Highly Diastereoselective Diels−Alder Reactions Using a Fructose Diacetonide Chiral Scaffold

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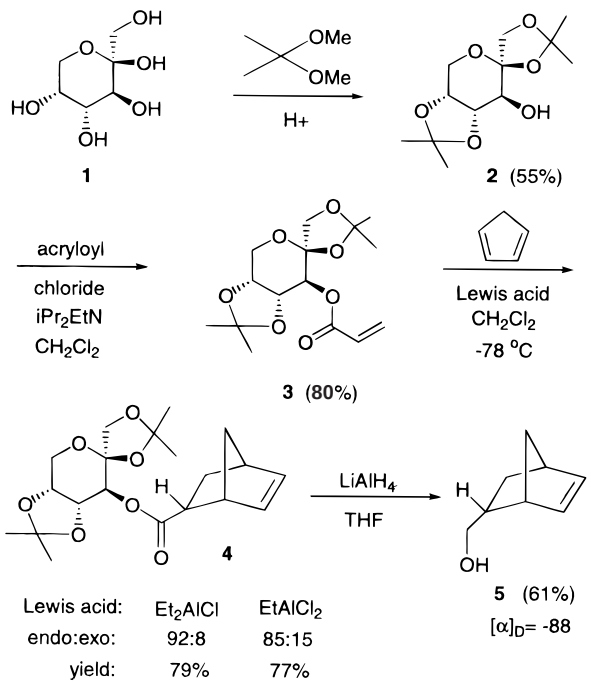
The Diels−Alder reaction is perhaps the most valuable synthetic method to construct a cyclohexene ring system. The use of Lewis acids to promote the [4 + 2]-cycloaddition reaction permits much lower temperatures and higher stereoselectivities to be achieved.[1] Although a considerable number of optically active molecules have been investigated to induce chirality in the Diels−Alder reaction, relatively fewer carbohydrates have been examined in this capacity.[2]

This avoidance is perhaps due to the potential for multiple sites of chelation with Lewis acids, and moreover, carbohydrates are topologically considerably more complex molecules than compounds with a single chiral center, such as amino alcohols.[2] Because of this complexity, carbohydrates are "bioinformational molecules" with important cellular communication properties on the cell's surface which rely on the stereochemistry and shape of a carbohydrate for protein interactions.[3] This stereochemical information could be also be viewed as an asset with a protected sugar constructed as a scaffold for the Diels−Alder reaction. One sugar that could be useful in this respect is fructose, which is abundantly available and its derivatives are readily prepared in very few steps.[4,5] Fructose diacetonide can be prepared in one step from fructose;[4b] however, it has not been used as a stereocontrol element in intramolecular Diels−Alder reactions. Herein, we will disclose results where high levels of both exo/endo selectivity (up to 99:1) and enantioselectivity were obtained in these cycloadditions. In addition, we have also examined the related intermolecular Diels−Alder reactions with fructose diacetonide. Useful levels of diastereo- and enantioselectivity were also obtained in those reactions (vide infra).

The first transformations to be examined were focused on intermolecular Diels−Alder reactions using fructose diacetonide **2**, arising from treatment with $HClO_4$ and 2,2-dimethoxypropane (Scheme 1).[4b,6] This chiral scaffold

Scheme 1



places the remaining unprotected C_3-hydroxyl in a highly biased steric environment, particularly when Lewis acids are available for chelation and can limit degrees of freedom in rotations about the alcohol appendage.

This latter effect was demonstrated in an intermolecular Diels−Alder reaction of **3**, prepared with an appended ester dienophile from the reaction of **2** with acryloyl chloride in 80% yield. The [4 + 2]-cycloaddition reaction with freshly distilled cyclopentadiene and a Lewis acid at −78 °C readily constructed norbornene ester **4**. Two aluminum-based Lewis acids, Et_2AlCl and $EtAlCl_2$, which are also good chelating agents were examined in this study. The best results were obtained from Et_2AlCl which gave a 92:8 ratio of diastereomers in 79% yield. Either exo- or endo-diastereomers of **4** could be readily isolated by flash column chromatography.

The new Diels−Alder bridged bicylic skeleton in **4** could be cleaved from its chiral fructose scaffold with $LiAlH_4$. This was followed by flash column chromatography to prepare norbornene alcohol **5** and recovered **2** in 61% and 70% yields, respectively. Compound **2** could be recycled if desired at this point. The optical rotation of **5** was compared to the literature with an $[\alpha]_D = -88$, EtOH(95%), $c = 0.98$ (lit.[7] $[\alpha]_D = -95$, EtOH(95%) and corresponds to good optical rotation and a reaction with a predictable stereochemical outcome.

The intramolecular Diels−Alder reaction, which gave better endo/exo results with auxiliary **2** is shown in Scheme 2. Deprotonation of **2** with ^{n}BuLi in THF produced lithium alkoxide **6**. Subsequent reaction with acid chloride triene **7**, prepared in five steps by literature methods, gave **8** in 58% yield.[8] The cycloaddition reaction

(1) Oh, T.; Reilly, M. *Org. Prep. Proc. Int.* **1994**, *26*, 129−158. (b) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289−332. (c) Narasaka, K. *Synthesis* **1991**, 1−11. (d) Ooi, T.; Maruoka, K. *J. Org. Chem. Jpn.* **1996**, *54*, 200−211.

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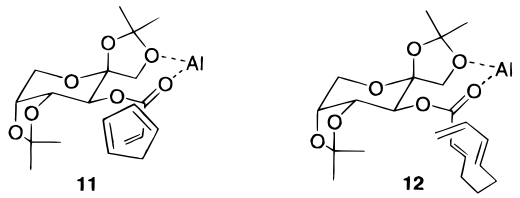
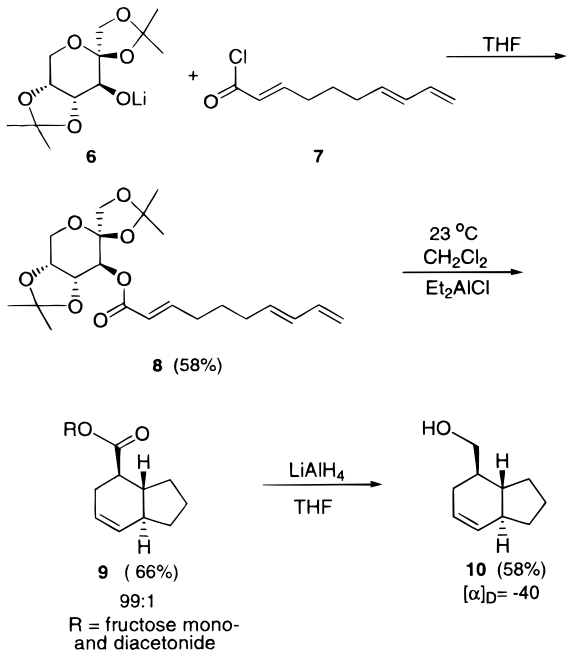


Figure 1. Diels-Alder transition states.

Scheme 2



of **8** in CH_2Cl_2 at ambient temperature for 24 h constructed the trans-fused bicycle **9** on the fructose scaffold in 66% yield (99:1, endo/exo). The fructose scaffold underwent some loss of one acetonide, however, this was inconsequential because both products underwent subsequent $LiAlH_4$ cleavage to the tetrahydroindane alcohol **10** with an optical rotation of $[\alpha]_D = -40$, EtOH(abs), $c = 1.9$ (opposite antipode lit.[8b] $[\alpha]_D = +45$, EtOH(abs), $c = 2.3$).

The orientation of the diene and dieneophile for each Diels−Alder reaction, shown in Figure 1, is interesting and deserves comment. In both proposed transition states **11** and **12**, the aluminum-based Lewis acid likely sits between the ester carbonyl and the most accessible and closest acetonide oxygen. Of the two acetonides in diacetone fructose, the anomeric isopropylidiene is less blocked by the *gem*-dimethyl functionality. The other acetonide has one of the two methyls tucked under the pyranose ring preventing effective coordination of the Lewis acid. The intermolecular reaction leading to **4** is clearly endo from its outcome, where the cyclopentadiene approaches from the least-hindered peripheral face of the dieneophile in **11**. The orientation in the intramolecular Diels−Alder leading to **9**, depicted as **12**, is similar and endo-disposed. The alkene in conjugation with the ester carbonyl in this case is a rotamer relative to acrylate **11** which now accommodates the terminal diene on the periphery of the molecule. The other rotamer brings the diene into a much more sterically hindered environment.

In summary, a new and highly effective chiral auxiliary, fructose diacetonide **2**, gave good results (92:8 endo:exo) for an intermolecular chiral Diels−Alder reaction with cyclopentadiene and Et_2AlCl. The intramolecular Diels−Alder with Et_2AlCl produced excellent endoselectivity (99:1, endo:exo).

Experimental Section

General Methods. Infrared (IR) spectra were recorded on an FT-IR spectrometer and were reported in wavenumbers (cm^{-1}). Proton (^1H NMR) nuclear magnetic resonance spectra were recorded at 300 MHz and carbon 13 (^{13}C NMR) nuclear magnetic spectra were recorded at 75 MHz on the same spectrometer. Chemical shifts were reported in ppm relative to chloroform (7.27 ppm) as an internal standard. All reactions were run under an inert atmosphere of argon using clean, oven dried reaction apparatus. All yields reported refer to isolated material were determined to be pure by NMR spectroscopy and thin-layer chromatography (TLC). GC spectra were recorded on a dedicated analytical capillary gas chromatograph using a 30m small bore GC column.

3-*O*-Acryloyl-1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose (3). Fructose diacetonide **2** (1.25 g, 4.8 mmol) was placed in CH_2Cl_2 (12 mL) with $^iPr_2EtN$ (3.34 mL, 19.2 mmol). The solution was cooled to 0 °C and acryloyl chloride (0.78 mL, 9.6 mmol) was added dropwise with a syringe. Reaction was stirred for 6 h at room temperature until done by TLC and the mixture was quenched with $NaHCO_3$ (aqueous saturated). After extraction with CH_2Cl_2 and drying over $NaSO_4$, the organic layers were rotary evaporated to give a brown crude oil. The crude material was subject to column chromatography to give compound **3** (1.21 g, 80% yield): ^1H NMR ($CDCl_3$) δ 6.47 (dd, $J = 17.4$, 1.5 Hz, 1H), 6.15 (dd, $J = 17.4$,10.5 Hz, 1H), 5.88 (dd, $J = 10.5$, 1.5 Hz, 1H), 5.18 (d, $J = 8.1$ Hz, 1H), 4.32 (dd, $J = 7.8$, 5.4 Hz, 1H), 4.22 (dd, $J = 5.4$, 1.5 Hz, 1H), 4.14 (dd, $J = 13.5$, 2.4 Hz, 1H), 4.08 (d, $J = 13.5$ Hz, 1H), 3.95 (d, $J = 9.3$ Hz, 1H), 3.80 (d, $J = 9.3$ Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H); ^{13}C NMR δ 165.6, 131.9, 127.8, 112.1, 109.7, 103.7, 74.9, 73.7, 71.7, 70.3, 60.4, 27.8, 26.5, 26.4, 26.0; IR (neat): 1731.6 (C=O), 1636.2 (C=C); exact mass for $C_{15}H_{22}O_7$ calcd 314.1366, found 314.1365.

General Procedure for the Intermolecular Diels−Alder Reactions. A solution of acrylate (1.0 equiv) in dry CH_2Cl_2 (0.1 M) was cooled at −78 °C under argon, a Lewis acid (1.8 M in toluene, 1.5 equiv) was added slowly, and the mixture was stirred for 10 min. Freshly distilled and precooled (0 °C) cyclopentadiene (10.0 equiv) was added. The mixture was stirred at −78 °C for 2 h until the reaction was complete by TLC or GC, then quenched with $NaHCO_3$ (aqueous saturated). The reaction mixture was extracted with CH_2Cl_2. The organic layers were dried over $NaSO_4$ and evaporated to a thick oil. The crude product was purified by flash chromatography on a silica gel column.

Diels−Alder Adduct 4: ^1H NMR ($CDCl_3$) δ 6.20 (dd, $J = 5.7$, 3.0 Hz, 1H), 5.95 (dd, $J = 5.7$, 2.7 Hz, 1H), 5.05 (d, $J = 8.1$, 1H), 4.26 (dd, $J = 7.8$, 5.1 Hz, 1H), 4.20 (dd, $J = 5.4$, 2.1 Hz, 1H), 4.14 (dd, $J = 13.2$, 2.4 Hz, 1H), 4.06 (d, $J = 13.5$ Hz, 1H), 3.90(d, $J = 9.3$ Hz, 1H), 3.75 (d, $J = 9.3$ Hz, 1H), 3.23 (s, 1H), 3.03 (m, 1H), 2.89 (s, 1H), 1.86 (dt, $J = 3.6$, 9.3 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.42 (m, 2H), 1.32 (s, 3H), 1.27 (d, $J = 7.8$, 1H); ^{13}C NMR δ 174.3, 138.3, 131.6, 111.9, 109.5, 103.9, 75.0, 73.7, 71.9, 70.2, 60.6, 50.0, 46.2, 43.2, 42.6, 28.8, 27.8, 26.5, 26.4, 26.0; IR (neat) 1738.3 (C=O); exact mass $C_{20}H_{28}O_7$ calcd 380.1835, found 380.1835.

Norbonyl Alcohol 5. This compound was prepared by $LiAlH_4$ reduction of the ester as described by Berson et al. and was identical in all respects to that previously published[7] (yield = 61%; $[\alpha]_D = -88°$ ($c = 0.98$, 95% EtOH); lit.[7] $[\alpha]_D = -95°$ (95% EtOH)) and recovered **2** (yield = 70%).

1,2:4,5-Di-*O*-isopropyl-*β*-D-fructopyranose-3-(*E*,*E*)-deca-2,7,9-trienoate (8). To a solution of **2** (1.55 g, 5.96 mmol) in

(8) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. (b) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269−2283. (c) Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4264−4267. (d) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825−4829.

anhydrous THF (27 mL) under argon at −78 °C was slowly added *n*-butyllithium (1.5 M in hexane, 3.61 mL, 5.41 mmol), the mixture was stirred for 10 min, and a solution of (*E*,*E*)-2,7,9-decatrienoyl chloride (**7**) (1.1 g, 5.96 mmol) in anhydrous THF (12 mL) was dropwise added with a syringe. The reaction mixture was stirred for 2 h at 0 °C and was quenched with NH_4Cl (aqueous saturated). The organic layers were dried on anhydrous $NaSO_4$ and concentrated by a rotary evaporator to give a crude yellow oil. The oil was subjected to flash column chromatography to afford **8** as a colorless oil (1.3 g, 58% yield): ^{1}H NMR ($CDCl_3$) δ 7.02 (dt, J = 15.6, 6.9 Hz, 1H), 6.28 (dt, J = 17.1, 10.2 Hz, 1H), 6.03 (dd, J = 15.6, 10.8 Hz, 1H), 5.85 (dt, J = 15.9, 1.5 Hz, 1H), 5.64 (dt, J = 15.3, 6.9 Hz, 1H), 5.17 (d, J = 7.8 Hz, 1H), 5.08 (d, J = 16.2 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 4.31 (dd, J = 7.8, 5.1 Hz, 1H), 4.21 (dd, J = 5.4, 1.8 Hz, 1H), 4.14 (dd, J = 13.5, 2.1 Hz, 1H), 4.07 (d, J = 13.2 Hz, 1H), 3.94 (d, J = 9.3 Hz, 1H), 3.80 (d, J = 9.3 Hz, 1H), 2.21 (q, J = 7.2 Hz, 2H), 2.10 (q, J = 7.2 Hz, 2H), 1.56 (q, J = 7.5 Hz, 2H), 1.55 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H); ^{13}C NMR δ 166.0, 150.6, 137.0, 134.0, 131.7, 120.7, 115.2, 112.0, 109.6, 103.8, 74.9, 73.7, 71.6, 69.8, 60.3, 31.9, 31.7, 27.8, 27.3, 26.5, 26.4, 26.0; IR (neat): 1728.1 (C═O), 1651.7 (C═C); exact mass $C_{22}H_{32}O_7$ calcd 408.2148, found 408.2148.

Intramolecular Diels−Alder Reaction of 8. To a solution of **8** (0.42 g, 1.03 mmol) in dry CH_2Cl_2 (11 mL) was added a crystal of BHT (ca. 3 mgs). The solution was cooled to −30 °C and Et_2AlCl (1.8 M in toluene, 0.8 mL) was dropwise added with a syringe. The reaction was stirred for 24 h and was quenched with $NaHCO_3$ (aqueous saturated). After filtration, drying over $NaSO_4$, and rotary evaporation, the resulting thick colorless oil, as a mixture of endo:exo diastereomers 99:1 (by capillary GC), was purified by chromatography on a silica gel column to give ester **9** as a colorless oil (150 mgs, 36% yield for the diacetonide and 30% for the monoacetonide; 66% total). Data for the diacetonide reported: ^{1}H NMR ($CDCl_3$) δ 5.80 (d, J = 9.9 Hz, 1H), 5.55 (m, 1H), 5.12 (d, J = 7.8 Hz, 1H), 4.24 (dd, J = 7.8, 5.1 Hz, 1H), 4.18 (dd, J = 5.4, 1.5 Hz, 1H), 4.11 (dd, J = 16.8, 2.4 Hz, 1H), 4.04 (d, J = 13.2 Hz, 1H), 3.93 (dd, J = 9.3, 2.1 Hz, 1H), 3.79 (dd, J = 9.3, 1.2 Hz, 1H), 2.55 (m, 1H), 2.38 (m, 2H), 1.86 (m, 2H), 1.66 (m, 2H), 1.51 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.22 (m, 2H), 0.82 (m, 2H); ^{13}C NMR δ 175.0, 129.7, 125.3, 111.9, 109.5, 103.7, 74.8, 73.7, 71.8, 69.9, 60.5, 45.6, 45.5, 44.2, 29.9, 29.0, 27.9, 27.8, 26.5, 26.2, 21.8; IR (neat) 1738.5 (C═O); exact mass $C_{22}H_{32}O_7$ calcd 408.2148, found 408.2148.

Tetrahydroindane Alcohol 10. This compound was prepared by $LiAlH_4$ reduction of the ester as described by Roush et al. and was identical in all respects to that previously published[8b] (58% yield; $[\alpha]_D$ = −40° (*c* = 1.9, absolute EtOH; lit.[8b] $[\alpha]_D$ = +45° (*c* 0.023 g/mL, EtOH)).

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Supporting Information Available: Copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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