Diastereoselective Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans via Cyclofunctionalization Reactions. Evidence of Stereoelectronic Effects

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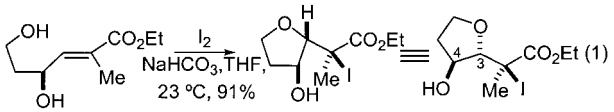
The work described herein considers the impact of stereoelectronic effects and allylic 1,3-strain in controlling the cyclofunctionalization reaction when a hydroxyl group is at the allylic position. The stereoelectronic arguments are supported by independent iodocyclization reactions performed using two secondary alcohols. The transition-state pathways involved in these reactions are established through a comparison of relative reaction rates. A bi-directional approach is used to demonstrate the potential of the iodocyclization reaction to differentiate a terminus in molecules with a pseudo C_2 axis of symmetry, showing that two-directional synthesis can be used to differentiate between alternative transition-state pathways.

Introduction

The asymmetric induction of new stereogenic centers is a central theme of chemistry research. The strategies used and the results obtained in this line of study are at the origin of many significant advances in organic chemistry and have served as an impetus to better define the factors that influence chemical reactivity. One strategy that has received considerable attention consists of electrophile-induced addition to an allylic π-system.[1] We have been particularly interested in cyclofunctionalization reactions involving electrophilic addition to an α,β-unsaturated ester bearing a substituent at the allylic position.[2] Our studies have shown that the outcome of such reactions can be predicted through the minimization of allylic 1,3-strain,[2] a controlling factor that we have taken advantage of for the synthesis of highly functionalized heterocycles, which are key synthons in the synthesis of natural products or segments thereof.[2c,d,3]

The present study considers the iodoetherification reaction[4] of a terminally disubstituted olefin bearing a hydroxyl group at the allylic position. As illustrated in eq 1, the reaction of substrate **1** with iodine in the presence of $NaHCO_3$ in THF gives compound **2** in a 91% yield.[5] The presence of a hydroxyl group induces allylic 1,3-strain to favor a trans relative stereochemistry between the C(3)−O and C(4)−O bonds of the cyclization product (compound **2**). Furthermore, the antiperiplanar addition of the oxygen to the double bond activated by the iodine (I_2) results in a product with a residual C−I bond anti to the newly formed C−O bond as in **2** (eq 1).



1 **2**

Transition states **A** and **B** could be used to rationalize trans product **2**, **A** being favored for steric reasons (Figure 1). However, considering that the substituent at the allylic position (OH) is an electron-withdrawing group, stereoelectronic arguments could be raised in favor of transition state **B**. It has been shown that the allylic hydroxyl group can have a significant stereodirecting effect on electrophilic additions to double bonds.[6] This study will focus on whether the hydroxyl group has any stereoelectronic effects[7] that can control diastereoselectivity, an aspect of cyclofunctionalization that has yet to be successfully elucidated.

To this end, our group has performed independent cyclofunctionalization reactions using secondary alcohols

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(1) For reviews of the effects of 1,3-allylic strain on conformation and stereoselectivity, see: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650.

(2) (a) Labelle, M.; Guindon, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2204. (b) Guindon, Y.; Slassi, A.; Ghiro, É.; Bantle, G.; Jung, G. *Tetrahedron Lett.* **1992**, *33*, 4257−4260. (c) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem.* **1994**, *59*, 1166. (d) Guindon, Y.; Murtagh, L.; Caron, V.; Landry, S. R.; Jung, G.; Bencheqroun, M.; Faucher, A.-M.; Guérin, B. *J. Org. Chem.* **2001**, *66*, 5427.

(3) Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett.* **1985**, *26*, 1185.

(4) Selected examples of iodoetherification reaction: (a) Tamaru, Y.; Harayama, H.; Bando, T.; Nagaoka, H.; Yoshida, Z. *Liebigs Ann.* **1996**, 223. (b) Fujioka, H.; Kitagawa, H.; Nagatomi, Y.; Kita, Y. *J. Org. Chem.* **1996**, *61*, 7309. (c) Seepersaud, M.; Blumenstein, M.; Mootoo, D. R. *Tetrahedron* **1997**, *16*, 5711. (d) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798. (e) Jordá-Gregori, J. M.; González-Rosende, M. E.; Sepúlveda-Arques, J.; Galeazzi, R.; Orena, M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1135. (f) Bew, S. P.; Barks, J. M.; Knight, D. W.; Middleton, R. J. *Tetrahedron Lett.* **2000**, *41*, 4447. (g) Bravo, F.; Castillón, S. *Eur. J. Org. Chem.* **2001**, 507.

(5) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701.

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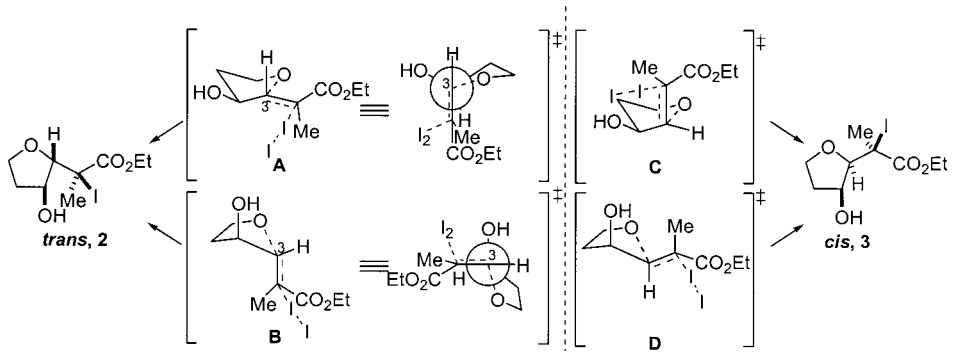


Figure 1. Proposed transition states for the iodoetherification of substrate **1**.

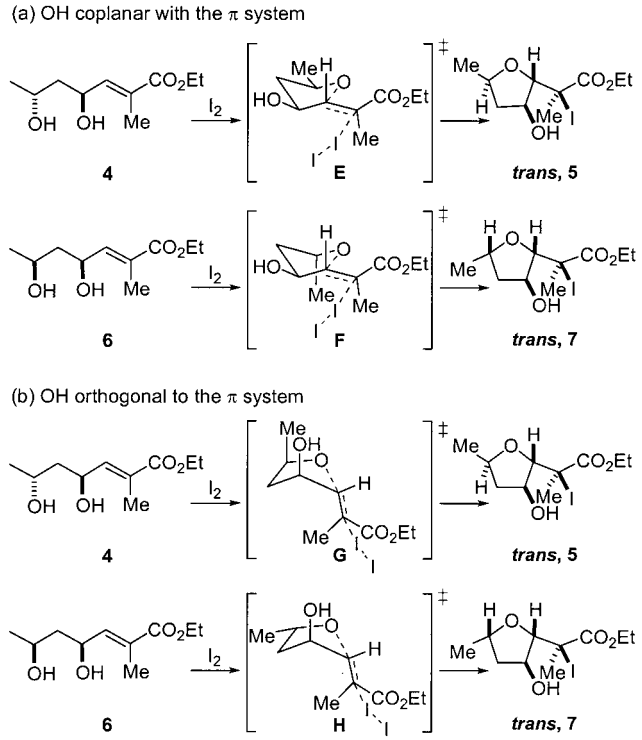


Figure 2. Proposed transition states for the iodoetherification of diols **4** and **6**.

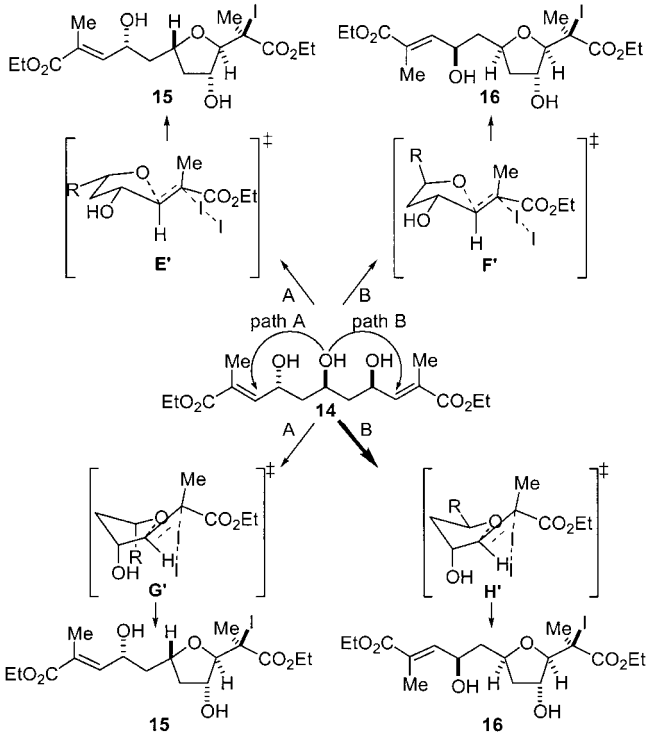


Figure 3. Two-directional synthesis.

4 and **6**. The transition states (cf. transition states **E**, **F**, **G**, and **H**, Figure 2) involved in these reactions were compared in terms of steric or steric/stereoelectronic effects to determine the relative reaction rates. The reasoning behind this strategy was that the anti diol **4** would cyclize faster than the syn diol **6** if steric effects were the only controlling factor in the reaction. If both allylic 1,3-strain and stereoelectronic effects were involved, **6** would react more rapidly than **4**. A complementary experiment featuring a bi-directional approach using **14** (Figure 3) was also proposed to ensure that both the syn and the anti diols would have the same chemical environment and to further support the findings from the competition reactions of **4** and **6**.

By shedding light on the critical role of stereoelectronic effects involved in the intramolecular addition of a nucleophile on an activated α,β-unsaturated ester, this study may contribute to a refinement of the transition state model normally used to rationalize such reactions. Furthermore, and at a more practical level, this work may provide an alternative application for bi-directional synthesis in the elucidation of reaction pathways.

Results and Discussion

Iodoetherification Reaction. The iodoetherification reactions studied herein normally proceed under kinetic control,[2] hence the importance of the transition-state energy. Complete reversibility of the electrophilic addition to the olefin is implied,[2b,8] allowing for selectivity during the cyclization step. The allylic hydroxyl involved in the iodocyclization reaction does not hydrogen bond to the nucleophilic oxygen (H-bond acceptor).[9] Although the exact nature of the intermediates is not yet known, it has been suggested that the intermolecular halo-

(6) (a) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 4114. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819. (c) Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079. (d) Tamaru, Y.; Higashimura, H.; Naka, K.; Hojo, M.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1045. (e) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, *26*, 5307.

(7) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*, 1st ed.; Baldwin, J. E., Ed.; Pergamon Press: Canada, 1983; Vol. 1.

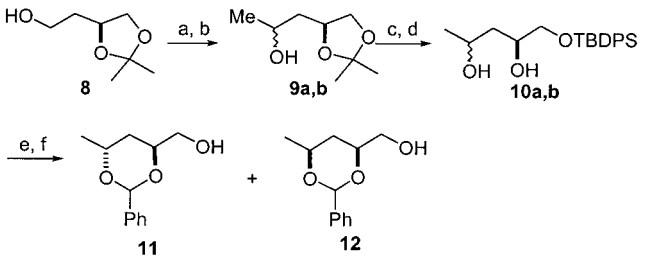
etherification reaction involves a fully developed halonium ion and that the cyclofunctionalization reaction proceeds through a π-complex before undergoing charge separation (Figure 1).[10] It should also be noted that the presence of a terminally disubstituted double bond forces the minimization of allylic 1,3-strain, an important steric constraint in the transition states proposed.

An analysis of these transition states, based on the minimization of the different torsional strains, would suggest that trans-predictive transition state **A** (Figure 1) is the lowest in energy while trans-predictive transition state **B** suffers from the presence of an axial hydroxyl and a gauche staggering within the ring. Nevertheless, these two transition states are preferred over cis-predictive transition states **C** and **D**, which are destabilized by two gauche effects and by allylic 1,3-strain, respectively.

Several additional points should be made about the electronic effects of both the ester (end-substituent of the olefin) and the allylic hydroxyl. First, the presence of the ester renders the olefin less reactive toward the electrophile.[2a] Second, most of the positive charge (in the onium or in the π-complex) is found on the olefin β-carbon. Given this, as well as for stereoelectronic reasons, an electron-withdrawing allylic hydroxyl at the equatorial position (transition state **A**, Figure 1) should be better aligned for maximizing conjugation of the σ^*_{C-O} orbital with either the π-system[11] or the carbonium ion, which results in a decrease in the rate of cyclization or an increase in the energy of the carbonium ion, respectively. Having the electron-withdrawing allylic group in an orthogonal position (i.e., axial as in **B**) with respect to the π-system might avoid the rate-retarding effect,[12] which would make transition state **B** the lowest in energy.[2a,13] Since both **A** and **B** lead to the same product, however, additional stereochemical information must be encoded into the substrates in order to differentiate between two trans-predictive transition states.

The search for the operative trans-predictive iodoetherification transition state begins with the following competition experiments involving anti diol **4** and syn diol **6** (Figure 2). In such competitions, the difference in reactivity of these diols is a reflection of the difference in energy of the respective transition states, which can in turn indicate whether the allylic hydroxyl substituents involved are axial or equatorial. The four possible transition states leading to the cyclized products **5** and **7** from the respective diols **4** and **6** are illustrated in Figure 2.

Scheme 1[a]



[a] Conditions: (a) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1.5 h, then DIAE; (b) MeMgBr, THF, −78 °C, 1 h, 52% in two steps; (c) 1 N HCl aq, THF, 24 h; (d) TBDPSCl, imidazole, DMF, 15 h, 63% in two steps; (e) $PhCH(OMe)_2$, *p*-TsOH, CH_2Cl_2, 15 h; (f) TBAF, THF, 1 h, 62% in two steps.

When minimization of torsional strain is the controlling factor in the iodoetherification reaction, the transition state possessing the equatorial hydroxyl group at the allylic carbon should be preferred (as in **A**, Figure 1). Given the steric interaction in **F** resulting from the presence of an axial methyl group, this transition state should be higher in energy than **E**, where all of the substituents are equatorial. In this case, the anti diol **4** will have cyclized faster than the syn diol. If both torsional strain minimization and stereoelectronic arguments are involved, then the preferred transition states will be those in which the hydroxyl group is orthogonal (as in **B**, Figure 1) to the π-system of the double bond (**G** and **H**, Figure 2). In this scenario, transition state **G** should be higher in energy than **H** due to the development of a transannular diaxial interaction, and the syn diol **6** will have reacted faster than the anti diol **4**.

In summary, the anti diol should cyclize faster than the syn when steric effects are the only controlling factor in the reaction. If both allylic 1,3-strain and stereoelectronic effects are involved, then the syn diol should react more rapidly.

Preparation and Cyclization of the Secondary Alcohols 4 and 6. The required substrates were prepared as illustrated in Scheme 1. The protected triol **8**[2a] was oxidized into the corresponding aldehyde, which was immediately subjected to a Grignard reaction using methylmagnesium bromide to give a 3:2 mixture of secondary alcohols **9a** and **9b**. Hydrolysis of the acetonides followed by selective protection of the primary alcohol, formation of the 1,3-benzylidene acetals, and subsequent fluoride treatment led to products **11** and **12**, which were easily separated. The relative configurations of the benzylidene acetals **11** (anti) and **12** (syn) were determined by the structures of cyclized products **5** and **7** (see below). Both compounds were subjected to a one-pot Swern oxidation/Wittig reaction to give, after hydrolysis, diols **4** and **6**, respectively (Scheme 2). These compounds were then independently subjected to iodoetherification conditions in THF.

As seen in Table 1, syn diol **6** gave compound **7** in good yield after 6 h of reaction at room temperature (entry 1). The unambiguous proof of structure for **7** was determined via crystallization and X-ray analysis of the corresponding dinitrobenzoate derivative **13**.[14] Interestingly, anti diol **4** seemed much less reactive, giving less than 20% conversion of the final product **5** after 24 h in THF at room temperature (Table 1, entry 2). The best yield

(8) In the case of halogen additions, onium intermediates are generally freely reversible. See: (a) Brown, R. S.; Gedye, R.; Slebocka-Tilk, H.; Buschek, J. M.; Kopecky, K. R. *J. Am. Chem. Soc.* **1984**, *106*, 4515. (b) Slebocka-Tilk, H.; Ball, R. G.; Brown, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 4504. (c) Bellucci, G.; Bianchini, R.; Ambrosetti, R. *J. Am. Chem. Soc.* **1985**, *107*, 2464. (d) Bellucci, G.; Chiappe, C.; Marioni, F. *J. Am. Chem. Soc.* **1987**, *109*, 515. (e) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E.; Liotta, D.; Monahan, R., III *J. Org. Chem.* **1987**, *52*, 4191.

(9) In the cyclofunctionalization reaction of an α,β-unsaturated ester, similar results were obtained for the free allylic alcohol, the OMe counterpart, and the allylic fluorine. See ref 2a.

(10) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672.

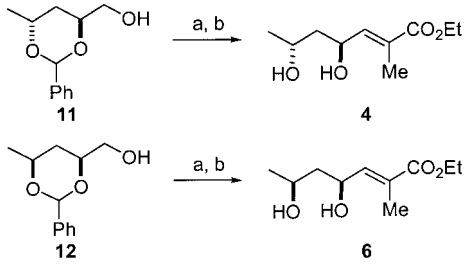
(11) Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc* **1985**, *107*, 1274.

(12) Endo alkoxy effect: Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(13) In support of these orthogonal arguments, see: Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650.

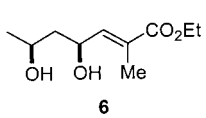
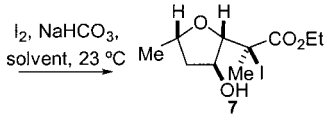
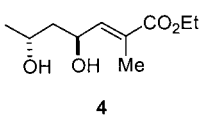
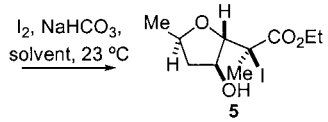
(14) See the Supporting Information.

Scheme 2[a]



[a] Conditions: (a) (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 45 min, then Et_3N; (ii) $Ph_3PC(Me)CO_2Et$, 23 °C, 15 h, 90%; (b) 70% AcOH/H_2O, 60 °C, 10 h, 70%.

Table 1. Iodoetherifications of Diols 4 and 6 under Kinetic Conditions

Entry	Substrate	Solvent	Reaction Time (h)	Yield (%)
				
	6		**7**	
1	**6**	THF	6	86
				
	4		**5**	
2	**4**	THF	24	20
3	**4**	CH_3CN	36	55

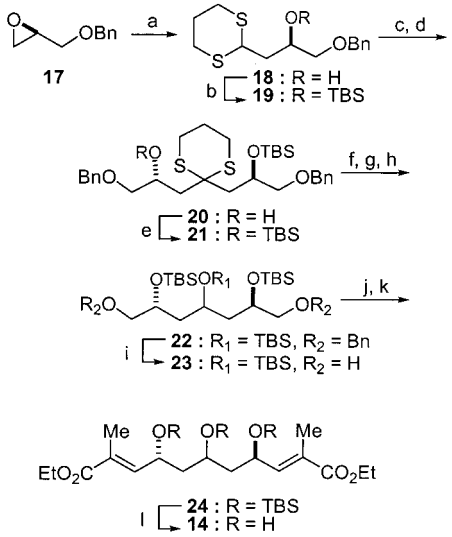
obtained (55%) was realized when acetonitrile was used as the solvent and the reaction was conducted for 36 h (Table 1, entry 3). In light of these results, we concluded that the transition state governing this type of reaction had to involve the allylic hydroxyl group in an orthogonal position, with respect to the π-system, as in both **B** (Figure 1) and **H** (Figure 2).

This exciting result led us to consider another experimental scenario that would further confirm our findings. An additional experiment involving a bi-directional approach was performed to ensure that no arguments of a physicochemical nature (i.e. solubility differences) could be raised to invalidate the results related thus far.

The Iodoetherification Reaction as a Diastereospecific Strategy for Group-Selective Terminus Differentiation. One way to ensure that the syn and the anti diols have the same chemical environment is to insert them into the same molecule and have both reactions (the syn diol cyclization versus the anti diol cyclization) compete against one another intramolecularly. To accomplish this, we considered substrate **14** (Figure 3), which has a diastereotopic carbon at the C-6 position due to a pseudo C_2 axis of symmetry. The choice of this substrate was based on the fact that the olefins in **14** could be differentiated through cyclization of the C-6 hydroxy group, inducing chirality at that position. This type of bi-directional approach corresponds to a Schreiber class C.[15] In this case however, the approach not only leads to a highly functionalized molecule but also helps to establish the preferred transition state.

As illustrated in Figure 3, the hydroxyl at the C-6 position in **14** can react through path A or path B to form

Scheme 3[a]



[a] Conditions: (a) 2-lithio-1,3-dithiane, BuLi, THF, 0 °C, 1 h, 97%; (b) TBSOTf, lutidine, CH_2Cl_2, 0 °C, 30 min, 96%; (c) BuLi, NaO-*t*-Bu; (d) **17**, hexane/THF, −78 °C, 1 h, 80%; (e) TBSOTf, lutidine, CH_2Cl_2, 0 °C, 30 min, 95%; (f) excess MeI, excess $CaCO_3$, CH_3CN/H_2O (4:1), reflux, 6 h, 37%; (g) $NaBH_4$, MeOH, 0−25 °C, 2 h; (h) TBSOTf, lutidine, CH_2Cl_2, 0 °C, 30 min, 75% from **21**; (i) H_2, cat. $Pd(OH)_2$, EtOH, 18 h, 94%; (j) Dess−Martin, CH_2Cl_2, 25 °C, 1.5 h, 100%; (k) $Ph_3PC(CH_3)CO_2Et$, toluene, 40 °C, 18 h, 70%; (l) HF, CH_3CN, 25 °C, 100%.

Scheme 4

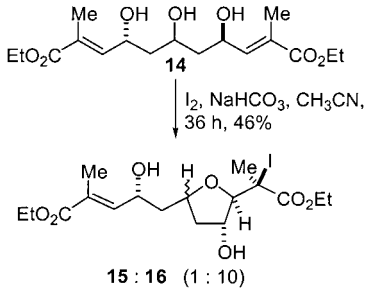
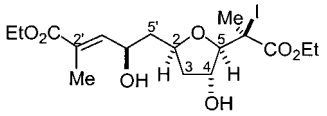


Table 2. NOE Values for Compound 16

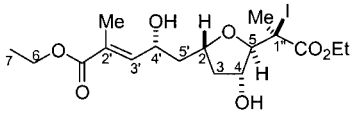


proton(s) irradiated	5-H	4-H	3α-H	3β-H/5′-H	2-H	2′-Me
5-H		2.0	1.8		3.4	1.2
4-H	2.6		1.4	4.6		1.4
2-H	4.0		4.3	2.7		

either of the two diastereoisomeric tetrahydrofurans **15** or **16**, respectively. Path A may involve transition state **E′** in which the allylic alcohol is equatorial and thus coplanar to the π-system. This transition state is analogous to transition state **E**, depicted in Figure 2, originating from anti diol **4**. Similarly, path B may involve transition state **F′** which mimics transition state **F** originating from syn diol **6**, the allylic alcohol again being coplanar to the π-system. Because of the axial orientation of the side chain (R), **F′** should be disfavored relative to **E′**. Thus, if the position of the hydroxyl group is equato-

(15) Schreiber, S. L. *Chemica Scripta* **1987**, *27*, 563.

Table 3. NOE Values for Compound 15



proton(s) irradiated	5-H	4-H	3α-H	3β-H	2-H/6-H	5′-H	5′-H	4′-H	3′-H	7-H	1″-Me/2′-Me
2-H/6-H	0.4	0.5		1.3		0.3	1.1	1.4	0.7	2.2	
4-H	2.0		1.1	4.0							
5-H		2.1	2.7					1.2			6.4
4′-H	0.4				3.4		1.8		3.3		10.2

rial in the transition state—stereoelectronic effects not being considered here—path A should predominate and anti product **15** should be formed preferentially. If the hydroxyl is orthogonal to the π-system, then trans-predictive transition states **G′** or **H′** should be involved in the process through paths A or B, respectively (Figure 3), and **16** would be favored, **G′** being higher in energy than **H′** due to a transannular diaxial interaction. On the basis of previous results, it was expected that path B, via transition state **H′**, would have the best competitive rate and that the reaction would favor **16** over **15**.

Substrate **14** was then synthesized as illustrated in Scheme 3. The optically active epoxide **17**[16] was reacted with a 2-lithio-1,3-dithiane followed by protection of the secondary alcohol **18** using TBSOTf. The resultant dithiane **19**[17] was then lithiated using BuLi in the presence of NaO*t*Bu,[18] and the resulting anion was condensed with epoxide **17** to give, after protection of the newly formed secondary alcohol by TBSOTf, product **21** in very good yield. The dithiane was then cleaved and the resulting ketone reduced with $NaBH_4$ before the resultant alcohol **22** was converted to a silyl ether to give pseudo C_2 symmetric product **23**. After hydrogenolysis of the benzyl ethers, the primary alcohols were oxidized into aldehydes using the Dess—Martin reagent.[19] This was followed by a Wittig extension to produce bilaterally the corresponding olefins. The final HF treatment led to the corresponding triol **14** in good yield (63%).

The iodoetherification conditions described before were then used on substrate **14** (Scheme 4). The reaction was stopped after 36 h. After workup, **16** was found to be the major compound in a 10:1 ratio over **15**, indicating once again that the hydroxyl group was orthogonal to the π-system in the operative transition state. It is important to note that from the single chiral center found in **17** (the epoxide), we were able to generate a molecule bearing five new stereogenic centers using a bi-directional approach. The relative stereochemistries of products **15** and **16** were supported by NOE, which revealed a network of enhancements consistent with the proposed structures (Tables 2 and 3). In particular, the strong interaction between H(2) and H(5) could under no circumstances be mistaken for a trans configuration in compound **16**.

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Conclusion

In conclusion, we have shown that both stereoelectronic effects and allylic 1,3-strain are important controlling factors in the cyclofunctionalization reaction when an electron withdrawing group is at the allylic position. We have provided support for the stereoelectronic arguments by showing that the syn diol reacts more rapidly than the anti diol. Using a bi-directional approach, we have also demonstrated the potential of the iodocyclization reaction to differentiate a terminus in molecules with a pseudo C_2 axis of symmetry. Two-directional synthesis is used to differentiate between alternative transition state pathways, a new approach that may contribute to a better understanding of chemical reactivity.

Experimental Section

(2*S*)-2-[(2*S*,3*S*,5*R*)-3-Hydroxy-5-methyltetrahydrofuran-2-yl]-2-iodopropionic Acid Ethyl Ester (5). To a solution of diol **4** (110 mg, 0.54 mmol) in MeCN (2.7 mL) were added successively $NaHCO_3$ (228 mg, 2.72 mmol) and I_2 (692 mg, 2.72 mmol). The mixture was stirred at room temperature for 36 h. The reaction mixture was then diluted with Et_2O and washed successively with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to give a yellow oil. Purification by flash chromatography (25% EtOAc in hexanes) offered an oil (110 mg, 62%). Re-purification by flash chromatography (10% EtOAc in benzene) provided pure **5**: $[\alpha]_D^{25}$ −20.5 (*c* 1.05, $CHCl_3$); IR (neat) ν_{max} 3490, 2980, 1725 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 4.48−4.42 (m, 1H), 4.18−4.12 (m, 1H), 3.90−3.79 (m, 2H), 3.64 (d, J = 4.5 Hz, 1H), 3.09 (d, J = 2.6, 1H), 2.11 (ddd, J = 5.4, 7.0, 13.0 Hz, 1H), 2.03 (s, 3H), 1.73 (ddd, J = 7.0, 8.0, 13.0 Hz, 1H), 1.14 (d, J = 6.0 Hz, 3H), 0.84 (t, J = 14.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0, 89.1, 78.1, 75.5, 62.4, 45.3, 42.0, 28.0, 21.4, 13.6; MS (CI) *m*/*e* 329 (MH^+), 311 ($MH^+ - H_2O$); HRMS calcd for $C_{10}H_{18}O_4I$ (MH^+) 329.0252. Found 329.0275.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **6**, **7**, **9**−**16**, and **18**−**24**. NMR spectra for compounds **5**, **9a**,**b**, **13**−**16**, and **21** as well as the ORTEP and tables of X-ray crystallographic data for compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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