JOC Article

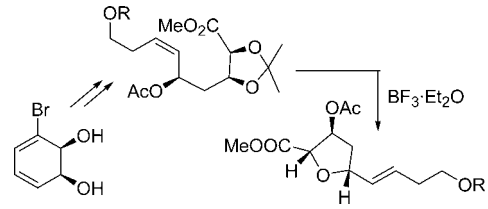
Stereoselective Synthesis of 3-Oxygenated-*cis*-dialkyl-2,5-substituted Tetrahydrofurans from Cyclohexadienediols

Margarita Brovetto* and Gustavo Seoane

Departamento de Química Orgánica, Facultad de Química, Universidad de la República, C.C. 1157, Montevideo, Uruguay

mbrovett@fq.edu.uy

Received March 5, 2008



The 3-oxygenated-*cis*-dialkyl-2,5-substituted tetrahydrofuran system, present in several natural products, was prepared with good selectivity by acidic cyclization of 5-alkene-1,2,4-triol derivatives. The starting alkenol was obtained in few steps from a chiral *cis*-diol resulting from microbial oxidation of bromobenzene. The study of the cyclization allowed the rationalization of all experimental results by assuming a complete ionization at the allylic position and a model close to the one proposed by Labelle for homoallylic induction in five-membered ring closures.

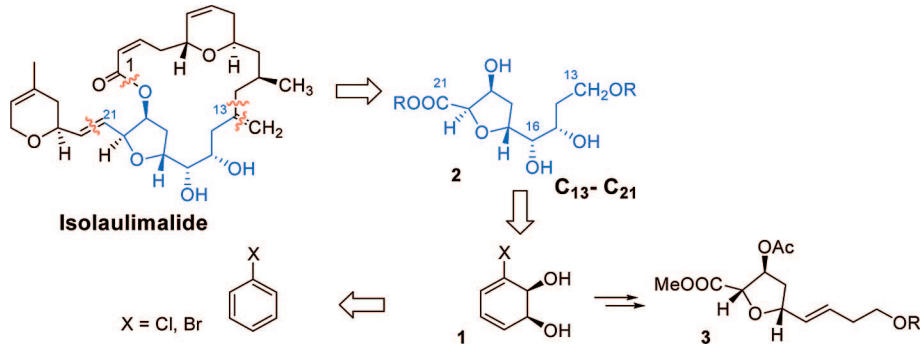
Introduction

2,5-Disubstituted tetrahydrofurans (THF) constitute important structural and functional subunits in various bioactive natural products including the group of cytotoxic polyethers,[1,2] polyether antibiotics,[3,4] antitumor acetogenins,[5–8] etc. As a result, the stereoselective construction of both *cis*- and *trans*-2,5-disubstituted tetrahydrofurans has drawn considerable attention from synthetic chemists. Several strategies have been described in this pursuit, namely, cyclization of 4-alkenols,[9–13] 3-alkenols,[14,15] and epoxy alcohols;[16–20] Ti-mediated coupling of acetylated γ-lactols or lactones with chiral enolates;[21,22] tandem 1,3-dipolar cycloaddition/electrophilic cyclizations supported on a polymer;[23] asymmetric [3 + 2]-annulation of chiral β-silyloxyallylsilanes;[24] cyclization of 1,4-diols[25,26] derived from several chiral templates; oxidative cyclization of 1,5-dienes;[27] etc. Many of these procedures suffer from moderate stereoselectivity and lengthy routes. In addition, only a few of the reported approaches led to the formation of either *cis*-[11,16,27] or *trans*-2,5-disubstituted THF.[9,13,15,21,22] Thus, the design and development of a simple and stereocontrolled strategy to construct 2,5-disubstituted

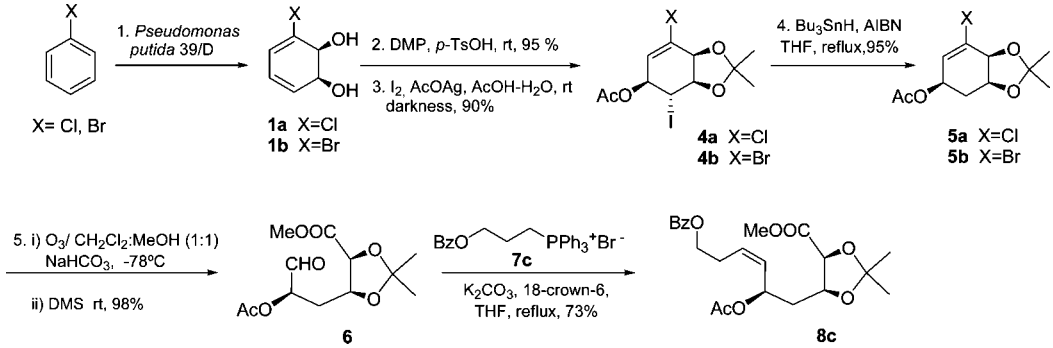
(1) Kang, S. H.; Lee, S. B. *Chem. Commun.* **1998**, 761–762.
(2) Matsuo, Y.; Suzuki, M.; Masuda, M. *Chem. Lett.* **1995**, 1043–1044.
(3) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3–72.
(4) O'Hagan, D. *Nat. Prod. Rep.* **1989**, *6*, 205–209.
(5) Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540.
(6) Hoppe, R. S.; Scharf, H. D. *Synthesis* **1995**, 1447–1464.
(7) Keinan, E.; Sinha, A.; Yazbak, A.; Sinha, S. C. *Pure Appl. Chem.* **1997**, *69*, 423–430.
(8) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275–308.
(9) Michael, J. P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1985**, *50*, 2416–2423, and references therein.
(10) Miura, K.; Hondo, T.; Okajima, S.; Hosomi, A. *Eur. J. Org. Chem.* **2006**, 3251–3258.
(11) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963–3964.
(12) Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1799–1803.
(13) Zhang, H.; Mootoo, D. R. *J. Org. Chem.* **1995**, *60*, 8134–8135.
(14) Bew, S. P.; Barks, J. M.; Knighta, D. W.; Middletona, R. J. *Tetrahedron Lett.* **2000**, *41*, 4447–4451.
(15) Kang, S. H.; Lee, S. B. *Tetrahedron Lett.* **1993**, *34*, 1955–1958.
(16) Arista, L.; Gruttadauria, M.; Thomas, E. J. *Synlett* **1997**, 627–628.
(17) Chattopadhyay, A.; Vichare, P.; Dhotare, B. *Tetrahedron Lett.* **2007**, *48*, 2871–2873.
(18) Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 2745–2748.
(19) Nakata, T.; Schmid, G.; Vranesic, M.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933–2935.
(20) Narayan, R. S.; Sivakumar, M.; Bouhlel, E.; Borhan, B. *Org. Lett.* **2001**, *3*, 2489–2492.
(21) Jalce, G.; Seck, M.; Franck, X.; Hocquemiller, R.; Figadere, B. *J. Org. Chem.* **2004**, *69*, 3240–3241.
(22) Pilli, R. A.; Riatto, V. B.; Vencato, I. *Org. Lett.* **2000**, *2*, 53–56.
(23) Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 10061–10062.
(24) Mertz, E.; Tinsley, J. M.; Roush, W. R. *J. Org. Chem.* **2005**, *70*, 8035–8046.
(25) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2005**, *7*, 4819–4822.
(26) Sharma, G. V. M.; Punna, S.; Prasad, T. R.; Krishna, P. R.; Chorghade, M. S.; Ley, S. V. *Tetrahedron: Asymmetry* **2005**, *16*, 1113–1123.
(27) Goksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433–3436, and references therein.

10.1021/jo800514k CCC: $40.75
Published on Web 06/27/2008

SCHEME 1. Chemoenzymatic Route to 3-Oxygenated-*cis*-2,5-substituted Tetrahydrofurans



SCHEME 2. Synthesis of 8c



tetrahydrofurans (THF) has assumed considerable importance in organic synthesis.[28,29]

During our studies on the chemoenzymatic synthesis of isolaulimalide[30–34] starting from cyclohexadienediols of microbial origin of type **1**,[35] we required a stereoselective route to the 3-hydroxy-*trans*-2,5-dialkyl tetrahydrofuran **2** present in the $C_{13}-C_{21}$ fragment, Scheme 1. However, during the manipulation of protecting groups in the acyclic precursor aiming at an intramolecular Williamson reaction, an unexpected cyclization afforded *cis*-2,5-trisubstituted THF, **3**, in good yields. Herein, we present a chemoenzymatic route to 3-oxygenated-*cis*-2,5-substituted tetrahydrofurans of type **3** starting from either chloro- or bromobenzene, as well as mechanistic studies accounting for the stereoselectivity of the cyclization.

Results and Discussion

The sequence started with the toluene dioxygenase-mediated oxidation of halobenzenes to produce enantiopure *cis*-diols, **1**, using *Pseudomonas putida* 39/D, Scheme 2.[35,36] From either diol **1**, acetylated halohydrins of type **4** were obtained in two steps, through acetonide protection of the diol functionality followed by acetoxyiodination using acetyl hypoiodite as source of halogen (Prévost reaction). The stereoselectivity of the halohydrin-forming reaction was thoroughly studied, varying the halonium donor, medium polarity, and temperature.[37] Best results were obtained under Prévost conditions, which afforded iodoacetates **4a** and **4b** in excellent yields and selectivity (99:1 dr). The major isomers present a coupling pattern for the H geminal to the iodine consisting of a triplet with $^3J_{H-H}$ 7.5−7.8 Hz, suggesting a *trans*-diaxial relationship with its neighbors. Further radical dehalogenation using tributyltin hydride gave acetates **5a** and **5b** in 95% yields, which were ozonized under reductive conditions to give aldehyde-ester **6**.

The excellent yield of the ozonolysis was obtained after some experimentation, trying different solvent mixtures and bases.[38] Best results were obtained in a 1:1 mixture of CH_2Cl_2/MeOH, in the presence of $NaHCO_3$ (3 equiv), using 8 equiv of DMS in the reductive step, Scheme 3. In our synthetic design for the $C_{13}-C_{21}$ fragment of Isolaulimalide, the aldehyde group in **6**, corresponding to C_{16} of the fragment, would react with a three carbon residue to give a *Z*-olefin, which would then be osmylated to give the requisite $C_{13}-C_{16}$ side chain. Owing to the presence of a labile α-acetoxy group in **6**, the mild conditions reported by Boden were chosen for the olefination.[39] Accordingly, different phosphonium salts were tried for the *Z*-selective Wittig-type olefination.[40] In all cases the selectivity was

(28) Harmange, J.-C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754.
(29) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261–290.
(30) Corley, D.; Herb, R.; Moore, R. E.; Sheuer, P. J. *J. Org. Chem.* **1988**, *53*, 3644–3646.
(31) Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, *77*, 5–778.
(32) Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159–162.
(33) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642–3644.
(34) Tanaka, J.; Higa, T.; Bernardinelli, G.; Jefford, C. *Chem. Lett.* **1996**, 255–256.
(35) Brovetto, M.; Schapiro, V.; Cavalli, G.; Padilla, P.; Sierra, A.; Seoane, G.; Suescum, L.; Mariezcurrena, R. *New J. Chem.* **1999**, *23*, 549–555.
(36) Vitelio, C.; Bellomo, A.; Brovetto, M.; Seoane, G.; González, D. *Carbohydr. Res.* **2004**, *339*, 1773–1778.
(37) Carrera, I.; Brovetto, M.; Seoane, G. *Tetrahedron* **2007**, *63*, 4095–4107.
(38) Brovetto, M. Cyclization studies of tetrahydrofuran rings as precursors of isolaulimalide. Ph.D. Thesis, Universidad de la República, 2006.
(39) Boden, R. M. *Synthesis* **1975**, 784–784.
(40) **General Procedure for the Phosphonium Salt.** Triphenylphosphine (1.7 mmol) was added to a solution of alkyl halide (1.6 mmol) in dry solvent (toluene or xylene) under a N_2 atmosphere. The reaction mixture was heated to reflux until consumption of the halide. When the reaction was complete, the solvent was removed under reduced pressure, and the residue was washed several times with dry hexanes until disappearance of triphenylphosphine by TLC. The resulting syrup was crystallized from a mixture of CH_2Cl_2/ Hexanes.

SCHEME 3. Optimization of Ozonolysis and Wittig Reactions

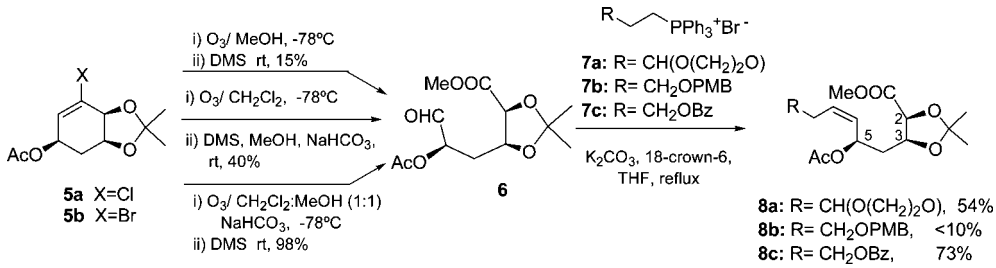
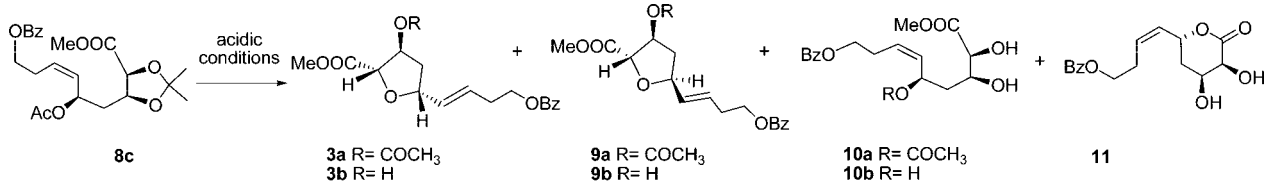


TABLE 1. Cyclization Studies of 8c in Acidic Conditions



		product, yield (%)				*cis*/*trans* ratio[a]		
entry	reaction conditions	**3a,b**	**9a,b**	**10a,b**	**11**	**a**	**b**	overall yield (%)
1	Dowex (50WX8-200), MeOH:H_2O (99:1), rt, 72 h			**10a**, 45; **10b**, 14	8			67
2	10% HCl, MeOH, rt, 24 h	**3a**, 14; **3b**, 20	**9a**, 29; **9b**, 20	**10b**, 33		7:1	1:1	89
3	$CuCl_2 \cdot 2H_2O$ (2eq), CH_3CN, 0 °C to rt, 24 h	**3a**, 40; **3b**, 2	**9a**, 10; **9b**, 2	**10a**, 44		4:1	1:1	98
4	$BF_3.Et_2O$ (2 eq), CH_2Cl_2, 0 °C, 72 h	**3a**, 52; **3b**, 0.5	**9a**, 6; **9b**, 0.5	**10a**, 13	8	9:1	1:1	80
5	$BF_3.Et_2O$ (2 eq), CH_2Cl_2, rt, 24 h	**3a**, 11; **3b**, 27	**9a**, 7; **9b**, 27			3:2	1:1	72 (87)[b]
6	$BF_3.Et_2O$ (2 eq), Toluene, −20 to 0 °C, 48 h	**3a**, 33; **3b**, 11	**9a**, 22; **9b**, 11			3:2	1:1	77

[a] The product distribution was determined by NMR on the crude of reaction, by integration of representative signals. The *cis*/*trans* isomers were not successfully separated by column chromatography or by HPLC. Basic characterization was performed on a 9:1 mixture, entry 4. [b] An additional 15% of a 7:3 *cis*/*trans* mixture of dihydropyranes **12** was also obtained (see structure in Scheme 4).

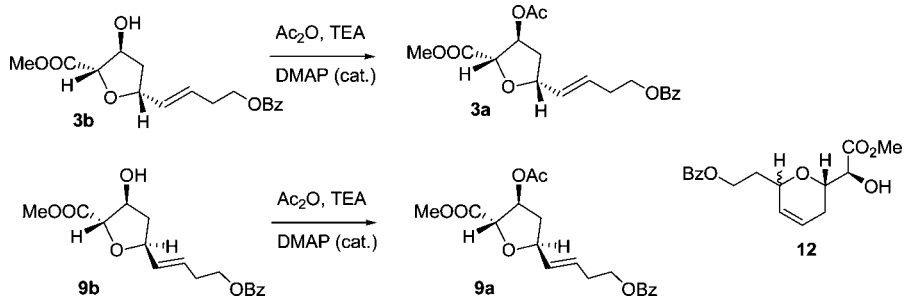
excellent; the *E*-isomer was not detected by NMR spectroscopy in any of the reaction mixtures. The *Z*-geometry of the double bond was assigned on the basis of the value of the corresponding coupling constants and NOE data for the olefinic protons: a $^3J_{H-H}$ of 10.5−10.8 Hz and NOE enhancements of 11% were found. The isolated yields were acceptable only for the phosphonium salt **7c**, and the corresponding compound **8c** was carried through, Scheme 3.

With olefin **8c** in hand, we were ready to perform some functional group manipulations in order to investigate the cyclization to the tetrahydrofuran ring. To this end, the allylic acetate had to be removed and the acetonide on C_2-C_3 replaced by a leaving group, thus allowing the allylic alcohol on C_5 to effect a displacement on C_2 (see Scheme 3 for numbering in **8c**). In this way the THF ring would be formed through an intramolecular Williamson reaction.[41] A number of acidic, basic, and also enzymatic conditions were tested for the deprotection of either the acetonide or the acetate group: Dowex resin 50WX8-200 (H^+ form), MeOH/H_2O (99:1), room temperature;[36] $CuCl_2 \cdot 2H_2O$, CH_3CN, 0 °C to room temperature;[42–44] $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C to room temperature;[45,46] K_2CO_3, MeOH, room temperature; [47] Bu_4NOH, CH_2Cl_2, room temperature; guanidine hydrochloride, TEA, MeOH/CH_2Cl_2 (9:1) room temperature;[48] *Candida antarctica* lipase A, MeOH, 30 °C; *Candida antarctica* lipase B, MeOH, phosphate buffer pH 7, 30 °C.[49] None of the conditions used produced the desired compounds in acceptable yields, the reactions being always complicated by concomitant nonselective deprotection of the remaining esters or other side reactions. In particular, under acidic conditions, the products of the reaction were mainly THF rings, Table 1.

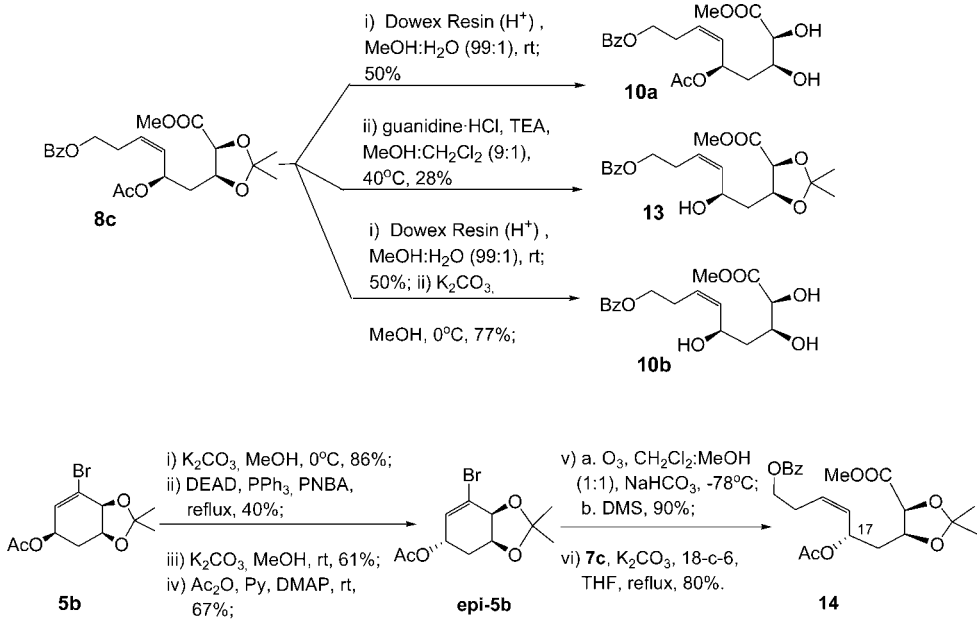
The use of a strongly acidic resin (entry 1) produced mostly the deprotection of the acetonide giving the diol **10a**, together with some triol, **10b**, which also lactonized to **11**. On the other hand, when using strong mineral or Lewis acids (entries 2−6), the main products were always THF rings of type **3** and **9**. It is interesting to note that both types of THF rings present an *E*-configuration of the double bond, thus suggesting a complete isomerization of the *Z*-olefin in **8c** along the reaction pathway (see below for mechanistic details). We found that mineral acids (entry 2) gave mostly THF rings with a free β-hydroxy group, corresponding to the type *b*, whereas Lewis acids favor the cyclization to form β-acetoxy THF rings of type *a*, except for entry 5. By inspecting the *cis*/*trans* ratio of THF rings (ratio **3**:**9**) a definite pattern is seen: the *cis*/*trans* ratio of acetylated THF rings (type *a*) always favors the *cis*-isomer (compound **3a**) in different proportions depending on the conditions used (from 6:4 to 9:1 *cis*/*trans*, entries 2−6), whereas for the free hydroxyl series (type *b*) the ratio is always 1:1, and remains constant regardless of the conditions (entries 2−6). This suggests

(41) Koert, U. *Synthesis* **1995**, 115–132.
(42) Aranda, G.; Cortés, M.; Maurs, M.; Azerad, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2013–2018.
(43) Ko, K.-Y.; Park, S.-T. *Tetrahedron Lett.* **1999**, *40*, 6025–6027.
(44) Saravanan, P.; Chadrasekhar, M.; Anand, R. V.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3091–3092.
(45) Kinderman, S. S. *Adv. Synth. Catal.* **2002**, *344*, 736–748.
(46) Prestat, G.; Baylon, C.; Heck, M. P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3829–3831.
(47) Schapiro, V.; Cavalli, G.; Seoane, G.; Faccio, R.; Mombrú, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2453–2459.
(48) Kunesch, N.; Miet, C.; Poisson, J. *Tetrahedron Lett.* **1987**, *28*, 3569–3572.
(49) (a) Berglund, Hult, K. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker Inc.: New York. (b) Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 611–633.

SCHEME 4. Stereochemistry of the *a* and *b* Series



SCHEME 5. Selective Deprotection of 8c and Synthesis of Epimer 14



that the cyclization to form THF rings of either type (*a* or *b*) proceeded by different mechanisms.

The stereochemical assignments of all compounds were done according to NOE experiments and *J* analysis performed on different isomeric mixtures (Figure 1). The data obtained for the *cis* and *trans* isomers agreed well with the NOE enhancements[50] and *J* values[30,33] reported in the literature for these systems.

Also, the stereochemistry of the deacetylated THF rings, corresponding to the *b* series, was assigned in a similar way by means of *J* analysis and NOE measurements. Moreover, additional evidence for the proposed structures of THF **3b** and **9b** was obtained by acetylation of the free alcohol, giving monoacetates of identical structure to **3a** and **9a**, Scheme 4.

Table 1 shows that, in addition to THF, other rings were formed in some of the conditions tested (entries 1, 4, and 5). In entry 1, the strongly acidic resin deprotected first the acetonide giving **10a**, which was identified by TLC in the reaction mixture. Further removal of the acetate afforded **10b**, which formed the corresponding lactone **11**. When using $BF_3 \cdot Et_2O$ (entries 4−6) different types of rings were formed, depending on the temperature and polarity of the reaction medium. Whereas the reaction in toluene afforded exclusively THF rings (entry 6), the use of the more polar dichloromethane gave also dihydropyranes (entry 5) and lactone **11** (entry 4). The formation of dihydropyranes **12** (15% yield of a 7:3 *cis*/*trans* mixture) involved the nucleophilic attack of the C_3-alcohol on the distal carbon of an allylic carbocationic species via an overall 6-*endo*-cyclization (vide infra). Lactone **11** was produced through removal of the acetonide protecting group and further lactonization (vide infra). The use of the milder Lewis acid $CuCl_2 \cdot 2H_2O$ afforded THF rings as the sole cyclic products (entry 3).

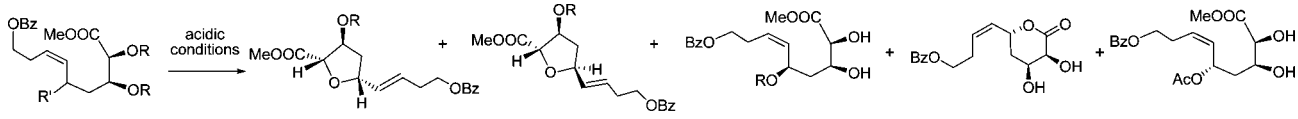
In summary, by an adequate choice of the reaction conditions, the acidic cyclization of **8c** led exclusively to THF rings, although variable *cis*/*trans* mixtures were produced. The highest *cis*/*trans* ratio was achieved for compound **3a** upon treatment of the precursor **8c** with $BF_3 \cdot Et_2O$ (2 equiv) in CH_2Cl_2 at 0 °C for 72 h, giving a 9:1 *cis*/*trans* mixture, representing a 52% yield of **3a**, entry 4. However, considering the long reaction time (72 h) and the presence of other cyclic products (8% of **11**), the reaction conditions chosen for preparative purposes corresponded to entry 3, giving 50% of a 8:2 *cis*/*trans* mixture in only 24 h (representing a 40% of **3a**), together with 44% deprotected diol **10a**, which can be recycled.[51]

It was previously mentioned that the presence of either an acetate or a free hydroxyl in the THF rings (corresponding to

(50) Durand, T.; Guy, A.; Vidal, J.-P.; Rossi, J.-C. *J. Org. Chem.* **2002**, *67*, 3615–3624.

(51) To establish the usefulness of the methodology, in one run the deprotected diol was separated and recycled to give, after acetonization (95%), an additional 17% of **3a**, which was thus obtained in a 57% overall yield.

TABLE 2. Cyclization of Selectively Protected 5-Alkene-1,2,4-triols[a]



8c R= CMe_2, R'= β-AcO
10a R= H, R'= β-AcO
13 R= CMe_2, R' = β-OH
10b R= H, R'= β-OH
14 R=CMe_2, R'= α-AcO

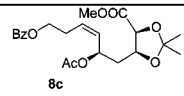
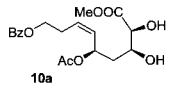
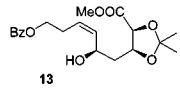
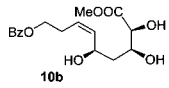
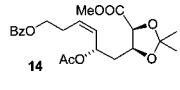
3a R= Ac
3b R= H

9a R= Ac
9b R= H

10a R= Ac
10b R= H

11

15

Entry	Acyclic precursor	Product yield (%)*					Overall yields (%)	Reaction time (h)
		3a,b	**9a,b**	**10a,b**	**11**	**15**		
1	 **8c**	**3a**, 40 **3b**, 2	**9a**, 10 **9b**, 2	**10a**, 44	--	--	98	24
2	 **10a**	**3a**, 13	**9a**, 3	starting material, **10a**, 80	--	--	16	72
3	 **13**	**3b**, 8	**9b**, 8	**10b**, 65	16	--	97	24
4	 **10b**	**3b**, 45	**9b**, 45	--	2	--	92	48
5	 **14**	**3b**, 3	**9b**, 3	--	--	76	82	48

[a] Reaction conditions: $CuCl_2.2H_2O$ (2 equiv), CH_3CN, rt. All reactions were run until consumption of the starting material, except for entry 2.

compounds **3** and **9** of type *a* or *b*, respectively) caused a significant shift in the *cis*/*trans* selectivity. In order to get some insight into the reasons for this selectivity change, we studied the acidic cyclization of selectively deprotected precursors, namely, diol **10a**, allylic alcohol **13**, triol **10b**, and the C_5 epimer of **8c**, acetate **14**.[52] These precursors were prepared by selective deprotection of **8c** and, for epimer **14**, through a Mitsunobu inversion of the allylic acetate in **5b**, Scheme 5.

The cyclizations were run as already mentioned (entry 3 of Table 1), using $CuCl_2 \cdot 2H_2O$ in acetonitrile, at room temperature, until TLC analysis indicated completion, Table 2.[42–44]

Analysis by TLC of the reaction mixtures indicated that, when both protecting groups were present (compounds **8c** and **14**), the more labile was always the acetonide (the only deprotected products found were **10a** and **15**, respectively). For compounds containing an allylic acetate (**8c**, **10a**, and **14**), migration of this group to the alcohol on C_3 was observed in the cyclized products, except for the epimeric acetate **14**. In this case the cyclic compounds were deacetylated, although they accounted for less than 10% of the product distribution (**3b** and **9b**). This seems to indicate that the migration is heavily dependent on conformational requirements (entries 1 vs 5). In addition, neither the TLC nor the ^1H NMR analysis of aliquots of the reaction mixtures was able to detect the intermediacy of the acyclic product containing the acetate migrated to the C_3 position, which is consistent with an active participation of the acetate in the cyclization process.

The protecting groups influence the *cis*/*trans* selectivity in a differential way. Whereas the acetonide produces no effect in the selectivity (compare entries 1 vs 2, and 3 vs 4), the acetate has a profound effect in the *cis*/*trans* ratio and its absence causes a total lack of selectivity (compare entries 1 vs 3, and 2 vs 4). Additionally, the configuration of the carbon atom bearing the acetate is determinant for the course of the reaction, giving high yields of THF rings only when using **8c** (for the epimer **14**, less than 10% of cyclized products are formed under the same conditions).

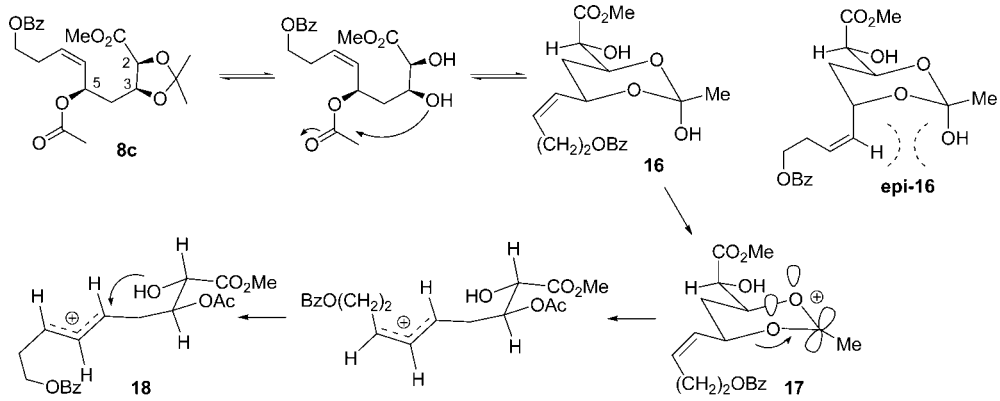
The rate of cyclization is also dependent on the protecting groups. It is much faster when both groups are present, giving the highest yield of THF rings in the shortest time (24 h, entry 1). The rate decreases with the removal of both (entry 4) or either one of the protecting group (entries 2 and 3).

For the allylic alcohol **13**, the reaction gave mostly the product of deprotection, triol **10b**, together with lactone **11** and a 1:1 mixture of THF rings. In addition, when the reaction was left to proceed until consumption of triol **10b**, the final product distribution was similar to entry 4. This separate experiment was monitored by TLC-scanning densitometry, which allows for rapid quantification of the different species using the UV spectrum of the benzoate.

Compound **8c** and its derivatives present multiple regio- and stereochemical routes for reaction under acidic conditions,

(52) The change of the acetate for other acyl protecting group, namely, benzoate, was also performed. When the benzoate **10c** (R = PhCO) was submitted to the cyclization conditions, clean deprotection of the acetonide was observed, giving the corresponding diol as the sole product in 85% yield.

SCHEME 6. Mechanistic Proposal for THF Compounds



namely, cyclizations to form THF, lactones, or dihydropyranes, and also simple deprotection of allylic alcohols and/or 1,2-diols. Under the conditions tested all derivatives afforded THF rings as the major cyclic products, although their reactions displayed ample variations in product distribution, ratesm and selectivities. However, based in the results presented in Tables 1 and 2, several features can be noticed:

(a) The rate of cyclization depends on the given arrangement of protecting groups.

(b) All detected products present the olefin of the side chain exclusively as the *E*-isomer, suggesting the formation of a fully developed carbocation, which can isomerize to the more stable configuration during the reaction.

(c) In all products the configurations of C_2 and C_3 are preserved whereas the configuration at C_5 is either retained (in THF **3**) or inverted (in THF **9**), which is consisting with a nucleophilic attack of the C_2-hydroxyl to C_5. This reinforces the previous point and prevents the consideration of competing mechanisms involving an S_N2-type attack on the allylic alcohol of C_5 (which would produce a different stereochemical outcome).

(d) The *cis*/*trans* selectivity to form THF rings depends on the reactions conditions (temperature, medium, and catalyst, Table 1) and mainly on the presence of the allylic acetate. It is noteworthy the effect on the selectivity produced by the presence of an acetyl protecting group on the allylic alcohol, suggesting the operation of two mechanistic pathways for cyclization, depending on the presence or absence of this functionality. On the other hand, the fact that the nonacetylated products (series *b*) can be converted into the products of series *a* by simple acetylation is consistent with mechanisms of similar type for both series.

All available data are consistent with the following mechanistic proposal. To start, let us consider the reaction of **8c**. The first step involves the removal of the acetonide group, freeing the 1,2-diol. In this event, the newly unmasked alcohol on C_3 reacts with the acetate on the allylic position to form a cyclic hemiorthoester (2-hydroxy-*m*-dioxane), **16**, presenting the two side chains in equatorial position, Scheme 6. This intermediate in the hydrolysis of orthoesters can react through acidic cleavage at different C−O bonds. According to the work by Deslongchamps[53,54] and others,[55] the hydrolysis of six-membered ring orthoesters is governed by stereoelectronic factors only, favoring the cleavage of the C−O bond presenting two *anti* periplanar lone pairs. In this case the reaction proceeds by cleavage of the exocyclic C−O bond, to form the dioxonium ion **17**. This species can form a stabilized allylic carbocation by cleavage of another C−O bond. In the acidic medium, the allylic carbocation can equilibrate to the more stable isomer, **18**, leading to the *E*-olefin at the end. The driving force for this outcome could be ascribed to the higher stability of the final cationic species which, being acyclic, is able to accommodate the corresponding orbitals for a better overlap than that achieved for the cyclic dioxonium counterpart. In a related work, the evolution of acyclic dioxonium cations to form tertiary carbocations has been observed during the reaction of orthoesters with olefins.[56] The net result is the migration of the acetate and concomitant formation of an allylic carbocation suitably configured to afford an *E*-olefin, which can proceed to form the cyclized products. Experimentally, only products with an *E*-olefin are observed.

For the epimeric acetate, **14**, the reaction is slower and there is no migration of acetate. This is consistent with the proposal, since in this case the formation of the corresponding hemiorthoester, **epi-16**, is prevented by severe 1,3-diaxial interaction between the olefin and the hydroxyl, Scheme 6. As a result, compound **14** gives mostly the free diol **15** (by removal of the acetonide) and less than 10% of cyclic products (through ionization of the acetate).

According to this proposal, the nonacetylated derivatives **10b** and **13** react through a different pathway not involving the intermediacy of an hemiorthoester. However, since their cyclization produces mixtures of THF rings with the configuration at C_5 retained and inverted (**3b** and **9b**, respectively), it is assumed that the allylic carbocation is formed. This species then proceeds to give the same type of THF products, although with different stereoselectivity.

As already mentioned, when the homoallylic alcohol is acetylated, the cyclization proceeds with good selectivity, which is lost for the free alcohol, Table 2. Unlike allylic stereocontrol, which has been frequently studied for electrophile-induced cyclization of hydroxy-alkenes,[57−] examples of homoallylic induction are scarce.[15,56,70–6978] Unfortunately, the distance between the involved centers in homoallylic stereocontrol turns their interaction much weaker and ill-defined. The available

(53) Deslongchamps, P.; Dory, Y. L.; Li, S. *Tetrahedron* **2000**, *56*, 3533–3537.

(54) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463–2490.

(55) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754–1769.

(56) Perron-Sierra, F.; Promo, M. A.; Martin, V. A.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 6188–6199.

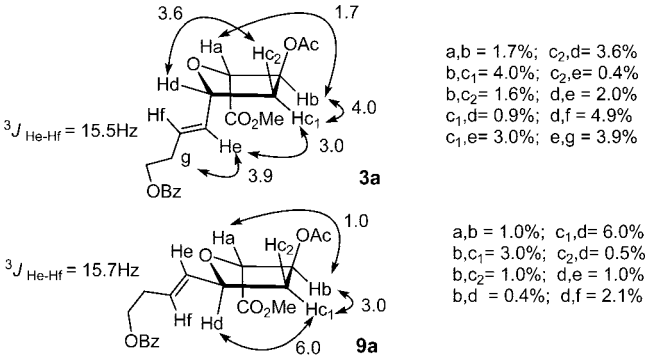
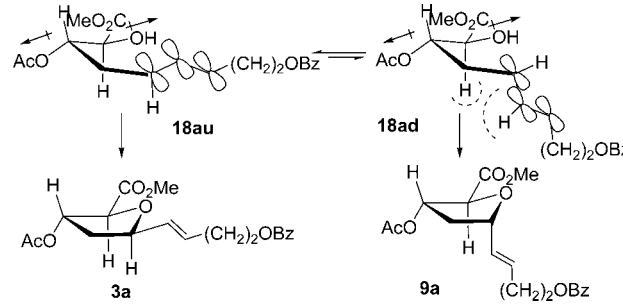


FIGURE 1. Selected NOE enhancements for compounds **3a** and **9a**.

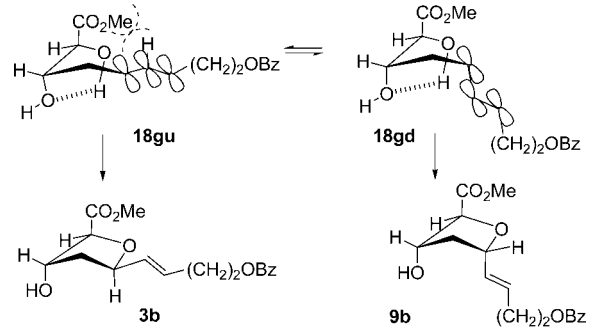
models for 5-*exo* cyclizations postulate a chairlike transition state with the homoallylic alkyl substituent disposed in equatorial position.[70,71] For electronegative substituents (i.e. F, OH, OMe), the axial position is preferred in the transition state.[71] Further substitution in other positions is not accounted for, constituting a limitation of the model. This is especially important when considering additional oxygenated substituents, which are able to interact through hydrogen bonding.[75,79] Another point is related to the geometrical arrangement of the substituents in a five-membered ring, where the positions are "quasi" equatorial and axial.

In our case the homoallylic substituent is either an acetate or a hydroxyl, and an explanation should be advanced for the intriguing selectivity difference. The product distribution we obtained may be rationalized using a model close to the one proposed by Labelle et al. for homoallylic induction cyclization reactions giving THF rings.[71] A chairlike transition state is assumed and the stereochemical outcome is

SCHEME 7. Homoallylic Induction for Cyclization Reaction Giving THF Rings, 3a and 9a



SCHEME 8. Homoallylic Induction for Cyclization Reaction Giving THF Rings, 3b and 9b



controlled by the relative conformation of the vicinal oxygenated substituents and the cationic moiety, Scheme 7. The cationic moiety can adopt two conformations (either up, **18au**, or down, **18ad**), and the preferred one, **18au**, results from steric reasons to avoid the hindrance in the α-face (of the type $A^{1,3}$-strain, as indicated in Scheme 7), which is absent in **18au**. For the nucleophilic terminus, in turn, the major product is consistent with the conformation **18au** having both substituents (carbomethoxy and acetate) in equatorial positions. In this conformation, both oxygenated polar groups (hydroxyl and acetate) are *anti*, which minimize their dipolar interaction. Thus, the preferred arrangement of the oxygenated functions is *anti*, based in electrostatic considerations. In this conformation the attack on the carbocation furnishes the *cis*-THF, **3a**, Scheme 7. The minor *trans*-THF, **9a**, is obtained by hydroxyl attack in conformation **18ad.**

This model may also explain other features of the cyclizations of different derivatives, such as the deacetylated **10b** and **13**. For the deacetylated compounds, the complete lack of stereoselection in the cyclizations may be the result of strong hydrogen bonding between the hydroxyl groups, which is not favored in the acetate **8c**, Scheme 8. As a result of hydrogen bonding the two hydroxyls are *gauche* (giving rise to the conformations **18g**), thus forcing the carbomethoxy group on C_2 to adopt an axial position. In this situation, the relative stability of the cationic moiety changes. The cationic end can adopt the conformation **18gd** (with the olefinic side chain down), in order to avoid the steric hindrance produced by the axial substituent on C_2 (of the type $A^{1,3}$ strain), which is present in **18gu**. Again, during the cyclization of the free diols, the presence of hydrogen bonding causes the C_2 substituent to adopt an axial position, which hinders the β-face and destabilizes the conformation **18gu**, and thus attack can occur to an equal extent on both faces of the cationic species, giving THF **3b** and **9b** in a 1:1 ratio, Scheme

(57) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819–5825.
(58) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672–677.
(59) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204–2210.
(60) Lipshutz, B. H.; Barton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1084–1086.
(61) Mihelich, E. D.; Hite, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7318–7319.
(62) Pougny, J. R.; Nassr, M. A. M.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1981**, 375–376.
(63) Reitz, A. B.; Nortey, S.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III *J. Org. Chem.* **1987**, *52*, 4191–4202.
(64) Reitz, A. B.; Nortey, S. O.; Maryuroff, B. E. *Tetrahedron Lett.* **1985**, *26*, 3915–3918.
(65) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483–4485.
(66) Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S.; Yosbida, Z. *J. Org. Chem.* **1987**, *52*, 4062–4072.
(67) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063–1066.
(68) Tamaru, Y.; Kawamura, S.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 2885–2888.
(69) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2–72.
(70) Andrey, O.; Landais, Y. *Tetrahedron Lett.* **1993**, *34*, 8435–8438.
(71) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533–4540.
(72) Bravo, P.; Resnati, G.; Viani, F.; Amone, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 839–840.
(73) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317–2327.
(74) Bedford, S. B.; Fenton, G.; Knight, D. W.; Shaw, D. *Tetrahedron Lett.* **1992**, *33*, 6505–6506.
(75) Bennett, F.; Bedford, S. B.; Bell, K. E.; Fenton, G.; Knight, D. W.; Shaw, D. *Tetrahedron Lett.* **1992**, *33*, 6507–6510.
(76) Bedford, S. B.; Bell, K. E.; Fenton, G.; Hayes, C. J.; Knight, D. W.; Shaw, D. *Tetrahedron Lett.* **1992**, *33*, 6511–6514.
(77) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Tetrahedron Lett.* **1990**, *31*, 5917–5920.
(78) Adam, W.; Saha-Moller, C. R.; Schmid, K. S. *J. Org. Chem.* **2001**, *66*, 7365–7371.
(79) Byon, C.; Gut, M. *J. Org. Chem.* **1976**, *41*, 3716–3722.

8. The presence of hydrogen-bonded conformations accounting for the formation of THF of the series *a* (**3a** and **9a**) can not be completely ruled out.

A particular case is compound **10a**, which reacts very slowly (80% starting material was recovered after 72 h of reaction). This can be explained through the formation of a chelate with the Lewis acid (Cu(II)), involving the two hydroxyl groups and the acetate. In this way once the complex is formed its stability makes it difficult to proceed with further reactions.

In summary several considerations on the mechanism of the cyclizations of 5-alkene-1,2,4-triol derivatives emerge:
(i) The protecting groups determine the course of the reaction. The acetate is actively involved not only in the *cis*/*trans* selectivity (Schemes 7 and 8) but also in the reaction rate. For the latter case, its participation in the formation of a cyclic hemiorthoester favors the generation of the allylic carbocation needed to cyclize (entries 1 vs 5). Also in this sense, the acetate accelerates the ionization compared to the free allylic alcohol (entries 1 vs 3). For the acetonide, even though this group is the first to be removed, under certain circumstances its presence seems to favor the cyclization (entries 1 vs 2), possibly through interaction with the Lewis acid, thus altering the electrostatic and steric environment.
(ii) Under the acidic conditions tried, the results are in agreement with the intermediacy of an allylic carbocationic species, whose formation is the rate determining step for the cyclization. Evidence for this proposal is found in the stereochemical outcome, the isomerization of the olefinic side chain, and the occasional formation of mixtures of dihydropyranes of type **12** (Table 1, entry 5).
(iii) The nature of the acids is determinant for the product distribution, operating on the relative reactivity of the different groups, allowing for several reaction pathways.
(iv) The selectivity of the reaction depends on the interplay between steric and stereoelectronic factors (Schemes 6, 7, and 8), among others, which determine the relative stability of intermediate species and conformations and, therefore, the final product distribution. The presence of conformations involving active participation of the Lewis acid by complexation can not be ruled out.

Conclusions

In this work we have shown the use of acidic conditions for the cyclization of 5-alkene-1,2,4-triol derivatives to produce 3-oxygenated-*cis*-dialkyl-2,5-substituted tetrahydrofurans with good selectivity. The product distribution is dependent on the choice of protecting groups and, to a minor extent, on the reaction conditions. Higher selectivity and shorter reaction time were obtained when using acetate and acetonide as protecting groups of the allylic alcohol and the diol, respectively.

The cyclization was studied by changing the protecting groups and the stereochemistry of the allylic alcohol. The results were rationalized assuming a complete ionization at the allylic position and a model close to the one proposed by Labelle for homoallylic induction in five-membered ring closures. It is expected that these results could be used as a guide in applications of these cyclizations, which are under way in our laboratory.

Experimental Section

General Procedure for the Prevost Reaction. To a stirred solution of cyclohexadienediol acetonide (1.9 mmol) and silver acetate (657 mg, 3.9 mmol) in acetic acid (20 mL) was added iodine (500 mg, 1.9 mmol) in small lots during 3 h. The mixture was protected from light and stirred at ambient temperature for 3 h. The precipitated silver iodide was filtered off, and the filtrate was diluted with CH_2Cl_2 (50 mL), neutralized with saturated aqueous $NaHCO_3$ (2 × 30 mL,), washed with water (2 × 30 mL), 20% aqueous solution of $NaHSO_3$ (2 × 30 mL), again with water (2 × 30 mL), and dried over Na_2SO_4. After filtration of the solids, the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using hexanes/ethyl acetate as eluant.

(1*R*,2*S*,5*S*,6*S*)-3-Chloro-6-iodo-1,2-isopropylidenedioxycyclohex-3-ene-5-yl Acetate (4a). Yellow crystalline solid; mp 102.0−103.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s,3H), 1.54 (s,3H), 2.13 (s,3H), 4.17 (t,1H, *J* 7.5 Hz), 4.61 (m, 2H), 5.54 (dd, 1H, *J* 3.2, 7.3 Hz), 5.99 (d, 1H, *J* 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 26.4 (HC-I), 26.6 (CH_3), 28.4 (CH_3), 72.6 (HC-O), 75.6 (HC-O), 79.2 (HC-O), 112.2 (C), 126.7 (CH), 133.8 (C), 170.3 (C═O); IR ν_{max} (KBr)/cm^{-1} 3000, 2920,1745, 1375; 1240, 1217; CIMS *m*/*z* (%) 372 (1, M^+), 357 (75, $M^+ - CH_3$), 313 (10, $M^+ -$ OAc), 255 (63, $M^+ -$ Ac $- C_3H_6O_2$), 146 (41), 128 (46), 43 (100, Ac^+); $[\alpha]^{25}_D$ +22° (*c* 0.8, $CHCl_3$). Anal. required for $C_{11}H_{14}O_4ClI$: C, 35.54; H, 3.80%. Found: C, 35.93; H, 4.26%.

General Procedure for the Dehalogenation Reaction. Bu_3SnH (174 mg, 0.6 mmol) was added to a mixture of 1,1′-azobis(cyclohexanecarbonitrile) (ABCC) (3 mg, 0.012 mmol) and compound **4a** or **4b** (0.4 mmol) in dry THF (15 mL) under an nitrogen atmosphere. The reaction mixture was refluxed for 2 h. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, ethyl acetate/hexanes, 15:85) to afford pure products **5a** or **5b**.

(1*S*,2*S*,5*R*)-3-Chloro-1,2-isopropylidenedioxycyclohex-3-ene-5-yl Acetate (5a). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s,3H), 1.50 (s,3H), 2.06 (s,3H), 2.13 (m,2H), 4.45 (m, 2H), 5.30 (qd, 1H, *J* 5.1 Hz), 6.08 (d, 1H, *J* 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 26.6 (CH_3), 28.3 (CH_3), 30.5 (CH_2), 66.7 (HC-O), 72.8 (HC-O), 75.1 (HC-O), 111.0 (C), 127.1 (CH), 135.6 (C), 170.9 (C═O); IR ν_{max} (KBr)/cm^{-1} 2988, 2936, 2876,1740, 1240; 1078, 1023; CIMS *m*/*z* (%) 246 (0.8, M^+), 231 (58, $M^+ - CH_3$), 187 (100, $M^+ -$ OAc), 129 (79), 111 (26), 59 (24, OAc^+), 43 (29, Ac^+); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{15}ClO_4$ $(M + Na)^+$ 269.0551, obsd 269.0559; $[\alpha]^{25}_D$ +30° (*c* 0.1, $CHCl_3$).

(1*S*,2*S*,5*R*)-3-Bromo-1,2-isopropylidenedioxycyclohex-3-ene-5-yl Acetate (5b). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s,3H), 1.52 (s,3H), 2.08 (s,3H), 2.15 (m,2H), 4.44 (td, 1H, *J* 6.0, 6.2 Hz), 4.55 (d, 1H, *J* 5.8 Hz), 5.24 (td, 1H, *J* 4.5, 4.7 Hz), 6.33 (d, 1H, *J* 4.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (CH_3), 26.6 (CH_3), 28.2 (CH_3), 30.4 (CH_2), 67.2 (HC-O), 72.9 (HC-O), 76.3 (HC-O), 110.0 (C), 126.6 (C), 131.3 (HC═), 170.8 (C═O); IR ν_{max} (KBr)/cm^{-1} 2986, 2936, 1736, 1647, 1238; 1078, 1032, 738; EIMS *m*/*z* (%) 290−292 (1, M^+), 275−277 (36, $M^+ - CH_3$), 190−192 (10, $M^+ -$ OAc $- C_3H_6$), 173−175 (39, $M^+ -$ OAc $- C_3H_7O$), 145−147 (9), 111 (7), 94 (12), 65 (14), 43 (29, Ac^+); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{15}BrO_4$ $(M + Na)^+$ 313.0046, obsd 313.0036, $[\alpha]^{25}_D$ +96° (*c* 2.7, $CHCl_3$).

Methyl (2*S*,3*S*,5*R*)-5-Acetoxy-2,3-isopropylidenedioxy-6-oxohexanoate (6). A mixture of O_2/O_3 (60% O_3 in O_2) was bubbled through a solution of compounds **5a** or **5b** (0.35 mmol) and $NaHCO_3$ (88 mg, 1.05 mmol) in CH_2Cl_2 (4 mL) and MeOH (4 mL) at −78 °C, until a blue color persisted. After removal of the excess of O_3 at −78 °C with N_2, dimethyl sulfide (2.8 mmol, 0.2 mL) was added, and the temperature was allowed to rise overnight until room temperature, whereupon the solvent was removed at reduced pressure. The residue was purified by column chromatography (10% deactivated silica gel, hexanes/ethyl acetate, 1:1) to afford com-

pound **6** as an oil (94 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s,3H), 1.57 (s,3H), 2.01 (m,1H), 2.11 (m,1H), 2.21 (s,3H), 3.79 (s,3H), 4.54 (m,1H), 4.68 (d, 1H, *J* 6.7 Hz), 5.23 (t, 1H, *J* 5.5 Hz), 9.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 25.9 (CH_3), 27.3 (CH_3), 31.2 (CH_2), 52.5 (CH_3), 73.5 (HC-O), 75.7 (HC-O), 77.4 (HC-O), 111.6 (C), 170.2 (C=O), 170.6 (C=O), 197 (CHO); IR ν_{max} (KBr)/cm^{-1} 3586, 3564,1755, 1738; 1439, 1373, 1242, 1221, 1093; CIMS *m/z* (%) 275 (0.1, M^++1), 259 (100, $M^+ - CH_3$), 217 (57, $M^+ - CH_3 - C_3H_6$), 199 (10, $M^+ - CH_3 - C_3H_6 - H_2O$), 157 (95, ($M^+$+1) − OAc − COOMe), 127 (18), 97 (25), 73 (15), 59 (17, AcO^+) 43 (95, Ac^+); $[\alpha]^{25}_D$ +1° (*c* 0.5, $CHCl_3$). Anal. required for $C_{12}H_{18}O_7$: C, 52.5; H, 6.6%. Found: C, 52.0; H, 7.0%.

General Procedure for the Wittig−Boden Reaction. A mixture of phosphonium salt (0.15 mmol), K_2CO_3 (0.15 mmol) and catalytic amounts of 18-Crown-6 in THF (12 mL) was refluxed under a N_2 atmosphere for 1 h. After that time a solution of aldehyde (0.10 mmol) in the minimum amount of THF was added dropwise. The system was kept under reflux until there was no more aldehyde by TLC. The reaction mixture was then filtrated through a small pad of silica gel and eluted with a 1:1 mixture of AcOEt/Hex. The filtrate was concentrated under reduced pressure, and the residue purified by flash chromatography.

Methyl (2*S*,3*S*,5*R*,6*Z*)-5-Acetoxy-9-benzoyloxy-2,3-isopropylidenedioxy-6-nonenoate (8c). Oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s,3H), 1.62 (s,3H), 1.80 (m,2H), 2.03 (s,3H), 2.66 (dtd,1H, *J* 1.6, 6.8, 21 Hz), 2.78 (dtd,1H, *J* 1.4, 7.9, 21 Hz), 3.77 (s,3H), 4.31 (ddd,1H, *J* 4.0, 6.7, 9.5 Hz), 4.40 (ddd,2H, *J* 4.0, 6.8, 9.3 Hz), 4.58 (d,1H, *J* 6.7 Hz), 5.44 (dd,1H, *J* 9.8, 10.6 Hz), 5.76 (m,2H), 7.45 (t,2H, *J* 7.7 Hz), 7.57 (dt,1H, *J* 1.2, 7.4 Hz), 8.05 (dd,2H, *J* 1.2, 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3), 25.9 (CH_3), 27.3 (CH_3), 27.8 (CH_2), 35.2 (CH_2), 52.3 (O-CH_3), 64.4 (O-CH_2), 68.1 (HC-O), 74.5 (HC-O), 77.7 (HC-O), 111.3 (C), 128.7 (CH=), 128.7 (CH=), 129.6 (CH=), 129.9 (HC=), 129.9 (HC=), 130.6 (C), 131.0 (HC=), 133.2 (HC=), 166.8 (C=O), 170.2 (C=O), 170.8 (C=O); IR ν_{max} (KBr)/cm^{-1} 2986, 2918, 2851, 1760, 1740, 1721, 1425, 1278, 1240, 1099, 713; EIMS *m/z* (%) 405 (10, $M^+ - CH_3$), 361 (6, $M^+ - AcO$), 302 (10, $M^+ - AcO - COOMe$), 181 (31, $M^+ - AcO - COOMe - BzOH$), 163 (40), 121 (38, $(C_7H_5O_2)^+$), 105 (100, $(C_7H_5O)^+$), 59 (6, AcO^+), 43 (18, Ac^+); UV:λ_{max} 232.0 nm; $[\alpha]^{25}_D$ −8.6° (*c* 2.5, $CHCl_3$). Anal. required for $C_{22}H_{28}O_8$: C, 62.86; H, 6.70%. Found: C, 62.80; H, 7.21%.

General Procedures for Deprotection of the Acetonide Group. Method A: Using Dowex Resin (H^+). Acetonide compound (0.04 mmol) was dissolved in a mixture of MeOH/H_2O (99:1) and stirred at room temperature with Dowex resin (H^+) until reaction was complete. The mixture was filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography.

Method B: Using Hydrochloric acid. Acetonide compound (0.03 mmol) was dissolved in 10% methanolic HCl and stirred at room temperature until reaction was complete. After neutralization with Amberlyst 21 (basic resin), the mixture was filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography.

Method C: Using Cupric Chloride. Solid $CuCl_2 \cdot 2H_2O$ (0.12 mmol) was added to the acetonide compound (0.06 mmol) dissolved in acetonitrile (5 mL) at 0 °C and stirred until the resulting blue-green solution reached room temperature. When the reaction was complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

Method D: Using Boron Trifluoride Etherate. A 10% (v/v) solution of $BF_3 \cdot Et_2O$ (0.005 mL, 0.004 mmol) in CH_2Cl_2 was added dropwise to a solution of acetonide compound (0.04 mmol) in CH_2Cl_2. The reaction was stirred at room temperature until consumption of starting material. When the reaction was complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

Methyl (2*S*,3*S*,5*R*,6*E*)-3-Acetoxy-9-benzoyloxy-2,5-oxy-6-nonenoate (3a). Oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (ddd,1H, *J* 5.4, 10.6, 13.8 Hz), 2.11 (s,3H), 2.12 (ddd,1H, *J* 0.6, 5.8, 13.8 Hz), 2.54 (dt,2H, *J* 6.4, 6.5 Hz), 3.77 (s,3H), 4.38 (t,2H, *J* 6.6 Hz), 4.48 (d,1H, *J* 1.2 Hz), 4.67 (ddd,1H, *J* 5.4, 7.4, 10.6 Hz), 5.41 (ddd,1H, *J* 0.5, 1.2, 5.3 Hz), 5.75 (dd,1H, *J* 7.6, 15.5 Hz), 5.87 (td,1H, *J* 6.6, 15.4 Hz), 7.45 (t,2H, *J* 7.8 Hz), 7.56 (dt,1H, *J* 1.2, 7.6 Hz), 8.04 (dd,2H, *J* 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3), 32.0 (CH_2), 38.5 (CH_2), 52.8 (O-CH_3), 64.2 (O-CH_2), 77.9 (HC-O), 81.4 (HC-O), 82.7 (HC-O), 128.7 (CH=), 128.7 (CH=), 129.9 (CH=), 129.9 (HC=), 130.4 (HC=), 130.7 (C), 132.4 (HC=), 133.3 (HC=), 166.8 (C=O), 170.4 (C=O), 171.1 (C=O); IR ν_{max} (KBr)/cm^{-1} 2984, 2916, 1740, 1603, 1450, 1242, 1047, 715; EIMS *m/z* (%) 303 (3, $M^+ - COOMe$), 240 (3, $M^+ - C_7H_6O_2$), 198 (4, $M^+ - C_7H_5O_2 - AcO$), 180 (51, $M^+ - C_7H_6O_2 - AcOH$), 148 (14), 122 (28, $(C_7H_6O_2)^+$), 121 (100, $(C_7H_5O_2)^+$), 105 (100, $(C_7H_5O)^+$), 93 (31), 77 (88, ϕ^+), 59 (16, AcO^+, $COOMe^+$); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_7$ (M + Na)$^+$ 385.1258, obsd 385.1269.

Methyl (2*S*,3*S*,5*R*,6*E*)-9-Benzoyloxy-3-hydroxy-2,5-oxy-6-nonenoate (3b). Oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (ddd,1H, *J* 5.5, 9.8, 13.3 Hz), 2.07 (ddd,1H, *J* 1.9, 5.7, 12.0 Hz), 2.19 (s,1H), 2.55 (dt,2H, *J* 6.3, 12.9 Hz), 3.78 (s,3H), 4.39 (t,2H, *J* 6.7 Hz), 4.40 (d,1H, *J* 1.7 Hz), 4.57 (m,1H), 4.70 (ddd,1H, *J* 6.7, 6.8, 6.8 Hz), 5.74 (dd,1H, *J* 7.5, 15.1 Hz), 5.84 (td,1H, *J* 8.5, 15.2 Hz), 7.45 (t,2H, *J* 7.8 Hz), 7.56 (dt,1H, *J* 1.2, 7.6 Hz), 8.04 (dd,2H, *J* 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9 (CH_2), 40.8 (CH_2), 52.6 (O-CH_3), 64.2 (O-CH_2), 76.3 (HC-O), 80.9 (HC-O), 85.3 (HC-O), 128.7 (CH=), 128.7 (CH=), 129.8 (CH=), 129.9 (HC=), 129.9 (HC=), 130.7 (C), 133.2 (HC=), 133.3 (HC=), 166.8 (C=O), 171.9 (C=O); IR ν_{max} (KBr)/cm^{-1} 3460 (broad), 2955, 2920, 1747, 1716, 1452, 1275, 1113, 713; EIMS *m/z* (%) 277 (5), 198 (27, $M^+ - C_7H_6O_2$), 180 (8, $M^+ - C_7H_6O_2 - COOMe - H$), 139 (33), 121 (54, $(C_7H_5O_2)^+$), 105 (100, $(C_7H_5O)^+$), 96 (47), 77 (70, ϕ^+), 59 (31, AcO^+, $COOMe^+$), 51 (33); HRMS (ESI) *m/z* calcd for $C_{17}H_{20}O_6$ (M + Na)$^+$ 343.1152, obsd 343.1147.

Methyl (2*S*,3*S*,5*S*,6*E*)-3-Acetoxy-9-benzoyloxy-2,5-oxy-6-nonenoate (9a). Oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (ddd,1H, *J* 3.7, 6.3, 13.6 Hz), 2.08 (s,3H), 2.54 (m,3H), 3.78 (s,3H), 4.38 (t,2H, *J* 6.7 Hz), 4.57 (d,1H, *J* 2.3 Hz), 4.75 (ddd,1H, *J* 7.0, 7.1, 7.1 Hz), 5.43 (ddd,1H, *J* 2.3, 3.7, 4.0 Hz), 5.74 (d,1H, *J* 7.6 Hz), 5.87 (m,1H), 7.45 (t,2H, *J* 7.8 Hz), 7.56 (dt,1H, *J* 1.2, 7.6 Hz), 8.04 (dd,2H, *J* 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3), 32.0 (CH_2), 38.3 (CH_2), 52.7 (O-CH_3), 64.2 (O-CH_2), 77.5 (HC-O), 80.7 (HC-O), 82.2 (HC-O), 128.7 (CH=), 128.7 (CH=), 129.5 (CH=), 129.9 (HC=), 129.9 (HC=), 130.7 (C), 132.7 (HC=), 133.3 (HC=), 166.8 (C=O), 170.6 (C=O), 171.3 (C=O); IR ν_{max} (KBr)/cm^{-1} 2984, 2916, 1740, 1603, 1450, 1242, 1047, 715; EIMS *m/z* (%) 303 (3, $M^+ - COOMe$), 240 (3, $M^+ - C_7H_6O_2$), 198 (4, $M^+ - C_7H_5O_2 - AcO$), 180 (51, $M^+ - C_7H_6O_2 - AcOH$), 148 (14), 122 (28, $(C_7H_6O_2)^+$), 121 (100, $(C_7H_5O_2)^+$), 105 (100, $(C_7H_5O)^+$), 93 (31), 77 (88, ϕ^+), 59 (16, AcO^+, $COOMe^+$); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_7$ (M + Na)$^+$ 385.1258, obsd 385.1269.

Methyl (2*S*,3*S*,5*S*,6*E*)-9-Benzoyloxy-3-hydroxy-2,5-oxy-6-nonenoate (9b). Oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (ddd,1H, *J* 5.3, 7.4, 12.8 Hz), 2.19 (s,1H), 2.42 (ddd,1H, *J* 6.3,

6.9, 13.3 Hz), 2.55 (td,2H, *J* 6.3, 12.9 Hz), 3.79 (s,3H), 4.39 (t,2H, *J* 6.7 Hz), 4.45 (d,1H, *J* 3.6 Hz), 4.58 (m,1H), 4.74 (m,1H), 5.75 (m,1H), 5.82 (m,1H), 7.45 (t,2H, *J* 7.8 Hz), 7.56 (dt,1H, *J* 1.2, 7.6 Hz), 8.04 (dd,2H, *J* 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0 (CH_2), 40.6 (CH_2), 52.6 (O-CH_3), 64.2 (O-CH_2), 76.1 (HC-O), 80.2 (HC-O), 84.4 (HC-O), 128.7 (CH═), 128.7 (CH═), 129.8 (CH═), 129.9 (HC═), 129.9 (HC═), 130.7 (C), 133.3 (HC═), 133.5 (HC═), 166.8 (C═O), 171.9 (C═O); IR ν_{max} (KBr)/cm^{-1} 3460 (broad), 2955, 2920, 1747, 1716, 1452, 1275, 1113, 713; EIMS *m*/*z* (%) 277 (5), 198 (27, $M^+ - C_7H_6O_2$), 180 (8, $M^+ - C_7H_6O_2 -$ COOMe− H), 139 (33), 121 (54, $(C_7H_5O_2)^+$), 105 (100, $(C_7H_5O)^+$), 96 (47), 77 (70, ϕ^+), 59 (31, AcO^+, $COOMe^+$), 51 (33); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{20}O_6$ $(M + Na)^+$ 343.1152, obsd 343.1147.

Acknowledgment. Support of this work from DINACYT (PDT 54, Ministerio de Educación y Cultura, Uruguay) is gratefully acknowledged. The authors thank Professor T. Hudlicky for providing the cultures of *P. putida* F39/D.

Supporting Information Available: Experimental details, ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800514K