# Studies Directed toward the Synthesis of Vancomycin and Related Cyclic Peptides

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## I. Introduction

In recent years considerable interest has been devoted to the vancomycin group of antibiotics which include the related glycopeptides of biological importance.[1] They are characterized by their clinical importance in treatment against emerging pathogens, such as the *Enterococci*, the coagulase-negative *Staphylococci*, the multiresistant *Staphylococcus aureus*, and the antibiotic-tolerant *Streptococci*. The most important among them is vancomycin (**1**), which has found clinical use in the last 35 years. In addition, recently, teicoplanin[2] (**2**) has also been introduced into clinical use. Further, the related avoparcin[3] has also been employed for several years as growth promoter in animal husbandary.

Although vancomycin and related antibiotics are often referred as "glycopeptides", they vary significantly, from other glycopeptide antibiotics such as bleomycin, phleomycins, tallysomycin, etc., both in structural and biological properties. Hence this terminology seems to be improper as it represents a broad family of biologically active sugar-containing peptide molecules.[4] Further, it is also commonly used for those "aglycons of the glycopeptides". To remove this ambiguity, all glycopeptides belonging to vancomycin group of antibiotics are better referred to as "dalbaheptides". They all have common structural features—a highly modified heptapeptide skeleton, and they all form specific complexation with *D*-alanine terminus of the bacterial cell wall component. The term "dalbaheptides" stands for DAL (D-alanyl-D-alanine), B (binding), A (antibiotic) with a heptapeptide structure.

Vancomycin (**1**), the first biologically active antibiotic reported in 1956 and was introduced in medical practice in the years 1956–1958,[5a] much before its structure was elucidated. Up to now more than 200 compounds having heptapeptide backbone similar to vancomycin have been reported.[5b] They all show *in vivo* activity particularly against gram-positive microorganisms. They are also recommended for the treatment of $\beta$-lactam-resistant infections and for the treatment of those who are sensitive to penicillins.[6]

In the present review a brief summary on structure, biosynthesis, and mode of action has been presented. However, the main emphasis will be devoted toward synthetic studies on vancomycin and related cyclic peptides.

### A. Structure and Characterization

The vancomycin group of antibiotics is stable, having molecular weights ranging from 1420 (vancomycin) to 2063 (ristocetin). They are produced by *Actinomycetes* belonging to the family of Streptomyces and Actinomyces. They are made up of seven amino acids, five of which are aryl amino acids and are common in all members of this class of compounds. The remaining two amino acids at position 1 and 3 help in classifying these into four types (Table 1).

In vancomycin type of compounds, the 1 and 3 amino acids are aliphatic, usually leucine and aspargine, respectively. Ristocetin type of products such as teicoplanin, aradacin, parvodicin, etc. are characterized by the presence of an extra 14-membered macrocycle which is formed by aryl ether bond occurring between two phenyl moieties of amino acids 1 and 3. On the other hand, compounds related to avoparcin type characterized by the presence of *p*-hydroxyphenylglycines in position 3 and 7. Finally, synmonicin is the only compound belonging to type 4 in which 1 position is a *p*-hydroxyphenylglycine and the amino acid 3 is methionine.

Further all these antibiotics differ by the presence of various substituents such as chlorine atoms and methyl or hydroxyl groups which can be present at different locations of five aryl residues of the aromatic amino acids. A benzylic hydroxyl is always present on the aryl amino acid 6 and rarely on 2.

Members of vancomycin group share similar heptapeptide back bone which usually carry one or more sugar substituents of different types. More than 20

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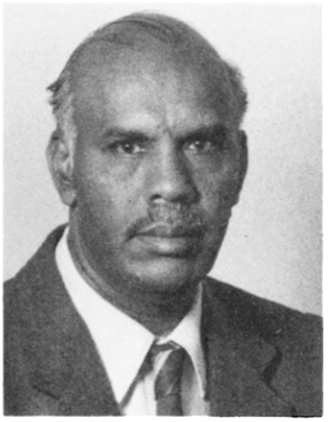
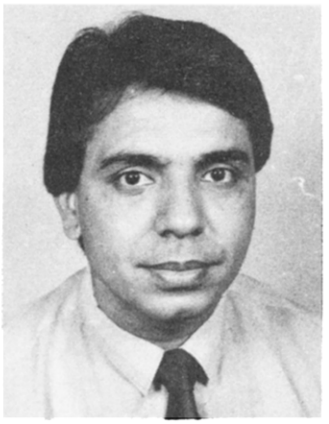


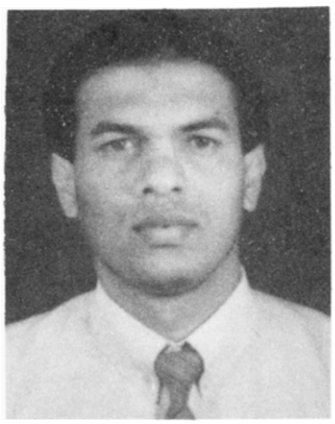
A. V. Rama Rao obtained his Ph.D. (tech.) from the Bombay University in 1964. He joined the National Chemical Laboratory (NCL), Pune as a Scientist in 1965 and contributed extensively in the area of natural products and synthetic dyes. He spent two years as a Postdoctoral Fellow (1975–1977) in Professor E. J. Corey's group at Harvard University. After his return, he was elevated as a Deputy Director and took over the Organic Chemistry Division at NCL as its Head. He moved to Hyderabad in 1985 to take over as the Director of the Indian Institute of Chemical Technology. He has received numerous honors and awards. He is a recipient of "Padmashree" in 1991, the prestigeous civilian award given by the President of India for his outstanding contributions to Organic Chemistry and Drug Technologies. He is known for his idea-based research with deep connection with chemical industry. He is known for his simple and thoughtful skills in the synthesis of several complex biologically active molecules. He has published 230 research papers and trained more than 60 Ph.D. students.



Mukund K. Gurjar was born in Nagpur, Maharashtra. He completed M.Sc. and Ph.D. degrees at the Nagpur University in 1974 and 1977, respectively. Later, he obtained the second Ph.D. degree working with Professor L. Hough from University of London on sucrochemistry in 1980. During the period of 1980–1982 he did postdoctoral work with Professor G. O. Aspinall, York University, Toronto, Canada. In 1982 he returned to India and joined the National Chemical Laboratory, Pune. In 1986 he moved to the Indian Institute of Chemical Technology, Hyderabad, where he is presently the Deputy Director. His research interests include carbohydrate chemistry, asymmetric synthesis of natural products, and development of new methodologies.

years passed between the isolation and structural elucidation of vancomycin. The structure was finally deduced by way of elaborate satisfactory purification and selective chemical degradation,[7] coupled with excellent use of NMR spectroscopy.[8] X-ray analysis[9] of a degradation product allowed the determination of the absolute configuration of vancomycin.

Vancomycin is probably one of the best examples in which elaborate purification techniques such as reverse-phase HPLC,[10] affinity chromatography,[11] and sophisticated analytical techniques such as high-field NMR[12a] and FAB-MS[12b] have been employed to

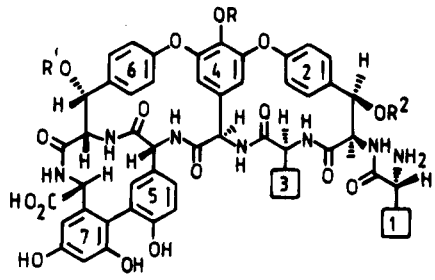


Laxma Reddy was born in 1963 in Karimnagar, A.P. He earned his M.Sc. in chemistry (1986) from Osmania University, Hyderabad, and received his Ph.D. in organic chemistry (1992) from the same University under the direction of Dr. A. V. Rama Rao (Director, Indian Institute of Chemical Technology) for his dissertation entitled "Synthesis of biologically active compounds". Since 1992 he was working as scientist–fellow at the Indian Institute of Chemical Technology, Hyderabad. His research interest includes the total synthesis of biologically active complex natural products and development of new methodologies.

A. Srinivasa Rao was born in Ramagundam, Andhra Pradesh. He completed his M.Sc. degree at the Osmania University in 1988. He is working with Dr. A. V. Rama Rao for his Ph.D. degree. Research interests include synthesis of biologically active compounds and new methodologies.

elucidate its structure.[10] Thus mild acid hydrolysis of vancomycin gave the biologically active aglycone.[11] The aglycon was subjected to various oxidative and reductive degradation studies which finally helped Williams' group[9] to simplify the structural aspects of its aglycon. On the basis of these studies, it was then deduced that this antibiotic is a heptapeptide type, built from two known amino acids (L-aspartic acid and *N*-methyl-D-leucine) and two complex, hitherto unknown building units (actinoidic acid and vancomycinic acid), accounting for the five aromatic amino acids. Actinoidinic acid is a common building unit occurring in each vancomycin type antibiotic. Similarly, the vancomycinic acid in vancomycin is a triamino-tricarboxylic acid; the two phenylserine units are symmetrically linked to the central *p*-hydroxyphenylglycine moiety through diphenyl ether bonds. The structure of vancomycin was finally obtained by X-ray analysis of the crystalline degradation product, formed by loss of ammonia. In 1981, Williams and his colleagues modified the three-dimensional structure obtained from X-ray measurements on the basis of their NMR studies on vanco-

**Table 1. General Characterization of Amino Acids in Vancomycin and Related Antibiotics[a]**



| type | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| vancomycin | Leu | β-OH Tyr | Asn | *p*-OHPhg | *p*-OHPhg | β-OHTyr | 3,5-OHPhg |
| ristocetin[b] | *p*-OHPhg | β-OHTyr | 3,5-OHPhg | *p*-OHPhg | *p*-OHPhg | β-OHTyr | 3,5-OHPhg |
| avoarcin | *p*-OHPhg | β-OHTyr | *p*-OHPhg | *p*-OHPhg | *p*-OHPhg | β-OHTyr | 3,5-OHPhg |
| synmonicin[c] | *p*-OHPhg | β-OHTyr | Met | *p*-OHPhg | *p*-OHPhg | β-OHTyr | 3,5-OHPhg |

[a] Leu = Leucine; β-OHTyr = β-hydroxytyrosine; Asn = aspargine; *p*-OHPhg = (*p*-hydroxyphenyl)glycine; 3,5-OHPhg = 3,5-dihydroxyphenylglycine; Met = Methionine. [b] Terminl carboxyl is $COOCH_3$. [c] Terminal amino group is $NCH_3$.

mycin. Finally, the structure of vancomycin represented as **1** was provided by Harris and coworkers[13] on the basis of extensive degradation and mechanism of transformations of degraded products, which helped the structural elucidation of other members of this class of compounds. Detailed structural elucidation is the subject of several papers and two reviews.[1,2]

## B. Biosynthesis

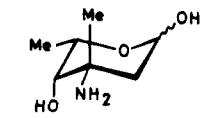
The vancomycin gross structure suggests a biosynthetic pathway derived by the condensation of seven amino acids followed by internal oxidation coupling with the respective phenolic units through C–C or C–O–C linkages. Obviously, the glycosylation is expected as the last step in its biosynthesis. Further, studies on the biosynthesis of vancomycin identified tyrosine as the precursor for *p*-hydroxyphenylglycine, and *m*-dihydroxyphenylglycine was derived from four acetate units.[14] The assembly of the seven amino acid units probably formed by a "multienzyme thiotemplate system". The glycosylating enzymes and the sequence of assembly enzymate reactions are not known.[2c]

## C. Mode of Action

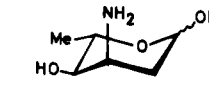
The molecular basis for the antibacterial activity of vancomycin has been well studied. Inspite of its clinical use for more than 35 years, establishment as the preferred drug for the treatment of multiresistant *Staphylococcus aureus* infections, and for several years not showing bacterial resistance to this drug, recent reports established that vancomycin is also not totally free from bacterial resistance. Several papers have dealt on the mode of its action including the recent excellent contribution from Williams' group.[15]

## D. Carbohydrate Components

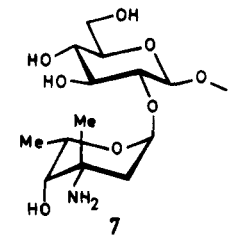
Vancomycin (**1**) and other members of this family are characterized by the presence of carbohydrate residues. These carbohydrate components are linked through *O*-glycosyl bonds. L-Vancosamine, 3-amino-2,3,6-trideoxy-3-*C*-methyl-L-hexose, was isolated from vancomycin antibiotic. The presence of the *C*-methyl group makes L-vancosamine, a unique branched chain amino sugar. L-Vancosamine forms a part structure of a disaccharide unit **7**, *O*-glucosylated at C-44 position.



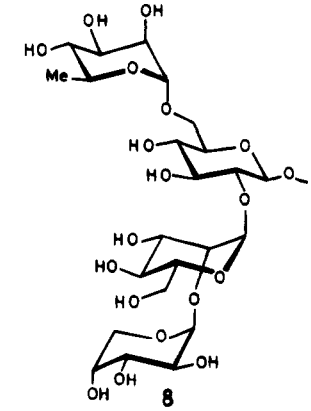
L-vancosamine



L-ristosamine



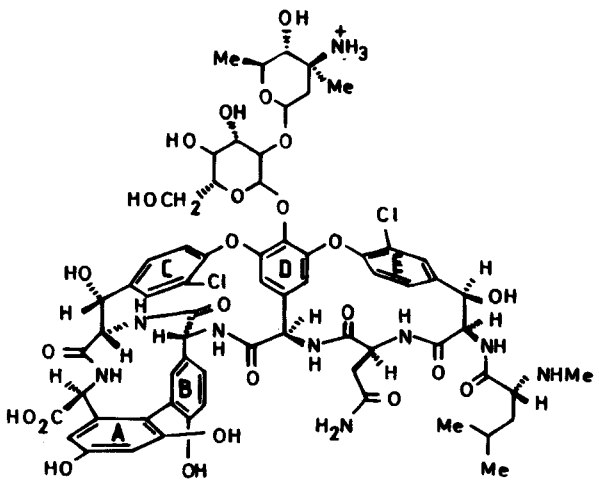
**7**



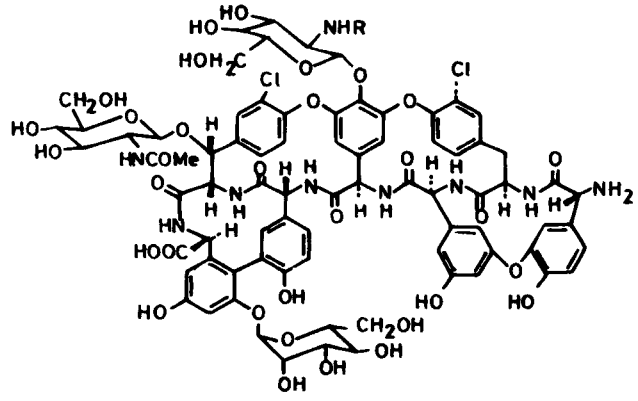
**8**

Structural elucidation of other antibiotics of this family revealed that a basic sugar component of each is an 3-amino-2,3,6-trideoxyhexose stereoisomer. L-Ristosamine (3-amino-2,3,6-trideoxy-L-ribohexose) was the amino sugar component of ristocetin (**3**) attached to the benzylic hydroxyl of ring C. Ristocetin also contains D-mannose and the tetrasaccharide unit **8** at the C-42 and C-56 centers. However, in teicoplanin (**2**) known sugars—two molecules of D-glucosamine and D-mannose—were present at the C-56, C-34, and C-42 positions, respectively. L-Ristosamine is present in another antibiotic, avoparcin, which also contains a disaccharide, 2-*O*-(3-amino-2,3,6-trideoxy-L-ribopyranosyl) D-glucopyranoside, at C-44, D-mannose at C-7, and L-rhamnose at C-59.

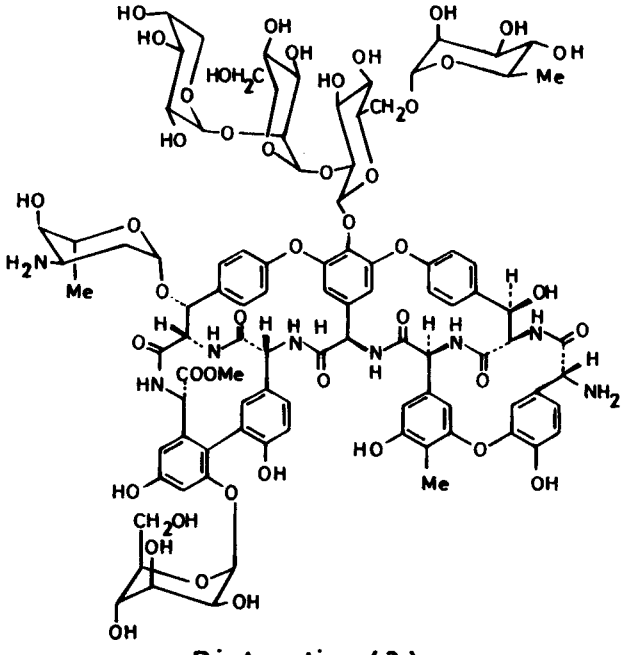
The synthesis of these stereoisomeric 3-amino-2,3,6-trideoxyhexoses has been a topic of interest. Several synthetic strategies involving both carbohydrate and non carbohydrate precursors have been



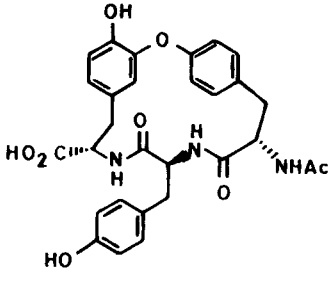
Vancomycin (1)



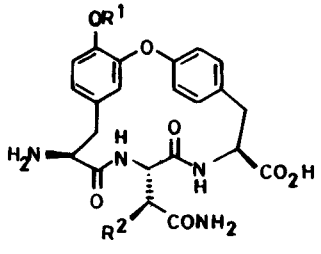
Teicoplanin (2)



Ristocetin (3)

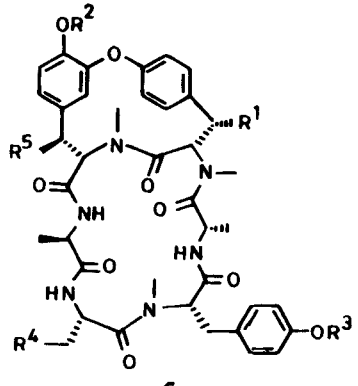


K - 13 (4)



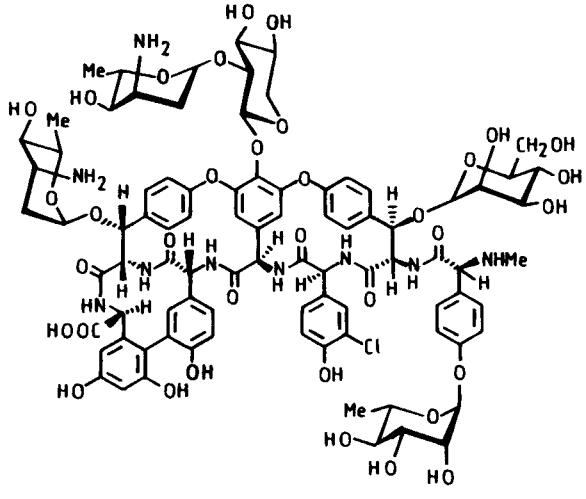
(5)

| $R^1$ | $R^2$ | |
|---|---|---|
| Me | OH | OF 4949-I |
| H | OH | OF 4949-II |
| Me | H | OF 4949-III |
| H | H | OF 4949-IV |



6

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | |
|---|---|---|---|---|---|
| OH | H | Me | H | H | Bouvaridin |
| H | H | Me | H | H | Deoxybouvaridin (RA-V) |
| H | H | Me | OH | H | RA-I |
| H | Me | H | H | H | RA-II |
| H | Me | Me | OH | H | RA-III |
| H | Me | Me | H | OH | RA-IV |
| OH | Me | Me | H | H | O-Methylbouvaridin (RA-VI) |
| H | Me | Me | H | H | O-Methyldeoxybouvaridin (RA-VII) |



β - Avoparcin

Figure 1.

developed. Since two review[16] articles have recently appeared covering exhaustively the synthetic aspect of amino deoxy sugars of vancomycin family, the detail discussion would be a redundant exercise and, therefore, deliberately omitted.

## II. Synthetic Studies toward Biaryl Ethers

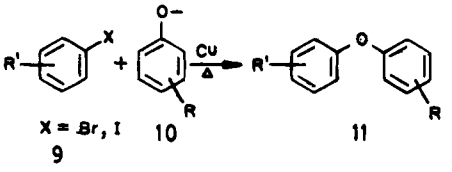
The molecular complexity of compounds of the vancomycin family provides yet another prospect for organic chemists to test their synthetic ingenuity.[17] From these attempts[18] it becomes more and more prominent that existing methodologies have limitations and therefore it is desirable to have new concepts at our disposal to think about synthetic strategies from a new perspective. This view holds true with the vancomycin family because so far not a single member of it has been synthesized, even-though vancomycin itself was isolated ~35 years ago. However, related cyclic peptides, which are simple in structure, formed the major targets of many synthetic chemists.[19] They have evaluated their new synthetic propositions with cyclic peptides. Since several structural elements are common between cyclic peptides and dalbaheptides, the knowledge gained from the synthesis of simple molecules such as K-13 (**4**) and OF-4949 I-IV (**5**), could in principle be expanded in designing synthetic protocols for the vancomycin family.

The compounds shown in Figure 1 are characterized by the presence of oxidatively coupled aromatic amino acids such as isodityrosine in cyclic peptides and diphenyl ether crossed-linked amino acids in dalbaheptides. The oxidative coupling reaction of aromatic substrates has been known for a long time, but the area has not been fully explored. The available procedures are indeed scanty. Basically the Ullmann condensation reaction[20] and recently developed thalium(III) trinitrate (TTN) oxidative coupling[21] are the main sources of assembling aromatic nuclei through ether linkages. Other methods,[22] however, are confined to specific examples.

### A. Ullmann Method

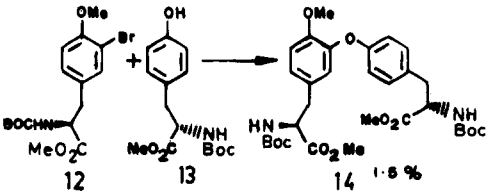
The Ullmann condensation reaction[23] involves the coupling of a halobenzene **9** with a phenol **10** in the presence of copper at high temperature and for a long reaction period to produce **11** (Scheme 1). These

**Scheme 1. Ullmann Reaction**



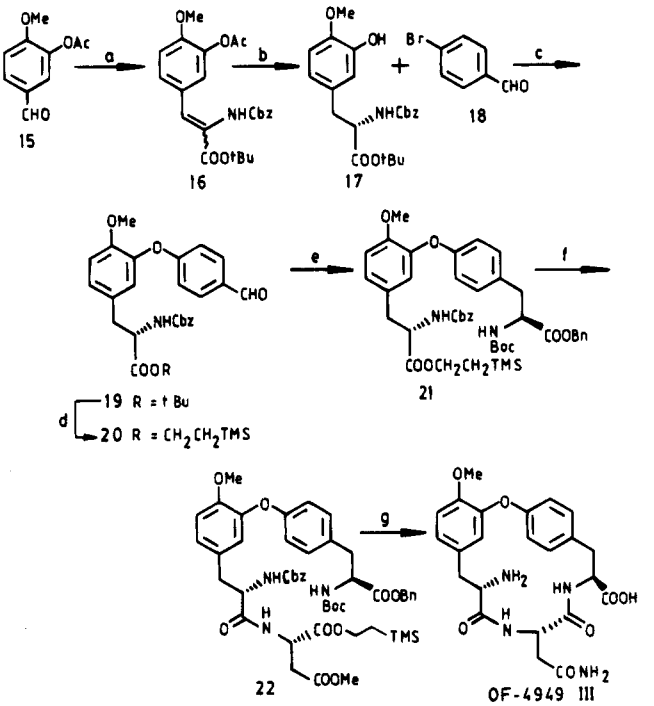

obligatory conditions of the Ullmann reaction are not naive toward those substrates which contain delicate functionalities and more importantly asymmetric carbon centers. This aspect is amicably demonstrated by the work done by Sano et al.[24] The Ullmann reaction between two tyrosine precursors (**12** and **13**) gave isodityrosine derivative **14** in only 1.5% yield (Scheme 2).

**Scheme 2. Isodityrosine Synthesis**




Not deterred with this observation, Schmidt et al.[25] modified the above strategy by using *p*-bromobenzaldehyde (**18**) as a coupling component which contained a rigid but useful funtionality for derivatizing the amino acid side chain. The didehydro amino acid **16** was synthesized by the condensation of the aldehyde **15** with phosphorylglycin derivative. Subsequent asymmetric hydrogenation with [Rh(DIPAMP)]$^+$ as a homogenous catalyst[26] gave the (*S*)-amino acid with 98% enantiomeric excess which was deactylated to **17** and coupled with *p*-bromobenzaldehyde (**18**) in the presence of CuO−pyridine at 130 °C to produce **19** in 93% yield. Its derived[27] 2-(trimethylsilyl)ethyl (TMS) ester **20** was subjected to successive olefination reaction and homogeneous asymmetric reduction as described earlier to obtain **21** with high diastereomeric excess. Hydrolysis of TMS-ethyl group and condensation with aspartic acid gave the tripeptide **22** which was converted into OF-4949 III by sequential reactions (Scheme 3).

**Scheme 3**[a]

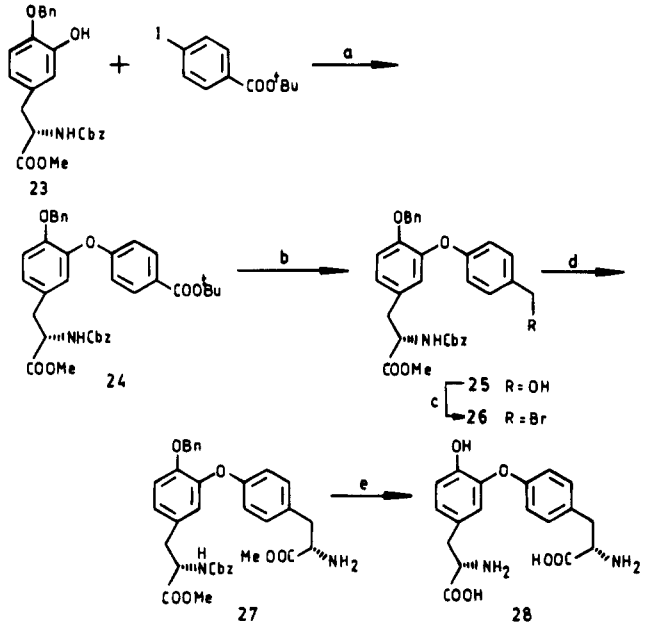



[a] (a) $(MeO)_2P(O)CH(NHCbz)(CO_2t\text{-Bu})$, KO*t*-Bu, $CH_2Cl_2$, 12 h; (b) (i) [Rh(DIPAMP)]$^+$, $H_2$, MeOH, 75 h, (ii) NaOH, MeOH, 15 h; (c) CuO, $K_2CO_3$, pyridine, 130 °C, 12 h; (d) (i) TFA, 20 °C, 5 h, (ii) DCC, $TMSCH_2CH_2OH$, DMAP, EtOAc, 12 h; (e) (i) $(MeO)_2P(O)CH(NHBoc)(CO_2Bn)$, KO*t*-Bu, $CH_2Cl_2$, 12 h, (ii) [Rh(DIPAMP)]$^+$, $H_2$, EtOH, 75 h; (f) (i) TBAF, DMF, 0.5 h, (ii) (S)-Asp-(OMe)-$OCH_2CH_2TMS$, EDCI, dioxane, 15 h; (g) (i) TBAF, DMF, 0.5 h, (ii) $C_6F_5OH$, DCC, EtOAc, 12 h, (iii) TMS-OTf, $CH_2Cl_2$, 2 h, (iv) $CHCl_3$, saturated $NaHCO_3$, 3 h, (v) Pd/C, $H_2$, $(CH_3)_2CHOH$, 20 h, (vi) saturated $NH_3$−MeOH, 120 h.

Boger's group[28] systematically studied, the activated Ullmann diaryl ether condensation reaction

with a view toward establishing optimal reaction conditions under which no racemization occurs and yields are maintained. For example, the condensation of the selectively protected (*S*)-DOPA **23** and *tert*-butyl *p*-iodobenzoate was promoted by $CuBr{\cdot}SMe_2$ in nitrobenzene at 130 °C to yield the diaryl ether derivative **24** (46%). Reduction of **24** gave the benzyl alcohol **25** which was converted into the primary bromide **26**. Treatment of **26** with Schollkopf's reagent[29] and hydrolysis produced **27**, while removal of protecting groups afforded isodityrosine (**28**) (Scheme 4).

**Scheme 4**[a]




[a] (a) NaH, $CuBr{\cdot}SMe_2$, $C_6H_5NO_2$, 130 °C, 8 h; (b) (i) 3.0 M HCl, EtOAc, 1.5 h, (ii) 1.0 M $BH_3{\cdot}THF$, THF, 0 °C, 3 h; (c) $CBr_4$, $PPh_3$, $Et_2O$; (d) (i) NaH (1 equiv), Schollkopf's reagent, THF, −78 °C, 14 h, (ii) 0.5 N HCl, THF; (e) 6.0 N HCl, 6 h.

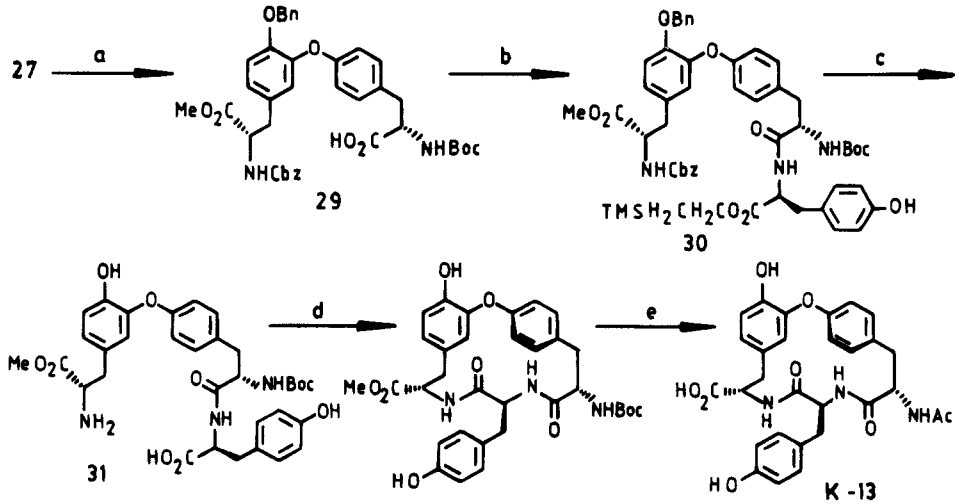
These authors[30,31] judiciously utilized the two above-mentioned biaryl ether intermediates **27** and **25** to complete the total synthesis of K-13 and OF-4949 III-IV, respectively. Compound **27** underwent the protection and deprotection sequence to produce the acid **29** whose coupling with protected (*S*)-tyrosine then furnished the tripeptide **30**. Removal of both TMS-ethyl ester and *N*-Cbz protecting groups led to the formation of the amino acid **31**, the cyclization and consequent deprotection of which produced K-13 in a well-defined synthetic approach[30] (Scheme 5).

In another sequence,[31] the biaryl ether benzyl alcohol **25** was first elaborated to produce chiral amino acid side chain **32** and then coupled with *N*-Boc-aspargine. The resulting tripeptide **33** was transformed in a straightforward way into the amino acid **34** which on cyclization **35** followed by deprotection completed the total synthesis of OF-4949 III. Alternatively, from the intermediate **35**, produced after macrocyclization, the hydroxyl group was methylated to obtain **36**. Removal of *N*-Cbz and hydrolysis of methyl ester produced the natural product OF-4949 IV (Scheme 6).

Evans' group[32] examined the synthesis of OF-4949-III and K-13 involving a common precursor **42** which was prepared by using diastereoselective direct azidation of imide enolate.[33] The oxidatively coupled cinnamic acid **39** was obtained by Ullmann reaction[23] between (*E*/*Z*)-*tert*-butyl 3-hydroxy-4-methoxycinnamate (**37**) and (*E*)-benzyl 4-bromocinnamate (**38**) in 91% yield (Scheme 7). By adopting a selective direct azidation technique, **39** was transformed into the α-azido carboximide **40** with 97.5:2.5 ratio of diastereomers. Subsequent transesterification[34] using titanium tetrabenzyl oxide in benzyl alcohol produced α-azidobenzyl ester which was reduced, hydrolyzed, and protected to give **41**. On the basis of similar methodology the introduction of second azido group was ensured which produced the above said common intermediate **42**.

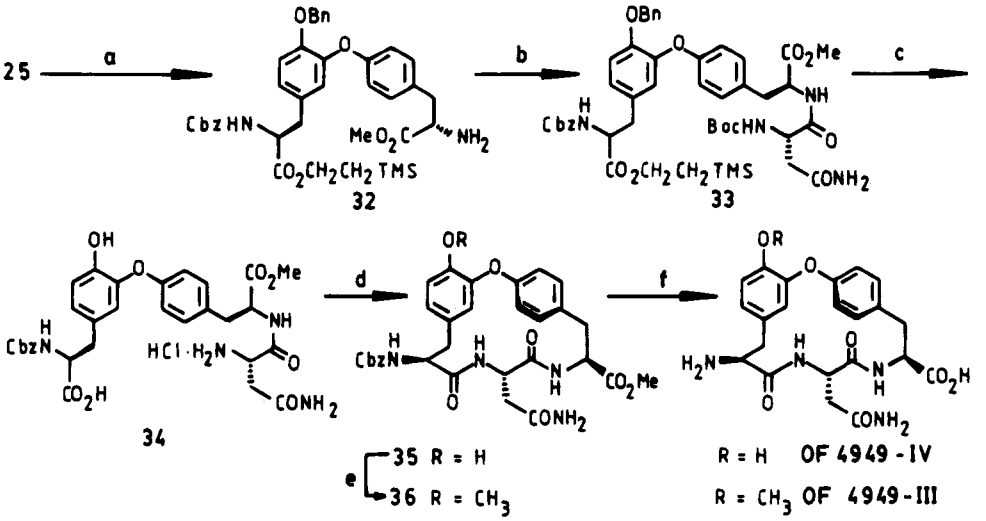
For K-13 synthesis, **42** was successively hydrolyzed, reduced, and coupled with (*S*)-*N*-Cbz-4-methoxyphenylalanine to give the tripeptide **43**, containing an active ester moiety. Among the different active esters[35] used for the construction macrocyclic amide bond Evans' group utilized the pentafluo-

**Scheme 5**[a]



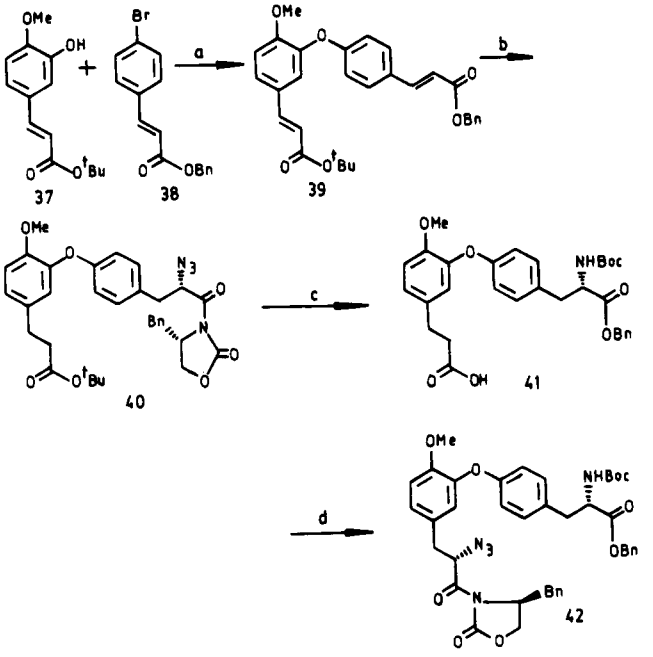

[a] (a) (i) TFAA, THF, 1 h, (ii) NaH (1 equiv), THF, 0 °C, 25 °C, 1 h, (iii) 10% $K_2CO_3$, MeOH−$H_2O$ (5:2), 6 h, (iv) $(Boc)_2O$, $K_2CO_3$, THF, 2 h; (b) (*S*)-tyrosine TMS ethyl ester, EDCI, $CH_2Cl_2$, 9 h; (c) (i) TBAF, DMF, 4 h, (ii) 10% Pd/C, $H_2$ (1 atm), 10% HCl (2 equiv), THF, 4 h; (d) DPPA, DMF, 0.008 M, pH 7 ($NaHCO_3$), 0 °C, 72 h; (e) (i) 3.0 M HCl, EtOAc, 2 h, (ii) $Ac_2O$, $NaHCO_3$, THF, 2 h, (iii) LiOH, THF−MeOH−$H_2O$ (3:1:1), 4 h.

**Scheme 6**[a]



[a] (a) (i) LiOH, THF–MeOH–$H_2O$, (ii) $TMSCH_2CH_2OH$, EDCl, (iii) $CBr_4$, $PPh_3$, $Et_2O$, 12 h, (iv) NaH (1 equiv), Schollkopf's reagent, THF, (v) 0.5 N HCl, THF, 11 h; (b) *N*-Boc-(*S*)-aspargine, EDCI, HOBT, DMF; (c) (i) 10% Pd/C, $H_2$ (1 atm), THF, 3 h, (ii) Cbz-Cl, $NaHCO_3$, THF, 3 h, (iii) TBAF, THF, 4 h, (iv) 3.0 M HCl–EtOAc, 0.5 h; (d) DPPA, $NaHCO_3$, DMF, 0.008 M, 0 °C, 72 h; (e) $CH_2N_2$, $Et_2O$, (f) (i) LiOH, THF–MeOH–$H_2O$, (ii) 10% Pd/C, $H_2$ (1 atm).

**Scheme 7**[a]



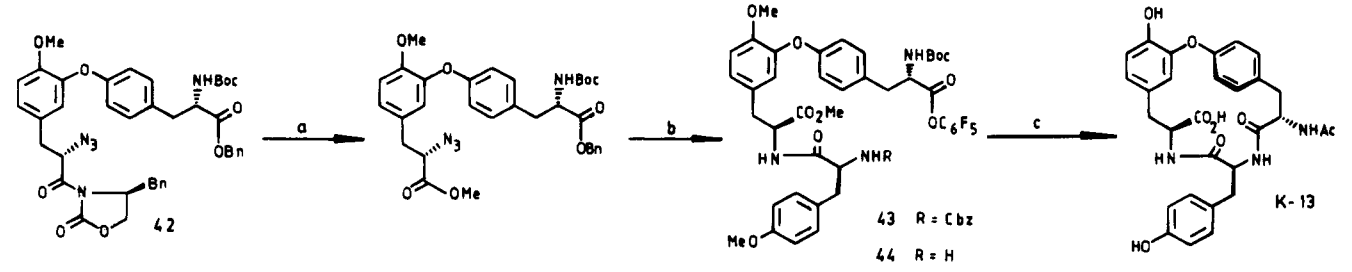
[a] (a) CuO, $K_2CO_3$, pyridine, 145 °C, (b) (i) 10% Pd/C, $H_2$, (ii) pivaloyl chloride, $Et_3N$, 0 °C, lithiated oxazolidinone, (iii) KHMDS, −78 °C, trisyl azide; (c) (i) $Ti(OBn)_4$, BnOH, (ii) Raney Ni, $H_2$, (iii) TFA, thioanisole, (iv) $(Boc)_2O$, $NaHCO_3$; (d) (i) pivaloyl chloride, $Et_3N$, 0 °C, lithiated oxazolidinone, (ii) KHMDS, −78 °C, trisyl azide.

rophenyl active ester primarily due to inherent higher reactivity. Finally **44** was macrocyclized and deprotected to give K-13 (Scheme 8).

In order to synthesize OF-4949-III, Evans' group first elaborated the aspargine side chain followed by conversion of oxazolidine group into the active ester **45**. Subsequent *N*-Boc deprotection, macrocyclization, and hydrogenolysis provided OF-4949-III (Scheme 9).

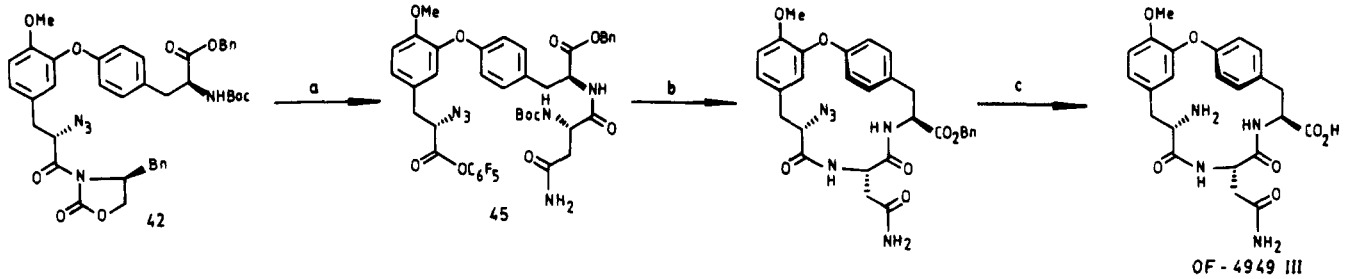
Rama Rao's group[36] expeditiously capitalized on the pronounced activity of halogen present in *o*-nitrohalobenzene toward Ullmann ether synthesis. This activation allows coupling with phenols to occur under mild conditions but more importantly the nitro group acts as a surrogate for *o*-hydroxy function present in all these natural products. This was illustrated in the synthesis of K-13. The Ullmann reaction of *N*-acetyl-L-tyrosine methyl ester with 3-bromo-4-nitrobenzaldehyde (**46**) at 110 °C in the presence of NaH and CuBr–DMS complex provided the biaryl ether **47** in 61% yield (Scheme 10). The introduction of alanine side chain (7:3 diastereomeric excess) followed by selective hydrolysis of methyl ester gave the acid **48**. A coupling reaction with (*S*)-tyrosine TMS-ethyl ester provided the diastereomeric mixture of tripeptide from which the major product **49** was isolated. Its conversion into the active ester **50** followed by cyclization gave **51**. In order to replace NHCbz with OH simple functional group

**Scheme 8**[a]



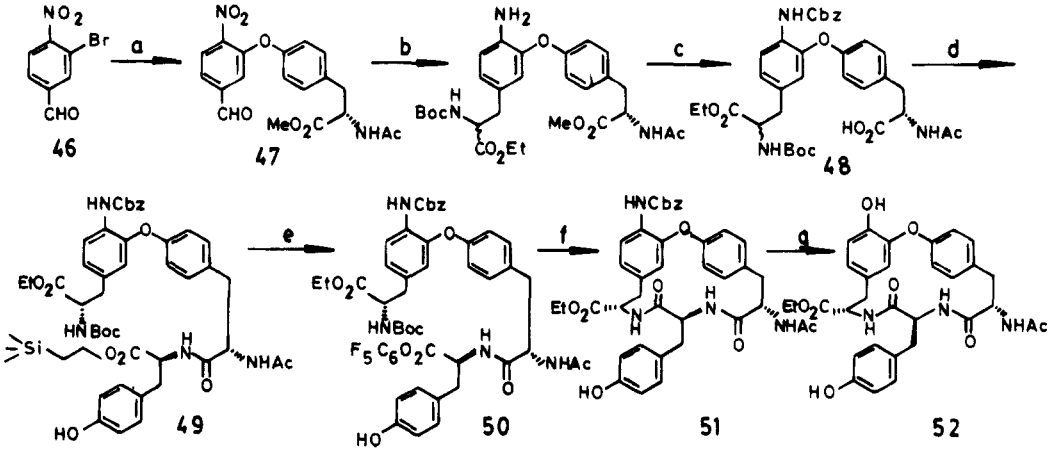
[a] (a) LiOOH, $CH_2N_2$; (b) (i) 10% Pd/C, $H_2$, (ii) *N*-Cbz-4-*O*-methyl-Tyr-$OC_6F_5$-$NaHCO_3$, (iii) $C_6F_5OH$, DCC; (c) (i) $H_2$, Pd(O), *N*-methylmorpholine, 2% EtOH–dioxane, 90 °C, (ii) TFA, thioanisole, (iii) $Ac_2O$, pyridine, (iv) AlBr, EtSH.

**Scheme 9**[a]




[a] (a) (i) TFA, thioanisole, (ii) *N*-Boc-Asn-OH, EDCI, HOBT, (iii) LiOOH, (iv) $C_6F_5OH$, DCC; (b) (i) TFA, thioanisole, (ii) 20% pyridine–dioxane, 90 °C; (c) $H_2$, Pd(O).

**Scheme 10**[a]



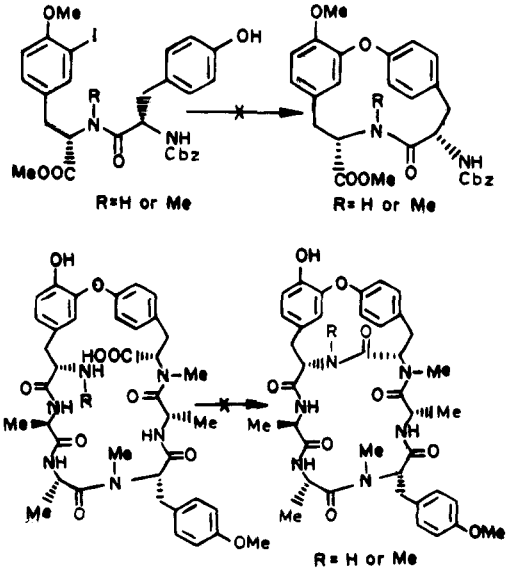

[a] (a) NaH, $CuBr{\cdot}SMe_2$, *N*-acetyl-(*S*)-tyrosine methyl ester, $C_6H_5NO_2$, 110 °C, 7 h; (b) (i) $(EtO)_2P(O)CH(NH\text{-}Boc)(CO_2Et)$, KO*t*-Bu, $CH_2Cl_2$, −60 °C, (ii) 10% Pd/C, $H_2$, MeOH; (c) (i) Cbz-Cl, DMAP, pyridine, $CH_2Cl_2$, 0 °C, (ii) LiOH, THF–MeOH–$H_2O$ (3:1:1), 0 °C; (d) 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 $3 \times 10^{-4}$ M conc. 90 °C; (g) (i) 10% Pd/C, $H_2$, MeOH, (ii) $HBF_4$, isoamyl nitrite, MeOH, 0 °C, (iii) $Cu(NO_3)_2{\cdot}3H_2O$, CuO, $H_2O$.

manipulations were carried out to provide the known K-13 ethyl ester (**52**) (Scheme 10).

Bouvardins and deoxybouvardins (**6**), the potent antitumor antibiotics, are characterized by the presence of an unusual structural framework, notably the 14-membered *N*-methylcyclicisotyrosine subunit incorporated in the 18-membered cyclichexapeptide skeleton.[37] Synthetic efforts on these novel bicyclic hexapeptides were initially hampered[38] because conventional macrolactamization or direct diaryl ether cyclization procedures did not succeed as illustrated in Scheme 11. However, Boger et al. investigated meticulously the synthetic designs of their preparation on the basis of the intramolecular Ullmann reaction as a key macrocyclization step.[39] For instance, the synthesis of RA-VII and deoxybouvardins described by the Boger's group involved[40] the preparation of **53** starting from (*S*)-*N*-acetyltyrosine methyl ester in four steps. Subsequent coupling with (*S*)-*N*-Boc-*N*-methyl-4-iodophenylalanine produced the dipeptide (**54**) whose intramolecular cyclization was effected in the presence of NaH–CuBr–$SMe_2$ at 130 °C followed by *N*-Boc-deprotection to yield the 14-membered cyclicisodityrosine derivative **55** in 24–30% yield. The tetrapeptide component, independently produced by conventional reaction, was then attached to **55** and deprotected to produce **56**. This resulting product **56** was elaborated to produce RA-VII and deoxybouvardin (Scheme 12).

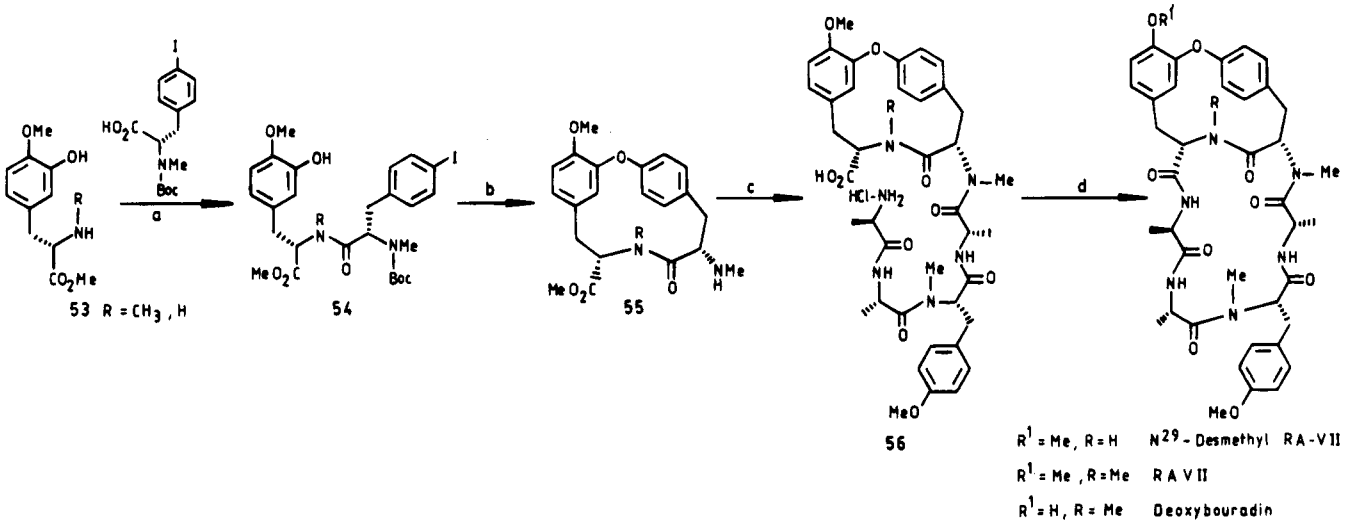
Recently Boger's group reported[41] the total synthesis of bouvardin based on the similar strategy as

**Scheme 11. Macrocyclization Studies**



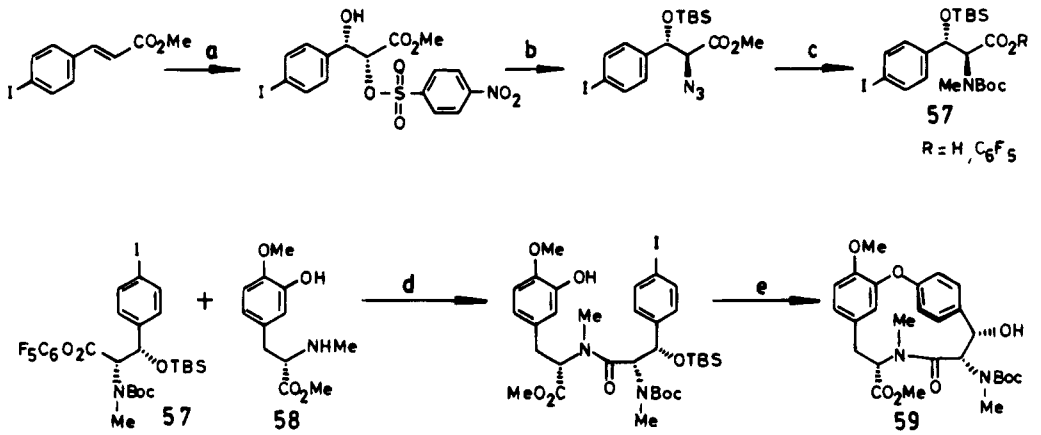

described above for deoxybouvardins. The key β-hydroxy-α-amino acid **57** was prepared by using Sharpless dihydroxylation reaction.[42] Coupling of the active ester of **57** (R = $C_6F_5$) with (*S*)-*N*,*O*-dimethyl-DOPA methyl ester (**58**) provided the dipeptide which was cyclized to give the product **59** (Scheme 13). Transformation of **59** into bouvardin was effected as discussed in their previous work.

**Scheme 12**[a]



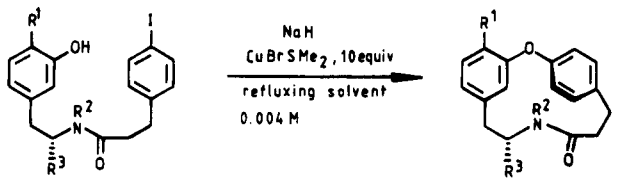

[a] (a) EDCI, HOBT, DMF, 16 h; (b) (i) NaH (2 equiv), CuBr–$SMe_2$ (10 equiv), collidine, 130 °C, 8 h, (ii) 3.0 M HCl–EtOAc, 1 h; (c) (i) EDCI, HOBT, tetrapeptide, DMF, 16 h, (ii) LiOH, THF–MeOH–$H_2O$ (3:1:1), 2 h, (iii) 3.0 M HCl–EtOAc, 1 h; (d) (i) DPPA (1.5 equiv), $NaHCO_3$ (5 equiv), DMF, 0 °C, 72 h, (ii) $BBr_3$, $CH_2Cl_2$, −78 °C 0 °C, 3 h.

**Scheme 13**[a]




[a] (a) (i) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH-$H_2O$, 25 °C, 20 h, (ii) *p*-$NO_2$-$C_6H_4$-$SO_2Cl$, $Et_3N$, $CH_2Cl_2$, 0–4 °C; (b) (i) $NaN_3$, DMF, 55 °C, 12 h, (ii) *t*-$BuMe_2SiOTf$, $Et_3N$, $CH_2Cl_2$, 5 h; (c) (i) $Ph_3P$, $H_2O$, THF, 45–50 °C, 10 h, (ii) $(Boc)_2O$, $K_2CO_3$, THF–$H_2O$, 25 °C, 3 h, (iii) KH–MeI, THF, 10 h, (iv) LiOH, THF–MeOH–$H_2O$, 4 h, 25 °C, (v) EDCI, $C_6F_5OH$, $CH_2Cl_2$, 8 h, 25 °C; (d) THF–DMF, 70 °C, 36 h; (e) (i) 2,6-lutidine, CuBr·$SMe_2$, 130 °C, 9 h, (ii) *n*-$Bu_4NF$, THF, 0 °C, 30 min.

**Table 2. Intramolecular Ullmann Macrocyclization**



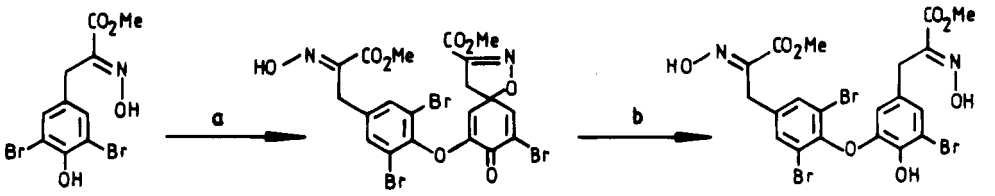

| $R^1$ | $R^2$ | $R^3$ | solvent | yield (%) |
|---|---|---|---|---|
| H | H | H | pyridine | 58 |
| H | $CH_3$ | H | pyridine | 49 |
| $OCH_3$ | H | H | pyridine | 46 |
| $OCH_3$ | $CH_3$ | H | pyridine | 45 |
| OH | H | $CO_2CH_3$ | pyridine | 51 |
| $OCH_3$ | H | $CO_2CH_3$ | pyridine | 51 |
| $OCH_3$ | H | $CO_2CH_3$ | dioxane | 31 |
| $OCH_3$ | H | $CO_2CH_3$ | collidine | 50 |

The Ullmann reaction is a reliable method to bring together two aromatic nuclei through ether linkage. Strategies, based on Ullmann reaction, have been successful in synthesizing compounds of cyclic peptide family such as K-13, OF-4949. In addition, the intramolecular macrocyclization through Ullmann reaction (Table 2) has been a major contribution in the synthesis of 14-membered cyclic isodityrosine subunit of bouvardin series. However, it should be noted that the Ullmann reaction, as discussed in preceding lines did require both high temperature and long hours. The application of the Ullmann reaction to the vancomycin family is still precluded. The lack of interest could perhaps be attributed to the presence of two diaryl ether linkages in vancomycin group where the performances of two Ullmann reactions may lead to unforseen difficulties.

## B. TTN Oxidative Coupling Method

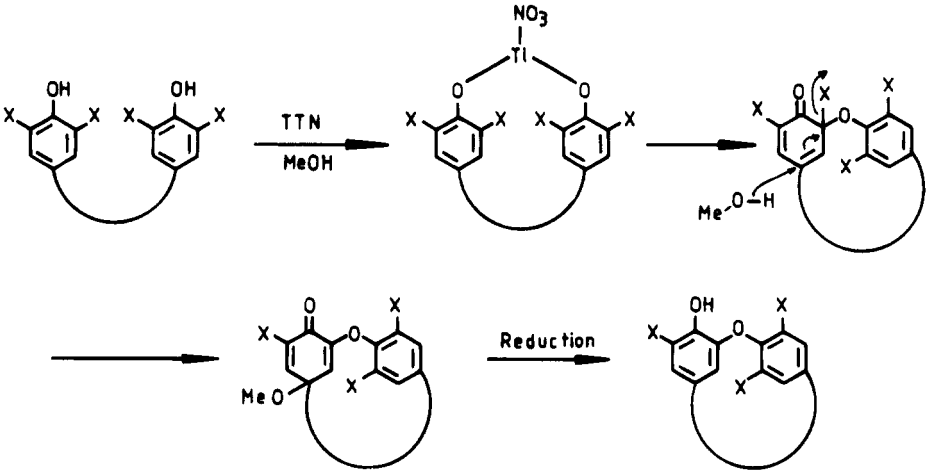
The concept of TTN oxidative phenolic coupling to prepare diphenyl ether was pioneered by Yamamura et al.[43] This brilliant biomimetic phenolic oxidation is increasingly being recognized as a useful and versatile method for effecting both intra- and intermolecular coupling (Scheme 14). In TTN cyclization, it is mandatory to utilize *O,O'*-dihalophenol which controls the oxidation potential and the regioselec-

**Scheme 14**[a]

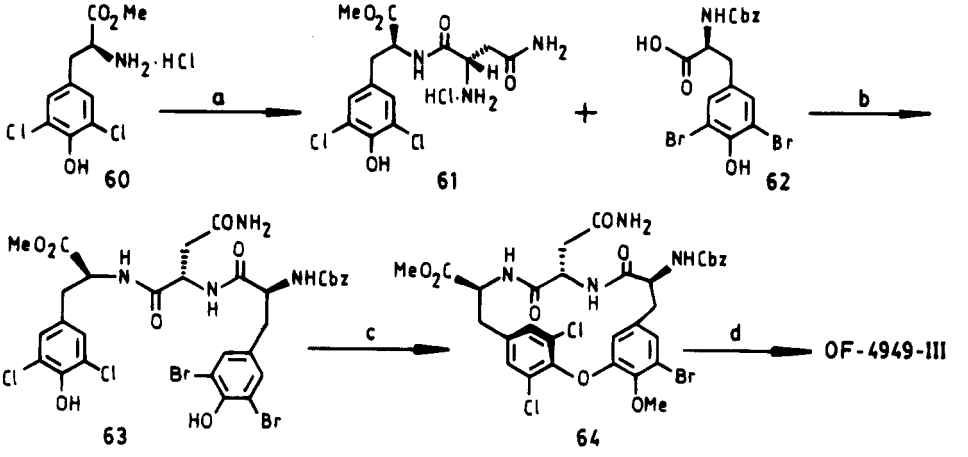


[a] (a) TTN, MeOH; (b) Zn–AcOH.

**Scheme 15. Mechanism of TTN Oxidative Coupling Reaction**



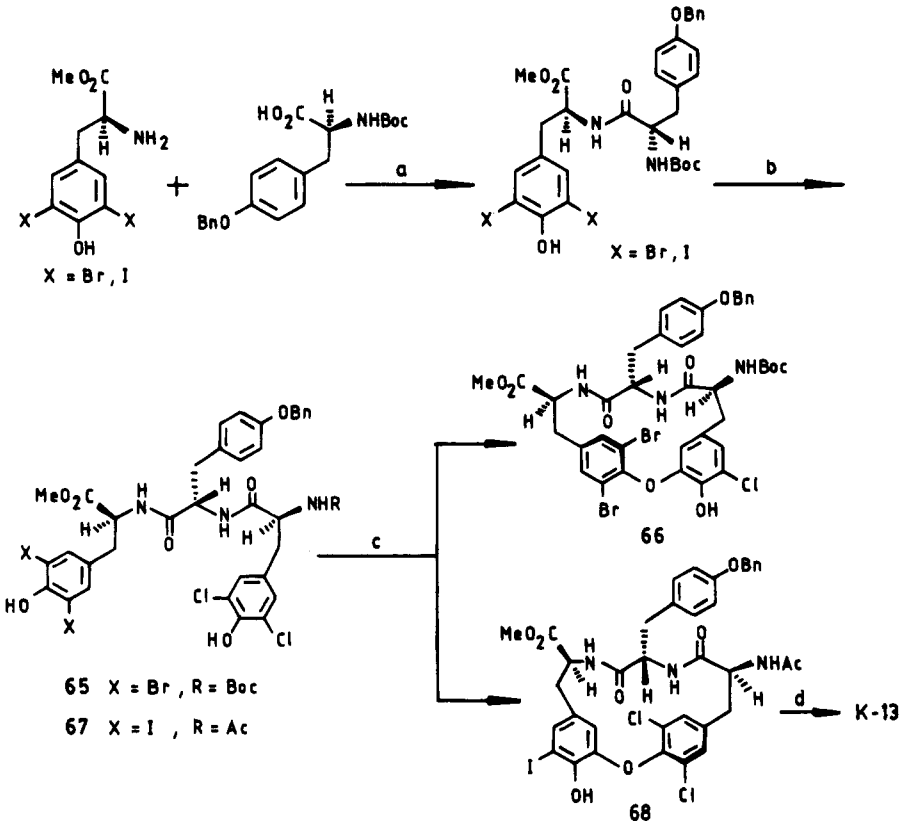
**Scheme 16**[a]



[a] (a) (i) (*S*)-*N*-Boc-aspargine, DCC, HOBT, *N*-methylmorpholine, (ii) HCl–dioxane; (b) DCC, HOBT, *N*-methylmorpholine; (c) (i) TTN, MeOH, (ii) Zn–AcOH, (iii) $CH_2N_2$, MeOH; (d) (i) $H_2$, Pd-black, HCl–THF, (ii) $(Boc)_2O$, $Et_3N$, dioxane, (iii) $H_2$, Pd-black, NaOAc, MeOH, (iv) NaOH, (v) HCl then NaOH.

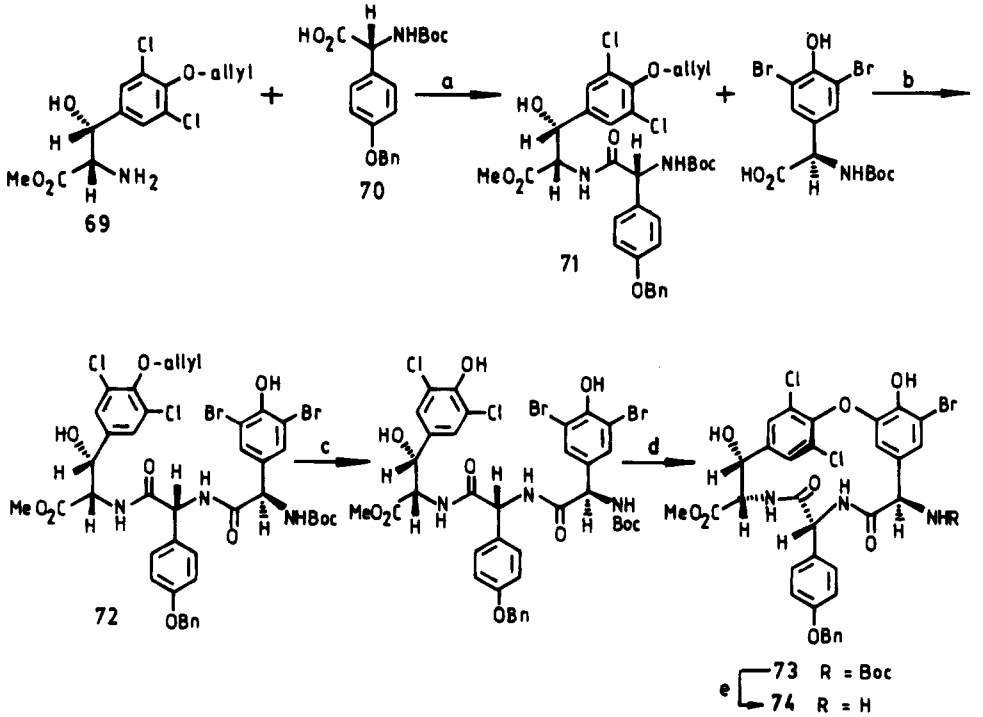
tivity.[18] The mechanism of TTN oxidation is delineated in Scheme 15. Yamamura and associates have examined the scope of this methodology in the synthesis of several diphenyl ether-containing natural products. For instance, in the synthesis[44] of OF-4949 III, the authors initially obtained the dipeptide **61** by the coupling reaction between suitably substituted (*S*)-tyrosine (**60**) and (*S*)-*N*-Boc-aspargine followed by *N*-Boc deprotection (Scheme 16). It was further condensed with (*S*)-*N*-Cbz-3,5-dibromotyrosine (**62**) to produce the tripeptide cyclization intermediate **63**. The crucial cyclization of **63** with TTN followed by reduction with Zn provided the diphenyl ether derivative **64**. Subsequent minor chemical modification on **64** completed the total synthesis of OF-4949 III. In an analogous fashion, Yamamura et al. formulated[45] the synthetic route to K-13; however, some unusual and interesting observations were noted during this exploration. For instance, the synthesis of the tripeptide intermediate **65** was first ensured by essentially the same procedure (Scheme 17). The TTN cyclization and conventional reduction of **65** produced the undesired cyclic product **66**. This unusual mode of cyclization was explained by considering stereochemical strain in the transition state. The prediction also suggested that replacement of bromine with iodine was obligatory to alter the course of this pathway. Accordingly, Yamamura et al. synthesized the modified iodo-substituted tripeptide **67** by the same route. Indeed, the TTN oxidation and Zn reduction of **67** provided the diphenyl ether **68**. With the oxidative coupling occurring in a desired direction, the total synthesis of K-13 was ensured as illustrated in Scheme 17.

**Scheme 17**[a]



[a] (a) DCC, HOBT, *N*-methylmorpholine, DMF; (b) (i) HCl–dioxane, (ii) (*S*)-*N*-acetyl-3,5-dichlorotyrosine, DCC, HOBT, *N*-methylmorpholine; (c) (i) TTN, MeOH–THF (1:2.5), (ii) Zn–AcOH; (d) (i) $H_2$, Pd-black, NaOAc, THF–MeOH (1:1), (ii) 1 N NaOH (aq) then Amberlite IR-120 ($H^+$).

**Scheme 18**[a]

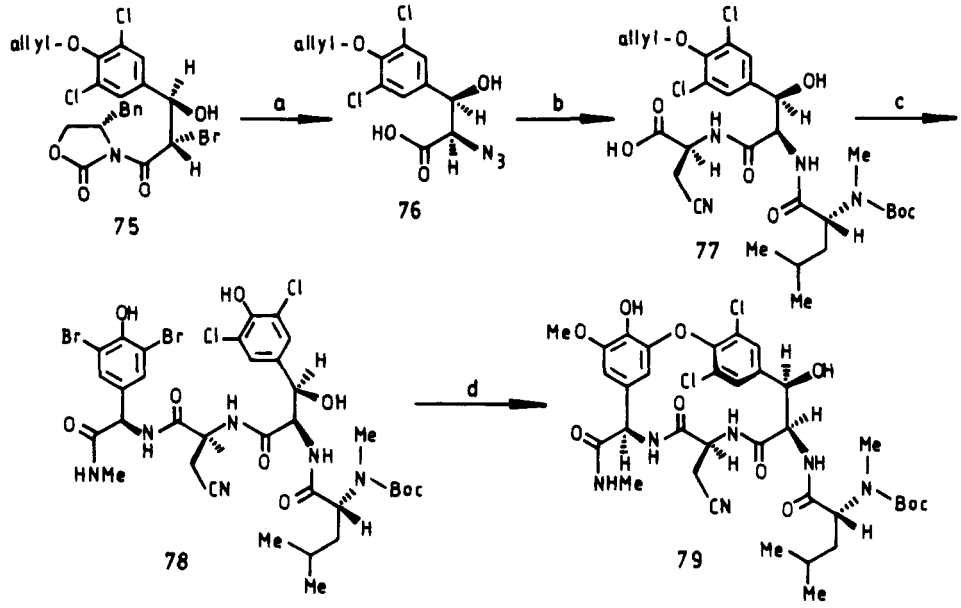


[a] (a) (i) Diisopropylcarbodiimide, HOBT; (b) (i) TFA, thioanisole, (ii) EDCI, HOBT; (c) $Bu_3SnH$, Pd(II); (d) (i) TTN, THF–MeOH (5:1), pyridine, (ii) $CrCl_2$; (e) TFA, thioanisole.

The most elaborate and truly fascinating demonstrations of TTN oxidative macrocyclization strategy were investigated by Evans' associates[46] in the synthesis of monocyclic and bicyclic C,D,E-phenyl ether fragments of vancomycin. The author's own methodology[47] was adopted to synthesize the key intermediates **69** and **76** which comprised the C and E rings of vancomycin.

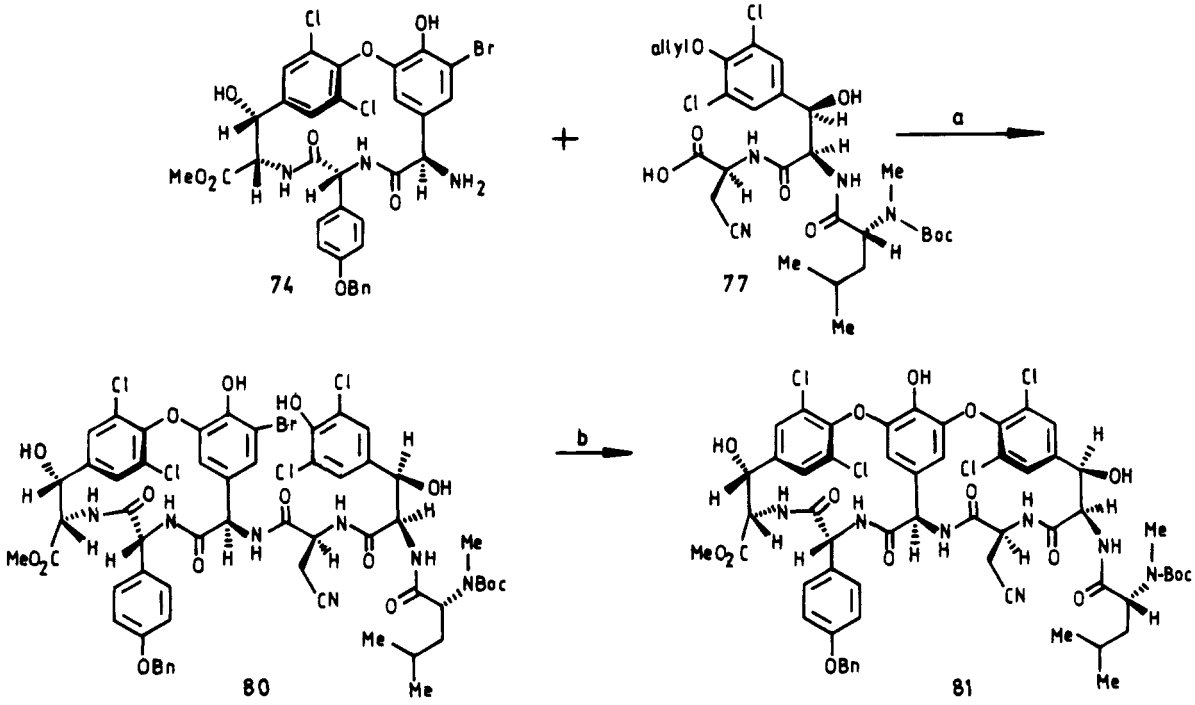
The coupling reaction between **69** and (*R*)-*N*-Boc-*p*-(benzyloxy)phenylglycine[48] (**70**) provided the dipep-

**Scheme 19**[a]



[a] (a) (i) $NaN_3$, DMSO, (ii) LiOOH; (b) (i) β-cyanoalanine TMS-ethyl ester, EDCI, HOBT, (ii) $SnCl_2$, MeOH, (iii) (*R*)-*N*-Boc-*N*-methylleucine, EDCI, HOBT, (iv) TBAF; (c) (i) (*R*)-*N*-Boc-3,5-dibromo-4-hydroxyphenylglycine *N*-methylamide, EDCI, HOBT, (ii) $Bu_3SnH$, Pd(II); (d) (i) TTN, $CH_2Cl_2$–MeOH (1:1), (ii) $CrCl_2$.

**Scheme 20**[a]

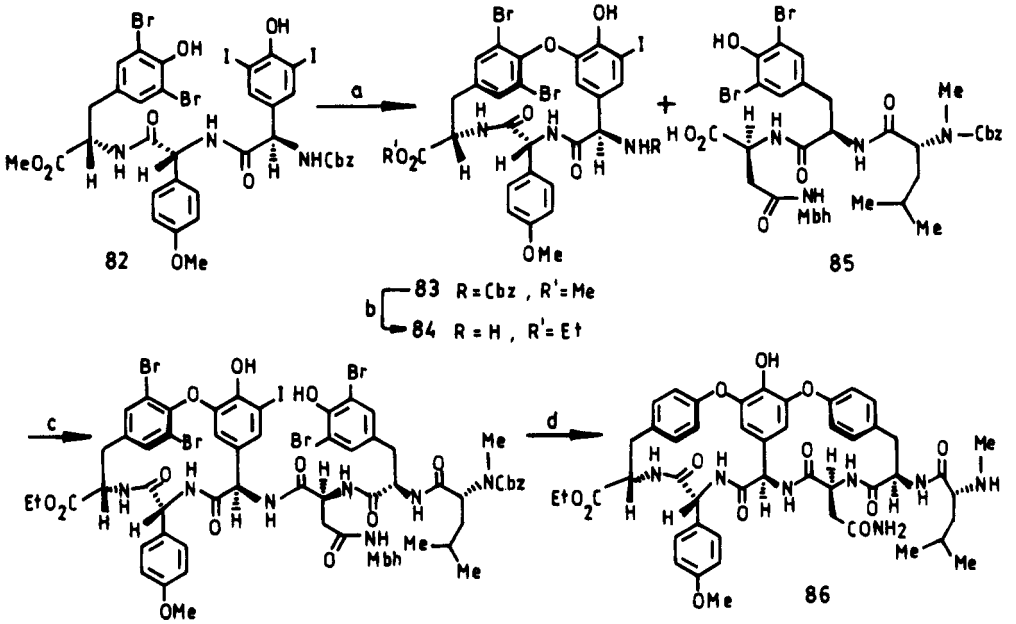


[a] (a) (i) Diisopropylcarbodiimide, HOBT, (ii) $Bu_3SnH$, Pd(II); (b) (i) TTN (5 equiv), $CH_2Cl_2$–MeOH (30:1), 1 mM concentration, 4 h, −23 °C, (ii) $CrCl_2$.

tide **71** with less than 1% racemization. Subsequent deprotection of *N*-Boc group and condensation with (*R*)-*N*-Boc-3,5-dibromophenylglycine yielded the tripeptide **72** with 4% racemization. After removal[49] of *O*-allyl group, cyclization was performed with excess of TTN. However, they modified the reduction step by using[50] $CrCl_2$ instead of Zn, which led to the formation of monocyclic oligopeptide intermediate **73** in 42% overall yield (Scheme 18).

The same group then synthesized the tetrapeptide cyclization intermediate **78** starting from α-bromocarboximide **75** (Scheme 19). Nucleophilic dis placement with $NaN_3$ and hydrolysis of oxazolidinone ring provided the α-azido acid **76** which was connected sequentially with (*S*)-β-cyanoalanine, and (*R*)-*N*-Boc-*N*-methyleucine through peptide bonds to yield **77**. By a general strategy **77** was further elaborated to the tetrapeptide **78** which on TTN oxidative coupling and $CrCl_2$ reduction furnished the biaryl ether **79**. The above results undoubtedly demonstrated the power of TTN oxidative macrocyclization in the preparation of monocyclic oligopeptides (**73** and

**Scheme 21**[a]




[a] (a) (i) TTN, MeOH–THF (1:19), (ii) Zn–AcOH; (b) (i) 30% HBr, AcOH, anisole, (ii) EtOH; (c) DCC, HOBT, *N*-methylmorpholine; (d) (i) TTN, MeOH, −10 °C, 8 h, (ii) Zn–AcOH, (iii) $H_2$, Pd-black, MeOH, (iv) 30% TFA in $CH_2Cl_2$, anisole.

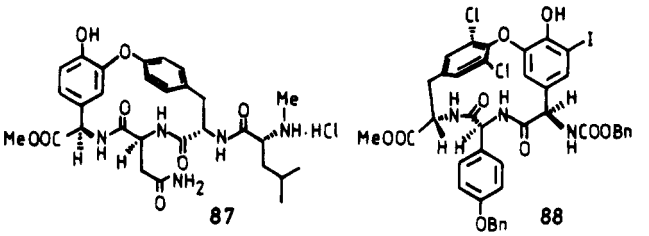
**79**). Obviously the more challenging fragment, namely bicyclic C,D,E-phenyl ether of vancomycin, then became their target molecule.

The two fragments **74** and **77**, as already described, were connected by a general strategy followed by deprotection of the *O*-allyl group to provide the hexapeptide intermediate **80** (Scheme 20). It was gratifying to note that final macrocyclization of **80** with TTN and $CrCl_2$ reduction occurred efficiently to furnish the first bicyclic compound **81** in 40% overall yield.

The structural framework of **81** correlates with C,D,E-phenyl ether fragment of vancomycin except for the additional two chlorine substituents in ring C and E. In principle selective hydrodechlorination could be expected to provide the actual C,D,E fragment; however, in practice, it could be a Herculean task. The concomitant formation of a number of possible analogues during dechlorination could not be ruled out.

Almost simultaneously, Yamamura et al. also examined[51] the synthesis of the model bicyclic hexapeptide fragment constituting C,D,E rings of vancomycin on the basis of their own TTN oxidative cyclization approach. The benzylic hydroxyls at the chiral centers at C-7 and C-22 of vancomycin were conspicuously absent from their model structures.

In accordance with their previous publication,[52] the synthesis of the tripeptide **82** was first accomplished (Scheme 21). Subsequent treatment with excess of TTN gave the monocyclic diphenyl ether **83** (43%) which was successively treated with HBr–AcOH and refluxed with ethanol to provide the ethyl ester **84** containing free $NH_2$ group. It was then coupled with the tripeptide **85** by a general strategy and subjected to second TTN oxidation and Zn reduction to afford the bicyclic diphenyl ether **86** (34.7%), characterized after reductive debromination and hydrolysis. Yamamura et al. also examined the model monocyclic tetrapeptide fragments **87** and **88** related to vancomycin antibiotic.

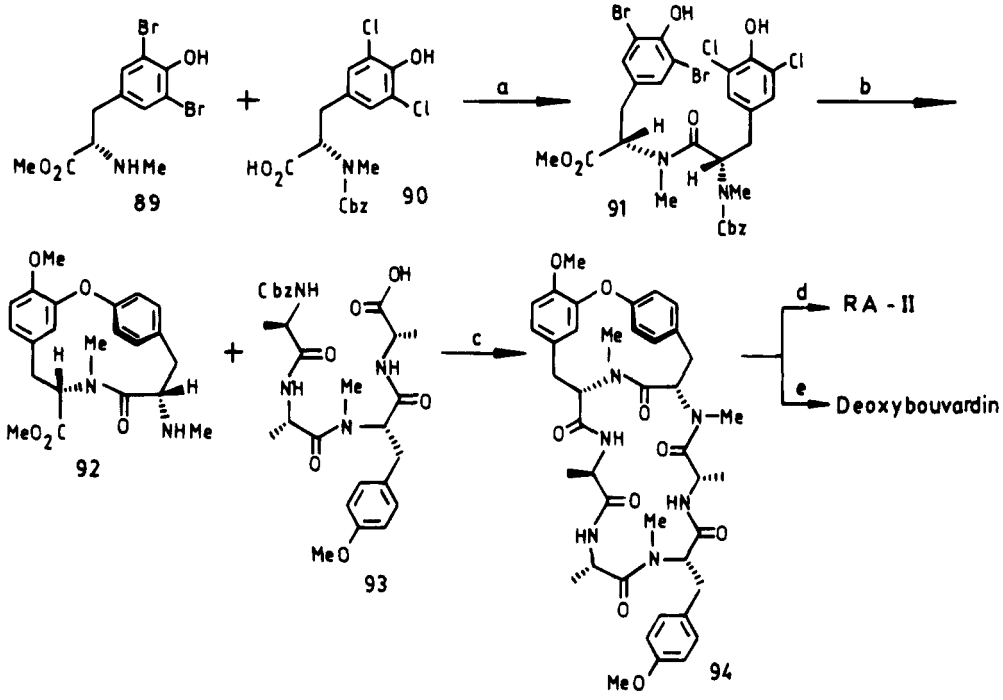



Inoue and co-workers examined[53] the synthesis of deoxybouvardins and RA-VII by the application TTN cyclization approach. (*S*)-*N*-Methyl-3,5-dibromotyrosine methyl ester (**89**) and (*S*)-*N*-methyl-*N*-Cbz-3,5-dichlorotyrosine (**90**) were coupled by a general strategy to give dipeptide **91**. The TTN cyclization of **91** occurred in 5.2% yield which was followed by Zn reduction, esterification, and hydrogenation to give **92**. Its condensation with the tetrapeptide **93** followed by macrocyclization in a conventional way to provide **94**. Manipulations of functional groups gave deoxybouvardins and RA-II (Scheme 22).

## C. Bromoquinone Substitution Method

Undoubtedly many impressive strategies and modifications in biaryl ether synthesis have been forwarded; their applications to the vancomycin family are fraught with many limitations. It is also pertinent to mention that many intricate problems of vancomycin synthesis have still remained unaddressed. For instance, no methodology has yet been successful in directly coupling the tyrosine derivatives to the centrally located *p*-hydroxyphenylglycine residue of vancomycin. Rama Rao and co-workers[54] have developed a complimentary but exceptionally potent methodology to construct oxidatively coupled aromatic nuclei under seemingly mild conditions, ensuring beyond doubt the stereochemical features

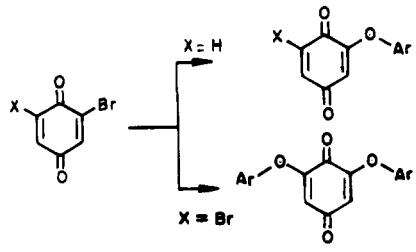
**Scheme 22**[a]




[a] (a) DCC, dioxane; (b) (i) TTN, MeOH, (ii) Zn–AcOH, (iii) $CH_2N_2$, $Et_2O$, MeOH, (iv) $H_2$, Pd/C, KOAc, MeOH; (c) (i) DCC, dioxane–$CH_2Cl_2$, (ii) 0.2 N NaOH, MeOH–MeCN, (iii) $H_2$, Pd/C, (iv) DCC, dioxane; (d) (i) $AlCl_3$, EtSH, (ii) $CH_2N_2$; (e) $AlCl_3$, $CH_2Cl_2$.

of reacting molecules and offering high yields of the product. Basically, the approach features the displacement[55] of bromine atoms of bromobenzoquinones with phenolic derivatives providing mono- or bis-(aryloxy)benzoquinones in good yields (Scheme 23).

**Scheme 23. Bromoquinone Substitution Reactions**

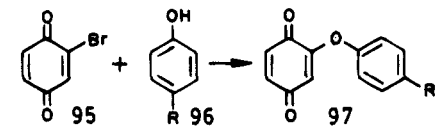



Subsequent manipulations of the benzoquinone skeleton to the corresponding aryl amino acid relied on the Pd-catalyzed cross-coupling reaction[56] of aryl triflates with alkenyltributyltin and the Sharpless asymmetric dihydroxylation reaction.[42]

2-Bromobenzoquinone (**95**) was coupled with *p*-cresol (**96b**) in the presence of KF or $K_2CO_3$ to afford the 2-(aryloxy)benzoquinone derivative **97b** in 85% yield. The efficacy of this reaction was substantiated by a number of displacement reactions carried out with a variety of phenoxides. It should be pointed out that the conditions for this displacement were mild and the chiral amino acid groups were tolerated in the phenoxide without any degree of racemization (Scheme 24).

Compound **97e** was chosen as the focal point for K-13 synthesis. Subsequent reduction of **97e** with dithionite provide the hydroquinone **98** which on direct trifluoromethanesulfonylation gave **99**, thus indicating the higher reactivity of the 1-hydroxyl group, probably due to hydrogen bonding (as steric

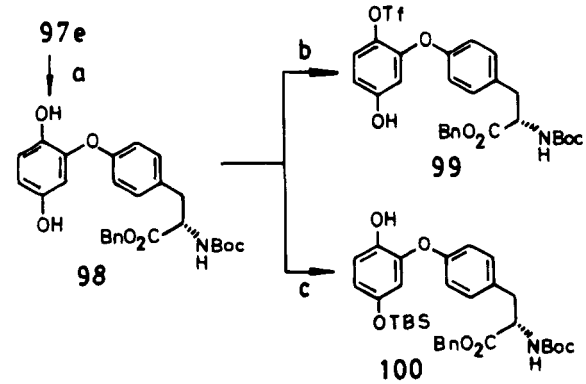
**Scheme 24. 2-Bromoquinone Substitution Reactions**




| | R | Yield % | | R | Yield % |
|---|---|---|---|---|---|
| a | H | 79 | d | (S)-$CH_2$-CH(NHBOC)-$CO_2Me$ | 81 |
| b | Me | 85 | | | |
| c | CHO | 78 | e | (S)-$CH_2$-CH(NHBOC)-$CO_2Bn$ | 80 |

factors suggest that the 4-hydroxyl group should be the preferred site of reaction) (Scheme 25). Therefore

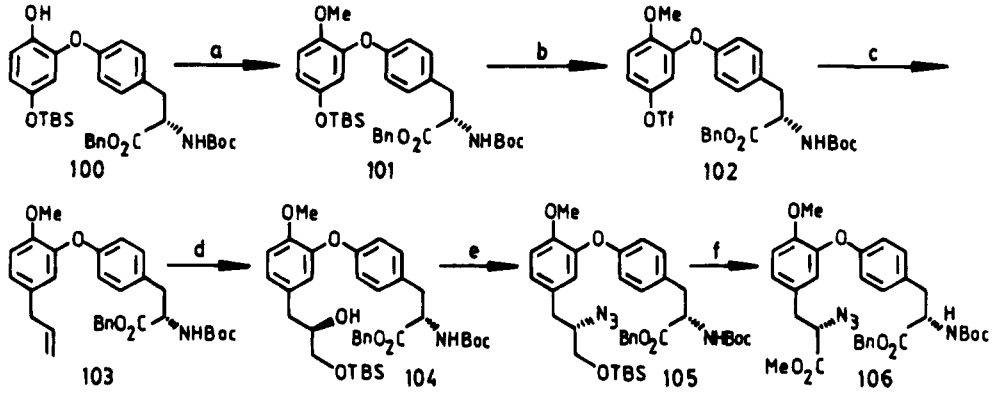
**Scheme 25**[a]




[a] (a) $Na_2S_2O_4$, $CHCl_3$–$H_2O$; (b) $Tf_2O$, Py, $CH_2Cl_2$, 2 h; (c) TBS–Cl, $Et_3N$, $CH_2Cl_2$, 5 h.

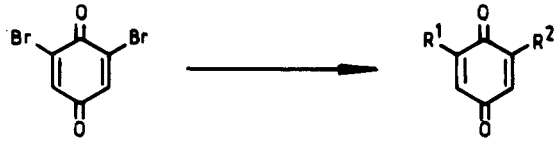
to obtain the 4-*O*-triflate derivative, hydroquinone **98** was reacted with 1 equiv of *tert*-butyldimethylsilyl (TBS) chloride to provide the 4-*O*-silylated derivative **100**, whose methylation with $K_2CO_3$ and dimethyl sulfate (DMS) gave **101** (Scheme 26). Successive desilylation and trifluoromethanesulfonylation of **101**

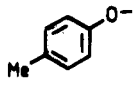
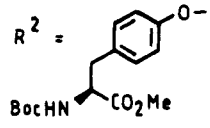
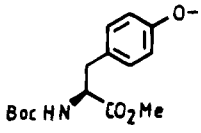
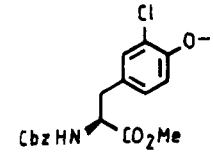
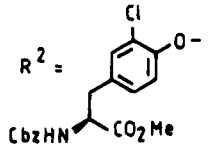
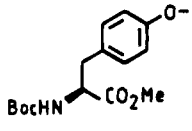
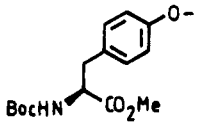
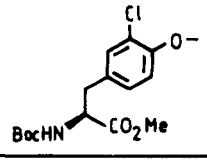
**Scheme 26**[a]




[a] (a) DMS, $K_2CO_3$, acetone, reflux; (b) (i) TBAF, THF, (ii) $Tf_2O$, pyridine, $CH_2Cl_2$; (c) allyltributyltin, $Pd(PPh_3)_4$, LiCl, dioxane, reflux; (d) (i) DHQDPCB, $K_2CO_3$, $K_3Fe(CN)_6$, $OsO_4$, *tert*-butyl alcohol–$H_2O$ (1:1), (ii) TBS–Cl, imidazole, cat. DMAP, $CH_2Cl_2$; (e) (i) MsCl, $Et_3N$, $CH_2Cl_2$, (ii) $NaN_3$, DMF, 90 °C; (f) (i) Jones reagent, acetone, (ii) $CH_2N_2$, ether.

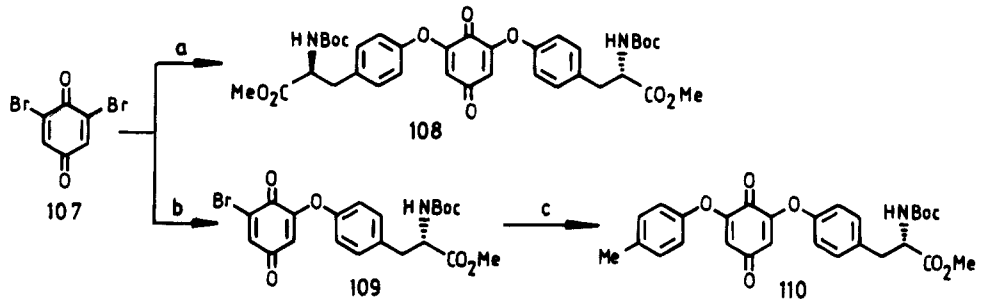
**Table 3. Mono- and Disubstution Reactions of 2,6-Dibromobenzoquinone**




| Entry | $R^1$ | $R^2$ | Reagent | Yield (%) |
|---|---|---|---|---|
| 1 | $R^1 = R^2 =$  | | KF | 75 |
| 2 | $R^1 = R^2 =$  | | KF | 72 |
| 3 |  |  | $K_2CO_3$ | 69 |
| 4 | $R^1 = R^2 =$  | | $K_2CO_3$ | 72 |
| 5 | Br |  | KF | 83 |
| 6 | Br |  | $K_2CO_3$ | 85 |
| 7 |  | Br | $K_2CO_3$ | 86 |

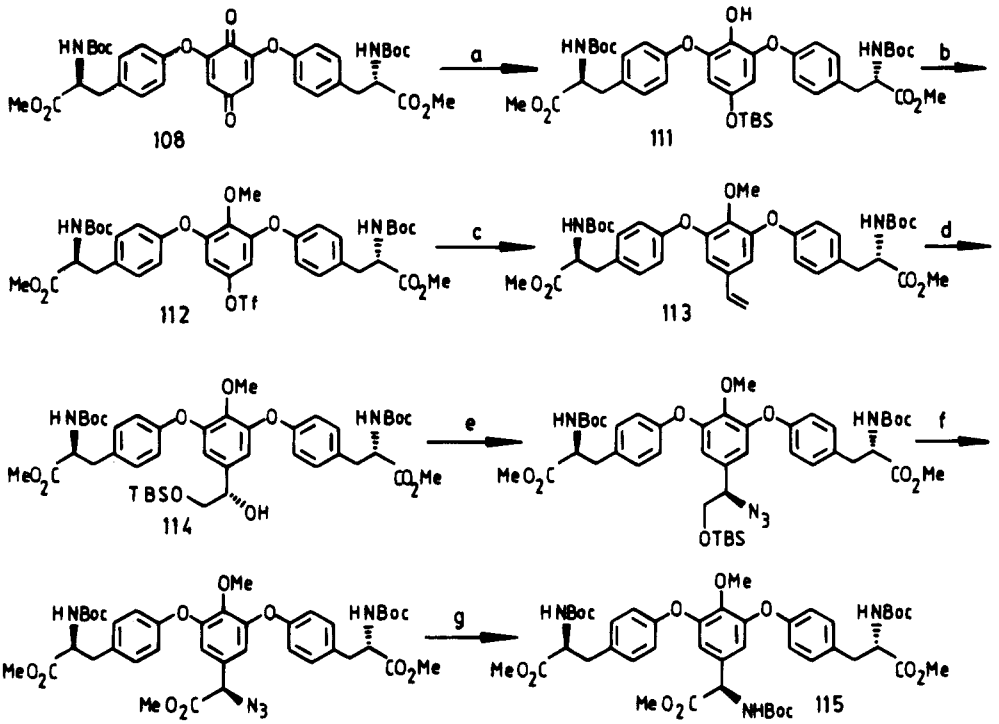
then gave the requisite 4-*O*-triflate derivative **102**. Its reaction[56] with allyl tributyltin in the presence of LiCl and $Pd(PPh_3)_4$ in refluxing dioxane gave the allyl derivative **103**, whose subsequent Sharpless asymmetric dihydroxylation reaction with dihydroquinidine–*p*-chlorobenzoate and mono-TBS-silylation produced **104** with 62% diastereomeric excess. Finally, **104** was transformed into the azido derivative via the mesylate followed by Jones' oxidation and *in situ* esterification[54] provided the key intermediate

**Scheme 27**[a]



[a] (a) (*S*)-*N*-Boc-tyrosine methyl ester (2 equiv), KF, DMF, 90 °C; (b) (*S*)-*N*-Boc-tyrosine methyl ester (1.0 equiv) KF, DMF, 90 °C; (c) *p*-cresol, KF, DMF, 90 °C.

**Scheme 28**[a]



[a] (a) (i) $Na_2S_2O_4$, $CHCl_3-H_2O$, (ii) TBSCl, $Et_3N$, $CH_2Cl_2$; (b) (i) DMS, $K_2CO_3$, acetone, reflux, (ii) TBAF, THF, (iii) $Tf_2O$, pyridine, $CH_2Cl_2$; (c) vinyltributyltin, $PdCl_2(PPh_3)_2$, DMF, 90 °C; (d) (i) DHQ-9-PHN, $K_2CO_3$, $K_3Fe(CN)_6$, $OsO_4$, *tert*-butyl alcohol–$H_2O$ (1:1), (ii) TBSCl, $Et_3N$, $CH_2Cl_2$; (e) (i) MsCl, $Et_3N$, $CH_2Cl_2$, (ii) $LiN_3$, DMF, 60 °C; (f) (i) TBAF, THF, (ii) Jones reagent, acetone, (iii) $CH_2N_2$, ether; (g) (i) 10% Pd/C, $H_2$ (1 atm), MeOH, (ii) $(Boc)_2O$, THF.

**106** (Scheme 26) which had been previously converted into K-13 by the Evans' group[32] (Scheme 8).

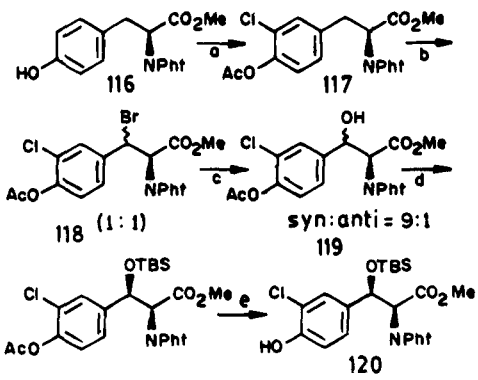
Attention was then focussed on the displacement reactions of 2,6-dibromobenzoquinone (**107**) with phenoxide in order to obtain 2,6-bis(aryloxy)benzoquinones.[57] Substitution of bromine atoms in **107** with 2 equiv of various tyrosine derivatives in the presence of KF or $K_2CO_3$ furnished the requisite bis(aryloxy)benzoquinones **108** in good yield. Careful examination of the reaction suggested that the substitution reaction probably occurred in a stepwise fashion. This provided an opportunity to attempt selective substitution of one bromine atom of **107** with 1 equiv of tyrosine derivative, leading to the formation of monobromomono(aryloxy)benzoquinone **109** in 81% yield. Not surprisingly, therefore compound **109** with 1 equiv of *p*-cresol furnished the diaryloxy derivative **110** (Scheme 27). This stepwise substitution reaction was particularly relevant in the synthesis of vancomycin because C and E rings present in the active center of the molecule contained stereogenically different β-hydroxytyrosine derivatives coupled through ether linkages. A number of phenol derivatives were introduced by the stepwise approach, generating bis(aryloxy)benzoquinones containing different aryl ether substitutions on benzoquinone[57] (Table 3).

The ability to introduce aryl ethers in a stepwise fashion was exploited in the synthesis of the model C,D,E-diphenyl ether fragment of vancomycin.

Compound **108** was converted into **111** by the strategy described earlier. Subsequent sulfonylation provided **112** which was reacted with vinyltributyltin and $PdCl_2$ $(PPh_3)_2$ as catalyst in DMF to give the styrene derivative **113**. The catalytic asymmetric dihydroxylation of **113** with dihydroquinine 9-*O*-(9-phenanthryl) (PHN) ether and selective TBS etherification provided **114** with 80% diastereomeric excess (Scheme 28).

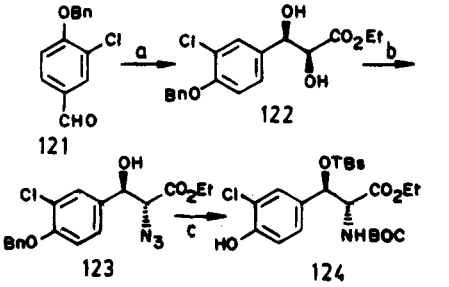
For the conversion of **114** into the chiral glycine side chain, Rama Rao adopted the strategy described for K-13 (Scheme 26) to obtain **115** representing

**Scheme 29**[a]



[a] (a) (i) $SO_2Cl_2$, ether, (ii) $Ac_2O$, pyridine, $CH_2Cl_2$; (b) NBS, AIBN, $CCl_4$, $h\nu$, reflux; (c) $AgNO_3$, acetone–$H_2O$; (d) (i) TBS–OTf, 2,4,6-collidine, $CH_2Cl_2$, 0 °C, (ii) separation; (e) NaOMe, MeOH.

**Scheme 30**[a]



[a] (a) (i) $Ph_3PCHCO_2Et$, benzene, (ii) DHQDPCB, $OsO_4$, $K_2CO_3$, $K_3Fe(CN)_6$, *t*-BuOH–$H_2O$; (b) (i) *p*-$NO_2C_6H_4SO_2Cl$, $Et_3N$, $CH_2Cl_2$, 0 °C, (ii) $NaN_3$, DMF, 50 °C; (c) (i) TBS–OTf, 2,4,6-collidine, $CH_2Cl_2$, 0 °C, (ii) $PtO_2$, $H_2$, $(Boc)_2O$, EtOAc.

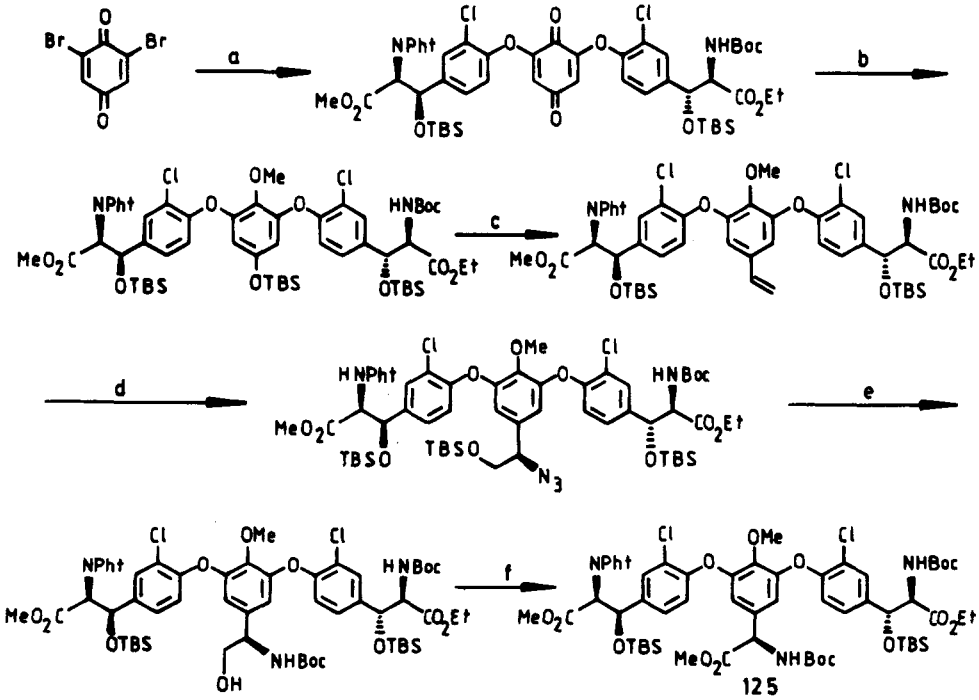
model C,D,E rings of vancomycin.[57]

The synthesis of vancomycinic acid[7] **125** (Scheme 31) by taking into account the quinone approach was also explored by Rama Rao's group.[58] The synthesis of β-hydroxytyrosines **120** (Scheme 29) and **124** (Scheme 30) constituting C and E rings of vancomycin were first pursued.[59] The route selected for the intermediate **120** involved a straightforward transformation of *N*-phthalidotyrosine derivative **116** into the corresponding methyl (*S*)-*N*-phthalido-3-chloro-4-acetyltryrosinate (**117**). Its benzylic bromination with NBS produced an almost 1:1 diastereomeric mixture of bromides **118**. The separation of diastereomers was not required because subsequent hydrolysis with aqueous silver nitrate provided the β-hydroxytyrosinate derivative **119** in a more respectable ratio of 9:1. The high degree of diastereoselectivity during the hydrolysis could be attributed to the preferential attack of the nucleophile (OH) on the carbocation from the sterically favoured β-face.[60] The pure isomer of **119** was transformed into **120** as shown in Scheme 29.

For the planned synthesis of the second hydroxytyrosinate **124**, the readily available 3-chloro-4-(benzyloxy)benzaldehyde (**121**) was olefinated and then subjected to Sharpless asymmetric dihydroxylation with dihydroquinine *p*-chlorobenzoate as chiral ligand to provide the diol **122** with 96% diastereomeric excess. The advantage of greater reactivity of the hydroxyl group at C-2 was then exploited to prepare the corresponding 2-azido derivative **123** via the nosylate intermediate.[61] Sequential reactions as shown in Scheme 30 furnished **124**.

Having obtained both the key intermediates **120** and **124**, all that remained was the stepwise introduction of these phenoxides onto the 2,6-dibromobenzoquinone ring followed by derivatization of chiral arylglycine as a central amino acid residue. This transformation is expeditiously described in Scheme 31.

**Scheme 31**[a]

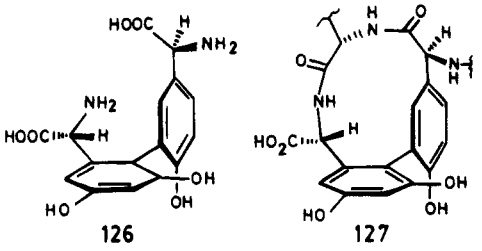


[a] (a) (i) $K_2CO_3$, 120, DMF, 0 °C, (ii) $K_2CO_3$, 124, DMF, 0 °C, (b) (i) $Na_2S_2O_4$, $CHCl_3$–$H_2O$, (ii) TBSCl, $Et_3N$, $CH_2Cl_2$, (iii) DMS, $K_2CO_3$, acetone; (c) (i) TBAF (0.5 equiv), THF, 0 °C, (ii) $Tf_2O$, pyridine, $CH_2Cl_2$, 0 °C, (iii) vinyltributyltin, LiCl, $Pd(PPh_3)_4$, 2,6-di-*tert*-butyl-4-methylphenol (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.

The above study constitutes the first synthesis of vancomycinic acid (**125**).[58]

## III. Synthetic Studies toward Biaryl Segment of Vancomycin

The biaryl amino acid (actinoidic acid, **126**) is a common segment in all the antibiotics of vancomycin family. This structural feature distinctly differs from biaryl systems of other naturally occurring compounds. The system in vancomycin is elegantly incorporated in a 12-membered cyclic structure **127** constituting rings 5 and 7 in its framework. 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. The abundantly present phenylglycine residues in vancomycin provide excellent manifestation for creative skills and also present opportunity to test the limits of current synthetic methodologies.[19] In spite of major advancements that have occurred in the synthesis of biaryl compounds, efforts directed toward vancomycin biaryl segment have been scarce. A recent review[62] on directed synthesis of biaryl compounds was published in 1990, however, the first report[63] on biaryl segment related to vancomycin appeared only in 1992. This review explicitly narrates strategies and tactics for the synthesis of biaryl compounds, many of which were indeed exploited for vancomycin. Synthesis of biaryl segment of vancomycin requires extensive investigations to address specific issues. For example, due to the presence of phenyl glycine residues in actinoidic acid any synthetic development requires significant attention to circumvent racemization. The possibility of atropisomerization across the biaryl axis provides yet another prospect to deal with. Above all, the assembly of 12-membered cyclic structure of vancomycin is a difficult proposition.



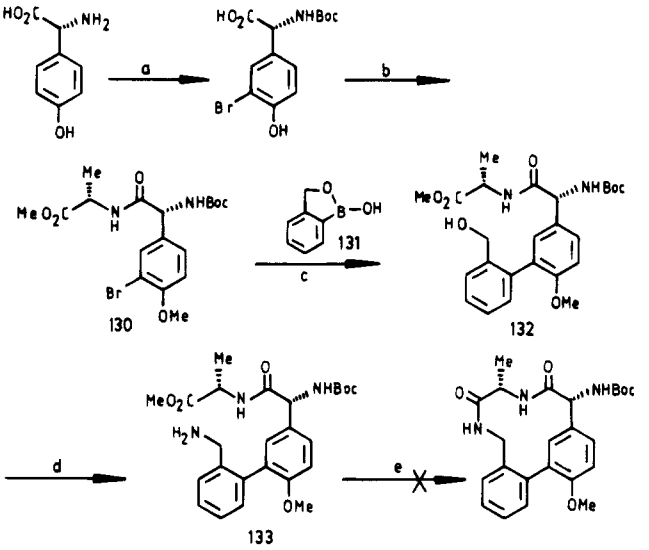
126 127

In principle, two major strategies can be evolved to synthesize the 12-membered biaryl macrocyclic structure **127** of vancomycin (Scheme 32). In the first instance, one can plan the synthesis of appropriately substituted biaryl diamino diacid intermediate **128** and then attempt cyclization through peptide bond leading to the 12-membered macrocyclic structure. Alternatively, one can plan the synthesis of a linear tripeptide **129** and then proceed for macrocyclization through C−C aryl coupling reaction.

The following are the synthetic strategies pertaining to the biaryl system of vancomycin. Except studies described by the Edwards' group[63] on attempted 12-membered macrocyclization, other studies are invariantly confined to the synthesis of only actinoidic acid derivative. On the other hand Evans' group[64] has synthesized the actual 12-membered macrocyclic system of vancomycin by adopting the second strategy wherein the aryl coupling of a linear tripeptide system was examined at a final stage.

In the synthetic strategy by the application of Suzuki biphenyl reaction[65] reported by Edwards' group,[63] (*R*)-4-hydroxyphenylglycine was converted into 3-bromo-4-hydroxyphenylglycine which was subsequently coupled with (*S*)-alanine methyl ester to provide the dipeptide **130** (Scheme 33). Treatment

**Scheme 33**[a]

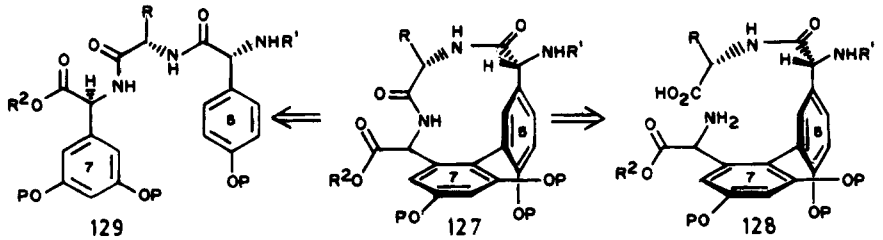


[a] (a) (i) $Br_2$, AcOH, (ii) $(Boc)_2O$; (b) (i) DCC, HOBT, (*S*)-alanine methyl ester, (ii) $K_2CO_3$, $(CH_3)SO_4$, DMF, 25 °C; (c) Pd(O), 131; (d) (i) $HN_3$, Mitsunobu conditions, (ii) $H_2$, 10% Pd/C, MeOH/$H_2O$; (e) (i) aqueous NaOH, (ii) HOBT, DMF, DCC.

of **130** with the borate **131** in the presence of Pd catalyst afforded the C−C biaryl derivative **132** whose functional group manipulation provided the amino acid precursor **133**, the macrocyclization of which under various conditions was, however, not successful; dimeric macrocycles were isolated instead.

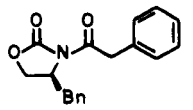
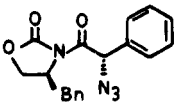
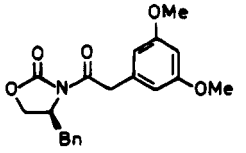
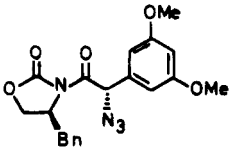
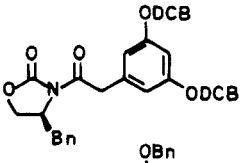
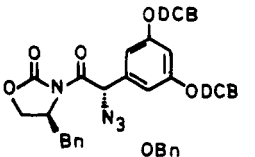
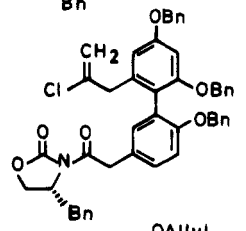
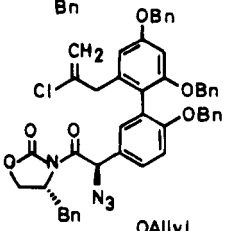
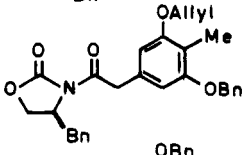
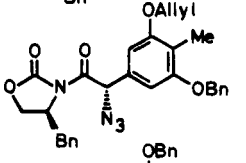
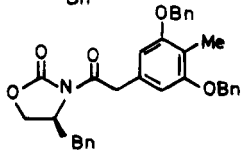
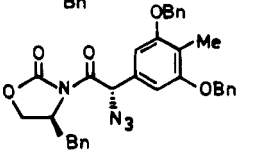
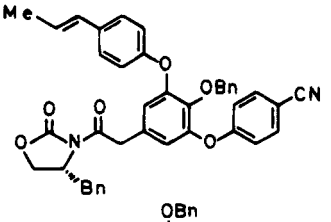
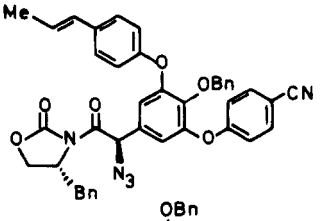
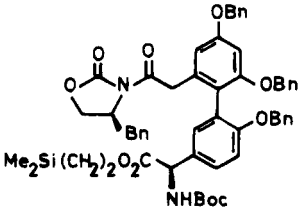
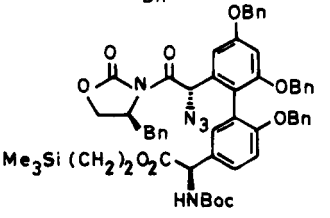
Evans et al. reported[66] asymmetric synthesis of the vancomycin-related α-azido aryl acetic acids by sponsoring their own direct azide transfer methodology.

**Scheme 32. Retrosynthesis of Biaryl Segment**



129 127 128

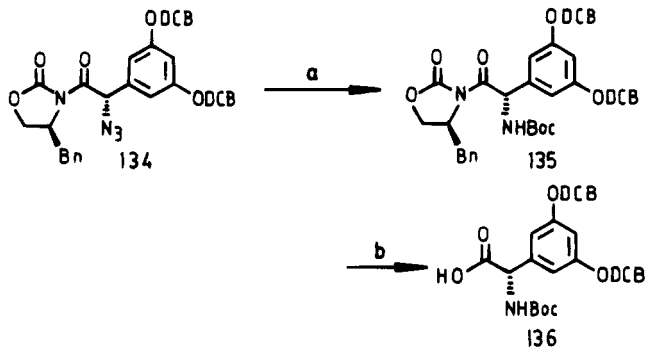
**Table 4. Electrophilic Azidation of Aryl Acetate-Deived Enolates**

| Entry | Substrate | Product | Stereoselection S : R | Yield (%) |
|---|---|---|---|---|
| 1 |  |  | 91 : 9 | 82 |
| 2 |  |  | 90 : 10 | 78 |
| 3 |  |  | 88 : 12 | 76 |
| 4 |  |  | <5 : 95 | 77 |
| 5 |  |  | 90 : 10 | 75 |
| 6 |  |  | 88 : 12 | 81 |
| 7 |  |  | 8 : 92 | 61 |
| 8 |  |  | | |
| | Atropoisomer A | | >95 : 5 | 60 |
| | Atropoisomer B | | 93 : 7 | 60 |

Synthesis of eight aryl glycines related to vancomycin family were accomplished by this method (Table 4). Most interesting results were observed with biaryl substrates in which the stereoselection upto 90% ee were observed (entry 8). Conversion of azido derivative **134** into the corresponding N-protected arylglycine (**135**) retaining benzyl ethers was appealing. Accordingly **134** was reduced with $SnCl_2$ in dioxane–water at ambient temperature followed by addition of $(Boc)_2O$ provided *N*-Boc imide in 96% yield (Scheme 34). Hydrolysis of oxazolidine ring by usual reaction gave *N*-Boc-arylglycine (**136**).

Rama Rao et al. directed[67] the efforts toward the biaryl system of vancomycin in which an intramolecular Pd-assisted aryl coupling was the strategic reaction.[68] During this investigation a sound protocol was also formulated[69] for the asymmetric synthesis of phenylglycine derivatives. The diastereoselective addition of TMSCN onto the Schiff's base **137** obtained from (*R*)-phenylglycinol and appropriate aromatic aldehyde formed (*S,R*)-**138** as a major diastereomer whose hydrolysis with HCl and oxidative cleavage with $Pb(OAc)_4$ provided (*S*)-arylglycine (**139**) (Scheme 35, Table 5).

**Scheme 34**[a]




[a] (a) (i) $SnCl_2$, dioxane–$H_2O$, (ii) $(Boc)_2O$, aqueous $NaHCO_3$; (b) LiOH, THF–$H_2O$, 0 °C.

**Table 5. Diastereoselectivity in Asymmeric Strecker Synthesis**

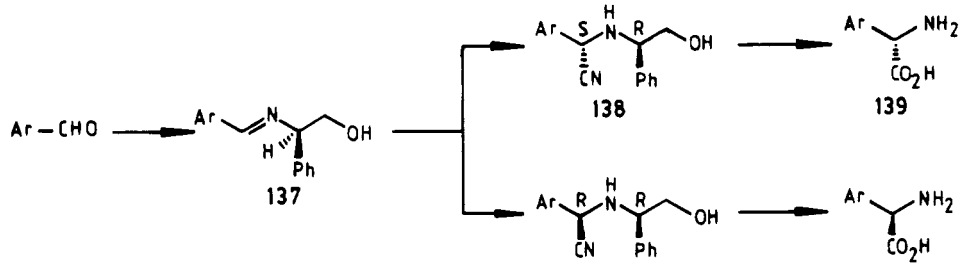
| Ar | (*RS*):(*RR*) | yield (%) |
|---|---|---|
| $C_6H_5$ | 82:19 | 92 |
| *p*-$CH_3$–$C_6H_4$ | 85:15 | 90 |
| *p*-$MeOC_6H_5$ | 90:10 | 95 |
| $C_6H_5$–$CH_2$ | 54:46 | 87 |

The intermolecular esterification of 3,5-dimethoxy-2-bromobenzoyl chloride (**140**) and 4-hydroxyphenylglycinol derivative **141** afforded the ester **142**. Aryl coupling reaction was performed in the presence of $Pd(PPh_3)_2Cl_2$–DMA at 110 °C to afford the lactone **143** which was converted into the aldehyde **144** by simple transformations. Subsequent derivatization of the Schiff's base **145** followed by addition of TMSCN, hydrolysis, and oxidation as described above gave **146** (Scheme 36).

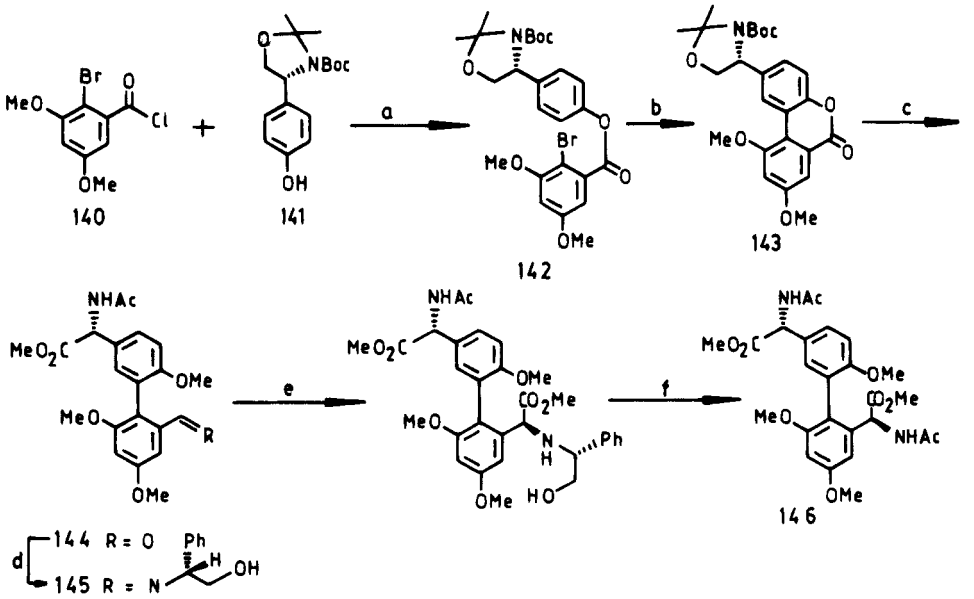
Zhu et al. reported[70] a convergent route to the protected racemic actinoidic acid **146**, a degradation product of vancomycin. They examined Mayer's oxazoline method[71] for regioselective cross coupling between two aromatic subunits **147** and **148**. The latter compound **147** was prepared by simple synthetic transformations (Scheme 37). The biaryl coupling product **149** was converted into the corresponding dialdehyde **150**. A single Strecker reaction carried out with TMSCN and methanolic $NH_3$ gave **151** which was hydrolyzed and acetylated to give the required product **146**.

An efficient second approach to the biaryl segment of vancomycin was developed[72] by Rama Rao and coworkers in which triphenylphosphine-catalyzed biaryl coupling of substituted aryl lithio compound **152** with Pd complex **153** of aromatic Schiff's base leading to **154** formed the basic theme of this approach (Scheme 38).[73] A wide range of substituted biaryls have been prepared using this approach (Table 6). Application of this methodology to the biaryl diamino diacid **146** of vancomycin was initiated with the formation of Pd complex **157** starting from 3,5-dimethoxybenzaldehyde (**155**). Treatment with aniline provided the Schiff's base **156** which was immediately

**Scheme 35. A New Approach to Chiral α-Arylglycine**

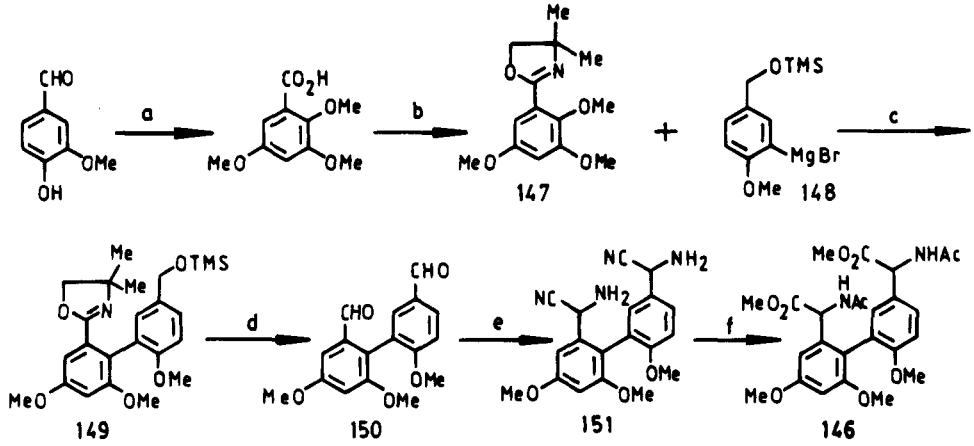



**Scheme 36**[a]



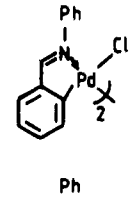
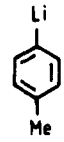
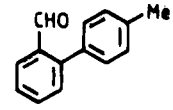
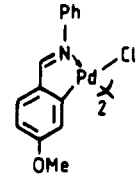
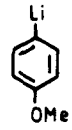
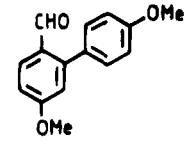
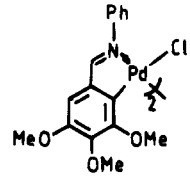
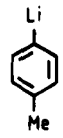
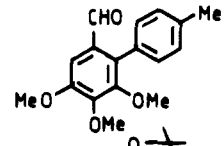
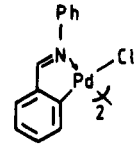
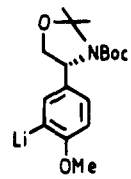
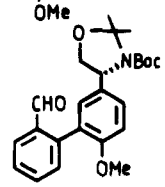
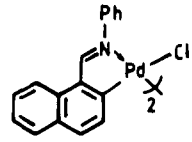
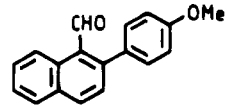

[a] (a) $Et_3N$, $CHCl_3$, 0 °C; (b) $Pd(PPh_3)_2Cl_2$, NaOAc, DMA, 110 °C; (c) (i) LAH, THF, (ii) DMS, $K_2CO_3$, acetone, (iii) NaH, BnBr, THF, (iv) PTSA, MeOH, (v) $Ac_2O$, $Et_3N$, $CHCl_3$, (vi) $K_2CO_3$, MeOH, (vii) PDC, DMF, (viii) $CH_2N_2$, (ix) $H_2$, Pd/C, MeOH, (x) PDC, $CH_2Cl_2$; (d) (*R*)-phenylglycinol,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

**Scheme 37**[a]

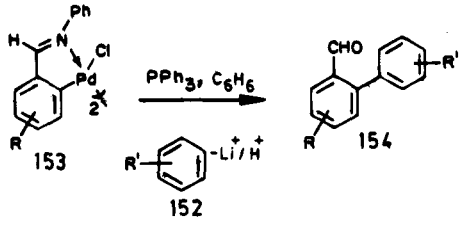


[a] (a) (i) $Br_2$, AcOH, (ii) KOH, $H_2O_2$, (ii) $K_2CO_3$, MeI, acetone, (iv) BuLi, THF, $CO_2$; (b) $Ph_3P-CCl_4$, 2-amino-2-methyl-1-propanol, pyridine–$CH_3CN$; (c) Mg, $BrCH_2CH_2Br$, THF; (d) (i) MeI, acetone, (ii) L-selectride, $CH_2Cl_2$, (iii) $HO_2CCO_2H$, (iv) PCC, $CH_2Cl_2$; (e) TMSCN, $NH_3$, MeOH; (f) (i) HCl, MeOH, (ii) $Ac_2O$, pyridine.

**Table 6. Biaryl Synthesis via Pd Complexes**

| Entry | Palladium complex | Aryllithium | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  |  |  | 48 |
| 2 |  |  |  | 43 |
| 3 |  |  |  | 35 |
| 4 |  |  |  | 38 |
| 5 |  |  |  | 31 |

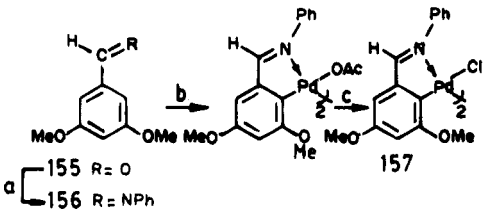
**Scheme 38. Preparation of Biaryls via Pd Complex**



treated with $Pd(OAc)_2$ followed by anionic exchange with saturated NaCl (Scheme 39). The complex was found to be stable at ambient temperature.

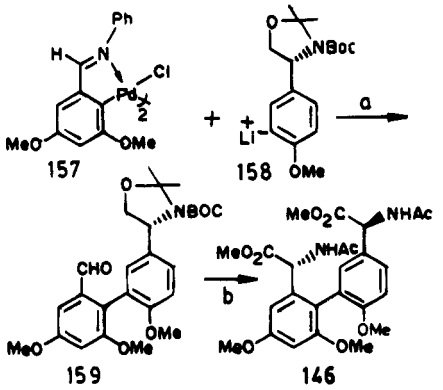
The lithiated derivative **158** was then condensed with this complex **157** in the presence of $PPh_3$ followed by hydrolysis to yield the biaryl aldehyde **159** (Scheme 40) which was already transformed into C-terminal biaryl diamino diacid **146** of vancomycin by the same group.[67]

**Scheme 39**[a]



[a] (a) Aniline; $CHCl_3$; (b) $Pd(OAc)_2$, $CH_3CN$; (c) saturated aqueous NaCl, acetone.

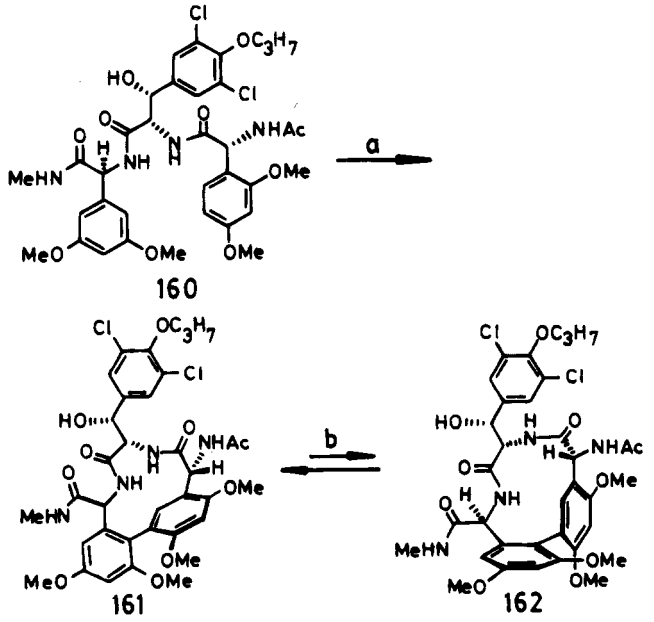
**Scheme 40**[a]



[a] (a) (i) $Ph_3P$, $C_6H_6$, room temperature, 2 h, (ii) 2% aqueous HCl; (b) ref 65.

Evans' group brilliantly examined[64] a biomimetic approach to synthesize macrocyclic actinoidic acid containing vancomycin subunit. The basic objective involved the preparation of a linear tripeptide intermediate followed by macrocyclization via aryl oxidative coupling. The linear tripeptide **160** was assembled by standard peptide coupling of appropriately substituted amino acids. Subsequent oxidative coupling was effected in the presence of $VOF_3$–$BF_3$·$OEt_2$ in TFA followed by addition of excess of Zn to afford the macrocycle **161** (Scheme 41). The atropisomeric

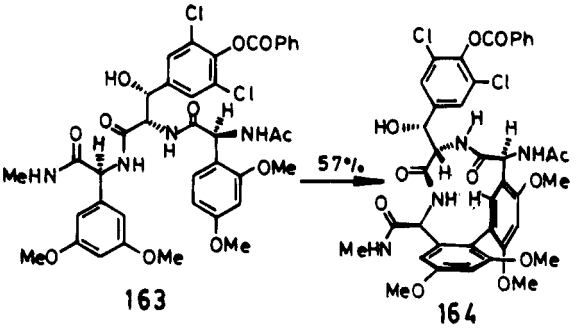
**Scheme 41**[a]



[a] (a) $VOF_3$, $BF_3$·$OEt_2$, $AgBF_4$, TFA, 0 °C, then Zn; (b) DMSO, 160 °C, 9 h.

structure of **161** was not in conformity with the natural biaryl configuration of vancomycin. Although isomerization to provide the natural biaryl acids configuration **162** was effected at 160 °C in DMSO, the ratio of 3.6:1 still favored the undesired isomer. They attributed[74] the undesired formation of atropisomer **161** to the $A^{(1,3)}$ strain between the ring 5 ortho methoxyl group and the adjacent $C_\alpha$-stereocenter. In order to substantiate this reasoning these authors carried out cyclization with the corresponding enantiomeric $C_\alpha$-stereomer **163**. As predicted the biaryl **164** had the atropisomerisation (97:3) related to the natural product (Scheme 42). On

**Scheme 42. Macrocyclization of $C_\alpha$ Epimer of 160**



the basis of these observations, it was envisaged that removal of *O*-methoxy group may thermally favor the natural atropisomeric structure of vancomycin. Accordingly the linear tripeptide, containing an acid labile 3,5-dichlorobenzyl group at the ortho phenolic group was designed essentially by the same sequence of reaction as noted earlier. In this case, the oxidative coupling of **165** was carried out with $VOF_3$ and TFA and TFAA as a solvent mixture to afford **166** in 58% yield (Scheme 43). Hydrogenolysis gave the free phenolic hydroxyl which was protected as a triflate and reductively removed with Pd(II) and triethylammonium formate. Removal of methyl groups and final atropisomerization in methanol at room temperature provided 11:89 mixture of **167** and **168**, the conformation of **168** was compatible with the natural product. The structural elucidation of these atropisomers **167** and **168** were brilliantly demonstrated by exhaustive NOE interactions as shown in Figure 2.

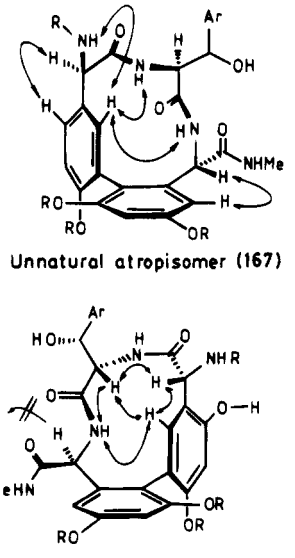
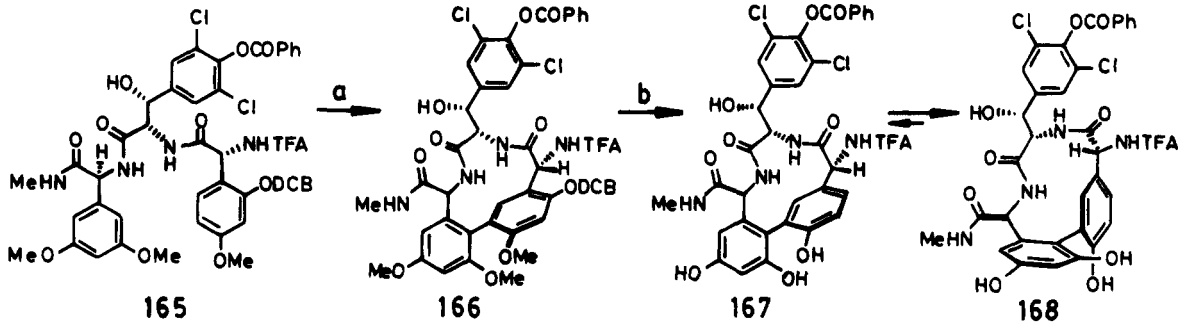


**Figure 2.** NOE interactions in **167** and **168**.

**Scheme 43**[a]




[a] (a) $VOF_3$, $BF_3$·$OEt_2$, TFA, TFAA, $CH_2Cl_2$, 0 °C, then Zn; (b) (i) Pd-black $H_2$, sonication, (ii) $PhNTf_2$, $Et_3N$, (iii) [1,1'-bis(diphenylphosphino)ferrocene]palladium chloride–$CH_2Cl_2$, $Et_3N$, $HCO_2H$, (iv) $AlBr_3$, EtSH.

## IV. Macrocyclization Studies toward Vancomycin and Related Compounds

Vancomycin and related antibiotics express antibacterial activity through their ability to antagonize bacterial cell wall biosynthesis by specific binding to the glycopeptides terminating in the sequence D-Ala-D-Ala. Investigations in the binding affinity and selectivity of vancomycin with D-Ala-D-Ala could not be taken up extensively because of a scarcity of compounds of dipeptide binding pockets. The complexicity of these molecules coupled with genuine difficulty in macrocyclization have spurred tremendous activities in this area.[75]

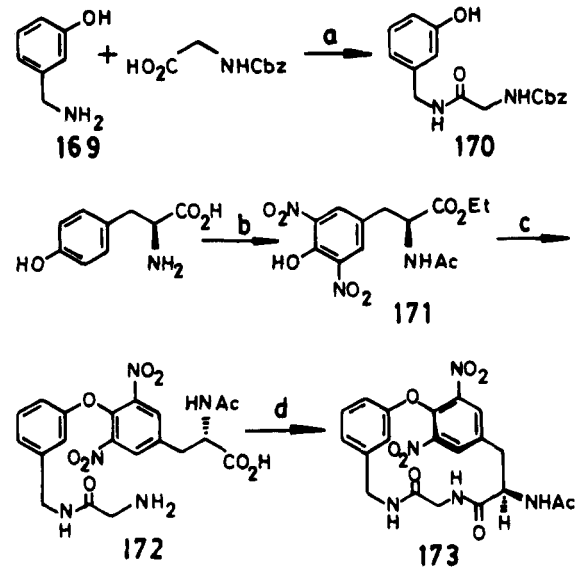
Development of appropriate synthetic methodology to construct 16-membered macrocyclic rings, composed of C-O-D and D-O-E structures of vancomycin has been a topic of extensive investigations. In TTN cyclization method discussed earlier, we have witnessed a powerful method to construct the 16-membered macrocycles of vancomycin, although the modalities of TTN oxidative coupling are not favorable. The 16-membered macrocyclic ring through amide bond (macrolactamization) was pioneered by Hamilton[76] and later by other workers with modest success. The Ullmann macrocyclization process for 16-membered ring system of vancomycin was reported by Boger. Additional studies to define the scope of this method with actual system remains to be seen.

### A. Macrolactamization

The first synthetic examination for carboxylate binding pocket of vancomycin analogue was reported by Hamilton and co-workers.[76] 3-Hydroxybenzylamine (**169**) and *N*-Cbz-glycine were coupled using *N*-methyl-2-chloropyridinium iodide to give **170**. In another sequence the product **171** was prepared from (*S*)-tyrosine via successive nitration, acetylation, and esterification. Subsequent tosylation of **171** and treatment with **170** gave the diphenyl ether whose Cbz and ethyl ester functions were removed in one step to provide **172**. Final cyclization was achieved using diphenylphosphoryl azide[77] in DMF at 0 °C for 4 days to produce **173** (Scheme 44).

The same group also synthesized[78] a model representing the right-hand ring of vancomycin. This ring is heavily involved in binding to carboxylic acids of D-Ala-D-Ala residue. The distinguish features of this model **177** were the presence of the N-terminal amino

**Scheme 44**[a]

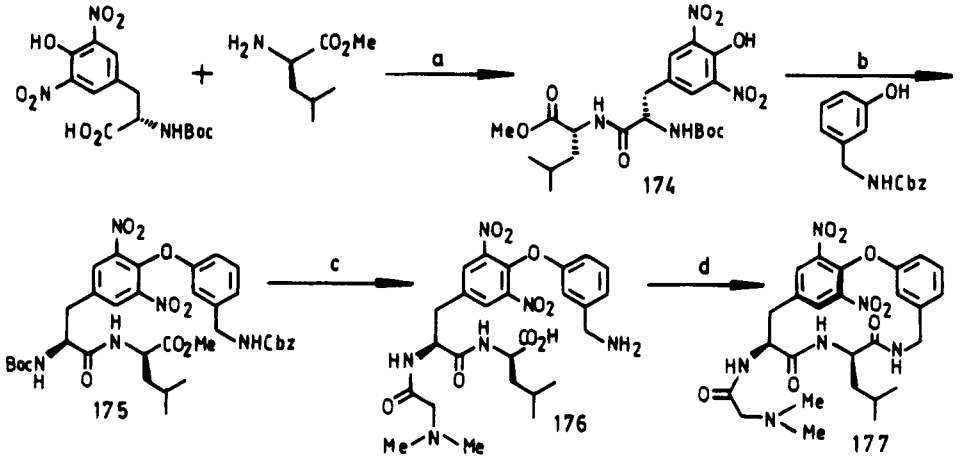



[a] (a) *N*-Methyl-2-chloropyridinium iodide, $Et_3N$; (b) (i) $HNO_3$, $H_2SO_4$, (ii) $Ac_2O$, (iii) EtOH, $MeC_6H_4SO_3H$; (c) $MeC_6H_4SO_2Cl$, pyridine; (d) (i) HCl, TFA, (ii) DPPA, DMF, 0 °C, 4 days.

group and the bulky isobutyl substituent on the central acid. Thus the required dipeptide **174** was produced by coupling (*S*)-*N*-Boc-3,5-dinitrotyrosine with (*R*)-leucine methyl ester. Subsequent tosylation and *in situ* reaction with *N*-Cbz-3-hydroxybenzylamine gave the diphenyl ether **175**. It was transferred into **176** by standard reaction and then subjected to the treatment of BOP–$Et_3N$ for 5 days to provide the macrocycle **177** in 10% yield (Scheme 45). They studied the complexation of **177** with cyanoacetic acid by $^1H$ NMR. The marked changes in the $^1H$ NMR spectrum (Figure 3) of the complex were consistent with an association involving proton transfer from acid to amine and consequent complexation of the carboxylate anion by multiple hydrogen bonding to amide groups of the receptors.

Brown and Crimmin[79-80] pioneered iodinium salt strategy to provide an amicable route to the cyclic peptide mimicing carboxylate binding pocket of vancomycin. The model chosen by these investigators was deliberately lacking in carboxyl terminus with a view toward circumventing problems of enantiospecific amino acid synthesis. The iodonium salt **178** was obtained from anisaldehyde by the treatment with iodosyl sulfate. Condensation with sodium salt of the dipeptide **179** gave the biphenyl ether derivative **180** in 59%. It was converted into the azido acid

**Scheme 45**[a]



[a] (a) BOP, $Et_3N$, $CH_2Cl_2$; (b) PTS–chloride, pyridine; (c) (i) 10% TFA–$CH_2Cl_2$, 0 °C, (ii) $Me_2NCH_2COCl$; (d) (i) HCl–TFA (1:2), (ii) BOP, $CH_2Cl_2$, 5 days.

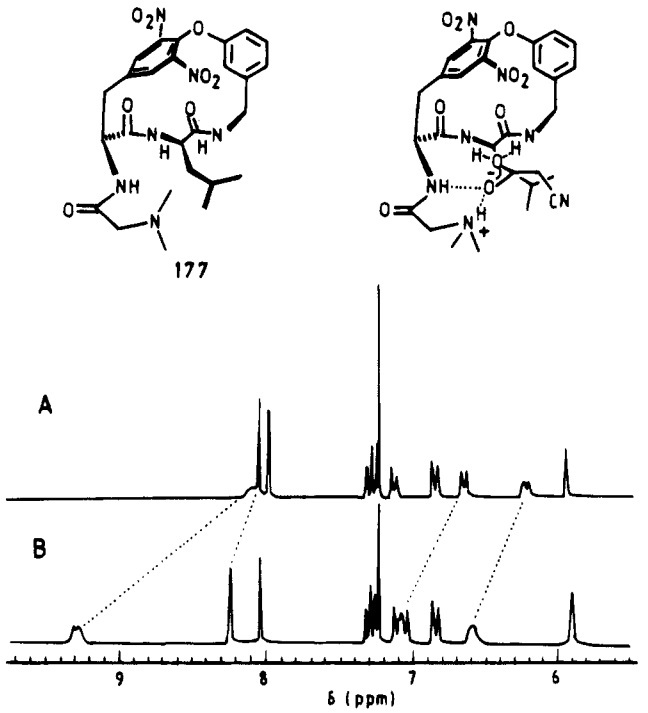
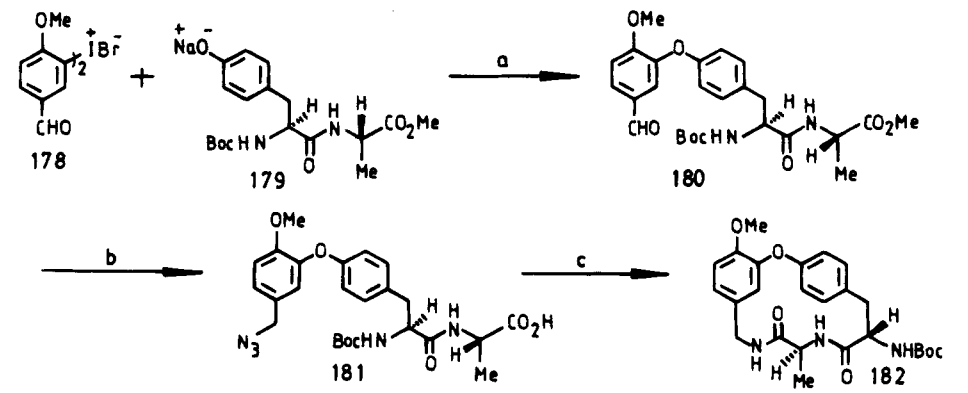


**Figure 3.** (A) Downfield region of $^1H$ NMR spectrum of **177** and (B) a 1:1 mixture of **177** and cyanoacetic acid.

**181** in three simple steps. Catalytic hydrogenation of **181** gave the amino acid which was macrocyclized in the presence of diphenylphosphorylazide–$Et_3N$ in DMF at 0 °C for 3 days to provide **182** in 9% yield (Scheme 46). The formation of cyclic dimer and polymeric material was also observed.

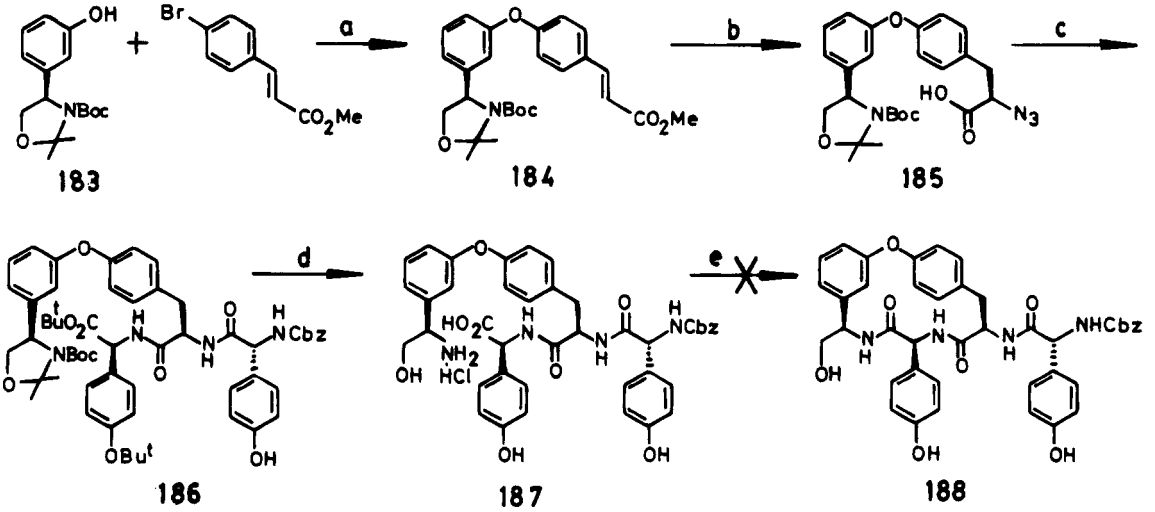
Williams and associates predicted,[81] on the basis of biological mode of action of vancomycin and other related antibiotics that the minimum structural requirement for the formation of carboxylate binding pocket should be a tetrapeptide. The configuration of the third N-terminus amino acid should be opposite to that of other three residues and furthermore the side chains at rings D and E should be cross-linked. This understanding led to the design of cyclic tetrapeptide **188**. Thus the (*R*)-3-hydroxyphenylglycinol derivative **183** was coupled with 4-bromocinnamic acid methyl ester under Ullmann conditions in refluxing pyridine to afford the diaryl ether product **184** in 50% yield (Scheme 47). Subsequent transformation utilizing Evans' methodology provided the dipeptide **185** which was converted into tetrapeptide **186** by a sequence involving deprotection and peptide bond formation. The derived amino acid **187** was subjected to cyclization but failed under various conditions tried. These authors examined a less strained model system **189** prepared by a simple strategy (Scheme 48). Cyclization attempts were performed under those conditions reported for the above product but again yielded no desired product

**Scheme 46**[a]



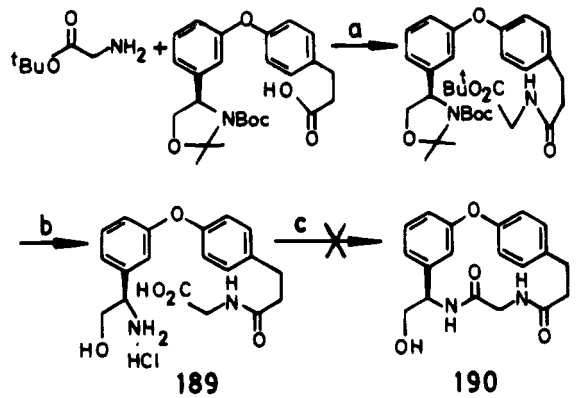
[a] (a) DMF, 90–95 °C; (b) (i) $NaBH_4$, MeOH, 0 °C, (ii) $PPh_3$, DIAD, $HN_3$, THF, (iii) NaOH, aqueous MeOH; (c) (i) 10% Pd/C, $H_2$, THF–$H_2O$ (1:1), (ii) DPPA, $Et_3N$, 2.5 nM, DMF, 3 days, −5 °C.

**Scheme 47**[a]



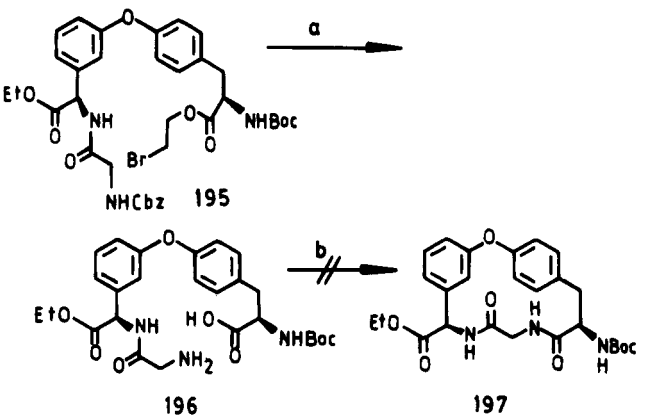
[a] (a) $K_2CO_3$, Py, CuCl; (b) (i) $H_2$, Pd–C, (ii) LiOH, THF–$H_2O$, 0 °C, (iii) Evans' methodology; (c) DCC, (*S*)-*O*-*tert*-butyltyrosine *tert*-butyl ester, $CH_2Cl_2$; (d) TFA; (e) various acyl activating agents.

**Scheme 48**[a]



[a] (a) EDCI, HOBT, $CH_2Cl_2$, *N*-methylmorpholine; (b) TFA; (c) various acyl activating agents.

**Scheme 49**[a]



[a] (a) (i) Zn, NaI, THF, $H_2O$, reflux, (ii) 1,3-cyclohexadiene, Pd/C, EtOH, reflux; (b) various coupling methods examined.

**190**. These failures were attributed to the inability of the macrocyclization intermediates to attain the conformations condusive to peptide bond formation.

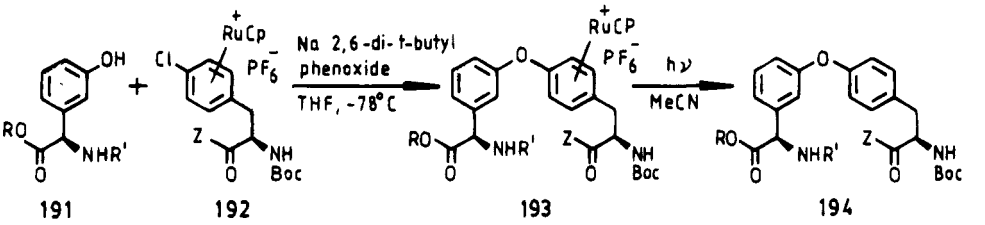
Pearson and associates[82–84] examined nucleophilic displacement of halobenzene–$MnCO_3$, FeCp, and RuCp cation complexes with phenoxides to construct biaryl ethers. For example, (*R*)-4-chlorophenylalanine–RuCp complexes **191** and (*R*)-3-hydroxyphenylglycine derivatives **192** were coupled[82] by using 2,6-di-*tert*-butylphenoxide as a base in THF at 0 °C to afford the coupled products **193** in good to excellent yields (Table 7). For demetalation, acetonitrile solutions of the coupled complexes were irradiated (sunlamp 275 W) in a quartz tube at room temperature for several hours to afford biaryl ethers **194**.

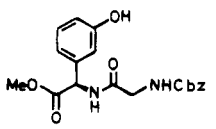
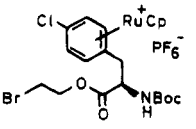
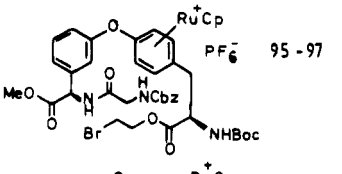
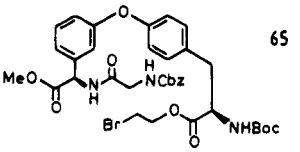
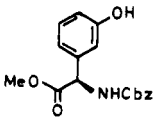
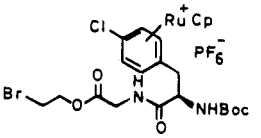
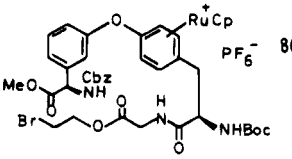
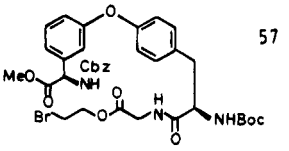
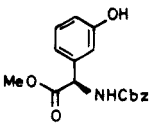
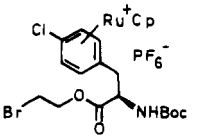
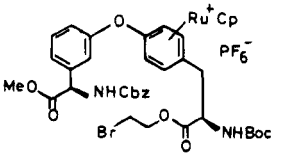
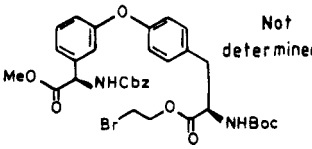
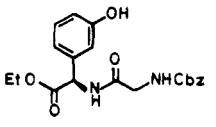
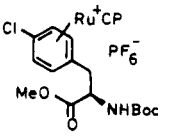
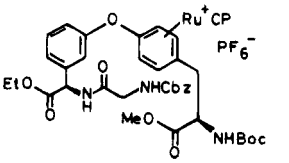
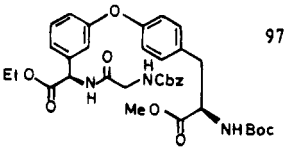
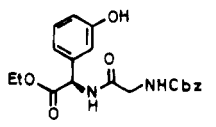
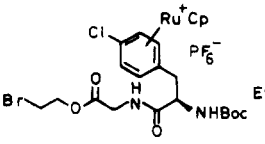
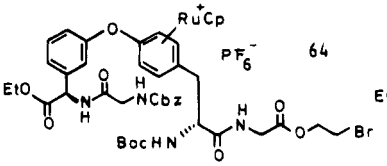
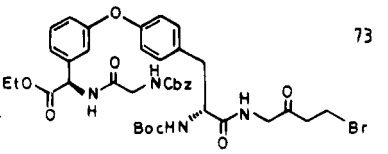
The same authors also studied[83] intramolecular macrolactamization for which the biaryl **195** was chosen as a model. Removal of bromoethyl ester blocking group and hydrogen-transfer hydrogenolysis gave the amino acid **196** whose intramolecular amide formation under various conditions uniformly failed to produce **197** (Scheme 49). In order to evaluate the influence of the conformation of these molecules and the effect on macrocyclization Pearson et al. reported[82] MM2 calculations. On the basis of these studies they inferred that conformational analysis does not provide adequate explanation for intramolecular cyclization. These observations markedly differ with Williams' notations which were described earlier.[81] A formal total synthesis of K-13 by the application of arene–ruthinium chemistry was reported.[84]

Chakraborty and Reddy[85] demonstrated for the first time the synthesis of N-terminal 14-membered ring of teicoplanin involving macrolactamization. The biphenyl ether **199** was first obtained by coupling between 3-methoxy-5-(methoxycarbonyl)phenoxide and iodonium salt (**198**). The elaboration of glycine side chain was carried out by diastereoselective Strecker synthesis developed by these authors[69] to afford **200**. Subsequent condensation with (*R*)-*N*-Cbz-tyrosine followed by dethioketalization provided the aldehyde **201** which was again subjected to diastereoselective Strecker reaction and hydrolysis. The resulting product **202** was macrocyclized by active ester technique to give **203** in 50% yield (Scheme 50).

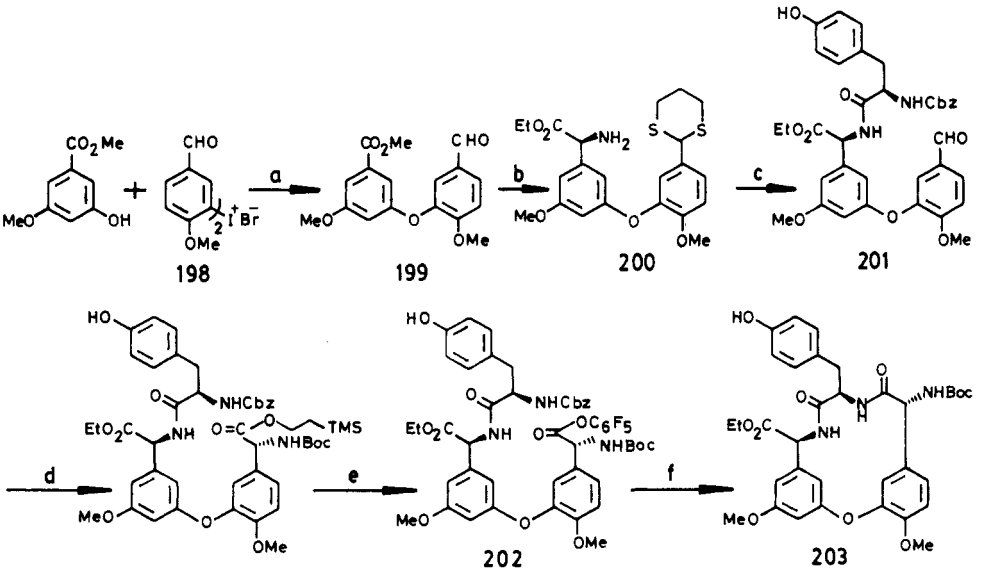
Synthesis of a 14-membered model for the CFG ring system of ristocetin-A was studied by Pearson and Shin.[86] The synthesis of macrocyclization tripeptide intermediate **204** was accomplished by involving arene–Mn–hexafluorophosphate and Scholkoff's bislactim enolate methodologies. Macro-

**Table 7. Synthesis of Biaryl Ethers via $RuCp^+PF_6^-$ complexes**



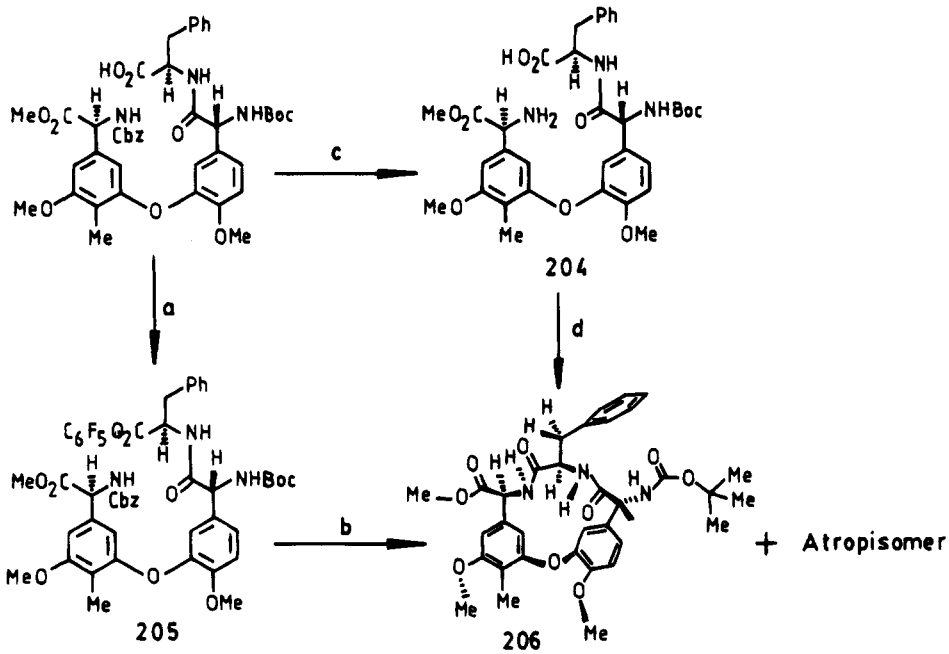

| Entry | Arylglycine (191) | Complex (192) | Product (193) (Yield %) | Demetalation Product (Yield %) (194) |
|---|---|---|---|---|
| 1 |  |  |  95-97 |  65 |
| 2 |  |  |  80-87 |  57 |
| 3 |  |  |  84 |  Not determined |
| 4 |  |  |  99.8 |  97 |
| 5 |  |  |  64 |  73 |

**Scheme 50**[a]




[a] (a) NaH, DMF; (b) (i) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, (ii) DIBAL-H, $CH_2Cl_2$, (iii) PCC, $CH_2Cl_2$, (iv) (*R*)-phenylglycinol, TMSCN, $CHCl_3$–MeOH, (v) EtOH–HCl, (vi) $Pb(OAc)_4$, $CH_2Cl_2$–MeOH, (vii) 3 N HCl; (c) (i) (*R*)-*N*-Cbz-tyrosine, DCC, HOBT, DMF, (ii) HgO, $HgCl_2$, $H_3CCN$–$H_2O$; (d) (i) (*S*)-phenylglycinol,TMSCN, $CHCl_3$, (ii) $TMSCH_2CH_2OH$, ether–HCl, (iii) $Pb(OAc)_4$, $CH_2Cl_2$–MeOH, (iv) 3 N HCl, (v) $(Boc)_2O$, $CH_2Cl_2$; (e) (i) TBAF, THF, (ii) $C_6F_5OH$, DCC, $CH_2Cl_2$; (f) (i) Pd/C, $H_2$, THF–HCl, (ii) $Et_3N$, dioxane (0.3 mM).

**Scheme 51**[a]



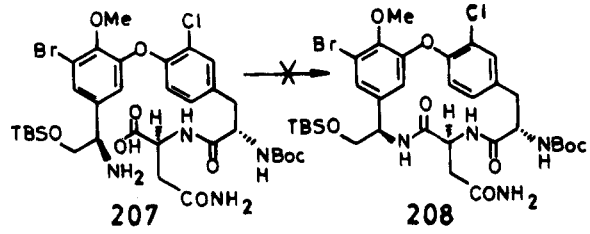

[a] (a) $C_6F_5OH$, EDCI, THF; (b) (i) Pd/C, $H_2$, EtOAc, (ii) $CHCl_3$, $NaHCO_3$; (c) Pd/C, $H_2$, EtOH; (d) EDCI, HOBT, $CH_2Cl_2$, 0 °C, 5 h.

cyclization of **204** with EDCI and HOBT gave a mixture of two atropisomers **206** where as cyclization via $C_6F_5$ active ester **205** provided cyclized product with correct configuration (Scheme 51).

## B. Biphenyl Ether Synthesis by Macrocyclization

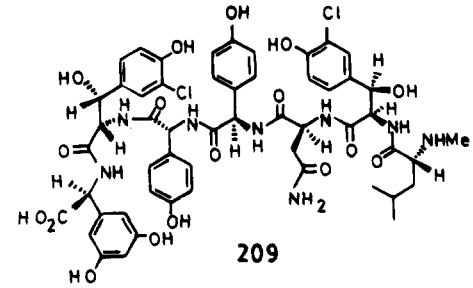
From the foregone discussion, it was clear that the formation of 16-membered lactam ring as in vancomycin is unfavorable. This was further strengthened by the failure[87] to bring the intramolecular amide bond formation of **207** to give the 16-membered model right-side portion **208** of vancomycin (Scheme 52).

**Scheme 52. Macrocyclization through Amide Bond Formation**




The only argument one could offer at this stage is that the linear peptide formed by the condensation of seven amino acids 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[51] and Evans[46] on the vancomycin synthesis. Both of them adopted TTN-promoted biaryl ether formation by a biomimitic approach. However, it is difficult to believe that TTN methodology will suit the synthesis of vancomycin as discussed previously.

The structure of vancomycin and other dalbaheptides indicate a biosynthetic pathway leading to the formation of linear peptide by condensation of seven amino acids of which five are aromatic amino acids as in case of vancomycin. The formation of the two 16-membered cyclic units (D-O-E and C-O-D) and the other 12-membered cyclic system (ABC) might have resulted by the oxidative cyclization between two aromatic units through C–O or C–C linkages. Vancomycin might have formed biogenetically from the peptide **209** by oxidative radical cyclization between 2 and 4, and 6 and 4 aromatic amino acids giving




rise to two 16-membered lactam rings. Further oxidative coupling between *p*-hydroxyphenylglycine unit (amino acid 5 and 7) resulted in the formation of the C–C coupling that occurs between the two aryl units. The conformation of the linear peptide **209** looks more favorable to undergo these transformations. Similarly, one can assume that teicoplanin might have resulted by the formation of additional cyclic ring formed by oxidative coupling between 1 and 3 aromatic segments giving rise to the C–O linkage.

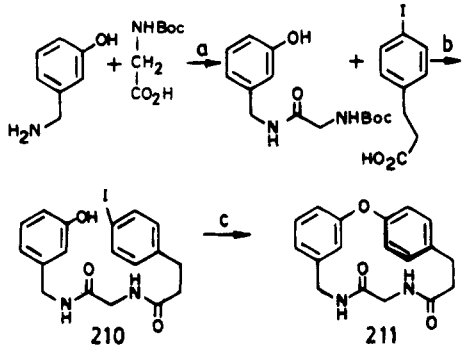
The ease of formation of the 16-membered cyclic system in vancomycin by biomimetic approach suggests that this is the most appropriate methodology that should be considered for synthesis. Boger's group[39-41] has also demonstrated that synthesis of deoxybouvardin, RA-VII as well as bouvardin could be achieved by intramolecular Ullmann reaction. Several approaches were attempted by first forming biaryl ether linkages but then failed in the intramo-

lecular 16-membered lactam formation. This suggests that the intramolecular cyclization between the two tyrosine derivatives (amino acids 2 and 6 in **209**) with the central *p*-hydroxyphenylglycine unit is the preferred approach.

### 1. Ullmann Macrocyclization

Boger et al.[88] examined the preparation of model 16-membered ring systems of vancomycin and ristocetin based on intramolecular Ullmann macrocyclization reaction. The two model systems **211** and **213** constituting C-O-D and D-O-E diphenyl ether ring of vancomycin were considered. The requisite macrocyclization substrates **210** and **212** were obtained by general procedures as shown in Schemes 53 and

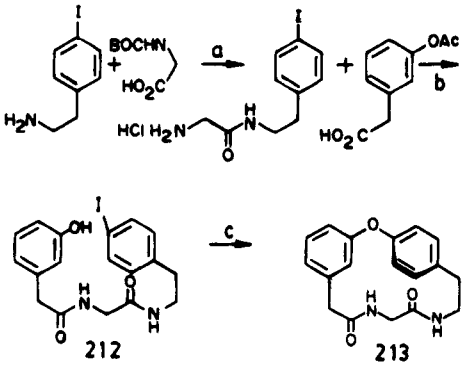
**Scheme 53**[a]




[a] (a) $ClCO_2Et$, $Et_3N$; (b) HCl–MeOH, $ClCO_2Et$, $Et_3N$; (c) MeCu (3 equiv), pyridine.

54. The Ullmann macrocyclization of **210** in the presence of NaH or $K_2CO_3$ with CuBr–DMS in pyridine at 130 °C provided **211** in 15–20% yields, however, with the use of MeCu improvement in the yield of **211** was observed. This was due to the facile formation of cuprous phenoxide. Similarly the substrate **212** was cyclized to give **213** in 31% yield (Scheme 54).

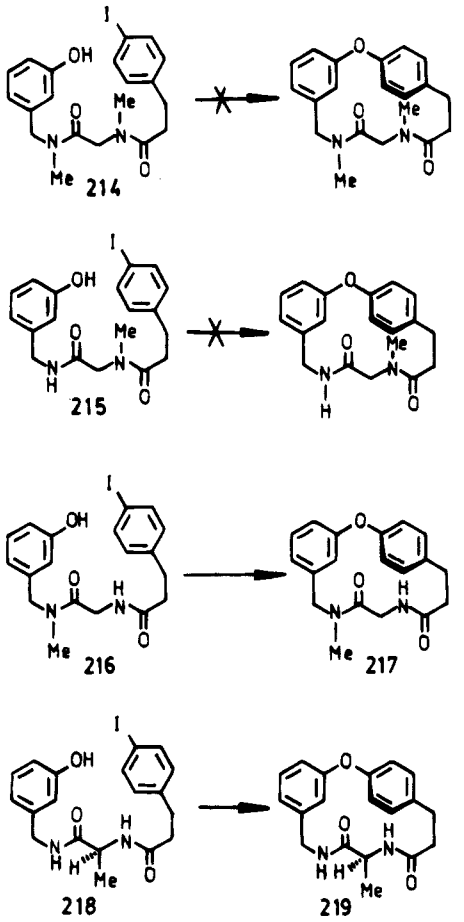
**Scheme 54**[a]




[a] (a) (i) $ClCO_2Et$, $Et_3N$, (ii) HCl–MeOH; (b) DCC; (c) MeCu (3 equiv), pyridine.

During the course of the above studies, the Boger group brilliantly analyzed the scope of Ullmann method in macrocyclizations. Particularly appealing observations were related to intramolecular N- or O-transacylation and oxidative cleavage of $-CH_2-NH-CO-$ bond. The possibility of racemization under the conditions was also considered. The group meticulously studied macrocyclization of substrates containing varying degrees of N-methylation. For instance, substrate **214** containing both $N^9$ and $N^{12}$ substituted with methyl groups which supposedly prevent both N- and O-transacylation and oxidative cleavage of amide was subjected to Ullmann macrocyclization reaction, however, no reaction was observed. The substrate **215** having a single $N^{12}$-methyl group also failed to yield the cyclized product (Scheme 55). Interestingly substrate **216** with $N^9$-

**Scheme 55. Ullmann Macrocyclization Studies**




methyl substituent underwent macrocyclization providing **217** with 27% yield. In order to propogate the Ullmann macrocyclization as an appropriate technology, the racemization-prone substrate **218** was cyclized in presence of pyridine as solvent to provide **219** in 60% yield, with only 5% racemization. The degree of racemization was indeed insignificant which was further minimized with the use of collidine as a solvent.

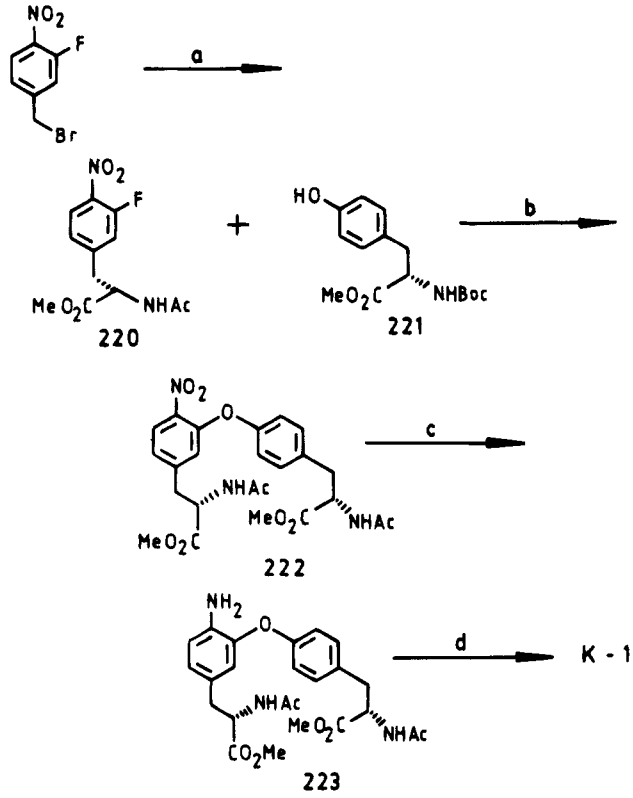
### 2. $S_NAr$ Method

On the basis of $S_NAr$ reaction of *o*-nitro-substituted aryl fluoride with phenoxide, Zhu and co-workers were the first to examine the synthesis of several cyclic peptides related to vancomycin family. It is well known that the nitro function activates halides placed at the ortho position toward the Ullmann reaction with phenoxides under seemingly mild condition. The nitro group also acts as a surrogate of a range of functional groups. The remarkable efficacy with which *o*-nitrofluoro group undergoes a displacement reaction with phenoxide is an attractive feature of this approach. The subtle reagents and mild

conditions will undoubtedly make this approach a powerful tool to complex natural products such as vancomycin. The $S_NAr$ strategy has been elaborately exercized in synthesis of quinolone antibiotics, wherein hydrolysis of fluoride ortho to nitro and its displacement with a nitrogen heterocycle are commonly practiced reactions.[89]

The French group reported[90] an elegant synthesis of K-13 by intermolecular $S_NAr$ approach in which (*S*)-3-fluoro-4-nitro-phenylalanine (**220**) was first prepared by alkylation of Scholkop's bislactim ether with 3-fluoro-4-nitrobenzyl bromide followed by hydrolysis and standard protection. Coupling of **220** with (*S*)-tyrosine derivatives **221** was effected in the presence of $K_2CO_3$–DMF at ambient temperature to give the biaryl ether **222** in high yield. Reduction of nitro with Fe–$FeSO_4$ produced **223** which has already been converted into K-13 by Rama Rao's group[36] (Scheme 56).

**Scheme 56**[a]

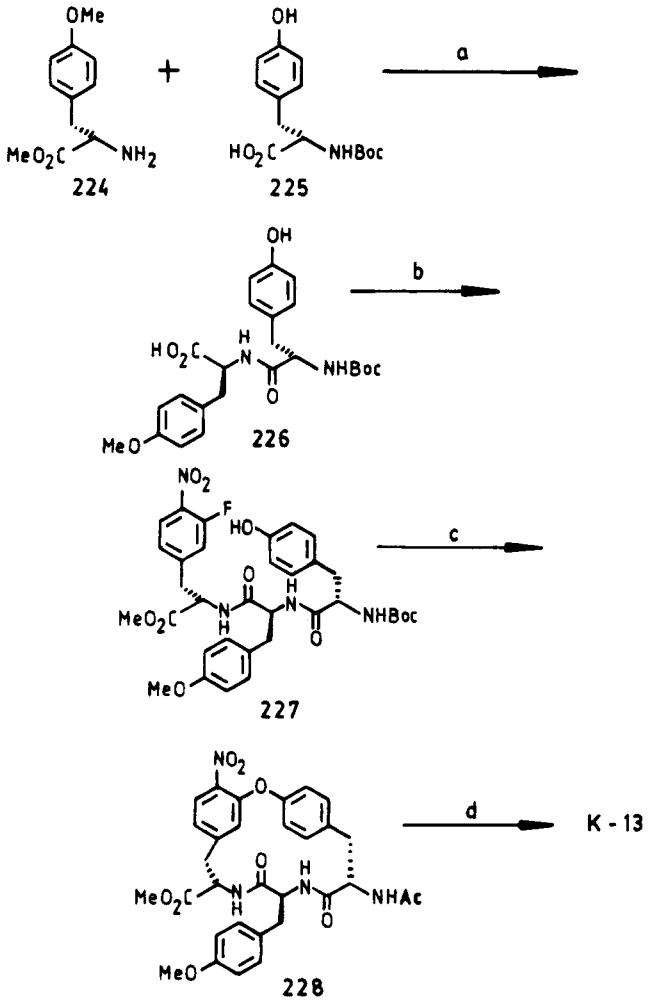



[a] (a) (i) Schollkopf's reagent, CuCN, THF, (ii) 0.25 N HCl, THF, MeCN, (iii) acetylation; (b) $K_2CO_3$, DMF, room temperature; (c) Fe–$FeSO_4$; (d) ref 33.

The same authors examined[91] an alternate but novel synthetic approach to K-13 in which they successfully implemented intramolecular $S_NAr$ reaction to construct the 17-membered cyclic structure of K-13. The dipeptide **226**, prepared from (*S*)-tyrosine derivatives **224** and **225**, was further coupled with (*S*)-3-fluoro-4-nitrophenylalanine to produce the linear tripeptide **227**. The macrocyclization was achieved with $K_2CO_3$ in DMF to obtain cyclic peptide **228** in 87% yield. Subsequent manipulation as delineated in Scheme 57 afforded K-13.

Zhu and associates also studied[92] the synthesis of triaryl diethers **234**, **235** and **240**, degradation products[7] of vancomycin and other related dalbaheptides,

**Scheme 57**[a]

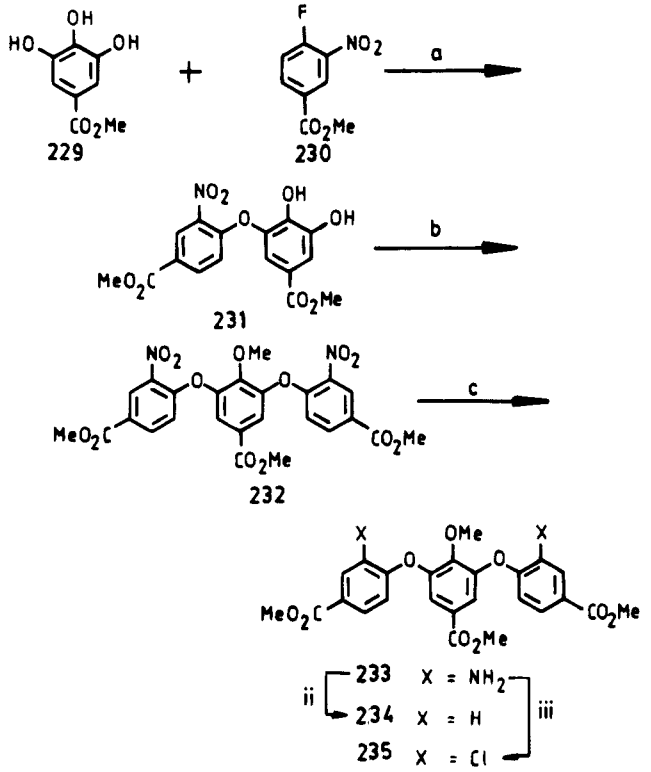



[a] (a) (i) DCC, HOBT, $CH_2Cl_2$–THF, (ii) $K_2CO_3$, MeOH–$H_2O$; (b) (*S*)-3-fluoro-4-nitrophenylalanine methyl ester, DCC, HOBT, $CH_2Cl_2$; (c) (i) $K_2CO_3$, 0.02 M in DMF, room temperature, (ii) TFA, (iii) $NaHCO_3$, $Ac_2O$, $CH_2Cl_2$; (d) (i) $H_2$, Pd/C, MeOH, HCl, (ii) $HBF_4$, *t*-BuONO, MeOH, 0 °C, then $Cu(NO_3)_2$, $3H_2O$, $Cu_2O$, $H_2O$.

in a stepwise $S_NAr$ reaction with gallic acid derivative. Compound **229** and methyl 3-nitro-4-fluorobenzoate (**230**) were employed in intermolecular $S_NAr$ reaction to produce biaryl ether **231**. Addition of a second equivalent of **230** followed by methylation gave the triaryl diether **232**, which was found to be suitable for obtaining **234** and **235** (Scheme 58). The $NO_2$ groups in **233** was reduced[93] and then diazotized in the presence of *tert*-butyl nitrite in DMF to give **234**, while the dichloro derivative **235** was prepared by treating **233** with *tert*-butyl nitrite in the presence of $CuCl_2$ in acetonitrile at 60 °C.[94] The $S_NAr$-based route developed for **240** involved the synthesis of nitro biaryl ether **237** starting from the ketal derivative **236** and the 4-nitro-3-fluorobenzoic acid methyl ester (**230**). This was followed by reduction of $NO_2$ group and deamination as described above to provide **238**. Deprotection of the ketal group of **238** and second $S_NAr$ reaction with **230** and methylation gave **239** whose nitro group was transformed into chloro to complete the synthesis of **240** (Scheme 59).

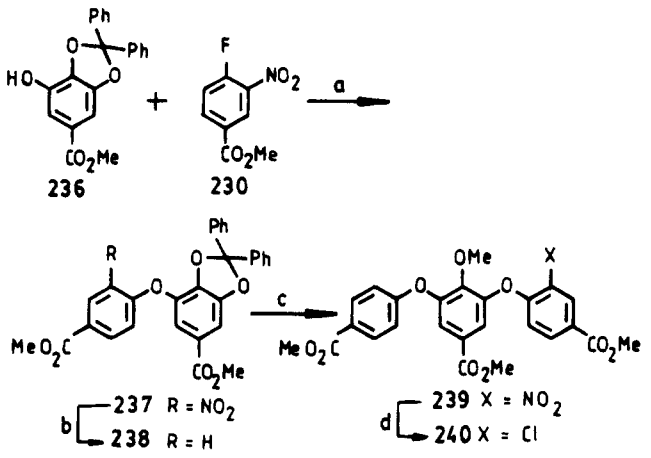
Beugelmans et al. revealed[95] a macrocyclization methodology related to the synthesis of vancomycin C-O-D diphenyl ether 16-membered ring systems by intramolecular $S_NAr$ reaction. Precursor **244** needed

**Scheme 58**[a]



[a] (a) $K_2CO_3$, DMF, room temperature; (b) 230, $K_2CO_3$, (ii) (i) $K_2CO_3$, MeI; (c) (i) Fe–$FeSO_4$ (3:1), $H_2O$, reflux, (ii) *t*-BuONO, DMF, 65 °C, (iii) *t*-BuONO, $CuCl_2$, $CH_3CN$, 60 °C.

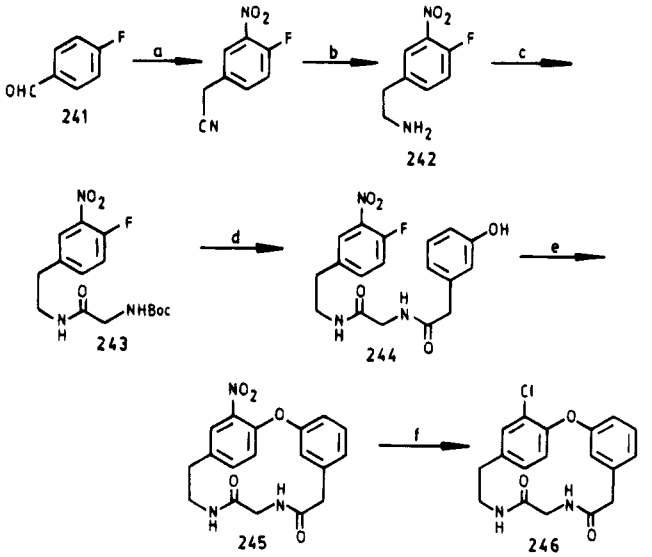
**Scheme 59**[a]



[a] (a) $K_2CO_3$, DMF, room temperature; (b) (i) Fe–$FeSO_4$, $H_2O$, (ii) *t*-BuONO, DMF, 65 °C; (c) (i) AcOH–$H_2O$ (4:1), reflux, (ii) $K_2CO_3$, 230, DMF, room temperature, (iii) $K_2CO_3$, MeI, DMF; (d) (i) Fe–$FeSO_4$, (ii) *t*-BuONO, $CuCl_2$, $CH_3CN$, 60 °C.

for C-O-D ring macrocyclization study was obtained from commercially available 4-fluorobenzaldehyde (**241**). The nitro substituent allows incorporation of masked chlorine atom as present in vancomycin. Nitration of **241** followed by reduction of aldehyde and cyanation produced the benzyl cyanide which was converted into phenylethylamine **242** by LAH–$AlCl_3$ mixture. The coupling of **242** with *N*-Boc-glycine produced the dipeptide **243**, which was deprotected and combined with 3-hydroxyphenylacetic acid to give **244**. The cyclization of **244** with $K_2CO_3$ in DMF at room temperature afforded **245** (95%) whose nitro was replaced with chlorine producing the model C-O-D ring **246** (Scheme 60).

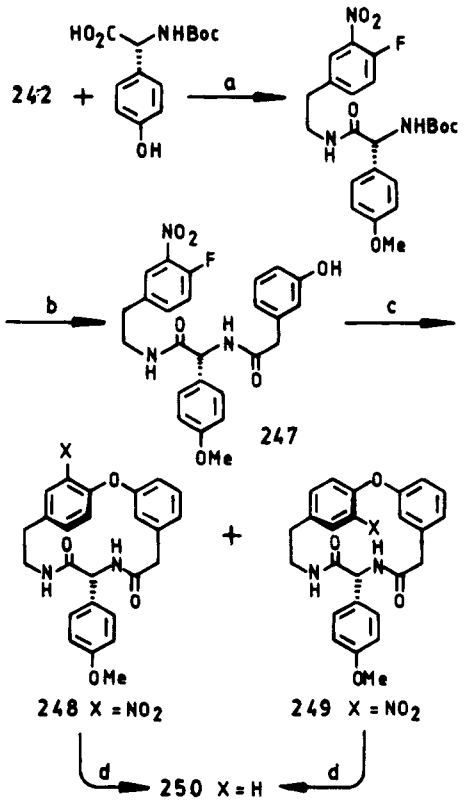
**Scheme 60**[a]



[a] (a) (i) $HNO_3$, $H_2SO_4$, (ii) $NaBH_4$, ether, (iii) $PBr_3$, toluene, (iv) $Et_4NCN$, $CH_3CN$; (b) $LiAlH_4$–$AlCl_3$; (c) *N*-Boc-glycine, DCC, THF–$CH_2Cl_2$; (d) (i) TFA, (ii) (*m*-hydroxyphenyl)acetic acid, DCCl; (e) $K_2CO_3$, DMF, 0.01 mol $dm^{-3}$; (f) (i) Fe–$FeSO_4$, (ii) *t*-BuONO, DMF, (iii) $NaNO_2$, concentrated HCl, CuCl–$CuCl_2$.

In a more elaborate study toward the C-O-D ring of vancomycin, Zhu et al. performed the macrocyclization of **247** by involving $S_NAr$ approach. The macrocyclic product was isolated as a atropisomers **248** and **249** in the ratio of 54:40 (Scheme 61). The

**Scheme 61**[a]



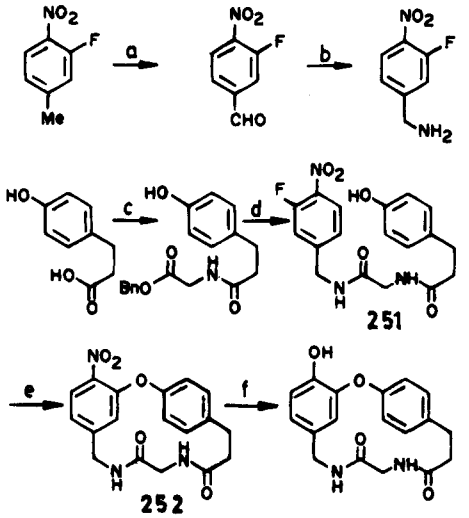
[a] (a) (i) DCC, (ii) MeI, $K_2CO_3$; (b) (i) TFA, (ii) DCC, (*m*-hydroxyphenyl)acetic acid; (c) $K_2CO_3$, DMF; (d) (i) Fe–$FeSO_4$, (ii) *t*-BuONO, DMF.

structures of these compounds were amicably assigned by $^1H$ NMR spectral analysis. Particularly notable feature of the $^1H$ NMR spectra of **248** and

**249** was the difference in chemical shifts for the proton H-17. The upfield shift from 8.05 ppm in compound **248** to 7.60 ppm in **249** explained that H-17 in **249** was disposed under the plane of the aromatic D ring and the shielding effect of diamagnetic anisotropy of the D ring compensated the shielding effect of the nitro group. Finally both the compounds **248** and **249** were converted into single product **250**.[95]

Rama Rao's group,[96] however, synthesized the macrocyclization intermediate **251** (Scheme 62) which

**Scheme 62**[a]



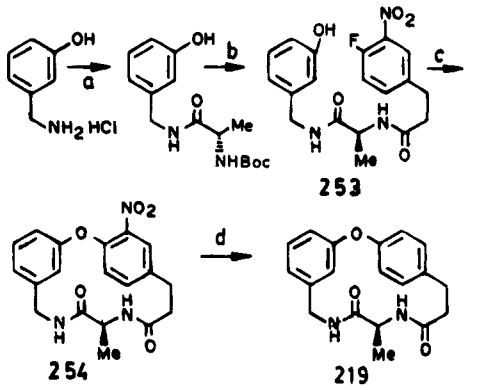
[a] (a) (i) $CrO_3$, $Ac_2O$, $H_2SO_4$, 0 °C, (ii) $H_2SO_4$, EtOH, $H_2O$; (b) $AcONH_4$, $NaBH_3CN$; (c) (i) DCC, HOBT, DMF, 0 °C, (ii) $BnO_2CCH_2NH_2$, DMF; (d) (i) Pd/C, $H_2$, EtOAc, (ii) 3-fluoro-4-nitrobenzylamine, DCC, HOBT, DMF; (e) NaH, 0.02 M in pyridine, room temperature; (f) ref 33.

was suitable to fabricate D-O-E model of vancomycin. In this case the nitro group acts as a masked hydroxy group of the centrally placed *p*-hydroxyphenylglycine residue of vancomycin. Treatment of **251** with sodium hydride in pyridine at room temperature gave the cyclic product **252** in 71% yield. Replacement of $NO_2$ with OH has been demonstrated by the group. This methodology was extended for the synthesis of K-13.[97]

Subsequently Beugelmans and associates also expanded[98] the limit of the above methodology to construct the model D-O-E ring related to vancomycin. The requisite precursor **253** was obtained by a route described in Scheme 63. Cyclization of the dipeptide **253** under the conditions developed by the group gave the cyclic product **254** in 88% yield. In order to determine the degree of racemization occurred during the cyclization step, the parent compound **254** was transformed into a known product[85] **219**. From this study the enantiomeric excess of the parent compound was found to be more than 90%.

The spectacular demonstration of intramolecular $S_NAr$ reaction was exemplified by Zhu and co-workers in 14-membered macrocyclization.[99] It is pertinent to mention the strains in this system do not allow easy formation of the 14-membered macrocycle and indeed very few methods are available for this endeavor. Zhu and co-workers have systematically studied 14-membered macrocyclization of **255** under various conditions with both X = F or Cl substituents

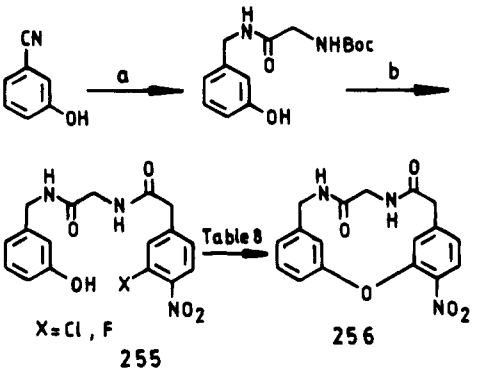
**Scheme 63**[a]



[a] (a) (*S*)-*N*-Boc-alanine, $ClCO_2Me$, $Et_3N$; (b) (i) TFA, (ii) 3-(4-fluoro-3-nitrophenyl)propionic acid, DCC; (c) $K_2CO_3$, DMF; (d) (i) $Fe-FeSO_4$, (ii) *t*-BuONO, DMF.

(Scheme 64, Table 8). They have attributed this facile macrocyclization to intramolecular recognition phenomena which may provide useful clues in designing newer approaches to macrocyclizations.

**Scheme 64**[a]



[a] (a) (i) $BH_3-THF$, then MeOH–HCl, (ii) $Et_3N$, EtOCOCl, *N*-Boc-glycine; (b) (i) TFA, (ii) EDCI, 3-fluoro-4-nitrophenylacetic acid or 3-chloro-4-nitrophenylacetic acid.

**Table 8. Base-Catalyzed 14-Membered $S_NAr$ Macrocyclizations**[a]

| X | base | addition | *T* (°C), *t* | yield (%) |
|---|---|---|---|---|
| F | $K_2CO_3$ | no | room temperature 20 h | 66 |
| F | CsF | no | room temperature 20 h | 62 |
| F | $K_2CO_3$ | 18-crown-6 | room temperature 6 h | 82 |
| Cl | $K_2CO_3$ | no | room temperature 2 days | no reaction |
| Cl | $K_2CO_3$ | no | room temperature 40, 24 h | degradation |
| Cl | $K_2CO_3$ | 18-crown-6 | room temperature 2 days | degradation |
| Cl | $K_2CO_3$ | no | room temperature 80, 6 h | 80 |

[a] All reactions were run at the concentration of 0.01M in DMF

## V. Conclusions

Vancomycin, isolated in 1956 from the fermentation broths of *Streptomyces orientalis*, belongs to the dalbaheptide family. It was introduced to the medical practice in 1958 much before its structure was elucidated. Over the period more than 200 compounds belonging to dalbaheptide group have been isolated, some of which such as teicoplanin and avoparcin have also found clinical uses. Vancomycin is characterized by the presence of seven amino acids, of which five belong to the groups of aryl amino acids. The presence of an unusual diphenyl ether cross-

linked amino acids and biaryl actinoidic acid segments make vancomycin an attractive target for synthesis. Related cyclic peptides represented by K-13 and OF-4949 which contain structural features analogous to vancomycin were extensively studied from a synthetic point of view. The knowledge from these studies has been aptly expanded to vancomycin and related antibiotics. Several synthetic strategies toward biaryl ether linkages have been developed. The first major share of this activity was related to the intermolecular Ullmann reaction which was particularly successful for K-13, OF-4949, etc. However, its application to vancomycin family was precluded.

Nature's biosynthetic approach to vancomycin occurs via radical cyclization of aromatic amino acids leading to C-C and C-O linkages. The biomimetic approach was explored by Yamamura and Evans for constructing monocyclic C-O-D and D-O-E and bicyclic C-O-D-O-E moieties. However, the presence of two chlorine atoms on rings C and E were undesirable. Selective removal of one from each ring to complete the synthesis of vancomycin segments was a difficult proposition.

Synthesis of biaryl ether substrate followed by macrolactamization was the second alternative. The macrocyclization through amide bond proved, unfortunately, to be a daunting task. Either the yields of macrocyclic compound were exorbitantly less or the reaction did not proceed in several cases studied. One of the difficult points in vancomycin synthesis is that the phenylglycine parts, being different from other amino acids, are epimerized very easily. For this reason, Ullmann approach does not always look promising.

The recently developed intra- and intermolecular $S_NAr$ approach via aryl fluoride displacement with phenoxide looks like the most appropriate technique to build biaryl ether structures such as K-13 and model C-O-D and D-O-E systems of vancomycin.

The commonly encountered biaryl 12-membered macrocycle segment of vancomycin family constituting ring A and B has been examined by several groups. The initial studies involving the preparation of biaryl segment first followed by macrolactamization was a failure. Evans' group brilliantly studied the biomimetic approach for 12-member biaryl system by constructing the linear tripeptide unit followed by oxidative biaryl coupling.

The biomimetic approach will continue to provide large inputs in planning and executing the total synthesis of vancomycin. The synthetic efforts are very important to evaluate the structure–activity relationship with the hope that a new analogue with better therapeutical efficacy will be discovered.

The synthetic studies on vancomycin have opened up several new avenues for chemists to develop their ingenuity. Several new concepts in structural elucidation studies have come out as a result of vancomycin synthesis. The work done by Evans' group on atropisomerization of biaryl segment of vancomycin constitute a fine example of this.

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