Exploration for Large-scale Stereoselective Synthesis of Unusual Amino Acids by using 4-Phenyloxazolidin-2-one as a New Chiral Resolution Reagent

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Individual isomers of β-branched α-amino acids have been stereoselectively and asymmetrically synthesized in high yield by a new method which uses 4-phenyloxazolidin-2-one as a novel chiral resolution reagent acting simultaneously as the auxiliary.

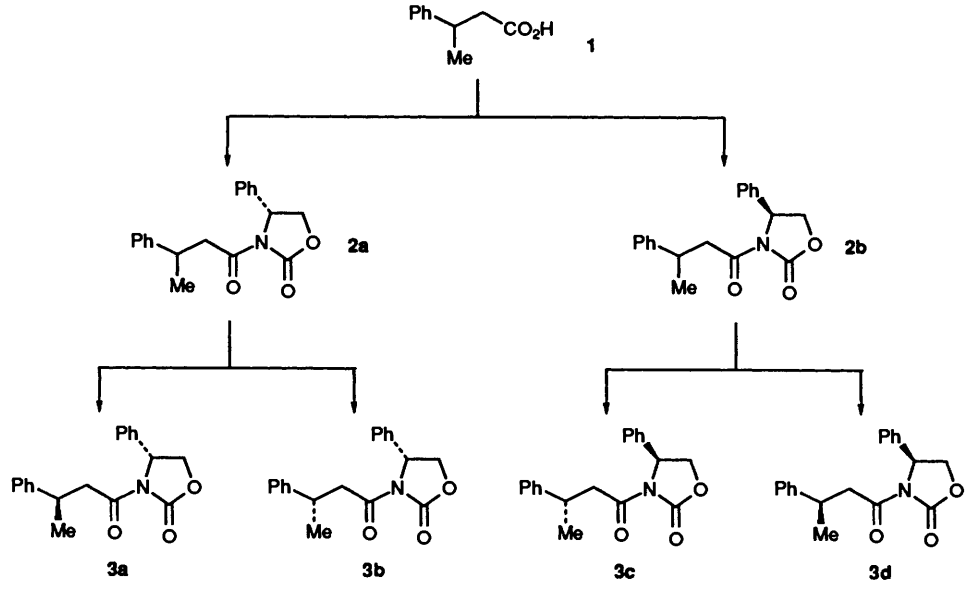
A central goal in peptide and protein research is the development of rational approaches to the design of peptide ligands with specific physical, chemical and biological properties.[1] It has been shown that the use of side-chain conformationally constrained analogues provides valuable insights into the mechanism of interaction and the involvement of amino acid side-chain groups in the binding of peptide ligands to their specific receptors, and consequent signal transduction.[2] Therefore, the asymmetric synthesis of all the individual isomers of unnatural amino acids has importance in achieving completely systematic studies of these targets.[3,4]

The asymmetric synthesis of several series of β-branched unusual amino acids has been studied in this laboratory with respect to synthetic methodologies and procedures.[4] However, the further exploration of these methods for practical and convenient large-scale asymmetric syntheses of these specialized amino acids still remains a central goal to meet the requirements of biologically active peptide molecular design. Here, we describe a new method for the large-scale synthesis of β-branched α-amino acids, in which (4*R*)- and (4*S*)-4-phenyl-oxazolidin-2-one, being used as novel chiral resolution reagents and simultaneously as the chiral auxiliary, provide complete stereoselectivity. Thus, optically pure (4*R*)- and (4*S*)- 4-phenyl-oxazolidin-2-one were coupled to racemic 3-phenylbutyric acid (commercially available) (**1**, Scheme 1), *via* the formation of the mixed anhydride with pivaloyl chloride, to yield either the (4*R*)- or (4*S*)-4-phenyl-3-(3-phenylbutyryl)oxazolidin-2-one **2a** and **2b**, respectively. The resulting diastereoisomeric mixtures were resolved into their optically pure isomers by classical crystallization from EtOAc–hexane (9:1). (4*R*)-4-Phenyl-3-[(3*R*)-3-phenylbutyryl]oxazolidin-2-one or (4*S*)-4-phenyl-3-[(3*S*)-3-phenylbutyryl]oxazolidin-2-one, **3a** and **3c**, crystallized first as the primary product, while **3b** and **3d** remained in solution until, upon further evaporation, they were obtained as a microfine crystalline mass.

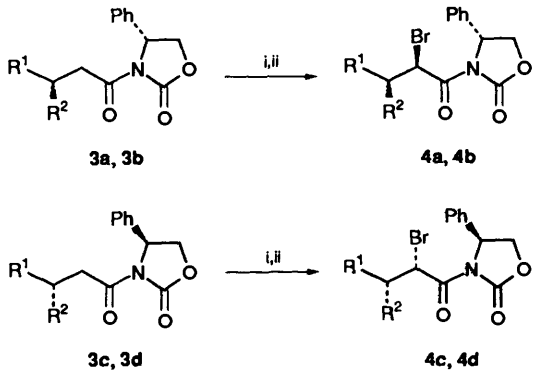
The bromination procedure utilized was similar to that described by Evans and co-workers.[3d] Thin layer chromatography proved to be a convenient method to monitor the reaction employing EtOAc–hexane (3:7). ^{1}H NMR (250 MHz) spectroscopy was used to determine the stereoselectivities of crude products by observation of the sharp α-protons doublets for **4a–d**.

The absolute stereoselectivity of the bromination and the consequent efficiency of induction can be attributed to the sterically hindered phenyl group of the auxiliary, as compared with our initial investigations using the original Evans auxiliary (Scheme 2).

The conversion of **4a–d** into the amino acids **7a–d** is demonstrated in Scheme 3. The bromides **4a–d** were subjected to S_N2 azide displacement using tetramethylguanidinium azide (TMGA) (prepared following a literature procedure[3d,4h]) in acetonitrile solution; the reaction required 6–10 h at room temperature. TLC, employing EtOAc–hexane–MeCN (3:9.5:1), was used to monitor the progress of the reaction. The

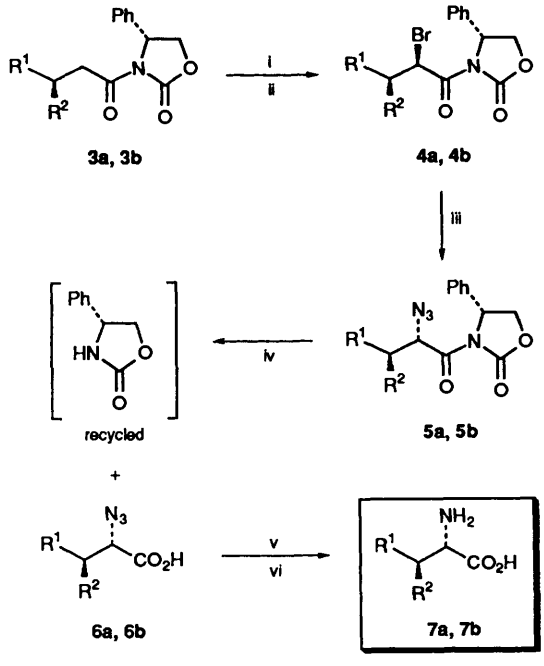


Scheme 1



R^1	R^2	Crude d.e. (%)	Yield (%)
Ph	Me	>99	99
Me	Ph	>99	88
Ph	Me	>99	94
Me	Ph	>99	91

Scheme 2 *Reagents and conditions:* i, Diisopropylethylamine (DIEA), CH_2Cl_2, dibutylboron triflate (Bu_2BOTf), −78 °C; ii, NBS



Yield (%) from compounds 3-7: **7a**(64), **7b**(66), **7c**(73) and **7d**(71)

Scheme 3 *Reagents and conditions:* i, DIEA, CH_2Cl_2, Bu_2OTf, −78 °C; ii, NBS, −78 °C; iii, TMGA, MeCN; iv, LiOH, H_2O_2; v, Pd–C, H_2; vi, ion-exchange resin

solid product appeared as the reactions approached completion, no racemization being observed in any of the cases examined in this study.

The removal and recovery of the chiral auxiliary from **5a–d** was achieved by using LiOH in the presence of hydrogen peroxide without any observed racemization. The resulting azido acids **6a–d** were subjected to hydrogenation (10% Pd–C) at 34–38 psi for 24–48 h. The crude amino acids **7a–d** were purified by ion-exchange chromatography on Amberlite IR-120 plus exchange resin. All physical properties were consistent with those of authentic products synthesized by alternative procedures.[4h,i]

In summary, this new method provides an efficient, and probably a general method for the large-scale asymmetric synthesis of unnatural β-branched α-amino acids. The application of this method to the synthesis of other unusual amino acids has shown preliminary success in our laboratories. The results in this report suggest that the chiral 4-phenyloxazolidin-2-ones, which can be recovered and recycled, may be applied to separate many other branched analogues of carboxylic acids.[5a] It should be mentioned that this method has been successfully applied in chiral separation, NMR and HPLC resolution for BOC α- and β-amino acids in our laboratories which will make it very easy to obtain optically pure both BOC D- and L-amino acids.[5a] It is possible that 4-phenyloxazolidin-2-one might also be used as a chiral probe[5b] in mechanistic studies, the sharp ^1H NMR signals for the oxazolidinone ring protons making identification very clear.

Experimental

To a −78 °C solution of racemic 3-phenylbutyric acid (20.6 g, 0.125 mol) in freshly distilled THF (560 cm^3) was added triethylamine (18.4 cm^3, 0.133 mol) and pivaloyl chloride (16.4 cm^3, 0.133 mol). After the mixture had been stirred for 30 min at −78 °C and 90 min at 0 °C it was recooled to −78 °C and transferred to a slurry of the lithiated (4*R*)-4-phenyloxazolidin-2-one prepared from butyllithium (1.60 mol dm^{-3} in hexane; 70.4 cm^3) and (4*R*)-4-phenyloxazolidin-2-one (16.4 g) in THF (480 cm^3) at −78 °C. The resulting mixture was stirred for 30 min at −78 °C and for a further 30 min at room temperature; it was then quenched with saturated aqueous $NaHCO_3$ (300 cm^3) and worked up by a known procedure[4h] to give the diastereoisomeric mixture (31.0 g). The mixture was crystallized from EtOAc–hexane (v/v 9:1) with **3a** appearing as the first crystals which were filtered off and washed with diethyl ether; **3b** remained in solution and after evaporation yielded a microfine mass with a few crystals of **3a**. The microfine mass was dispersed in diethyl ether (600 cm^3) with crystals precipitating to the bottom of the vessel. These were filtered off and washed by diethyl ether. The combined crystals yielded 11.3 g of **3a**. The microfine mass was crystallized from diethyl ether and the remaining mass was further purified through silica gel chromatography (eluted with 30% EtOAc in hexane) to give 17.4 g of **3b**. The combined yield of **3a** and **3b** is 93% from **2a**.

Acknowledgements

This work has been supported by U.S. Public Service Grant CA 57723 and NIDA Grants DA 06284 and DA04248.

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Paper 4/05024J
Received 16*th August* 1994
Accepted 16*th August* 1994