Novel Anionic Reagents for the Stereoselective Synthesis of γ-Hydroxy-α-amino-acids. An *X*-Ray Crystallographic Study of 2*R*(*S*)-Benzoylamino-*N*-t-butyl-4*R*(*S*)-hydroxy-4-(4-methoxyphenyl)-3*R*(*S*)-methylbutanamide

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The isoxazoline *trans*-ArCH–CH(Me)–C(=NO)CONHBu^t and oxime *threo*-ArCH(OH)CH(Me)C(=NOSiMe$_2$Bu^t)CONHBu^t, prepared respectively from 4-methoxybenzaldehyde (ArCHO) and the anions MeCH=C(N̄–Ō)C(=NBu^t)Ō and MeCH=C(N̄–OSiMe$_2$Bu^t)C(=NBu^t)Ō, were reduced stereoselectively (25:1) and benzoylated to produce the title amide which was characterised by an *X*-ray analysis.

The γ-hydroxy-α-amino-acid unit occurs widely in diverse natural products. Examples include the nikkomycins[1] (neopolyoxins[2]) which are a group of nucleoside chitin synthetase inhibitors produced by *Streptomyces tendae* or *cacaoi* subsq. *asoensis*. The molecules are of interest as potential insecticides.[3] Herein we report a highly stereoselective synthesis[4] of the *N*-terminal amino-acid (**7**) of nikkomycin B (**1**) that illustrates the use of novel carbanion chemistry.

The oxime (**2**)‡ was readily obtained from 2-oxobutanoic acid by reaction with 1,1-dichloro-2-oxapropane,[5] t-butylamine–triethylamine, and finally hydroxyammonium chloride–triethylamine without isolation of any intermediates. Crystallisation gave (**2**) (68%, m.p. 99—100 °C) as a single geometric isomer most probably (*Z*) on account of hydrogen bonding. On reaction with t-butylchlorodimethylsilane and imidazole in *N*,*N*-dimethylformamide (DMF) (**2**) gave the *O*-silyl oxime (**8**) (98%).

The oximes (**2**) and (**8**) were respectively converted into the yellow trianion (**3**) and dianion (**9**) *via* reaction with n-butyllithium or t-butyl-lithium (Scheme 1). Both condensed cleanly with 4-methoxybenzaldehyde to produce, after quenching with acetic acid, the γ-hydroxy-α-hydroxyimino-amides (**4**) (87%) and (**10**) (74%). Although (**4**) was produced with negligible (59:41) diastereoselection the hydroxyimino-amide functionality of the product was of a single (*Z*)-geometry. In contrast (**10**) was obtained as a mixture of geometric isomers and yet with complete (>49:1) diastereoisomeric control. The preparative shortcomings of the trianion (**3**) were, however, readily overcome. The reaction of (**4**) with trifluoroacetic acid gave the isoxazoline (**5**) (100%, m.p. 98—99 °C) exclusively as the *trans*-isomer [^{1}H n.m.r. δ 5.22 (1H, d, *J* 10 Hz)]. In the preparation of (**5**) the isolation of (**4**) is unnecessary: condensation of (**3**) with 4-methoxybenzaldehyde followed by trifluoroacetic acid gave (**5**) (73%).

Reduction of the isoxazoline (**5**) using lithium aluminium hydride followed by benzoylation gave the amides (**11**) (67%, m.p. 177.5—178 °C) and (**12**) (29%, m.p. 175—176 °C). The diastereoselectivity of reduction was dramatically enhanced using either sodium bis(2-methoxyethoxy)aluminium hydride (Red-al) or lithium di-t-butoxyaluminium hydride when (**11**) was formed in yields of 82 and 81% and (**12**) in yields of 5 and 4% respectively. We have also prepared (**11**) (36%) and (**12**) (2%) from the oxime (**2**) directly and without any isolation of intermediates (Scheme 1). As proof of the *threo*-configuration (**10**) was reduced with lithium aluminium hydride and the product amines benzoylated to give only (**11**) (51%) and (**12**) (22%).

Having established these transformations, the oxime (**2**) was readily converted into the nikkomycin B amino-acid (**7**). Reduction of the isoxazoline (**5**) using Red-al followed by hydrolysis with ethanolic hydrochloric acid at reflux gave (**6**) (62%). However, hydrolysis using hydrogen bromide in acetic acid at reflux gave the nikkomycin *N*-terminal amino-acid (**7**) (56%) identical with the authentic material.[4]

(**1**)

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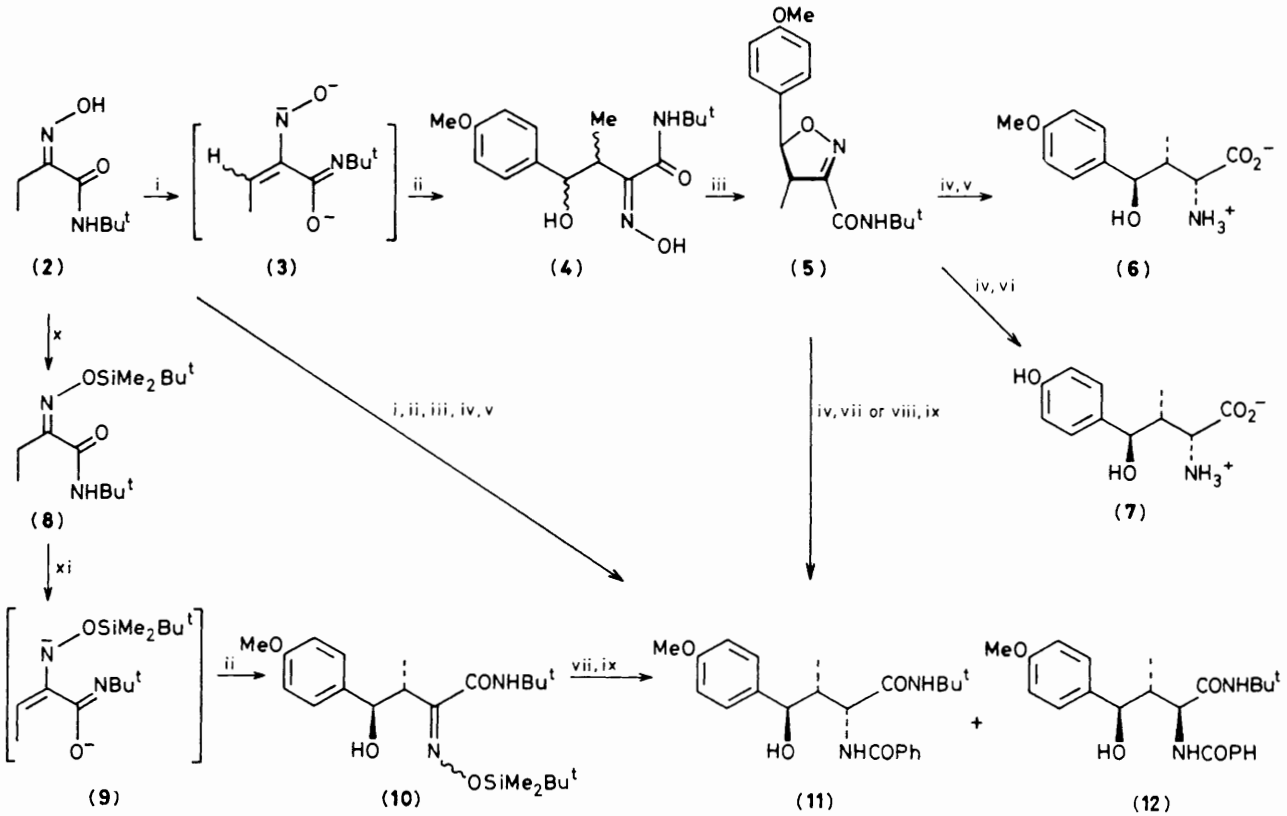
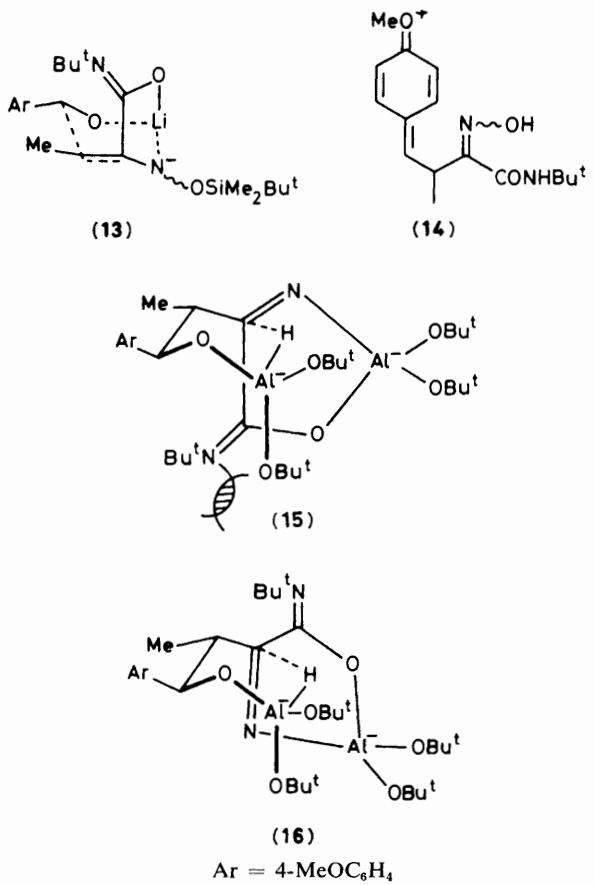
‡ All formulae with the exception of (**1**) refer to racemic modifications.



Scheme 1. *Reagents:* i Bu^{n}Li (3.1 equiv.), tetrahydrofuran (THF), tetramethylethylenediamine (TMEDA), −78 to 0 °C; ii, 4-MeOC$_6$H$_4$-CHO, THF, TMEDA, −78 °C; HOAc; iii, CF_3CO_2H, CH_2Cl_2, 25 °C; iv, Red-al (10 equiv.), THF, −78 to 25 °C; v, HCl, EtOH, heat; vi, HBr, HOAc, heat; vii, $LiAlH_4$ (10 equiv.), THF, −78 to 25 °C; viii, $LiAlH_4$ (10 equiv.), Bu^{t}OH (20 equiv.), THF, −78 to 25 °C; ix, PhCOCl, Et_3N, CH_2Cl_2; x, Bu^{t}SiMe$_2$Cl, DMF, imidazole; xi, Bu^{t}Li (2.1 equiv.), THF.



Ar = 4-MeOC$_6$H$_4$

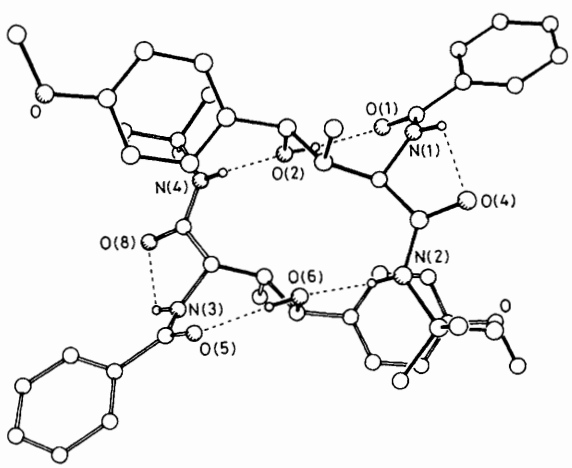


Figure 1. The molecular structure of (**11**) showing the pattern of intra- and inter-molecular hydrogen bonds for the two crystallographically independent molecules. Hydrogen bond distances (Å): O(1) · · · O(2) 2.76, O(1) · · · H 1.89, N(1) · · · O(4) 2.60, H · · · O(4) 2.14, O(5) · · · O(6) 2.73, O(5) · · · H 1.89, N(3) · · · O(8) 2.61, H · · · O(8) 2.15; N(2) · · · O(6) 2.99, H · · · O(6) 2.13, N(4) · · · O(2) 2.98, H · · · O(2) 2.08.

These results require both substantiation and mechanistic comment. All new compounds were fully characterised by spectral and microanalytical data with the exception of (**4**) which could not be obtained microanalytically pure. In addition the structure of (**11**) was unequivocally established by an *X*-ray crystallographic study *vide infra*. We consider that the dianion (**9**) had the (*E*)-geometry and reacted with 4-methoxybenzaldehyde *via* the transition state (**13**). In con-

trast, the trianion (**3**) was a geometric mixture and hence condensed stereorandomly. Secondly, formation of the isoxazoline (**5**) from (**4**) is fully consistent with the intermediacy of the cation (**14**) and cyclisation proceeding *via* thermodynamic control. The production of (**11**) and (**12**) with similar diastereoselectivities from the reduction of (**5**) or (**10**) is consistent with a common intermediate. The diastereoselection of reduction of the isoxazoline (**5**) is opposite to that observed on the lithium aluminium hydride reduction of simple *trans*-4,5-disubstituted isoxazolines.[6] We consider that the reduction of both (**5**) and (**10**) proceeded preferentially *via* the intermediate (**16**) rather than (**15**).

Crystal data: for (**11**), $C_{23}H_{30}N_2O_4$, M = 398.50, monoclinic, a = 17.336(2), b = 10.025(1), c = 26.157(4) Å, β = 102.26(1)°, U = 4 442 Å^3, space group $P2_1/n$, Z = 8 (2 independent molecules in the asymmetric unit), D_c = 1.20 g cm^{-3}. 4 557 Independent reflections were measured on a diffractometer ($\theta < 50°$) using Cu-K_α radiation, and of these 3 701 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The structure was solved by direct methods and refined anisotropically to R 0.046.§ The two molecules adopt identical conformations. Unambiguous location and refinement of all amide and hydroxy hydrogen atoms has revealed a pattern of both intra- and inter-molecular hydrogen bonds (Figure 1). The former, between the hydroxy oxygen O(2) and the amide oxygen O(1), and between the amide nitrogen N(1) and amide oxygen O(4) (crystallographic numbering), serve to stabilise the overall conformation of the molecule. The latter between N(2) and O(6) and between N(4) and O(2) link the two crystallographically independent molecules forming a DL hydrogen bonding dimer.

Clearly the α-hydroxyimino-amide anions (**3**) and (**9**) are useful for the stereocontrolled preparation of γ-hydroxy-α-amino-acids. The highly stereoselective reduction of both the oxime (**10**) and the isoxazoline (**5**) deserve particular emphasis.

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§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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