REINVESTIGATION OF THE DIELS-ALDER REACTION OF (E)-(R)-4,5-DI-O-ISOPROPYLIDENEPENT-2-ENOATES AND CYCLOPENTADIENE

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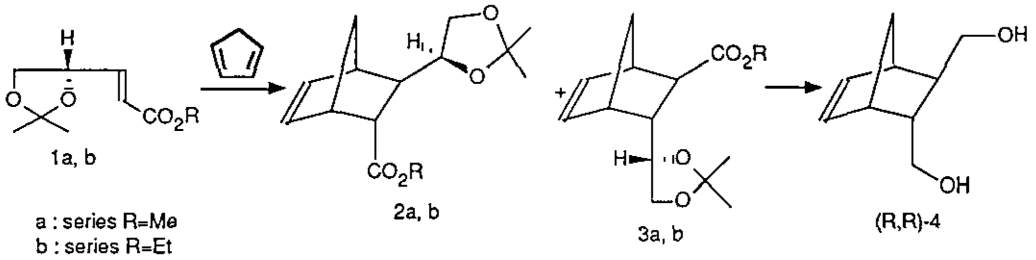
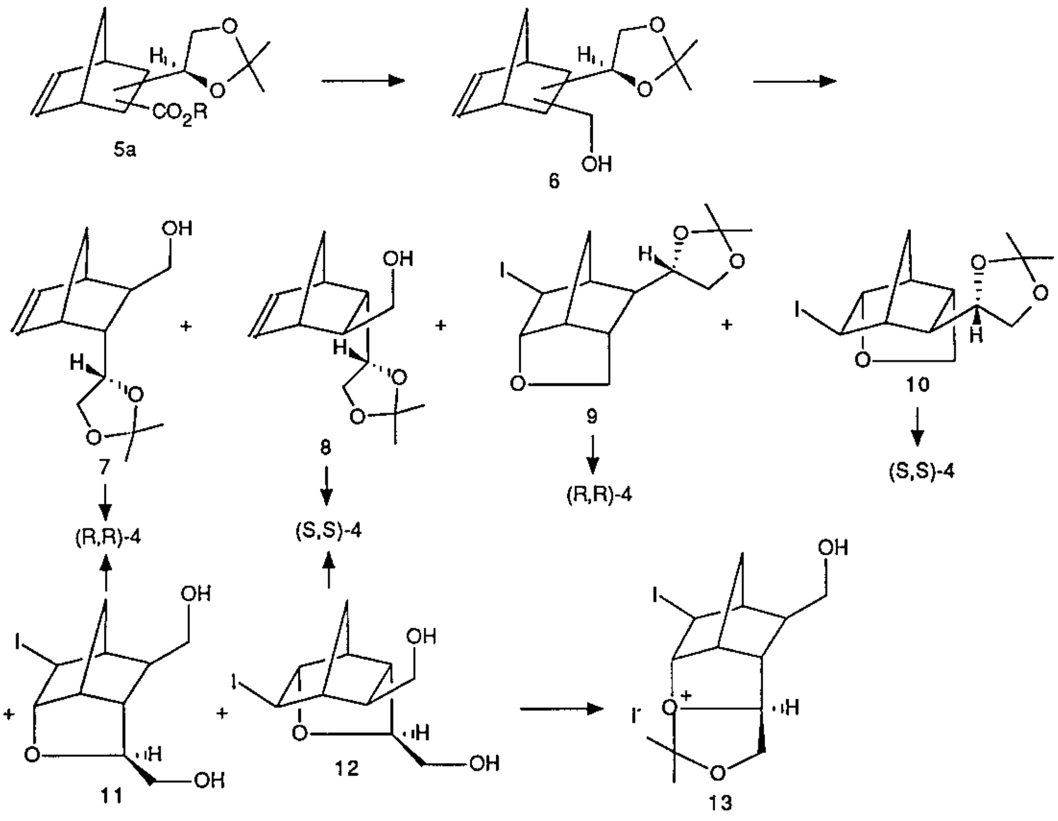
Abstract——Diels-Alder reaction between (*E*)-(*R*)-4,5-di-*O*-isopropylidene-pent-2-enoates and cyclopentadiene under both uncatalyzed and catalyzed conditions has been reinvestigated. Contrary to the preceding reports, no high diastereofacial selection has been observed under both conditions.

Mulzer and Kappert first reported that the Diels-Alder reaction between methyl (*E*)-(*R*)-4,5-di-*O*-isopropylidenepent-2-enoate (**1a**) and cyclopentadiene under uncatalyzed conditions proceeded with high diastereofacial selection to give a 2:3 mixture of the *endo*-ester (**2a**) and the *exo*-ester (**3a**) in an excellent yield.[1] Encouraged by this interesting finding we carried out the same reaction using the ethyl ester (**1b**) under Lewis acid catalyzed conditions which resulted in the formation of a 3~4:1 mixture of two adducts at much lower reaction temperature.[2] We believed that the reaction proceeded with extremely high diastereofacial selection to give a mixture of the *endo*-(**2b**) and the *exo*-(**3b**) adducts since the *bis*-diol directly derived from the mixture showed virtually the same optical rotation values[3] to those reported for (2*R*,3*R*)-2,3-dihydroxy-methyl-5-norbornene (*R*,*R*)-**4**. However, we now have found the high diastereofacial selectivity described in the preceding reports should be corrected by the following experimental results.

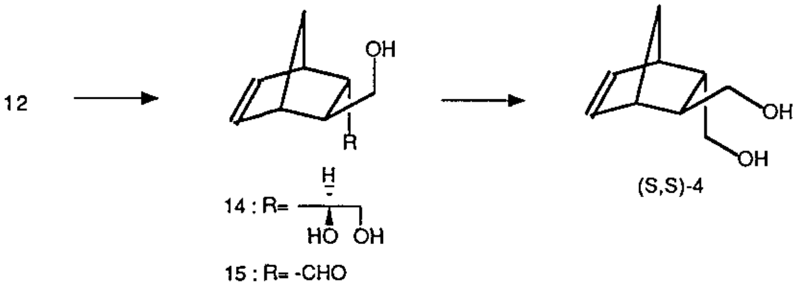


Scheme 1

First, we reinvestigated the reaction between the methyl ester (**1a**) and cyclopentadiene under uncatalyzed conditions.[1] The dienophile (**1a**) was heated with an excess (6.7 equiv) of the diene at 80 °C to afford a mixture of the adducts (**5a**), in 92% yield, which appeared as two spots on a tlc plate (SiO_2). The mixture, without separation, was reduced with lithium aluminum hydride to give a mixture of the primary alcohols (**6**), quantitatively, which still appeared as two spots on a tlc plate (SiO_2). Upon treatment with iodine (2 equiv) in aqueous THF (80%) containing sodium hydrogen carbonate (5 equiv),[4] this mixture furnished four iodo-ethers, (**9**) (28.3%), (**10**) (8.7%), (**11**) (42.2%) and (**12**) (9.8%), and two unchanged alcohols, (**7**) (4.8%) and (**8**) (6.2%), which could be separated by silica gel chromatography. When reaction time was prolonged, both of the unchanged two were gradually transformed into the corresponding iodo-ethers, (**11**) and (**12**), with loss of the isopropylidene group probably *via* an oxonium intermediate, such as **13** (Scheme 2). The structure of the isolated products was unambiguously determined by converting them into the optically active diol (**4**) on sequential reductive cleavage by zinc, acid hydrolysis [for (**9**)~(**10**)], cleavage with sodium periodate, and reduction with sodium borohydride as exemplified by the conversion of **12** into (*S,S*)-**4**.[5] We could



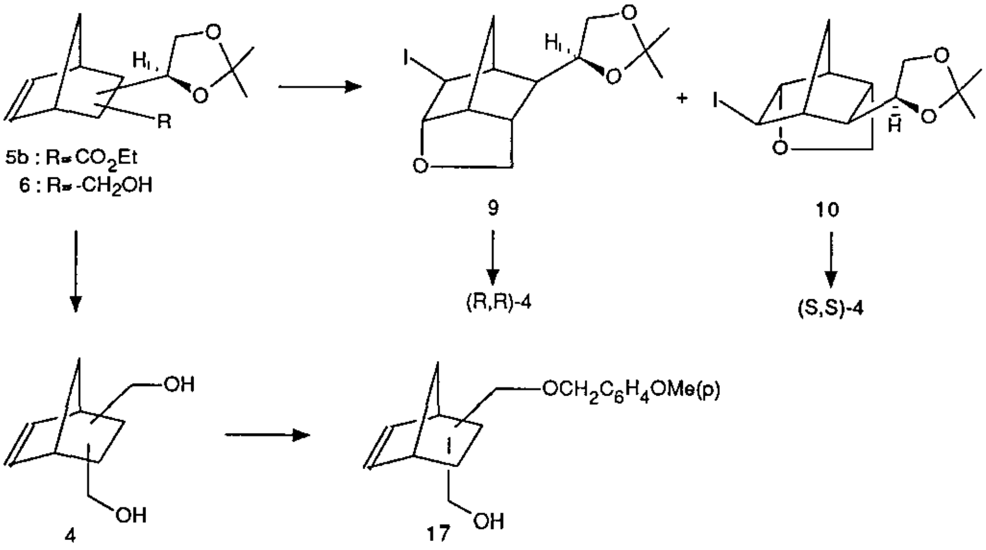
Scheme 2



Scheme 3

now conclude that diastereofacial selectivity and *endo*/*exo*-stereoselectivity in the uncatalyzed conditions were 3:1 and 1:1.7, respectively.

Next, we reexamined the reaction under the Lewis acid catalyzed conditions.[2] The dienophile (**1b**) was reacted with an excess diene (10 equiv) in methylene chloride at -20 °C in the presence of the same equivalents of diethylaluminum chloride to give a mixture of the adducts (**5b**) in 90 % yield. Reduction of the mixture with lithium aluminum hydride afforded a mixture of the primary alcohols (**6**) in 95% yield. Upon treatment with iodine (2 equiv) in aqueous THF (80%) containing sodium hydrogen carbonate (5 equiv), the mixture (**6**) afforded a mixture of the iodo-ethers, **9** (66%), **10** (17%) , **11** (9%), and **12** (2%), which were separated by silica gel chromatography. Each of the iodides was



Scheme 4

converted into the corresponding diol (**4**) [(*R*,*R*)-4[5] from **9** and**11**, (S,S)-4[5] from **10** and **12**], respectively. As appeared, high diastereofacial selectivity could not be observed even in the catalyzed conditions (3.9:1), though generation of the *exo*-ester adducts was greatly reduced (1:7.5). The diastereofacial selectivity estimated from the yields of two iodo-ethers was further supported by converting the mixture (**4**) into the mixture of the monobenzyl ether (**17**). Thus, the mixture of the diol (**4**) was first converted into the mixture of the iodo-ether (**16**) which on sequential *p*-methoxybenzylation (*p*-methoxybenzyl chloride, NaH) and reductive treatment (Zn, MeOH, rt) gave the *endo*-alcohol mixture (**17**). Examination of ^{1}H-nmr spectrum (500 MHz) of the MTPA ester of **17** revealed that the mixture was consisted of 15 parts of (*R*,*R*)-**17** and 4 parts of (*S*,*S*)-**17** which was consistent with the above estimation.

We also tried the same Lewis acid catalyzed cycloaddition using the methyl ester (**1a**) in place of the ethyl ester (**1b**) to give the adduct mixture (**5a**) in quantitative yield. On the same conversion above this mixture furnished the four iodo-ethers, **9** (38 parts), **10** (10 parts), **11** (5 parts), and **12** (1 parts) in a similar total yields, indicating diastereofacial and *endo*/*exo*-selectivities in 7:2 and 10:1, respectively.

References and Notes

1. J. Mulzer and M. Kappert, *Tetrahedron Lett.*, 1985, **26**, 1631.
2. S. Takano, A. Kurotaki, and K. Ogasawara, *Synthesis*, 1987, 1075.
3. We believe that the analytical sample we used in the preceding report[2] was derived from the fractions containing the major component (**2b**) which has been partly separated during chromatographical purification of the adduct mixture. The diol (**4**) obtained from the present mixture (**5b**) showed much lower optical rotation values: $[\alpha]_D^{18}$ +13.0° (*c* 1.08, $CHCl_3$).
4. Cf. M. D. Dowle and D. I. Davies, *Chem. Soc. Rev.*, 1979, **8**, 171.
5. The all diols (**4**) obtained in the present experiment possessed almost the same optical rotation values: $[\alpha]_D$ |23.1°| ±1.4° ($CHCl_3$).
6. S. Takano, A. Kurotaki, M. Takahashi, and K. Ogasawara, *Synthesis*, 1986, 403.

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