Pergamon

Tetrahedron Letters, Vol. 38, No. 51, pp. 8777-8780, 1997

0040-4039/97 $17.00 + 0.00

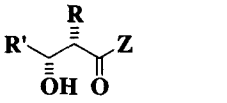
PII: S0040-4039(97)10378-1

Synthesis of Chiral α- Substituted β-Hydroxy Acid Derivatives on Solid Support

Ashok V Purandare* and Sesha Natarajan
Discovery Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute
PO Box 4000, Princeton, NJ 08543.

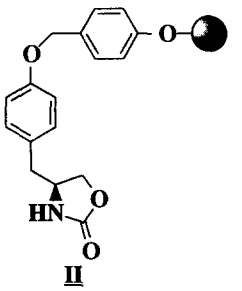
Abstract: Enantioselective aldol condensation using solid supported chiral auxiliary was used for the synthesis of α-substituted-β-hydroxy acid and ester. The solid phase synthesis proceeded with high degree of enatioselectivity, as is observed in solution chemistry. © 1997 Elsevier Science Ltd.

Aldol condensation is an important two component carbon-carbon bond forming reaction. The scope of this reaction has been expanded by advances made in asymmetric version of aldol condensation.[1] The ability to vary two components in aldol condensation offers a great potential to synthesize numerous compounds using combinatorial approaches. Indeed Kurth et al had elegantly used aldol condensation on solid support to generate diverse set of compounds.[2]



Z = OH, OR_2
R & R' = alkyl, aralkyl

I



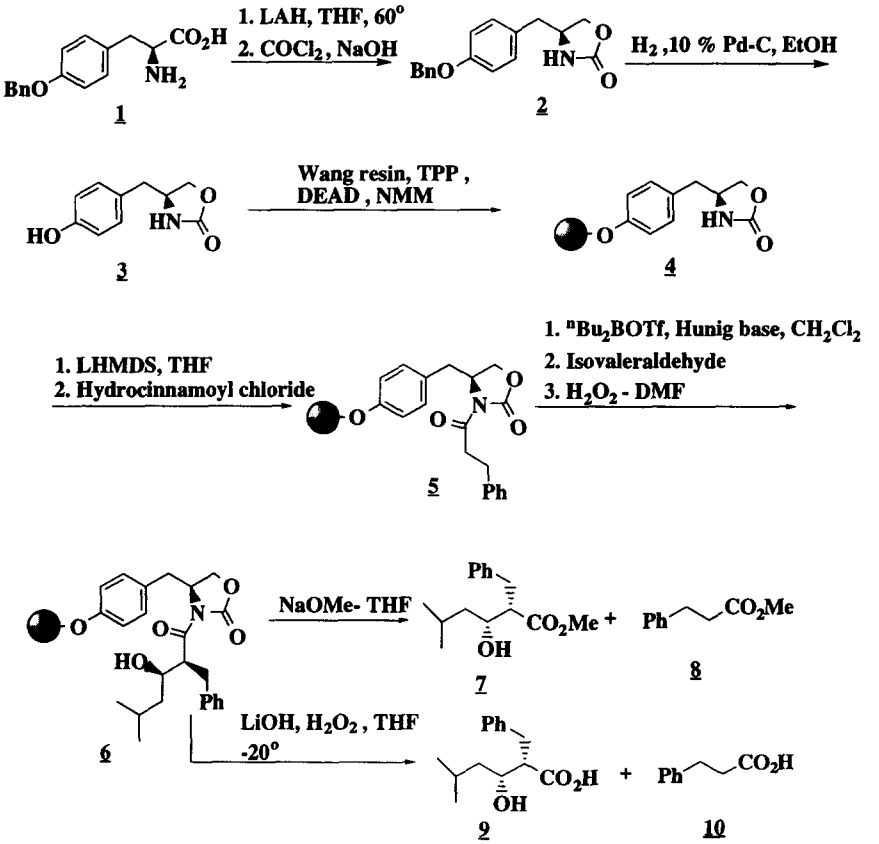
II

We herein report our studies directed towards developing asymmetric aldol reaction on solid support to generate chiral α-substituted-β-hydroxy carboxylic acid derivatives shown by the general structure **I**. To accomplish the objective, we required an immobilized[3] chiral auxiliary attached through a linker (**II**) to a solid support. We envisaged that the oxazolidinone (**3**) derived from L-tyrosine would serve a dual purpose - phenolic OH for attachment to a resin and oxazolidinone as the chiral auxiliary to carry out the aldol condensation.

The oxazolidinone (**3**) was prepared in 3 steps from commercially available O-benzyl L-tyrosine (**1**). Thus O-benzyl-L-tyrosine was reduced to amino alcohol which was subsequently treated with phosgene (in toluene) to give the protected oxazolidinone (**2**) in 82% yield (from **1**). Debenzylation of **2** with hydrogen over $Pd(OH)_2$ gave the required chiral scaffold (**3**) (**Scheme 1**). Compound **3** was then attached to solid support using Mitsunoubu reaction.[4] The extent of loading of oxazolidinone on resin **4** was determined on the basis of

elemental analysis which showed ratio of N:O to be 1:3.5 (theoretical 1:4). The resin was also characterized by gel phase C^{13}NMR and FT-IR. N-acylation of immobilized chiral auxiliary was carried out by first lithiation with excess (2.0 eq) of LiHMDS at -20° followed by treatment with a representative acid halide, hydrocinnamoyl chloride, to give the acylated resin (**5**). Also, when acylation was attempted using modified conditions reported by Mathre et al[5], it was equally successful. The progress of the reaction was monitored by FT-IR which clearly showed two distinct carbonyl peaks at 1699 and 1782 cm^{-1} and disappearance of 1758cm^{-1} peak , confirming the total conversion. The resin-bound compound **5** was also characterized by gel phase C^{13}NMR.

Scheme 1



Aldol condensation with a representative aldehyde, isoveraldehyde was investigated under several conditions i.e., changing reaction temperature, number of equivalents of boron reagent and number of repetitive treatments (**Table 1**). For the analysis of the results of each reaction, the resulting products were cleaved as methyl ester from the resin using sodium methoxide in THF at -20°. The best product ratio of 90:10 (**7**:**8**) was obtained when the resin was treated twice, each time with 2.0 equivalents of boron reagent (each treatment followed by 3 times wash with anhydrous methylene chloride) followed by addition of 4.0 equivalents of aldehyde.[6,7]

Table 1

	Eq of Bu_2BOTf	Eq of Hunig Base	Eq of aldehyde	Reaction temp	Ratio **7** : **8**
1	2.0	2.0	4.0	-78	15 : 85
2	2.0	2.0	4.0	-20	60 : 40
3	4.0	4.0	8.0	-20	50 : 50
4	2 X 2.0	2 X 2.0	4.0	-20	90 : 10

HPLC and H^1 NMR of the product revealed that it was predominantly a single diastereomer (20:1). The stereochemical outcome of the reaction was determined by synthesizing the compound **7** in solution[8] and comparing the HPLC with the product obtained from solid phase reaction. The major product from the solid phase reaction was the expected *syn* diastereomer, thus maintaining the stereochemical integrity. As the Evans aldol protocol is known to yield a single major enantiomer when such a chiral auxiliary is used, our experiments show that same results are obtained when the reactions are carried out on the solid support.

The resin upon treatment with 1.0 M aqueous $LiOH\text{-}H_2O_2$ in DMF gave the corresponding carboxylic acids, namely **9** and **10** in approximately same ratio and similar diastereomeric purity. Initial attempts to cleave the product as substituted amides using primary amines were not successful.

In conclusion, we have shown that enantiospecific aldol condensation of Evans and co-workers can be successfully carried out on solid phase, analogous to the procedure practiced in solution chemistry. The methodology described here will be applicable for the preparation of library of α-substituted-β-hydroxy acids and esters.

* To whom correspondence should be addressed

REFERENCES AND NOTES:

1. Evans, D. A; Bartoli, J.; Shih, T. L.; *J. Am. Chem. Soc.* **1981**, *103,* 2127.
2. Kurth, M. J.; Randall, L. A.; Chen, C.; Melander, C.; Miller, R. B.; McAllister, K.; Reitz, G; Kang, R.; Nakatsu, T.; Green, C.; *J. Org. Chem.* **1994**, *59*, 5862.
3. Allin, S. M.; Shuttleworth, S. J; *Tetrahedron Letters* **1996**, *37,* 8023.
4. Richter, L. H.; Gadek, T. R.; *Tetrahedron Letters.* **1994**, *35,* 4705.
5. Ho, G. J; Mahtre, D. J; *J. Org. Chem.* **1995**, *60*, 2271.
6. General Experimental Procedure For Aldol Condensation:
Resin (**4**) (150 mg, 0.108 mmol) (dried overnight over P_2O_5) was allowed to swell in methylene chloride under argon atmosphere for 30 minutes in a jacketed fritted funnel fitted with a joint and stopcock. The suspension was cooled to -20° C. Diisopropylethylamine (42 mL, 0.24 mmol) followed by di-n-butylboron triflate (0.22 mL, 0.22 mmol, 1.0 M solution in CH_2Cl_2) were added dropwise while the suspension was being vortexed. The resin turned deep red color. The reaction mixture was vortexed for additional 45 minutes at -20°C and then the solution was removed by applying pressure with argon gas. The resin was washed (2 X 5 mL) with dry methylene chloride. Methylene chloride (5 mL) was added to swell the resin. The resin was retreated with diisopropylethylamine (42 mL, 0.24 mmol) and di-n-butylboron triflate (0.22mL, 0.22 mmol, 1.0 M solution in CH_2Cl_2). Isoveraldehyde (36 mL, 0.43 mmol) was added in dropwise manner while the resin was slowly vortexed. The reaction mixture was allowed to shake for 4 h at -20° and then quenched by addition of 2.0 M aqueous solution of Na_2HPO_4 in DMF and vortexed further for 1h at 0°. The reaction mixture was drained and successively washed with DMF (2 X 5 mL) and THF (2 X5 mL).The resin was then treated with 10% hydrogen peroxide in DMF (4:1) for 1 h. The reagent was drained and then the resin was washed with DMF, THF, CH_2Cl_2 (each 3 X 5 mL) and finally with methanol.
7. Procedure For Cleavage (to ester):
A solution of sodium methoxide (1.0 mL, 25% solution in methanol) was added to a cooled (-20°) suspension of resin (**6**) (125 mg) in THF (4 mL) placed in a fritted funnel fitted with a stopcock. The reaction mixture was vortexed for 1 h and the reaction was quenched by addition of acetic acid (20 mL). The solution was filtered and the filtrate was concentrated in vacuo to a crude mixture containing **7** and **8**. The crude was purified by column chromatography (silica gel, hexane-ethyl acetate; 8:2) to furnish analytically pure **7** (26 mg) and **8** (3mg).
8. Compound **7** was prepared in solution in following manner : 1) (S)-4-Benzyl-2-oxazolidinone, nBuLi, hydrocinnamoyl chloride, THF, -78° to 0°; 2) nBu_2BOTf, Hunig base, isoveralaldehyde, Na_2HPO_4, H_2O_2, CH_2Cl_2, -20° to 0°; 3) NaOMe, THF, -20° .

(*Received in USA* 15 *September* 1997; *accepted* 7 *October* 1997)