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Planar Tether Control Groups and π-Facial Selectivity: Intramolecular Cycloadditions for Polycyclic Systems

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Abstract: The direct synthesis of the fused ring systems **11** (R = Me, H) and the decalin **14** are described. The use of a planar tether control group (either aromatic ring or double bond) greatly facilitates the key Diels-Alder cycloadditions. A second intermolecular cycloaddition of **14** with cyclopentadiene afforded the tetracyclic adduct **17**. The interaction between the allylic ethers and diene substituents influences the facial selectivity observed in these examples.

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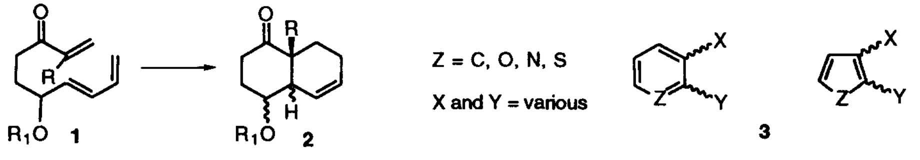
We required a direct route to various tricyclo[8.4.0^{1,6}.0^{8,13}]tetradecanes (dehydroanthracenes) and related carbocycles. Attractive approaches involved the direct incorporation of an aromatic ring in a [4 + 2] cycloaddition precursor with subsequent functional group modification or alternatively the synthesis of a decalin intermediate via a Diels-Alder reaction followed by attachment of a third ring. The Diels-Alder reaction is one of the most efficient construction methods for carbocyclic systems.[1] 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. Thus Diels-Alder cycloaddition of trienes, such as **1**, usually afford complex mixtures and require high temperatures to generate the adducts **2**.[2,3] Limiting the flexibility in the side chain, through the incorporation of a planar moiety (such as an olefin or aromatic or heterocyclic ring, *e.g.* **3**), should enhance the transition state interaction between the reactive components (X, Y) and facilitate a variety of intramolecular reactions (pericyclic, free radical, dipolar, enolate, metal mediated, etc.). Various examples of this beneficial effect have appeared in the literature but a systematic study does not appear to have been reported. Representative reactions include intramolecular alkylations for 10-membered rings,[4] radical cyclizations,[5] olefin metathesis,[6] and cycloaddition of metal carbenes.[7] The effect on intramolecular [4 + 2] cycloadditions should also be significant, provided the group selected promotes the achievement of a dominant transition state. We have established that this is the case and wish to report the behaviour of both aromatic rings and double bonds as planar tether control groups. In addition, these groups supply useful functionality in the

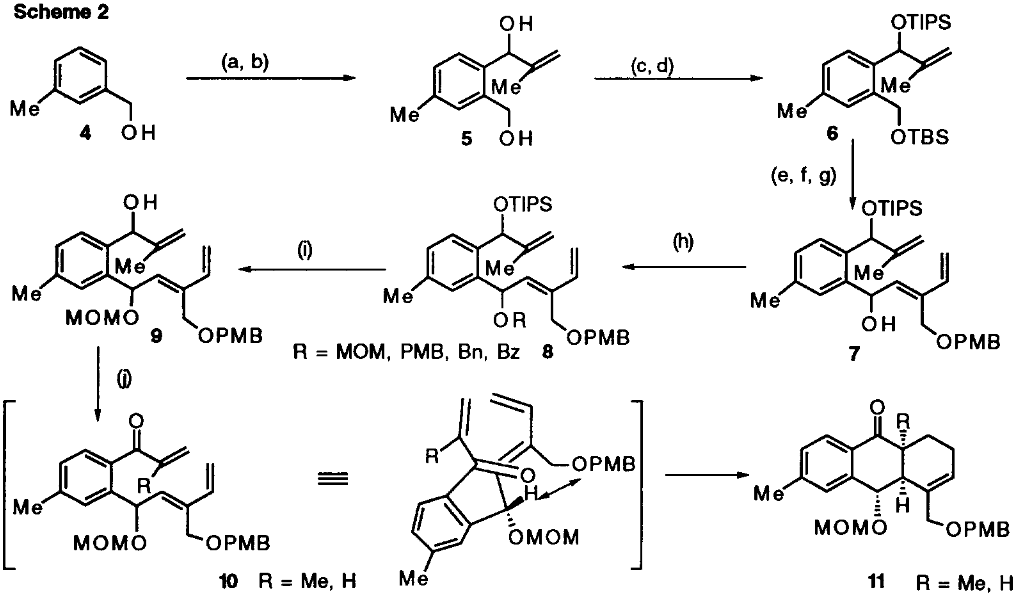
Scheme 1



adduct for subsequent synthetic manipulations, as illustrated by the conversion of **14** to the tetracyclic nucleus **17**.

The triene alcohol **9** was synthesized from 3-methylbenzyl alcohol (**4**) as illustrated (Scheme 2). Directed *ortho*-metallation[8] of **4**, followed by condensation with methacrolein produced diol **5**. Differential silyl protection of the respective alcohols to give **6**. Selective desilylation under acid catalyzed conditions released the primary alcohol which was oxidized to the aldehyde with Dess-Martin reagent and condensed with the organolithium reagent derived from (*Z*)-1-iodo-2-(*p*-methoxybenzyloxy)methyl-1,3-butadiene[9] to afford **7**. The secondary alcohol was protected in various ways to provide the family represented by **8** (MOM, PMB, Bn, Bz). The triisopropylsilyl group in the corresponding methoxymethyl ether was removed with tetrabutylammonium fluoride to provide **9**. Initially, this allylic alcohol **9** was treated with Dess-Martin reagent at room temperature (21 °C) in the expectation that the ketone **10** (R = Me) would be produced. Instead the major product (70%) was the single adduct **11** (R = Me) accompanied by a small amount of ketone. For improved efficiency it was best to run the reaction in refluxing dichloromethane for 2 hours which increased the yield to 95%. This result illustrated the dramatic improvement that arose from restricting the rotational freedom in the side chain due to the presence of the aromatic ring. Thus, the required diene-dienophile interaction was

Scheme 2

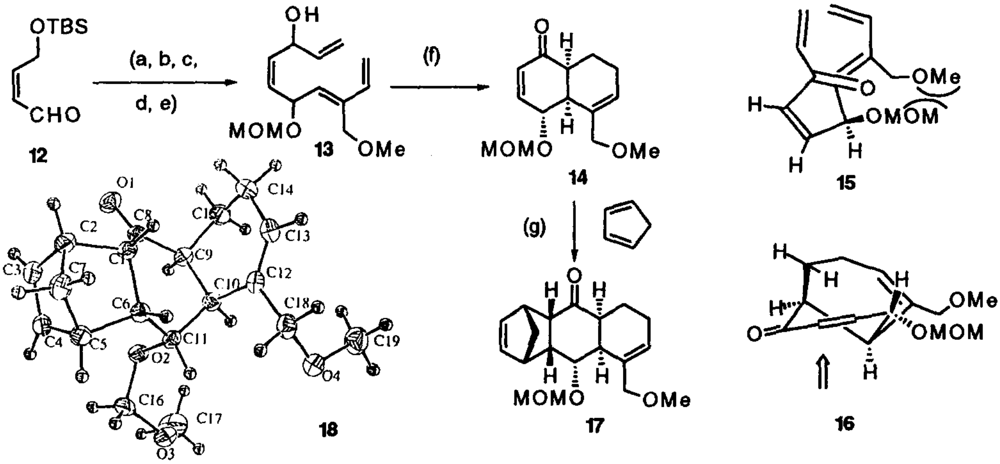


(a) ^{n}BuLi, pentane, TMEDA; (b) $CH_2{=}C(Me)CHO$, -78 °C, 55%; (c) TBSCl, imidazole, CH_2Cl_2, 21 °C, 78%; (d) TIPSOTf, collidine, CH_2Cl_2, 21 °C, 97%; (e) PPTS, 99% EtOH, 21 °C, 89%; (f) Dess-Martin Ox., CH_2Cl_2, 21 °C, 89%; (g) (*E*)$LiCH{=}C(CH_2OPMB){-}CH{=}CH_2$, THF, -78 °C, 86%; (h) MOMCl, $^{i}PrEt_2N$, CH_2Cl_2, 97%; (i) TBAF, THF, 21 °C, 86%; (j) Dess-Martin Ox., CH_2Cl_2, 48 °C, 95%.

readily achieved. X-ray analysis[10] confirmed a single diastereomer had been produced. This adduct arose from preferential addition *anti* to the methoxymethyl ether substituent via an *endo* transition state as illustrated. This orientation places the MOM group in an axial position so it avoids the 1,3-allylic interaction with the bulky group on the diene (arrow) that occurs in the *endo* approach from the opposite face (hydrogen and ether are interchanged). Other ether substitutents (PMB, Bn, Bz, *cf.* **8**) in **10** did not alter the π-facial selectivity observed but the yields were reduced (52-83%). This stereochemical preference is consistent with related diene-allylic ether cycloadditions.[11] In a parallel fashion, following the procedures above from **4**, the ketone **10**, (R = H) was synthesized and cyclized to give **11** (R = H) as a single adduct (69%).

To examine the influence of a *cis*-olefin, (Z)-2-butene-1,4-diol was converted to the aldehyde **12** (Scheme 3) and this material condensed with the methoxy substituted lithiodiene related to step (g) Scheme 2.[9] The new secondary alcohol was protected as a methoxymethyl ether. Deprotection of the primary alcohol, oxidation, and addition of vinylmagnesium bromide afforded the tetraene alcohol **13**. As in the previous examples, Dess-Martin oxidation in refluxing dichloromethane provided the cycloaddition products directly in 73% yield. However, this cycloaddition was less selective as a ~2:1 mixture of the methoxymethyl ether epimers was obtained, in which the major adduct **14** again arose from *endo-anti* addition. The hydroxymethyl protecting group plays a significant role and helps determine the π-facial selectivity. This homoallylic interaction was camouflaged in the aromatic series due to the size of the ether groups. Reduction in the steric demands of this group (Me vs PMB) minimizes the *syn* periplanar, 1,3-interaction in the transition state for the MOM epimer **15**. Consequently, cyclization in a *syn* direction is now energetically more favourable and addition may occur from this face. Alteration of the size of the diene substituent therefore permits some control of the facial selectivity. Roush and coworkers have employed a vinyl bromide substituent for this purpose in related studies.[12]

Scheme 3



(a) (E)LiCH=C(CH$_2$OMe)-CH=CH$_2$, THF, -78 °C, 86%; (b) MOMCl, ^{i}PrEt$_2$N, CH$_2$Cl$_2$, 97%; (c) TBAF, THF, 21 °C, 86%; (d) Swern Ox. (e) CH=CHMgBr, -78 °C (f) Dess-Martin, CH$_2$Cl$_2$, 48 °C, 73%; (g) Et$_2$AlCl, CH$_2$Cl$_2$, 0 °C, 87%.

Cyclopentadiene reacted readily with the enone **14** at 0 °C in the presence of diethylaluminum chloride to generate the tetracyclic ketone **17** in 87% yield (*syn/anti*, 9:1). This adduct arose from addition of the cyclopentadiene *syn* to the methoxymethyl ether substituent in an *endo* manner as illustrated (**16**). This approach avoids the diaxial interaction with the methylene group in the adjacent ring and is consistent with the pattern observed for 4-*t*-butyldimethylsiloxycyclohexenone[13] and related systems.[11] This influence was ascribed to the favourable interaction with the developing orbital at the β-carbon. The relative stereochemistry was established unambiguously by X-ray analysis (**18**).[14] Unfortunately, cycloaddition with 2-trimethylsiloxybutadiene in the presence of diethylaluminum chloride failed even at elevated temperatures, although, cyclohexenones frequently require additional electron withdrawing groups for successful adduct formation.[15]

In conclusion, planar 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. In addition, they supply useful functionality for subsequent synthetic manipulation. For these cycloadditions an allylic ether function may be employed to influence the facial selectivity in combination with a diene substituent. The ether also encourages *syn* addition in intramolecular [4 + 2] cycloadditions. Clearly chiral tether control groups that facilitate attainment of the requisite transition state would be even better. Our investigations in this area, in which the tether control group also imparts asymmetry, will be reported shortly.

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10. Crystal data for **11**: Size 0.20 x 0.30 x 0.40 mm^{-3}; Orthorombic space group P bac; Unit cell: a = 22.966(1), b = 27.903(1), c = 7.976(2) Å, Z = 8, T = -150 °C, D_c = 1.254 g cm^{-3}; Mo-Kα radiation: 4619 reflections measured, 2646 observed, R = 0.060; R_w = 0.073
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14. Crystal data for **17**: Size 0.20 x 0.20 x 0.20 mm^{-3}; Monoclinic space group 21/c; Unit cell: a = 11.5034(3), b = 9.66010(2), c = 14.9000(3) Å, Z = 4, D_c = 1.283 g cm^{-3}; Mo-Kα radiation: 11,411 reflections measured, 2694 observed, R = 0.027; R_w = 0.043
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