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Isopropylidene Acetals: Tether Control Groups for Asymmetric Intramolecular Diels-Alder Reactions

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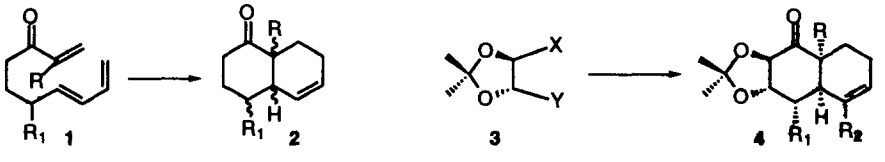
Abstract: The beneficial influence of appropriately placed tartrate and carbohydrate derived isopropylidene acetal tether control groups, to facilitate the asymmetric synthesis of substituted decalins by intramolecular Diels-Alder reactions, is described. In all cases the *cis* fused adducts **10**, **12**, **14**, **16** and **18** were formed from an *endo* transition state in which the isopropylidene acetal also determined the π-facial selectivity. Ring cleavage of appropriate adducts afforded functionalized cyclohexenes. © 1997 Elsevier Science Ltd.

The Diels-Alder reaction is one of the most efficient construction methods for the preparation of carbocyclic systems.[1] Consequently it continues to be employed for a variety of synthetic objectives and receive increased scrutiny and study. Frequently, the intramolecular variant offers improved regiochemical and stereochemical control. It also allows the construction of more than one ring simultaneously.[2] Unfortunately, intramolecularity by itself is often insufficient to ensure the best levels of stereoselectivity. Diels-Alder cycloadditions of trienes, such as **1**, usually afford complex mixtures and require high temperatures to generate the adducts **2**.[2,3] We have established that limiting the flexibility in the tether, by incorporation of a planar moiety (aromatic ring or olefin), has a dramatic effect on intramolecular [4 + 2] cycloadditions.[4] The required reaction temperature was lowered and a dominant adduct was produced as a consequence of the restricted rotational freedom that enhanced favorable diene-dienophile overlap.

Scheme 1



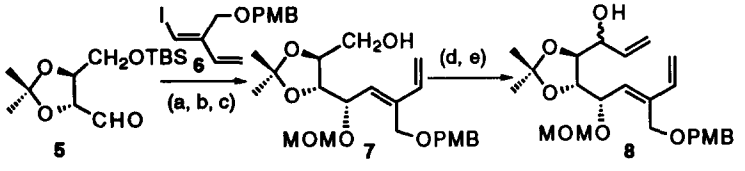
The best tether control groups should facilitate the achievement of a dominant transition state, induce the desired asymmetry, and contain useful functionality that may be used in the product for subsequent synthetic manipulations. Chiral, nonracemic tartrate and carbohydrate derived isopropylidene acetals fulfill these criteria and can be synthesized easily. In addition, they are usually available in both optical series. Thus the stereochemical environment dictated by the presence of the rigid isopropylidene group depicted in **3** should enhance the transition state interaction between the reactive components **X** and **Y** to facilitate a variety of intramolecular reactions (pericyclic, free radical, dipolar, enolate, metal mediated, etc.). A suitable diene/dienophile combination would lead to **4**. We wish to report our initial application of these ideas for the

rapid, stereocontrolled construction of highly functionalized decalins and as a stereodefined route to substituted cyclohexenes after ring cleavage.

Previous strategies to increase the level of regio- and stereochemical control in intramolecular cycloadditions have included the use of cleavable control groups such as silyl acetyl tethers[5] which may contain stereocenters,[6] conformationally restricted diester spacers,[7] as well as chiral Lewis acids,[8] chiral auxiliaries,[9] magnesium chelation,[10] and chiral copper complexes.[11] The ring cleavage products of appropriate adducts constitute an intermolecular cyclohexene synthesis, while the bicyclo[4.4.0] nucleus can be used independently or expanded. Isopropylidene acetals hold promise for the control of many intramolecular reactions although only a few cases of this beneficial effect have appeared in the literature and a systematic study does not appear to have been reported. Representative examples include radical cyclizations[12] and 2-azaallyl cycloadditions.[13] In addition, the behavior of 1,7,9-decatriene-3-ones bearing isopropylidene acetals adjacent to the diene have been examined by Roush and coworkers[14] in their synthesis of nargenicin A_1. However, to obtain the required stereoselectivity it was necessary to employ a transannular cycloaddition sequence with a bromide substituent in the diene.[15] In contrast, our studies have demonstrated that placement of the acetonide β to both the diene and dienophile improved the stereoselectivity for the synthesis of substituted decalins.

The required triene precursors were prepared from the known *tert*-butyldimethylsilyl ether-aldehyde **5**.[16] Condensation of this aldehyde (Scheme 2), with the organolithium reagent derived from the halogen-metal exchange of (*Z*)-1-iodo-2-(*p*-methoxybenzylmethyloxy)-1,3-butadiene (**6**),[17] afforded the secondary alcohol as a 2:1 epimeric mixture. The major diastereomer was separated, protected as its methoxymethyl ether, and desilylation effected with *n*-tetrabutylammonium fluoride to give **7** (94%). Subsequent Swern oxidation and vinyl magnesium bromide addition yielded the trienol **8**. The remaining substrates were synthesized in a parallel manner with the exception of **15** and **17**. For **15** a sequence was developed from (L)-arabinose,[18] while (L)-ascorbic acid[19] served as the starting material for **17**.

Scheme 2



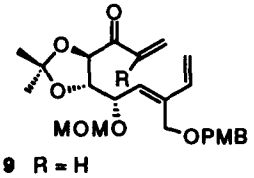
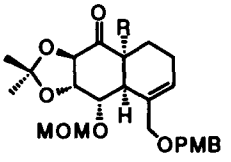
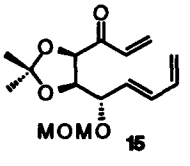
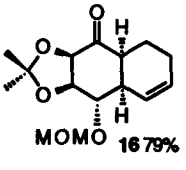
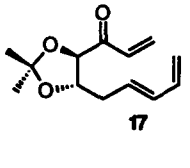
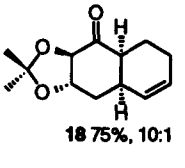
(a) *s*-BuLi, THF, -78 °C, ~2:1, 93%, (b) MOMCl, *i*-Pr_2EtN, CH_2Cl_2,77%; (c) *n*-Bu_4NF, THF, 94%; (d) $COCl_2$, DMSO, CH_2Cl_2, -78 °C, 40 min; Et_3N, 93%; (e) CH_2=CHMgBr,THF, -78 °C, 97%.

In several cases the intermediate ketones were not isolated, but were cyclized directly to avoid a mixture of adduct and enone. Thus the allylic alcohol precursors for **9**, **15**, and **17** were oxidized with Dess-Martin periodinane and cycloaddition proceeded *in situ*. For example, oxidation of **8** generated the trienone **9** which cyclized directly to **10** in refluxing dichloromethane (75%). The alkyl substituted dienophiles were less reactive and the isolated ketones **11** and **13** were cyclized efficiently (82%, 97%) in toluene (110 °C). X-ray analysis[20] of **10** confirmed the *cis* ring junction was formed exclusively (preferentially for **18**).

The decalins **10**, **12**, **14**, and **18** arose from preferential addition via an *endo* transition state in which the bridging unit adopted a chair-like conformation, as illustrated in Figure 1. The number of possible transition states was reduced due to the presence of the isopropylidene unit which was constrained to a diequatorial conformation. Previous studies[4, 21] with planar control groups indicated that the interaction between the C_6 and C_8 substituents determined the π-facial selectivity. Applied to **9**, **11**, and **13**, the preferred orientation placed the

MOM group in an axial position to avoid the potential 1,3-allylic interaction that would have occurred in the *endo* approach from the opposite face. Clearly these interactions were not important in this series due to the dominant influence of the cyclic acetal. Removal of both substituents did not alter the resultant stereochemistry in the adduct **18**.

Table Cycloaddition Summary

triene	conditions	adduct
		
9 R = H **11** R = CH_2CH_2OTPS **13** R = CH_2CH_2C-($CMe{=}CH_2$)=CMe_2	48 °C, 4 h 110 °C, 18.5 h 110 °C, 17 h	10 75% 12 82% 14 97%
 **15**	21 °C, 1.5 h	 **16** 79%
 **17**	48 °C, 21 h	 18 75%, 10:1

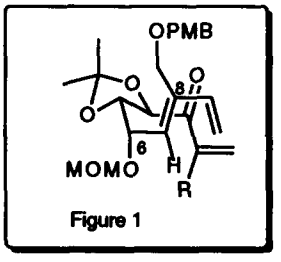


Figure 1

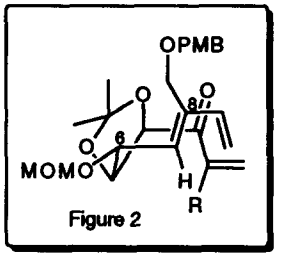
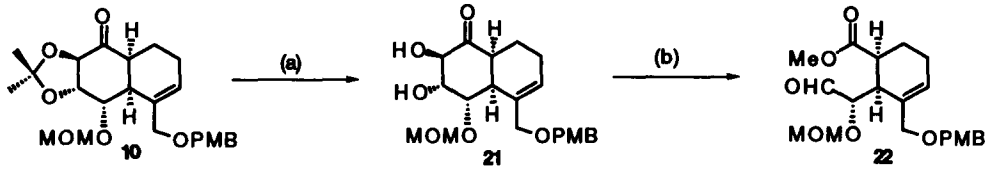


Figure 2

The *cis* isopropylidene acetal **15** cyclized readily at ambient temperature to afford the adduct **16**. Thus epimerization of an acetal center improved the efficiency of the reaction and led to the same stereochemical result. In this instance the preferred *endo* transition state was achieved from the boat-like conformation represented in Figure 2, which placed the diene and dienophile in close proximity for facile cyclization.

Scheme 3



(a) 10% aq. HCl/THF, 2.3 h, 91%; (b) $Pb(OAc)_4$, MeOH, C_6H_6, 0 °C, 12 min, 86%.

Hydrolysis of the acetal in **10** afforded the diol **21** and oxidative ring cleavage with lead tetraacetate generated the aldehyde-ester cyclohexene **22** in which the various substituents can be readily differentiated.

In summary, these diverse examples of intramolecular [4 + 2] cycloadditions have established the general utility of tartrate and carbohydrate derived isopropylidene acetals as asymmetric tether control elements for the construction of bicyclo[4.4.0] ring systems. The stereoselectivity was determined by the influence of the cyclic acetal unit rather than the other substituents. These concepts are currently being expanded to encompass other intramolecular reactions including our total synthesis of taxoids.[22]

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