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5-Deoxy-5-alkyl-1,2-*O*-isopropylidene-α-D-Xylofuranoses as Chiral Auxiliaries in Asymmetric 1,4-Addition Reaction

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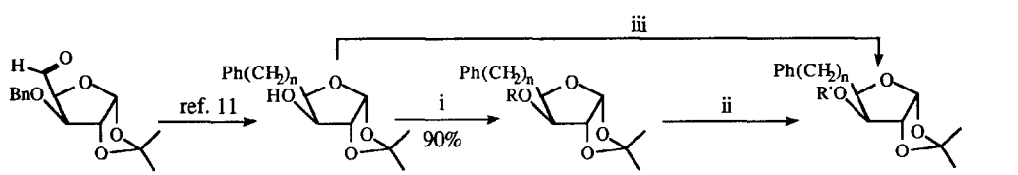
Abstract: Two deoxy-sugar based chiral auxiliaries (**2** and **5**) have been prepared. Their α,β-unsaturated esters were treated with different cuprate reagents to give the 1,4-addition adducts in good chemical yield and good diastereoselectivity.

Amino acids and terpenoids are often used as chiral auxiliaries in asymmetric synthesis.[1] Carbohydrates, however, have been extensively employed as starting materials in the construction of polyfunctional compounds containing one or more centers of chirality[2], but less often used as chiral auxiliaries in control of stereoselectivity.[3-9] Carbohydrates exhibit considerable complexing abilities towards metal ions because of their poly-oxygenated functionalities. The diastereoselectivities were not good in some cases for which the reactions involve several possible chelated intermediates.[3a] For the use of these complexing properties selectively in control of stereoselectivity, deoxygenation of certain oxygen-containing groups attached to the sugar skeleton is needed. Consequently, we prepared two chiral auxiliaries 1,2-*O*-isopropylidene-5-phenyl-5-deoxy-α-D-xylofuranose (**2**, white solid, mp = 96.0–96.5 °C, $[\alpha]_D$ –13.2 , c = 1.7 in $CHCl_3$) and 1,2-*O*-isopropylidene-5-phenylmethyl-5-deoxy-α-D-xylofuranose (**5**, white solid, mp = 86–87 °C, $[\alpha]_D$ –5.3 , c = 1.3 in $CHCl_3$).

We converted readily available 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose (**1**)[10] to **2** and **5** in 67% and 79% yields, respectively, on a large scale[11] (Scheme 1). Esterification of the



Reagents : (i) *trans*-RCH=CHCOCl, NaH, THF, 0 °C (R = Me or Ph); (ii) R^1MgBr, CuBr-Me_2S, Me_2S-THF, –78 °C; (iii) rac-R^1RCHCH_2COCl, NaH, THF, 0 °C (R^1 = phenyl, vinyl, allyl, isopropyl, ethyl, or *n*-heptyl)

Scheme 1

free hydroxy groups at C–3 in **2** and **5** with an α,β-unsaturated acyl chloride provided optically pure esters in high yields (Scheme 1). We believe that the phenyl group on each chiral auxiliary can increase the π-facial selectivity by through space π–π interaction between π-orbitals of the phenyl ring and the α,β-unsaturated ester moiety[12] (**3a**, **3b**, **6a**, and **6b**). Herein, we describe our results on the asymmetric 1,4-addition reaction by using these two chiral auxiliaries.

Table 1: The 1,4-Addition of R^1MgBr to α,β-Unsaturated Esters Catalyzed by CuBr-Me_2S

entry	starting material	R^1 =	$[\alpha]_D$ in $CHCl_3$	yield % [a]	% d. e.	configuration of the new chiral center
1	**3a**	ph	–46.5 (c = 2.06)	74	95[b,c]	*S*
2	**3a**	vinyl	–36.1 (c = 1.22)	68	>90[b]	*S*
3	**3a**	allyl	–33.9 (c = 1.12)	69	87[b]	*R*
4	**3a**	*n*-heptyl	–27.9 (c = 2.44)	70	>90[b]	*R*
5	**3a**	ethyl	–29.4 (c = 1.91)	65	>90[b]	*R*
6	**3a**	i-propyl	–26.2 (c = 1.91)	72	>90[b]	*S*
7	**3b**	vinyl	–17.7 (c = 3.38)	69	75[c]	*S*
8	**3b**	allyl	–14.1 (c = 1.42)	71	>90[b]	*R*
9	**3b**	n-heptyl	–14.7 (c = 1.63)	67	58[c]	*R*
10	**3b**	ethyl	–12.0 (c = 2.00)	89	58[c]	*R*
11	**3b**	*i*-propyl	–12.7 (c = 1.57)	69	75[c]	*S*
12	**6a**	phenyl	–22.7 (c = 0.97)	71	83[c]	*S*
13	**6a**	vinyl	–17.0 (c = 0.59)	80	>90[b]	*S*
14	**6a**	allyl	–7.7 (c = 0.78)	82	—[d]	—[d]
15	**6a**	*n*-heptyl	–11.6 (c = 3.60)	80	—[d]	—[d]
16	**6a**	ethyl	–10.3 (c = 2.30)	85	—[d]	—[d]
17	**6a**	*i*-propyl	–7.7 (c = 1.55)	75	80[b]	*S*
18	**6b**	vinyl	–1.4 (c = 9.95)	81	79[c]	*S*
19	**6b**	allyl	–0.8 (c = 9.95)	75	66[b]	*R*
20	**6b**	*n*-heptyl	–8.0 (c = 3.00)	90	70[c]	*R*
21	**6b**	ethyl	–14.3 (c = 1.85)	73	70[c]	*R*
22	**6b**	*i*-propyl	–3.6 (c = 1.66)	72	69[c]	*S*

[a] Satisfactory ^1H, ^{13}C NMR, IR, and HRMS results were obtained . [b] The % d. e. was determined by ^{13}C NMR. [c] The % d. e. was determined by ^1H NMR. [d] The % d. e. can not be determined by ^1H NMR, ^{13}C NMR, or HPLC.

The typical procedure for the conjugated additions is as follows. To a mixture of CuBr·Me_2S (205.6 mg, 1.05 mmol) and Me_2S–THF (3.0 mL, 1:1) was added a THF solution of Grignard reagent (2.1 mmol)

at –78 °C with stirrring under nitrogen for 10 min[13]. To this brownish solution was added α,β-unsaturated ester (0.50 mmol) in 2.5 ml of THF. After 2 h of stirring at –78 °C, the resultant dark green mixture was poured into aqueous NH_4Cl at 0 °C with vigorous stirring. A usual workup gave crude mixture, which was purified by silica gel column chromatography. The results summarized in the Table show that this reaction worked almost equally well for vinylic cuprate reagents (such as phenyl and vinyl groups), secondary alkyl cuprate reagent (such as isopropyl group), and primary alkyl cuprate reagents (such as allyl, ethyl, and *n*-heptyl groups). These reactions gave moderate-to-good yields (Table 1). In order to determine the sereoselectivity by spectroscopic methods, we converted compounds **2** and **5** to the 1:1 diastereomeric isomers of compounds **4a**, **4b**, **7a**, and **7b** by reacting them with racemic R^1RCHCH_2COCl (R^1 = phenyl, vinyl, allyl, isopropyl, ethyl, or *n*-heptyl; R = methyl or phenyl) in the presence of NaH (Scheme 1). In comparison the ^1H NMR or ^{13}C NMR spectra of these authentic samples with those obtained from our approach, the ratio of two diastereomers could be determined for all entries except 14–16. Usually, the ^1H NMR of the anomeric protons (C_1-H) or the ^{13}C NMR of the new stereogenic centers (β to the carbonyl group) for both diastereomers appeared at different chemical shifts. Nevertheless, stereoisomers from entries 14–16 showed identical ^1H and ^{13}C NMR spectra. Furthermore, they were inseparable by HPLC (DuPont Zorbax Sil 4.6 mm ID x 25 cm, Table 1). In general, the 1,4–addition of the crotonates gave better diastereoselectivities than those of cinnamates for each chiral auxiliariy.

The *S* configuration of the new stereogenic center of the major products (entries 1 and 12) were proved to be S by comparison of their spectral data with those of the optically pure authentic samples, which were made by reacting of compounds **2** and **5** with (*S*)-3-phenylbutyryl chloride[14] in the presence of NaH. We rationalize that this stereochemical outcome results from the addition of cuprate reagents to

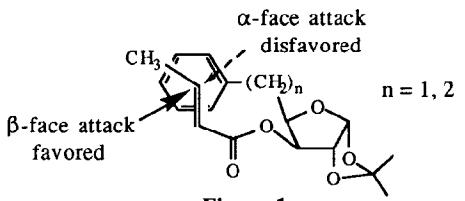


Figure 1

α,β-unsaturated esters away from the bulky phenyl group as we expected. In this process, the *s-trans* relationship of the C=O/C=C disposition the crotonate moiety is the most favorable one as shown in Figure 1.[15] Presumably, the chelation among the metal ion with oxygen atoms from C=O and C_2-O groups might enhance the rigidity of this conformation. Further work on the application of these chiral auxiliaries in asymmetric synthesis is under investigation in our laboratory.

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