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Generalized Approach from Sugars to Enantiomerically Pure Tetra-*C*-Substituted Carbocycles

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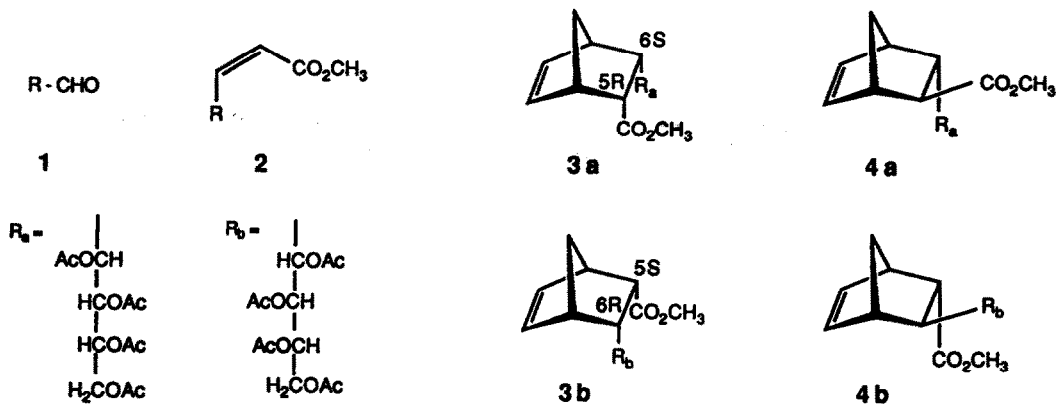
Abstract: A set of *cis*-dienophiles (**2**, **6**, **9**) derived from D- or L-arabinose reacts with high yield and stereospecificity to give enantiomerically pure 5,6-disubstituted norbornenes.

The Diels—Alder reaction is one of the most powerful methods for stereoselective construction of rings with synchronous creation of multiple asymmetric centers.[1] The study of asymmetric versions of this reaction has focused on the design of chiral dienophiles,[2] dienes,[3] and catalysts.[4] Considerable progress in this area has been achieved by using sugar precursors as a chiral pool of reagents.[5,6] Despite extensive development of available chiral dienophiles, only a few acyclic *cis*-1,2-disubstituted chiral dienophiles have been made.[3b,c] In connection with our studies on asymmetric Diels—Alder reactions using acyclic unsaturated sugars[5a,b,c,e] as dienophiles, we needed to prepare and evaluate *cis*-1,2-disubstituted dienophiles in order to expand and generalize a synthesis[5] of carbocycles having four functionally different carbon side-chains of defined and controllable absolute stereochemistry.

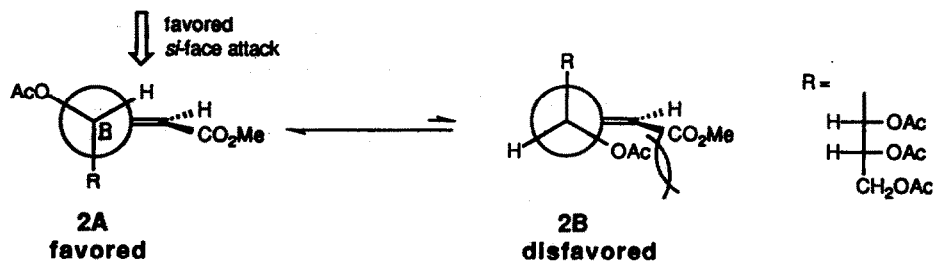
Horner–Emmons alkenation of (+)-*aldehydo*-D-arabinose 2,3,4,5-tetraacetate (**1a**) with bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)-phosphonate[7] gave 91% of (+)-methyl (*Z*)-4,5,6,7-tetra-*O*-acetyl-2,3-dideoxy-D-*arabino*-hept-2-enonate (**2a**) with high stereoselectivity (*Z*:*E* 20>1); m.p. 68°C, $[\alpha]_D$ +16° (*c* 1, chloroform). Diels—Alder reaction of **2a** under thermal conditions[5] with an excess of cyclopentadiene gave (+)-methyl (5*R*,6*S*)-6-*endo*-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)bicyclo[2.2.1]hept-2-eno-5-*endo*-carboxylate (**3a**), in 95% yield, and contaminated by a small proportion (<5%) of another isomer. Recrystallization gave pure **3a**, 81%; m.p. 103°C, $[\alpha]_D$ +7.8° (*c* 1, chloroform).

Relative configurations of the newly formed carbon centres C-5 and C-6 were assigned by ^{1}H-NMR comparison with the ^{1}H-NMR spectra of the known[5b,c] 5,6-*trans* isomers **4a** and **4b**. The relatively-low field shift of H-5 in **3** (δ 3.01) indicated the ester group to be *endo*, (δ 2.71, H-5 in **4b**, δ 1.66, H-5 in **4a**), and the large coupling constant ($J_{5,6}$ 9.3 Hz in **3a**) showed the *cis* relationship ($J_{5,6}$ 4.7 Hz in the *trans* isomers[5b,c] **4a**, **4b**). The 5*R*,6*S* absolute configurations were verified by *X*-ray structure analysis in conjunction with the known D-*arabino* configuration of the sugar chain.



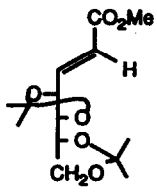
The same sequence of reactions applied to (-)-*aldehydo*-L-arabinose 2,3,4,5-tetraacetate (**1b**) furnished the dienophile **2b** (m.p. 68°C, $[\alpha]_D$ -15.8°) and the enantiomerically pure L-*arabino*-(5*S*,6*R*)-norbornene analogue **3b** (m.p. 103.5°C, $[\alpha]_D$ -7.9°).

These results accord with predictions based on the Trost model.[9] The observed high diastereofacial selectivity is attributed to conformational restriction at the allylic centre in dienophiles **2**. The confomer **2A** is expected to be more favored than **2B** which has severe allylic strain between the methoxycarbonyl and acetyl groups. The diene attacks preferentially from the *si* -face of the favored conformer **2A** to give **3**.



The butenolide **6** provides an opportunity to test the foregoing hypothesis in that the lactone ring locks the dienophile in the conformation that is disfavored for the acyclic dienophiles **2**. The lactone **6** was prepared from 1:4 (trans: cis) mixture of isopropylidenated enonated **5** by deacetonated (p-TsOH, MeOH) and subsequent acetylation. The Diels–Alder reaction gave two products **7** (70%) and **8** (11%) only from the *re* -face attack. Structures of the products were again established by NMR spectroscopy and that of **7** firmly consolidated[8] by X-ray crystallography. These two assignments of absolute configurations revealed that the diene attacked the dienophile **6** exclusively from the *re* -face. This butenolide **6** can have only one confomer **6A**, (which is depicted as the unfavorable conformation in the acyclic dienophiles **2**) because of the γ-lactone ring. Therefore the attack of diene would be favored from the *re* - face of the conformer **6A**. The

consistency in the diastereofacial selectivities for **2** and **6** supports previous hypothesis of conformational restriction in the acyclic dienophile **2** and its analogues.



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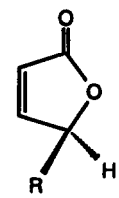

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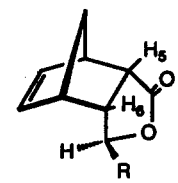

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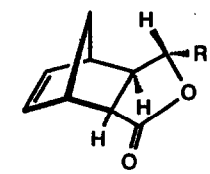

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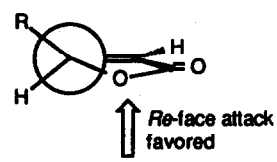
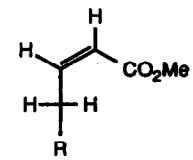


6A



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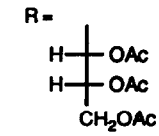

The *cis*-enonate **9**, which is deoxygenated at the allylic position, reacted with cyclopentadiene to give a mixture of all four possible adducts. The diasterofacial selectivity was negligible ane the *endo*, *exo* ratio (6.5: 1, by ^{1}H-NMR) was similar to that observed with butenolide **6**. This result demonstrates that the stereocenter at the allylic position alone determines the diasterofacial selectivity of the Diels–Alder reaction with these acyclic dienophiles.

These results complement earlier work[5] on analogous *trans*-dienophiles. The excellent yield and high facial selectivity observed here, coupled with the ready availability of both enantiomers of arabinose, offer both practicality and versatility in this approach to stereochemically defined tetra-*C*-substituted cyclopentanes. Use of different dienes provides extension to other cycloalkanes and heterocycles. Four different C-functionalities are available for synthetic elaboration; hydroxylation—glycol cleavage of the double bond in the norbornene gives[5e] dialdehydes in which the two aldehyde groups show differential reactivity.

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