Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 371–374

TETRAHEDRON: *ASYMMETRY*

New glyco-oxazolidin-2-ones as chiral auxiliaries in boron-mediated asymmetric aldol reactions

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Received 29 October 1999; accepted 11 November 1999

Abstract

Two new chiral glyco-oxazolidin-2-one auxiliaries based on D-glucose are described. Some *N*-acyl derivatives were synthesized and used in dialkylboron-mediated asymmetric aldol reactions. All reactions delivered as the major diastereomer those predicted by the Zimmerman–Traxler model and were separated by column chromatography and mostly isolated in moderate to good yields.

Chiral oxazolidin-2-ones as introduced and developed by Evans and co-workers[1] have become versatile auxiliaries for various reactions in modern stereoselective synthesis. Based on a very simple approach to glyco-oxazolidin-2-ones, that was discovered in our laboratory in cooperation with Hungarian colleagues,[2] we recently reported on the D-xylose derived glyco-oxazolidin-2-ones 3,5-*O*-isopropylidene- and 3,5-*O*-benzylidene-α-D-xylofurano[1,2-d]oxazolidin-2′-one for the same purposes. Their practical value in the resolution of racemic carboxylic and sulfonic acids, in diastereoselective α-alkylations, α-acylations, α-halogenations and aldol reactions has been demonstrated.[3]

The success of these acetal protected reagents in stereoselective synthesis encouraged us to look for other glyco-oxazolidin-2-ones as chiral auxiliaries. We decided to explore the applicability of the two new compounds 3,5,6-tri-*O*-methyl-1-deoxy-α-D-glucofurano[1,2-d]-1′,3′-oxazolidin-2′-one **4** and 3,5,6-tri-*O*-pivaloyl-1-deoxy-α-D-glucofurano[1,2-d]-1′,3′-oxazolidin-2′-one **7**. Both are prepared from very inexpensive D-glucose. The use of methyl ether protecting groups in **4** and pivaloyl protecting groups in **7** were chosen to obtain auxiliaries that are more stable towards acidic conditions in order to employ them in reactions the previous auxiliaries could not be used for. Another interesting aspect is the different steric demand of these protecting groups. Because of their importance in the asymmetric construction of carbon–carbon bonds we decided to examine the performance of these new auxiliaries in some aldol additions.

The first step in the synthesis of auxiliary **4** was the permethylation of 1,2-*O*-isopropylidene-α-D-glucofuranose **1** (Scheme 1).[4] After 1,2-deprotection of obtained compound **2** the resulting derivative **3** was converted into the target compound **4**.[2]

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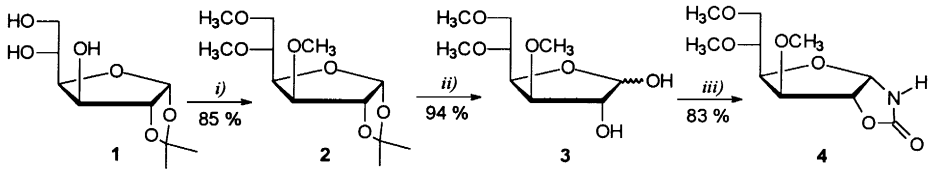
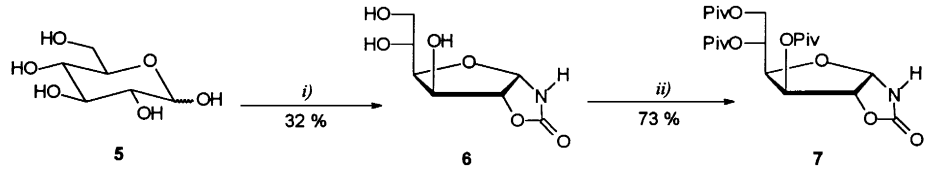
0957-4166/00/$ - see front matter
PII: S0957-4166(99)00503-0



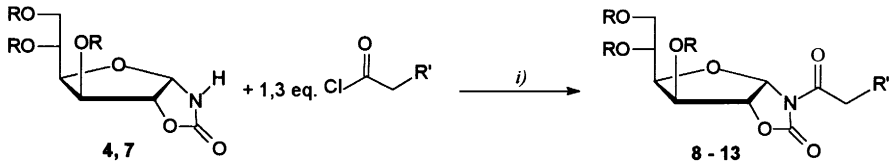
Scheme 1. Synthesis of 3,5,6-tri-*O*-methyl-1-α-D-glucofurano[1,2-d]-1′,3′-oxazolidin-2′-one **4**. Reagents: (i) MeI, NaOH, DMF, 3.5 h, rt; (ii) acetic acid 50%, 100°C, 5 h; (iii) KOCN, NaH_2PO_4, H_2O, 2 h, 60°C

The synthesis of the pivaloyl protected auxiliary **7** was started by addition of potassium cyanate to D-glucose (Scheme 2).[2] The resulting oxazolidin-2-one **6** was smoothly converted into target compound **7** by addition of pivaloylchloride and pyridine in dichloromethane.[5]



Scheme 2. Synthesis of 3,5,6-tri-*O*-pivaloyl-1-deoxy-α-D-glucofurano[1,2-d]-1′,3′-oxazolidin-2′-one **7**. Reagents: (i) KOCN, NaH_2PO_4, H_2O, 2 h, 60°C; (ii) 1.2 equiv. pivaloychloride, pyridine, CH_2Cl_2, rt, 3 d

A number of different *N*-acyl substrates of both auxiliaries were easily prepared in good yields by accommodating Kunieda's technique using *N*,*N*-dimethyl-aminopyridine as catalyst[6] in order to study the steric influence of the substituents in the α-position of the *N*-acyl moiety on the diastereoselectivity (Scheme 3, Table 1).



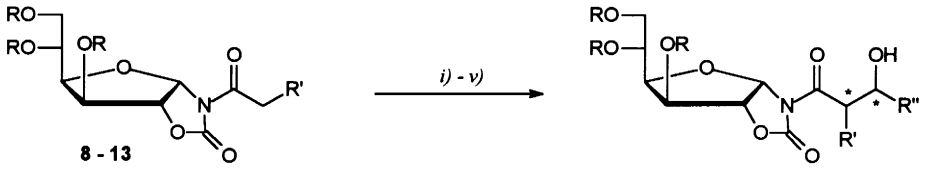
Scheme 3. *N*-Acylation procedure. Reagents: (i) 1.2 equiv. Et_3N, 0.2 equiv. DMAP, CH_2Cl_2, rt, 1 h

Table 1
N-Acylation products of auxiliaries **4** and **7**

auxiliary	R	R'	N-acyl derivative	yield
4	$-CH_3$	$-CH_3$	**8**	97 %
4	$-CH_3$	$-C_2H_5$	**9**	91 %
4	$-CH_3$	$-C_6H_5$	**10**	44 %
7	-Piv	$-CH_3$	**11**	87 %
7	-Piv	$-C_2H_5$	**12**	98 %
7	-Piv	$-C_6H_5$	**13**	71 %

The formation of the boron enolates using dibutylboryltrifluoromethanesulfonate (*n*-Bu_2BOTf) and diisopropylethylamine (DPEA) and the subsequent aldol condensation was carried out by adapting a method by Evans et al. (Scheme 4, Table 2).[7] For the reaction of the methyl ether protected *N*-acyl derivatives, dichloromethane was used as solvent, whereas diethyl ether was the solvent of choice for the reaction of the pivaloyl protected *N*-acyl precursors. The diastereomeric ratios were determined by ^1H NMR spectroscopy. In most cases it was possible to separate the major diastereomer by simple column chromatography in yields varying from 23 to 70%.

The high selectivities can be explained by applying the widely accepted Zimmerman–Traxler pericyclic chair-like transition state model.[8] A non-chelated transition state is assumed to be responsible for



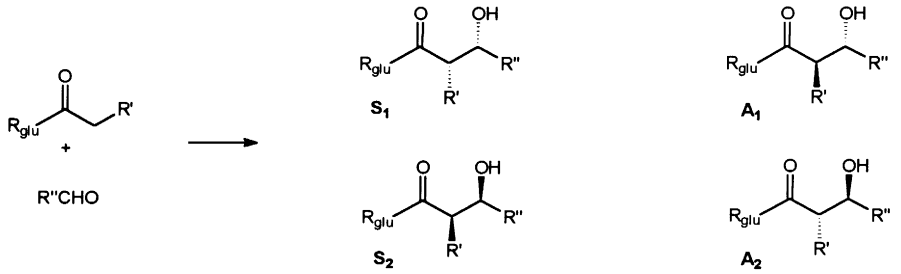
Scheme 4. Boron-mediated aldol reaction. Reagents: (i) 1.2 equiv. iPr$_2$NEt, 1.15 equiv. n-Bu$_2$BOTf, 0°C, 30 min; (ii) 1.1 equiv. R′′CHO, −78°C, 20 min; (iii) 0°C, 1 h; (iv) pH 7 – phosphate buffer:methanol (2:3); (v) methanol:H_2O_2 (2:1)

Table 2
Results of boron-mediated aldol reactions

	educt	aldehyde R''CHO	diastereomeric ratio[a]	configuration of major product	isolated yield of major product[b]
8	(R' = -CH_3)	-CH_3	8 : 1	S_1	52 %
8	(R' = -CH_3)	-$CH_2CH_2CH_3$	13 : 1	S_1	62 %
8	(R' = -CH_3)	-$CH(CH_3)_2$	8 : 1	S_1	67 %
8	(R' = -CH_3)	-C_6H_5	3 : 1	S_1	70 %
9	(R' = -CH_2CH_3)	-CH_3	3 : 1	S_1	[c]
9	(R' = -CH_2CH_3)	-$CH_2CH_2CH_3$	5 : 1	S_1	29 %
9	(R' = -CH_2CH_3)	-$CH(CH_3)_2$	3 : 1	S_1	21 %
9	(R' = -CH_2CH_3)	-C_6H_5	5 : 1	S_1	30 %
10	(R' = -C_6H_5)	-$CH(CH_3)_2$	5 : 1	A_2	[c]
11	(R' = -CH_3)	-CH_3	12 : 1	S_1	[c]
11	(R' = -CH_3)	-$CH_2CH_2CH_3$	16 : 1	S_1	43 %
11	(R' = -CH_3)	-$CH(CH_3)_2$	16 : 1	S_1	59 %
11	(R' = -CH_3)	-C_6H_5	8 : 1	S_1	47 %
12	(R' = -CH_2CH_3)	-CH_3	9 : 1	S_1	66 %
12	(R' = -CH_2CH_3)	-$CH_2CH_2CH_3$	6 : 1	S_1	50 %
12	(R' = -CH_2CH_3)	-$CH(CH_3)_2$	8 : 1	S_1	53 %
12	(R' = -CH_2CH_3)	-C_6H_5	3 : 1	S_1	53 %
13	(R' = -C_6H_5)	-$CH(CH_3)_2$	8 : 1	A_2	23 %

[a]Determined by 500 MHz ^{1}H NMR spectroscopy using 1 D Win NMR software from Bruker.
[b]After column chromatography.
[c]The major product could not be isolated in pure form.

the formation of the observed S_1 and A_2 major products. The four possible configurations are shown in Scheme 5.



Scheme 5. The four possible diastereomers

In the case of the non-arylic *N*-acyl derivatives this can be explained by the formation of a *Z*-enolate which is attacked from its less hindered *re*-face. However, the phenylacetyl derivatives **10** and **13** give rise to the *E*-enolate which is attacked from the *si*-face, resulting in the expected A_2 product. Not surprisingly, the observed selectivities are usually higher for the auxiliary **7** with its sterically more demanding pivaloyl protecting groups.

The absolute configurations were determined by the cleavage of some of the β-hydroxy acids from the auxiliaries using lithium hydroperoxide[9] and subsequent comparison of the specific rotations with literature values. It should be noted that the auxiliaries could always be recovered in high yields.

The structures of all isolated compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy, MS measurements, and microanalyses. According to these studies, **4** and **7** can be used as efficient chiral auxiliaries in stereoselective boron-mediated aldol reactions. Further investigations are in progress.

References

1. Evans, D. A.; Takaks, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109–1127.
2. (a) Kovács, J.; Pintér, I.; Lendering, U.; Köll, P. *Carbohydr. Res.* **1991**, *210*, 155–166; (b) Kovács, J.; Pintér, I.; Töth, G.; Györgydeák, Z.; Köll, P. *Carbohydr. Res.* **1993**, *239*, 95–106; (c) Kovács, J.; Pintér, I.; Abeln, D.; Kopf, J.; Köll, P. *Carbohydr. Res.* **1994**, *257*, 97–106; (d) Kovács, J.; Pintér, I.; Köll, P. *Carbohydr. Res.* **1995**, *272*, 255–262.
3. (a) Köll, P.; Lützen, A. *Tetrahedron: Asymmetry* **1995**, *6*, 43–46; (b) Köll, P.; Lützen, A. *Tetrahedron: Asymmetry* **1996**, *7*, 637–640; (c) Lützen, A.; Köll, P. *Tetrahedron: Asymmetry* **1997**, *8*, 29–32; (d) Lützen, A.; Köll, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1193–1206.
4. Ciucanu, I.; Kerek, F. *Carbohydr. Res.* **1984**, *131*, 209–217.
5. Kunz, H.; Harreus, A. *Liebigs Ann. Chem.* **1982**, 41–48.
6. Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185–4188.
7. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
8. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1922.
9. Evans, D. A.; Britton, T.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.