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Tether-Controlled Cycloadditions for the Asymmetric Synthesis of Decalins: Increased Selectivity in Acetonitrile Solvent

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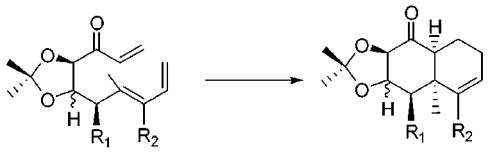
ABSTRACT



The beneficial influence of *cis*-isopropylidene acetal tether control groups, to facilitate the asymmetric synthesis of substituted decalins by intramolecular Diels–Alder reactions, is described. Compared to *trans*-acetonides, these cases proceed under milder conditions to afford the *cis*-fused adducts from an *endo* transition state. An unusual acetonitrile solvent effect exerts a dramatic influence on the diastereoselectivity. This strategy leads to the chiral nonracemic bicyclo[4.4.0]decane core of diverse natural products.

A large number of natural products contain a decalin (bicyclo[4.4.0]decane) ring system as an important structural component.[1] These compounds, particularly the terpenoids, display a surprisingly wide array of biological activities that may have medicinal potential. Figure 1 illustrates two representative oxygenated examples. The fungal metabolite K-76 (**1**)[2] displays both anticomplement and antiinflammatory activity with potential for the treatment of arthritis, while phytocassane E (**2**)[3] is an antifungal agent.

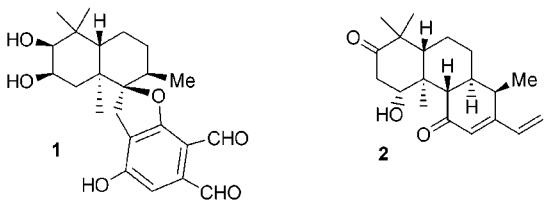


Figure 1. Oxygenated terpenoids.

Motivated in part by our interest in the synthesis of taxoids,[4] we have established that planar "tether control groups" (aromatic rings, *cis* double bonds) in the side chain have a dramatic influence on the ease of cyclization of substituted trienes in intramolecular Diels−Alder reactions.[5]

Subsequent research has demonstrated that tartrate and carbohydrate derived *trans*-isopropylidene acetals provide a significant improvement.[6] They limit the flexibility of the side chain to impose a restricted geometry on the reactive

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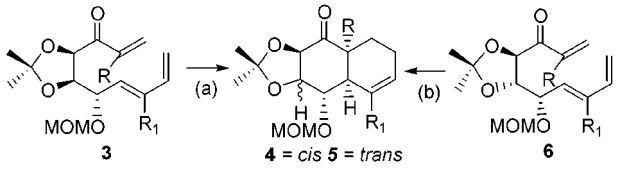
components and afford chiral nonracemic adducts. In addition, they are usually available in both optical series. We wish to report that *cis*-isopropylidene acetals are even better for inducing the overlap required for facile cyclization. There is a significant rate increase which will permit lower reaction temperatures. In addition, it should be possible to employ sterically encumbered dienes to generate the core nuclei of **1** and **2**. These advantageous features are illustrated in Scheme 1 with highly substituted, closely related, acetal

Scheme 1. Comparison of *cis* and *trans* Acetal Cycloadditions



3 R = CH_2CH_2C-($CMe{=}CH_2$)=CMe_2, R_1 = $CH{=}CH_2$
(a) 0 °C, 1 h, 74%.

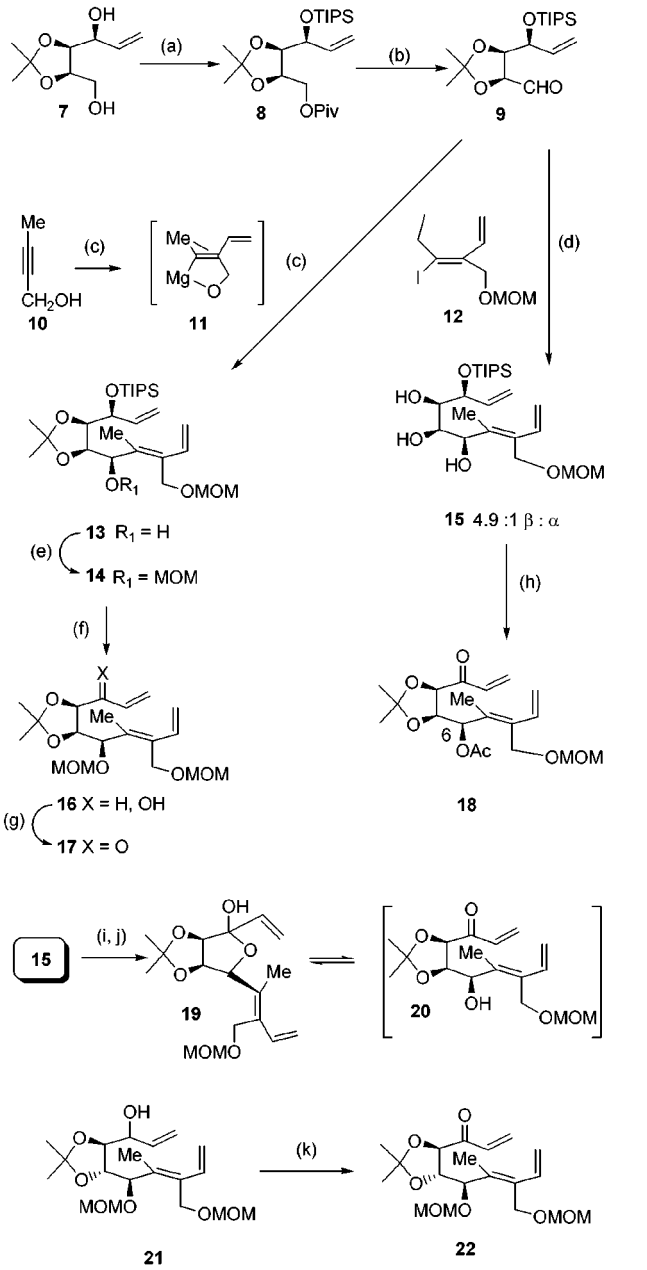
6 R = CH_2CH_2C-($CMe{=}CH_2$)=CMe_2, R_1 = CH_2OPMB,
(b) 110 °C, 17 h, 97%.

isomers. Ketone **3** cyclized to the decalin **4** at 0 °C without the aid of Lewis acid, while the *trans* isomer **6** required heating in refluxing toluene for 17 h. Thus, epimerization of an acetal center improved the cycloaddition reaction and led in both cases to the *cis*-decalin adduct. The fact that the *cis* tether reaction is faster is consistent with the fact that the transition state geometry resembles that of the *cis*-fused bicyclo[4.3.0]decene, which is less strained than the *trans*-acetal-*trans*-fused isomer.

It is usually difficult to conduct cycloadditions with an "inside" substituent which inhibits the formation of the required s-*cis*-diene conformer.[7] However, the application of this strategy to the synthesis of terpenoid skeletons requires this inside methyl group on the diene.

To investigate the potential of a *cis*-acetonide unit to circumvent this difficulty, the diol **7** was synthesized (Scheme 2) from D-isoascorbic acid.[8] Selective protection of the primary alcohol with pivaloyl chloride was followed by exposure to triisopropylsilyl triflate in the presence of collidine at 0 °C to yield **8** (92%) (Scheme 2). Reduction with diisobutylaluminum hydride (DIBAL-H) gave the primary alcohol, and oxidation with Dess−Martin periodinane afforded aldehyde **9**. The requisite diene unit was derived from the carbometalation of 2-butynol (**10**) with vinylmagnesium chloride to generate magnesium chelate **11**,

Scheme 2. Synthesis of Triene Precursors



(a) PivCl, Py, CH_2Cl_2, 21 °C, 2 h; TIPSOTf, collidine, CH_2Cl_2, 0-21 ° C, 23 h, 99%; (b) DIBAL-H, CH_2Cl_2, -78- 21 °C, 2 h; Dess-Martin periodinane, CH_2Cl_2, 0-21 °C, 1.5 h, 86%; (c) **10**, $CH_2{=}CHMgCl$,C_6H_{12}, 80 °C,19 h; -78-21 °C,15 h; THF, -78-21 °C, 15 h, 43%; (d) **12**, *t*-BuLi, THF, -78 °C,10 min, 79 %; (e) MOMCl, *i*-$PrNEt_2$; (f) TBAF, THF, 0-21 °C,15 h, 52%; (g) Dess-Martin periodinane, CH_2Cl_2, 21-40 °C, 4 h, 65%; (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 21 °C, 24 h; TBAF, THF, 0 °C,10 min; Dess-Martin periodinane, CH_2Cl_2, 21 °C, 2 h, 89%; (i) TBAF, THF, 0 -21°C, 15 min, 98%; (j) MnO, MeCN, in situ, Scheme 3; (k) Dess-Martin periodinane, CH_2Cl_2, 21 °C, 2 h, 80%;

which was condensed with aldehyde **9**.[9] The stereochemistry of secondary alcohol **13** arises from chelation-controlled attack on the carbonyl face *anti* to the acetonide so the two adjacent oxygen substituents bear a *syn* relationship.

(7) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 315. Weinreb, S. M., ref 7a, p 401. Boyes, D. L., ref 7a, p 451. Roush, W. R., ref 7a, p 513. Granum, K. A.; Merkel, G.; Mulder, J. A.; Debbins, S. A.; Hsung, R. P. *Tetrahedron Lett.* **1998**, *39*, 9597.

(8) Cohen, N,; Banner, B. L.; Loprest, R. J.; Wong, F.; Rosenberger, M.; Liu, Y.-Y.; Thom, E.; Liebman, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661. (b) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336. (c) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217.

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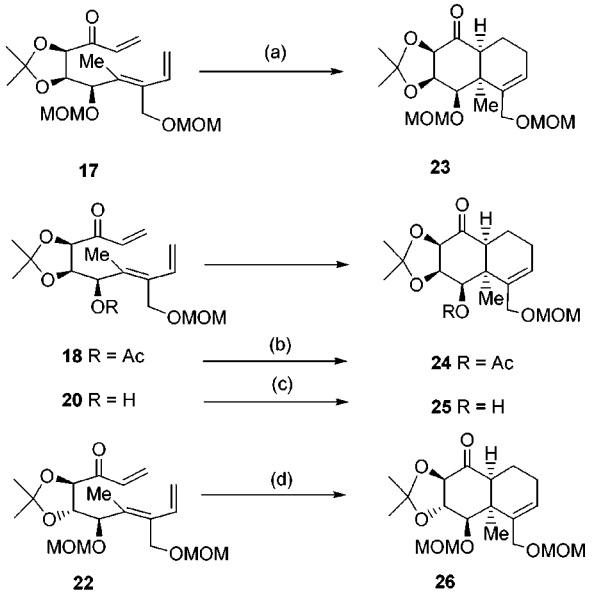
To obtain a preliminary indication of the cumulative effects of the *cis*-acetate and the methyl substituent on the diene, the hydroxyl groups in **13** were reacted simultaneously with chloromethyl methyl ether in the presence of diethylisopropylamine to provide the bis-methoxymethyloxy ether **14**. The silyl group was removed with tetrabutylammonium fluoride to afford the allylic alcohol **16**. Oxidation of this secondary alcohol **16** with Dess−Martin periodinane in dichloromethane generated decatriene ketone **17** in situ, which cyclized spontaneously to **23** at room temperature (21 °C) over 60 h or more efficiently in 4 h at 40 °C during the oxidation reaction (87%) (Scheme 3). The mild conditions

Scheme 3. Cycloadditions of Substituted Dienes



(a) Dess-Martin periodinane, CH_2Cl_2, 21 °C, 60 h, or 40 °C, 4 h, 87%; (b) $CHCl_3$, 21 °C, 14 d, or CH_3CN, 40 °C, 4 h, 95%; (c) MnO_2, $CHCl_3$,reflux, 100 h, or MeCN, 70 °C, 100 h, 95 % at 70% conversion; (d) Toluene, sealed tube, 220 °C, 24h, 72%.

for this cycloaddition of a sterically encumbered system are particularly expedient.

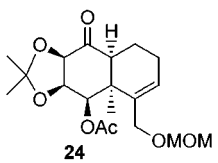
For natural product syntheses, differentiation of the hydroxyl groups is required. Consequently iododiene **12**[10] was prepared from **10** via **11**, and the derived lithium salt condensed with **9** to afford alcohol **15** in which the α-hydroxy diastereomer predominated.[11]

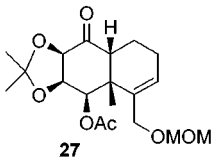
Protection of the secondary alcohol as its acetate, removal of the silyl ether, and Dess−Martin periodinane oxidation afforded the highly substituted cycloaddition precursor **18**. In this instance the ketone could be isolated, but as summarized in Table 1 (entry 1) at room temperature (21 °C) it cyclized slowly over 2 weeks to the decalin. Treatment of the dienes with Lewis acid did not facilitate cycloaddition but led to decomposition. As expected, higher temperatures reduced the level of selectivity.

(10) Wong, T.; Tjepkema, M. W.; Audrain, H.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **1996**, *37*, 755.

(11) Tjepkema, M. W.; Wilson, P. D.; Audrain, H.; Fallis, A. G. *Can. J. Chem.* **1997**, *75*, 1543.

Table 1. Solvent Effects: Cycloaddition Diastereoselectivitiy Ratios





entry	solvent	temp. °C	**24:27** ratio	time, h
1	$CDCl_3$	20	7.0:1	>300
2	$CDCl_3$	40	5.3:1	60
3	$CDCl_3$	60	4.2:1	20
4	C_6D_6	40	2.4:1	100
5	CD_3CN	40	23:1	60
6	Dioxane-d_8	40	2.7:1	100

>95% yield with >98% conversion

However, the most intriguing result is reflected in the data for entry 5, in which the ratio of **24**/**27** increased to 23:1 with acetonitrile as the solvent at 40 °C. In comparison, entry 2 in chloroform under similar conditions afforded a 5.3:1 ratio. Generally, the rates and stereoselectivities of Diels−Alder reactions are immune to significant solvent effects.[12] Experiments conducted in water, in which substantial rate enhancements are observed, are an exception.[13] Normally the diastereofacial selectivity is not affected in aqueous conditions unless the components are partially water-soluble.[14] In these examples the adduct ratios are influenced by the hydrogen-bond donating ability of the solvent.

It seems likely that this "acetonitrile effect" is a consequence of the preferred association of the solvent dipole with the oxygen atoms on the top face of the molecule. This interaction may resemble the type of charge-transfer and $\pi-\pi$ interactions encountered in aromatic systems.

If hydrogen bonding is important, then a free hydroxyl on the underside of the molecule should reduce the diastereomeric ratio. To examine this possibility and provide an additional, differentially functionalized adduct, alcohol **15** was treated with tetrabutylammonium fluoride and oxidized with manganese dioxide (Scheme 2). The expected ketone **20** was not isolated but rather hemiacetal **19** was formed preferentially. In refluxing chloroform the lactol and keto forms are in equilibrium and the *cis* diastereomer **25** was generated in a ratio of 5:1. This value increased to 11:1 in

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(13) (a) Rideout, D.; C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *103*, 7817. (b) Engberts, J. B. F. N. *Pure Appl. Chem.* **1995**, *67*, 823. (c) Meijer, A.; Sijbreu, O.; Engberts, J. B. F. N. *J. Org. Chem.* **1998**, *63*, 8989.

(14) Lubineau, A.; Augé, J.; Lubin, N. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3011. (b) Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Royo, A. J.; Salvatella, L. *J. Phys. Org. Chem.* **1992**, *5*, 230.

acetonitrile at 70 °C (95% yield). This implies that the nitrile is not hydrogen bonded to the free hydroxyl. Instead, in these cases the acetonitrile solvent influences the facial preference and improves the stereoselectivity of these cyclizations.[15] It is possible that this phenomenon may be observed in other oxygen-rich systems in the presence of acetonitrile.

There are four possible transition state geometries for these decatrienones; Figure 2 illustrates the two most important

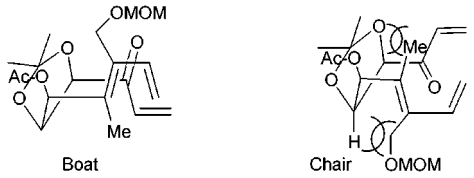
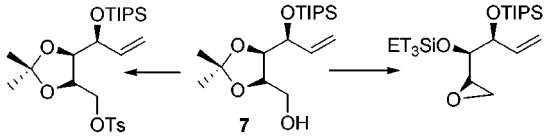


Figure 2. Cycloaddition *endo* transition state conformations.

endo conformations. Previous investigations have established that *cis*-fused boatlike transition states are usually favored in related systems.[16] As illustrated, the boatlike orientation is clearly preferred compared to the competing chairlike conformation, due to the minimization of nonbonded interactions in the boatlike arrangement.

(15) Preparation of a diene which lacked this hydroxyl was also of interest for comparison with the examples in Scheme 2 and because it is absent in several skeletons of interest. The tosylate and the epoxide below were synthesized independently from the alcohol **7**, but various organometallic-based coupling procedures failed.



Finally, additional evidence, which demonstrated the distinct synthetic advantage of *cis* compared to *trans* acetonides as control elements in intramolecular Diels−Alder precursors, was provided by **22** (Scheme 3). Compound **17** cyclized at 21 °C (above) and yet **22**, its C5 acetal epimer, required 24 h in a sealed tube at 220 °C to generate the corresponding adduct **26** in 72% yield.

In conclusion, we have established the advantage of *cis*-acetonides as tether control groups for the synthesis of decalins from highly substituted decadienones. Epimerization studies of these adducts, to prepare the requisite *trans* isomers for selected targets, are in progress. This protocol is particularly useful for difficult substitution patterns. The stereoselectivity is enhanced when acetonitrile is the solvent, as a consequence of its association with the oxygen-rich keto-acetal dienophile. This strategy will afford rapid entry to highly oxygenated multicyclic skeletons.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **3**−**6**, **17**−**18**, and **22**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For an excellent discussion of related intramolecular transition states, see: (a) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915. (b) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502. (c) Roush, W. R. Stereochemical and Synthetic Studies of the Intramolecular Diels−Alder Reaction. *Adv. Cycloaddition* **1990**, *2*, 91. For recent, related examples of decalin lactones, see: (d) Kim, P.; Nantz, M. H.; Kurth, M. J.; Olmstead, M. M. *Org. Lett.* **2000**, *2*, 1831. (e) Jung, M. E.; Huang, A.; Johnson, T. W. *Org. Lett.* **2000**, *2*, 1835.