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# Dihydroxyacetone Variants in the Organocatalytic Construction of Carbohydrates: Mimicking Tagatose and Fuculose Aldolases

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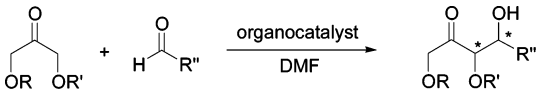


Dihydroxyacetone variants have been explored as donors in organocatalytic aldol reactions with various aldehyde and ketone acceptors. The protected form of dihydroxyacetone that was chosen for in-depth study was 2,2-dimethyl-1,3-dioxan-5-one, **1**. Among the catalysts surveyed here, proline proved to be superior in terms of yield and stereoselectivities in the construction of various carbohydrate scaffolds. In a fashion analogous to aldolase enzymes, the de novo preparation of L-ribulose, L-lyxose, D-ribose, D-tagatose, 1-amino-1-deoxy-D-lyxitol, and other carbohydrates was accomplished via the use of **1** and proline. In reactions using 2,2-dimethyl-1,3-dioxan-5-one **1** as a donor, (*S*)-proline can be used as a functional mimic of tagatose aldolase, whereas (*R*)-proline can be regarded as an organocatalytic mimic of fuculose aldolase.

## Introduction

Carbohydrates constitute an important class of biomolecules. Like nucleic acids and proteins, carbohydrates play a key role in many physiological processes such as cell recognition and metabolic function. They are also important in medicinal chemistry where, for example, they are used in antibiotic agents[1] and have potential as anticancer therapeutics and vaccines.[2]

The stereochemical complexity of carbohydrates has made their de novo synthesis a formidable challenge, one that has thus far been very successfully tackled via the use of enzymes.[3] Among enzymes used in carbohydrate synthesis, the C−C bond-forming aldolases have received significant attention. A wide variety of naturally occurring aldolase enzymes are available that enable efficient coupling of carbonyl compounds, wherein any given aldolase typically operates on a select set of carbonyl compounds.

In an attempt to mimic the activity of enzymes in catalytic asymmetric synthesis, we have actively developed the utility of organocatalysts such as proline and other chiral amines.[4] Like enzymes, organocatalysts can effectively catalyze aldol addition reactions providing for the direct coupling of aldehyde and ketone donors to various aliphatic and aromatic acceptors with excellent stereoselectivities.[5] These studies have allowed us to effectively recapitulate the activity of two of nature's aldolases, DERA aldolase, with its unique ability to use both aldehydes and ketones as donors in aldol reactions, and threonine aldolase,

(1) (a) Ritter R. T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3508−3533. (b) Wong, C.-H.; Bryan, M. C.; Nyffeler, P. T.; Liu, H.; Chapman, E. *Pure Appl. Chem.* **2003**, *75*, 179−186. (c) Wrodnigg, T. M.; Sprenger, F. K. *Mini-Rev. Med. Chem.* **2004**, *4*, 437−459.

(2) Barchi, J. J., Jr. *Curr. Pharm. Des.* **2000**, *6*, 485−501.

(3) (a) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994. (b) Machajewski, T. D.; Wong, C.-H.; Lerner, R. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374. (c) Takayama, S.; McGarvey, G. J.; Wong, C.-H. *Chem. Soc. Rev.* **1997**, *26*, 407−415. (d) Wymer, N.; Toone, E. J. *Curr. Opin. Chem. Biol.* **2000**, *4*, 110−119. (e) Koeller, K. M.; Wong, C.-H. *Nature* **2001**, *409*, 232−240.

(4) For reviews see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (c) Allemann, C.; Gordillo, R.; Clemente, F.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558. (d) Dalko, P. I.; Moisan, L. *Angew Chem., Int. Ed.* **2004**, *43*, 5138−5175. (e) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580. For recent work see: (f) Suri, J. T.; Steiner, D. D.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 3885−3888. (g) Steiner, D. D.; Mase, N.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2005**, *44*, 3706−3710. (h) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2507. (i) Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 1577−1580. (j) Chowdari, N. S.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 867−870. (k) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 3541−3544.

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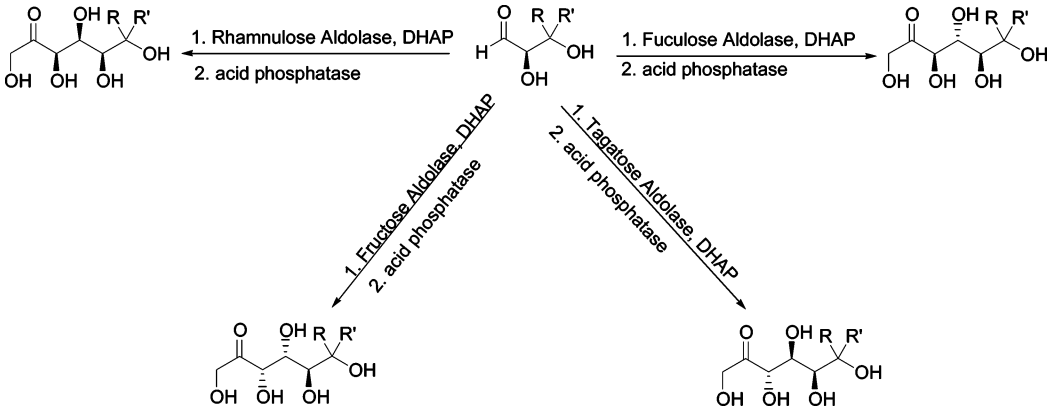
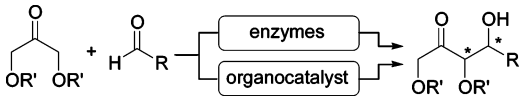
**SCHEME 1. Aldolase-Catalyzed Assembly of Sugars**




which provides expedient access to $\beta$-hydroxyamino acids.[4k] Dihydroxyacetone phosphate dependent aldolases are a particularly intriguing class of aldolases that catalyze the aldol addition of dihydroxyacetone phosphate (DHAP) to a range of aldehyde acceptors, forming a new C−C bond while creating two hydroxy-substituted stereogenic centers. Typically, these reactions take place with complete stereocontrol, and with the appropriate aldolase enzyme, all four stereoisomeric products can be generated with high levels of stereocontrol (Scheme 1).[6]

To approach the powerful chemistry available through the DHAP aldolases, we studied the aldolization of dihydroxyacetone (DHA). In aqueous media, DHA serves as a donor in the proline-catalyzed aldol reaction; however, enantioselectivities are poor.[5k] These studies prompted us[7] and others[8] to further investigate the use of protected forms of DHA in carbohydrate synthesis, with the ultimate goal of mimicking the DHAP aldolase enzymes and achieving complete stereocontrol without the substrate restrictions endemic of natural enzymes (Scheme 2). Herein we describe a full account of our investigation.

**SCHEME 2**




## Results and Discussion

**Dihydroxyacetone Analogues as Donors.** We initially studied various protected forms of DHA to determine the most general and synthetically useful derivative for further reactions. In DMF, unprotected DHA gave no reaction with nitrobenzaldehyde when stirred at room temperature in the presence of 20 mol % (*S*)-proline (Table 1, entry 1). Symmetric protection of DHA with benzyl or silyl groups (entries 2−4) or monosubstitution of one of the hydroxy groups with a silyl, phthalimido, or benzyl group (entries 5 and 6) gave no product.[9]

When the hydroxy groups in the substrate were constrained through an alkyl linker (entries 7−13), the aldol reaction with nitrobenzaldehyde ensued at room temperature. The cyclohexanone-like structure (entries 7 and 8) gave slightly superior results in terms of stereoselectivity; however, 2,2-dimethyl-1,3-dioxan-5-one **1** (entries 9−11) was chosen because it was more accessible via synthesis[10] or commercial sources. Interestingly, an increase in steric bulk on the donor resulted in a decrease in stereocontrol (entries 12 and 13).[11] Attempts to reproduce published studies concerning the use of L-alanine as a catalyst

(5) For references on organocatalyzed aldol reactions see: (a) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734−735. (b) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 1040−1041. (c) Mase, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2004**, *43*, 2420. (d) Mase, N.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2003**, *5*, 4369. (e) Cordova, A.; Notz, W.; Barbas, C. F., III *J. Org. Chem.* **2002**, *67*, 301. (f) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F., III *Tetrahedron Lett.* **2002**, *43*, 9591. (g) Sakthivel, K.; Notz, N.; Bui, T.; C. F. Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260. (h) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (i) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (j) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (k) Cordova, A.; Notz, W.; Barbas, C. F. III *Chem. Commun.* **2002**, *67*, 3034. (l) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (m) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799. (n) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620. (o) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785. (p) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343. (q) Hartikaa, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831. (r) Torii, H.; Nakakai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983−1986. (s) Martin, H. J.; List, B. *Synlett* **2003**, 1901. (t) Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445. (u) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755. (v) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141. (w) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (x) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji; M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958−961. (y) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q. Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285−9289.

(6) (a) Takayama, S.; McGarvey, G. J.; Wong, C.-H. *Annu. Rev. Microbiol.* **1997**, *51*, 285−310. (b) Fessner, W.-D.; Walter, C. *Top. Curr. Chem.* **1996**, *184*, 97−194. (c) Fessner, W.-D. In *Microbial Reagents in Organic Synthesis*; Servi, S., Ed.; Kluwer Academic Publishers: Dordrecht, 1992; Vol. 381, pp 43−55. (d) Henderson, I.; Sharpless, K. B.; Wong C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 558−561.

(7) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 1383−1385.

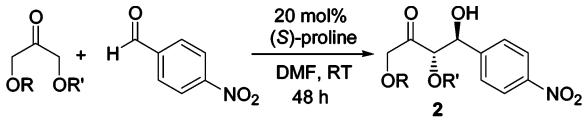
(8) (a) Enders, D.; Grondal, C. *Angew Chem., Int. Ed.* **2005**, *44*, 1210−1212. (b) Ibrahem, I.; Cordova, A. *Tetrahedron Lett*. **2005**, *46*, 3363−3367. (c) Attempts to reproduce published studies concerning the use of L-alanine as a catalyst for the synthesis of **2h** under the conditions described by Córdova failed. Under these conditions, **2h** was obtained in only 24% yield and 78% ee; see: Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun*. **2005**, 3586−3588. (d) Westermann, B.; Neuhaus, C. *Angew Chem., Int. Ed.* **2005**, *44*, 4077−4079. (e) Enders, D.; Palecek, J.; Grondal, C. *Chem. Commun.* **2006**, 655−657. (f) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329−337.

(9) Westermann and Neuhaus tested dihydroxyacetone phosphate as a substrate for the Mannich reaction and observed no reaction; see ref 8d.

(10) (a) Hoppe, D.; Schmincke, H.;. Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 687−694. (b) Forbes, D. C.; Ene, D. G.; Doyle, M. P. *Synthesis* **1998**, 879−882. (c) Carman, R. M.; Handley, P. N. *Aust. J. Chem.* **2001**, *54*, 769−776. (d) Enders, D.; Voith, M.; Ince, S. J. *Synthesis* **2002**, 1775−1779.

(11) Kim, K. S.; Hong, S. D. *Tetrahedron Lett.* **2000**, *41*, 5909−5913.

**TABLE 1. Aldol Reaction of Dihydroxyacetone Analogs with Nitrobenzaldehyde**




| entry | R,R' | product | %yield[a] | *anti*:*syn*[b] | %ee[b] |
|---|---|---|---|---|---|
| 1 | H,H | **2a** | - | - | - |
| 2 | Bn,Bn | **2b** | - | - | - |
| 3 | TIPS, TIPS | **2c** | - | - | - |
| 4 | H, TMS | **2d** | - | - | - |
| 5 | H, NPhth | **2e** | - | - | - |
| 6 | H, Bn | **2f** | - | - | - |
| 7 | -$CH_2$- | **2g** | 89 | 2:1 | 92 |
| 8 | | | 91 | 15:1 | 94[c] |
| 9 | -$C(CH_3)_2$- | **2h** | 89 | 2:1 | 60 |
| 10 | | | 90 | 6:1 | 93[c] |
| 11 | | | 86 | 16:1 | 95[c,d] |
| 12 | -$C(C_5H_{10})$- | **2i** | 85 | 5:1 | 59 |
| 13 | | | 62 | 5:1 | 67[c] |

[a] Isolated yield after column chromatography. [b] Determined by chiral-phase HPLC analysis. [c] Performed at 4 °C. [d] 20 mol % of (*S*)-2-pyrrolidine-tetrazole[6k] used as catalyst.

for the synthesis of **2h** under the conditions described by Córdova failed.[8c]

**Aldehyde Acceptors.** The scope of the proline-catalyzed reaction was then explored using **1** and various aromatic and aliphatic substrates. As indicated in Table 2, activated benzaldehydes as well as heterocyclics were suitable acceptors when the reaction was conducted in DMF at subambient temperature. Reactions gave good yields (60−89%), high enantioselectivities (84−95% ee), and diastereoselectivities (drs) that ranged from 2:1 to 6:1.

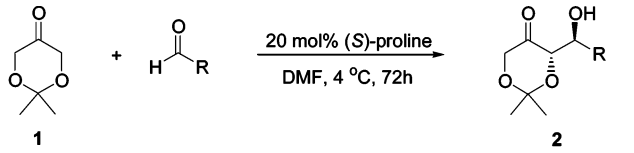
The aliphatic acceptors were better substrates than the others tested in terms of stereocontrol. The aldol products were obtained in moderate yields with excellent diastereo- and enantioselectivities (Table 3). For example, the nonbranched aldehydes (entries 1−3) gave dr's that ranged from 10:1 to 55:1 and ee's of 98%. Adducts were obtained from branched aldehydes (entries 4−6) with excellent ee's and dr's of up to 99:1. Significantly, the polyols and aminols that were formed are protected carbohydrates (entry 1, L-ribulose) and azasugars (entry 3), compounds that are otherwise most efficiently prepared via enzymatic reactions[3b] or via purification from the chiral pool.[12]

The synthesis of various carbohydrates was completed using a two-step reduction-deprotection sequence. A gamut of reducing agents were tested with aldol adduct **3f** to determine reagents with the potential to provide selective access to *anti*- and *syn*-1,3-diols (Table 4). The *anti*-selective reduction of adduct **3f** could be achieved using L-selectride (entry 1), $NaBH(OAc)_3$ (entry 11), $LiBH_4$ (entry 12), or $NaCNBH_3$ (entry 13). None of the reducing agents provided the *syn*-1,3-diol products in significant amounts, although some stereocontrol resulted when $Me_4NBH(OAc)_3$ and $Bu_4NBH_4$ (entries 6 and 10) were used.

If the hydroxy group in the aldol adduct was protected with *tert*-butyldimethylsilyl (TBS), the diastereoselectivity was reversed providing the *syn*-1,3-diol products in good yield (Scheme 3). Deprotection of the reduced products was carried out using Dowex resin to provide the carbohydrates L-lyxose and D-ribose. Conversion of the aldehydes into the oximes **6** and comparison to authentic samples provided further structural proof of the prepared sugars (Scheme 4).

From **3c**, the phthalimide protected aminosugar **7** was prepared (Scheme 5). Reduction of **3c** allowed for the prepara-

**TABLE 2. Aldol Reaction of 1 with Aromatic Acceptors**

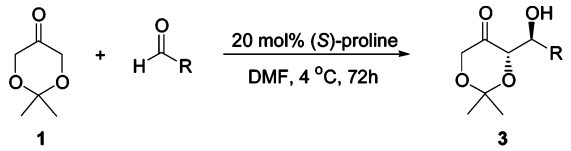



| entry | R | product | %yield[a] | *anti*:*syn*[b] | %ee[c] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **2j** | 0 | - | - |
| 2 | *p*-$NO_2C_6H_5$ | **2h** | 90 | 6:1 | 93 |
| 3 | *p*-$BrC_6H_5$ | **2k** | 60 | 3:1 | 94 |
| 4 | *p*-$CNC_6H_5$ | **2l** | 88 | 4:1 | 84 |
| 5 | $C_4H_3S$ | **2m** | 90 | 2:1 | 92 |
| 6 | $C_4H_3O$ | **2n** | 70 | 3:1 | 92 |

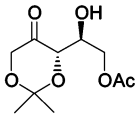
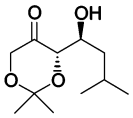
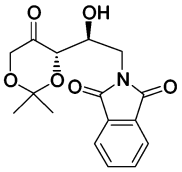
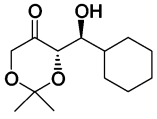
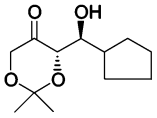
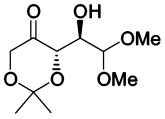
[a] Isolated yield after column chromatography. [b] Determined by $^1H$ NMR and HPLC analysis. [c] Determined by chiral-phase HPLC analysis.

(12) Ekeberg, D.; Morgenlie, S.; Stenstrom, Y. *Carbohydr. Res.* **2002**, *337*, 779−786.

**TABLE 3. Aldol Reaction of 1 with Aliphatic Acceptors**




1 3

| entry | R | product | %yield[a] | *anti*:*syn*[b] | %ee[cd] |
|---|---|---|---|---|---|
| 1 | $CH_2OAc$ |  **3a** | 60 | >15:1 | 98 |
| 2 | $CH_2{}^iPr$ |  **3b** | 75 | 10:1 | 98 |
| 3 | $CH_2Phth$ |  **3c** | 75 | 55:1 | 98 |
| 4 | $CH_2{}^iPr$ |  **3d** | 71 | 99:1 | 94 |
| 5 | $C_5H_9$ |  **3e** | 67 | 99:1 | 97 |
| 6 | $CH(OMe)_2$ |  **3f** | 60 | 18:1 | 98 |

[a] Isolated yield after column chromatography. [b] Determined by $^1$H NMR and HPLC analysis. [c] Determined by chiral-phase HPLC analysis. [d] Aldol products were converted to 3,5-dinitrobenzoate esters for ee determination by HPLC.

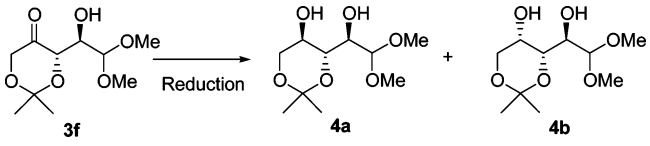
tion of aminosugar 1-amino-1-deoxy-D-lyxitol **9**, a carbohydrate traditionally isolated from the chiral pool of naturally occurring sugars.[13]

In contrast to the *anti*-selective reduction of **3f** using L-selectride, the phthalimido protected adduct **3c** was diastereoselectively reduced to the *syn*-1,3-diol product **8**. Subsequent deprotection with trifluoroacetic acid (TFA) and methylamine-induced cleavage of the phthalimido group afforded **9** in 60% yield.

In addition to simple achiral aldehyde acceptors, we also explored the use of chiral acceptors. The readily available acetonide protected (*S*)-glyceraldehyde **10** proved to be a good

(13) Blanc-Muesser, M.; Defaye, J.; Horton, D. *Carbohydr. Res.* **1979**, *68*, 175−187.

**TABLE 4. Stereoselective Reduction of Aldol Adduct 3f**




3f 4a 4b

| entry | reagent | condition | ratio **4a**:**4b**[a] (% yield) |
|---|---|---|---|
| 1 | L-selectride | −78 °C, THF | >20:<1 (62%) |
| 2 | DIBAL-H | −78 °C, THF | ca. 1:1 |
| 3 | DIBAL-H | −78 °C, toluene | ca. 1:1 |
| 4 | $NaBH_4$ | −20 °C, MeOH | 6.3:1 |
| 5 | Red-Al | −78 → −20 °C, toluene | 4.2:1 |
| 6 | $Me_4NBH(OAc)_3$ | −40 → −20 °C, MeCN, AcOH | 1:1.4 |
| 7 | $Cl_3SiH$ | $Et_3N$, $CH_2Cl_2$ | complex mixture |
| 8 | $NaBH_4$, $CeCl_3$ | 0 °C, MeOH | 1.5:1 |
| 9 | $LiAlH_4$ | −78 °C, THF | 1.6:1 |
| 10 | $Bu_4NBH_4$ | −20 °C, $CH_2Cl_2$ | 1:2.7 |
| 11 | **$NaBH(OAc)_3$** | **−20 °C, $CH_2Cl_2$, AcOH** | **>20:<1 (69%)** |
| 12 | $LiBH_4$ | −78 °C, THF | >20:<1 |
| 13 | $NaCNBH_3$ | −20 °C, $CH_2Cl_2$, AcOH | >20:<1 |

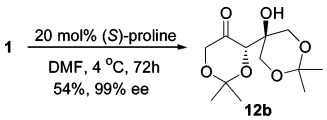
[a] Determined by $^1$H NMR.

substrate, allowing for the synthesis of acetonide-protected D-tagatose[6] (Scheme 6) that readily crystallized to afford X-ray quality crystals (see Supporting Information). In a similar fashion, D-psicose can be prepared from (*R*)-glyceraldehyde, as has recently been reported.[8a]

The galactose-derived **12** was prepared and utilized as an acceptor. The reaction of **1** with **12** in the presence of (*R*)-proline afforded **13** as a single diastereomer in 60% yield along with the self-aldol product of **1** (Scheme 7).[14]

Product **13** with its nine-carbon backbone is classified as a "higher carbon sugar", which have gained attention because of their potential as antibiotics. 3-Deoxy-D-manno-2-octulosonic acid is an essential component necessary for the growth of Gram-negative bacteria and inhibitors of its synthesis are antibiotics.[15] Typical synthetic routes for higher carbon sugars involve homologation of lower carbon sugars and require the introduction of new stereogenic centers in a controlled manner. Protocols involving Wittig olefination of C6 sugars and

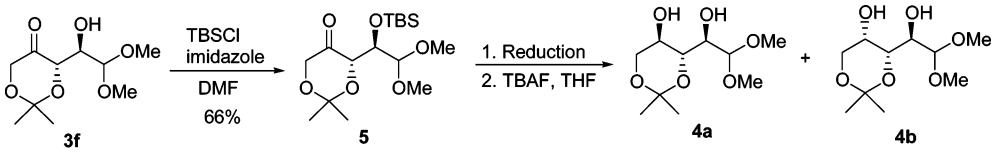
(14) The self-condensation of **1** is a competing side reaction giving acetonide protected dendroketose **12b**.




12b

(15) (a) Ungm, F. M. *Adv. Carbohydr. Chem. Biochem*. **1981**, *38*, 323. (b) Iwasa, T.; Kusuka, T.; Suetomi, K. *J. Antibiot.* **1978**, *31*, 511−518. (c) Harada, S.; Kishi, T. *J. Antibiot.* **1978**, *31*, 519−524. (d) Harada, S.; Mizuta, E.; Kishi, T. *Tetrahedron* **1981**, *37*, 1317−1327. (e) Takatsuki, A.; Arima, K.; Tamura, G. *J. Antibiot.* **1971**, *24*, 215−223. (f) Takatsuki, A.; Tamura, G. *J. Antibiot.* **1971**, *24*, 224−231. (g) Takatsuki, A.; Tamura, G. *J. Antibiot.* **1971**, *24*, 232−238. (h) Takatsuki, A.; Kawamura, K.; Okina, M.; Kodama, Y.; Ito, T.; Tamura, G. *Agric. Biol. Chem.* **1977**, *41*, 2307−2309. For references on analogues of 3-deoxy-D-manno-2-octulosonic acid, see: (i) Claesson, A.; Luthman, K.; Gustafsson, K.; Bondesson, G. *Biochem. Biophys. Res. Commun.* **1987**, *143*, 1063. (j) Molin, H.; Ring, B. G. *Tetrahedron Lett.* **1985**, *26*, 617. (k) Norbeck, D. W.; Kramer, J. B. *Tetrahedron Lett.* **1987**, *28*, 773. (l) Norbeck, D. W.; Kramer, J. B.; Lartey, P. A. *J. Org. Chem.* **1987**, *52*, 2174. (m) Tadanier, J.; Lee, C. M.; Wittern, D.; Wideburg, N. *Carbohydr. Res.* **1990**, *201*, 185. (n) Tadanier, J.; Lee, C. M.; Hengeveld, J.; Rosenbrook, W., Jr.; Whittern, D.; Wideburg, N. *Carbohydr. Res.* **1990**, *201*, 209.

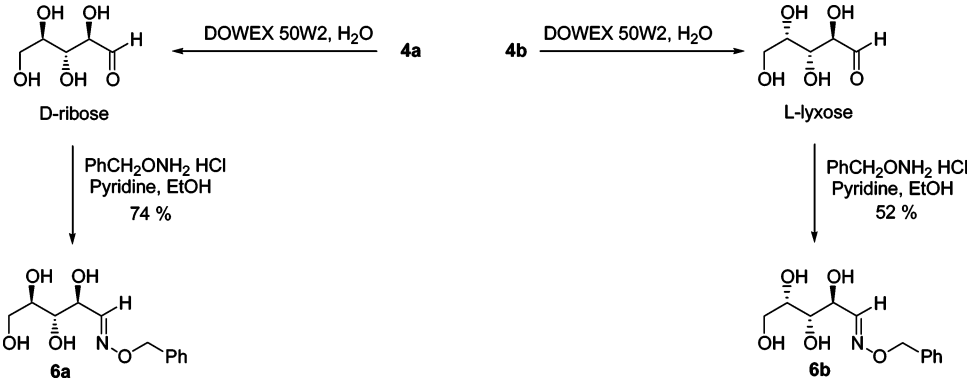
**SCHEME 3. Protection/Reduction Sequence To Selectively Afford *syn*-1,3-Diols**



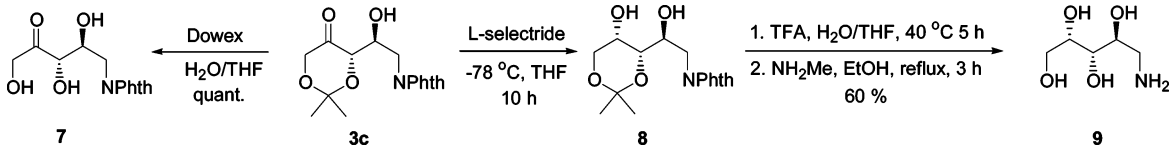

| Entry | Reducing Agent | Condition | Yield[a] | Ratio (**4a**:**4b**)[b] |
|---|---|---|---|---|
| 1 | L-Selectride | -78 °C, THF | 93 | <1: >20 |
| 2 | $LiBH_4$ | - 20 °C | 99 | 1:9 |

[a] Isolated yield. [b]Determined by $^1H$ NMR.

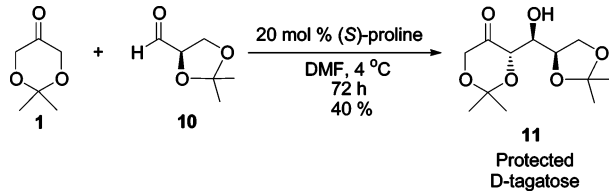
**SCHEME 4. Preparation of d-Ribose and L-Lyxose and Conversion into the Corresponding Oximes 6**



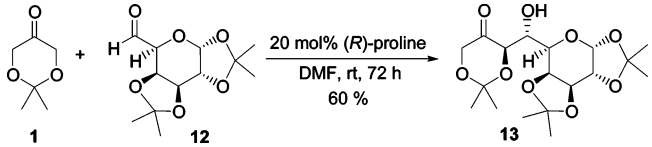

**SCHEME 5. Preparation of Amino Sugars 7 and 9**




**SCHEME 6. Preparation of Acetonide-Protected D-Tagatose**




**SCHEME 7. Preparation of Higher Carbon Sugar 13**




subsequent osmylation,[16] intramolecular C-glycosidations,[17] enzyme-mediated aldolizations,[18] and 1,3-dipolar cycloadditions[19] have been employed for synthesis of higher carbon sugars. With the appropriate aldehyde acceptor the preparation of various higher carbon sugars may become more facile via organocatalysis. Current studies are underway to investigate this possibility.

**Ketone Acceptors.** In our initial studies concerning the cross-aldol of **1** with a variety of aldehydes, in some reactions we noted a side product formed by the self-aldolization of **1**.[14] This finding encouraged studies of crossed-ketone aldol reactions. We examined the reaction of **1** with various ketone acceptors. An initial solvent screen was performed with diethyl ketomalonate **14** as the acceptor (Table 5). Dichloromethane gave the highest yield, albeit with almost no enantioselectivity. Among the other nonsymmetric ketones that were tested, only ethyl trifluoropyruvate **16** (Table 6) proved to be a useful substrate.[20] A solvent screen of **1** with **16** revealed $CH_2Cl_2$ to be the optimum solvent, giving an *anti*:*syn* ratio of 85:15 and >99% ee for the *anti* product (entry 1).

A catalyst screening that utilized various additives as well as the tetrazole-based catalyst[5r] and a diamine-based catalyst[5c] (entries 8 and 9, Table 7) indicated that proline was superior in terms of yield and stereoselectivities and that, at a cost to yield,

(16) (a) Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S. Bennett, F.; Taylor, I. D. *Org. Biomol. Chem.* **1986**, 815−821. (b) Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S. *Org. Biomol. Chem.* **1986**, 823−828. (c) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1986**, *150*, 35−51. (d) Brimacombe, J. S.; Kabir, A. K. M. S. *Carbohydr. Res.* **1986**, *158*, 81−89.

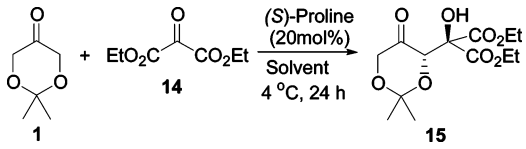
(17) Craig, D.; Pennington, M. W.; Warner, P. *Tetrahedron* **1999**, *55*, 13495−13512.

(18) Bedarski, M. D.; Waldmann, H. J.; Whitesides, G. M. *Tetrahedron Lett.* **1986**, *27*, 5807.

(19) Paton, R. M.; Young, A. A. *Org. Biomol. Chem.* **1997**, 629−635.

(20) (a) Torok, B.; Abid, M.; London, G.; Esquibel, J.; Torok, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew Chem., Int. Ed.* **2005**, *44*, 3086−3089. (b) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901−904. (c) Gathergood, N.; Juhl, K.; Poulsen, T. B.; Thordrup, K.; Jorgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 1077−1085. (d) Bogevig, A.; Gothelf, K. V.; Jorgensen, K. A. *Chem.−Eur. J.* **2002**, *8*, 5652−5661. (e) Prakash, G. K. S.; Yan, P.; Torok., B.; Olah, G. A. *Synlett* **2003**, *4*, 527−531.

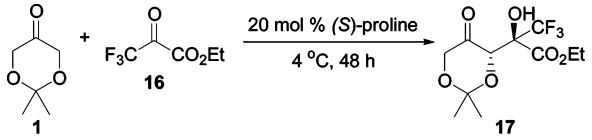
**TABLE 5. Solvent Effects on the Aldol Reaction of 1 with Diethyl Ketomalonate 14**

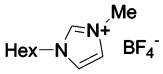



| entry | solvent | % yield[b] | % ee[c] |
|---|---|---|---|
| 1 | DMF | 26 | 3 |
| 2 | $CH_2Cl_2$ | 54 | 1 |
| 3 | $CH_2Cl_2$ [a] | 40 | 3 |
| 4 | MeCN | 12 | 2 |
| 5 | toluene | 39 | 1 |
| 6 | THF | 38 | 4 |

[a] 3 hreaction time. [b] Isolated yield after column chromatography. [c] Determined by chiral-phase HPLC analysis.

**TABLE 6. Solvent Effects on the Aldol Reaction of 1 with Ethyl Trifluoropyruvate 16**




| Entry | solvent | %yield[a] | *anti*:*syn*[b] | %ee[c] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 41 | 85:15 | >99 / 38 |
| 2 | $CH_2Cl_2$[d] | 91 | 80:20 | 60 / 56 |
| 3 | DMSO[d] | 14 | 49:51 | 23 / 46 |
| 4 | NMP | 4 | 91:9 | 30 / - |
| 5 | DMF | 5 | 80:20 | 25/ 36 |
| 6 |  | 19 | 53:47 | 49 / >99 |
| 7 | $CHCl_3$ | 44 | 79:21 | 34 / 57 |
| 8 |  | 15 | 66:34 | 55 / 70 |

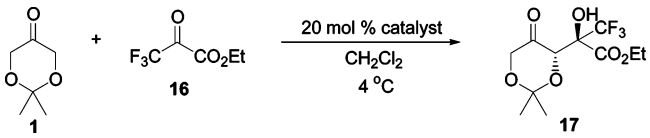
[a] Isolated yield after column chromatography. [b] Determined by $^1$H NMR and HPLC analysis. [c] Determined by chiral-phase HPLC analysis. [d] Reaction conducted at room temperature.

high dr's can be obtained upon the addition of water to the reaction (entries 6 and 7). To the best of our knowledge, this is the first time that the aldol adduct **17** has been prepared; it may possess interesting biological properties because of its unique trifluoro-substituted polyhydroxy structure.[21]

## Conclusions

Dihydroxyacetone variants have been explored as donors in organocatalytic aldol reactions with various aldehyde and ketone acceptors. The protected form of dihydroxyacetone that was chosen for in-depth study was 2,2-dimethyl-1,3-dioxan-5-one **1** because of its well-developed chemistry and commercial availability.[22] Among the catalysts surveyed here, proline proved to be superior in terms of yield and stereoselectivities in the construction of various carbohydrate scaffolds. Our studies reveal that (*S*)-proline can be used as a functional mimic of tagatose aldolase, whereas (*R*)-proline can be regarded as an organocatalytic mimic of fuculose aldolase in reactions using 2,2-dimethyl-1,3-dioxan-5-one **1** as a donor. In a fashion analogous to aldolase enzymes, the de novo preparation of L-ribulose, L-lyxose, D-ribose, D-tagatose, 1-amino-1-deoxy-D-lyxitol, and other carbohydrates was accomplished via the use of **1** and proline. Many of the aldol acceptors aldehydes used in our study have not been reported in studies of the natural enzymes. Attempts to use (*S*)-alanine as a catalyst were unsatisfactory.[8c] Unlike the natural aldolase derivates, the scope of proline-catalyzed reactions extends to ketone acceptors and highly protected sugars. Our studies have also revealed effective methodologies for accessing *anti*- or *syn*-1,3-diols, expanding the scope of synthons and carbohydrates and their derivatives that are accessible with our approach. Further studies are underway to explore the synthesis of higher carbon sugars via organocatalysis.

**TABLE 7. Catalyst Screen for the Aldol Reaction of 1 with Ethyl Trifluoropyruvate 15**




| entry | catalyst | additive | time | % yield[a] | *anti*:*syn*[b] | % ee[c] |
|---|---|---|---|---|---|---|
| 1 | (±)-proline | | 24 h | 31 | 86:14 | |
| 2 | (*S*)-proline | | 3 h | 4 | 90:10 | >99/33 |
| 3 | (*S*)-proline | | 48 h | 41 | 85:15 | >99/38 |
| 4 | **(*S*)-proline** | | **264 h** | **83** | **87:13** | **>99/54** |
| 5 | (*S*)-proline[d] | | 72 h | 78 | 75:25 | 40/62 |
| 6 | **(*S*)-proline** | **$H_2O$ (5 equiv)** | **48 h** | **3** | **>95:1** | **>99/−** |
| 7 | (*S*)-proline | $H_2O$ (2 equiv) | 72 h | 28 | 92:8 | 86/20 |
| 8 | cat1[e] | | 48 h | 39 | 79:21 | 58/75 |
| 9 | cat2[f] | TFA (1 equiv) | 48 h | 11 | 87:13 | >99/37 |

[a] Isolated yield after column chromatography. [b] Determined by $^1$H NMR and HPLC analysis. [c] Determined by chiral-phase HPLC analysis. [d] 30 mol % catalyst used. [e] (*S*)-2-Pyrrolidine-tetrazole. [f] (*S*)-(+)-1-(2-Pyrrolidinyl-methyl)-pyrrolidine.

## Experimental Section

**General Experimental Procedure for the Aldol Reaction.** To a glass vial charged with DMF (200 $\mu$L) were added ketone (0.5 mmol), aldehyde (0.1 mmol), and (*S*)-proline (0.02 mmol, 2.3 mg), and the reaction was stirred at ambient temperature or at 4 °C until the reaction was complete as shown by TLC. Then, a half-saturated $NH_4Cl$ solution and ethyl acetate were added with vigorous stirring, the layers were separated, and the organic phase was washed with brine. The organic phase was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired aldol product.

**General Procedure for Derivatization of Aliphatic Substrates for HPLC Analysis.** The aldol adduct (1 equiv) in $CH_2Cl_2$ (1 mL/0.5 mmol) was treated with 3,5-dinitrobenzoyl chloride (1.1 equiv) and DMAP (1.1 equiv) and stirred for 1 h. The solution was filtered through a small plug of silica gel and analyzed by HPLC.

**(4*R*,5*R*)-4-((*R*)-1-Hydroxy-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-ol (4a).** To a solution of **3f** (20.0 mg, 0.0854 mmol) in $CH_2Cl_2$ (0.25 mL) were added AcOH (0.050 mL) and $NaBH(OAc)_3$ (27.1 mg, 0.128 mmol) at −20 °C. After stirring for 5 h, the mixture was poured into saturated $NaHCO_3$ and extracted

(21) Baasner, B.; Hagemann, H.; Tatlow, J. C.; Eds. Organofluorine compounds. In *Houben-Weyl, Methods of Organic Chemistry*; Thieme-Verlag: Stuttgart, 1999/2000; Vol. E 10a−c and papers cited therein.

(22) For a recent review on dihydroxyacetone derivatives, see: Enders, D.; Voith, M.; Lenzen, A. *Angew Chem., Int. Ed.* **2005**, *44*, 2−23.

with EtOAc. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The obtained residue was purified on silica gel to give **4a** (15.1 mg, 69%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.38 (s, 3H), 1.47 (s, 3H), 3.49 (s, 3H), 3.52 (s, 3H), 3.64 (dd, $J$ = 8.8, 11.2 Hz, 1H), 3.73 (dd, $J$ = 6.4, 9.2 Hz, 1H), 3.81−3.86 (m, 2H), 3.93 (dd, $J$ = 5.2, 11.2 Hz, 1H), 4.46 (d, $J$ = 3.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 19.5, 28., 29.70, 55.9, 56.5, 63.9, 65.3, 72.3, 75.0, 103.3. HRMS $C_{10}H_{20}NaO_6$(M + Na): calcd 259.1152, obsd 259.1149. $[\alpha]^D_{25} = -7.3$ ($c$ = 0.52, MeOH).

**(*S*)-4-((*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,2-dimethoxyethyl)-2,2-dimethyl-1,3-dioxan-5-one (5).** To a solution of compound **3f** (0.174 mg, 0.744 mmol) in DMF (2.0 mL) were added imidazole (0.127 g, 1.87 mmol) and TBS-Cl (0.168 g, 1.11 mmol) at room temperature. After stirring for 24 h, the mixture was poured into saturated $NH_4Cl$ and extracted with EtOAc. The combined organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The obtained residue was purified on silica gel to give the target product (0.170 g, 66%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.09 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 1.44 (s, 3H), 1.47 (s, 3H), 3.40 (s, 3H), 3.46 (s, 3H), 3.89 (d, $J$ = 16.0 Hz, 1H), 4.06 (dd, $J$ = 2.0, 7.2 Hz, 1H), 4.22 (dd, $J$ = 1.6, 16.0 Hz, 1H), 4.34 (dd, $J$ = 1.6, 3.2 Hz, 1H), 4.59 (d, $J$ = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −4.9, −4.6, 18.1, 22.9, 24.9, 25.8, 55.6, 56.0, 67.1, 73.5, 77.7, 100.2, 105.4, 202.1. HRMS $C_{16}H_{32}NaO_6Si$ (M + Na): calcd 371.1866, obsd 371.1856. $[\alpha]^D_{25} = -88.3$ ($c$ = 0.69, MeOH).

**(2*S*,3*S*,4*R*,*E*)-2,3,4,5-Tetrahydroxypentanal *O*-Benzyl Oxime (6a).** Dowex 50W2-100 (54.0 mg) was added to a solution of **4a** (83.0 mg, 0.351 mmol) in $H_2O$ (2.0 mL). After stirring at room temperature for 6.5 h, the resin was removed by filtering through a glass filter. The solution was concentrated in vacuo. The residue (51.4 mg, 0.342 mmol) was dissolved in EtOH (1.0 mL), and pyridine (0.042 mL, 0.513 mmol) and benzyloxyamine HCl salt (82.0 mg, 0.513 mmol) were added to the solution. After stirring for 24 h, the mixture was diluted with EtOAc and saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over $Na_2SO_4$, and evaporated. The obtained residue was purified on silica gel to give the target product (74% over two steps). $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 3.56−3.68 (m, 3H), 3.77 (m, 1H), 4.35 (dd, $J$ = 4.8, 7.2 Hz, 1H), 5.07 (s, 2H), 7.27−7.36 (m, 5H), 7.51 (d, $J$ = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 64.8, 68.4, 72.7, 74.6, 77.1, 128.9, 129.2, 129.4, 139.2, 153.8. HRMS for $C_{12}H_{17}NNaO_5$ ($MNa^+$): calcd 278.0999, obsd 278.1004. $[\alpha]^D_{25} = 62.2$ ($c$ = 1.0, MeOH).

**(2*S*,3*S*,4*S*,*E*)-2,3,4,5-Tetrahydroxypentanal *O*-Benzyl Oxime (6b).** The standard sample was prepared from **4b** by the same method as described for **6a**; yield 52% over two steps. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 3.30−3.32 (m, 3H), 3.60 (m, 1H), 4.22 (dd, $J$ = 7.2, 8.0 Hz, 1H), 5.06 (s, 2H), 7.27−7.36 (m, 5H), 7.50 (d, $J$ = 7.2 Hz, 1H). $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 64.5, 70.4, 71.7, 73.4, 76.8, 128.8, 129.3, 129.4, 139.2, 152.8. HRMS for $C_{12}H_{17}NNaO_5$ ($MNa^+$): calcd 278.0999, obsd 278.1004. $[\alpha]^D_{25} = 0.27$ ($c$ = 1.0, MeOH).

**2-((2*S*,3*S*)-2,3,5-Trihydroxy-4-oxopentyl)isoindoline-1,3-dione (7).** Compound **3c** (0.05 mmol, 18 mg) dissolved in $H_2O$ (200 $\mu$L) and THF (300 $\mu$L) was stirred with Dowex 50WX2-100 resin (prewashed with $H_2O$) for 12 h at room temperature. The solution was filtered and the filtrate was concentrated to give the final product without purification (yield 99%). $^1$H NMR (*d*-DMSO, 500 MHz): $\delta$ 7.88−7.82 (m, 4H), 5.70 (d, J = 5.3 Hz, 1H), 5.31 (d, $J$ = 5.4 Hz, 1H), 4.90 (t, $J$ = 5.9 Hz, 1H) 4.32 (dq, $J_1$ = 6.0 Hz, $J_2$ = 19.4 Hz, 2H), 4.03−3.96 (m, 2H), 3.73 (dd, $J_1$ = 9.2 Hz, $J_2$ = 13.8 Hz, 1H), 3.56 (dd, $J_1$ = 3.13 Hz, $J_2$ = 13.1 Hz, 1H). $^{13}$C NMR (*d*-DMSO, 125 MHz) $\delta$ 211.0, 167.9, 134.1, 131.7, 122.8, 76.3, 69.0, 66.4, 41.0. HRMS for $C_{13}H_{13}NNaO_6$ ($MNa^+$): calcd 302.0635, obsd 302.0634. $[\alpha]^D_{25} = -23.9$ ($c$ = 1.0, THF/$H_2O$, 1:1).

**Compound 12.** Commercially available 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (2.5 g, 9.61 mmol) was dissolved in EtOAc (70 mL), and IBX (28.8 mmol, 8.1 g) was carefully added.[23] The suspension was heated to reflux for 4 h, and then the precipitate was removed via filtration. The EtOAc was concentrated in vacuo to give aldehyde **12** in quantitative yield. $^1$HNMR ($CDCl_3$, 500 MHz): $\delta$ 9.618 (1H), 5.67 (d, $J$ = 4.9 Hz, 1H), 4.62 (ddd, $J_1$ = 2.45 Hz, $J_2$ = 7.80 Hz, $J_3$ = 11.5 Hz, 2H), 4.38 (q, $J$ = 2.45 Hz, 1H), 4.19 (d, $J$ = 2.13 Hz, 1H), 1.51 (s,3H), 1.44 (s,3H), 1.35 (s, 3H), 1.31 (s, 3H). $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ 24.2, 24.8, 25.8, 26.0, 70.4, 70.5, 71.7, 73.2, 96.2, 109.0, 110.0, 200.3. HRMS for $C_{12}H_{19}O_6$ ($MH^+$) calcd 259.1176, obsd 259.1182.

**Acknowledgment.** This study was supported by the Skaggs Institute for Chemical Biology.

**Note Added after ASAP Publication.** There was an error in the page range of ref 8a and ref 8f was missing in the version published ASAP April 6, 2006; the revised version was published April 12, 2006.

**Supporting Information Available:** Product characterization data of **2k**−**n**, **3d**, **3f**, **4a**, **13**, **15**, **17**; $^1$H and $^{13}$C NMR spectra of **2k**−**n**, **3d**, **3f**, **4a**, **5**, **6a**, **6b**, **13**, **15**, **17**; X-ray ortep diagram and CIF file of **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0602017

(23) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003.