Pergamon

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Tetrahedron Letters 44 (2003) 4261–4263

TETRAHEDRON LETTERS

A versatile and efficient synthesis of (2*S*)-2-(hydroxymethyl)-*N*-Boc-2,3-dihydro-4-pyridone☆

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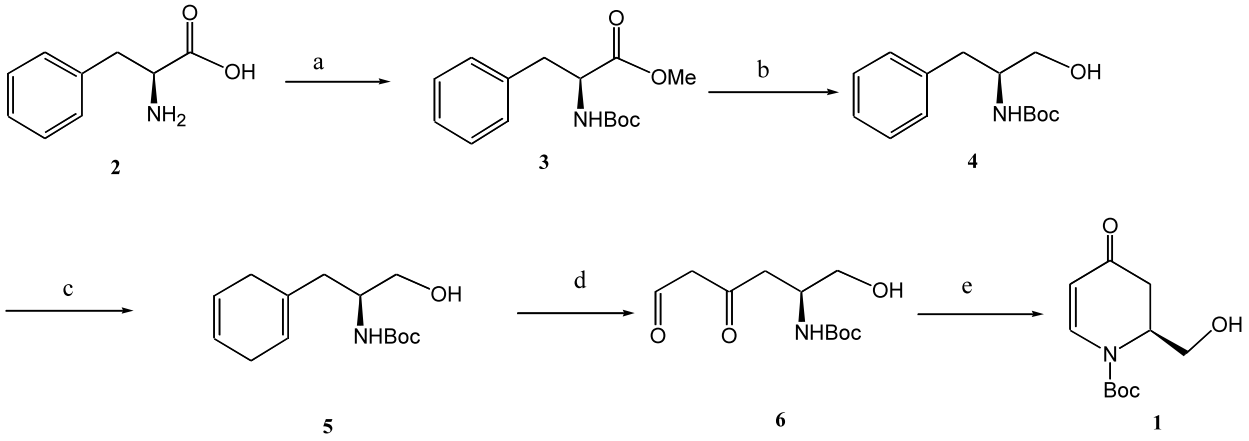
Received 6 January 2003; revised 21 March 2003; accepted 4 April 2003

Abstract—A versatile and efficient method for the preparation of (2*S*)-2-(hydroxymethyl)-*N*-Boc-2,3-dihydro-4-pyridone from L-(−)-phenylalanine **2** utilising the aromatic system as a masked β-keto aldehyde was developed. The key step in the sequence is an intramolecular cyclisation of **6** to give 2,3-dihydropyridin-4-ones.

2,3-Dihydro-4-pyridones and their *N*-acyl derivatives are interesting building blocks for a large variety of nitrogen-containing heterocycle syntheses. The amino-enone moiety can be used in various reactions leading to key intermediates and is also particularly useful in the synthesis of biologically active compounds and alkaloids.[1] Therefore, some general methods for the synthesis of chiral dihydropyridones have been reported. Comins and co-workers synthesised dihydro-4-pyridones with the use of organometallics and 1-acyl pyridinium salts.[2] Dallemagne et al. converted β-aryl-β-amino acids to dihydropyridones via δ-aryl-δ-amino-β-ketoketones and also by condensing the β-aryl-β-amino acids with β-ketoesters.[3] Another method involves the reaction of aromatic imines with the Danishefsky's diene (hetero Diels–Alder reaction) in the presence of a chiral catalyst to form dihydropyridin-4-ones.[4] A racemic synthesis of dihydropyridones by the condensation of a Schiff's base with β-diketones has also been reported.[5] In particular the chiral dihydropyridones of Type **1** (Scheme 1) have been utilised for the synthesis of some chiral piperidine skeletal natural products e.g. (+)-dienomycin C,[2e] (+)-deoxoprosopinine,[2g] and 1-deoxynojirimycin.[2d] Herein we report a novel and simple method for the synthesis of **1** starting from 3-aryl-2-aminopropanol **4** (obtained from aryl amino



Scheme 1. *Reagents and conditions*: (a) AcCl, MeOH, reflux, 3 h, then $(Boc)_2O$, Et_3N, THF, 0°C–rt, 8 h, 95%; (b) LiCl, $NaBH_4$, EtOH, THF, 0°C–rt, 12 h, 82%; (c) Li, (100 equiv.)/liq. NH_3, THF, −78°C, EtOH, 1 h; (d) O_3, EtoAc, −78°C, 1.5 h, then H_2, $Pd(OH)_2$ rt, 3 h; (e) PPTS/THF, −20°C, 1 h, 43% (overall yield for three steps).

☆ IICT Communication Number: 021206.

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0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00888-8

acids) in three steps, using Birch reduction and ozonolysis.[6]

Compound **4** is commercially available and can also be easily prepared from L-(−)-phenylalanine in three steps. L-(−)-phenylalanine **2** was converted to *N*-Boc-methyl ester **3** in the presence of acetyl chloride and methanol followed by treatment with $(Boc)_2O$. The resultant ester **3** was reduced to alcohol **4** using $LiBH_4$. Birch reduction of **4** gave the corresponding dihydro derivative **5** which on ozonolysis followed by quenching the resultant ozonide with $H_2/Pd(OH)_2$ yielded the β-keto aldehyde **6**. Compound **6** without isolation was subjected to acid-catalysed cyclisation to give the dihydro-4-pyridinone **1**.[7]

This method is novel and general in nature to obtain the skeleton of a 2,3-dihydro-4-piperidinone, by using an appropriate amino-aryl precursor.

Acknowledgements

A.S.K. thanks the CSIR, New Delhi for a research fellowship (S.R.F.). One of the authors (B.H.) thanks the UGC, New Delhi for financial assistance. We also thank Dr. J. S. Yadav and Dr. G. V. M. Sharma for their support and encouragement.

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7. **Typical experimental procedure**: (2*S*)-2-(hydroxymethyl)-*N*-(*tert*-butoxycarbonyl)-2,3-dihydro-4-pyridone, **1**
To a solution of lithium (5.57 g, 796.7 mmol) in liquid ammonia (200 mL) at −78°C (cooling was maintained with acetone/dry ice in a cold finger and cold bath) was added *N*-Boc-phenylalaninol **4** (2.0 g, 7.96 mmol) in dry THF (15 mL). The acetone/dry ice bath was replaced by a CCl_4/dry ice bath and stirred for 2 h, after which time the reaction mixture was cooled to −78°C. The blue solution was stirred for 1 h and dry EtOH (10 mL) and solid NH_4OAc (5.0 g) was added and the reaction mixture was brought to rt. After all the ammonia had evaporated the residue was partitioned between EtOAc/H_2O. The aqueous layer was separated and extracted with EtOAc (2×20 mL) and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo to afford *N*-Boc-dihydro derivative **5** (2.54 g) as a colourless oil, which was taken to the next step without any purification. (The crude ^1H NMR showed a 3:2 ratio of dihydroproduct **5** to starting material **4**, both compounds have the same R_f value on TLC).
A dilute stream of ozone was passed into a solution of crude *N*-Boc-dihydro derivative **5** (2.5 g) in EtOAc (25 mL) at −78°C for 1 h, the reaction mixture turned light blue.

The reaction mixture was brought to rt then flushed with oxygen. To the solution was added $Pd(OH)_2$ (0.018 g) which was then stirred under a hydrogen atmosphere for 3 h. The reaction mixture was filtered through Celite and concentrated to give *N*-Boc-β-ketoaldehyde **6** which was immediately used in the next step.

To a solution of *N*-Boc-β-ketoaldehyde **6** in THF (20 mL) at −20°C, PPTS (0.025 g) was added and the resulting mixture stirred under nitrogen for 1 h. The reaction mixture was poured onto an ice-cold solution of $NaHCO_3$ and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with water (50 mL), brine (20 mL), dried (Na_2SO_4), concentrated and purified by column chromatography to afford **1** (0.54 g) as a syrup and *N*-Boc-phenylalaninol **4** (0.59 g) was also recovered. Based on recovery the overall yield for the three steps was 43%.

Spectral data for compound **1**: $[\alpha]_D^{25} = -26.96$ (*c* 1.8, $CHCl_3$); IR (KBr, cm^{-1}): 3477, 3256, 2915, 1730, 1599.4, 1469, 1342, 1289, 1216, 1146, 1071, 985, 858, 764, 630; ^1H NMR (200 MHz, $CDCl_3$): δ 1.56 (s, 9H), 2.57 (d, 1H, $J = 21.3$ Hz), 2.85 (dd, 1H, $J = 7.6$, 21.3 Hz), 3.62–3.90 (m, 2H), 4.62–4.78 (m, 1H), 5.25 (d, 1H, $J = 7.6$ Hz), 7.78 (d, 1H, $J = 7.6$ Hz).; ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.98, 36.77, 53.79, 61.26, 83.83, 105.92, 142.65, 151.64, 192.95; MS (*m*/*z*): 227 (M+), 171, 154, 127, 96, 86, 57, 41.