A new process for the synthesis of (*2S*,*3S*)-2-ethyl-3-methylvaleramide

Cuifen Lu, Taotao Lu, Qunqi Nie, Guichun Yang and Zuxing Chen*

Hubei Collaborative Innovation Center for Advanced Organochemical Materials & Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules, Hubei University, Wuhan 430062, P.R. China

A new process for synthesis of (*2S*,*3S*)-2-ethyl-3-methylvaleramide has been developed via the key step of a diastereoselective alkylation reaction using non-cross-linked polystyrene (NCPS) supported (*4S*)-2-phenylimino-2-oxazolidine as a chiral auxiliary. This method is efficient with the target product obtained in 99.24% ee and 38.4% overall yield and the chiral auxiliaries can be recovered quantitatively by simple filtration.

Keywords: synthesis, (*2S*,*3S*)-2-ethyl-3-methylvaleramide, chiral auxiliary, diastereoselective alkylation

Valnoctamide (2-ethyl-3-methylvaleramide, Nirvanil®, VCD), endowed with anticonvulsant properties, is used clinically as a mild tranquiliser in several European countries.[1] Valnoctamide contains two stereogenic carbon atoms and exists commercially as a mixture of four stereoisomers. Bialer and co-workers have demonstrated that individual VCD stereoisomers exhibits different pharmacokinetics and/or pharmacodynamics profiles, and their preclinical testing showed that the (*2S,3S*)-2-ethyl-3-methylvaleramide isomer ((*2S,3S*)-VCD) is more potent and selective in various pain and antiepileptic models.[2–4]

Recently optically pure (*2S,3S*)-VCD has been synthesised by several researchers.[5–9] Bialer and co-workers have reported a stereoselective synthetic method for both stereoisomers (*2S,3S*)-VCD and (2*R*,3*S*)-VCD using chiral oxazolidinone auxiliaries.[5] This method required the use of the highly reactive and expensive alkylating agent ethyl triflate due to the low nucleophilicity of the enolate. Later Li and co-workers developed an efficient and scaleable synthesis of (*2S,3S*)-VCD using (1*S*,2*S*)-pseudoephedrine as a chiral auxiliary.[6] Although kilogram quantities of (*2S,3S*)-VCD can be provided, the high cost of the auxiliary and the problems encountered with its recycling are major drawbacks. Analogously, Yang and co-workers have reported a stereoselective synthetic method for both stereoisomers (*2S,3S*)-VCD and (2*R*,3*S*)-VCD using chiral 2-phenylimino-2-oxazolidine auxiliaries,[7] but they also encountered difficulties in the recovery of chiral auxiliaries. Alexakis and co-workers have recently reported a highly enantioselective synthetic method by the asymmetric copper-catalysed addition of dialkylzinc to enals followed by organocatalysed one-pot aldehyde α-functionalisation.[8] However, separation of the organocatalyst from the product is still the issue that needs to be addressed in this method. Chen and co-workers have reported a synthetic method for (*2S,3S*)-VCD by a stereoselective catalytic reaction under the catalysis of a bio-enzyme.[9] A bio-enzyme is a kind of highly effective biological catalyst, but high temperature, acid, alkali and heavy metal ions can lead to deactivation.

The non-cross-linked polystyrene (NCPS) supported 2-phenylimino-2-oxazolidine chiral auxiliary, developed by our group,[10] has proved to be particularly efficient in terms of stereoselectivity and yield in asymmetric alkylation reactions. Most importantly, this NCPS supported chiral auxiliary is easily recovered quantitatively by simply filtration. So it is a good candidate to synthesise optically pure drugs. In a previous paper, we have reported asymmetric synthesis of both (*R*)-and (*S*)-arundic acids,[11] and we now report the synthesis of (*2S,3S*)-VCD using NCPS supported 2-phenylimino-2-oxazolidine as a chiral auxiliary through the key step of a diastereoselective α-alkylation with a stereogenic centre at the β-position which might have an influence on the stereoselectivity of α-alkylation.

* Correspondent. E-mail: chzux@hubu.edu.cn

Results and discussion

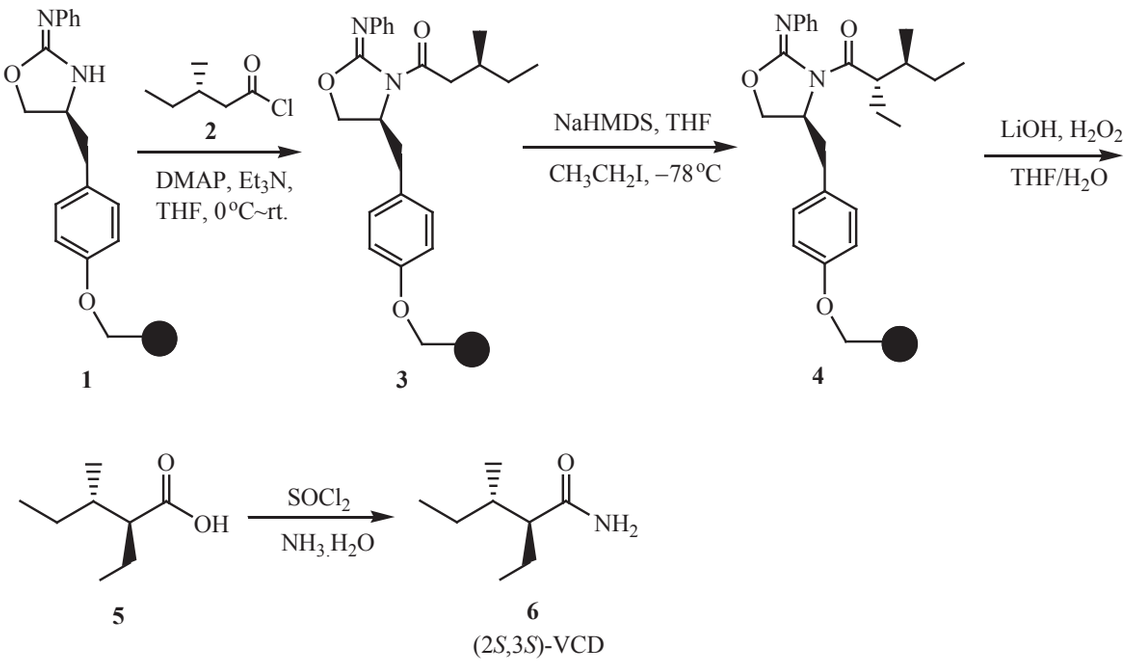
As shown in Scheme 1, the diastereoselective alkylation reaction induced by NCPS supported 2-phenylimino-2-oxazolidine was the key step in the total synthesis of (*2S,3S*)-VCD. First, NCPS supported (*4S*)-2-phenylimino-2-oxazolidine chiral auxiliary **1** reacted with the key intermediate (3S)-methyl valeroyl chloride **2** which was prepared according to a literature procedure, in the presence of Et_3N and DMAP to give NCPS supported (4*S*)-*N*-isovaleryl-2-phenylimino-2-oxazolidine **3**. The enolate of **3** was generated by reaction with NaHMDS at –78 °C for 1 h. followed by the addition of ethyl iodide yielding the alkylated product **4**. The alkylated product **4** was treated with $LiOH/H_2O_2$ at 0 °C in THF/H_2O to afford (*2S,3S*)-2-ethyl-3-methylvaleric acid **5** along with the recovery of the chiral auxiliary **1**, while the endocyclic cleavage problem may be overcome by deploying the more nucleophilic species LiOOH for hydrolysis.[12] (*2S,3S*)-2-ethyl-3-methylvaleric acid **5** was treated with $SOCl_2$ and $NH_3.H_2O$ respectively as previously reported [6] to afford (*2S,3S*)-VCD **6** in good overall yield (38.4%) and high enantiomeric purity (99.24% ee), which was analysed by chiral GC. Moreover, NCPS supported chiral auxiliary **1** was recovered in 92.4% yield. The ee (99.24%) is slightly higher than the ee (99.0%) of (*S*)-arundic acid, so we deduced that the stereogenic centre at the β-position may have a positive effect on the stereoselectivity of α-alkylation.

Conclusion

In conclusion, (*2S,3S*)-VCD was synthesised in 99.24% ee and 38.4% overall yield through the key step of a diastereoselective alkylation using NCPS supported (4*S*)-2-phenylimino-2-oxazolidine as a chiral auxiliary. This method is efficient and the chiral auxiliary can be recovered quantitatively by simple filtration.

Experimental

All organic solvents were dried by standard methods. TLCs were performed on precoated plates of silica gel HF254 (0.5 mm, Yantai, P.R. China). Separations by flash chromatography were performed on 300–400 mesh silica gel (Yantai, P.R. China). Melting points were measured on a WRS-1A digital melting point apparatus. Optical rotations were measured using a sodium D line on WZZ-2B automatic polarimeter. IR spectra were recorded with an IR-spectrum one (PE) spectrometer. ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded with a Varian Unity INOVA 600 spectrometer in $CDCl_3$ by using TMS as an internal standard. GC analyses were carried out on a Shimadzu GC-2010 chromatograph. The column used was an Agilent



Scheme 1 Synthesis of (*2S,3S*)-2-ethyl-3-methylvaleramide.

Cyclodex-B chiral capillary column (30 mm × 0.25 mm × 0.25 μm). The carrier gas was argon, the flow was set at 1.5 mL min^{-1}, injector at 250 °C, column at 120 °C.

NCPS supported (4S)-N-((3'S)-methyl)-pentyl-2-phenylimino-2-oxazolidine (**3**): Et_3N (116 mL, 0.85 mol) and DMAP (18 g, 0.142 mol) were added to a stirred solution of NCPS supported (*4S*)-2-phenylimino-2-oxazolidine **1** (500 g, 0.71 mol, loading: 1.42 mmol g^{-1} polymer) in CH_2Cl_2 (1 L), and then (*3S*)-methyl valeroyl chloride (124 g, 0.92 mol) in CH_2Cl_2 (0.1 L) was added dropwise to the reaction mixture at 0 °C. The resulting mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (0.1 L), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 0.5 L), and then the organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold EtOH and the precipitated solid was filtered and dried at 65 °C for 2 h under vacuum to afford polymer **3** (515 g). IR (NaCl): υ = 1705, 1683, 1510, 757, 699 cm^{-1}; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.9, 158.1, 145.0, 139.2, 130.5, 130.0, 129.2, 128.9, 128.5, 127.9, 125.6, 115.1, 69.9, 56.0, 44.1, 40.3, 31.8, 31.4, 29.3, 29.1, 19.2, 11.1.

NCPS supported (4S)-N-((2'S)-ethyl-(3'S)-methyl)-pentyl-2-phenylimino-2-oxazolidine (**4**): Polymer **3** (515 g) in anhydrous THF (1 L) was added to a dry round-bottomed flask under a nitrogen atmosphere was added. The solution was cooled to –78 °C and 2.0 M NaHMDS (0.42 L, 0.84 mol) was added, and the solution was allowed to stir at –78 °C for 1 h. Then, ethyl iodide (137 mL, 1.7 mol) was added and the solution was stirred for 2 h at –78 °C and progressively warmed to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (0.1 L) and extracted with CH_2Cl_2 (3 × 0.5 L). The combined organic layers were dried with $MgSO_4$, filtered, and most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold EtOH and the precipitated solid was filtered and dried at 65 °C for 2 h *in vacuo* to afford polymer **4** (506 g). IR (NaCl): υ = 1715, 1674, 1510, 758, 701 cm^{-1}; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.9, 158.0, 145.2, 145.1, 130.2, 129.3, 129.1, 128.8, 128.5, 127.9, 127.6, 125.5, 113.6, 112.5, 69.9, 56.5, 44.1, 40.3, 31.8, 31.4, 31.3, 29.2, 29.0, 19.1, 11.1.

(*2S,3S*)-*2-Ethyl-3-methylvaleric acid* (**5**): The polymer **4** (506 g) was treated with LiOH (26.7 g, 1.1 mol) and 30% H_2O_2 (0.38 L, 3.3 mol) at 0 °C in a 4 : 1 mixture of THF/H_2O (1 L). The reaction was stirred at room temperature overnight and then concentrated under reduced pressure. The organic layer was extracted with CH_2Cl_2 (3 × 0.5 L), concentrated, precipitated in cold EtOH, filtered to recover quantitatively the chiral auxiliary **1** (462 g, 92.4% recovered yield). Acidification of the aqueous layer to pH = 1 and extraction with EtOAc furnished the chiral carboxylic acid **5** as a faint yellow oil (64.5 g, 63% overall yield). $[\alpha]_D^{20}$ = +2.24 (*c* 1.45, MeOH), lit.[6] $[\alpha]_D^{20}$ = +2.0 (*c* 1.0, MeOH); IR (NaCl): υ = 1704, 1416, 940 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 2.23 – 2.19 (m, 1H), 1.66 – 1.65 (m, 2H), 1.56 – 1.53 (m, 2H), 1.24 – 1.19 (m, 1H), 0.95 – 0.89 (m, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): 182.2, 52.0, 36.4, 26.5, 22.4, 16.2, 12.1, 11.1.

(2S,3S)-2-Ethyl-3-methylvaleramide (**6**): The chiral carboxylic acid **5** (64.5 g, 0.45 mol) was added dropwise to $SOCl_2$ (36 mL, 0.5 mol) at room temperature, and the reaction mixture was stirred for 1.5 h. After evaporation under reduced pressure to get rid of the excess $SOCl_2$, 25% $NH_3.H_2O$ (0.28 L, 2.0 mol) was added to the residue at 0 °C, and the reaction mixture was warmed to room temperature and stirred for 1 h. The slurry was dissolved in a 1 : 1 mixture of acetone/water (0.4 L) at 65 °C and cooled to 0 °C over 12 h. The solid was collected by filtration and recrystallised from a mixture of petroleum ether and EtOAc (20/1, V_1/V_2) to give (*2S,3S*)-VCD **6** as a white crystalline solid (39.2 g, 38.4% overall yield). Chiral GC indicated 99.24% (*2S,3S*), 0.34% (2*R*,3*S*) and 0.42% (2*S*,3*R*) isomers. M.p. 130 °C, lit.[6] 131.5 °C; $[\alpha]_D^{20}$ = –11.2 (*c* 1.0, MeOH), lit.[6] $[\alpha]_D^{20}$ = –12.1 (*c* 1.0, MeOH); IR (NaCl): υ = 3373, 3188, 2966, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 6.29 (s, 1H), 5.72 (s, 1H), 1.91–1.87 (m, 1H), 1.60–1.51 (m, 4H), 1.20–1.16(m, 1H), 0.94–0.87 (m, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 178.2, 53.9, 36.6, 26.4, 23.0, 16.6, 12.2, 10.9.

We gratefully acknowledge the National Natural Sciences Foundation of China (No. 20772026 and 21042005) and the Natural Sciences Foundation of Hubei Province in China (No. 2010CDA019) for financial support.

Received 15 January 2014; accepted 17 March 2014
Paper 1402403 doi: 10.3184/174751914X13975731462355
Published online: 6 May 2014

References

1 J.E.F. Reynolds, *Martindale: the extra pharmacopoeia*, 31st edn. Pharmaceutical Press: London, 1996; p. 742.
2 S. Barel, B. Yagen, V. Schurig, S. Soback, F. Pisani, E. Perucca and M. Bialer, *Clin. Pharmacol. Ther.*, 1997, **61**, 442.
3 A.J. Hutt and S.C. Tan, *Drugs*, 1996, **52**, 1.
4 N. Isoherranen, H.S. White, B.D. Klein, M. Roeder, J.H. Woodhead, V. Schurig, B. Yagen and M. Bialer, *Pharmac. Res.*, 2003, **20**, 1293.
5 M. Roeder, O. Spiegelstein, V. Schurig, M. Bialer and B. Yagen, *Tetrahedron: Asymmetry*, 1999, **10**, 841.
6 B.-F. Li, R.M. Hughes, J. Le, K. McGee, D.J. Gallagher, R.S. Gross, D. Provencal, J.P. Reddy, P. Wang, L. Zegelman, Y. Zhao and S.E. Zook, *Org. Process. Res. Dev.*, 2009, **13**, 463.
7 G.C. Yang, L.D. Zhang, C.F. Lu, Z.X. Chen and H. Su, 2013, CN 102875407A.
8 A. Quintard and A. Alexakis, *Adv. Synth. Catal.*, 2010, **352**, 1856.
9 J.G. Chen, B.F. Li and T. Sun, 2013, CN 102876744A.
10 F.Q. Hu, D.X. Xia, C.F. Lu, Z.X. Chen and G.C. Yang, *Eur. J. Org. Chem.*, 2010, 5552.
11 C.F. Lu, L.D. Zhang, H. Su, G.C. Yang and Z.X. Chen, *J. Chem. Res.*, 2012, 678.
12 S.D. Bull, S.G. Davies, S. Jones and H.J. Sanganee, *J. Chem. Soc., Perkin Trans., 1*, 1999, 387.