Pergamon

Tetrahedron Letters 43 (2002) 2577–2580

TETRAHEDRON LETTERS

Studies toward the total synthesis of RP-66453

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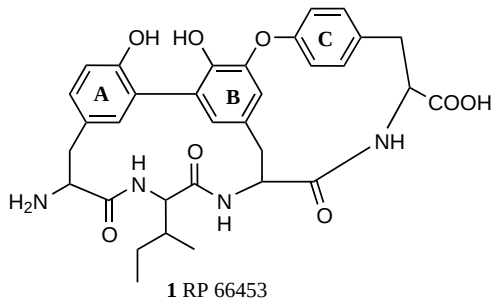
Received 23 January 2002; revised 11 February 2002; accepted 13 February 2002

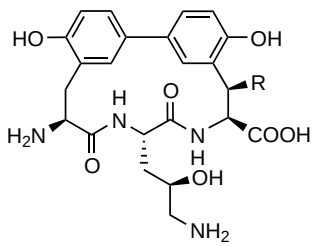
Abstract—Synthesis of a bicyclic A-B-O-C ring system of RP-66453, an neurotensine receptor antagonist, with an *endo* aryl–aryl and an *endo* aryl–aryl ether bond is described. An alternative synthetic strategy starting from the construction of functionalized B-O-C cycloisodityrosine unit is also detailed.

Isolated from an *Actinomycetes* strain, RP-66453 (**1**) (Fig. 1) and its semi-synthetic derivatives bind specifically to the neurotensine receptor and are claimed to be useful for treating psychosis, Alzheimer's and Parkinson's diseases.[1] Structurally, it is characterized by the presence of (a) a 15-membered macrocycle with an *endo* aryl–aryl bond (A-B), reminiscent of biphenomycin antibiotics (**2**);[2,3] and (b) a strained 14-membered biaryl ether containing *meta*,*para*-cyclophane (B-O-D). Notably, the similar cycloisodityrosine unit with reversed peptide coupling sequence has been found in the family of anti-tumor agent, named RA series (e.g. RA-VII, **3**).[4,5] Although the gross structure of RP-66453 has been determined from detailed spectroscopic studies by Helynck and co-workers at Rhône-Poulenc Rorer,[6] the absolute configuration of the five stereocenters as well as the possible atropisomerism of the biaryl axis remained unknown.

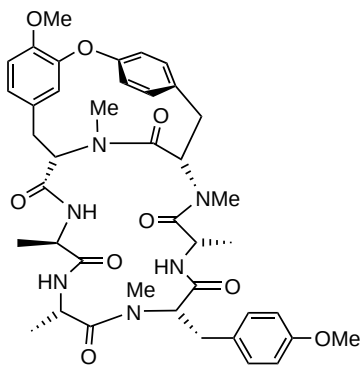
From a synthetic perspective, RP-66453 is a challenging molecule because of the inherent ring strain associated with its two-bridged macrocyclic ring systems. We have been engaged in a program aiming at the total synthesis and stereo-structural elucidation of RP-66453 and have reported a synthesis of a fully functionalized AB macrocycle.[7] A recent report from Boger's group[8] dealing with the preparation of cycloisodityrosine unit of the same natural product prompted us to detail in this letter our approaches to the A-B-O-C bicycle (**4**) as well as the appropriately functionalized B-O-C macrocycle (**5**).



1 RP 66453



2a biphenomycin A, R = OH
2b biphenomycin B, R = H



3 RA-VII

Figure 1.

Keywords: neurotensine receptor antagonist; RP 66453; macrocycle; biaryl; biaryl ether; intramolecular S_NAr reaction.

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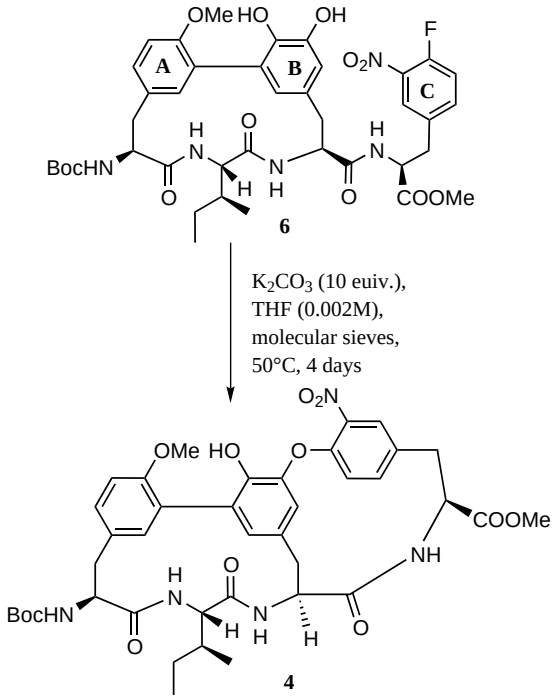
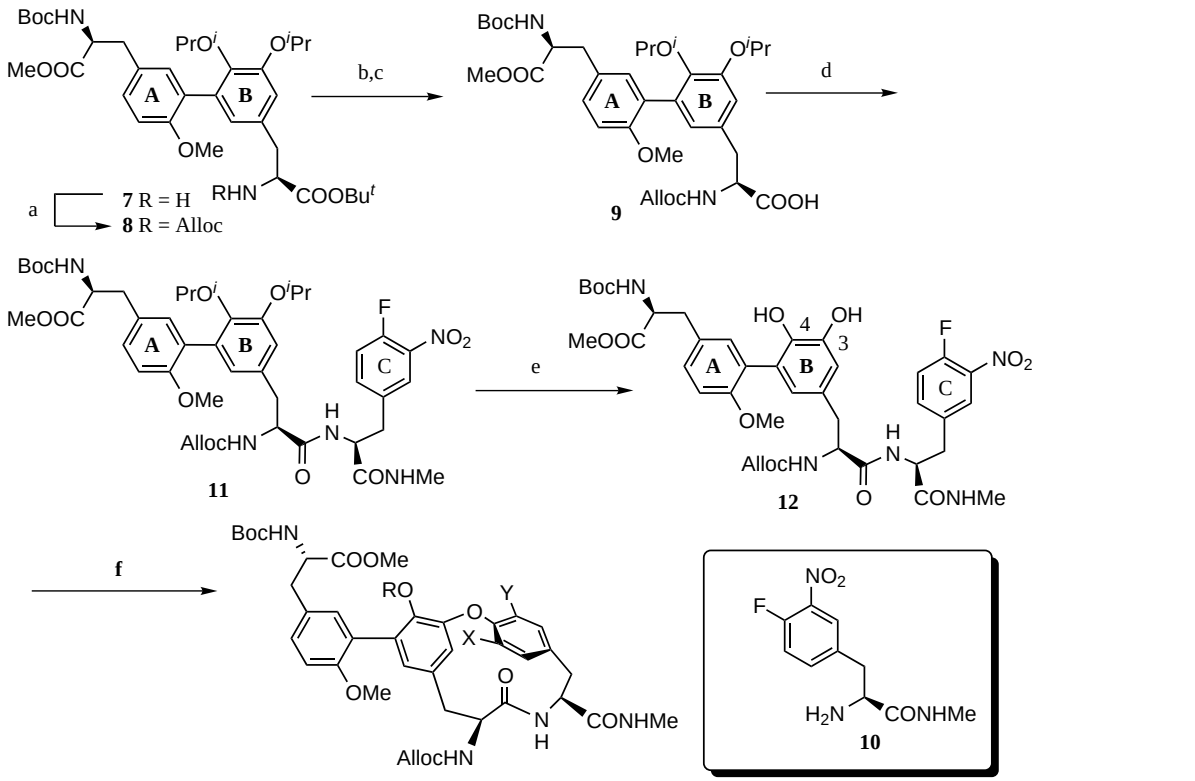
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00307-6

The intramolecular S_NAr reaction developed in our group has been demonstrated to be very efficient in construction of the biaryl ether containing macrocycles.[9] A number of complex natural products have since been synthesized using this cycloetherification methodology as a key ring closure step.[10] Therefore, we initially planned to access the skeleton of RP-66453 by constructing A-B, then A-B-O-C bicycle. For this purpose, the biphenyl ring system was synthesized by a key macrolactamization strategy. Subsequent introduction of (L)-4-fluoro-3-nitro phenyl alanine methyl ester[11] and functional group manipulation led to the compound **6** ready for the second macrocyclization studies.[12] However, the cyclization of **6** was found to be particularly difficult. Dozens of reaction conditions varying bases (K_2CO_3, CsF, DBU, NaH), solvents (DMF, DMSO, MeCN, THF), additives (18-crown ether, molecular sieves) and temperature were examined. The only conditions that allowed us to isolate the desired bicyclic system **4** (Scheme 1) [yield: about 15%, MS (ESI), $m/z=812$ $(M+Na)^+$, 828 $(M+K)^+$] consist of performing the cycloetherification of **6** in THF at 50°C in the presence of potassium carbonate and molecular sieves.[13]

The low yield of the cycloetherification reaction made the overall sequence via biphenyl A-B macrocycle inad-



Scheme 1.



Scheme 2. *Reagents and conditions*: (a) Alloc, K_2CO_3, dioxane–H_2O, room temperature, 96%; (b) TFA, room temperature; (c) Boc_2O, aqueous $NaHCO_3$, dioxane, 91%; (d) EDC (1.3 equiv.), HOBt (1.3 equiv.), **10** (1.2 equiv.), Et_3N (1.4 equiv.), 85%; (e) BCl_3 (5 equiv.), CH_2Cl_2, −78°C, then Boc_2O, THF, $NaHCO_3$, room temperature, 70%; (f) K_2CO_3, DMF, then MeI, 60%.

equate for the total synthesis of this natural product. Consequently, an alternative synthetic sequence, i.e. construction of B-O-C cyclophane followed by formation of the biphenyl macrocycle A-B was investigated. The synthesis started from the known biaryl bisamino acid **7**,[7] synthesized by a key Suzuki coupling[14] and a chiral quaternary ammonium salt catalyzed enantioselective alkylation of glycine template[15] (Scheme 2). The *N*-allyloxycarbamate protection of the amine under standard conditions provided **8**. Removal of a *tert*-butyl ester without touching the *N-tert* butyloxycarbamate under the recently described conditions ($ZnBr_2$, CH_2Cl_2) met with marginal success.[16] On the other hand, a two-step sequence involving the mild acidic treatment of **8** followed by reintroduction of *N*-Boc function produced acid **9** in excellent overall yield. Coupling of this acid with methyl amide **10** mediated by EDC–HOBt furnished **11**, which was then transformed to phenol **12** upon selective removal of isopropyl ether (BCl_3, CH_2Cl_2).

In sharp contrast to the cyclization of **6**, the key size-selective ring-forming process based on the intramolecular S_NAr reaction proceeded smoothly.[5,17] Thus, treatment of **12** in DMF (0.002 M) in the presence of potassium carbonate furnished the 14-member cyclophane as a mixture of two atropisomers in a 3/1 ratio. The 15-membered *para,para* cyclophane resulting from the nucleophilic attack of the ring B 4-hydroxy function was not formed because of its inherent higher ring strain. The instability of cyclophane **13** towards flash chromatography purification prompted us to examine the one-pot tandem cyclization/methylation processes. Thus, when the cycloetherifcation of **12** under defined conditions (K_2CO_3, 0.002 M in DMF) deemed complete by TLC analysis, an excess of methyl iodide was introduced to the reaction mixture to promote the methylation of the remaining free hydroxy function. Under these conditions, the desired cycloisodityrosine **5** was reproducibly isolated in greater than 60% yield.

In conclusion, we reported two synthetic approaches to the bicyclic ring system of RP-66453. The higher yield obtained in the cyclization of **12** relative to that of **6** clearly indicated the appropriate direction to be pursued. Further work is in progress and will be reported in due course.

Acknowledgements

We thank CNRS for financial support. A doctoral fellowship from this institute to S. Boisnard is gratefully acknowledged. We thank Professor Potier for his interest in this work.

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