

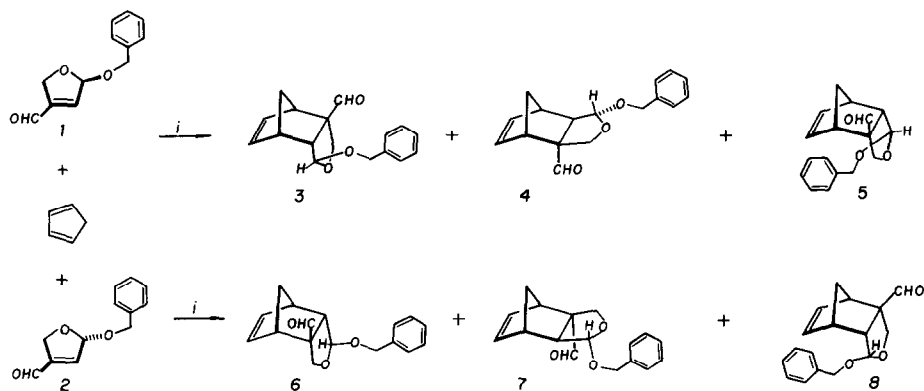
ASYMMETRIC DIELS-ALDER REACTION BETWEEN THE CHIRAL ISOPRENE UNITS 2-(R)-
AND (S)-BENZYLOXY-2,5-DIHYDRO-4-FURANCARBOXALDEHYDE AND CYCLOPENTADIENE

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Summary: The title Diels-Alder reaction gave a mixture of enantiomerically pure adducts with complete norbornane-type monoterpene skeletons. The *exo/endo* ratio of the products changed from approximately 4:1 at 5^o to 2:1 at 165^o.

Synthesis of enantiomerically pure compounds by the Diels-Alder route has received great attention recently¹. In most cases, chiral acrylates and $\alpha\beta$ -unsaturated ketones have been used as dienophiles, whereas few (if any) examples with chiral $\alpha\beta$ -unsaturated aldehydes have been reported. Since the chiral dienophiles are usually derived from natural products with multiple chiral centers, easy accessibility to both enantiomers is rare.



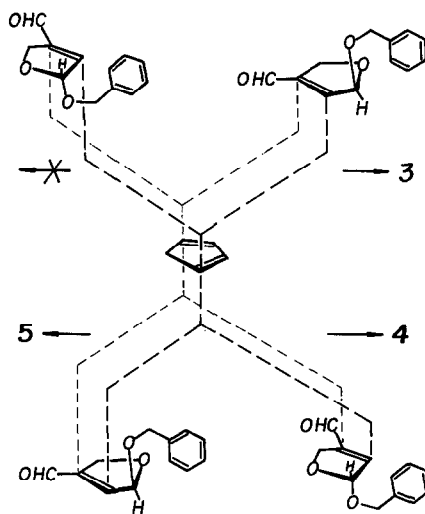
Scheme 1.

We now report the Diels-Alder reaction (both with and without catalyst) between cyclopentadiene² and the new chiral isoprene units 2-(R)- and (S)-benzyloxy-2,5-dihydro-4-furancarboxaldehyde (**1** and **2**) as depicted in Scheme 1. The aldehydes **1** and **2** were conveniently prepared³ in six steps from D- and L-arabinose, respectively, in an over-all isolated yield of 20%.

Table 1. Product distribution in the Diels-Alder reaction between **1** and cyclopentadiene^a.

Reaction temp. (°)	Reaction time (h)	Product yield (%) ^b		
		3	4	5
-20	212 ^c	82	18	<1
5	66 ^c	81	18	1
25	66	76	22	2
25	1 ^d	76	18	6
50	24 ^e	63	18	2
50	40	75	22	3
70	16	73	24	3
110	2	73	22	5
165	<2	63	32	5

a) 1 equiv. of **1**, 3 equiv. of cyclopentadiene, and 14 equiv. of toluene; b) determined by capillary gas chromatography; c) incomplete conversion of **1**; d) with 0.1 equiv. of Eu(fod)₃. e) isolated yield.



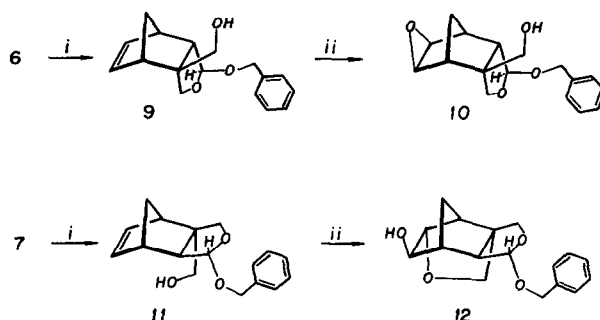
Scheme 2

Treatment of **1** at different temperatures with three equivalents of cyclopentadiene² in toluene followed by chromatography gave a mixture of **3** ($[\alpha]_D^{23} -113^\circ$, c 0.6, CDCl₃), **4** ($[\alpha]_D^{23} -119^\circ$, c 0.8, CDCl₃), and **5** ($[\alpha]_D^{23} -19^\circ$, c 1.8, CDCl₃) in the yields shown in Table 1. The yield of the mixture was virtually quantitative. The reaction was slow at, or below, room temperature, whereas higher temperatures, or the addition of Eu(fod)₃, increased the reaction rate⁴ (Table 1). The aldehyde **2** gave **6** ($[\alpha]_D^{23} +114^\circ$, c 0.7, CDCl₃), **7** ($[\alpha]_D^{23} +118^\circ$, c 0.4, CDCl₃), and **8**, analogously. It should be noted that **3-8** are potentially useful for inter alia the preparation of enantiomerically pure norbornane-type mono- and sesquiterpenes. The structures of the products were determined by nmr and by chemical transformations as shown below.

Phenyl groups have been used to selectively block reagent attack¹. In the present case, the benzyloxy protecting group makes the attack of cyclopentadiene occur preferentially from the least hindered side of **1** and **2** (Scheme 2). At temperatures below 0°, the uncatalysed reaction runs with virtually complete diastereofacial selection, whereas at higher temperatures

a small amount of the diastereoisomer 5 (or 8) was produced by *exo* addition (Scheme 2) of cyclopentadiene to the more hindered side of 1 (or 2). The preponderance of the *exo* mode of addition is in contrast to the outcome of most Diels-Alder additions with $\alpha\beta$ -unsaturated carbonyl dienophiles⁵, although other such exceptions are known⁶.

The ¹H- and ¹³C-nmr spectra of 3-5 were fully analysed and found to be in accord with the structures. The "anomeric" proton signals of 3 and 4 were sharp singlets (as expected from the Karplus equation⁷), whereas with 5, a doublet ($J=5.9$ Hz) was found. Reduction of 6 and 7 with sodium borohydride in ethanol gave the alcohols 9 (91%; $[\alpha]_D^{23} +110^\circ$, c 3, CDCl₃) and 11 (93%; $[\alpha]_D^{23} +93^\circ$, c 2, CDCl₃), respectively (Scheme 3). Treatment of 9 and 11 with *m*-chloroperbenzoic acid gave the epoxide 10 ($[\alpha]_D^{23} +64^\circ$, c 1, CDCl₃) and the ether 12 (m.p. 104-105^o; $[\alpha]_D^{23} +96^\circ$, c 0.6, CDCl₃), as anticipated from other epoxidations of norbornenes^{8,9}. Comparison of the ¹H- and ¹³C-nmr chemical shifts and coupling constants of 10 and 12 with literature data⁹ established the structures and confirmed the *exo/endo* ratio discussed above.



Scheme 3. i) NaBH₄, EtOH, 23^o; ii) *m*-CPBA, CH₂Cl₂, 23^o.

Most enantioselective Diels-Alder reactions utilise dienophiles that carry reusable chiral auxiliaries¹. The single chiral centre of the present dienophiles 1 and 2 was initially formed by Fisher glycosidation of D- and L-arabinose, respectively¹⁰. When the four chiral centers of the carbon skeleton in 3-8 have been induced by the original one (which is in reality only a protecting group), the latter can be conveniently removed by processes that produce only relatively dispensable products such as benzyl alcohol and toluene. The further use of 1 and 2 in total synthesis of chiral natural products will be reported in due course.

Acknowledgments: We are grateful to M. Levin for technical assistance. This work was supported by the Swedish Natural Science Research Council and The Swedish Board for Technical Development.

References and notes

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- 2 All new compounds had satisfactory combustion analysis data and ^1H - and ^{13}C -nmr spectra in full accord with the structures. For an improved method for the preparation of cyclopentadiene on a laboratory scale, see: G. Magnusson, *J. Org. Chem.* **1985**, 50, 1998.
- 3 Enantiomerically pure **1** and **2** were prepared by LiBr-induced ring-contraction of benzyl 2,3-anhydro- β -D- and L-ribofuranoside¹⁰, essentially as described for epoxycyclohexanols¹¹. Detailed procedure and reaction mechanism will be published elsewhere. Aldehyde **1** had m.p. 44-49 $^\circ$; $[\alpha]_{\text{D}}^{23}$ +89 $^\circ$ (c 0.7, CDCl_3); **2** had m.p. 43-49 $^\circ$; $[\alpha]_{\text{D}}^{23}$ -90 $^\circ$ (c 0.8, CDCl_3).
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(Received in UK 1 September 1985)