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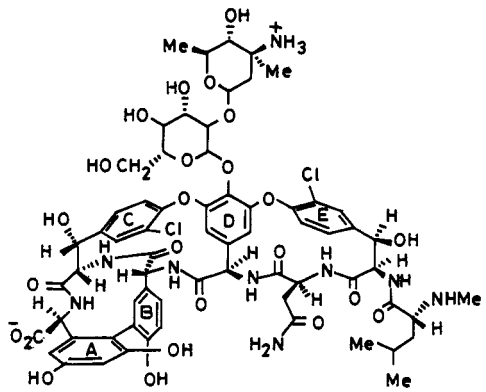
Studies directed on the synthesis of Vancomycin and related cyclic peptides

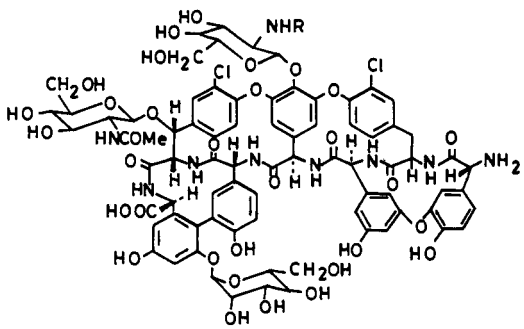
A V Rama Rao

A V Rama Rao Research Foundation
AVRA House, Habshiguda, Hyderabad 500 007, India

In recent years considerable interest has been devoted to the vancomycin group of antibiotics, which include related glycopeptides of biological importance. The most important among them is vancomycin (**1**), the first biologically active antibiotic reported in 1956, and was introduced into medical practice by 1958, much before its structure was elucidated. In addition, recently, teicoplanin (**2**) has also been introduced into clinical use. They are produced by *Actinomycetes*, belonging to the family of *Streptomyces* and *Actinomyces*. They are made up of seven amino acids and are common in all members of this class of compounds (Ref.1).

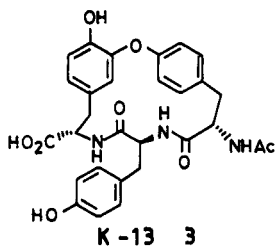


Vancomycin 1

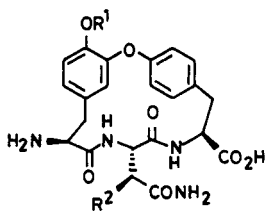


Teicoplanin 2

The molecular complexity of vancomycin provide yet another prospect for organic chemists to test their synthetic ingenuity. During the past one decade several groups have targeted their efforts in this direction. From these attempts, it became more and more prominent, that the existing methodologies have limitations and it is therefore desirable to have new concepts at our disposal to think about synthetic strategies from a new perspective. For this reason, several related cyclic peptides, such as K-13 (**3**), OF 4949 I-IV (**4**) and Bouvardins (**5**), formed the major target of many synthetic chemists (Ref.1). The knowledge gained from the synthesis of these compounds, could in principle be expanded to design the synthetic protocols for the vancomycin family.



K-13 3



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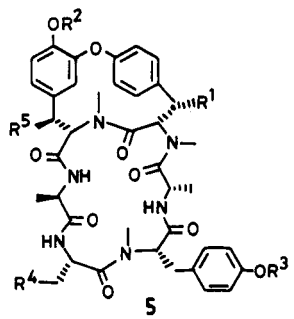


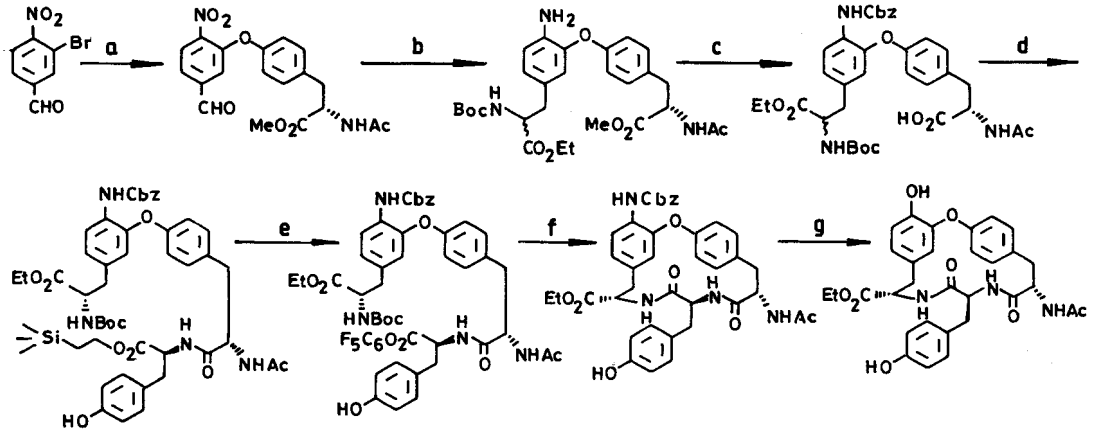
5

The Ullmann reaction has traditionally been a rigorous method for constructing diphenyl ether linkages. The high temperature and long reaction periods have been its major bottlenecks in using this reaction (Ref.2). Schmidt (Ref.3) has improved this methodology and was the first to report the synthesis of OF 4949. A careful study was made by Boger on the Ullmann condensation to establish optimal conditions to synthesize K-13 and OF 4949 (Ref. 4). Evan's group extended this methodology to synthesis of K-13 and OF 4949 involving a common precursor, which was prepared by using diastereoselective directed azidation of imide enolate (Ref. 5).

The concept of thalium trinitrate (TTN) oxidative phenolic coupling to prepare diphenyl ether was pioneered by Yamamura et al (Ref.6). However, in this approach it is mandatory to utilize O,O-dihalophenol, which control the oxidative potential and the regioselectivity. Yamamura et al made use of this approach for the synthesis of OF 4949 and K-13 (Ref.7). The most elaborate and truely fascinating approach for the synthesis of vancomycin by TTN oxidative macrocyclization was investigated by Evans (Ref. 8). The main drawback in this approach is to remove selectively one halogen atom from each aromatic ring which in practice it could prove to be an herculean task.

My personal group at IICT initiated work on the synthesis of K-13 in 1992 and capitalized on the pronounced activity of halogen present in o-nitrohalobenzene towards Ullmann ether synthesis (Ref.8). This activation allows coupling with phenols to occur under mild conditions but more importantly the nitro group acts as a surrogate for ortho hydroxy function present in all these compounds including vancomycin (Ref.9)(Scheme 1).

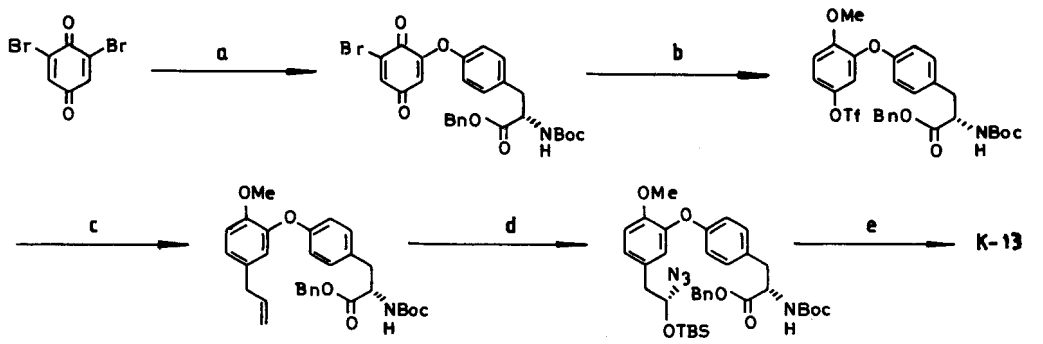
Scheme-1



(a) NaH, $CuBrSMe_2$, N-acetyl-(S)-tyrosine methyl ester, $C_6H_5NO_2$, 110°C, 7 h; b) (i) $(EtO)_2P(O)CH(NH\text{-}Boc)(CO_2Et)$, KOt-Bu, CH_2Cl_2, -60 °C, ii) 10% Pd/C, H_2, MeOH, c) i) Cbz-Cl, DMAP, pyridine, CH_2Cl_2, 0°C, ii) LiOH, THF-MeOH-H_2O (3:1:1), 0°C, d) HOBT, DCC, CH_2Cl_2, 0°C, (S)-tyrosine TMS ethyl ester; e) i) TBAF, DMF, ii) C_6F_5OH, DCC, CH_2Cl_2; f) i) TFA, thioanisole, CH_2Cl_2, ii) dioxane-pyridine (5:1) at $3x10^{-4}$ M conc. 90°C; g) i) 10% Pd/C, H_2, MeOH, ii) HBF_4, isoamyl nitrite, MeOH, 0°C, iii) $Cu(NO_3)_2.3H_2O$, CuO, H_2O.

In our endeavour to find a simple and elegant approach for the synthesis of isodityrosine unit, retaining the stereochemical features of the reacting molecules, we attempted to replace the two ortho-bromine atoms in the 2,6-dibromobenzoquinone by one or two substituted phenols to give the corresponding mono or disubstituted benzoquinone. Subsequent manipulation of the benzoquinone moiety to the corresponding aryl amino acid was relied on the Pd-catalyzed cross coupling reaction of the aryl triplet with alkyl tributyltin followed by Sharpless asymmetric dihydroxylation reaction. By this approach we have demonstrated for the first time the synthesis of K-13 (Scheme 2) and extended this methodology for the synthesis of the model C-D-E diphenyl ether fragment of vancomycin (Ref.10).

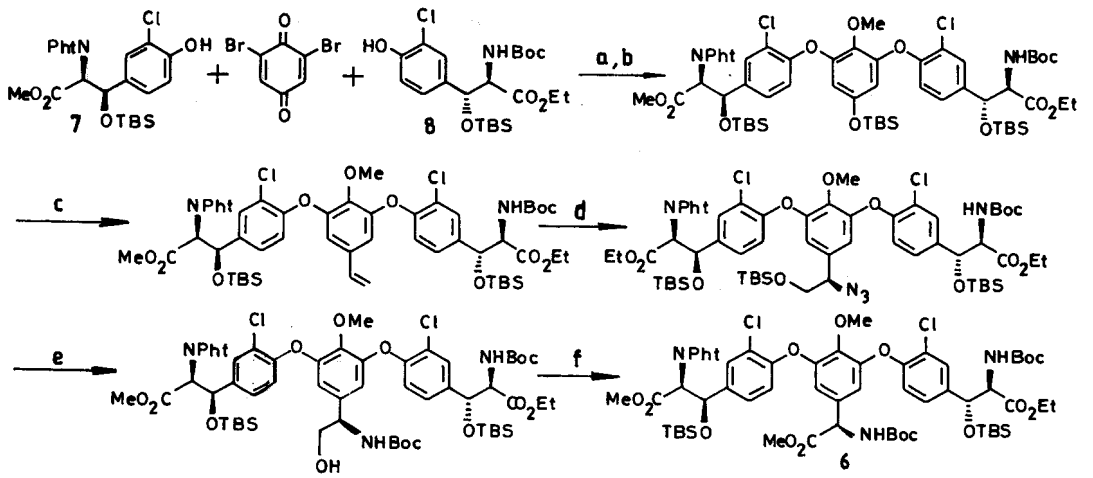
Scheme-2



a) (S)-N-Boc-tyrosine benzyl ester (1 eq.), KF, DMF, 90°C, b) i) $Na_2S_2O_4$, $CHCl_3$-H_2O; ii) TBS-Cl, Et_3N, CH_2Cl_2, 5 h; iii) DMS, Acetone, K_2CO_3, reflux, iv) H_2, Pd/C, v) TBAF, THF, vi) TF_2O, Py, CH_2Cl_2; c) i) alkyltributyltin, $Pd(PPh_3)_4$, LiCl, dioxane, reflux; d) i) DHQDPCB, K_2CO_3, $K_3Fe(CN)_6$, OsO_4, t.BuOH-H_2O (1:1), ii) TBS-Cl, imidazole, cat. DMAP, CH_2Cl_2, iii) MsCl, Et_3N, CH_2Cl_2, iv) NaN_3, DMF, 90°C, e) i) Jones reagent, acetone; ii) CH_2N_2 ether.

We then moved on to the synthesis of vancomycinic acid (**6**) by stepwise introduction of the phenoxides of **7** and **8** (Ref.11) onto the 2,6-dibromobenzoquinone ring followed by derivatization of chiral arylglycine as a central amino acid residue. This sequence of reactions is described in scheme 3 (Ref.12).

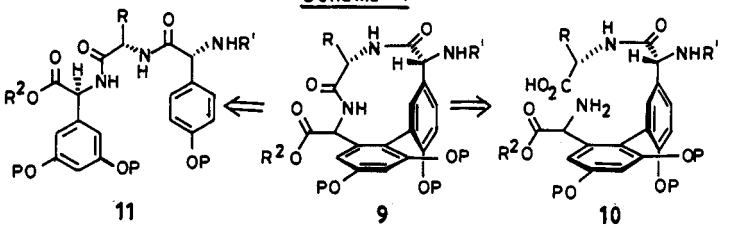
Scheme-3



a) i) K_2CO_3, 7, DMF, 0°C; ii) K_2CO_3, 8, DMF, 0°C; b) i) $Na_2S_2O_4$, $CHCl_3$-H_2O; ii) TBSCl, Et_3N, CH_2Cl_2; iii) DMS, K_2CO_3, acetone; c) i) TBAF, (0.5 equiv.), THF, 0°C; ii) Tf_2O, pyridine, CH_2Cl_2, 0°C; iii) vinyltributyltin, LiCl, $Pd(PPh_3)_4$, 2,6-di-tert-butyl-4-methylphenol (cat.), dioxane, 90°C; d) i) DHQ-9-PHN, OsO_4, K_2CO_3, $K_3Fe(CN)_6$, t-BuOH-H_2O (1:1); ii) TBSCl, Et_3N, CH_2Cl_2; iii) MsCl, Et_3N, CH_2Cl_2; iv) NaN_3, DMF, 50°C; e) i) PtO_2, H_2, $(Boc)_2O$, EtOAc; ii) TBAF (0.5 equiv.), THF, 0°C; f) i) PDC, DMF; ii) CH_2N_2, ether.

Our next goal was to synthesise the biaryl segment (AB Segment) of vancomycin which is common in all the vancomycin group of compounds isolated so far. The 12-membered biaryl macrocycle of vancomycin contains unusual (S)-3,5-dihydroxyphenylglycine along with (R)-4-hydroxyphenylglycine coupled together in an unprecedented biaryl linkage. In principle, two major strategies could be evolved to synthesize the 12-membered biaryl segment (**9**), either by obtaining the biaryl diamino diacid (**10**) and then achieving the 12-membered unit or by the synthesis of a linear tripeptide (**11**) and then proceed for macrocyclization through C-

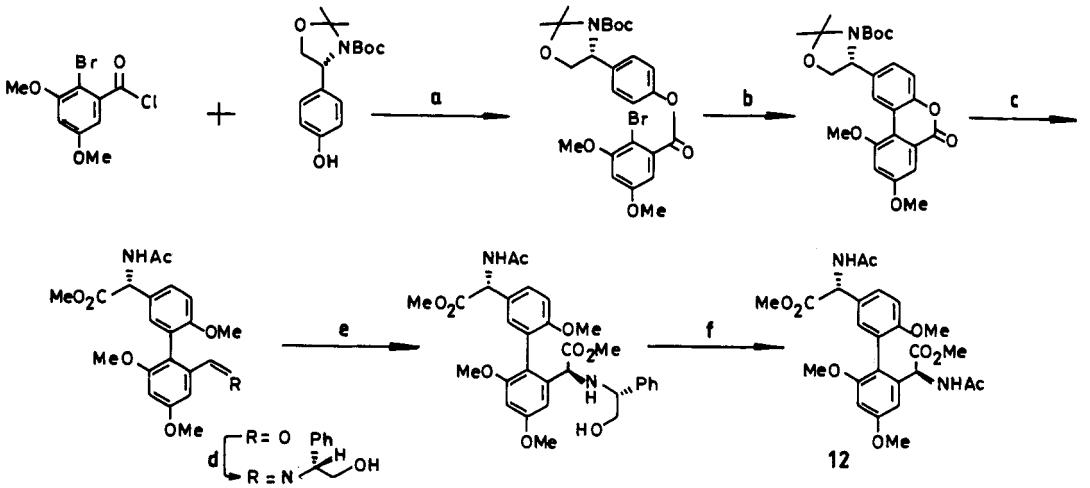
Scheme-4



11 9 10

C aryl coupling reaction (Scheme 4). We choose the 1st approach in which an intramolecular Pd-assisted aryl coupling was the strategic reaction. During this investigation a sound protocol was also formulated for the synthesis of phenylglycine derivatives (Ref.13) and the same is extended in our final synthesis of the AB-biaryl segment (**12**) of vancomycin (Scheme 5) (Ref.14).

Scheme-5



12

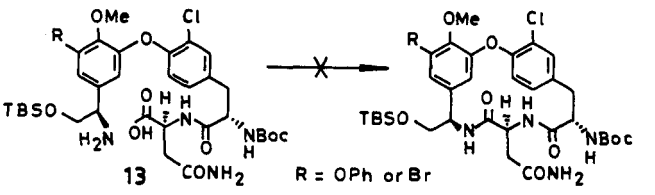
a) Et_3N, $CHCl_3$, 0°C; b) $Pd(PPh_3)_2Cl_2$, NaOAc, DMA, 110°C; c) i) LAH, THF; ii) DMS, K_2CO_3, acetone; iii) NaH, BnBr, THF; iv) PTSA, MeOH; v) Ac_2O, Et_3N, $CHCl_3$; vi) K_2CO_3, MeOH; vii) PDC, DMF; viii) CH_2N_2; ix) H_2, Pd/C, MeOH; x) PDC, CH_2Cl_2; d) (R)-phenylglycinol, $CHCl_3$-MeOH (3:1); e) i) TMSCN; ii) HCl-MeOH; f) i) LTA, CH_2Cl_2-MeOH; ii) HCl (aq.); iii) Ac_2O, Et_3N.

Not satisfied with the overall yields of the above approach, we have looked into an alternate method in which triphenyl phosphine-catalysed biaryl coupling of a substituted aryl lithio compound of the aromatic Schiff's base leading to form **12** is the basic theme of our approach (Ref.15). In the interm period Evans group came out with a biomimetic approach to synthesize macrocyclic actinoidic acid containing the AB segment of vancomycin (Ref.16).

Having successfully synthesized the vancomycinic acid (**6**) constituting the C-D-E segment and the biaryl portion of AB segment of vancomycin (**12**), our next attempt was to achieve macrocyclization with other two amino acids. We made several attempts to achieve the 16-membered macrocyclization through amide bond formation from a model segment related to vancomycinic acid **13** but could not achieve the desired goal (Scheme 6). Several groups have also made extensive investigations in this direction but unfortunately failed to build the 16-membered macrocycle system through amide bond formation (Ref.1). The only argument one could offer at this stage is that the linear peptide formed by the condensation of seven amino acids (**14**) is more suitable to undergo oxidative coupling between two aromatic amino acid units via C-O or C-C linkages as seen in vancomycin. This concept is further supported by the contributions of Yamamura and Evans on the

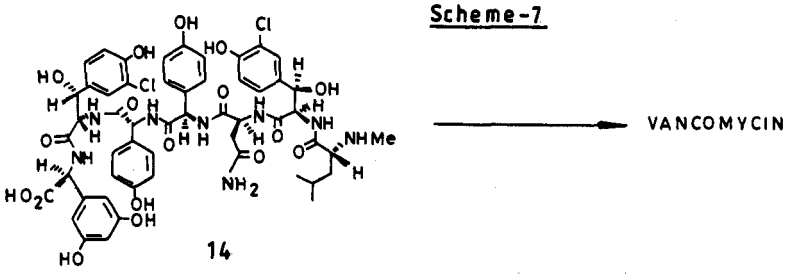
vancomycin synthesis . Both of them adopted TTN-promoted biaryl ether formed by a biomimitic approach. However, it is difficult to believe that TTN methodology will suit the synthesis of vancomycin due to several in built hurdles indicated earlier.

Scheme - 6



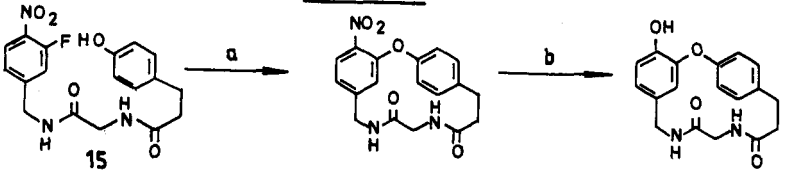
The ease of formation of the two 16-membered cyclic systems in vancomycin by biomimetic approach suggests that this is the most appropriate methodology that should be considered. Boger's group has also demonstrated that synthesis of deoxybouvardin and bouvardin could be achieved by intramolecular Ullmann ether formation (Ref.17). The intramolecular cyclization between the two tyrosine units (amino acids **2** and **6** in **14**) with the central p-hydroxyphenyl glycine unit (**4**) is the preferred approach (Scheme 7).

Scheme-7



Earlier (Ref.9), we have demonstrated that the Ullmann reaction between N-acetyl-L-tyrosine methyl ester with 3-bromo-4-nitrobenzaldehyde at 110° in presence of NaH as base provided the biaryl ether which was then elaborated for the synthesis of K-13 (See Scheme 1). We then conceived that this S_NAr reaction should further facilitate by replacing the bromo group by fluorine. Thus, we demonstrated the formation of a 16-membered cyclic peptide model related to vancomycin family by treating the intermediate **15** with sodium hydride in pyridine in 71% yield (Scheme 8) (Ref.18). Replacement of nitro with OH has been demonstrated by us earlier in the synthesis of K-13. This approach was further extended for the synthesis of K-13 using K_2CO_3 as base and DMF as solvent (Ref.19).

Scheme - 8

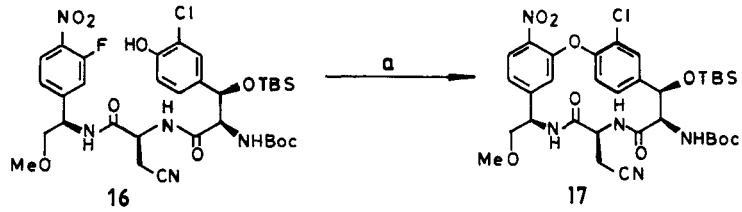


a) NaH, 0.02 M in pyridine, room temperature; b) Ref. 9.

Beugelman and his co-workers have simultaneously examined the synthesis of several cyclic peptides related to vancomycin family via arylfluoride displacement and effected intramolecular macrocyclization under mild conditions in good yield (Ref.20). This methodology was later extended by Boger (Ref.21) and Evans (Ref.22) groups in building model carboxylate-binding pocket of C-O-E rings of vancomycin. All these groups obtained the two atropisomers (nitro group either in the 16-membered ring or outside).

In our continued efforts to study the optimum conditions for the synthesis of the 16-membered cyclic system present in vancomycin group of compounds, we achieved the synthesis of a model 16-membered right hand side system present in Teicoplanin (**2**) (Ref.23). We have also succeded in synthesizing the right hand binding pocket of vancomycin (**17**) from the tripeptide (**16**) under mild conditions (Scheme 9). Further work in this direction is being actively perceived in our group (Ref. 24).

Scheme - 9



Having established the most appropriate methodology for the synthesis of the 16-membered cyclic system present in vancomycin and having the various synthons such as the β-hydroxy tyrosinates, and the AB biphenyl segment on hand, our next goal is to complete the total synthesis of vancomycin. Inspite of several advances made by us and others on vancomycin synthesis, it still remains as one of the most difficult tasks and offers further new avenues to organic chemists in trying their ingenuity in tackling the synthesis of complex natural products.

Acknowledgments : I am indebted to all my colleagues for their dedication in carrying out this work on vancomycin and related antibiotics.

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