Highly Stereoselective Diels-Alder Reactions Achieved on Some Hexopyranosidic Templates

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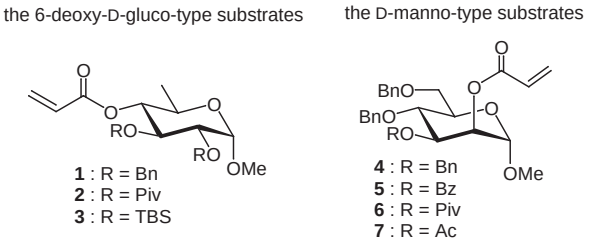
Abstract: The Diels-Alder reactions of some carbohydrate derivatives, as chiral acrylic esters, with cyclopentadiene proceed highly diastereoselectively to provide the adducts carrying a norbornene carboxylate. By reductive removal of the carbohydrate templates from the adducts, both 2*S* and 2*R*-enriched 5-norbornene-2-methanol are obtained.

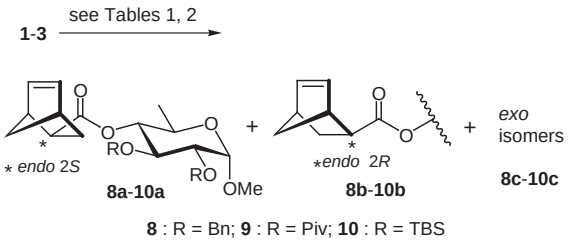
Key words: asymmetric synthesis, diastereoselectivity, Diels-Alder reaction, cyclopentadiene, norbornene derivatives

The design of chiral auxiliaries based on readily available natural products, which would serve as a stereocontrolling factor, is one of the promising approaches in the field of asymmetric synthesis.[1] Several carbohydrate derivatives are sources of chiral nonracemic materials, from which synthetically useful auxiliaries have been devised.[2] We have investigated the utility of hexopyranose derivatives as chiral templates for asymmetric carbon-carbon bond forming reactions. Recently, we reported the highly stereoselective 1,4-additions of organocopper reagents[3] or alkyl radicals[4] to carbohydrate derived chiral crotonyl esters. In this communication, we report the preliminary results on the intermolecular Diels-Alder reaction based on our carbohydrate template concept.[5] The substrates **1**-**7**, which were used for the present asymmetric Diels-Alder reaction, were conventionally prepared from known methyl α-D-glycopyranosides (Scheme 1). As the dienophile part, these substrates possess an acryloyl ester moiety at C-4 for methyl 6-deoxy-α-D-glucopyranosides, i.e., **1**-**3**,[6,7] or at C-2 for methyl α-D-mannopyranosides, i.e., **4**-**7**.[8]



Scheme 1

First, we investigated the Diels-Alder reactions of the 6-deoxy-D-glucosidic substrates **1**-**3** with cyclopentadiene (Scheme 2). The results under thermal conditions are shown in Table 1. In every case, the Diels-Alder reaction proceeded at room temperature to provide the adduct as a mixture of diastereomers (*endo* 2*S*, *endo* 2*R*, and *exo* isomers).[9] The ratio of the *endo*/*exo* isomers and the diastereomeric ratio of the *endo* adducts (**8a**-**10a**:**8b**-**10b**) were determined based on each ^{1}H NMR analysis. In the case of **1**, a modest diastereoselectivity was observed for **8a**:**8b** (entry 1). The reaction of **2** or **3**, which possesses a bulkier substituent (R = Piv or TBS) at C-3, afforded *endo* 2*S* adduct **9a** or **10a**, respectively, with improved diastereoselectivity (entries 2 and 3). However, the observed *endo*/*exo* selectivity was not sufficiently high in every case. The absolute stereochemistry of the newly introduced stereogenic centers in the norbornene ring was determined by comparison with the reported optical signs for known 5-norbornene-2-carboxylic acid and/or -2-methanol,[10] after removal of the carbohydrate templates. In the case of the substrate **3**, the mixture of the *endo* adducts **10a**/**10b** was obtained by removing the minor *exo* adducts by chromatographic separation on silica gel (Scheme 3). Removal of the carbohydrate templates from the mixture of **10a**/**10b** was conducted by reductive cleavage using DIBAL-H to provide (2*S*) enriched 5-norbornene-2-methanol **11**.[11] The carbohydrate template **12** was recovered efficiently. Benzoylation of the (2*S*) enriched **11** and HPLC analysis (serial connection of Chiralcel OD+OD-H; hexane:EtOH = 300:1) of the resulting benzoate verified that the enantiomeric ratio (2*S*:2*R*) of **11** was 97:3.



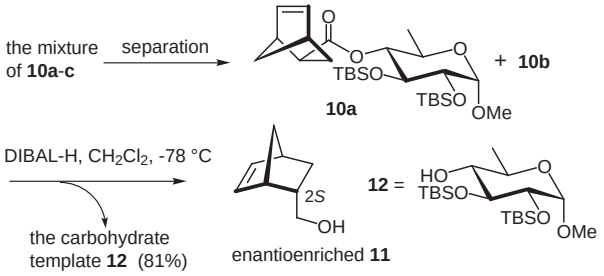
Scheme 2

The results of the Diels-Alder reaction of **1** or **2** conducted in the presence of $EtAlCl_2$ as Lewis acid are shown in Table 2. Both Diels-Alder reactions proceeded at -78 °C to provide a mixture of the *endo* adducts **8a**/**8b** or **9a**/**9b** predominantly although the combined yield of two *endo*-adducts was modest in every case (entries 1 and 2). In the case of **2**, however, highly diastereoselective formation of the *endo* adduct **9b** was observed. Interestingly, the π-facial selectivity in the Lewis acid mediated *endo* mode Diels-Alder reaction of **2** was opposite to that observed

Table 1 Diels-Alder Reaction of the 6-Deoxy-D-gluco-type Substrates **1**-**3** under thermal conditions[a]

entry	substrate	yield[b]	*endo* : *exo*[c]	**a** : **b**[c]
1	**1**	96	79 : 21	71 : 29
2	**2**	96	89 : 11	87 : 13
3	**3**	97	80 : 20	>95 : 5

[a]Cyclopentadiene, CH_2Cl_2, rt, 2-5 days. [b]Combined yield of diastereomeric adducts (%). [c]Determined by ^1H NMR analysis.



Scheme 3

under the thermal conditions (entry 2 in Table 1 vs. entry 2 in Table 2). We propose a plausible transition state mechanism to interpret this reverse π-facial selectivity observed for the substrate **2** under the thermal or the Lewis acid mediated conditions (Figure). In the case of the thermal conditions, the dienophile part is apt to exist in *s-cis, syn* conformation. Then cyclopentadiene approaches from the less hindered side by reason of avoiding the steric hindrance expected by the presence of the substituent at C-3 such as pivaloyloxy group in the case of **2** (**TS 1**). Consequently, the *endo* 2*S* adducts **9a** or **10a** were obtained predominantly. On the other hand, in the presence of $EtAlCl_2$, the dienophile part is likely to change to *s-trans, syn* conformation as a result of the Lewis acid coordination to acryloyl carbonyl. Cyclopentadiene favorably approaches to the dienophile part from the less hindered side (**TS 2**). As a result, the *endo* 2*R* adduct **9b** was obtained predominantly in the latter conditions.

Table 2 Diels-Alder Reaction of the 6-Deoxy-D-gluco-type Substrates **1**-**3** in the presence of $EtAlCl_2$[a]

entry	substrate	yield[b]	*endo* : *exo*[c]	**a** : **b**[c]
1	**1**	63	>95 : 5	*ca.* 1 : 1
2	**2**	79	>95 : 5	10 : 90
3	**3**	NR[d]	---	---

[a]$EtAlCl_2$ (2 eq), cyclopentadiene, CH_2Cl_2, -78 °C, 15 min. [b]Combined yield of diastereomeric adducts (%). [c]Determined by ^1H NMR analysis. [d]Reaction did not take place.

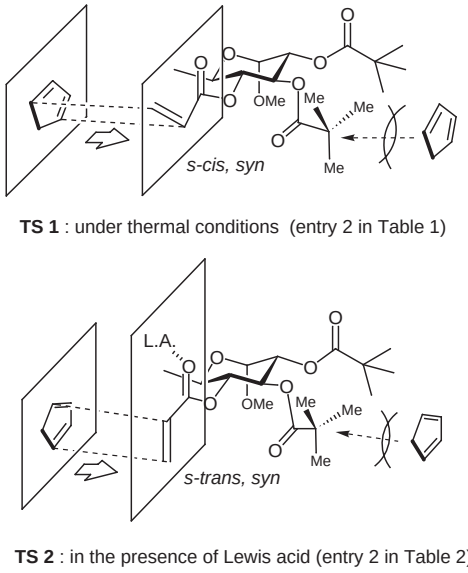
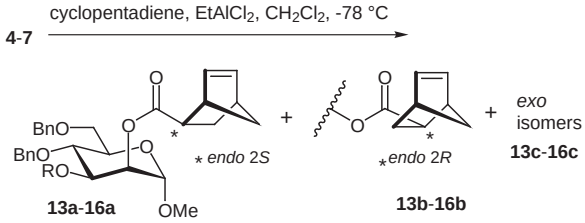


Figure A Plausible Transition States Mechanism for the Diels-Alder Reactions of the 6-Deoxy-D-glucosidic Substrate **2**

Next, we investigated the Diels-Alder reactions of the D-mannopyranosidic substrates **4**-**7** with cyclopentadiene in the presence of Lewis acid[12] (Scheme 4). The results are summarized in Table 3. In every case, the Diels-Alder reaction proceeded at -78 °C to afford a mixture of two *endo* adducts **13a**/**13b** - **16a**/**16b** with high *endo*/*exo* selectivity. The substrates **5**-**7** possessing an acyloxy substituent at C-3 afforded the respective *endo* 2*R* adducts **14b**-**16b** with remarkable diastereoselectivity (entry 1 vs. entries 2-4). Furthermore, the diastereomerically homogeneous *endo* 2*R* adduct **16b** was separated from other adducts by chromatographic separation on silica gel (Scheme 5).[13] After reductive cleavage of the carbohydrate moiety, enantiomerically pure (2*R*)-*endo*-5-norbornene-2-methanol **17**[14] was obtained. The carbohydrate template **18** was recovered in good yield. The Diels-Alder reactions of **5**-**7** afford *endo* 2*R*-adducts in good diastereoselectivity, however, at present we have no reasonable explanation for this stereochemical outcome.



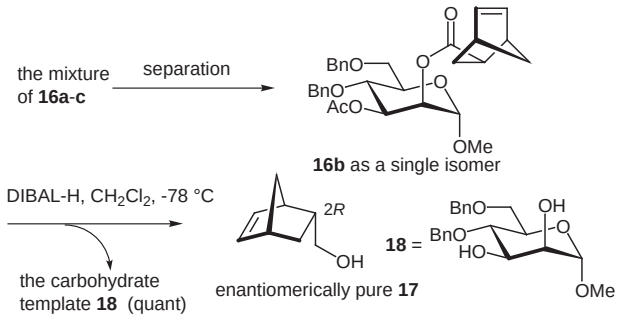
Scheme 4

We also investigated the influence of the stoichiometry of $EtAlCl_2$ on the Diels-Alder reaction by using **2** or **5** as the substrate. The results are shown in Table 4. Although the

Table 3 Diels-Alder Reaction of the D-Manno-type Substrates **4**-**7** in the presence of $EtAlCl_2$[a]

entry	substrate	yield[b]	*endo* : *exo*[c]	**a** : **b**[c]
1	**4**	83	>95 : 5	33 : 67
2	**5**	84	>95 : 5	9 : 91
3	**6**	89	>95 : 5	14 : 86
4	**7**	98	>95 : 5	11 : 89

[a]$EtAlCl_2$ (2 eq), cyclopentadiene, CH_2Cl_2, -78 °C, 15 min. [b]Combined yield of diastereomeric adducts (%). [c]Determined by ^1H NMR analysis.



Scheme 5

endo/*exo* selectivity was independent of the stoichiometry of $EtAlCl_2$, the larger equiv of $EtAlCl_2$ provided the higher diastereoselectivity in the π-facial selectivity. On the other hand, decrease of $EtAlCl_2$ to 1 equiv or less caused significant decrease of the yield in the case of **2**. The increase of Lewis acid certainly accompanies with the coordination of $EtAlCl_2$ to the neighboring acyloxy group, which results in the formation of a more effective asymmetric environment.

Table 4 Influence of $EtAlCl_2$ Stoichiometry[a]

entry	substrate	$EtAlCl_2$ (eq.)	yield[b] (%)	*endo* : *exo*[c]	**a** : **b**[c]
1	**2**	1	*ca.* 30[c]	>95 : 5	12 : 88
2	**2**	2	79	>95 : 5	10 : 90
3	**2**	4	85	>95 : 5	8 : 92
4	**5**	1	83	>95 : 5	17 : 83
5	**5**	2	85	>95 : 5	9 : 91
6	**5**	4	84	>95 : 5	10 : 90

[a]$EtAlCl_2$, cyclopentadiene, CH_2Cl_2, -78 °C, 15 min. [b]Combined yield of diastereomeric adducts (%). [c]Determined by ^1H NMR analysis.

In summary, we have found a novel asymmetric Diels-Alder reaction methodology realized on the carbohydrate templates. The present work provides a practical method to prepare optically active chiral norbornene derivatives. In some cases, the predominant *endo* adducts can be readily separated from the other diastereomers. Removal of the carbohydrate templates from the *endo* adducts provides enantiomerically enriched or pure (2*S*) or (2*R*)-*endo*-5-norbornene-2-methanol.

Acknowledgement

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References and Notes

(1) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995. Rück, K.; Kunz, H. *Chiral Auxiliaries in Cycloadditions*; Wiley: New York, 1995.
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(5) A representative report on the Diels-Alder reaction on carbohydrate template, see: Kunz, H.; Müller, B.; Schanzenbach, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 267.
(6) The 6-deoxy-D-gluco-type acrylates **1**-**3** were prepared analogously to the preparation of the corresponding crotonyl esters described in references 3 and 4.
(7) All purified new compounds were fully characterized by ^1H and ^{13}C NMR, IR, and HRMS.
(8) The D-manno-type acrylate **4** was prepared from methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (Eby, R.; Webster, K. T.; Schuerch, C. *Carbohydr. Res.* **1984**, *129*, 111) by acryloylation. The substrates **5**-**7** were prepared from methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside (Kong, F.; Schuerch, C. *Carbohydr. Res.* **1983**, *112*, 141) by regioselective acryloylation of the 2-OH,*via* a metal chelate as descried in the preparation of methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside by Eby et al., followed by acylation (benzoylation for **5**, pivaloylation for **6**, or acetylation for **7**) of the 3-OH.
(9) A typical procedure for the Diels-Alder reaction under thermal conditions: To a solution of **3** (38.1 mg, 0.083 mmol) in CH_2Cl_2 (2 mL) was added cyclopentadiene (0.10 mL) at 0 °C. The reaction mixture was stirred for 5 days at room temperature and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/EtOAc = 80:1) to give a mixture of **10a**, **10b** and **10c** as a colorless oil (42.2 mg, 97%).
(10) Berson, J. A.; Walia, J. S. Remanick, A.; Suzuki, S.; Reynolds-Warnhoff, P.; Willner, D. *J. Am. Chem. Soc.* **1961**, *83*, 3986. Also, see: Ref.5.
(11) The optical rotation of enantioenriched **11**:$[\alpha]^{22}_D$-69 (*c* 0.195, EtOH). For (2*S*)-*endo*-5-norbornene-2-methanol: Lit.[5] $[\alpha]_D$ -76.6 (95% EtOH).
(12) The Diels-Alder reactions of the substrates **4**-**7** under thermal conditions underwent with no significant π-facial selectivities (d.r. of two *endo* adducts was ca. 1: 1 in every case).

(13) A typical procedure for the Diels-Alder reaction in the presence of Lewis acid: The reaction was conducted under an argon atmosphere. To a solution of **7** (477.1 mg, 1.01 mmol) in CH_2Cl_2 (20 mL) was added 1.0 M solution of $EtAlCl_2$ in hexane (2.1 mL, 2.1 mmol) at −78 °C. After the mixture was stirred at –78 °C for 40 min, cyclopentadiene (0.25 mL) was added dropwise over 10 min. The mixture was stirred at –78 °C for 15 min and quenched with 1 M aq. HCl (2 mL). The mixture was allowed to warm to room temperature, diluted with 1 M aq. HCl (40 mL) and extracted with CH_2Cl_2 (40 mL × 2). The combined organic layers were dried and concentrated in vacuo. The residue was purified on silica gel chromatography (hexane/EtOAc = 5:1) to provide 467.3 mg (86%) of **16b** as a colorless oil, and 68.1 mg (12%) of an inseparable mixture of **16a** and *exo*-adducts **16c**.

(14) The optical rotation of enantiopure **17**:$[\alpha]^{22}_{D}$+76 (*c* 0.215, EtOH). For (2*R*)-*endo*-5-norbornene-2-methanol: Lit. $[\alpha]^{22}_{D}$ +76.1 (*c* 0.9, EtOH) (Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc*. **1975**, *87*, 6908).

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