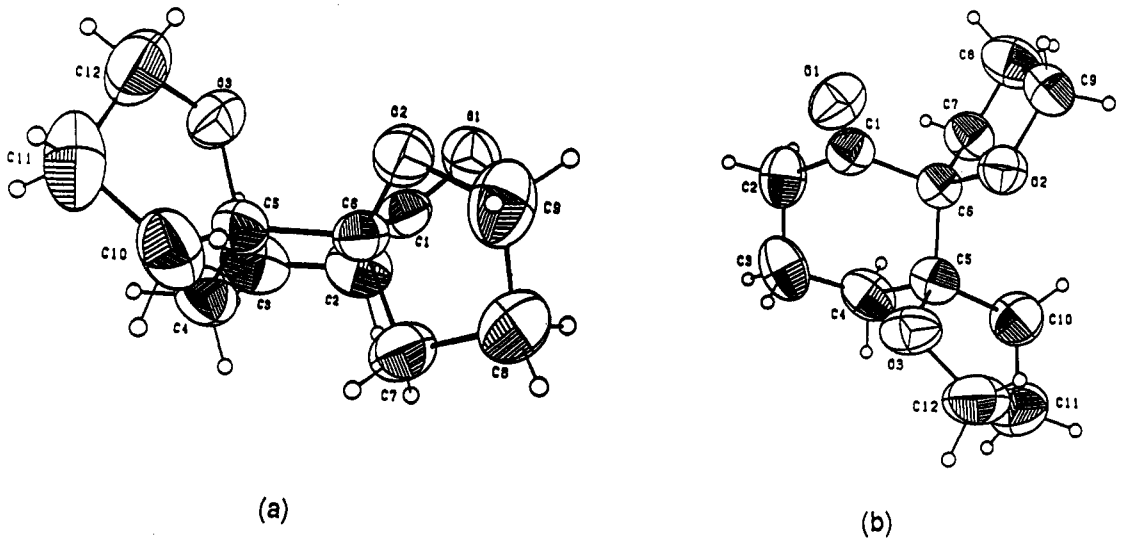


**Figure 3.** Computer-generated perspective drawing of **22** as determined by X-ray crystallography: (a) side view; (b) top view. The atom numbering is arbitrary.

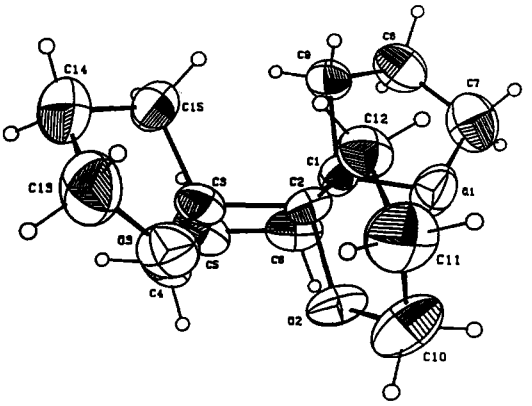


**Figure 4.** Computer-generated perspective drawing of **9** as determined by X-ray crystallography. The atom numbering is arbitrary.

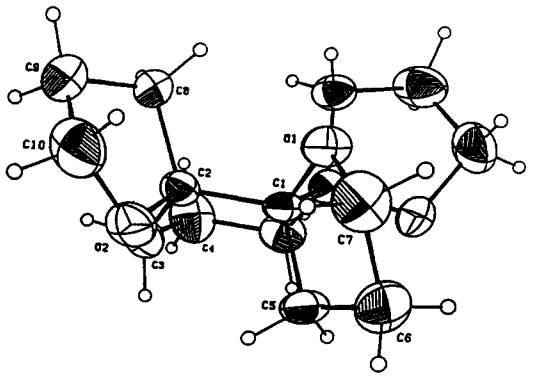


**Figure 5.** Computer-generated perspective drawing of **11** as determined by X-ray crystallography. The atom numbering is arbitrary.

the steric outcome of organometallic addition reactions to spirocyclic α-alkoxy ketones such as **14** and **20**, although guided by the ability of the reagent to chelate with the alkoxy substituent,[32] is not as highly stereoselective as often encountered in acyclic systems.[32,33] This dropoff in the level of stereocontrol is utilitarian when the "capping" sequence is being implemented because both spiro tetrahydrofuran end products are made available from a common precursor. Thus, the formation of **15** and **16** in a 5:1 ratio upon reaction of **14** with allylmagnesium bromide provides for quantities of the latter alcohol adequate to produce **8** concurrently with **7** on a reasonable scale.

Since the stereoselectivity of the ring expansion remains an open question, the lack of strong adherence to Cram's chelation rule may not be of any consequence in transformations exemplified by the conversion of **20** to **22** and **23**. This aspect of the question will form the subject of future work.

Our investigation does confirm that the ring expansion process is completely dominated by the aptitude of the quaternary carbon to undergo the pinacol-related 1,2-shift with the greatest facility. This regioselectivity conforms to expectations based upon the intermediacy of oxonium ions such as **G** and **H**, where migration of the more electron-rich neighboring σ-bond is strongly induced. Despite the specific advantages offered by this high regiocontrol, the ring expansion process appears to be limited by thermodynamic considerations, at least under conditions of simple acid catalysis. Thus, the need arises to offset such lack of reactivity if medium-ring cyclic arrays ($m > 2$ in **1** and **2**) are going to be obtained.

The utility of the "capping" reaction in the present context needs to be stressed. The efficiency with which a carbonyl group can be transformed into a spiro tetrahydrofuran subunit is certainly attractive. In addition, the picture that emerges is that the acid-promoted variant exhibits stereochemical consequences almost as retention-selective as the monotosylate-mediated alternative. The intramolecular $S_N2$ pathway is adopted to a large extent, once again demonstrating the relative importance of this previously unappreciated mechanistic option.[11]

The product spiro ethers are highly interesting compounds in their own right. The crystal structures of **9** and **11** reveal that their ground-state conformations feature a minimum of repulsive interactions. The stabilization gained by the gauche orientation of three C–O bonds would appear to reach its maximum value in those arrangements illustrated in Figures 4 and 5. The gauche effect is not confined to this pair of compounds but is reflected also in the conformations adopted by ketone **22** (Figure 3) and the trans dispiro system **8**. Less information is available regarding the precise structural features of **7** and **10**. However, their highly dynamic nature is considered to be a reflection of the existence of closely balanced energetic

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(33) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879. (b) Keck, G. E.; Abbott, D. E. *Ibid.* **1984**, *25*, 1883. (c) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422. (d) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1986**, *27*, 3223; *J. Am. Chem. Soc.* **1988**, *110*, 484.

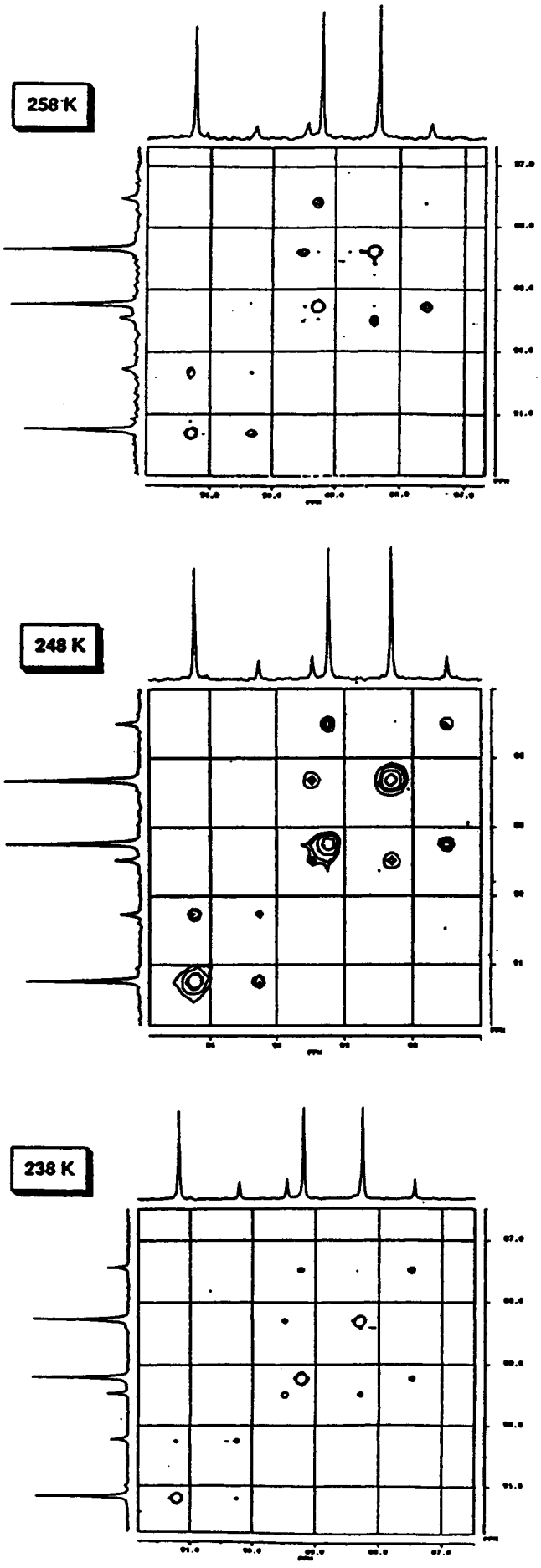



**Figure 6.** Contour plots of the 2-D EXSY spectra of **10** recorded in toluene-$d_8$ solution at the three temperatures indicated.

forces in at least two conformations. Clearly, the mutual orientational relationships of the C–O bonds on the six-membered ring core govern the shapes adopted by these systems and tip the balance toward a molecular geometry where electrostatic stabilization is maximized.

Since only modest effort has been devoted to exploring how changes in polytetrahydrofuran structure affect the strength and specificity of oxophilic cation complexation, modifications of the sort described here gain importance. The results involving **7–11**, a relatively small subset, already disclose that considerable variation in binding capacity can be achieved. As a result, the optimization of chelation efficiency gives every indication of being a realizable goal of the future.

## Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. $^1$H NMR spectra were recorded at 300 MHz and $^{13}$C NMR spectra at 75 or 20 MHz on Bruker AC 300 and AF-80 instruments as indicated. Mass spectra were recorded on a Kratos MS-30 instrument by Mr. Dick Weisenberger at The Ohio State University Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All separations were carried out under flash chromatography conditions on Merck silica gel $HF_{254}$. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use.

**1-(4,5-Dihydro-2-furyl)cyclopentanol (13).** A solution of freshly distilled 2,3-dihydrofuran (3.77 g, 4.06 mL, 54 mmol) in dry THF (200 mL) was cooled to −78 °C and treated with *tert*-butyllithium (1.1 equiv) for 30 min. The solution was warmed to 0 °C for a further 30 min before being returned to −78 °C, at which point cyclopentanone (4.11 g, 49 mmol) was introduced neat via cannula. The reaction mixture was slowly allowed to warm to room temperature during 3 h, recooled to −78 °C, and treated with excess saturated $NaHCO_3$ solution. Following separation of the organic phase, washing with brine (2×), drying, and evaporation gave a thick colorless oil. Kugelrohr distillation (oven temperature 120–130 °C, 1.5 Torr) gave pure **13**: IR (neat, cm$^{-1}$) 3600–3300, 1600; $^1$H NMR (80 MHz, $CDCl_3$) $\delta$ 4.90 (t, $J$ = 2.4 Hz, 1 H), 4.40 (t, $J$ = 9.4 Hz, 2 H), 2.65 (td, $J$ = 9.3, 2.4 Hz, 2 H), 2.20–1.50 (m, 9 H); $^{13}$C NMR (75 MHz, $C_6D_6$) ppm 163.15, 93.10, 79.48, 70.40, 39.07, 30.23, 24.30.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.65; H, 9.20.

**(*S**)-1-Oxaspiro[4.5]decan-6-one (14).** A solution of **13** (1.53 g, 9.94 mmol) in $CH_2Cl_2$ (200 mL) was added to Dowex-50X4-400 (5.25 g before washing) in $CH_2Cl_2$ (800 mL) and stirred at room temperature for 20 h. The mixture was filtered through Celite, the filtrate was evaporated under reduced pressure (no heat), and the residue (1.47 g, 96%) was chromatographed on silica gel (elution with petroleum ether–ether 85:15): IR (neat, cm$^{-1}$) 1725; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.89 (dt, $J$ = 8.3, 1.6 Hz, 1 H), 3.76 (dt, $J$ = 8.3, 1.3 Hz, 1 H), 2.66 (m, 1 H), 2.31 (m, 2 H), 1.51–1.97 (m, 9 H); MS $m/z$ ($M^+$) 154.0994, obsd 154.0963.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 69.98; H, 9.19.

**(5*S**,6*R**)-6-Allyl-1-oxaspiro[4.5]decan-6-ol and (5*S**,6*S**)-6-Allyl-1-oxaspiro[4.5]-decan-6-ol (15 and 16).** A solution of allylmagnesium bromide in ether was prepared from Mg turnings (1.41 g, 58.4 mmol) in anhydrous ether (20 mL) and allyl bromide (4.01 g, 32.9 mmol) in the same solvent (12 mL). A solution of **14** (2.108 g, 13.7 mmol) in ether (13 mL) was added dropwise to the Grignard solution, stirring was maintained for 1 h, and the mixture was poured into a mixture of ether (100 mL) and saturated $NH_4Cl$ (100 mL). The ether layer was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (elution with petroleum ether–ether 9:1) to give **15** and **16** as a colorless oily mixture (1.53 g, 94%), which was directly hydroborated.

Rechromatography of this mixture permitted the isolation of isomerically pure **15** as a mobile, colorless oil: IR (neat, cm$^{-1}$) 3560–3400; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.90 (m, 1 H), 5.07 (m,

2 H), 3.83 (m, 2 H), 2.25 (d, $J$ = 7.1 Hz, 2 H), 2.15 (s, 1 H), 2.05 (m, 2 H), 1.95–1.65 (m, 3 H), 1.55 (m, 5 H), 1.30 (m, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 134.27, 117.12, 87.33, 74.42, 67.76, 38.77, 33.90, 33.49, 31.10, 26.05, 22.12, 21.93; MS $m/z$ ($M^+$) calcd 196.1464, obsd 196.1465.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.54; H, 10.26.

**(5*S**,6*R**)-6-Hydroxy-1-oxaspiro[4.5]decane-6-propanol and (5*S**,6*S**)-6-Hydroxy-1-oxaspiro[4.5]decane-6-propanol (17 and 18).** A solution of the 15/16 mixture (1.0 g, 5.10 mmol) in dry THF (15 mL) at 0 °C was treated with the borane–THF complex (5.1 mL of 1.0 M, 5.1 mmol). The mixture was stirred at 0 °C for 1 h, at which point sodium hydroxide (5.1 mL of 3 M, 15.3 mmol) was introduced rapidly followed by hydrogen peroxide (2 g of 30%, ~16 mmol). Stirring was maintained at 0 °C for a further hour. The customary workup[11] and silica gel chromatography (elution with petroleum ether–ether 2:3, to pure ether, to pure ethyl acetate) gave 542 mg (50%) of 17 and 118 mg (11%) of 18.

For 17: colorless crystals, mp 54–55 °C (from petroleum ether–ether); IR ($CHCl_3$, $cm^{-1}$) 3620, 3550, 3400; $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 3.70–3.46 (m, 4 H), 2.70–2.50 (br s, 2 H), 2.05–1.90 (m, 12 H), 1.90–1.80 (m, 1 H), 1.80–1.65 (m, 2 H), 1.65–1.40 (m, 8 H), 1.29–1.05 (m, 4 H); $^{13}$C NMR (75 MHz, $C_6D_6$) ppm 87.63, 74.40, 67.52, 63.14, 33.49, 33.41, 30.96, 30.40, 26.67, 25.93, 22.82, 22.01; MS $m/z$ ($M^+$) calcd 214.1569, obsd 214.1553.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.12; H, 10.34.

For 18: colorless plates, mp 86–87 °C (from ethyl acetate–ether); IR ($CHCl_3$, $cm^{-1}$) 3610, 3575, 3400; $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 3.69 (dd, $J$ = 15, 6.0 Hz, 1 H), 3.58 (dd, $J$ = 15, 7.1 Hz, 1 H), 3.45 (m, 2 H), 2.20 (dt, $J$ = 12.5, 7.5 Hz, 1 H), 2.06 (br s, 1 H), 1.85–1.47 (m, 4 H), 1.65–1.47 (m, 6 H), 1.47–1.32 (m, 3 H), 1.32–1.15 (m, 3 H); $^{13}$C NMR (75 MHz, $C_6D_6$) ppm 87.70, 75.04, 67.83, 63.40, 34.59, 33.15, 31.83, 31.13, 26.93, 26.35, 23.22, 22.03; MS $m/z$ ($M^+$) calcd 214.1569, obsd 214.1572.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.31; H, 10.44.

**(5*R**,6*S**)-1,7-Dioxadispiro[4.0.4.4]tetradecane (7).** To a solution of 17 (150 mg, 0.7 mmol) in triethylamine (0.6 mL) containing a catalytic quality of 4-(dimethylamino)pyridine was added a solution of $p$-toluenesulfonyl chloride (160 mg, 0.84 mmol) in $CH_2Cl_2$ (2.5 mL). The reaction was stirred at room temperature for 16 h and partitioned between $CH_2Cl_2$ (50 mL) and water (50 mL). The organic layer was washed with 2 M HCl (2×) and brine, dried, and concentrated. Silica gel chromatography (elution and petroleum ether–ether 9:1) gave pure 7 (118 mg, 84%) as a colorless oil: IR (neat, $cm^{-1}$) 1445; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.83 (t, $J$ = 6.5 Hz, 4 H), 1.95–1.62 (m, 12 H), and 1.35 (m, 4 H); $^{13}$C NMR (see Figure 1); MS $m/z$ ($M^+$) calcd 196.1436, obsd 196.1433.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.79; H, 10.25.

**(5*S**,6*S**)-1,7-Dioxadispiro[4.0.4.4]tetradecane (8).** Diol 18 (14.4 mg, 0.67 × $10^{-4}$ mol) was treated as described above with triethylamine (0.1 mL), DMAP (cat. amount), and $p$-toluenesulfonyl chloride (15.3 mg, 0.8 × $10^{-4}$ mol) in $CH_2Cl_2$ (0.25 mL). Column chromatography afforded 10.5 mg (79%) of 8, a colorless oil: IR (neat, $cm^{-1}$) 1450, 1080–1040; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.77 (m, 4 H), 2.18 (dt, $J$ = 12.1, 7.8 Hz, 2 H), 2.02–1.75 (m, 4 H), 1.70–1.40 (m, 8 H), 1.26 (m, 2 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 87.23; 67.88, 36.59, 31.23, 26.81, 23.38; MS $m/z$ ($M^+$) calcd 196.1463, obsd 196.1430.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.27; H, 10.36.

**Acid-Catalyzed Cyclization of 17.** A solution of diol 17 (198 mg, 0.93 mmol) in toluene (30 mL) containing a catalytic amount of $p$-toluenesulfonic acid was heated to reflux under argon for 20 h. The reaction mixture was cooled and poured into a mixture of ether (30 mL) and saturated $NaHCO_3$ solution (20 mL). The organic phase was washed with brine, dried, and evaporated. GC analysis of the crude product mixture indicated the 7:8 ratio to be 18:1. Silica gel chromatography (elution with petroleum ether–ether 9:1) furnished 114 mg (63%) of pure 7.

A repeat reaction on a 0.42-mmol scale gave 7 and 8 in a 14:1 ratio and 62% yield.

**Acid-Catalyzed Cyclization of 18.** Heating 18 (34 mg, 1.59 × $10^{-4}$ mol) in toluene (15 mL) containing catalytic $p$-toluenesulfonic acid afforded a 7:8 ratio of 1:15. Column chromatography (silica gel, elution with petroleum ether–ether 9:1) gave 13.3 mg (43%) of 8.

A repeat reaction on a 1.07 × $10^{-4}$ mol scale afforded a 1:14 ratio of 7 and 8 in 57% yield.

**1-(4,5-Dihydro-6-furyl)cyclobutanol (19).** 2,3-Dihydrofuran (3.15 g, 45 mmol) in dry THF (150 mL) was lithiated as described above. Cyclobutanone (3.0 g, 42.9 mmol) in THF (10 mL) was introduced via cannula. The reaction mixture was then stirred at −78 °C for 2.5 h, allowed to warm to room temperature during 4 h, and worked up as before. Kugelrohr distillation gave pure 19 (4.97 g, 83%) as a colorless oil, bp 85–110 °C at 0.1 Torr: IR (neat, $cm^{-1}$) 3500–3300, 1650, 1140, 1070; $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 4.68 (t, $J$ = 2.5 Hz, 1 H), 4.03 (t, $J$ = 9.3 Hz, 2 H), 2.39 (td, $J$ = 9.3, 2.5 Hz, 2 H), 2.31–2.08 (m, 5 H), 1.67 (m, 2 H); $^{13}$C NMR (75 MHz, $C_6D_6$) ppm 161.94, 93.27, 72.33, 70.43, 35.21, 30.17, 13.31; MS $m/z$ ($M^+$) calcd 140.0838, obsd 140.0882.

**(*S**)-1-Oxaspiro[4.4]nonan-6-one (20).** A solution of 19 (992 mg, 7.09 mmol) in $CH_2Cl_2$ (40 mL) was added to a magnetically stirred suspension of Dowex-50X4-400 resin (950 mg after washing and drying) in the same solvent (480 mL) and stirred at room temperature for 20 h. Workup and solvent evaporation gave 20 as a colorless, mobile oil (940 mg, 95%), which was homogeneous by TLC, etc.: IR (neat, $cm^{-1}$) 1740; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.94 (t, $J$ = 3.0 Hz, 2 H), 2.26 (m, 2 H), 2.15–1.65 (series of m, 8 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 218.49, 86.46, 68.96, 35.80, 35.18, 32.29, 25.89, 18.11; MS $m/z$ ($M^+$) calcd 140.0837, obsd 140.0843.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.79; H, 8.68.

**(5*S**,6*R**)- and (5*R**,6*R**)-6-(4,5-Dihydro-2-furyl)-1-oxaspiro[4.4]nonan-6-ol (21).** Lithiation of 2,3-dihydrofuran (2.67 g, 38.5 mmol), introduction of 20 (4.90 g, 35 mmol) as a THF solution (30 mL), workup, and Kugelrohr distillation furnished 550 mg (75%) of a 1:1 mixture of epimeric alcohols 21 (bp 130–160 °C at 0.4 Torr): colorless oil; IR (neat, $cm^{-1}$) 3500–3350, 1680; $^1$H NMR (300 MHz, $C_6D_6$) $\delta$ 5.01 (t, $J$ = 2.5 Hz, 1 H), 4.79 (t, $J$ = 2.5 Hz, 1 H), 4.10 (m, 2 H), 3.96 (td, $J$ = 9.8, 0.9 Hz, 2 H), 3.67 (t, $J$ = 6.3 Hz, 2 H), 3.62 (t, $J$ = 6.6 Hz, 2 H), 3.50 (s, 1 H), 2.53–2.0 (series of m, 12 H), 1.97–1.75 (m, 5 H), 1.72–1.40 (series of m, 8 H); MS $m/z$ ($M^+$) calcd 210.1256, obsd 210.1260.

**Ring Expansion of 21.** A solution of alcohols 21 (5.25 g, 25 mmol) in $CH_2Cl_2$ (300 mL) was stirred with Dowex-50X4-400 (4.7 g) in $CH_2Cl_2$ (1.4 L) overnight at room temperature. Workup followed by column chromatography (silica gel, elution with petroleum ether–ether 80:20 → 50:50) afforded in order of elution 2.39 g of 23 and 2.05 g of 22 (total yield of 88%).

For 22: colorless rhombic crystals, mp 48.5–50 °C (from petroleum ether): IR (film, $cm^{-1}$) 1715; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.89 (m, 4 H), 2.67 (m, 1 H), 2.35 (m, 1 H), 2.20 (m, 1 H), 2.10–1.50 (series of m, 11 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 210.26, 93.45, 88.94, 69.06, 68.85, 37.42, 34.09, 31.37, 26.04, 25.58, 20.35 (1 C not observed); MS $m/z$ ($M^+$) calcd 210.1256, obsd 210.1226.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.74; H, 8.65.

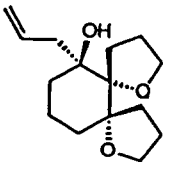
For 23: colorless oil; IR (neat, $cm^{-1}$) 1715; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.85 (m, 4 H), 2.48 (m, 2 H), 2.23 (m, 1 H), 2.1–1.8 (m, 9 H), 1.55 (m, 2 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 210.11, 93.85, 88.73, 69.08, 68.72, 37.96, 35.59, 32.07, 29.61, 26.58, 26.24, 20.37; MS $m/z$ ($M^+$) calcd 210.1255, obsd 210.1254.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.73; H, 8.56.

**Conversion of 22 to 9 and 10.** Ketone 22 (1.28 g, 6.1 mmol) was added to an ethereal solution of allylmagnesium bromide in the predescribed fashion. Precipitation of the white alkoxide was noted during this process. The standard workup and silica gel chromatography afforded 614 mg (~32%) of a mixture of trans alcohol 26 and an unknown impurity (4:1) together with 744 mg (48%) of pure cis alcohol 27.

For 26: impure colorless oil isolated as the diol and characterized as the trispiro ether 10.

For 27: colorless needles, mp 50.5–51.5 °C (from cold petroleum ether); IR (film, $cm^{-1}$) 3420; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.00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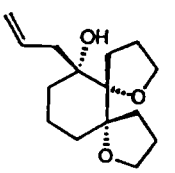
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(complex m, 1 H), 5.75 (br s, 1 H), 5.03 (m, 2 H), 4.15 (m, 1 H), 3.92 (m, 3 H), 2.42 (dd, $J$ = 13.2, 5.8 Hz, 1 H), 2.10–1.50 (series of m, 12 H), 1.45–1.25 (m, 3 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 134.90, 116.53, 90.87, 89.60, 77.88, 71.01, 69.24, 40.83, 36.03, 34.43, 33.54, 32.16, 26.55, 25.10, 16.85; MS $m/z$ ($M^+$) calcd 252.1725, obsd 252.1695.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.58.

To a solution of impure **26** (526 mg, 2.09 mmol) in cold (0 °C) THF (5 mL) was added the borane–THF complex (2.09 mL of 1.0 M, 2.09 mmol) via syringe. The reaction mixture was stirred at 0 °C for 1 h and treated sequentially with sodium hydroxide (2.09 mL of 3 M, 6.27 mmol) and hydrogen peroxide (0.8 mL of 30%, 6.57 mmol). Workup and silica gel chromatography gave the diol as a thick colorless oil which crystallized on standing (267 mg, 47%).

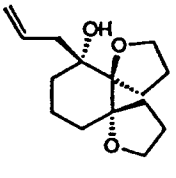
To this diol (189 mg, 0.7 mmol) in triethylamine (2 mL) were added $p$-toluenesulfonyl chloride (167 mg, 0.88 mmol) dissolved in triethylamine (0.5 mL) and $CH_2Cl_2$ (0.5 mL). After overnight stirring and the usual workup, there was isolated 125 mg (71%) of **10**, a colorless oil: IR (neat, cm$^{-1}$) 1450, 1070; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.95–3.70 (m, 5 H), 3.57 (m, 1 H), 2.43 (br s, 1 H), 2.27 (br s, 1 H), 2.10–1.25 (series of m, 16 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 90.80, 88.89 (2 C), 70.02, 67.73, 67.25, 36.55 (br), 34.70, 32.59, 31.55 (br, 2 C), 27.24, 26.88, 25.31, 19.52; MS $m/z$ ($M^+$) calcd 252.1725, obsd 252.1728.

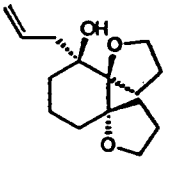
Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H. 9.59. Found: C, 71.46; H, 9.49.

Comparable hydroboration of **27** (252 mg, 1 mmol) afforded 147 mg (54%) of diol as a thick colorless oil. A 139-mg (0.51 mmol) sample was monotosylated and cyclized in the predescribed manner. There was isolated 110 mg (85%) of **9**, colorless rods, mp 83–84 °C (from cold petroleum ether): IR ($CHCl_3$, cm$^{-1}$) 1060; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.96 (t, $J$ = 6.6 Hz, 2 H), 3.86 (m, 2 H), 3.67 (AB q, $J_{gem}$ = 15.4, $J_{vic}$ = 7.8 Hz, 2 H), 2.02–1.55 (series of m, 15 H), 1.37 (dt, $J$ = 6.0, 3.4 Hz, 2 H), 1.15 (m, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 91.98, 88.50, 69.75, 66.96, 32.36, 31.59, 27.61, 27.06, 26.25, 20.45; MS $m/z$ ($M^+$) calcd 252.1725, obsd 252.1741.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.46; H, 9.77.

**Conversion of 23 to 10 and 11.** Allylation of ketone **23** (1.71 g, 8.14 mmol) in the predescribed manner afforded 1.88 g of a thick colorless oil that solidified on standing. Recrystallization of this material from cold petroleum ether provided 1.03 g of cis alcohol **29**. The mother liquor was concentrated and chromatographed on silica gel (elution with petroleum ether–ether 9:1 → 8:2) to give 77 mg of **28** and an additional 193 mg of **29**.


28


29

For **28**: colorless oil; IR (neat, cm$^{-1}$) 3480; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.93 (m, 1 H), 5.10 (m, 2 H), 4.39 (br s, 1 H), 3.89 (m, 4 H), 2.32 (m, 2 H), 2.12 (m, 1 H), 2.00–1.78 (series of m, 6 H), 1.62 (m, 6 H), 1.38 (m, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 134.98, 116.66, 88.74 (2 C), 76.19, 70.07, 68.28, 33.91, 32.97, 32.62, 27.20, 27.02, 24.91, 16.71; MS $m/z$ ($M^+$) calcd 252.1725, obsd 252.1725.

For **29**: colorless crystals, mp 58–59 °C (from petroleum ether); IR ($CHCl_3$, cm$^{-1}$) 3545, 1645, 1080; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.90 (m, 1 H), 5.08 (m, 2 H), 3.85 (m, 2 H), 3.78 (m, 1 H), 3.61 (m, 1 H), 2.30 (m, 4 H), 2.10–1.75 (series of m, 7 H), 1.72–1.30 (series of m, 6 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 134.69, 117.60, 91.09, 88.64, 77.54, 69.98, 66.85, 40.68, 35.59, 33.30, 31.84, 29.07, 27.54, 26.74, 19.01 (1 C not observed); MS $m/z$ ($M^+$) calcd 252.1725 obsd 252.1746.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.36; H, 9.57.

Hydroboration–oxidation of **28** (200 mg, 0.87 mmol) in THF (5 mL) at 0 °C with the borane–THF complex (0.87 mmol) in the usual way afforded 191 mg (81%) of diol. Cyclization of a sample (100 mg, 0.37 mmol) with $p$-toluenesulfonyl chloride (78 mg, 0.4 mmol) in triethylamine and $CH_2Cl_2$ and workup followed by column chromatography gave **11** (72 mg, 77%) as a colorless crystalline solid, mp 86.5–87 °C (from petroleum ether): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.80 (m, 4 H), 3.60 (m, 2 H), 2.20 (m, 4 H), 2.02–1.69 (series of m, 6 H), 1.65–1.35 (series of m, 7 H), 1.20 (m, 2 H); $^{13}$C NMR (75 MHz, $CDCl_3$) ppm 91.37, 88.53, 69.33, 36.03, 29.94, 29.67, 27.81, 27.03, 20.60; MS $m/z$ (M) calcd 252.1725, obsd 252.1738.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H. 9.59. Found: C, 71.41; H, 9.69.

Comparable processing of **29** (252 mg, 1 mmol) led to the isolation of diol (200 mg, 74%). Cyclization of this material (189 mg, 0.7 mmol) via its monotosylate as described earlier led to the isolation of **10** (125 mg, 71%), identical in all respects to the trispiro compound characterized above.

**Acid-Catalyzed Cyclizations Leading to 9–11.** The diol derived from **29** (47 mg, 0.17 mmol) was heated in dry toluene (25 mL) containing 4 mg of $p$-toluenesulfonic acid at the reflux temperature under a Soxhlet extractor containing $CaH_2$ for the removal of water as described for **17**. Workup as described gave a yellow oil (35 mg). Column chromatography (silica gel, elution with petroleum ether–ether 85:15) gave the trispiro product **10** (26 mg, 59%) as a pure colorless oil.

Analogous treatment of the diol derived from **28** (60.6 mg, 0.22 mmol) furnished 14.4 mg (25%) of a colorless oil consisting of an 8:1 mixture of **11** and **10**.

Heating the diol derived from **27** (147 mg, 0.58 mmol) in the same manner except for only 2 h gave 75 mg (55%) of **9**, mp 83–84 °C, and 2.6 mg (2%) of **10**.

Heating the diol derived from **26** (104 mg, 0.39 mmol) as before for 5.5 h afforded a 14:1 mixture of **10** and **9**. Silica gel chromatography (elution with petroluem ether–ether) led to the isolation of 14 mg (14%) of **10**.

**Addition of 5-Lithio-2,3-dihydrofuran to 14.** The reaction of **12** with **14** was carried out in the manner described earlier for the preparation of **13**. Starting with 797 mg (5.2 mmol) of the ketone, Kugelrohr distillation (135–145 °C at 1.0 Torr) afforded 922 mg (79%) of a thick colorless oil from which crystals slowly deposited. NMR analysis indicated the initial composition of the oil to be a 1.5:1 mixture of **24** and **25**. The colorless crystals of **24** were washed 5 times with petroleum ether–ether (95:5) and dried at 30 mmHg to give tubular prisms (517 mg, 47%), mp 55–59 °C: IR ($CHCl_3$ cm$^{-1}$) 3580, 1650; $^1$H NMR (80 MHz, $CDCl_3$) $\delta$ 4.85 (t, $J$ = 2.6 Hz, 1 H), 4.25 (t, $J$ = 9.5 Hz, 2 H), 3.80 (t, $J$ = 6.7 Hz, 2 H), 2.63 (td, $J$ = 9.5, 2.6 Hz, 2 H), 2.40–1.30 (m, 13 H); MS $m/z$ ($M^+$) calcd 224.1412, obsd 224.1434.

**Complexation Studies.**[28a] All glassware involved was base-washed and rinsed sequentially with acetone and distilled, demineralized water (2×) prior to drying. Host solutions were prepared in acid-free $CDCl_3$ in the 0.014 to 0.020 M concentration range. Experiments were conducted simultaneously on four–six samples of the identical polyether plus a blank. The mean value of the absorbance ($A$) was used in the calculations. Two or more determinations were carried out until good duplication was realized. All measurements of volume was done by difference. Volumes of <0.4 mL were transferred in Hamilton gas tight syringes. Care was taken at all times to avoid evaporation of the $CDCl_3$ solutions.

To each of two graduated distillation receiver flasks containing a micro magnetic stirring bar was introduced the host solution (0.4 mL). A solution of the alkali metal picrate in water (0.5 mL) followed. The tubes were stoppered and placed in a water bath at 20 °C. The contents of the tubes were stirred as rapidly as possible for 5.0 min (stopclock) before centrifugation to produce two clear layers. For each tube, a 50- to 150-$\mu$L aliquot (depending on color intensity) of the chloroform layer was removed and transferred to a 5-mL volumetric flask. Dilution to the mark with

$CH_3CN$ produced solutions suitable for UV measurement. A blank sample was similarly prepared with 0.4 mL of host solution and 0.5 mL of demineralized water.

UV measurements were made on a Uvikon 930 spectrophotometer. The same cell was used as reference on each occasion and the pair of cells were always oriented in the same way inside the spectrophotometer. The cells were "zeroed" in the instrument at 380 nm. The extraction constants ($K_{ex}$) were calculated using equilibrium equation (2) in ref 28b from the concentration of picrate salt measured in the original $CDCl_3$ layer. Correction for the water solubility of hosts was made by measurement of $K_d$ for hosts ($CHCl_3/H_2O$) according to the literature method.[28b] The following $K_d$ values were determined: 15-crown-5, 0.17; 12-crown-4, 0.20; **9**, 0.05; **11**, 0.05; **10**, 0.06; **7**, 0.03.

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**Registry No.** **7**, 141411-92-9; $Na^+$ $Pic^-$ **7**, 141412-06-8; $K^+$ $Pic^-$ **7**, 141412-08-0; **8**, 141436-74-0; **9**, 134178-97-5; $Na^+$ $Pic^-$ **9**, 141412-10-4; $K^+$ $Pic^-$ **9**, 141412-12-6; **10**, 134236-71-8; $Na^+$ $Pic^-$ **10**, 141507-83-7; $K^+$ $Pic^-$ **10**, 141507-87-1; **11**, 134236-72-9; $Na^+$ $Pic^-$ **11**, 141507-81-5; $K^+$ $Pic^-$ **11**, 141507-85-9; **13**, 129529-77-7; **14**, 141411-93-0; **15**, 141411-94-1; **16**, 141436-75-1; **17**, 141411-95-2; **18**, 141411-96-3; **19**, 134179-00-3; **20**, 141411-97-4; *trans*-**21**, 141411-98-5; *cis*-**21**, 141411-99-6; **22**, 141412-00-2; **23**, 141412-01-3; **24**, 141412-02-4; **25**, 141412-03-5; **26**, 141412-04-6; **27**, 141505-51-3; **28**, 141505-52-4; **29**, 141505-53-5; cyclopentanone, 120-92-3; 2,3-dihydrofuran, 1191-99-7; cyclobutanone, 1191-95-3.

**Supplementary Material Available:** $^1H$ NMR spectra of **19**, **21**, **24**, and **28** together with X-ray experimental procedures, tables of bond distances and angles, final fractional coordinates, thermal parameters for **9**, **11**, **22**, and **24**, and ORTEP diagram of **24** (25 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

# Regio- and Stereochemical Course of the Ring Expansion of Bridged Bicyclic Ketones to Spirocyclic α-Keto Tetrahydrofurans

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The regio- and stereochemical aspects of oxonium-promoted pinacol-like rearrangements have been investigated starting from the bridged bicyclic ketones (±)-norcamphor, (1*R*)-(−)-fenchone, and (1*R*)-(−)-3,3-dimethyl-1-vinyl-2-norbornanone. 1,2-Addition of 5-lithio-2,3-dihydrofuran to these substrates provided alcohols that smoothly underwent acid-catalyzed ring expansion. Whereas bridgehead carbon migration was observed in the first and third examples, the alternative available 1,2 Wagner–Meerwein shift operated in the fenchone series. In every instance, a substantial kinetic preference for formation of the O-exo spirotetrahydrofuranyl ketone was noted. Positioning of the dihydrofuranyl unit in sterically congested endo environments as accomplished by condensation of the α-lithio vinyl ether with (1*R*)-(+)-camphor, (1*S*)-(+)-7,7-dimethyl-1-vinyl-2-norbornanone, and (1*S*)-(−)-apocamphor was accompanied by increased hydrolytic sensitivity. Second-stage ring expansion of two of the spirocyclic ketones was characterized by continued adherence to anticipated migratory aptitudes. However, loss of stereochemistry occurred both at the original α carbon and at the newly introduced stereogenic center. These observations and relevant control experiments are most consistent with a push–pull fragmentation scheme leading to a ring-opened oxonium ion–enol pair that, because they are tethered, find it possible to cyclize. Prior to final bonding, either terminus may rotate relative to the other. The kinetic and thermodynamic interrelationships of these phenomena are discussed.

The ability of 4,5-dihydrofurans bearing a carbinol substituent at C-2 to function as oxonium ion initiators of pinacol-like rearrangements has come to light recently.[4] Even in its simplest form, this transformation affords spirotetrahydrofuranyl ketones holding considerable synthetic potential as precursors to ionophores.[5] More widespread utilization of the reaction in organic synthesis would appear dependent on elucidation of its intrinsic characteristics. One of these is regiochemistry. Since ring expansion of the alcohols proceeds under acid catalysis, the expectation is that the migrating center most able to bring electron density to the neighboring cationic carbon will be transferred preferentially. However, should the flanking groups be closely balanced in their electronic make-up, will secondary factors such as the relative spatial orientation of the dihydrofuran ring hold relevance? Questions of this ilk can best be answered by suitable examination of topologically well-defined substrates.

Another key feature of these processes is their stereochemical course. Once again, an attractive way of systematically investigating stereoselectivity is to construct a series of molecules in which conformational variables are constrained.

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(3) Author to whom inquiries regarding the X-ray crystallographic analyses should be made.
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