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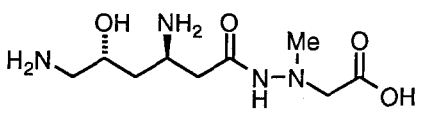
Asymmetric Synthesis of (+)-Negamycin

Stephen G. Davies* and Osamu Ichihara[1]

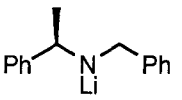
The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK.

Abstract: (+)-Negamycin was synthesised employing the highly diastereoselective conjugate addition of lithium (α-methylbenzyl)benzylamide in the key step. The synthesis was completed in 13 steps starting from ethyl 4-chloroacetoacetate with an overall yield of 24 %.

Negamycin **2** is an unusual pseudopeptide antibiotic which possesses a strong inhibitory activity against Gram-negative bacteria and exhibits very low acute toxicity. Since its discovery by Umezawa *et al.*[2] in 1970 from the culture filtrate of three strains closely related to *Streptomyces purpeofuscus*, negamycin has attracted a great deal of synthetic interest.[3-10] We have previously described methodology for the asymmetric synthesis of a variety of β-amino acid derivatives using the highly diastereoselective conjugate addition of the lithium amides derived from α-methylbenzylamine,[11] which is potentially applicable for the synthesis of the δ-hydroxy-β-lysine fragment of negamycin. Here we wish to report an asymmetric total syntheses of (+)-negamycin, using the asymmetric Michael addition of lithium (*R*)-(α-methylbenzyl)benzylamide **1**[12] as the pivotal step.



(+)-Negamycin **2**



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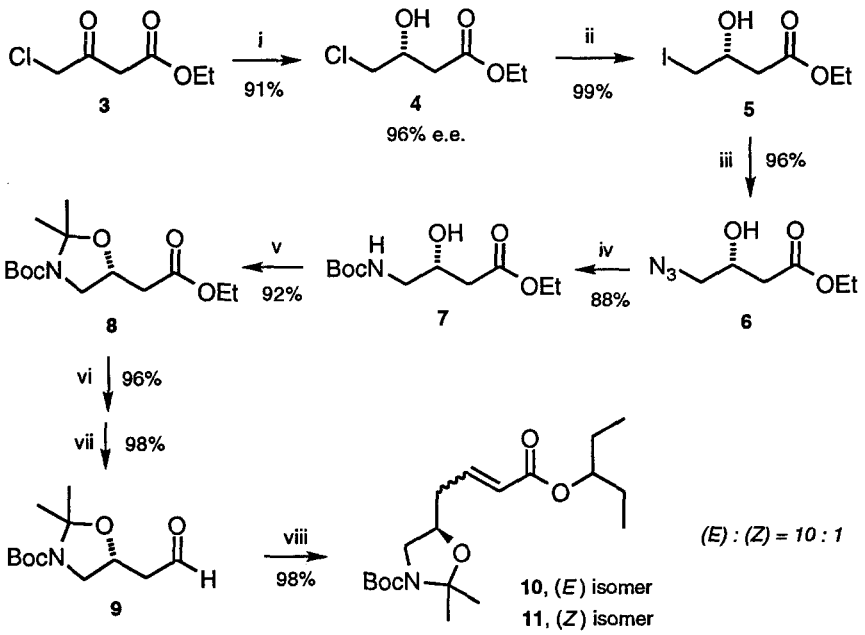
The synthesis of the key intermediate, α,β-unsaturated ester **10**, is illustrated in Scheme 1. The synthesis was initiated with the asymmetric reduction of the commercially available ethyl 4-chloroacetoacetate **3**. The hydrogenation of **3** under 4-5 atm of hydrogen at 100°C using (*S*)-BINAP-Ru(II) complex[13] as a catalyst afforded γ-chloro-β-hydroxy ester **4**[14] in good yield with excellent enantioselectivity (96%).[20] Treatment of **4** with a large excess of sodium iodide in acetone gave an essentially quantitative yield of the iodo ester **5**.[21] The azide **6**[22] was obtained by the smooth displacement of the iodo group in **5** with sodium azide. Hydrogenation of the azide **6** and protection of the resulting amino group were performed by treating **6** with palladium on activated carbon under atmospheric pressure of hydrogen in the presence of di-*t*-butyl dicarbonate,[15] and the *N*-Boc protected amino ester **7** was obtained in 88% yield {$[\alpha]_D^{20}$ +6.6 (c 1.08, $CHCl_3$)}. Acetonide protection of **7** was then effected by treatment with dimethoxypropane in acetone. After chromatographic

purification of the crude product, fully protected γ-amino-β-hydroxybutanoate **8** was obtained in high yield {$[\alpha]_D^{20}$ -26.8 (c 2.7, $CHCl_3$)}. Although the attempt to convert the ester **8** directly to the aldehyde **9** by DIBAL reduction was unsuccessful, the more conservative two step sequence was found to be efficient. Thus, the ester **8** was treated with sodium *bis*(2-methoxyethoxy)aluminium hydride, affording the corresponding alcohol in 97% yield. The alcohol was then subjected to the Swern oxidation to give the desired aldehyde **9** in excellent yield {$[\alpha]_D^{20}$ -27.5 (c 2.05, $CHCl_3$)}.

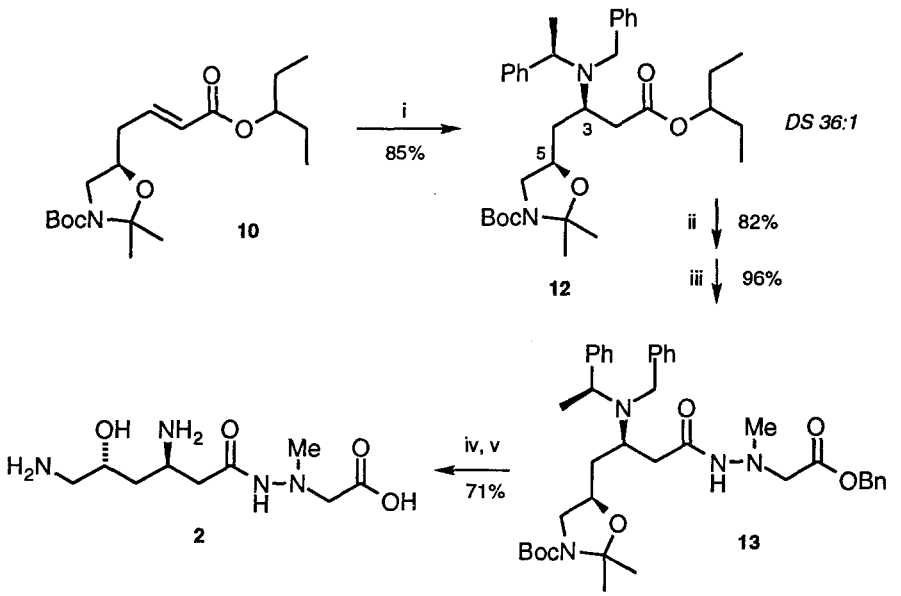


Scheme 1. *Reagents:* i) H_2, (*S*)-Ru[BINAP]Cl_2; ii) NaI; iii) NaN_3; iv) H_2, Pd(C), $(Boc)_2O$; v) $(CH_3O)_2C(CH_3)_2$, CSA; vi) sodium *bis*(2-methoxyethoxy)aluminium hydride; vii) DMSO, oxalyl chloride, $(^iPr)_2EtN$; viii) 3-pentyl-(triphenylphosphoranylidene)acetate

The Wittig reaction of **9** with 3-pentyl (triphenylphosphoranylidene)acetate in toluene at 60°C afforded (**10**+**11**) in essentially quantitative yield. ^1H nmr spectroscopic analysis of the crude products indicated a 10:1 selectivity of double bond formation in favour of the (*E*)-isomer. The (*E*)-isomer **10** {$[\alpha]_D^{20}$ -17.9 (c 2.1, $CHCl_3$)} and the (*Z*)-isomer **11** {$[\alpha]_D^{25}$ -12.7 (c 2.2, $CHCl_3$)} were readily separable by column chromatography on silica gel. With this key intermediate **10** in hand, the critical asymmetric Michael addition of the lithium amide (*R*)-**1**, was attempted (Scheme 2). The α,β-unsaturated ester **10** reacted readily with the lithium amide at -78°C in THF to afford the Michael adduct **12** in 85% yield {$[\alpha]_D^{21}$ -23.9 (c 2.0, $CHCl_3$)}. Determination of the diastereomeric excess of the products by ^1H nmr spectroscopy at ambient temperature was hampered by the broad signals presumably caused by the restricted ^{t}BuOCO-N bond rotation in the adduct **12**. Running the spectrum at 90°C, however, gave satisfactorily sharp signals, and the diastereomeric ratio was determined to be 36:1. Considering the enantiomeric purity of **10** (96%) reflecting the enantioselectivity of the Ru-BINAP reduction of **3**, the major and minor diastereoisomers should be epimeric at C5 not at C3, and the Michael addition of the lithium amide **1** is essentially completely diastereoselective. It should be noted that the sense of diastereoinduction in the conjugate addition of **1** is highly predictable.

Although the absolute configuration of the newly created stereogenic centre at C3 in **12** had not been confirmed at this stage, we assigned the stereochemistry of **12** as shown in the Scheme 2 according to the precedence accumulated in our laboratory, and this was confirmed later by the successful transformation of **12** into negamycin.

Having constructed the δ-hydroxy-β-lysine fragment, our efforts were then devoted to the coupling of the two fragments and completion of the synthesis. LiOH-mediated hydrolysis of the bulky ester moiety on adduct **12** proceeded readily affording the corresponding acid. Assembly of the acid and the hydrazinoacetic acid fragment was achieved by a DCC-mediated coupling reaction. Treatment of the mixture of the acid and the PTSA salt of benzyl (1-methylhydrazino)acetate[16] with DCC in the presence of triethylamine and HOBt at room temperature afforded the coupling product **13** in 82% yield {$[\alpha]_D^{25}$ -9.8 (c 0.8, $CHCl_3$)}. It was also shown that the mixed anhydride method (Et_3N, $ClCO_2Et$, DCM, -15°C, 70%) is also effective for this coupling.



Scheme 2. *Reagents:* i) **1**; ii) LiOH, MeOH/THF/Water; iii) benzyl (1-methylhydrazino)acetate PTSA salt, DCC, Et_3N, HOBt; iv) TFA, THF/Water; v) H_2, $Pd(OH)_2/C$

The *t*-butoxycarbonyl and acetonide protecting groups in **13** were removed by treatment with trifluoroacetic acid in THF/water. The crude product was then subjected to hydrogenolysis without purification. Catalytic hydrogenolysis over palladium hydroxide (Pearlman's catalyst) under 6 atm of hydrogen at ambient temperature removed all three benzyl groups to provide a crude sample of negamycin. Ion-exchange chromatography (Amberlite CG50) afforded (+)-negamycin **2** in 71% yield for the two step sequence $[\alpha]_D^{20}$ +2.7 (c 1.55, H_2O) {lit.[2] $[\alpha]_D^{29}$ +2.5 (c 2, H_2O)}. The spectroscopic and physical data including ^1H and ^{13}C nmr, IR, m.p. and specific rotation for the synthetic material were in excellent agreement with those of the natural product.[4,10,17,18]

In summary, the total synthesis of (+)-negamycin **2** was achieved in an overall yield of 24% over 13 steps starting from the commercially available chloroacetoacetate **3**.

References and Notes

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20. $[\alpha]_D^{21}$ +20.7 (c 7.33, $CHCl_3$) {lit.[14], for (*R*)-**4** of 97% enantiomeric purity, $[\alpha]_D^{21}$ +20.9 (c 7.71, $CHCl_3$)}.
21. $[\alpha]_D^{20}$ +10.0 (c 2.99, EtOH) {lit.[19], for (*S*)-**5**, $[\alpha]_D^{20}$ -10.9 (c 3.0, EtOH)}.
22. $[\alpha]_D^{20}$ +7.1 (c 4.13, MeOH) {lit.[19], $[\alpha]_D^{20}$ +7.4 (c 4.05, MeOH)}.
23. All new compounds, except the aldehyde **9**, exhibited satisfactory spectroscopic (^1H and ^{13}C nmr, IR, MS) and combustion analysis data. The aldehyde **9** was fully characterised as its 2,4-dinitrophenylhydrazone including elemental analysis.

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