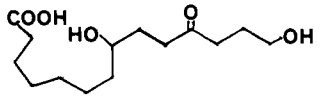
independently synthesized from the dihydroxy keto acid **9** by the following sequence: (1) lactonization of the 1-isopropyl-4-*tert*-butyl-2-thiolimidazole[9] ester using the double activation method[5a] to give **10** in 78% yield and (2) reduction by sodium borohydride in ethanol at 0 °C.[10]



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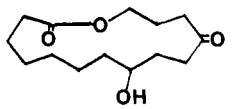
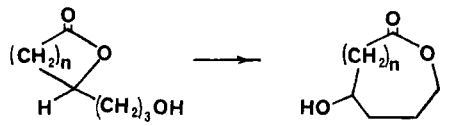


10

A number of other informative experiments on translactonization have been performed which can be summarized briefly (items I–IV below).

I. The 8-membered hydroxy lactone **11**,[11a] the lower homologue of **2**, undergoes ring expansion (3 mol % *p*-toluenesulfonic acid in methylene chloride, 24 h, 0 °C) somewhat more slowly and less efficiently[12] than **2**, to form the 11-membered lactone **12** in 69% yield.

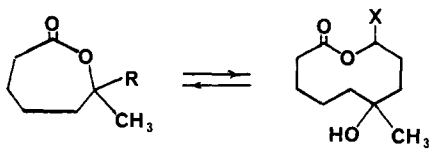


11, n = 5
13, n = 4

12, n = 5
14, n = 4

II. The 7-membered hydroxy lactone **13**[11b] does not undergo observable ring expansion to the 10-membered lactone **14** (3 mol % *p*-toluenesulfonic acid in methylene chloride, 6 h, 25 °C) and is converted (65%) only to polar materials.[12] In this case it is probable that the 7-membered lactone **13** is more stable than the 10-membered isomer **14.**

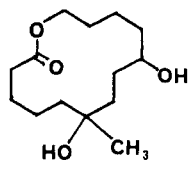
III. The 7-membered lactone **15**[13] is converted by storage at 23 °C either neat or in chloroform solution for 3 days into an equilibrium mixture of **15** and **16** (ratio 35:65). The same mixture is generated rapidly (<1 h) at 0 °C with 1 mol % *p*-toluenesulfonic acid in methylene chloride.



15, R = $(CH_2)_3OH$
17, R = $(CH_2)_2CH(CH_2)_4OH$ (OH)

16, X = H
18, X = $(CH_2)_4OH$

IV. The 7-membered lactone **17** undergoes translactonization to form an equilibrium mixture of **17** and the 10-membered isomer **18** (ratio 1:1). However, under either basic or acidic equilibration conditions none of the 14-membered lactone **19** which is to be expected from further translactonization



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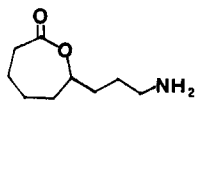

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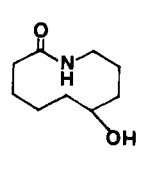

21

can be detected, clearly because of an unfavorable rate rather than unfavorable equilibrium.[5] The ring expansion **18** → **19** (by four members) necessitates an 8-membered cyclic transition state which is evidently much more difficulty attained than the 7-membered cyclic structure involved in the other translactonization processes outlined above. It seems likely that the general translactonization scheme indicated by eq a is generally workable only for $y = 1$, 2, or 3 and not $y = 4$.

Based on relative stabilities of various lactone ring sizes[5] and the constraint that $y = 1$, 2, or 3 in eq a, the following ring expansions can be expected to be most favorable (in terms of lactone ring size):

$$8 \rightarrow 11 \rightarrow 13 \text{ or } 14$$

$$9 \rightarrow 12 \rightarrow 14 \text{ or } 15$$

$$10 \rightarrow 13$$

In these instances ring expansion may also be facilitated by the presence of one or more substituents which can be accommodated more readily on the larger ring. Finally it seems likely that the basic approach outlined here will also serve for the synthesis of macrocyclic lactams, e.g., **20** → **21.** This and other extensions of our work are being pursued.[14]

References and Notes

(1) For a recent review, see K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977).
(2) Synthesized from the pyrrolidine enamine of cyclooctanone by the sequence (1) reaction with ethyl acrylate in dioxane at reflux for 1 h and aqueous cleavage of the enamine adduct so obtained, (2) ester saponification using 2 N sodium hydroxide in aqueous methanol at reflux for 6 h, (3) Baeyer–Villiger reaction with excess 20% peracetic acid in ethyl acetate at 50–60 °C.
(3) Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for each compound described herein using a purified and chromatographically homogeneous sample.
(4) This result is quite general in our experience; i.e., translactonization proceeds more rapidly under catalysis by *p*-toluenesulfonic acid than by DBN.
(5) This instability is indicated by the generally low rates of formation of 9-membered lactones:[5a–c] (a) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974); (b) C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *ibid.*, **99**, 2591 (1977); (c) E. J. Corey, D. J. Brunelle, and P. J. Stork, *Tetrahedron Lett.*, 3405 (1976); as well as by thermodynamic data for cycloparaffins:[5d] (d) V. Prelog, *Bull. Soc. Chim. Fr.*, 1255 (1960).
(6) See (a) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970); (b) T. Mukaiyama, R. Matsueda, and H. Marayama, *Bull. Chem. Soc. Jpn.*, **43**, 1271 (1970); (c) K. Lloyd and G. T. Young, *J. Chem. Soc. C*, 2890 (1971); (d) T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.*, **95**, 4763 (1973).
(7) Prepared by reaction of 3-bromopropanol with 1.2 equiv of *tert*-butyldimethylsilyl chloride and 2 equiv of imidazole in DMF at 0 °C for 6 h followed by aqueous workup and distillation.
(8) The ^1H NMR spectrum clearly indicates that this product corresponds to structure **7** rather than the isomeric 9-membered lactone, which obviously is a reaction intermediate.
(9) E. J. Corey and D. J. Brunelle, *Tetrahedron Lett.*, 3409 (1976).
(10) The keto acid **9** was prepared from **5** by hydrolysis with 2 N sodium hydroxide in aqueous methanol at reflux for 24 h.
(11) Synthesized from (a) cycloheptanone or (b) cyclohexanone by a sequence paralleling that used for **2.**
(12) Very polar by-products, quite possibly linear polyesters, were also formed.
(13) Synthesized from 10-methyl-4-octal-3-one (C. H. Heathercock and J. E. Ellis, *Tetrahedron Lett.*, 4995 (1971)) by (1) oxidation with permanganate–periodate, (2) Baeyer–Villiger reaction, and (3) reduction of carboxyl to CH_2OH as for **2.**
(14) This work was supported by a grant from the National Institutes of Health.

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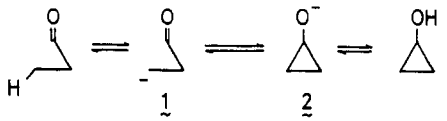
Homoenolate Anion Precursor. Reaction of Ester Homoenol Silyl Ether with Carbonyl Compounds

Sir:

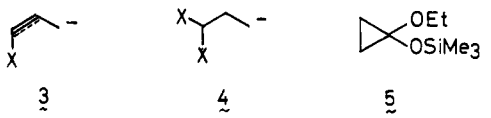
Recognition of homoenolization[1] is a much newer event compared with that of enolization, and synthetic chemists have not paid any significant attention to this phenomenon (formation of **1** or **2**) until quite recently.[2]

However, the concept of homoenolate anion **2** has become one of the major subjects with respect to polarity inversion[3] (or



1 2

Umpolung),[4] and an increasing number of papers have been published in regard to the homoenolate anion equivalent[5] and related species.[6] Since homoenolate anion **2** itself does not normally show nucleophilic reactivities toward carbon electrophiles,[7] every effort has been centered on carbanion which structurally resembles anion **1.** All of the previous simple equivalents fall into two classes, **3**[5a] and **4.**[5b] Since allylic anion

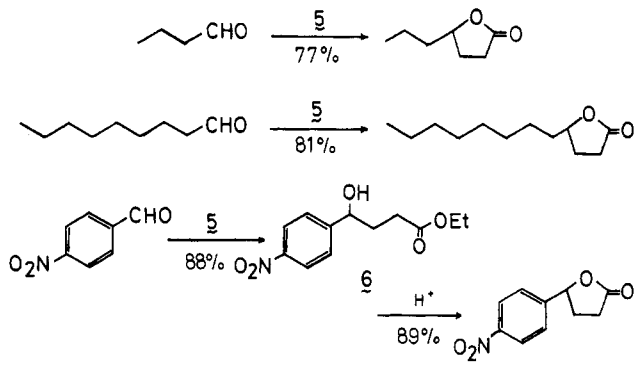


3 4 5

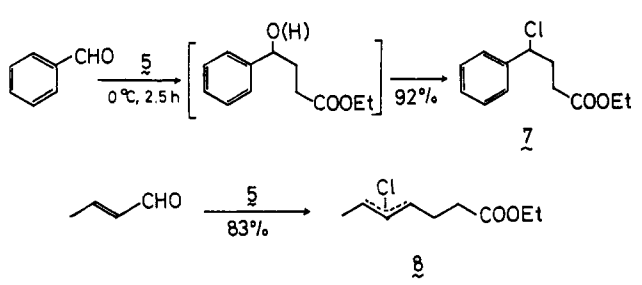
3 has an ambident character, the major drawback most frequently encountered is the formation of positional isomers (α-alkylation).[5a] Here we wish to suggest that homoenol silyl ether, silylated cyclopropanol itself, can work well as a homoenolate anion precursor, which, in both a conceptual and an operational sense, is the simplest solution ever offered to the problem.

1-Ethoxy-1-trimethylsiloxycyclopropane (**5**) is a stable and distillable oil and is available in good yield by reductive silylation of ethyl 3-chloropropanoate.[8] We found that addition of this cyclopropane to a carbonyl compound is readily achieved with the aid of $TiCl_4$ (~1 equiv). The reaction is the first example of an ester homoenolate anion equivalent that is shown to add onto carbonyl compounds.[5c]

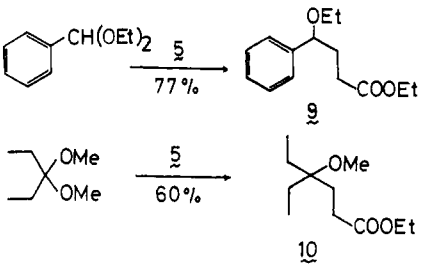
Cyclopropane **5** smoothly reacts below 0 °C with aliphatic aldehydes, giving γ-lactones in high yields.[9] *p*-Nitrobenzaldehyde also reacted with **5** to give uncyclized adduct **6** after the usual workup.



In some instances, chlorination of the hydroxyl group emerged as a side reaction. For example, benzaldehyde and enals afforded chlorinated esters in high yields on prolonged exposure to the reaction conditions. The reaction of crotonaldehyde and **5** gave **8** as an isomeric mixture[10] whose allylic chloride moiety was hydrolytically unstable. With enals, chlorination reaction is as fast as the addition reaction, and short reaction period also afforded **8** as a major product. Virtually no such chlorination was observed with adduct **6.**

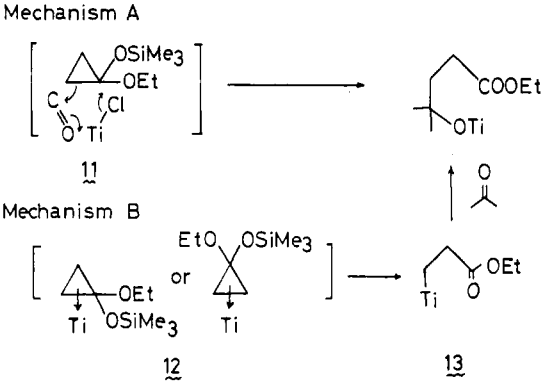


Aromatic acetals can also be the electrophile of this reaction. Thus, adduct **9** formed in good yield. Again, a longer reaction period transformed **9** to **7.** Ketals also reacted under the influence of an equivalent of $TiCl_4$. The adduct was isolated as the γ-methoxy ester **10** with its tertiary ether intact. Ketones, however, failed to give adducts in isolable quantities.



9 10

Two mechanistic rationales are conceivable for the present reaction. One involves a transition state schematically depicted as **11,** in which direct interaction of the carbonyl carbon with the σ bond of cyclopropane is postulated (mechanism A). Another explanation assumes the occurrence of electrophilic attack of metal halide on the ring (mechanism B).



11 12 13

The fact that common Lewis acids other than $TiCl_4$ were totally ineffective, or gave different products does not favor mechanism A.[11] On the other hand, coordination of heavy metals with a cyclopropane ring, e.g., **12,** is well documented.[12] Mercury(II) is known to react with cyclopropanols forming open-chain organomercury compounds.[13] In addition, the second step of mechanism B appears reasonable in view of the stability of alkyltitanium(IV) compounds[14] and their reactivities.[14,15]

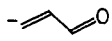
The reaction mechanism and generality of such an approach for the coupling of strained molecules and electrophiles are of our current interest.

Acknowledgment. We thank Professor Akio Yamamoto for advices about the reaction mechanism.

References and Notes

(1) A. Nickon, J. L. Lambert, J. E. Oliver, D. F. Covey, and J. Morgan, *J. Am. Chem. Soc.*, **98,** 2593 (1976); see also ref 2.
(2) For a comprehensive review on the chemistry of cyclopropanols, see D. H. Gibson and C. H. DePuy, *Chem. Rev.*, **74,** 605 (1974).
(3) D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7,** 147 (1974).
(4) D. Seebach and D. Enders in "New Synthetic Methods", Vol 2, Verlag Chemie, Weinheim, 1975, pp 65–70.
(5) (a) E. J. Corey and D. E. Cane, *J. Org. Chem.*, **35,** 3405 (1970); K. Oshima, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **48,** 1567 (1975) and *J. Am. Chem. Soc.*, **95,** 7926 (1973); A. Evans, G. C. Andrews, and B. Buckwalter, *ibid.*, **96,** 5560 (1974); W. C. Still and T. L. MacDonald, *ibid.*, **96,** 5561 (1974); K.-H. Geiss, B. Seuring, R. Pieter, and D. Seebach, *Angew. Chem.*, **86,** 484 (1974); D. Seebach, K.-H. Geiss, and M. Pohmakotr, *ibid.*, **88,** 449 (1976); H. Ahlbrecht and G. Rauchschwalbe, *Synthesis*, 417 (1973); H. W. Thompson and B. S. Huegi, *J. Chem. Soc., Chem. Commun.*, 636 (1973). (b) G. Büchi and H. Wüest, *J. Org. Chem.*, **34,** 1122 (1969); K. Kondo and D. Tsunemoto, *Tetrahedron Lett.*, 1007, 1387 (1975). (c) Two-step approach which involves final oxidation of the latent acyl carbon to attain the requisite oxidation level: P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37,** 1947 (1972); B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95,** 5321 (1973).

(6) Various procedures for anion formulated as i have been devised: E. J. Corey,



i

B. W. Erickson, and R. Noyori, *J. Am. Chem. Soc.*, **93,** 1724 (1971); T. Nakai, H. Shiono, and M. Okawara, *Tetrahedron Lett.*, 3625 (1974); Y. Leroux and C. Roman, *ibid.*, 2585 (1973); T. Cohen, D. A. Bennett, and A. J. Mura, Jr., *J. Org. Chem.*, **41,** 2506 (1976); P. T. Lansbury and R. W. Britt, *J. Am. Chem. Soc.*, **98,** 4578 (1976); M. Wada, H. Nakamura, T. Taguchi, and H. Takei, *Chem. Lett.*, 345 (1977); see also E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *J. Am. Chem. Soc.*, **94,** 4395 (1972), and ref 5b.

(7) (a) Cyclopropanols react with proton and halogenating agents.[2] (b) An attempt to effect a fluoride catalyzed reaction of **5** failed; cf. R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **99,** 1265 (1977).

(8) K. Rühlmann, *Synthesis*, 236 (1971).

(9) (a) Preparation of 4-hydroxyheptanoic lactone illustrates the standard reaction conditions. A solution of **5** (6.09 g, 35 mmol) in 10 mL of methylene chloride was added during 5 min to a thick yellow suspension of $TiCl_4$ (6.26 g, 33 mmol) and propanal (2.16 g, 30 mmol) in 20 mL of methylene chloride at −78 °C under nitrogen. The resulting dark brown solution was stirred for 15 min at −78 °C, and for 1 h at 0 °C, and quenched by slow addition of water. The crude product consisted mainly of the expected lactone. Treatment of the crude lactone with *p*-toluenesulfonic acid hydrate in refluxing benzene gave, on distillation, 2.96 g (77%) of the lactone, bp 76–78 °C (2.3 mm). (b) All final compounds in the text were fully characterized by spectral data and elemental composition. All yields referred to are isolated (TLC or distillation) yields.

(10) Distilled product showed two methyl doublets of equal intensities at δ 1.57 (J = 7 Hz) and at δ 1.74 (J = 5 Hz) on NMR. IR spectrum exhibited only a trans olefinic bond at 967 cm^{-1} of medium intensity.

(11) (a) $BF_3{\cdot}Et_2O$, $AlCl_3$, Cp_2TiCl_2, and $ZrCl_4$ brought about only very slow consumption of starting materials and/or gave complex mixture. $SnCl_4$ reacted with **5,** even in the presence of an acetal to give a β-stannyl ester in good yield. (b) We have not yet been successful to effect the coupling of **5** with aliphatic acetals and benzoyl chloride. This observation strongly contrasts with the high reactivities of enol silyl ethers with these substrates (T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 15 (1974); E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, **99,** 961 (1977); R. E. Donaldson and P. L. Fuchs, *J. Org. Chem.*, **42,** 2032 (1977)). (c) Although another type of cyclopropane ring cleavage to form allylic cation is possible (initiated by coordination of $TiCl_4$ with the acetal moiety of **5**), we have not detected any products of such an origin.

(12) K. C. Bishop III, *Chem. Rev.*, **76,** 461 (1976).

(13) (a) C. H. DePuy and R. H. McGirk, *J. Am. Chem. Soc.*, **96,** 1121 (1974). (b) For the reactions of mercury(II) with cyclopropanes in general, see K.-P. Zeller and H. Straub in "Methoden der Organischen Chemie," E. Muller, Ed., Bend XII/2b, Georg Thieme Verlag, Stuttgart, 1974, pp 201–206.

(14) (a) A review: P. C. Wailes, R. S. P. Coutts, and H. Weigold, "Organometallic Chemistry of Titanium, Zirconium, and Hafnium", Academic Press, New York, N.Y., 1974. (b) D. F. Herman and W. K. Nelson, *J. Am. Chem. Soc.*, **75,** 3877 (1953); J. Causse, R. Tabacchi, and A. Jacot-Guillarmod, *Helv. Chim. Acta*, **55,** 1560 (1972).

(15) Attempts to detect a species like **13** on low temperature ^1H NMR have thus far been unsuccessful. We thank Professor T. Nakai and Mr. K. Tanaka for helping us to carry out the measurement.

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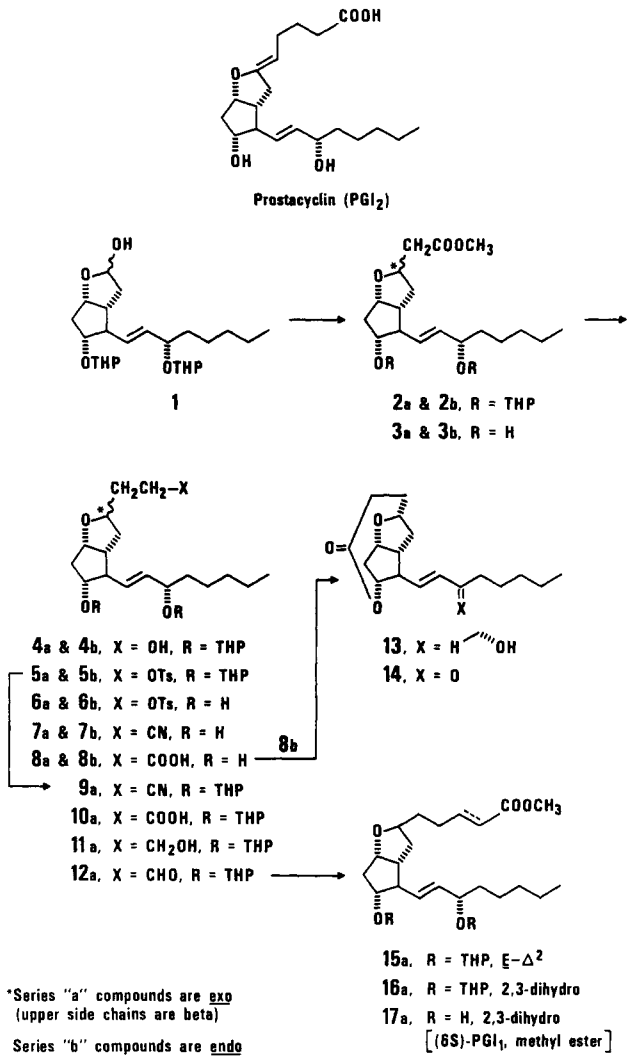
Stereoconfiguration of 5,6-Dihydroprostacyclins

Sir:

Recent communications have described the isolation,[1] biology,[1] synthesis, and stereochemistry[2-4] of prostacyclin (PGI_2),[5] a remarkable new prostaglandin which appears to have an important role in preventing thrombosis.[1] From a pharmaceutical standpoint, prostacyclin suffers a serious disadvantage in that it is rapidly hydrolyzed to the less active 6-oxo-$PGF_{1\alpha}$ even at pHs as high as 7.6.[2] Reduction of the acid-labile enol ether double bond should lead to chemically stable analogues (PGI_1s) which hopefully will retain the desirable characteristics of PGI_2. Past developments indicate that much effort will occur on the synthesis of PGI_1 analogues and it becomes desirable, therefore, to have a way of determining the configuration of isomers at C-6 by some simple procedure.[6] This communication describes an unambiguous assignment



of configuration for PGI_1 isomers at C-6 and, in concert with Johnson's[4,6] NMR observations of PGI_1 isomers, a method of distinguishing such isomers in future analogues of PGI_1.

Reaction of lactol **1**[7] with trimethylphosphonoacetate and potassium *tert*-butoxide (tetrahydrofuran, 20 °C, 2 h) afforded 82% of a mixture of **2a** and **2b,** which was not readily separated by chromatography. Depyranylation (20:10:1 acetic acid–water–tetrahydrofuran at 40 °C for 4 h) of the mixture and repeated chromatographic purification (on E. Merck silica gel 60, 40–63 μ, 40–60% acetone in methylene chloride) gave 16% *endo*-carboxy side-chain isomer **3b** (mp 47–48 °C, R_f 0.41 on silica gel TLC plate with 4:6 acetone–methylene chloride) and 68% *exo*-carboxy side-chain isomer **3a** (R_f 0.35).[8]

To generate a definitive assignment of configuration at C-6 (prostaglandin numbering)[9] in these PGI_1 analogues, we set out to construct a short bridge between C-6 and C-11, a feat possible only with the isomer having the upper side chain in the endo configuration. Thus, **3a** and **3b** were repyranylated (dihydropyran, pyridine hydrochloride, 25 °C, 16 h) to give **2a** (R_f 0.59, silica gel plate, 1:1 ethyl acetate–hexane) and **2b** (R_f 0.67), respectively. Reduction of each isomer with lithium aluminum hydride gave **4a** and **4b,** respectively, each of which was treated with *p*-toluenesulfonyl chloride and pyridine (25 °C, 5 h) to give **5a** and **5b.** Depyranylation (as above) gave **6a** (84% from **3a,** R_f 0.33, silica gel plate, ethyl acetate) and **6b** (62% from **3b,** R_f 0.37), respectively. Each isomer (**6a** and **6b**) was treated with methanolic sodium methoxide and with potassium *tert*-butoxide in tetrahydrofuran in an effort to demonstrate formation of a cyclic ether[10] with one of them via an