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Asymmetric Synthesis of Actinoidic Acid Derivatives

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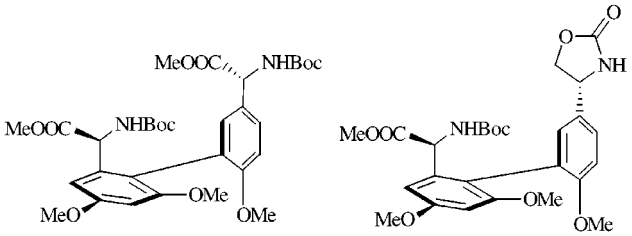
ABSTRACT



Synthesis of fully protected actinoidic acid derivative 3 and selectively protected biaryl bisamino acid 4, intermediates for vancomycin total synthesis, are reported.

Vancomycin (**1**) and related glycopeptide antibiotics have attracted multidisciplinary interest for decades due to their clinic importance.[1] Indeed, together with teicoplanin, they are the drug of last resort for the treatment of infections due to methicillin-resistant *Staphylococcus aureus* and other Gram positive organisms resistant to β-lactam antibiotics. The complex molecular architecture and the recent emergence of vancomycin-resistance phenomenon have rendered them attractive synthetic targets.[2] The intensive research efforts have culminated in three landmark total syntheses of vancomycin aglycon.[3] In connection with our work aimed at developing a new strategy toward the construction of AB−COD rings,[4] an efficient synthesis of suitably protected biaryl diamino diacid units common to the 12-membered AB ring of all glycopeptides of this family was required. Asymmetric synthesis of such compounds was not trivial as one not only has to construct a sterically congested biaryl moiety[5] but also has to introduce two very racemization prone aryl glycines.[6] Controlling the axial chirality posed yet another synthetic problem which has recently been addressed.[7,8]

Previously, we reported a synthesis of racemic actinoidic acid derivative (**2**) employing Meyers's oxazoline chemistry.[9] With a view to developing a more convergent synthesis, we decided to use a suitably protected D-phenylglycinol as a nucleophilic partner in the intermolecular nucleophilic

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substitution reaction (S_NAr). We report now the realization of such a strategy featuring a key coupling reaction between two oxazolines (**5** and **6**, Figure 1). The characteristic feature

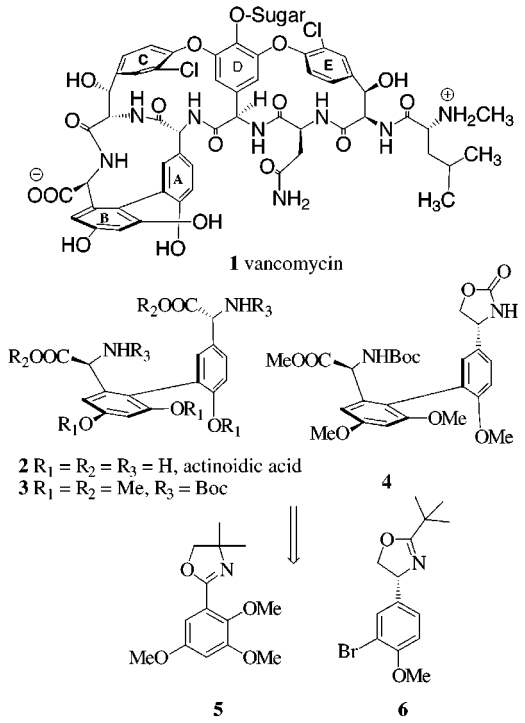


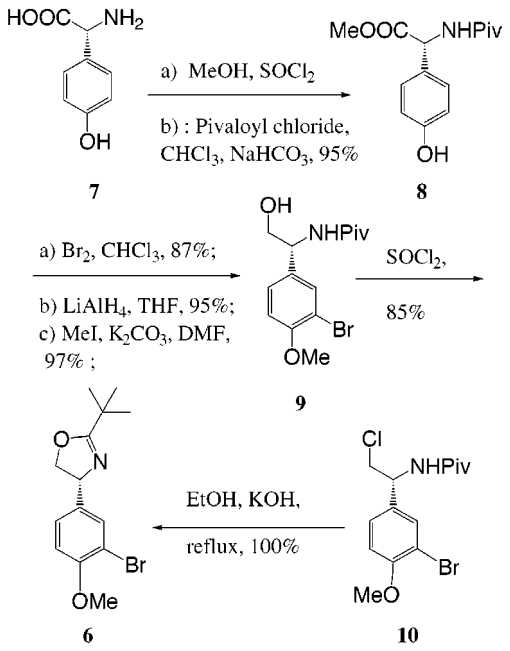
Figure 1.

of this synthesis is the exploitation of two distinct roles of oxazoline, one as an activating group for S_NAr reaction[10] and the other as a protecting group for the chiral amino alcohol derived from D-phenylglycine.[11]

The synthesis of oxazoline (**6**) was shown in Scheme 1. Esterification of D-phenylglycine (**7**) followed by acylation with pivaloyl chloride gave compound **8**, which was transformed into amino alcohol **9** in three straightforward steps. Protection of the phenol group of **9** as its methyl ether was best carried out after reduction of the ester function in order to avoid any exposure of racemization-prone methyl 4-hydroxyphenylglycinate to the basic conditions. Thionyl chloride induced ring closure of hydroxyamide (**9**) afforded oxazoline (**6**) in 85% yield together with a small amount of chloroamide (**10**). The latter can be converted to the desired oxazoline under basic conditions in quantitative yield (KOH, EtOH, reflux).[12]

Formation of Grignard reagent from **6** using the entrainment method[13] followed by addition of oxazoline **5**[9] gave biaryl **11** in 87% yield as a mixture of two atropisomers in

Scheme 1



a one-to-one ratio (Scheme 2).[14] Apparently, chirality transfer from the sp^3 carbon center to give biaryl asymmetry was negligible, which is in fact not unexpected. The coupling reaction has to be carried out under strictly anhydrous and inert conditions in order to get reproducibly high yields. The main side reaction was the demethylation of compound **5**. This coupling reaction is one of the few examples wherein Meyers's reaction has been used for the construction of a biaryl bisoxazoline compound.[10,11] To fully demonstrate the dual role of oxazoline, a selective transformation of these functions was required. After surveying various reaction conditions, the one developed by Feuer[15] was found to fulfill this demanding task nicely. Thus, treatment of biaryl **11** with trifluoroacetic acid in anhydrous methanol gave amino ester **12** which was immediately *N*-protected using CbzOSu to afford *N*-CBz derivative **13** in 77% overall yield. No acyl migration was observed in either step. The B ring oxazoline was perfectly stable under these conditions and was subsequently converted into an aldehyde following a three-step sequence. Thus, heating the acetone solution of **13** in the presence of methyl iodide followed by reduction of the so-produced oxazolinium salt with L-Selectride to oxazolidine and acidic workup (aqueous citric acid) provided **14** in excellent overall yield.[16]

Asymmetric Strecker reaction was projected for the introduction of the second amino acid unit. Phenylglycinol was first attempted as a chiral auxiliary.[5a,17] Although the

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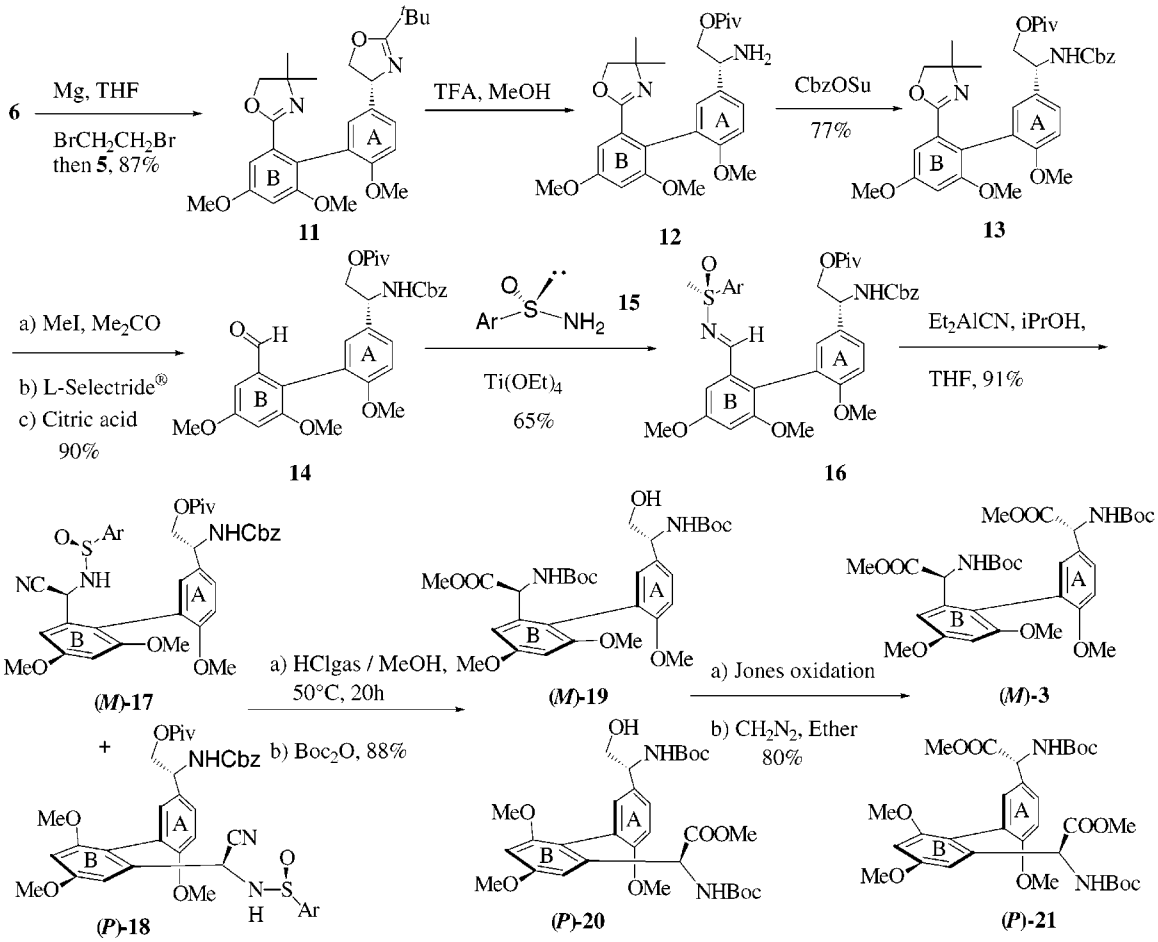
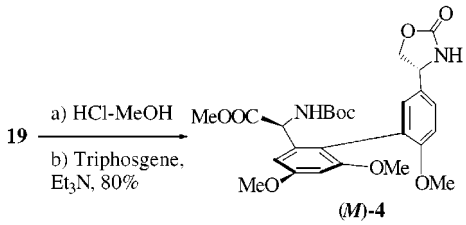
Scheme 2



chemical yield was excellent, chiral induction was moderate at best. Chiral sulfinimines were next examined as substrates in view of their high performance in the asymmetric synthesis of amino acids.[18] Condensation of aldehyde **14** with (*S*)-*p*-toluenesulfinamide (**15**), derived from S_S (−)-Andersen reagent, in the presence of titanium tetraethoxide[19] gave the desired sulfoximine (**16**) which was then reacted with diethylaluminum cyanide in the presence of 2-propanol to provide amino nitrile with excellent diastereoselectivity.[20] Indeed, only two separable diastereomers were detectable from NMR spectra which were assigned and later comfirmed by CD spectra to be two atropisomers. The *S* configuration was attributed to the newly created chiral carbon center according to Davis' empirical model.[18] Hydrolysis of amino nitrile to amino ester was realized by heating a solution of **17** in anhydrous methanol saturated with gaseous HCl to give compound **19** after protection of amino groups. Both *N*-Cbz and *O*-pivaloyl functions were removed under these conditions. Jone's oxidation of alcohol to acid followed by esterification gave, after purification, diastereomerically pure **3** with over a 70% yield.[21] Following the same sequence, **18** was converted to **21** with similar efficiency. Partial epimerization (5−10%) at one of the two chiral carbon centers occurred during this last transformation.[22] However, both **3** and **21** can be separated from their respective epimers, epi-**3** and epi-**21**. Analysis of NMR spectra of these compounds indicated that atropisomerization did not take place. Finally, comparison of the CD spectra of **19** and **20** with those of actinoidic acid derivatives reported in the literature allowed us to determine their axial chirality to be *M* and *P*, respectively (Scheme 3). It follows, therefore, that

Scheme 3



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17 and **18** and **3** and **21** must have the configurations depicted in Scheme 2.[23]

Differentiation of the two amino acid functionalities of **19** is possible. Thus, deprotection of *N*-Boc under mild acid conditions followed by treatment with triphosgene in the presence of triethylamine gave oxazolidinone **4** which can be engaged in the synthesis of the AB−COD ring of vancomycin.

In conclusion, we have developed an asymmetric synthesis of biaryl bisamino acids common to vancomycin-type glycopeptides. The dual role of oxazoline as an activating group for promoting biaryl formation and as a protecting group of chiral vicinal amino alcohols was demonstrated in this synthesis.

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Supporting Information Available: Full experimental details and characterization data for compounds **3**, **4**, and **11**−**21** and the CD specta of compounds **19** and **20**. This material is available free of charge via the Intenet at http://pubs.acs.org.

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