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A Concise Route to Biaryls : Formal Synthesis of Biaryl Diamino Diacid (AB Segment) of Vancomycin

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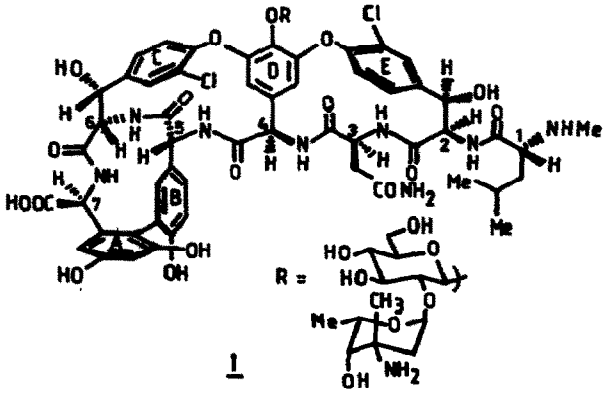
Abstract : An efficient approach to the AB segment of vancomycin involving triphenylphosphine-catalysed coupling of the substituted aryl lithio compound (**13**) with palladium complex (**14**) of aromatic Schiff base derived from 3,5-dimethoxybenzaldehyde is described.

In recent years vancomycin (**1**)[1], has been of much interest to synthetic chemists in view of its structural complexity and biological activity. Although known for over thirty years, no total synthesis of any member of this family has been achieved. However several reports have appeared on the synthesis of some simpler segments of this molecule[2]. In addition our group[3] and Evans group[4] have reported the synthesis of biaryl diamino diacid segment (AB unit), common to all members of this family of antibiotics.



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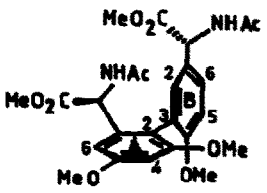
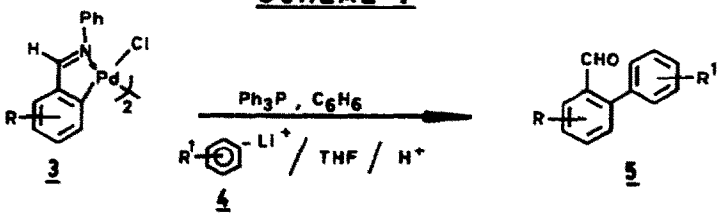


2

In our efforts towards achieving the total synthesis of vancomycin, our plan was to develop an efficient synthesis of the biaryl diamino diacid (AB segment) **2** and the biaryl ether cross linked amino acid segments (CD and E rings). Herein we disclose a highly simplified alternative approach for the synthesis of AB biaryl diamino diacid segment (**2**) based on a methodology[5,6] that Schiff bases derived from substituted aromatic aldehydes could be conveniently ortho alkylated via the five membered palladium complex. The essence of the reaction as shown in the scheme I is that di-μ-chloro-bis[ortho-(N-phenylformimidoyl)aryl)]di-palladium (**3**) reacts with aryl lithium (**4**) in THF at r.t. to give neatly the biaryl **5**.

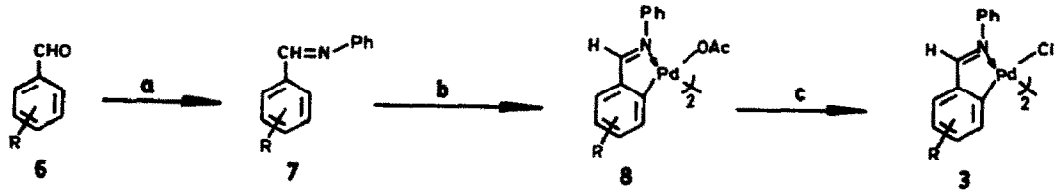
The Pd-complex of the aryl Schiff's base **3** was prepared as shown in scheme II. Schiff's base **7**, obtained by treating the aldehyde **6** with aniline in chloroform, was immediately treated with palladium (II) acetate[7] (see typical experimental procedure) in acetonitrile to afford bis-acetato bridged complex **8**, which on anionic exchange with saturated aq.NaCl in acetone

SCHEME-I



gave the chlorobridged complex **3**. The complex was split into two ligand-co-ordinated monomers with the help of triphenylphosphine and the monomer on treatment with aryl lithium cleanly afforded the functionalised biphenyl **5**. The reaction is quite general as can be seen from the conversion of various aryl aldehydes into biaryls (see table).

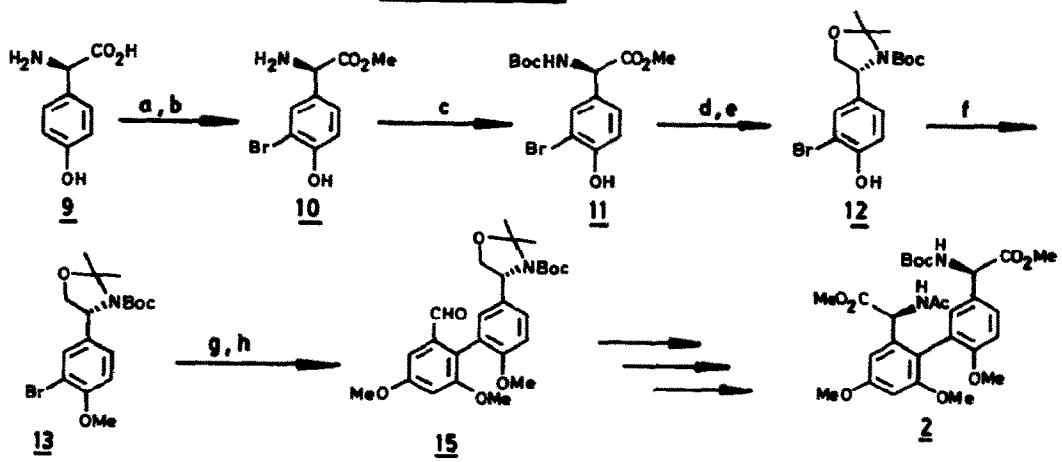
SCHEME-II

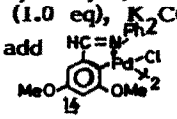


a) Aniline (1.0 eq), $CHCl_3$, RT, 1-2 h, 100%; (b) $Pd(OAc)_2$ (1.0 eq), CH_3CN, RT, 4-5 h, 80%; c) Saturated aq.NaCl, Acetone, RT, 2h, 90%.

Being convinced that a wide range of substituted biaryls can be prepared using this approach, we ventured to apply the methodology to the main project on hand i.e. the synthesis of AB biaryl system present in vancomycin which is shown in scheme III.

SCHEME-III

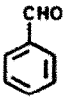
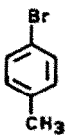
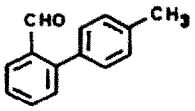
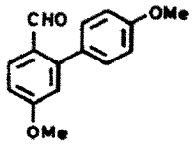
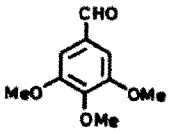
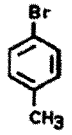
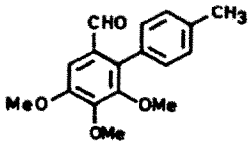
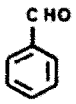
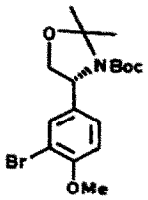
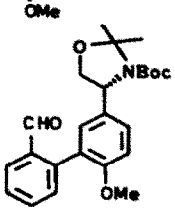
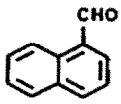
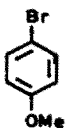
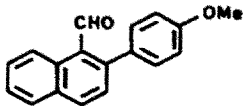


a) Br_2 (1.05 eq), AcOH, RT, 6h; b) $SOCl_2$ (1.2 eq), MeOH, RT, 7h, (90%, two steps); c) $(Boc)_2O$ (1.1 eq), $NaHCO_3$ (1.5 eq), CH_2Cl_2, RT, 2h, 95%; d) LAH (2.0 eq), THF, RT, 10h, 80%; e) 2,2-dimethoxypropane, PTSA, 96%; f) DMS (1.0 eq), K_2CO_3 (1.5 eq), acetone, RT, 3h, 95%; g) BuLi (1.0 eq), -78°C, THF, 30 min, then add  , PPh_3 (2.0 eq), C_6H_6, RT, 2h, 30%; h) 2% HCl, 10 min.

(R)-p-Hydroxyphenyl glycine (**9**) on selective monobromination with Br_2/AcOH followed by esterification ($SOCl_2$, MeOH) gave the bromo ester **10**, which on treatment with Boc anhydride afforded the protected amino ester **11**. Reduction of the ester group with LAH and subsequent protection as acetonide afforded the bromophenol **12**. The phenolic hydroxyl group was then converted to its methyl ether by treatment with DMS/K_2CO_3 in acetone to get **13**, which was lithiated with BuLi and coupled to the palladised-Schiff's base **14**, prepared from 3,5-dimethoxybenzaldehyde (as described in the experimental procedure) to afford the biaryl unit **15**[8]. We have earlier reported[3] a method to elaborate this biaryl aldehyde **15** to the C-terminal biaryl diamino diacid moiety of vancomycin.

Table

The reaction of the palladium complexes of Schiff bases with aryl lithium in the presence of triphenylphosphine

S.No.	Arylaldehydes	Arylhalides	Products	Time (h)	Yield (%)
1				1	48
2				1	43
3				1.5	35
4				2	38
5				1.5	31

Thus, the simplicity and efficacy of this route to biaryls has been extended to the synthesis of AB segment of vancomycin.

Typical Experimental Procedure: To the Schiff base (0.5 g, 2.8 mmol) in acetonitrile (10 ml), $Pd(OAc)_2$ (0.62 g, 2.8 mmol, 1.0 eq.) was added and stirred at room temperature for 3-5 h. Acetonitrile was removed under reduced pressure, diluted with chloroform (50 ml), washed with water. The organic phase was dried (Na_2SO_4), concentrated and purified by column chromatography (silica gel, finer than 200 mesh, 0.5% ethanol in ethyl acetate). Further purified by recrystallisation from dichloromethane/n-hexane to give yellow crystals (75-85%). The Pd-complex was dissolved in acetone (5 ml) and stirred with saturated aq.NaCl (0.5-1.0 hr) to afford the chlorobridged complex which was filtered off. To a suspension of this complex (1.0 mmol) in dry benzene (5 ml), TPP (2.2 mmol) was added and stirred for 30 min. Aryl lithium (2.0 mmol) (prepared from the corresponding aryl bromide and BuLi in THF) was added to the Pd-complex and continued stirring for additional 1-2 hrs. The reaction mixture was hydrolyzed with dil. HCl and extracted into ether. Purification by column chromatography gave the biaryls in 30-48% yield.

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