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Asymmetric synthesis of a highly functionalized β-amino acid: the key amino acid of sperabillins B and D

Stephen G. Davies * and Osamu Ichihara †

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

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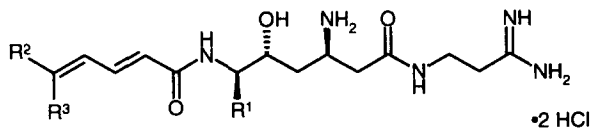
Abstract

The asymmetric synthesis of the highly functionalized (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoic acid, the key amino acid fragment of sperabillins B and D, was achieved by an asymmetric Michael addition of lithium (*R*)-(α-methylbenzyl)allylamide **10** to (*E*,*E*)-2,5-heptadienoate establishing the C-3 stereogenic centre, the information from which was propagated to the C-5 and C-6 centres by a highly stereoselective iodocyclocarbamation reaction.

The sperabillins are novel antibiotics isolated in 1986 from the culture filtrates of *Pseudomonas fluorescens* by the research group of Takeda Chemical Industries.[1] The structures of the sperabillins including the absolute configurations were elucidated by the degradation study by Hida et al.,[2] and confirmed by the total synthesis of sperabillin D by Natsugari et al. in 1991.[3] The primary feature of the structures is a 3,6-diamino-5-hydroxyhexanoic (or heptanoic) acid moiety, and two fragments, 2,4-hexadienoic acid and 3-aminopropanamidine attached to it at the N- and C-termini, respectively, through amide linkages (Fig. 1). In vitro, the sperabillins exhibit considerable inhibitory activity towards Gram-positive and Gram-negative bacteria including antibiotic-resistant strains.[1] Moreover, they show



sperabillins A-D

A **1** ; R¹=H, R²=H, R³=Me
B **2** ; R¹=Me, R²=H, R³=Me
C **3** ; R¹=H, R²=Me, R³=H
D **4** ; R¹=Me, R²=Me, R³=H

Figure 1.

* Corresponding author. E-mail: steve.davies@chem.ox.ac.uk
† Present address; Oxford Asymmetry International plc, 151 Milton Park, Abingdon OX14 4SD, UK.

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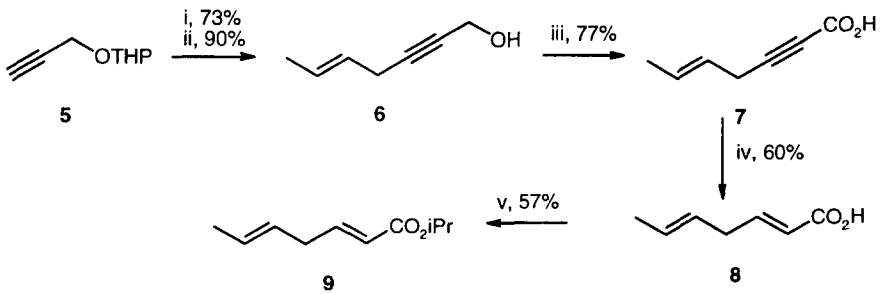
much stronger protective effects in vivo than that expected from the in vitro potencies. They also show inhibitory activity on human tumour cells in vitro and in vivo.[4]

The fact that the key amino acid fragment of sperabillins A and C is the same constituent as that of negamycin made us interested in the syntheses of the sperabillins, since our synthetic route previously developed for the synthesis of negamycin could readily be applied.[5] However, the amino acid **19**, the principal component of sperabillins B and D, is the 6-methyl congener of the key amino acid of negamycin. The additional stereogenic centre at C-6 makes its synthesis even more challenging. Herein, we wish to describe the asymmetric synthesis of **19**. Our synthetic strategy toward the synthesis of **19** involves construction of the stereogenic centre at C-3 via the asymmetric Michael addition of the lithium amide **10**.[6] This stereocentre is then used to control the stereochemistry at C-5 and C-6 via an iodocyclocarbamation reaction, the pivotal step of this strategy.[7,8]

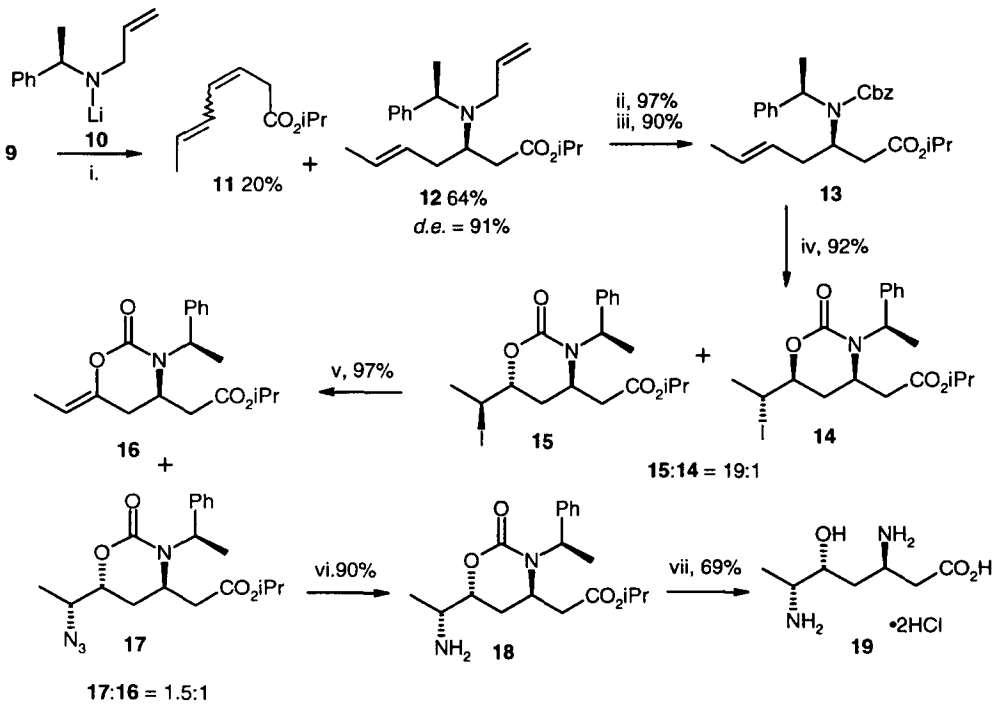
First, our effort focused on the preparation of isopropyl (*E*,*E*)-2,5-heptadienoate **9**. After examining several different approaches, the unconjugated dienoate was prepared as shown in Scheme 1. The Grignard coupling reaction of the *O*-THP protected propargyl alcohol **5** with crotyl bromide in the presence of a copper(I) salt afforded the coupled product in 73% yield.[9] Treatment of the coupled product with a catalytic amount of *p*-toluenesulfonic acid in methanol smoothly removed the THP protecting group, affording hept-5-en-2-yn-1-ol **6** in good yield. Jones oxidation of the ynol **6** provided a 77% yield of the acid **7**. Reduction of the triple bond in **7** using a chromium(II) reagent in DMF/water was completely *trans*-selective and (2*E*,5*E*)-2,5-heptadienoic acid **8** was obtained in 60% yield.[10,11] The coupling constant for the C-2 olefinic proton in the ^{1}H NMR (15.5 Hz) was consistent with the assigned *trans* double bond geometry. Although the initial attempts at esterification of **8** were not encouraging due to extensive isomerization of the double bonds, treatment with boron trifluoride etherate in dry isopropanol afforded the unconjugated dienoate **9** in 57% yield.[12]



Scheme 1. Reagents: (i) EtMgBr, CuCl, crotyl bromide; (ii) PTSA, MeOH; (iii) CrO_3, H_2SO_4; (iv) $CrSO_4$, DMF, water; (v) *i*PrOH, BF_3–Et_2O

The Michael addition of the lithium (α-methylbenzyl)allyamide (*R*)-**10** to the unconjugated dienoate **9** proceeded smoothly at −78°C to afford the adduct **12** with good diastereoselectivity (*d.e.*=91%) in 64% yield, along with a 20% yield of the isomerized ester **11**, presumably via the trienolate, as an inseparable mixture by column chromatography (Scheme 2).[6] Although this mixture could be separated by Kugelrohr distillation, the material was best purified after the removal of the allyl group. Thus, the mixture containing the adduct **12** was subjected to the deallylation reaction using tetrakis(triphenylphosphine)palladium(0) as a catalyst in the presence of *N*,*N*-dimethylbarbituric acid as an allyl group scavenger.[13,14] The smooth deallylation afforded the β-amino ester in good yield after chromatographic purification. The deallylation product was then treated with 6 equiv. of dibenzyl dicarbonate in the presence of a minimal amount of DCM at rt to furnish the desired Cbz derivative **13** in 90% yield.[15] With the requisite Cbz derivative **13** in hand, the crucial iodocyclocarbamation was attempted. Treatment of **13** with I_2 in DCM at 0°C followed by chromatographic purification of the crude products

gave a pale yellow solid (92%); the ^{1}H NMR spectrum of which showed the predominant formation of a single diastereoisomer. Integration of the multiplets due to the C-3 protons of the major diastereoisomer (δ 3.98) and the minor diastereoisomer (δ 3.88) indicated a *d.e.* of 90% for the cyclization. The major diastereoisomer was found to be the desired 3,5-*trans*-isomer **15** {$[\alpha]_D^{25}$ +30.9 (*c* 0.95, $CHCl_3$)} and readily separable from the *cis*-isomer **14** by recrystallization from hexane/EtOH. The C-6 configuration of **14** and **15** was initially assigned assuming *anti* addition across the double bond; this stereochemical assignment was unambiguously confirmed by X-ray crystallographic analysis of **15**.[16]



Scheme 2. Reagents: (i) (*R*)-**10**; (ii) $Pd(PPh_3)_4$, DCM, *N*,*N*-dimethylbarbituric acid; (iii) $(Cbz)_2O$, DCM; (iv) I_2, DCM, 0°C; (v) NaN_3, DMF; (vi) H_2, Pd/C; (vii) 5N HCl, reflux

The observed stereochemistry is consistent with the transition state model shown in Fig. 2. In this model the bulky α-methylbenzyl group occupies a pseudo-equatorial position. The highly unfavourable steric interaction between the α-methylbenzyl and C-2 methylene favours the ester side chain occupying a pseudo-axial position. To avoid a 1,3-diaxial interaction with this axially positioned side chain, the ene moiety occupies a pseudo-equatorial position and attack of the carbonyl oxygen from the back side of the iodonium intermediate generates the stereogenic centres that have the absolute configuration found in **15**.

With the correct stereochemical disposition of the amino, hydroxy and iodo stereogenic centres

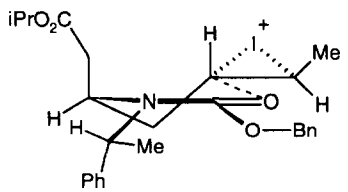


Figure 2.

secured, displacement of the iodide with sodium azide was then attempted. Treatment of **15** with sodium azide in DMF at 120°C afforded the desired azide **17** as well as the elimination product **16** as an inseparable mixture (**17**:**16**=1.5:1). The azide **17** and the elimination product **16** were best separated after reduction of the azide. Thus, the mixture was subjected to hydrogenolysis over Pd/C under one atmosphere of hydrogen to afford the aminocarbamate **18** in almost quantitative yield after column chromatography {$[\alpha]_D^{25}$ +33.6 (*c* 0.67, $CHCl_3$)}. Hydrolysis of the carbamate and ester moieties and concomitant cleavage of the *N*-benzyl bond were achieved by treatment of **18** with 5N HCl under reflux, and chromatographic purification of the crude products using Amberlite XAD-II resin afforded **19** as hygroscopic powder in 69% yield. The analytical data for this material including $^1H/^{13}C$ NMR and specific rotation were in good agreement with those reported in the literature: $[\alpha]_D^{25}$ −3.1 (*c* 0.68, H_2O) {lit. $[\alpha]_D^{25}$ −2.7 (*c* 0.58, H_2O)}.[2]

In conclusion, (3*R*,5*R*,6*R*)-3,6-diamino-5-hydroxyheptanoic acid, the key amino acid of sperabillins B and D, was synthesized as its dihydrochloride **19** in enantiomerically pure form, starting from *O*-THP protected propargyl alcohol **5** in 12 steps.[17] The synthesis demonstrates the synthetic utility of the asymmetric Michael addition of lithium (α-methylbenzyl)allylamide **10** with the stereochemical information being propagated through a highly stereoselective iodocyclocarbamation.

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