Improving the Regioselectivity in the Cyclic Iminocarbonate Rearrangement: Enantioselective Synthesis of the Paclitaxel Side Chain

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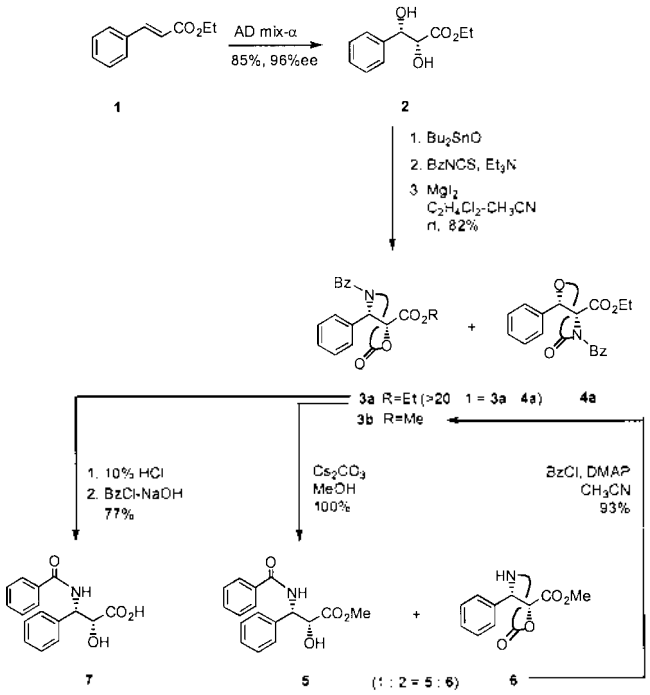
β-Amino-α-hydroxy acids represent an important class of compounds with wide biological activities.[1] In particular, *N*-benzoyl-*syn*-phenylisoserine, the C-13 side chain of Paclitaxel, has been the target of numerous synthetic efforts as the interest in and the paucity of the anti-cancer agent has prompted a wide search for alternative sources for the parent drug and its fragments.[2-9] A key in the side chain synthesis is the stereocontrol of the C-2/C-3 vicinal carbons, and various strategies have been devised to address the relative (*syn*) as well as absolute (2*R*,3*S*) stereocontrol. These include asymmetric 1,2-induction,[3] use of chiral auxiliary,[4] enzymatic resolution,[5] and those employing powerful asymmetric oxidation processes such as catalytic asymmetric epoxidation,[6] dihydroxylation[7] and aminohydroxylation[8] (followed by stereospecific functional group transformations as necessary).

Employing Sharpless's asymmetric dihydroxylation (AD) as the key step, one faces two issues in the synthesis of the Paclitaxel side chain: the regiocontrol and the stereocontrol, particularly in a *relative* sense (*i.e.*, diastereocontrol). Thus, a (2*R*,3*S*)-cinnamate diol, available *via* the AD, needs to be converted to *N*-benzoyl-(2*R*,3*S*)-phenylisoserine with a substitution of *N*-benzoyl group *regioselectively* at the C-3 and with *net-retention of configuration*. A reaction sequence involving an *N*-benzoyl substitution with inversion of configuration at C-3, a perhaps more straightforward synthetic plan that would require (2*R*,3*R*)-cinnamate diol starting material, is not applicable as anti(*erythro*)-diols are not directly accessible *via* AD process.[10,11] While the reported syntheses solved the issue of regiocontrol by taking advantage of the fact that the C-3 was activated as benzylic, this could cause the stereocontrol to be less than complete during the necessary double inversion (net-retention) *N*-substitution steps due to the participation of S_N1-type reaction pathways. Thus, one AD-based synthesis endured an incomplete (6 : 1) regioselection.[7a] while another suffered from a modest (4 : 1) diastereoselection.[7b]

Our solution to this double-faced problem is to use the cyclic iminocarbonate rearrangement, which we reported recently (Scheme 1).[12] The rearrangement converts *syn*-diols (AD products) to protected *syn*-amino alcohols in a one-pot operation: the configurations at both carbinol carbons are retained. Thus, ethyl *trans*-cinnamate (**1**) was dihyroxylated using AD-mix-α to give the (2*R*,3*S*)-cinnamate diol (**2**, 85% yield, 96%ee[13]), which was subjected to the cyclic iminocarbonate rearrangement protocol. While the original procedure (using tetrabutylammonium bromide as the nucleophile) had been initially reported to produce preferentially the C-2 nitrogen isomer (**4a**, the "wrong" regioisomer for the synthesis of the side-chain, 1:2.7 regioselectivity),[12a] subsequent works led to a discovery that using LiI nucleophile in acetonitrile/$C_2H_4Cl_2$ reversed the regioselection of the rearrangement toward the desired C-3(benzylic)-nitrogen isomer (**3a**, 3 : 1 regioselectivity).[12b] *Further optimizations of the reaction conditions have now resulted in a great improvement in regioselectivity* (>20 : 1 for the desired isomer **3a**, 82% combined yield) when the rearrangement was performed with MgI_2 as the nucleophile in acetonitrile/$C_2H_4Cl_2$ at room temp. No diastereomeric products were observed and the enantiomeric purity of the product was confirmed to be as high as that of the starting diol **2**.[13] The stereochemical integrity, therefore, was fully maintained during the rearrangement. The high diastereoselectivity is presumably due to the fact that the rearrangement (**2** → **3a**) involves an intramolecular (cyclic) nucleophilic substitution step and the *syn*-diastereomer, as obtained, is also thermodynamically more stable. Therefore, an S_N1-type reaction pathway, if present at all, would also yield the net retention diastereomer preferentially.[14] For an additional advantage, the desired regioisomer **3a** conveniently crystallized out from the crude product (hexane-ethyl acetate).

The rearranged product, ethyl 1-benzoyl-5-(*S*)-phenyloxazolidin-2-one-4-(*R*)-carboxylate (**3a**), is only a short distance away from the Paclitaxel side chain. It has been reported that various deprotection methods under basic or acidic solvolytic conditions usually remove the *N*-benzoyl group first.[12a] Nevertheless, we sought to cleave selectively the carbonyl group of the oxazolidinone ring, while leaving the *N*-benzoyl group intact, as this would lead to a very atom-economic route to the Paclitaxel side chain. Although our endeavor was met with a partial success, we have devised an efficient synthetic process for our target compound, nonetheless.

When the *N*-benzoyl-oxazolidinone **3a** was treated with Cs_2CO_3 in anhydrous methanol, a mixture of products was obtained, consisting of the oxazolidinone ring-opened product **5** and the *N*-debenzoylated compound **6** in a 1 : 2 ratio (100% combined yield). *N*-Benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester (**5**), the methyl ester of the Paclitaxel side chain, crystallized out from hexane-ethyl acetate (28% yield from **3a**, 97%ee). The *N*-debenzoylated compound, 5-(*S*)-phenyl-



Scheme 1

oxazolidin-2-one-4-(*R*)-carboxylate methyl ester (**6**), recovered from the mother liquor, could be re-*N*-benzoylated to give compound **3b** (BzCl, DMAP, 93% yield), which may be recycled to furnish additional amounts of the product **5**.

Alternatively, the oxazolidinone **3a** was subjected to exhaustive hydrolytic conditions (10% HCl, reflux for 7 days), and without isolation of the resulting phenylisoserine, the crude hydrolyzed product was *N*-benzoylated under Schotten-Baumann conditions to yield *N*-benzoyl-(2*R*,3*S*)-phenylisoserine (**7**) in 77% (from **3a**). The stereochemical integrity was sustained through the harsh and prolonged reaction conditions.[15]

In conclusion, we have achieved a very efficient synthesis of the Paclitaxel side chain, *N*-benzoyl-(2*R*,3*S*)-phenylisoserine, in a three-step sequence employing as key steps the asymmetric dihydroxylation and the regio- and diastereoselective cyclic iminocarbonate rearrangement processes.

Experimental procedure for the MgI_2-catalyzed cyclic iminocarbonate rearrangement. To a solution of (2*R*,3*S*)-cinnamate diol ethyl ester (213 mg, 1.0 mmol) in dichloroethane (15 mL), dibutyltin oxide (305 mg, 1.2 mmol) was added. The mixture was heated to reflux for 4 hr with a concomitant removal of water using a Dean-Stark trap. Benzoyl isothiocyanate (0.187 mL, 1.4 mmol) and triethylamine (0.142 mL, 1.0 mmol) were added and the mixture was heated to reflux for further 2 hr. After it was cooled to rt, the mixture was diluted with MeCN (30 mL) and MgI_2 (304 mg, 1.0 mmol) was added. It was then stirred at rt overnight. Aqueous extractive work-up (EtOAc - *aq.* $NaHCO_3$, *dil.* HCl, then brine) yielded the crude product (277 mg, 82%, > 20 : 1 regioisomeric mixture **3a** : **4a**). Crystallization from hexane-EtOAc produced pure ethyl 1-benzoyl-5-(*S*)-phenyloxazolidin-2-one-4-(*R*)-carboxylate (**3a**, 75%).[16]

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References and Notes

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13. The enantiomeric purity was determined by chiral HPLC (Pirkle column; hexane-^{i}PrOH gradient eluent).
14. When an *anti*(*erythro*)-diol was subjected to the MgI_2-catalyzed rearrangement protocol, the corresponding *syn*(*trans*)-diastereomeric oxazolidinone was obtained, via an apparent *inversion* of configuration at one carbinol carbon. This observation implies a thermodynamic control of stereoselectivity (as opposed to stereospecificity).
15. $[\alpha]_D$ -39.4 (*c* 0.83, EtOH); Lit.[7a] $[\alpha]_D$ 35.5 (*c* 1.07, EtOH). Anal. Calcd for $C_{16}H_{14}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.01; H, 5.36; N, 4.91.
16. A full characterization of this compound has been reported elsewhere (see reference 12a).