Tetrahedron Vol. 44, No 15, pp. 4793 to 4796, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + 00
Pergamon Press plc

STEREOSELECTIVE SYNTHESIS OF ISOVALINE (IVA) AND IVA-CONTAINING DIPEPTIDES FOR USE IN PEPTIDE SYNTHESIS [1]

K Nebel and M Mutter*

Institute of Organic Chemistry, University of Basel
St. Johanns-Ring 19, CH-4056 Basel, Switzerland

(*Received in Germany* 4 *May* 1988)

Abstract The stereoselective synthesis of isovaline (2-amino-2-methylbutyric acid) and the stereochemical pathway via the key intermediate 2 is described For use in peptide synthesis, this α,α-dialkyl amino acid is incorporated into N-protected dipeptide derivatives in high yields. Special emphasis was put on the upscaling-problem

Due to their pronounced helix-inducing potential, some α,α-dialkyl amino acids have attracted great attention in the design of peptides with tailor-made conformational features [2] Several routes for the stereoselective synthesis of these conformationally constrained amino acids have been reported over the last few years.[3] However, convenient methods for the preparation in large scale needed for their incorporation into peptides are still lacking.[4] We describe here an efficient procedure for the synthesis of both enantiomers of isovaline, the optically active homologue of the well-known Aib [5] Further, their conversion into optically active dipeptide derivatives which are key intermediates in peptide chemistry is reported.[6]

This synthesis takes advantage of the "principle of self reproduction of chirality centers", introduced by Seebach et al [3a], a strategy exhibiting some favourable features. Both enantiomers of the amino acid are equally well accessible (vide infra). The diastereoselectivities of the alkylations are good Additionally, the by-products of the hydrolysis of heterocyclic compounds such as 2 can easily be removed For the synthesis of an α,α-ethyl-methyl amino acid, the oxazolidinone derivative 1 proved to be a most useful intermediate In particular, the high stereoselectivity in the ring closure reaction and the ease of isolation should be mentioned.[7,8]

Starting from 0 9 mol of D-alanine, 1 was obtained with a 50% yield by a single crystallization step from CH_2Cl_2/Et_2O in the final stage of the synthesis [7,8a] No other diastereomer could be detected by ^{1}H-NMR (400 MHz) and the $[\alpha]_D^{20}$ -value of -220° (c=1 0, $CHCl_3$) agrees well with the one obtained by Fadel and Salaün for the enantiomer of 1

Alkylation of the lithium enolate of 1 with ethyl iodide was first unsuccessful, possibly because of ring-opening leading to an N-acyliminium species [9] A further problem was the lability of configuration at C(2).[10] Alkylation without cosolvent or working with a delay period of 1 hr or more between generation of the enolate (either by means of LHMDS or LDA) and addition of the electrophile resulted in varying amounts of racemic alkylation product (2 and its enantiomer). Moreover, the diastereoselectivity of the alkylation reaction could not be determined by standard gas chromatographic analysis because of extensive and non-reproducible signal-doubling (presumably due to epimerization at C(2))

Elaboration of this key step resulted in the procedure outlined in scheme 1 (see also experimental procedures), giving access to compound 2 in comparatively good yields[3,8]

Scheme 1

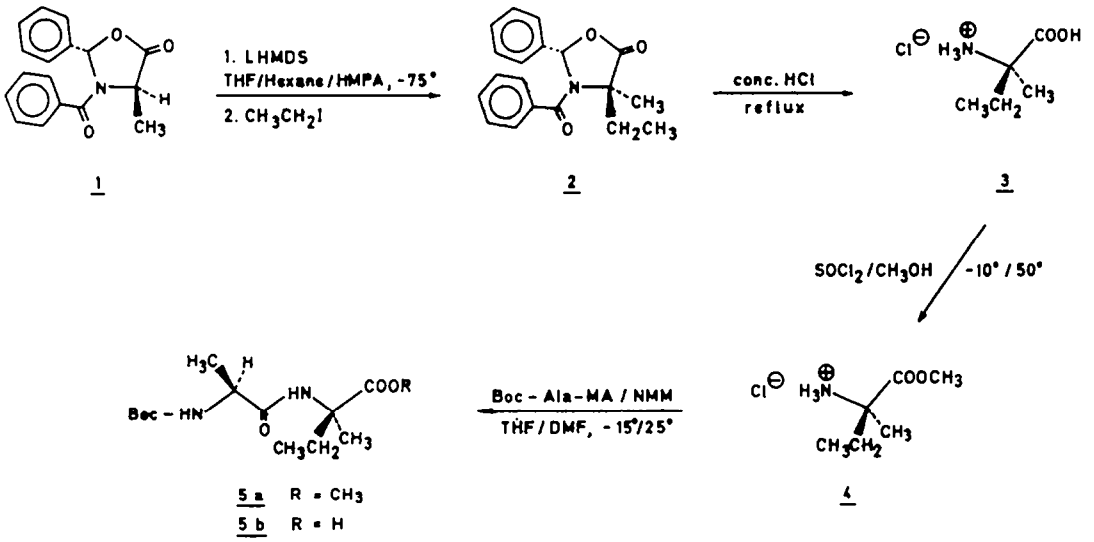
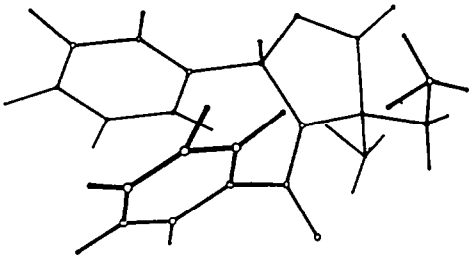


Figure 1



Perspective drawing of 2, derived from the X-ray analysis.

The relative configurations at C(2) and C(4) in compound 2 were determined by single crystal X-ray analysis (figure 1).[11] The absolute configuration at C(4) was established by gas chromatographic analysis of a derivative of 3 on a chiral phase[12] and by optical rotation ($[\alpha]^{20}_{D}$ = -10.5°, c=2, H_2O, raw product 3). According to these results the electrophile (EtI) approaches the enolate from the Re-side, i.e. trans to the phenyl group at C(2) (ul-1,3-course of reaction). Furthermore, this allows us to deduce the stereochemistry of 1 (as well as its enantiomer described by Fadel and Salaün[8a]) on grounds of the stereochemical course of similar alkylation reactions.[3a]

After hydrolysis of 2, a simple extraction with CH_2Cl_2 removed the by-products benzaldehyde and benzoic acid[7] The hydrochloride 3 was converted into the methyl ester 4 by the method of Brenner[13] (the reaction was repeated twice). From 4 the N-protected dipeptide derivatives 5 were prepared (cf experimental procedures) As the N-protected dipeptide acid 5b is the reagent of choice for the incorporation of Iva into larger peptides[6], the main purification was carried out at this stage Gas chromatographic analysis (W. A. König) of a hydrolysate of 5b gave an ee-value greater than 99.8% for isovaline

We may conclude that the procedure described represents an efficient strategy for the synthesis of optically pure isovaline-containing derivatives for use in peptide synthesis. Most notably, this approach can equally be applied to the synthesis of the enantiomer of 3, i.e. (S)-isovaline hydrochlori-

de, by starting from L-alanine for the preparation of the enantiomer of 1. We have focused on the work with (R)-isovaline as this enantiomer is especially suited for stabilization of a right-handed helix[5b]

Experimental Procedures

Melting points were determined with a hot-block microscope and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. NMR spectra were measured on Varian EM 390 and VXR 400 spectrometers using tetramethylsilane as internal standard. Mass spectra were determined on a VG 70-250.

(2S, 4R)-3-Benzoyl-4-ethyl-4-methyl-2-phenyl-1,3-oxazolidin-5-one (2).
A 0.4 M solution of 1 in THF/HMPA (4:1, v/v) at -75° C was added over 20 minutes by Ar-pressure to a pre-cooled (-75° C) solution of LHMDS (lithium hexamethyldisilazide) in THF/hexane (3:1, v/v, 0.4 M). After 10 minutes 1.5 eq. of freshly distilled ethyl iodide was added in one portion. The mixture was stirred at -75° C (3 hrs) and then allowed to warm up to room temperature overnight. Half-sat. NH_4Cl-solution was added and the THF removed in vacuo. Then, Et_2O was added and the phases separated. The organic layer was washed with $NaHCO_3$- and half-sat. NaCl-solutions. After drying (Na_2SO_4), filtration and removal of the solvent, the raw product was suspended in Et_2O (2 could also be purified by crystallization from isopropanol). Compound 2 was obtained with a 90% yield from 240 mmol of 1. A ds-value greater than 95% was estimated by ^{1}H-NMR (400 MHz) for the raw product. By means of a gas chromatographic analysis (W. A. König) of a hydrolysate of 2 less than 0.1% of (S)-Iva was found.
^{1}H-NMR (DMSO-D_6, 60° C, δ/ppm): 7.4-7.05 (10H, m), 6.91 (1H, s), 2.45-2.2 (1H, broad); 1.95-1.8 (4H, m), 0.99 (3H, t, J=7.5Hz). **^{13}C-NMR** (DMSO-D_6, 60° C, δ/ppm): 174.1, 168.2 (broad), 136.3, 135.8, 129.6, 129.3; 128.3, 128.0; 126.6, 125.9, 89.4; 63.6; 28.6 (broad), 23.9 (broad), 8.2. **MS** (CI, NH_3, m/z): 310 (m^++1), 294, 264, 210; 162; 160, 122, 108; 105, 94, 85, 72. **IR** (KBr, ν/cm^{-1}): 3060, 2970, 2930, 2870; 1785, 1650. $[\alpha]_D^{rt}$=-181° (c=1.2, $CHCl_3$). mp=141-142.5° C. $C_{19}H_{19}NO_3$ requires C,73.77; H,6.19, N,4.53. Found C,73.61, H,6.22, N,4.47.

(R)-Isovaline hydrochloride 3 (HCl*(R)-Iva-OH).
150 mmol 2 were suspended in 500 ml conc. HCl-solution. After an argon flush, the mixture was heated under reflux for 3 hrs under Ar. After filtration and removal of the HCl-solution, the white precipitate was dried over P_2O_5/KOH. The raw product (quantitative yield) was converted into the ester without further purification.

(R)-Isovaline methylester hydrochloride 4 (HCl*(R)-Iva-OCH_3).
Freshly distilled $SOCl_2$ (1.1 eq.) was added slowly at a temperature <-5° C to a solution of 3 and dry CH_3OH (7.5 eq.). The mixture was heated under reflux for 3 hrs. Thereafter, 1 eq. of $SOCl_2$ was added at a temperature <-5° C, followed by heating under reflux (2 hrs). This was repeated once. The solvent was removed in vacuo, then 7.5 eq. of dry CH_3OH were added and evaporated. 4 was obtained with a nearly quantitative yield and used without purification in the synthesis of the dipeptides.
Free isovaline methylester ((R)-Iva-OCH_3) was obtained by the following procedure: 4 together with 1 eq. dicyclohexylamine was thoroughly mixed and distilled at 10 Torr. The yield (50 mmol) was 65% (from 3).
^{1}H-NMR (DMSO-D_6, 50° C, δ/ppm): 3.61 (3H, s), 1.75-1.65 (2H, broad), 1.63-1.43 (2H, m), 1.18 (3H, s), 0.78 (3H, t, J=7.5 Hz). **^{13}C-NMR** (DMSO-D_6, 50° C, δ/ppm): 177.4 (s), 57.6 (s), 51.5 (q), 33.7 (t); 25.4 (q); 8.3 (q). $[\alpha]_D^{rt}$=-9.2° (c=3.0, $CHCl_3$). bp_{10Torr}=55-62° C.

Boc-L-Ala-(R)-Iva-OH (5b).[14]
A 0.5 M solution of 4 and 1 eq. NMM (N-methyl-1,4-morpholine) in DMF was added after 3 minutes to the pre-formed mixed anhydride (MA) of Boc-alanine and isobutyl chloroformate (1 eq., 1 M) together with 1 eq. NMM in THF at -15° C. After 1hr at -15° C, 0° C and room temperature resp., the usual work-

up gave 5a as a viscous oil Hydrolysis of 5a in CH_3OH/2 M NaOH (2:1, v/v, 3 eq. base) for 90 minutes at 40° C gave pure 5b (30 mmol) with a 80% overall yield from 2 after workup and crystallization from CH_3CN or CH_3NO_2.

^{1}H-NMR (DMSO-D_6, 25° C, δ/ppm) 12.7-12.5 (1H, broad), 7.60 (1H, s); 6.99 (1H, d, J=7.5Hz); 4.0-3.8 (1H, m); 2.0-1.7 (2H, m); 1.38 (9H, s); 1.35 (3H, s); 1.15 (3H, d, J=7Hz); 0.73 (3H, t, J=7.5Hz) **^{13}C-NMR** ($CDCl_3$, 25° C, δ/ppm): 176.9 (s), 172.7 (s), 156.0 (s); 80.6 (s); 60.9 (s), 50.1 (d), 29.1 (t); 28.3 (q); 22.7 (q), 18.6 (q), 8.4 (q). **MS** (FAB, glycerol, m/z): 289 (m^++1), 233; 215; 189, 187, 133; 118; 93. **IR** (KBr, v/cm^{-1}) 3370; 3290; 2980; 2940, 2880; 2540, 1720, 1630 $[\alpha]_D^t$=-45° (c=1.2, CH_3OH). $C_{13}H_{24}N_2O_5$/0.37.CH_3NO_2 (^{1}H-NMR) requires: C,51.65, H,8.14, N,10.68 Found: C,51.34; H,8.27; N,10.36. Gas chromatographic analysis (W.A. König) of a hydrolysate (6M HCl, 110° C, 24 hrs) of 5b (^{t}Bu-NH-CO-Iva-O-^{i}Pr derivative) on a XE-60-L-valine-(S)-α-phenylethylamid phase gave an ee-value >99.8%.

Boc-L-Ala-(S)-Iva-OH.

This diastereomer of 5b was obtained with a 75% yield (250 mmol) according to the described procedure. However, crystallization from AcOEt was most convenient.

^{1}H-NMR (DMSO-D_6, 25° C, δ/ppm): 12.6-12.5 (1H, broad); 7.64 (1H, s); 6.95 (1H, d, J=7.5Hz); 4.0-3.8 (1H, m), 1.95-1.7 (2H, m), 1.38 (9H, s); 1.36 (3H, s); 1.16 (3H, d, J=7Hz); 0.74 (3H, t, J=7.3Hz). **^{13}C-NMR** (DMSO-D_6, 25° C, δ/ppm): 175.0 (s), 171.7 (s); 154.9 (s); 78.0 (s); 58.6(s); 49.7(d); 28.8(t); 28.1(q); 21.9(q), 17.9(q), 8.0(q). **MS** (FAB, glycerol, m/z). 289 (m^++1), 233, 189; 133, 118. **IR** (KBr, v/cm^{-1}): 3360, 3337, 2990, 2950, 2890; 2535, 1725, 1715, 1635, 1540, 1510. $[\alpha]_D^t$=-32° (c=1.1, CH_3OH) $[\alpha]_D^t$=-14° (c=1.0, DMF) mp=162-166° C $C_{13}H_{24}N_2O_5$ requires C,54.15; H,8.39; N,9.72. Found: C,54.27, H,8.49, N,9.70

Acknowledgment The authors wish to thank the Swiss National Science Foundation for financial support

References and Notes

1) Dedicated to Professor Ch. Tamm on the occasion of his 65th birthday.
2) a) Fauchère, J.-L. Adv. Drug Res., (1985), 15, 29. b) Mutter, M., Altmann, K.-H. Makromol. Chem.(1986), 145/46, 211
3) a) Seebach, D., Imwinkelried, R., Weber, T. in Modern Synthetic Methods 1986, Vol. 4, Scheffold, R. edit., Springer-Verlag, (1986), p. 125 b) Schöllkopf, U. Top. Curr. Chem., (1983), 109, 65.
4) a) Subramanian, P. K., Woodard, R. W. Synth. Commun., (1986), 16, 337. b) Belokon, Y. N., Bakhmutov, V. I., Chernoglazova, N. I., Kochetkov, K. A., Vitt, S. V., Garbalinskaya, N. S., Belikov, V. M. J. Chem. Soc. Perkin Trans. 1, (1988), 305
5) a) Bosch, R., Brückner, H., Jung, G.; Winter, W. Tetrahedron, (1982), 38, 3579. b) Benedetti, E., Toniolo, C., Hardy, P., Barone, V., Bavoso, A., Di Blasio, B.; Grimaldi, P.; Lelj, F.; Pavone, V., Pedone, C., Bonora, G. M., Lingham, I. J. Am. Chem. Soc., (1984), 106, 8146 c) Alb: Venkataram Prasad, B. V.; Balaram, P. CRC Crit. Rev. Biochem., (1984), 16, 307
6) a) Schmitt, H., Jung, G. Liebigs Ann. Chem., (1985), 321 b) Wipf, P., Heimgartner, H. Helv. Chim. Acta, (1986), 69, 1153
7) Beck, A. K., Seebach, D. Chimia, in press
8) a) Fadel, A.; Salaün, J. Tetrahedron Lett., (1987), 28, 2243. b) Karady, S., Amato, J. S.; Weinstock, L. M. Tetrahedron Lett., (1984), 25, 4337.
9) a) Neelakantan, L. J. Org. Chem., (1971), 36, 2256 b) Speckamp, W. N.; Hiemstra, H. Tetrahedron, (1985), 41, 4367
10) a) Agami, C., Rizk, T. Tetrahedron, (1985), 41, 537 b) 2a, p. 155.
11) We are grateful to M. Zehnder and A. Riesen (University of Basel) for performing the X-ray analysis of compound 2.
12) We thank W. A. König (University of Hamburg) for this analysis.
13) Brenner, M., Huber, W. Helv. Chim. Acta, (1953), 36, 1109.
14) Anderson, G. W.; Zimmermann, J. E., Callahan, F. M. J. Am. Chem. Soc., (1967), 89, 5012.