Synthesis of Enantiomerically Pure (2*S*)-2-*endo*-Hydroxymethyl-5-norbornene by Diels−Alder Reaction Based on a New Fructose-Derived Auxiliary

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Introduction

During our previous work[1] on the use of carbohydrate derivatives for asymmetric induction,[2] we showed that methyl methylene-arabinoside **A** was an efficient template in the asymmetric Diels−Alder reaction of an acrylate with cyclopentadiene (CPD)[1b] (Scheme 1). However, *β*-D- or α-L-arabinopyranosides are relatively expensive, and the synthesis of **A** involves a direct methyl glycosylation during the methylenation of arabinose, which is not selective.[3] Tedious separation of the anomers is only possible on the corresponding acrylates.

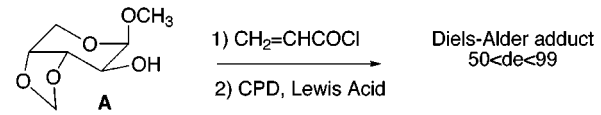
We needed an auxiliary suitable for large scale applications as, for example, the synthesis of enantiomerically pure (2*S*)-2-*endo*-5-norbornene derivatives.[4] Then, we turned our attention toward the design of a more accessible sugar-derived acrylate having the same favorable conformational structure as arabinose for efficient asymmetric Diels−Alder reactions.

Results and Discussion

Because the relative configuration of adjacent C-3, C-4, and C-5 carbons of D-fructose is the same as for C-2, C-3, and C-4 in D-arabinose, we decided to synthesize a 4,5-*O*-methylene acetal of D-fructose with the equatorially attached 3-OH remaining free. We have shown[5] that direct methylenation of D-fructose led to 2,3:4,5-di-*O*-methylene-*β*-D-fructopyranose and not to 1,2:4,5-di-*O*-methylene-*β*-D-fructopyranose. Consequently, we first protected the anomeric and the 2-OH positions to obtain spirotriol **3**. Then, methylenation of **3** led to the desired stable and crystalline tricyclic product **4** with the requisite structural pattern (Scheme 2).

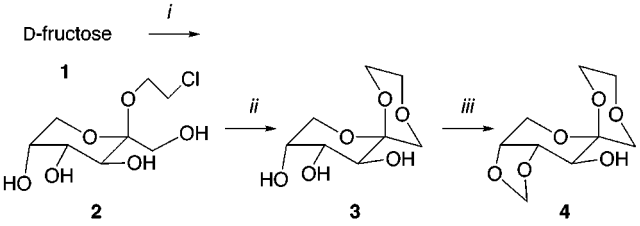
The synthesis of spiro **3** was carried out as described in the literature.[6] Methylenation of **3** was achieved in 76% yield, through a well-established three-step sequence without isolation of the intermediates.[5] Nevertheless, we have shown that after the first step a 80/20 mixture of the trimethoxymethyl ether (tri-MOM ether) of **3** and the MOM ether of **4** was obtained. This mixture was entirely transformed into the MOM ether of **4** during the dioxolane-forming second step, and finally, the last MOM ether protection was cleaved during the third step.

Scheme 1



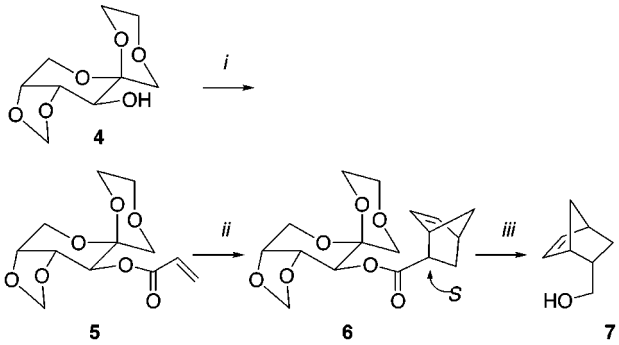
methyl 3,4-*O*-methylene-β-D-arabinopyranoside

Scheme 2



[a] *i* - $Cl(CH_2)_2OH$, CH_3COCl, 75%; *ii* -1M MeONa, MeOH, 94%; *iii* - 76%: a) DMM, Amberlyst 15, 4 h; b) TsOH,CH_2Cl_2, 12 h; c) MeOH 2%H_2O, TsOH, 6 h.

Scheme 3



[a] *i* - CH_2=CHCOCl, Et_3N, CH_2Cl_2, -30 °C→ RT, 12 h, 71%; *ii* - $SnCl_4$, CPD, CH_2Cl_2, 0 °C, 40 min, >99%; *iii* - $LiAlH_4$, 93 %

Alcohol **4** was transformed into acrylate **5** with acryloyl chloride in the presence of Et_3N. The Diels−Alder reaction with CPD was carried out at 0 °C with 2 equiv of $SnCl_4$ as Lewis acid. The acrylate was consumed in 40 min (TLC). After workup and rapid purification through a short pad of silica, adduct **6** was isolated in quantitative yield. ^{1}H NMR and HPLC analysis[1c] showed the presence of only 2% of the *exo* adduct along with *endo*-**6** as a major diastereomer (Scheme 3). This result and those employing $EtAlCl_2$ as Lewis acid are presented in Table 1. The diastereomeric ratios were determined by 400 MHz ^{1}H NMR analyses by integrating the signals of the ethylenic protons of the norbornene moiety.[1c]

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(2) (a) Kunz, H.; Rück, K. *Angew. Chem.* **1993**, *105*, 355. (b) Hultin, P. G.; Earle, M. A.; Sudharshan, M. *Tetrahedron* **1997**, *53*, 14823. (c) Seyden-Penne, J. In *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley: New York, 1995.

(3) Nouguier, R.; Gras, J.-L.; Giraud, B. Virgili, A. *Bull. Soc. Chim. Fr.* **1991**, 128, 945.

(4) For the synthesis of enantiopure norbornene adducts see, for exemple: (a) Bezuidenhoudt, B. C. B.; Castle, G. H.; Geden, J. V.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 7451. (b) Kitagawa, O.; Izawa, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 4447. (c) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095. (d) Helmchen, G.; Ihrig, K.; Schindler, H. *Tetrahedron Lett.* **1987**, *28*, 183. (e) Helmchen, G.; Abdel Hady, A. F.; Hartmann, H.; Karge, R.; Krotz, A.; Sartor, A.; Urmann, M. *Pure Appl. Chem.* **1989**, *61*, 409.

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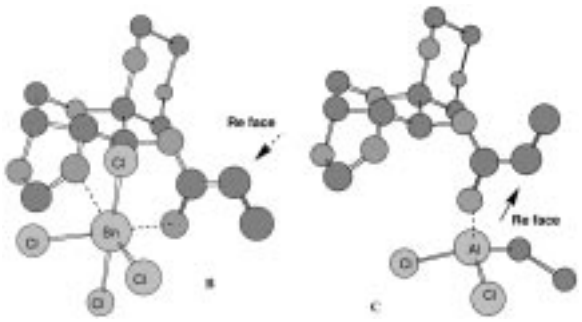

Figure 1. CSC Chem3Dpro drawing of chelates **B** and **C**. Only the geometry of the sugar acrylate **5** has been optimized by MM2 calculations.

Table 1. Reaction of 5 with CPD (4 equiv) in CH_2Cl_2 under Different Conditions: % of the *S*, *R*, and *exo* adducts of 6

			product (%)			
Lewis acid (2 equiv)	reaction time	temp (°C)	(2*S*)-**6** *endo*	(2*R*)-**6** *endo*	(2*R* + 2*S*)-**6** *exo*	yield (%)
$SnCl_4$	40 min	0	>99	<1	2	>99
$EtAlCl_2$	40 min	0	75	25	5	>99
$EtAlCl_2$	6 h	−78	90	10	1	96

As expected, the acrylate **5** proved excellent for asymmetric induction in this reaction. It can favorably compare with the previously used acrylate of arabinoside **A**, with the advantage of cooling at 0 °C rather than at −78 °C. This seems to be due to the resemblance of the two sugar templates: the acrylate is equatorial, and the adjacent oxygen of the methylene acetal function is also equatorial, in a $^1C_4$ pyranoside chair conformation. This geometry favors, with a bidentate Lewis acid[7] like $SnCl_4$, the chelate **B** represented in Figure 1. The CPD approaches from the less hindered *Re* face of the chelate with the acrylate in an s-cis conformation, and the de is very high.

As already observed[1b,8] with arabinose acrylates, when $EtAlCl_2$ is employed as Lewis acid, the de is not so high. These results can be explained on the basis of the complex **C**, shown to prefer a conformation where the C═O/C═C bonds of the acrylate are s-trans disposed.[4c] The *Re* face of the chelate is less hindered by the methylene acetal protection than the *Si* face by the spiro-2-dioxanyl substitution.

The $LiAlH_4$ reduction[9] of the cycloadduct **6** led to the desired norbornenol **7** and to recovered auxiliary **4**.

Conclusion

We have shown that the acrylate of the protected fructose derivative **4** is an efficient new chiral auxiliary for $SnCl_4$-mediated asymmetric Diels−Alder reaction with CPD.

The transformation of cheap and abundant D-fructose into the 1,2-*O*-ethylene-fructose **3** and the protection as the methylene acetal **4** are very easy, highly selective and can be scaled up to large quantities. These protections are very stable toward an excess of $SnCl_4$ at 0 °C. The auxiliary **4** is crystalline and easily handled and recovered and can be used for the synthesis of pure (2*S*)-2-substituted-5-norbornene derivatives.

Experimental Section

General Methods. Unless otherwise noted, starting materials were obtained from commercial suppliers and used as received. All reactions were carried out under argon atmosphere. Tetrahydrofuran (THF) was distilled under argon from sodium/benzophenone prior to use. MeOH-free CH_2Cl_2 was distilled over P_2O_5, and Et_3N was distilled over KOH. Melting points are uncorrected. Coupling constants (*J*) are reported in Hz.

1,2-*O*-ethylene-*β*-D-fructopyranose (3). To a solution of acetyl chloride (5 mL) in 2-chloroethanol (200 mL) was added portionwise anhydrous powdered D-fructose (27 g, 0.15 mmol). The mixture was stirred for 2 h at room temperature. The solid was filtered off and washed twice with EtOH and then with Et_2O. After drying under vacuum, **2** (27.3 g, 75%) was obtained as a white solid, mp 148 °C. Crude fructoside **2** (25.5 g, 105 mmol) was added to a 1 M solution of MeONa in MeOH (200 mL). The mixture was heated under reflux for 45 min, cooled, and neutralized by Amberlite IR-120 resin (prior to use, the resin was washed with distilled water and then with hexanes). After filtration, the solution was decolorized for 20 min with activated carbon Norit A. Filtration and evaporation led to a slightly yellowish syrup; crystallization for 12 h in 2-propanol (100 mL) gave 18.4 g (85%) of a white solid, mp 133 °C. Concentration of the filtrate and purification of the residual syrup by chromatography on silica gel with 10% → 40% MeOH in $CHCl_3$ as eluent gave 2 g (9%) of a second crop of **3**. If the 2-propanol used for crystallization was not dried, **3** crystallized as a semihydrate. Anal. Calcd for $C_8H_{14}O_6 \cdot 0.5H_2O$: C, 44.65; H, 7.02. Found: C, 44.60; H, 7.00.

1,2-*O*-ethylene-4,5-*O*-methylene-*β*-D-fructopyranose (4). A slurry of fructopyranose **3** (10.3 g, 50 mmol), dimethoxymethane (DMM) (100 mL), and amberlyst 15 resin (5.1 g) was vigorously stirred in a round-bottom flask topped with a Soxhlet containing 4 Å molecular sieves (200 g) and filled with DMM. The mixture was refluxed for 12 h at such a temperature that refluxing DMM returned in the reaction flask after percolation on the molecular sieves. After filtration and evaporation of the DMM, the residue was dissolved in CH_2Cl_2 (100 mL) containing 0.7 g of *p*-toluenesulfonic acid, and the mixture was refluxed for 12 h. To this solution was added 50 mL of MeOH containing 2% of water, and the CH_2Cl_2 was slowly evaporated. MeOH (50 mL) and *p*-TsOH (0.7 g) were added, and the mixture was refluxed for 6 h. The reaction mixture was neutralized with solid K_2CO_3 and filtered. The solid was washed with CH_2Cl_2, and the filtrate was concentrated. Purification by chromatography on silica gel with 0% → 5% MeOH in CH_2Cl_2 as eluent gave 8.2 g (76%) of a white solid: mp[10] 173 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.20 (s, 1H), 5.00 (s, 1H), 4.23−4.13 (m, 2H), 4.05−3.88 (m, 4H), 3.76−3.55 (m, 4H), 3.38 (t, J = 7.9 1H), 2.40 (d, J = 7.9, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 95.1, 94.8, 76.0, 74.5, 69.8, 68.5, 65.5, 60.2, 59.3. Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found:[10] C, 49.51; H, 6.49. $[\alpha]^{24.5}_D$ −150 (*c* 0.46, 95% EtOH).[10]

3-*O*-acryloyl-1,2-*O*-ethylene-4,5-*O*-methylene-*β*-D-fructopyranose (5). To a solution of **4** (1.1 g, 5 mmol) in MeOH-free CH_2Cl_2 (12 mL) cooled at −40 °C were added Et_3N (2 mL, 15 mmol) and acryloyl chloride (0.8 mL, 10 mmol), and the mixture was stirred for 12 h at room temperature. The mixture was cooled at 0 °C and acidified with 1 N HCl. The organic layer was washed with 1 N HCl and saturated $NaHCO_3$, dried over Na_2SO_4, concentrated, and purified by chromatography on silica

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(8) Shing, T. M. K.; Lloyd-Williams, P. *J. Chem. Soc., Chem. Commun.* **1987**, 423. This reference was inadvertently omitted in ref 1b but quoted in ref 1c.

(9) The adduct may be saponified without C-2 epimerization with $LiOH/H_2O$/THF at room temperature. See ref 4c for experimental procedure.

(10) After second purification of a small amount on silica gel with EtOAc as eluent.

gel with Et_2O as eluent to give 0.97 g (71%) of the acrylate: ^1H NMR ($CDCl_3$, 200 MHz) δ 6.50 (dd, J = 17.3, 1.4, 1H), 6.22 (dd, J = 17.3, 10.4, 1H), 5.92 (dd, J = 10.4, 1.4, 1H), 5.20 (s, 1H), 4.98 (s, 1H), 4.88 (d, J = 8.1, 1H), 4.40 (dd, J = 8.1, 5.4, 1H), 4.21 (d, J = 13.5, 1H), 4.06 (dd, J = 5.3, 2.4, 1H), 4.0−3.9 (m, 1H), 3.90 (dd, J = 13.5, 2.4, 1H), 3.75−3.70 (m, 1H), 3.65−3.55 (m, 3H), 3.38 (d, J = 11.9, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.9, 132.4, 127.5, 94.9, 94.6, 74.7, 73.2, 69.5, 68.0, 65.3, 60.3, 59.3. Anal. Calcd for $C_{12}H_{16}O_7$: C, 52.92; H, 5.92. Found: C, 52.73; H, 6.01. $[\alpha]^{25}_D$ −178 (*c* 0.72, $CHCl_3$).

Diels−Alder Reaction of 5 with Cyclopentadiene. A solution of the acrylate (2.72 g, 10 mmol) in MeOH-free CH_2Cl_2 (80 mL) was cooled at −40 °C. $SnCl_4$ (2.34 mL, 20 mmol) was added slowly, and the mixture was stirred for 15 min. The cooling bath was replaced by an ice bath, and freshly distilled cyclopentadiene (6.6 g, 40 mmol) was added. The mixture was stirred at this temperature for 40 min (TLC) until the reaction was complete, and then finely ground $Na_2CO_3 \cdot 10H_2O$ (12 g, 40 mmol) was added. The cooled (0 °C) reaction mixture was filtered, the solid was washed with cooled CH_2Cl_2, and the excess of CPD and solvent was evaporated under vacuum at 0 °C. The residue was purified by chromatography on a short pad of silica gel with 1% → 30% Et_2O in CH_2Cl_2 as eluent to give 3.37 g (>99%) of the adduct: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.21 (dd, J = 5.7, 3.1, 1H), 5.95 (dd, J = 5.7, 2.8, 1H), 5.13 (s, 1H), 4.94 (s,1H), 4.70 (d, J = 8.0, 1H), 4.33 (dd, J = 8.0, 5.3, 1H), 4.01 (dd, J = 5.3, 2.4, 1H), 4.16 (d, J = 13.4, 1H), 3.97−3.90 (m, 1H), 3.88 (dd, J = 13.4, 2.4, 1H), 3.8−3.7 (m, 1H), 3.60−3.55 (m, 2H), 3.54 (d, J = 11.8, 1H), 3.33 (d, J = 11.8, 1H), 3.37 (broad s, 1H), 3.05 (dt, J = 9.3, 4.0, 1H), 2.90 (broad s, 1H), 1.92 (ddd, J = 11.9, 9.3, 3.7, 1H), 1.45−1.38 (m, 2H), 1.29 (d J = 8.2, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 138.4, 132.0, 95.0, 94.7, 74.8, 73.5, 69.1, 68.2, 65.6, 60.4, 59.4, 50.0, 46.0, 43.4, 42.6, 28.5. Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.33; H, 6.56. Found: C, 60.30; H, 6.52.

(2*S*)-*endo*-2-Hydroxymethyl-5-norbornene (7). To a slurry of $LiAlH_4$ (0.35 g, 9 mmol) in anhydrous Et_2O at 0 °C was slowly added a solution of the adduct (3 g, 9 mmol) in THF, and the reaction mixture was stirred at room temperature for 1 h and refluxed for 1 h. Solid $Na_2SO_4 \cdot 10H_2O$ (6 g, 18 mmol) was added to the cooled reaction mixture. After filtration, the solid was washed twice with ether, and the ethereal layer was washed with brine, dried over Na_2SO_4, concentrated, and purified by chromatography on silica gel first with Et_2O/CH_2Cl_2 2/8 as eluent to give 1.02 g (93%) of the norbornenol **7** (>98% *endo* by 400 MHz ^1H NMR), $[\alpha]^{25}_D$ −93 (*c* 0.5, 95% EtOH), lit[11] (*endo*) −95, (*exo*) −23.9 and then with $MeOH/CH_2Cl_2$ 1/9 to give 1.86 g (95%) of recovered **4** identical to an original sample. ^1H NMR of **7** ($CDCl_3$, 200 MHz) δ 6.09 (dd, J = 5.7, 3.0, 1H), 5.91 (dd, J = 5.7, 3.0, 1H), 3.36 (dd, J = 10.5, 6.6, 1H), 3.18 (dd, J = 10.5, 8.9, 1H), 2.88 (broad s, 1H), 2.76 (broad s, 1H), 2.4−2.1 (m, 2H), 1.76 (ddd, J = 11.6, 9.2, 3.8, 1H), 1.40 (dq, J = 8.4, 2.0, 1H), 1.21 (m, 1H), 0.46 (ddd, J = 11.6, 4.4, 2.5, 1H).

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