Communications

A Radical Approach to Asymmetric Aldol Synthesis†

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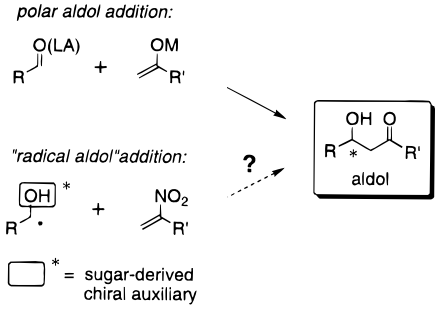
Asymmetric versions of the aldol addition reaction continue to attract the attention of organic chemists.[1] A major impetus for synthetic developments in this area comes from the variety of antibiotics that incorporate aldol retrons directly into their structures. While most practical asymmetric aldol reactions still rely on (stoichiometric) chiral auxiliaries to control developing stereochemistry, catalytic systems utilizing enzymes[2] as well as chiral Lewis acids[3] have now been reported. The aldol addition of enolates (or their equivalents) to aldehydes and ketones generally proceeds by a polar addition type of mechanism.[4] This usually has certain implications regarding functional group compatibility, aldol substitution pattern, etc., which must be taken into account. We now report a conceptually novel approach to asymmetric aldol synthesis based on the stereocontrolled addition of a chiral hydroxyalkyl radical equivalent[5] to a nitroalkene. It is further shown that the free aldol can be released (without dehydration) and the sugar-derived chiral auxiliary efficiently processed for reuse.



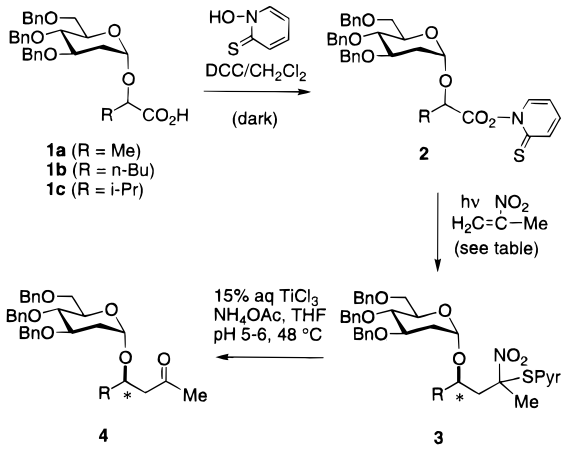
The sequence begins with the hydroxy acid glycosides **1**, which are readily prepared by acid-catalyzed addition of the corresponding α-hydroxy ester (stereochemistry irrelevant)[6] to tri-*O*-benzyl-D-glucal followed by saponification. Following a modified version of Barton's protocol,[7] these carboxylic acids were converted to their PTOC esters **2** and irradiated with a sunlamp in the presence of 2-nitropropene at the indicated temperature (see Table 1 and Scheme 1). The clean formation of adducts corresponding to **3** was detected by TLC but it was difficult to evaluate the ρ-diastereoselectivity at this stage since thiopyridyl ether formation (α to the nitro group) was stereorandom. Conversion of the geminal nitro thioether functionality to a ketone was best accomplished by first filtering the crude reaction mixture through silica gel (to remove DCU) and then exposing the unresolved adducts to buffered reductive Nef conditions.[8] As shown in Table 1, the protected aldols **4** could be obtained in excellent overall yields from **1** (better than 90% per step in optimized cases). The kinetic diastereomer ratios (**4**/**dia-4**) were readily determined by comparing the crude ^{1}H NMR spectra with those of deliberately prepared mixtures.[9]

Table 1

entry	substrate	reaction *T* (°C)	overall yield (%)	ρ-ds (**4**/**dia-4**)
1	**1a**	−78	77	5/1
2	**1b**	−78	74	6/1
3	**1c**	−78	47[a]	7/1
4	**1a**	−100	69	7/1
5	**1b**	−100	50	8/1

[a] 16% of the decarboxylative rearrangement product i-PrCH(O-Sugar)SPyr was isolated as well.

Scheme 1



Glycoside cleavage with concomitant production of the free aldol represented a potential difficulty because of the ease with which the aldol product can suffer dehydration. Attempted use of our previously elucidated conditions for auxiliary removal (PPTS/MeOH)[5] failed to give any detectable aldol product. However, exposure of **4** to PhSH + BF_3·OEt_2, according to Danishefsky et al.,[10] resulted in clean conversion to the 2-deoxythioglycosides

† Dedicated to Professor Paul Dowd on the occasion of his 60th birthday.

(1) Review: Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317−338.

(2) Cf. Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 7585−7591.

(3) (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077−4078. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *Ibid.* **1994**, *116*, 8837−8838. (c) Keck, G. E.; Krishnamurthy, D. *Ibid.* **1995**, *117*, 2363−2364.

(4) There is some evidence that a SET mechanism can intervene with aromatic aldehydes: Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1986**, *51*, 472−476.

(5) Garner, P. P.; Cox, P. B.; Klippenstein, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4183−4184.

(6) Racemic α-hydroxy esters **1b** and **1c** were conveniently prepared from their cyanohydrins: Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55−56.

(7) Barton, D. H. R.; Togo, H.; Zard, S. Z. *Tetrahedron* **1985**, *41*, 5507−5516.

(8) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367−4373.

(9) Approximately equimolar mixtures of **4** and **dia-4** were obtained by adding (±)-RCH(OH)CH_2COMe (from the hydroxide-catalyzed aldol reaction of RCHO and MeCOMe: Dubois, J. E. *Ann. Chim.* **1951**, *6*, 406−486) to tri-*O*-benzyl-D-glucal.

(10) Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5720−5749.

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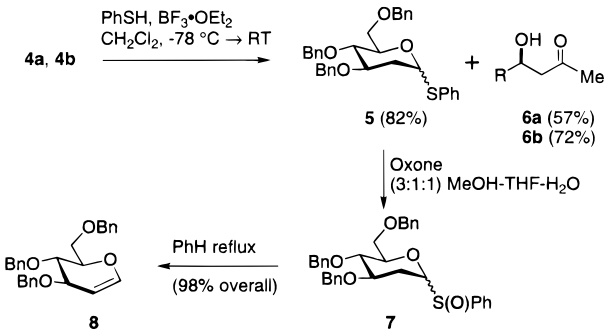
Scheme 2



5 (as a mixture of anomers) and the free aldol **6** (Scheme 2). Consistent with the TS model that we had proposed previously,[5] the negative optical rotations observed for the free aldols indicated that the newly-formed stereocenter had the *R*-configuration.[11] Free aldols **6** could be obtained in >90% ee (Mosher ester analysis)[12] from protected aldols **4** that had been purified (enriched) by flash chromatography. To complete the auxiliary recovery cycle, the thioglycosides **5** were oxidized with Oxone and the resulting sulfoxides heated to induce sulfenic acid elimination. This two-step procedure afforded the starting glucal **8** in very good yield. Finally, we hypothesize that the somewhat eroded ρ-selectivity of radical addition (relative to our results with methyl acrylate)[5] simply reflects an earlier TS with the more reactive nitropropene trap. Studies addressing this issue will be the subject of a future paper.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4a**−**c**, **5**, **6a**,**b**, and **8** (17 pages).

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(11) Cf. Fauve, A.; Veschambre, H. *J. Org. Chem.* **1988**, *53*, 5215−5219.

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.