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Studies on the Total Synthesis of RP 66453: Synthesis of Fully Functionalized 15-Membered Biaryl-Containing Macrocycle

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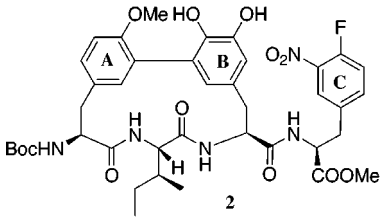
ABSTRACT



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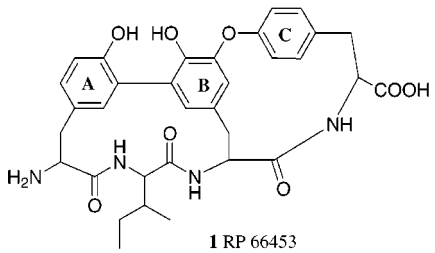
Palladium-catalyzed Suzuki cross-coupling, Corey's enantioselective alkylation of glycine template, and macrolactamization are key steps in an efficient synthesis of the 15-membered macrocycle 2.

RP-66453 (**1**, Figure 1)), a novel secondary metabolite, has been isolated from an *Actinomycetes* strain by Helynck and co-wokers at Rhône-Poulenc Rorer.[1] The plane structure has been deduced from detailed spectroscopic studies. However, the absolute configuration of the five asymmetric carbon centers as well as the possible atropisomerism of the biaryl axis remains unknown at the present time. This new bicyclic compound binds very specifically to the neurotensine receptor from guine-pig ($IC_{50} = 30\ \mu g/mL$). Subsequent structural modification has led to the discovery of potent neurotensin antagonists, claimed to be useful for treating psychose, Alzheimer's, and Parkinson's disease, etc.[2]



1 RP 66453

Figure 1.

Structurally RP 66453 belongs to a growing family of complex macrocycles that includes the vancomycin class antibiotics,[3] chloropeptin[4] and kistamine[5] to name a few. The characteristic structural feature of these natural products is the presence of macrocycles with both *endo* aryl−aryl and *endo* aryl−aryl ether bonds. The complex molecular architecture and important bioactivities have made them attractive yet challenging synthetic targets. Indeed, these molecules

(1) Helynck, G.; Dubertret, C.; Frechet, D.; Leboul, J. *J. Antibiot.* **1998**, *51*, 512−514.

(2) Clerc, F. F.; Dubroeucq, M. C.; Helynck, G.; Leboul, J.; Martin, J. P. FR 2720066, November 24, 1995.

(3) (a) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1173−1193. (b) Zhu, J. *Exp. Opin. Ther. Pat.* **1999**, *9*, 1005−1019.

(4) Matsuzaki, K.; Ikeda, H.; Ogino, T.; Matsumoto, A.; Woodruff, H. B.; Tanaka, H.; Omura, S. *J. Antibiot.* **1994**, *47*, 1173−1174.

(5) Naruse, N.; Oka, M.; Konishi, M.; Oki, T. *J. Antibiot.* **1993**, *46*, 1812−1818.

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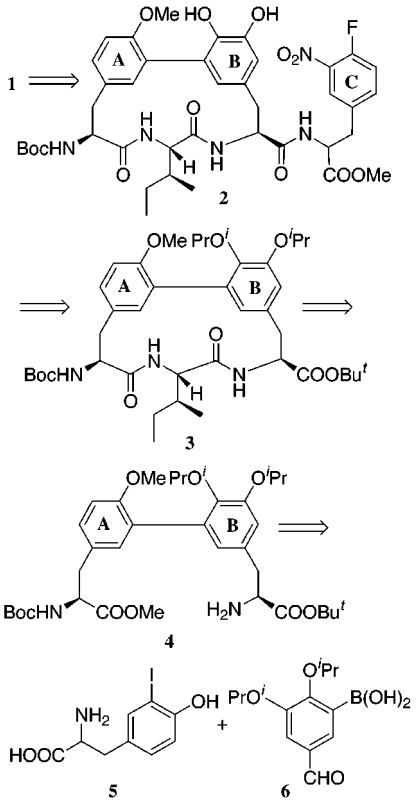
have provided impetus for the development of numerous new synthetic methodologies.[6]

To the best of our knowledge, no synthetic work on RP 66453 has been reported.[7] Scheme 1 summarizes one of the

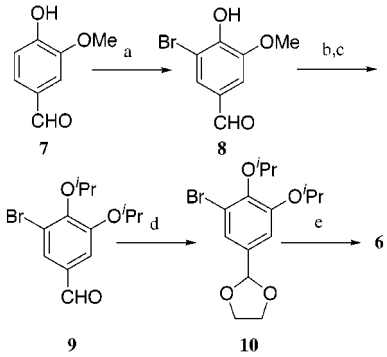
Scheme 1. Retrosynthetic Analysis



synthetic strategies being pursued in our laboratory. In a forward sense, a sequence of macrolactamization[8] and intramolecular S_NAr reaction[9] is projected for the assemblage of A−B and B−O−C macrocycles, respectively. To proceed with the synthesis, all asymmetric carbon centers are arbitrarily assigned as *S* configuration, keeping in mind that the convergent approach would allow one to easily modulate the stereochemical issue.

One of the building blocks, arylboric acid **6**, was synthesized as shown in Scheme 2. Bromination of vanillin in acetic acid gave regioselectively 5-bromovanillin in excellent yield.[10] Two-step protective group interchange gave, after acetal formation, the bromide **10**. The protection of phenol

Scheme 2[a]



[a] Reaction conditions: (a) Br_2, acetic acid, 90%; (b) $AlCl_3$, Py, CH_2Cl_2, 98%; (c) K_2CO_3, ^iPrBr, DMSO, 83%; (d) ethylene glycol, benzene, pTsOH, Dean−Stark, 91%; (e) (i) BuLi, $B(OMe)_3$, THF, −78 °C; (ii) 3 N HCl, 67%.

as an isopropyl ether was based on our previous observation that it can be easily removed from the complex molecular structure under mild conditions.[11] Lithium−bromide exchange followed by addition of trimethyl borate provided, after acidic workup and flash chromatography, the pure arylboric acid **6** in 67% yield.

A palladium-catalyzed Suzuki cross-coupling reaction[12] between methyl L-*N*-Boc-3-iodo-4-methoxyphenyl alanate **11**[13] and **6** under standard conditions gave the biaryl **12** in higher than 85% yield. The cross-coupling of in situ generated aryl borate with **11** also produced the same compound, but with less efficiency.[14] Reduction of the aldehyde, mesylation of the resulting benzyl alcohol, and Finkelstein bromination gave the benzyl bromide **13** in 56% overall yield (Scheme 3). It was observed that the amino ester function of **12** was unusually prone to reduction. Thus, treatment of **12** with $NaBH_4$ in MeOH led to the formation of a diol as a major byproduct even at −78 °C. However, this side reaction was avoided by simply changing the solvent from MeOH to THF. Following Corey's procedure,[15] alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with bromide **13** in the presence of a catalytic amount of *O*(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**14**, 0.1 equiv) produced, after chemoselective hydrolysis of the imine function (THF, aqueous citric acid, SiO_2), the orthogonally protected biaryl bisamino acid derivative **4** in 65% yield. Only one diastereomer was detectable from NMR

(6) For a review on vancomycin synthesis, see: Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096−2152.

(7) For an approach to the total synthesis of Chloropeptin, see: (a) Carbonnelle, A.; Gonzalez-Zamora, G.; Beugelmans, R.; Roussi, G. *Tetrahedron Lett.* **1998**, *39*, 4471−4472. (b) Elder, A. M.; Rich, D. H. *Org. Lett.* **1999**, *1*, 1443−1446.

(8) For an alternative strategy involving the formation of an aryl−aryl bond as a key cyclizaion step, see refs 6, 7, and the following. (a) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527−6530. (b) Carbonnelle, A.-C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477−3480.

(9) (a) Zhu, J. *Synlett* **1997**, 133−144. (b) Burgess, K.; Lim, D.; Martinez, C. I. *Angew. Chem., Int. Ed.* **1996**, *35*, 1077−1078. (c) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045−5065.

(10) Bromination of 3,4-dihydroxybenzaldehyde gave the wrong regioisomer. Anhoury, M. L.; Crooy, P.; De Neys, R.; Eliaers, J. *J. Chem. Soc., Perkin Trans. I* **1974**, 1015−1017.

(11) Bois-Choussy, M.; Vergne, C.; Neuville, L.; Beugelmans, R.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 5795−5798.

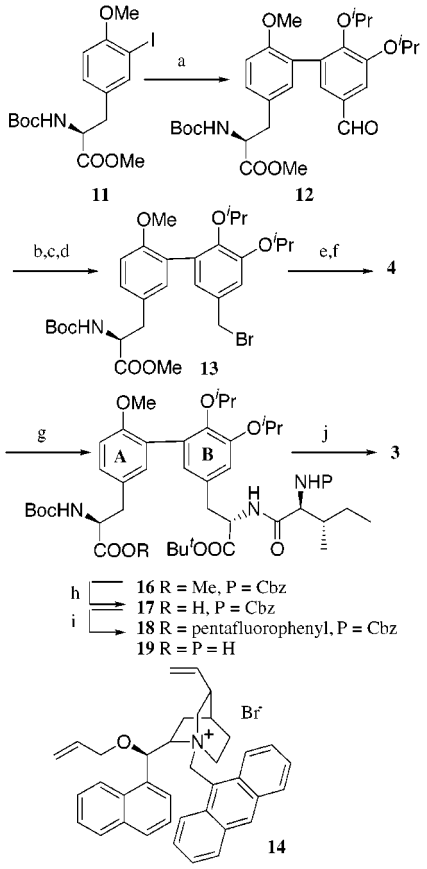
(12) Suzuki, A. In *Metal-catalyzed cross-coupling reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49−97.

(13) Prepared in four conventional steps from L-tyrosine; for iodination procedure, see: Chiarello, J.; Joullié, M. M. *Synth. Commun.* **1988**, *18*, 2211−2223.

(14) Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501−6503.

(15) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. See also: Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598.

Scheme 3[a]



[a] Reaction conditions: (a) $Pd(PPh_3)_4$, aqueous Na_2CO_3, DME, 90 °C, 85%; (b) $NaBH_4$, THF, −78 °C, 80%; (c) MsCl, Et_3N, CH_2Cl_2; (d) LiBr, Me_2CO, 69%; (e) CsOH·H_2O **14**, $Ph_2C{=}NCH_2$-COOBu^t; (f) 15% aqueous citric acid, THF, SiO_2, 65%; (g) EDC, HOBt **15**, 90%; (h) LiOH, THF−H_2O; (i) EDC, C_6F_5OH, CH_2Cl_2; (j) Pd/C, cyclohexene, *tert*-butyl alcohol, Hunig's base, 95 °C, 70%.

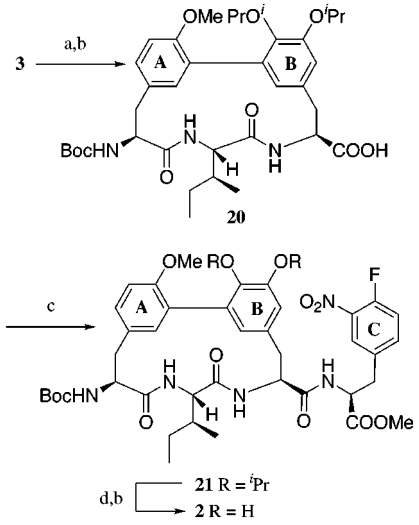
spectroscopy. Since the existing chiral center is far away from the reaction site, it is reasonable to assume that the newly created asymmetric carbon is *S* configured according to Corey's empiric model. Coupling of **4** with (2*S*,3*S*) *N*-Cbz isoleucine (**15**)[16] mediated by EDC and HOBt provided compound **16** in 90% yield. The methyl ester on the A ring was selectively converted into the activated ester **18** via saponification and esterification with pentafluorophenol. One-pot hydrogenolysis of the *N*-Cbz function and macrolactamization were best realized under transfer hydrogenation conditions. Thus, heating a solution of **18** in *tert*-BuOH in the presence of Pd/C, cyclohexene, and Hunig's base provided the 15-membered biaryl macrocycle **3** in 70% yield (three steps from **16**).[17] Using *tert*-BuOH instead of MeOH or EtOH as the solvent is essential in order to avoid the competitive trans-esterification. Cyclization of *seco*-acid **19** mediated by HATU[18] has also been examined, leading to macrocycle **3** in only 27% yield.

(16) (2*S*,3*S*) isoleucine is commercially available.

(17) (a) Shcmidt, U.; Zäh, M.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1002−1004. (b) Heffner, R. J.; Jiang, J.; Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 10181−10189.

With compound **3** in hand, we next turned our efforts to the elaboration of the 14-membered macrocycle with an *endo* aryl−aryl ether bond. Treatment of compound **3** with TFA followed by Boc_2O under standard conditions furnished the acid **20**, which was coupled with methyl L-4-fluoro-3-nitrophenylalanine[19] to provide tetrapeptide **21** in 92% yield (Scheme 4). Selective hydrolysis of *tert*-butyl ester in the

Scheme 4[a]



[a] Reaction conditions: (a) TFA; (b) Boc_2O, dioxane, aqueous $NaHCO_3$, 98%; (c) EDC, HOBt, L-methyl 4-fluoro-3-nitrophenyl alanate, 92%; (d) BCl_3, CH_2Cl_2, 82%.

presence of the *N*-Boc function using $ZnBr_2$ was found to be sluggish.[20] Finally, removal of the isopropyl ether with BCl_3 provided compound **2**, a precursor for investigating the intramolecular S_NAr reaction. While the ^1H NMR spectrum of compound **21** showed two sets of peaks at room temperature that coalesced when it was recorded at 333 K in DMSO-d_6, that of compound **2** displayed only one set of peaks at room temperature. This result indicated that the energy barrier of atropisomerism in such a ring system is relatively low in accord with our previous observation.[8b]

The cyclization of **2** was performed by varying the base (NaH, K_2CO_3, K_2CO_3/crown ether 18-C-6, CsF, K_2CO_3/$CaCO_3$, DBU], the solvent (THF, DMF, DMSO), and the temperature (0 to 40 °C). Unfortunately, none of these conditions allowed us to isolate the desired bicyclic compound. A degradation of starting material was observed in most of the reaction conditions examined. The B−O−C macrocycle is structurally reminiscent of the cycloisodityrosine unit found in the RA series whose synthesis has been a subject of many recent efforts.[21,22] A total synthesis

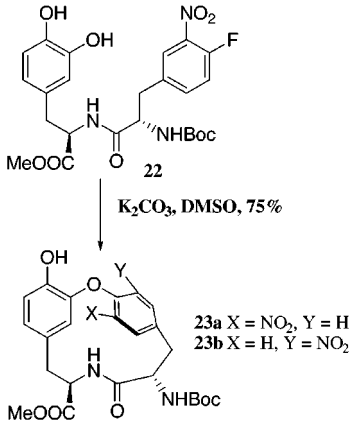
(18) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

(19) Vergne, C.; Bois-Choussy, M.; Ouazzani, J.; Beugelmans, R.; Zhu, J. *Tetrahedron: Asymmetry* **1997**, *8*, 391−398

(20) Wu, Y. Q.; Limburg, D. C.; Wilkinson, D. E.; Vaal, M. J.; Hamilton, G. S. *Tetrahedron Lett.* **2000**, *41*, 2847−2849.

(21) For reviews, see: (a) Rama, R. A. V.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135−2167. (b) Yamamura, S.; Nishiyama, S. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 1029−1039.

Scheme 5



of RA-VII featuring a key cyclization of dipeptide **22** to cycloisodityrosine **23** has been reported by our laboratory (Scheme 5).[23] In view of this result, we tentatively attributed the failure of the present cyclization to the unfavorable conformational property of the compound **2**.

In conclusion, we have reported a synthesis of the fully functionalized A−B biaryl macrocycle **2** of RP-66453 featuring a key macrolactamization step. An alternative ring construction sequence, i.e., C−O−B and then C−O−B−A−A, is being actively pursued in our group.

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Supporting Information Available: Full experimental details and characterization data for compounds **2**−**4**, **6**, **8**−**10**, **12**, **13**, **16**−**18**, **20**, and **21**. This material is available free of charge via the Intenet at http://pubs.acs.org.

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(23) Bigot, A.; Tran Huu Dau, M. E.; Zhu, J. *J. Org. Chem*. **1999**, *64*, 6283−6296.