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A Concise and Efficient Synthesis of Protected Actinoidic Acid, the Degradation Product of Vancomycin

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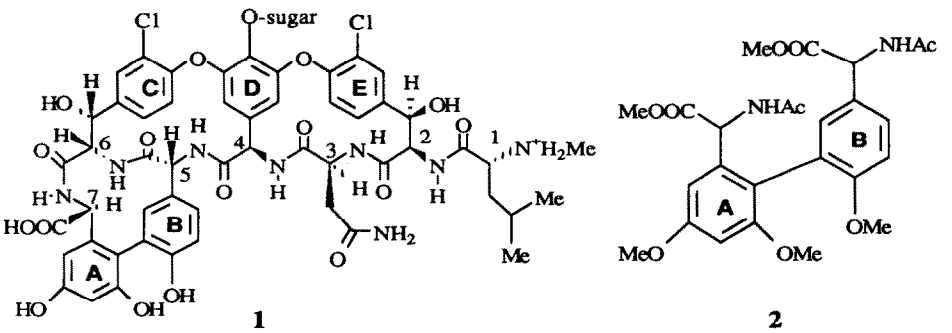
Abstract: Protected actinoidic acid **2**, one of the degradation products of vancomycin, has been efficiently synthesized by a convergent route which is amenable to large scale application as well as to asymmetric synthesis.

Since the discovery of the glycopeptide antibiotic vancomycin **1**[1] (Figure 1), many other structurally related compounds, including ristocetin A[2], teicoplanin[3], avoparcin[4], ristomycin[5] and actaplanin[6] have been isolated and characterized.



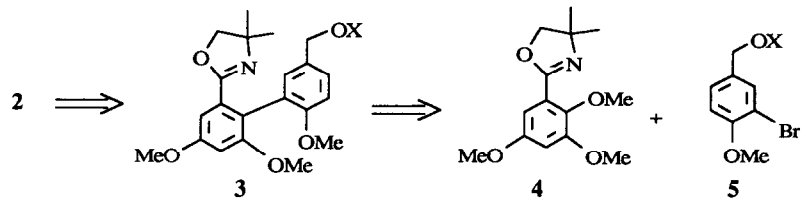
1 **2**

Figure 1

The architectural complexity and biological activity of vancomycin have inspired numerous synthetic works[7]. However, many difficult problems remain in constructing this molecule, one of them is the synthesis of biaryl amino acid **2** (Figure 1, lower left biaryl 5/7 macrocyclic portion) which has been obtained by degradation of all members of the vancomycin family and is essential in forming the binding pocket[1]. One of the major obstacles towards the synthesis of **2** is the construction of the highly substituted biaryl system. From our preliminary studies, we learned that neither the palladium catalyzed cross coupling reactions[8] (between 2-tributylstannyl-3,5-dimethoxy-diethylbenzamide and *o*-bromoanisole) nor the ligand coupling conditions[9] (2-tributylstannyl-3,5-dimethoxy-diethylbenzamide and *p*-*t*-butylphenol in the presence of $Pb(OAc)_4$) nor the

photostimulated $S_{RN}1$ reaction[10] (between 2-bromo-3,5-dimethoxyphenylglycine derivatives and *p*-hydroxyphenylglycine) led to the desired biaryl compound.

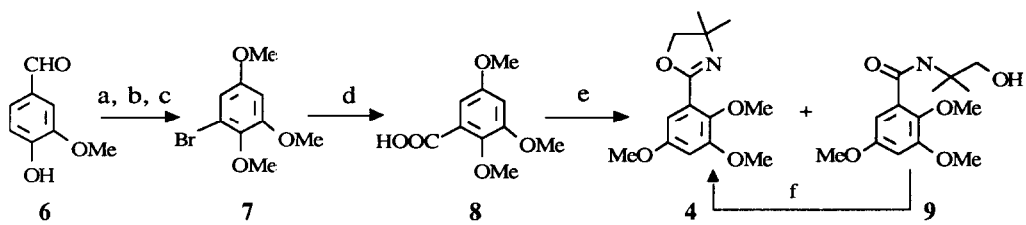
To date, only one synthesis of **2** was reported[11] where the biaryl intermediate was prepared in 25% yield via an intramolecular palladium catalyzed aryl coupling reaction. We describe herein a convergent and efficient synthesis of protected actinoidic acid **2** via the basic strategy depicted in scheme 1.



Scheme 1

Biaryl **3** was considered as key intermediate in our synthesis and Meyer's oxazoline method[12] was envisaged for achieving regioselective cross-coupling between the two aromatic subunits **4** and **5**. The realisation of this scheme in practice is described below.

2,3,5-trimethoxybenzoic acid **8**, the precursor of oxazoline **4**, was prepared starting either from vanillin **6**[13] (scheme 2) or 3,5-dimethoxybenzoic acid[14]. Though both methods gave satisfactory overall yields, the former was preferred on large scale synthesis. The acid **8** was converted to the oxazoline **4** by Vorbrüggen's procedure[15]. The amide **9** which was always isolated as minor product could, however, be quantitatively transformed into **4** by $SOCl_2$ treatment.

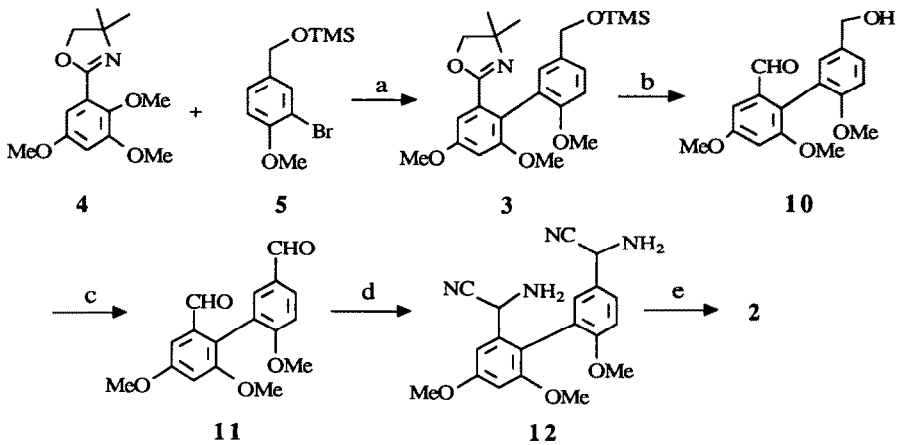


reagents and conditions: a: Br_2, AcOH, 100%; b: KOH, H_2O_2, 92%; c: K_2CO_3, Me_2CO, MeI, 72%;
d: BuLi, THF, CO_2, 92%; e: Ph_3P-CCl_4, Py-CH_3CN, 2-amino-2-methyl-1-propanol, 87%; f: $SOCl_2$, 100%.

Scheme 2

Compound **5** was readily prepared in 77% yield from *p*-hydroxybenzaldehyde by bromination with Br_2 in $CHCl_3$, followed by methylation, reduction and trimethylsilylation. Other bromination conditions, e.g., Br_2 in AcOH, NBS in DMF or CCl_4 gave increased amount of 3,5-dibromo-4-hydroxybenzaldehyde.

With the two precursors for the biaryl coupling in hand, the stage was set for the preparation of the key intermediate **3**. To the Grignard reagent of **5**, prepared by the entrainement method[16], was added 2,3,5-trimethoxyphenyloxazoline **4** and refluxing for 4 hrs furnished *key biaryl coupling product 3 in 80% yield* [17] (Scheme 3). The transformation of oxazoline to aldehyde function was performed in three steps (one pot). Thus, the compound **3** was first converted to oxazolinium salt by heating the acetone solution with methyliodide, which was reduced to the corresponding oxazolidine using L-selectride^R in CH_2Cl_2[18], acidic workup gave the biaryl aldehyde **10** in 70% yield. Using $NaBH_4$ as reducing agent led to a low yield of aldehyde due to the over reduction of oxazolidine to aminoalcohol.



reagents and conditions: a: Mg, $BrCH_2CH_2Br$, THF, 80%; b: i) MeI, Me_2CO; ii) L-selectride^R, CH_2Cl_2; iii oxalic acid, H_2O, 70%; c: PCC, CH_2Cl_2, 79%; d: TMSCN, NH_3, MeOH, 100%.; e: i) MeOH, HCl; ii) Py, Ac_2O, 77%

Scheme 3

The functionalities of compound **10** could allow us to perform two distinct Strecker synthesis in order to introduce two differently protected aminoacids with the appropriate configuration. However, this refinement was not necessary for the synthesis of racemic degradation product **2** and **10** was oxidized to the dialdehyde **11**. A single Strecker reaction carried out with two eq. of TMSCN in MeOH-NH_3[19] on **11** then afforded bisaminonitrile **12** in quantitative yield. This latter, on treatment with methanolic HCl gave the corresponding methyl ester and acetylation (Py-Ac_2O) then afforded the protected actinoidic acid **2** as the mixture of diastereoisomers in 77% yield. One major diastereoisomer could be separated from others by conventional chromatography which had physical data[20] in accordance with that of the degradation product of vancomycin family glycopeptide[4].

In conclusion, the protected actinoidic acid has been synthesized in 18% overall yield featuring a high yield coupling reaction of the Grignard reagent derived from **5** with oxazoline **4**. The synthesis is amenable to

large scale application and can also be implemented in the asymmetric version. This result will be reported in due course.

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20 m.p. 206-208°C.(lit[4]: 199-201°C); IR(cm^{-1}): 3510, 3010, 2950, 1744, 1675, 1603, 1507, 1211; ms(m/z): 502, 470, 459, 443, 401.; ^1H NMR ($CDCl_3$): 2.03, 2.06(s, 6H), 3.61, 3.68, 3.70, 3.75, 3.85 (s, 15H), 5.4 (s, 1H), 5.43 (d, *J*=6.2Hz, 1H), 6.44(d, *J*=2.3Hz, 1H), 6.50 (d, *J*=2.3Hz, 1H), 6.94(d, *J*=8.4Hz, 1H), 7.04 (d, *J*=2.3Hz, 1H), 7.40 (dd, *J*=2.3, 8.4Hz, 1H), 7.75 (brs, 2H). In CD_3OD-one drop of $CDCl_3$: 2.00, 2.03 (s, 6H), 3.59, 3.66, 3.74, 3.82 (s, 15H), 5.28 (2H), 6.54(d, *J*=2.1Hz, 1H), 6.56(d, *J*=2.1Hz, 1H), 6.96(d, *J*=2.3Hz, 1H), 7.01(d, *J*=8.4Hz, 1H), 7.35(dd, *J*=2.3 and 8.4Hz, 1H).

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