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Synthesis of the reported structure of the naturally occurring siderophore nocardimicin B

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ABSTRACT

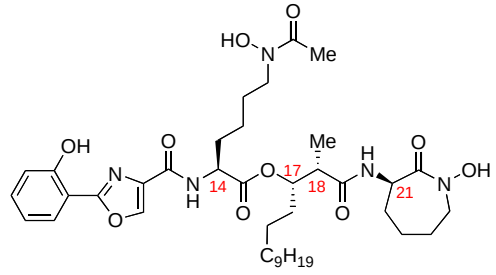
A total synthesis of the reported structure of the naturally occurring siderophore nocardimicin B is reported: the synthetic material appears to be diastereomeric with the natural product.

The nocardimicins, exemplified by nocardimicin B **1**, are a series of nine siderophores isolated from culture broths of *Nocardia* sp.,[1,2] and are the first examples of siderophores that exhibit inhibitory activity against the muscarinic M3 receptor. Structurally, the nocardimicins are closely related to other siderophores such as nocobactin NA,[3] formobactin,[4] the amamistatins,[5–7] the mycobactins[8–11] and brasilibactin A,[12–14] represented by the general structure **2** (with or without the 9,10-double bond) (Fig. 1). Although the full stereochemical assignment of nocardimicin B was not published in the original 2005 Letter,[1] it was subsequently disclosed at a conference in 2006.[15] Thus by a series of degradation experiments, and by comparison with known amino acid derivatives or with β-hydroxy acid derivatives prepared using Evans aldol chemistry, Ikeda et al. proposed the (*S*,*S*,*S*,*R*)-stereochemistry shown in structure **1**. We now report the first synthesis of compound **1**.

Although related siderophores such as mycobactin S,[10] amamastatin-A[6] and -B,[7] and brasilibactin A[13,14] have already been synthesised, our approach to the building blocks of nocardimicin B was somewhat different. Thus the oxazole-4-carboxylic acid **5** was obtained from 2-benzyloxybenzonitrile **3** using the rhodium carbene methodology developed in our laboratory,[16–19] and elsewhere.[20] The nitrile **3** reacted with dimethyl diazomalonate in the presence of a catalytic amount of dirhodium tetraacetate to give 5-methoxyoxazole-4-carboxylate **4** in good yield. Subsequent removal of the unwanted methoxy group was readily achieved by treatment with lithium triethylborohydride,[20] and the ester was hydrolysed to give the oxazole-4-carboxylic acid **5** (Scheme 1). Attempts to convert the nitrile **3** into a 5-unsubstituted oxazole directly by rhodium-catalysed reaction with ethyl formyldiazoacetate were less satisfactory (cf. Ref. 20).

The synthesis of the second fragment, the protected *N*-hydroxylysine derivative **8**, was based on the method developed by Fennell and Miller,[21] using the dibenzoyl peroxide oxidation of Boc-Lys-OMe acetate followed by acetylation to give **6**. Removal of the benzoyl group and reprotection as the *O*-benzyl derivative **7** was followed by hydrolysis to reveal the required carboxylic acid **8** (Scheme 2).

The β-hydroxycarboxylate fragment **14** was prepared using Paterson *anti*-aldol methodology.[22] Thus the (*R*)-ketone **9**, derived from lactate in two steps,[22] underwent boron-mediated aldol reaction with dodecanal under the conditions developed by Paterson to give the *anti*-aldol product **10**, which was subsequently protected as its TBS-ether **11.** Standard manipulation of the aldol product by borohydride reduction to diol **12**, oxidative cleavage to



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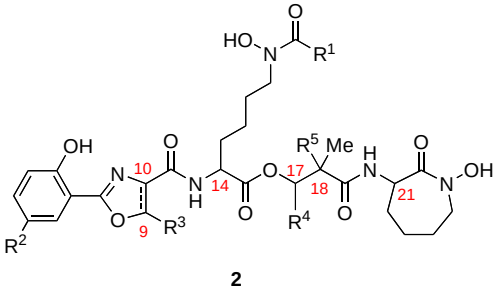

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Figure 1.

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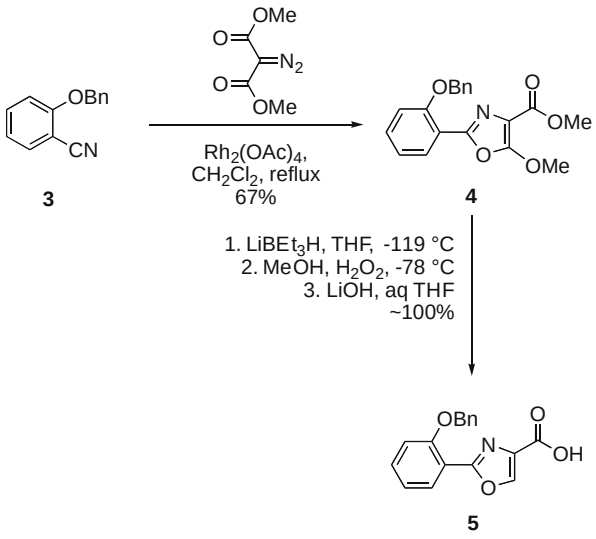
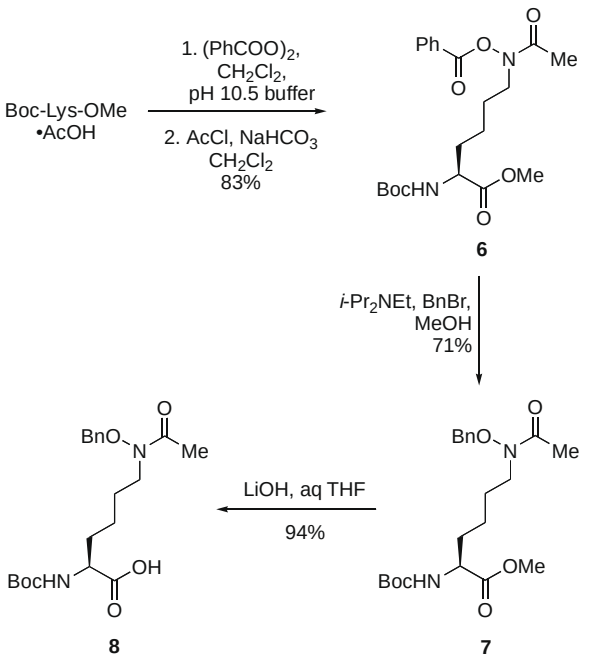
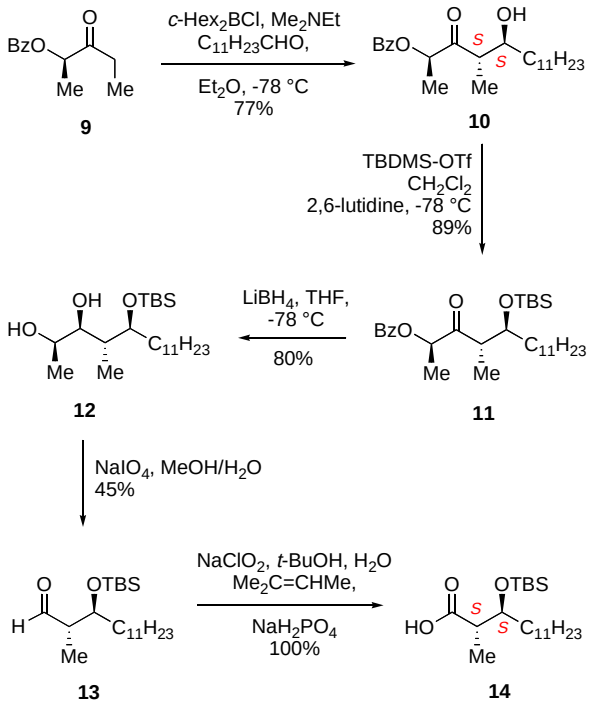


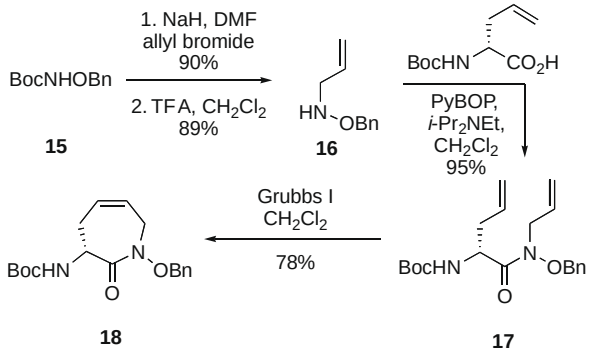
Scheme 1.



Scheme 2.



Scheme 3.



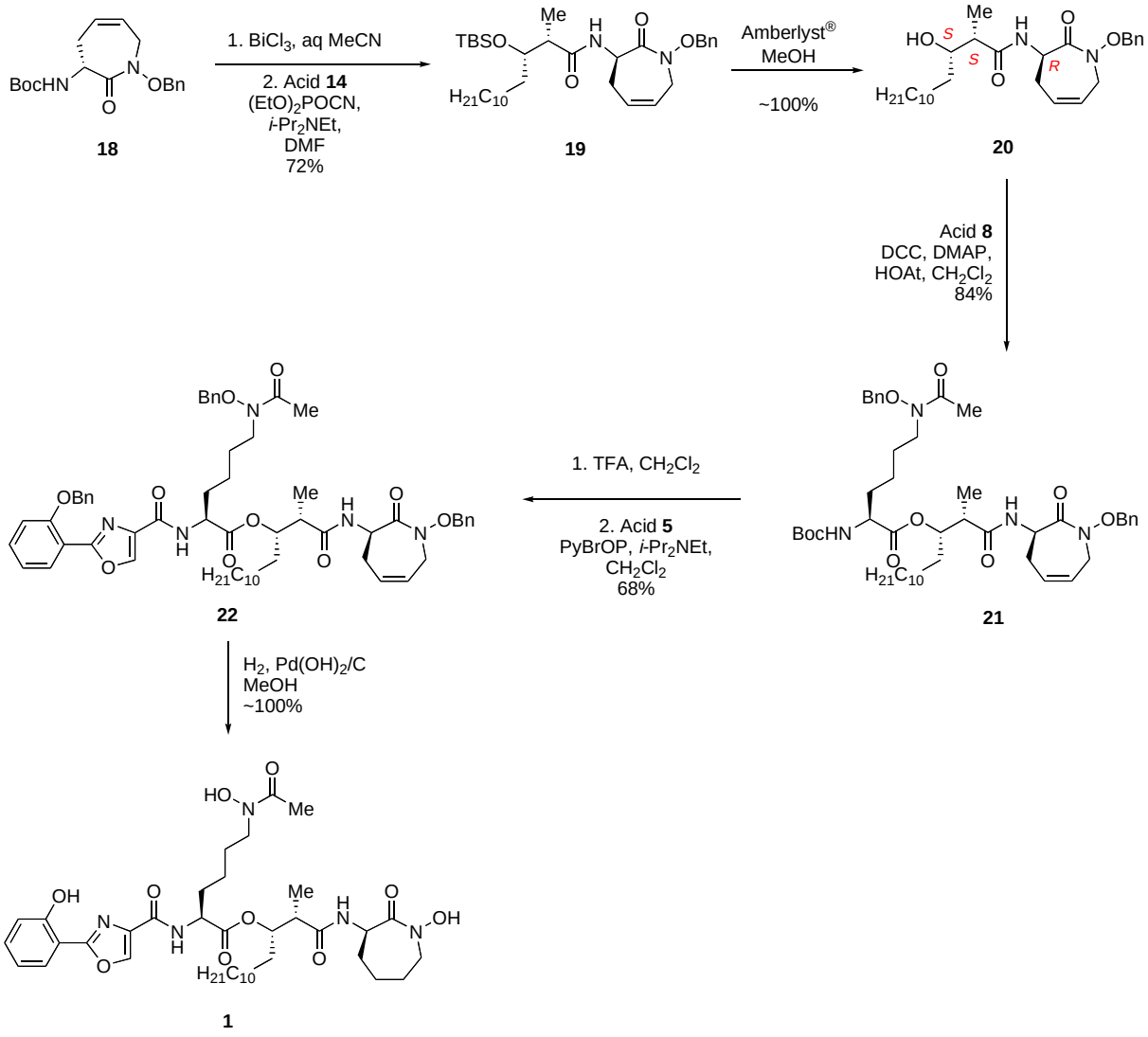
Scheme 4.

aldehyde **13** and a final Pinnick oxidation gave the β-hydroxy acid derivative **14** (Scheme 3).

The final fragment required for the synthesis of nocardimicin B is the caprolactam **18**, and this was prepared from *O*-benzyl-*N*-Boc-hydroxylamine **15** using a ring-closing metathesis (RCM) strategy,[23] as outlined in Scheme 4. Straightforward conversion into *N*-allyl-*O*-benzylhydroxylamine **16** was followed by amide coupling to (*R*)-Boc-allylglycine to give the diallyl compound **17**, treatment of which with Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] resulted in the desired RCM reaction to give the caprolactam **18** in 78% yield (Scheme 4).

With the four key fragments in hand, it remained to connect them by forming the one ester and two amide bonds. The Boc-group in (*R*)-lactam **18** was removed under mild conditions using bismuth trichloride in acetonitrile,[24] and the resulting amine was coupled with the (*S*,*S*)-hydroxy acid derivative **14** to give the amide **19**. Removal of the silicon protecting group was followed by carbodiimide-mediated coupling of the secondary alcohol to the acid **8** to give the ester **21** in good yield. Removal of the Boc-group and coupling to the oxazole acid **5** then gave the complete nocardimicin B framework **22**. Finally, treatment with hydrogen in the presence of Pearlman's catalyst resulted in hydrogenation of the alkene and hydrogenolysis of the three benzyl protecting groups to deliver compound **1** (Scheme 5), the ^{1}H and ^{13}C NMR spectra of which are consistent with the structure.

However there are a number of small differences between the ^{1}H and ^{13}C NMR spectra of the synthetic compound **1** and those reported for the natural product.[1] Furthermore, the optical rotations also differ {$[\alpha]_D = -5.9$ (*c* 0.4, MeOH) and +8.4 (*c* 0.4, MeOH) for natural and synthetic material, respectively}. The final evidence that the compounds differ came from LC–MS studies carried out by Dr. Ikeda. Although both natural and synthetic materials have identical UV and mass spectra, they do not co-elute on HPLC. Therefore the evidence appears to suggest that the compounds are diastereomers of each other, and further experiments are under way to define, more precisely, the nature of the stereochemical dif-



Scheme 5.

ference(s) between the compounds, and whether the structure of the natural product needs to be reassigned.

Acknowledgement

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