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Hetero Diels–Alder Reaction involving (*E*)-3-(*tert*-Butyldimethylsiloxy)-1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)buta-1,3-diene and *p*-Nitrobenzaldehyde

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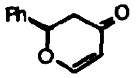
Abstract: The title reaction, when carried out in carbon tetrachloride in the presence of a catalytic amount of $Eu(fod)_3$, leads mainly to the *cis*-cycloadduct **6a**; the product undergoes isomerisation to its epimer **7a** in the presence of the catalyst in dichloromethane.

The discovery, by Danishefsky and his group,[1] that Lewis acids such as $ZnCl_2$ and $BF_3.OEt_2$ can induce the cyclocondensation of 1-oxy-3-siloxybuta-1,3-dienes and aldehydes to give 2,3-dihydropyran-4-ones, *e.g. rac*-**1**, has had a notable impact on the synthesis of pyranoid systems.[2] Although cycloaddition products are considered to intervene in certain cases,[3] the opportunity to study such labile species became possible when it was found that they could be isolated from reactions catalysed by soluble lanthanide complexes.[4] In a quest for stereopure 2,3-dihydropyran-4-ones such as **1**, the Yale workers prepared a series of dienes incorporating menthyl auxiliaries and studied their reactions with benzaldehyde in the presence of europium(III) complexes.[5] The best result was achieved using the diene **2a** and (+)-$Eu(hfc)_3$[6] in hexanes at −20 °C; a 96:4 mixture of the *cis*-cycloadducts **3a** and **4a** (arising from *endo*-cycloadditions) was produced, from which the major product was isolated in 60% yield after crystallisation. Treatment of compound **3a** with trifluoroacetic acid afforded the enantiopure dihydropyranone **1**, which served as a precursor of L-glucose.[5]



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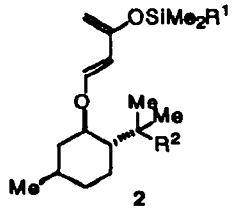

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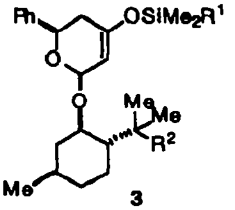

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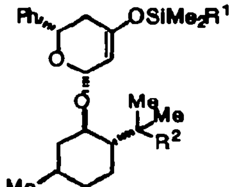

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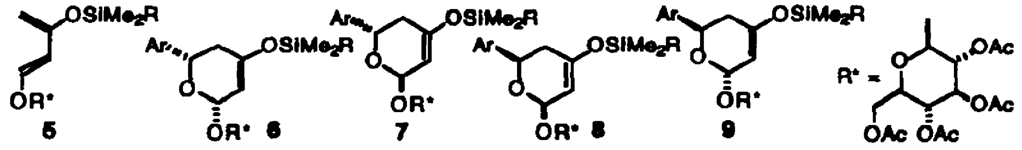
a; $R^1 = Bu^t$, $R^2 = Ph$ **b**; $R^1 = Me$, $R^2 = H$

Having developed the dienes **5a**[7] and **5b**[8] and shown that they undergo *endo*-cycloadditions in a stereoselective manner with cyclic dienophiles under thermal conditions, we were interested in assessing their reactivity towards aromatic aldehydes. Based upon the known diastereofacial selectivity of the dienes **5a** and **5b** towards electron-deficient alkenes[7–9] and the established preference for aromatic aldehydes to undergo *endo*-selective cycloadditions with 1-oxy-3-siloxybuta-1,3-dienes in the presence of europium(III) complexes,[4,5] we expected that cycloadducts of type **6** would predominate over their counterparts of types **7**–**9**. As well as laying the foundations for a new protocol for the elaboration of (1→1)-linked disaccharides, we envisaged that the technology would lead to the synthesis of antipodes of the dihydropyranone **1** and its relatives. We now report on some of our findings.



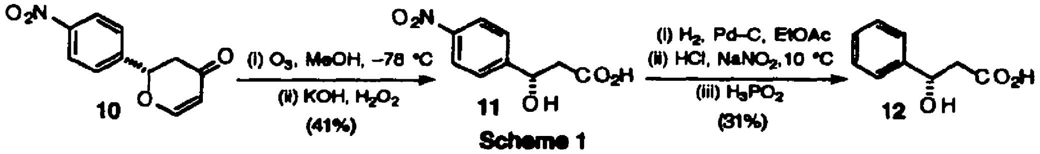
5 **6** **7** **8** **9**

a; R = Bu^t **b**; R = Me   **a**; R = Bu^t, Ar = p-NO$_2$C$_6$H$_4$ **b**; R = Me, Ar = p-NO$_2$C$_6$H$_4$

Preliminary studies indicated that the reactions of the dienes **5a** and **5b** with benzaldehyde in the presence of europium(III) complexes were very sluggish, a problem that was remedied by the substitution of p-nitrobenzaldehyde for benzaldehyde. Although the cycloadducts arising from the reaction of the diene **5b** with p-nitrobenzaldehyde were too sensitive to work with, those produced in the corresponding reaction of the diene **5a** were easily handled. Accordingly, the last-cited reaction was subjected to a detailed examination.

The reaction of the diene **5a** with p-nitrobenzaldehyde in dichloromethane was conducted over a 24 hour period in the presence of catalytic amounts (5 mol%) of (+)-Eu(hfc)$_3$, (–)-Eu(hfc)$_3$ and Eu(fod)$_3$.[10] The first reaction gave rise largely to a 55:45 mixture of the *cis*-cycloadducts **6a** and **8a** together with small amounts of compounds **7a** and **9a**.[11] Mainly an 80:10:10 mixture of the cycloadducts **6a**, **7a** and **8a** was produced in the reaction involving (–)-Eu(hfc)$_3$; crystallisation of the mixture from diethyl ether–light petroleum provided the major cycloadduct **6a**,[12] m.p. 116–117 °C, $[\alpha]_D$ –68 (c 0.33, CH$_2$Cl$_2$), in 39% yield. The reaction involving Eu(fod)$_3$ afforded largely a 28:62:10 mixture of the cycloadducts **6a**, **7a** and **9a**; crystallisation of the mixture from diethyl ether–light petroleum gave compound **7a**,[12] m.p. 142–144 °C, $[\alpha]_D$ –41 (c 0.29, CH$_2$Cl$_2$), in 34% yield.

That compounds **6a** and **7a** shared a common stereochemistry at the benzylic position was established by their conversion into the same dihydropyranone, shown to possess the stereostructure **10**. Thus, brief treatment of compound **6a** with trifluoroacetic acid provided the dihydropyranone **10**[12] (71% yield after chromatography), $[\alpha]_D$ +58 (c 0.54, CH$_2$Cl$_2$) {m.p. 110–111 °C and $[\alpha]_D$ +59 (c 0.39, CH$_2$Cl$_2$) after crystallisation}. Similar treatment of compound **7a** gave the dihydropyranone **10** (87% yield after chromatography), $[\alpha]_D$ +60 (c 0.43, CH$_2$Cl$_2$) {m.p. 110–111 °C and $[\alpha]_D$ +62 (c 0.45, CH$_2$Cl$_2$) after crystallisation}. The absolute stereochemistry of compound **10** was provisionally assigned on the basis of its dextrorotatory behaviour {compound **1** is reported[5] to show $[\alpha]_D$ –96.3 (c 0.87, CHCl$_3$)} and confirmed by its conversion into (3S)-3-hydroxy-3-(p-nitrophenyl)propanoic acid **11**,[12] m.p. 139–142 °C, $[\alpha]_D$ –9.8 (c 0.5, MeOH), and thence into (3S)-3-hydroxy-3-phenylpropanoic acid **12**,[13] m.p. 116–117 °C (lit., 118–119 °C), $[\alpha]_D$ –17 (c 0.4, EtOH) [lit., –18.9 (c 2.3, EtOH)], as shown in Scheme 1.



Scheme 1

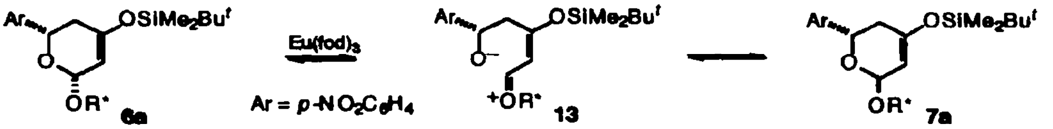
Clearly, the major cycloadduct obtained in the reaction catalysed by (–)-Eu(hfc)$_3$ possessed the stereostructure **6a** whereas that isolated from the Eu(fod)$_3$ catalysed reaction possessed the stereostructure **7a**. Whilst it was apparent that (–)-Eu(hfc)$_3$ represented a "matched" catalyst and (+)-Eu(hfc)$_3$ a "mismatched"[14] catalyst, it was surprising to detect a significant amount (~10%) of compound **7a** (formally, an "exo"-cycloadduct) using the former catalyst. Even more surprising was the finding that compound **7a** was the major product in the Eu(fod)$_3$ catalysed reaction. Further studies of the last-cited reaction, in which the effects of time and solvent were examined (Table 1), served to clarify the situation.

Table 1. Outcome of cycloaddition reactions of the diene **5a** with *p*-nitrobenzaldehyde in the presence of Eu(fod)$_3$ (2 mol%).

Solvent	Time	**6a**:**7a**:**8a**:**9a**[11]	**6a**+**7a**:**8a**+**9a**
CH_2Cl_2	24 h	49:39:5:7	88:12
CH_2Cl_2	96 h	14:72:4:10	86:14
$CHCl_3$	28 h	72:16:6:6	88:12
$CHCl_3$	118 h	46:46:trace:8	92:8
CCl_4	24 h	87:5:8:trace	92:8
CCl_4	113 h	82:9:9:trace	91:9
PhH	24 h	83:6:8:3	89:11
PhH	52 h	79:11:5:5	90:10
PhH	118 h	68:22:3:7	90:10
PhMe	24 h	79:9:9:3	88:12
PhMe	52 h	76:12:6:6	88:12
PhMe	132 h	71:19:4:6	90:10

It became apparent that the ratios of the cycloadducts **6a**:**7a**:**8a**:**9a** changed with time. However, although the rate of change depended upon the solvent, being most rapid in dichloromethane, the ratios of the cycloadduct pairs **6a**+**7a**:**8a**+**9a** remained constant at ~90:10 throughout the reaction. In a control experiment, it was established that the *cis*-cycloadduct **6a** underwent isomerisation in dichloromethane in the presence of Eu(fod)$_3$ (2 mol%) to give, after 71 hours, a 14:86 mixture of compounds **6a** and **7a**.

It therefore appears that the Eu(fod)$_3$ catalysed reactions lead initially to ~90:10 mixtures of the *cis*-cycloadducts **6a** and **8a** and that the stereoselectivity is largely independent of solvent. Epimerisation of the cycloadducts **6a** and **8a**, induced by the catalyst, then occurs to give their thermodynamically more stable *trans*-counterparts **7a** and **9a**,[15] the extent of epimerisation being dependent upon the time of reaction and the nature of the solvent. Presumably, the isomerisations proceed by way of ion-pair-like intermediates, *e.g.* **13**, as illustrated in Scheme 2 for the **6a**→**7a** conversion. A similar situation probably prevails for the (–)-Eu(hfc)$_3$ catalysed reaction, since when it was conducted in toluene for 24 hours only an 89:11 mixture of the *cis*-cycloadducts **6a** and **8a** was detected.



Scheme 2

On a preparative scale, the use of Eu(fod)$_3$ (2 mol%) in carbon tetrachloride (25 cm^3) over 24 hours proved very effective in transforming the diene **5a** (1.5 mmol) and *p*-nitrobenzaldehyde (1.5 mmol) into the *cis*-cycloadduct **6a**; after crystallisation, the last-cited compound was obtained in 80% yield.

The foregoing results are significant in a number of respects. They show that the diene **5a** exerts a useful degree of diastereofacial selectivity towards *p*-nitrobenzaldehyde in a hetero Diels–Alder reaction catalysed by Eu(fod)$_3$.[16] Surprisingly, the achiral catalyst performs at least as well as (–)-Eu(hfc)$_3$, which represents a "matched" catalyst with respect to the diene **5a**. As well as providing a practical route to the *cis*-cycloadduct **6a**, which serves as a precursor of the dihydropyranone **10**,[17] a new protocol for the synthesis of (1→1)-linked disaccharides[18] is in hand. Finally, the ability of Eu(fod)$_3$ to catalyse the **6a**→**7a** isomerisation is of note because of the fragility of the reactant and product.

Acknowledgements

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6 This is an abbreviation for tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).

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10 This is an abbreviation for tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium(III).

11 The ratio was estimated by 300 MHz ^{1}H NMR spectroscopy (CDCl$_3$) from the integrals of the broad quartets (separation 1.5 Hz) at δ 5.70 and 5.67, attributed to the 2-hydrogen atoms of the *cis*-cycloadducts **6a** and **8a**, and of the broad doublets (separation 3.5 Hz) at δ 5.48 and 5.64, ascribed to the 2-hydrogen atoms of the *trans*-cycloadducts **7a** and **9a**.

12 The spectral and analytical properties of new compounds were consistent with their assigned structures.

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15 It is well established for related cycloadducts, lacking 4-siloxy substituents, that *trans*-products are favoured over their *cis*-counterparts and that *cis*→*trans* isomerisations can be induced under acidic conditions (Jurczak, J.; Bauer, T.; Jarosz, S. *Tetrahedron* **1986**, *23*, 6477–6486).

16 It is noteworthy that the diene **2b** showed only a modest selectivity towards benzaldehyde in deuteriochloroform in the presence of Eu(fod)$_3$; the reaction was inferred to give a 33:67 mixture of the cycloadducts **3b** and **4b** (see ref. 5).

17 For other routes to enantioenriched representatives of this synthetically versatile class of compounds, see: Gao, Q., Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979–988; Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951–1952; Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312; Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907–6910; Togni, A. *Organometallics* **1990**, *9*, 3106–3113; Faller, J. W.; Smart, C. J. *Tetrahedron Lett.* **1989**, *30*, 1189–1192.

18 For a related strategy for the synthesis of (1→3)- and (1→4)-linked disaccharides, see: David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2521–2525 and references cited therein.

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