# Communications

#### Natural Product Synthesis

## Total Synthesis of an Atropdiastereomer of RP-66453 and Determination of Its Absolute Configuration\*\*

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RP-66453 (1), a secondary metabolite, was isolated from an *Actinomycetes* strain by Helynck and co-workers at Rhône–Poulenc Rorer.<sup>[1]</sup> This new bicyclic compound binds very selectively to the neurotensin receptor from guinea pigs  $(IC_{50} = 30 \ \mu g m L^{-1})$ . Subsequent structural modification has led to the discovery of potent neurotensin antagonists claimed to be useful for treating psychosis and Alzheimer's and Parkinson's diseases.<sup>[2]</sup> Structurally, RP-66453 belongs to a growing family of macrocycles that include the vancomycin class of antibiotics,<sup>[3]</sup> chloropeptin,<sup>[4]</sup> and kistamine.<sup>[5]</sup> The presence of strained macrocycles with both *endo* aryl–aryl and aryl–aryl ether bonds is the common structural feature of these complex and medicinally relevant natural products.



Figure 1. Structure of RP-66453 (1).

The connectivity of RP-66453 (1) was 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 remained to be solved. Intrigued by its potent bioactivity and with the hope to determine its absolute configuration, we and Boger's group embarked on the total synthesis of RP-66453.<sup>[6,7]</sup> From a synthetic perspective, RP-66453 (1) is a challenging target because of the inherent ring strain associated with its two bridged macrocyclic ring systems. We communicate herein the first total synthesis of all-*S*-configured RP-66453, which, in combination with spectroscopic studies, also led to the

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assignment of the absolute configuration of the natural product as aR(M), S, S, S, S, S.

Our approach is depicted retrosynthetically in Scheme 1. In forward sense, a sequence of  $S_NAr$ -based cycloetherification<sup>[8]</sup> for the formation of the highly strained 14-membered



Scheme 1. Retrosynthetic analysis of RP-66453 (1).

B-O-C cyclophane **3** followed by an intramolecular Suzuki– Miyaura coupling reaction<sup>[9]</sup> for the construction of the 15membered ring in **2** would complete the construction of the elusive A-B-O-C bicyclic skeleton of RP-66453. To proceed with the synthesis, we arbitrarily assigned all asymmetric carbon centers the *S* configuration, keeping in mind that the convergent approach would facilitate the incorporation of each fragment with desired stereochemistry.

The synthesis began with commercially available (S)-dopa and (S,S)-isoleucine (Scheme 2). Coupling of (S)-dopa methyl ester (6) with (S,S)-N-Boc isoleucine (7) provided the dipeptide 8 in 94% yield. Subsequent hydrolysis of the methyl ester followed by amidation with the hydrochloride salt of (S)-methyl 4-fluoro-3-nitrophenylalanate (9)<sup>[10]</sup> afforded the tripeptide 5 in 78% overall yield. The sizeselective ring-forming process based on the intramolecular S<sub>N</sub>Ar reaction proceeded smoothly.<sup>[11]</sup> Thus, stirring a solution of 5 (0.0026 M) in DMSO in the presence of cesium fluoride at room temperature gave the corresponding 14-membered meta, para-cyclophane. Without purification, the crude reaction mixture was submitted to one-pot sequential iodination and methylation to provide the two separable atropisomers 10a and 11a in 48% overall yield (1.3:1 ratio) from the linear tripeptide 5. Similarly, a sequence of cycloetherification/ bromination/methylation provided the two atropisomers 10b and 11b in 62% overall yield. It is worthy of note that the halogenation reaction must be performed before the Omethylation, otherwise the halogenation takes place exclu-



**Scheme 2.** Synthesis of the B-O-C ring. a) EDC, HOBt, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, RT, 94%; b) LiOH, THF/H<sub>2</sub>O, RT, then compound **9**, EDC, HOBt, Et<sub>3</sub>N, DMF, RT, 77%; c) CsF, DMSO (0.0026 M), RT, 2 h; d) NIS, DMF, then K<sub>2</sub>CO<sub>3</sub>, Mel, 48% overall yield of **10a** and **11a** from **5**; e) NBS, DMF, then Mel, 62% overall yield of **10b** and **11b** from **5**. Abbreviations: DMF = N,N-dimethylformamide, DMSO = dimethyl sulfoxide, EDC = 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole hydrate, NBS = N-bromosuccinimide, NIS = N-iodosuccinimide, RT = room temperature.

sively at the position *para* to the diaryl ether linkage.<sup>[12]</sup> Thus judicious selection of the reaction sequence allowed us to use the readily available and cheap (S)-dopa as starting material, reducing significantly the length of the overall synthetic sequence.<sup>[13]</sup>

The production of two atropisomers is of no consequence since the planar chirality will be destroyed in subsequent synthetic operations. We nevertheless determined their planar chirality by NOE studies<sup>[14]</sup> and continued the synthesis with the atropisomerically pure compounds 10a and 11a. Removal of the *N*-Boc function from 10a followed by coupling with arylboronate **13**, obtained in turn from the (S)-3-iodotyrosine derivative 12 by the method of Miyaura et al.<sup>[15]</sup> furnished the tetrapeptide **14** (Scheme 3). Due to the high ring strain imposed by the B-O-C ring, closing the second ring by means of an intramolecular Suzuki-Miyaura coupling was expected to be difficult.<sup>[16,17]</sup> In the event, the best results were obtained when we heated a solution of 14 in toluene/ H<sub>2</sub>O to 90°C in the presence of potassium carbonate and a catalytic amount of [PdCl<sub>2</sub>(dppf)]. Under these conditions the desired bicycle 16 was obtained reproducibly in about 40% yield as a single atropstereoisomer. The choice of solvent was critical since the cyclization carried out in other solvents (DMF, DMSO, toluene/methanol) but under otherwise identical conditions afforded a complex reaction mixture. Finally,



**Scheme 3.** Completion of the synthesis of bicycle **2**. a)  $[PdCl_2(dppf)]$ , bis(pinacolato)diboron, KOAc, DMSO, 80%; b) LiOH, THF/H<sub>2</sub>O (1:1), RT, quantitative; c) 1) **11 a**, 7% HCl in MeCN, RT, aqueous (KHCO<sub>3</sub>) workup, then **13**, EDC, HOBt, Et<sub>3</sub>N, DMF, RT, 87%; d)  $[PdCl_2(dppf)]$ , toluene/H<sub>2</sub>O (30:1), K<sub>2</sub>CO<sub>3</sub>, 90°C, 40%; e) Pd/C, H<sub>2</sub>, MeOH; f) NaNO<sub>2</sub>, H<sub>3</sub>PO<sub>2</sub>, Cu<sub>2</sub>O, THF/H<sub>2</sub>O (6:1), 42%; g) AlBr<sub>3</sub>, EtSH, 55%. Abbreviation: dppf=1,1'-bis(diphenylphosphano)ferrocene.

reductive removal of the nitro function provided the fully protected all-S-configured bicycle **17**. Following the same sequence, the atropisomer **11a** was converted into **17** in a similar overall yield. On the other hand, cyclization of bromide **15** gave the bicycle **16** in only about 5% yield under identical conditions. Treatment of **17** with AlBr<sub>3</sub> in the presence of EtSH removed all the protecting groups (two methyl ethers, one methyl ester, and one *N*-Boc function) to provide the desired bicyclic compound **2** in 55% yield.

The spectroscopic data (<sup>1</sup>H NMR, COSY) and the highresolution mass spectrum of bicycle **2** are in accord with its structure, but they, as well as the optical rotation, differ from those of the natural product (**2**: +208 (c=1, MeOH); RP-66453 (**1**): -181 (c=1, MeOH)). However, a simple experiment demonstrated that **1** and **2** differ only in their axial chirality and that the chiral carbon centers of the natural product **1** are all *S*-configured as in compound **2**. Indeed,

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heating a solution of **1** in DMSO at 150°C for 3 h gave exclusively the compound **2** without any detectable decomposition. Conversely, compound **2** was perfectly stable at the same temperature, indicating that compound **2** is the thermodynamically more stable atropstereoisomer. Similarly, compound **18**, which was synthesized from the natural product by a two-step sequence (Scheme 4) was irreversibly converted



**Scheme 4.** Derivatization of RP-66453 (1). a) Boc<sub>2</sub>O, MeOH, Et<sub>3</sub>N; b) CsF, DMF, MeI, 50°C, 80%. Boc<sub>2</sub>O = di-*tert*-butyl dicarbonate.

into 17 when a a solution in DMSO was heated at 150 °C. The similarity of the spectra of the pairs 1 and 18, 2 and 17 indicated that there was no major conformational perturbation upon protection of the peripheral functional groups of the bicyclic structure. These results demonstrate that axial chirality was preserved during the deprotection of 17 to give 2. Scheme 5 summarizes the chemical transformations that



*Scheme 5.* Evidence of atropisomerism between RP-66453 (1) and compound 2. a) DMSO, 150°C, 3 h, quantitative; b) Boc<sub>2</sub>O, MeOH, Et<sub>3</sub>N, then CsF, DMF, MeI, 50°C, 80%; c) AlBr<sub>3</sub>, EtSH, CH<sub>2</sub>Cl<sub>2</sub>, 55%.

proved the atropisomerism between RP-66453 (1) and the synthetic compound 2. The activation energy  $(E_a)$  for the isomerization of 1 to 2 was calculated to be 16.9 kcalmol<sup>-1</sup>.

The <sup>1</sup>H NMR spectra of both **1** and **2** exhibit a single set of signals in [D<sub>6</sub>]DMSO or in CD<sub>3</sub>OD indicating that they exist as single conformers. Based on the known absolute configuration of the peptide chain, the axial chirality of both compounds **17** and **18** was deduced from NOE studies as shown in Figure 2.<sup>[18]</sup> For compound **18**, it is evident from the ROESY spectrum that all amide bonds are *trans* by observing the NOEs between NH<sup>36</sup>–H<sup>2</sup>, NH<sup>29</sup>–H<sup>31</sup>, NH<sup>25</sup>–H<sup>27</sup>. The aR(M) configuration of the axial chirality of compound **18**,



**Figure 2.** Stereochemistry of the natural product RP-66453 (1): (*aR*, *S*, *S*, *S*, *S*, *S*, *S*) and the synthetic compound **2**: (*aS*, *S*, *S*, *S*, *S*, *S*).

hence that of RP-66453 (1), was evidenced by the following characteristic NOEs:  $H^{27}$  with  $H^{23}$ ,  $H^{25}$ ,  $H^{13}$ ,  $H^{15}$ ,  $H^9$ ;  $H^{13}$  with  $H^{27}$ ,  $H^{28'}$ ,  $H^{25}$ ,  $H^{17}$ ,  $H^{20}$ ,  $H^{21}$  and  $H^{15}$  with  $H^{28}$ ,  $H^{27}$ ,  $H^{31}$ ,  $H^9$ . This stereochemical assignment also nicely explains the unusual upfield shift of protons  $H^{27}$  ( $\delta = 3.63$  ppm in [D<sub>6</sub>]DMSO) and NH<sup>25</sup> ( $\delta = 4.22$  ppm in [D<sub>6</sub>]DMSO) of RP-66453, both of which are located under the aromatic C ring. Although the ROESY spectra of compound **17** did not provide useful NOE correlations for the determination of its axial chirality, an *aS*(P) configuration was assigned, since chemical experiments indicated that **17** is an atropisomer of **18**. Drieding models showed that for atropisomer **17**, the proton  $H^{27}$  is completely out of the influence of aromatic ring current in contrast to that of **18**.

In conclusion, we have developed a convergent synthesis of all S-configured diastereoisomer of RP-66453 (aS, S, S, S, S, S). The synthesis is notable for its brevity, partly because functionalized amino acids can be used directly in our approach. By combination of chemical evidence and NMR data, the absolute configuration of RP-66453 (1) was determined to be (aR, S, S, S, S). It is interesting to note that nature created RP-66453 with a thermodynamically less stable atropisomer, while laboratory synthesis using intramolecular Suzuki–Miyaura coupling as the last ring-closure step produced the thermodynamically more stable isomer.

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- [1] G. Helynck, C. Dubertret, D. Frechet, J. Leboul, J. Antibiot. 1998, 51, 512-514.
- F. F. Clerc, M. C. Dubroeucq, G. Helynck, J. Leboul, J. P. Martin, FR 2720066 (WO 9532218), 1995 [*Chem. Abstr.* 1996, 124, 233154x and 124, 233155y].
- [3] a) D. H. Williams, B. Bardsley, Angew. Chem. 1999, 111, 1264–1286; Angew. Chem. Int. Ed. 1999, 38, 1173–1193; b) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, Angew. Chem. 1999, 111, 2230–2287; Angew. Chem. Int. Ed. 1999, 38, 2096–2152; c) J. Zhu, Expert Opin. Ther. Pat. 1999, 9, 1005–1019.
- [4] K. Matsuzaki, H. Ikeda, T. Ogino, A. Matsumoto, H. B. Woodruff, H. Tanaka, S. Omura, J. Antibiot. 1994, 47, 1173–1174.
- [5] N. Naruse, M. Oka, M. Konishi, T. Oki, J. Antibiot. 1993, 46, 1812–1818.
- [6] a) S. Boisnard, A.-C. Carbonnelle, J. Zhu, Org. Lett. 2001, 3, 2061–2064; b) S. Boisnard, J. Zhu, Tetrahedron Lett. 2002, 43, 2577–2580.
- [7] a) P. J. Krenitsky, D. L. Boger, *Tetrahedron Lett.* 2002, 43, 407–410; b) P. J. Krenitsky, D. L. Boger, *Tetrahedron Lett.* 2003, 44, 4019–4022.
- [8] a) J. Zhu, Synlett 1997, 133–144; b) J. S. Sawyer, Tetrahedron 2000, 56, 5045–5065.
- [9] N. Miyaura, A. Suzuki, Chem. Rev. 1995, 95, 2457-2483.
- [10] C. Vergne, M. Bois-Choussy, J. Ouazzani, R. Beugelmans, J. Zhu, *Tetrahedron: Asymmetry* 1997, 8, 391–398.
- [11] a) A. Bigot, J. Zhu, *Tetrahedron Lett.* 1998, 39, 551–554; b) A. Bigot, E. Tran Huu Dau, J. Zhu, *J. Org. Chem.* 1999, 64, 6283–6296.
- Bromination of (S)-dopa gave exclusively the undesired (S)-2-bromo-4,5-dihydroxyphenylalanine, see: S. Kirschbaum, H. Waldmann, J. Org. Chem. 1998, 63, 4936-4946.
- [13] For the synthesis of selective protected L-dopa from tyrosine, see ref. [7] and a) D. L. Boger, D. Yohannes, J. Org. Chem. 1987, 52, 5283-5286; b) M. E. Jung, T. I. Lazarova, J. Org. Chem. 1997, 62, 1553-1555; c) C. Chen, Y.-F. Zhu, K. Wilcoxen, J. Org. Chem. 2000, 65, 2574-2576.
- [14] In the NOESY spectra, characteristic NOE crosspeaks between protons H<sup>a</sup> and H<sup>b</sup>, between protons H<sup>a</sup> and H<sup>c</sup> were observed for compounds 10 and 11, respectively.
- [15] T. Ishiyama, M. Murata, N. Miyaura, J. Org. Chem. 1995, 60, 7508-7510.
- [16] Aryl-Aryl bond formation by intramolecular Suzuki-Miyaura coupling see: a) A. M. Elder, D. H. Rich, Org. Lett. 1999, 1, 1443-1446; b) W. Li, K. Burgess, Tetrahedron Lett. 1999, 40, 6527-6530; c) A.-C. Carbonnelle, J. Zhu, Org. Lett. 2000, 2, 3477-3480; d) V. Lobrégat, G. Alcaraz, H. Bienaymé, M. Vautier, Chem. Commun. 2001, 817-818.
- [17] In our hands formation of the B-O-C cyclophane followed by macrolactamization failed to afford the complete A-B-O-C bicycle (S. Boisnard, Ph.D. Thesis, Université Paris-Sud, 2001), although the 15-membered A-B ring can be prepared efficiently by macrolactamization (refs. [6a,7b]).
- [18] Due to the overlap of several key signals in the <sup>1</sup>H NMR spectra of RP-66453 (1) and 2 in DMSO, we performed NOE studies on their derivatives 18 and 17, respectively.