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Preparation of the 14-membered L,L-cycloisodityrosine subunit of RP 66453

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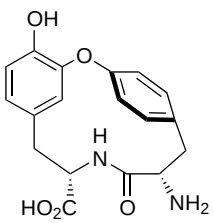
Abstract—The synthesis of the reversed 14-membered L,L-cycloisodityrosine **9** constituting an appropriately functionalized BC ring system of RP 66453 is detailed.

The strained, 14-membered cyclophane ring system of cycloisodityrosine (**1**) is found in several natural products including piperazinomycin,[1] bouvardin and deoxybouvardin (**2**),[2] and RA-VII.[3,4] In the course of screening for novel compounds that bind the neurotensin receptor, RP 66453 (**3**) was isolated from an *Actinomycetes* strain and partially characterized.[5] These studies concluded that **3** contains a cycloisodityrosine subunit, albeit with a reversed orientation of the amide central to the 14-membered ring, but they did not lead to the assignment of the relative or absolute stereochemistry of **3**.



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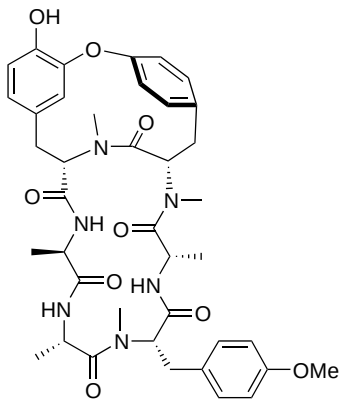

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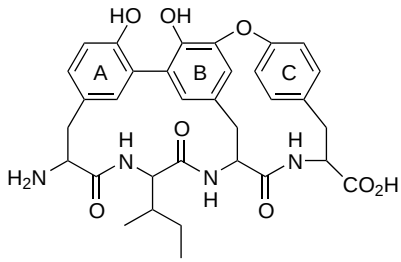

3

One of the most striking features distinguishing the cycloisodityrosine subunit of **3** from that found in prior series is the reversed orientation of the amide central to the 14-membered ring. Ring closure of the typical cycloisodityrosine subunit found in the deoxybouvardin series has only been achieved by diaryl ether formation,[1–4,6] and it was found to be significantly more synthetically challenging than the analogous ring closures of the 16-membered diaryl ethers found in vancomycin or teicoplanin.[7] Consequently and as a prelude to efforts on the total synthesis and structural confirmation of RP 66453,[8] we have been interested in the synthesis and characterization of the reversed cycloisodityrosine subunit found in **3**. Herein, we report the synthesis of the 14-membered L,L-cycloisodityrosine subunit **9** constituting an appropriately functionalized BC ring system of RP 66453 through diaryl ether macrocyclization enlisting a phenoxide nucleophilic aromatic substitution reaction of an *o*-fluoronitroaromatic.

The preparation of the BC ring system of RP 66453 began with functionalized amino acid **4**, readily prepared from tyrosine.[9] Bromination of **4** with *N*-

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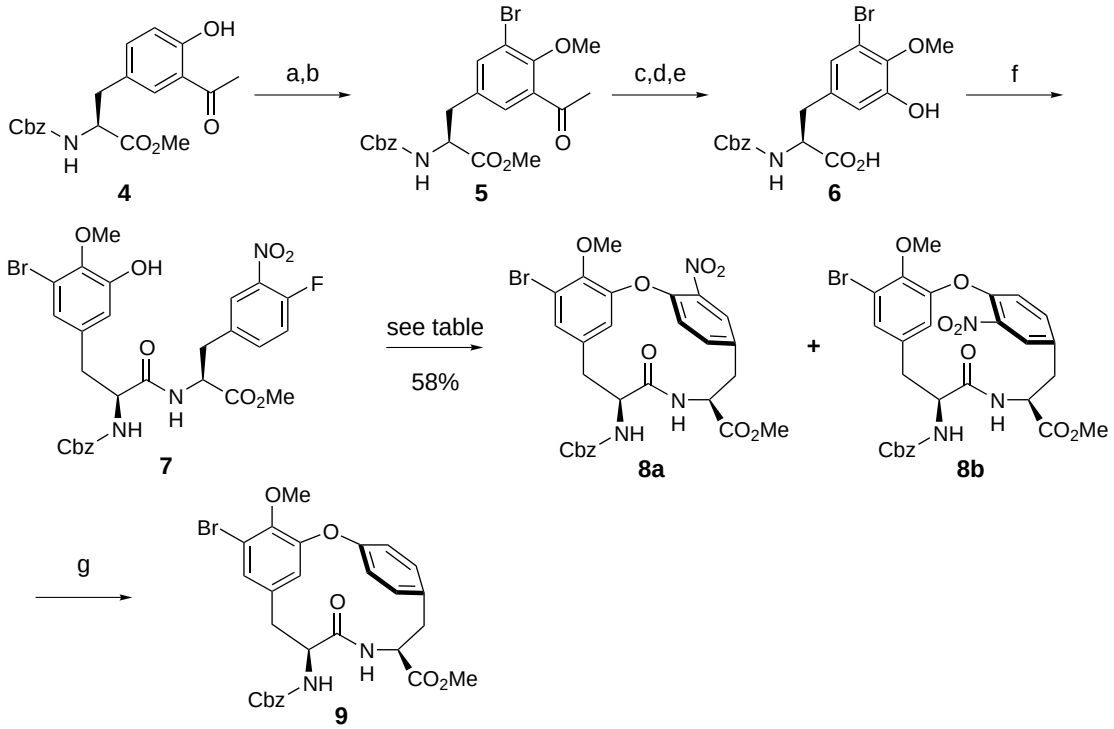


Scheme 1. *Reagents and conditions*: (a) NBS, CH_3CN, 25°C, 18 h, 99%; (b) K_2CO_3, MeI, DMF, 25°C, 5 h, 94%; (c) CF_3CO_3H, CH_2Cl_2, reflux, 2 days, 61%; (d) HCl, dioxane, 25°C, 2 h, 88%; (e) LiOH, THF/H_2O, 0°C, 90 min, 68%; (f) EDCI, HOAt, 4-F-3-NO_2-phenylalanine methyl ester, DMF, 25°C, 18 h, 85%; (g) Al–Hg, $Et_2O/EtOH/H_2O$, 25°C, 1 h; HBF_4, *t*-BuONO, 0°C, 10 min; H_3PO_2, 25°C, 1 h, 40%.

bromosuccinimide[10] followed by *O*-methylation with iodomethane provided **5** (Scheme 1). Baeyer–Villiger oxidation with trifluoroperacetic acid, cleavage of the resulting acetate, and hydrolysis of the methyl ester with lithium hydroxide gave carboxylic acid **6**. This was coupled to L-4-fluoro-3-nitrophenylalanine methyl ester[11] to provide the cyclization precursor **7**.

Key ring closure of **7** to **8**[12,13] via the intramolecular aromatic nucleophilic substitution reaction smoothly proceeded at room temperature under a range of conditions (Table 1). All reactions were carried out at a 2 mM concentration of **7** in degassed, anhydrous solvent using five equivalents of base. The most favorable yield of cyclophane **8** was obtained in DMSO with potassium carbonate as the base. Slower reactions were observed in DMF, but comparable conversions were observed if CsF versus K_2CO_3 was used to promote the reaction. Cyclization of **7** resulted in a 1:1 mixture of atropisomers **8a** and **8b**, which were not separated.

Table 1. Reaction conditions for conversion of **7** to **8**

Base	Solvent	Temp. (°C)	Time (h)	Yield (%)
K_2CO_3	DMF	25	18	<10
K_2CO_3	DMSO	25	18	58
K_2CO_3	DMSO	25	4	34
CsF	DMF	25	18	51
CsF	DMF	0	6	33
CsF	DMSO	25	4	41

Without optimization, removal of the nitro group was accomplished in three steps. Aluminum amalgam reduction provided the aniline, which was immediately carried on to the next step without purification, and diazotization with fluoroboric acid and *t*-butyl nitrite followed by reduction of the diazonium salt with hypophosphorous acid gave a single product **9**.[14] The single crystal X-ray structure of **9**[15] shown in Fig. 1 confirmed that the stereochemistry of both chiral centers was preserved in the *S* configuration and that no apparent epimerization of the labile ester center occurred under the basic conditions of the ring closure reaction.

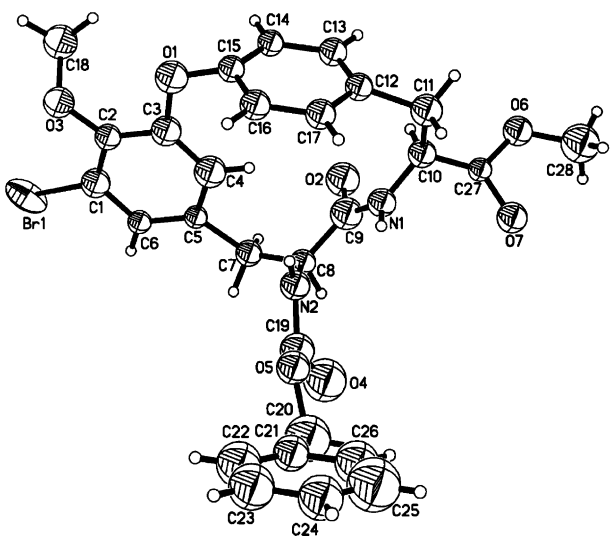
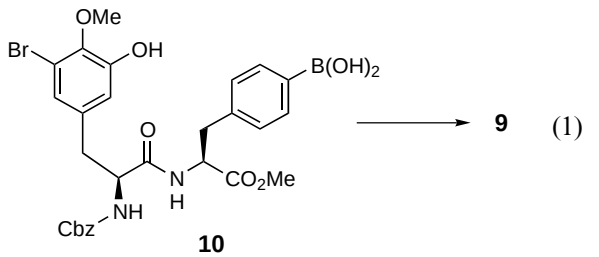


Figure 1. ORTEP diagram of **9**.

An alternative $Cu(OAc)_2$-promoted[16] closure of the boronic acid **10** was also examined (3 equiv. $Cu(OAc)_2$, 5 equiv. of pyridine or collidine, 1 mM CH_2Cl_2, 25°C, 5 days) and found to be less successful, providing low conversions to **9** (9%) and a mixture of the corresponding acyclic phenol or phenylalanine derivatives derived from oxidation or reduction of the boronic acid (Eq. (1)).



(1)

In conclusion, the L,L-isomer of a fully functionalized BC ring system of RP 66453, which constitutes an unusual reversed 14-membered cycloisodityrosine, has been assembled through use of a key diaryl ether macrocyclization reaction enlisting a phenoxide nucleophilic aromatic substitution reaction of an *o*-fluoronitroaromatic. Extension of this work in the total synthesis of RP 66453 is in progress and will be disclosed in due course.

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12. For **7**: $[\alpha]_D^{25}$ +23 (*c* 0.08, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.74 (d, 1H, $J=5.9$ Hz), 7.32 (m, 6H), 7.10 (dd, 1H, $J=8.6$, 10.5 Hz), 6.85 (d, 1H, $J=1.9$ Hz), 6.73 (s, 1H), 6.72 (s, 1H), 6.44 (s, 1H), 5.54 (d, 1H, $J=7.7$ Hz), 5.07 (dd, 2H, $J=12.3$, 22.2 Hz), 4.78 (dd, 1H, $J=6.2$, 12.8 Hz), 4.38 (d, 1H, $J=7.0$ Hz), 3.83 (s, 3H), 3.71 (s, 3H), 3.15 (m, 1H), 3.02 (dd, 1H, $J=6.1$, 13.7 Hz), 2.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 170.9, 155.8, 153.7, 150.4, 143.9, 137.1, 136.7, 136.1, 134.3, 133.2, 128.8, 128.5, 128.2, 126.8, 125.1, 118.6, 116.4, 116.2, 67.5, 61.1, 56.3, 53.2, 53.0, 37.6, 37.0; IR (film) ν_{max} 3311, 3065, 2952, 1652, 1538, 1435, 1351, 1251, 993, 842 cm^{-1}; MALDIFTMS (DHB) m/z 670.0791 (M^++Na, $C_{28}H_{27}BrFN_3O_9$ requires 670.0807).
13. For **8**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, 1H, $J=1.8$ Hz), 7.66 (dd, 1H, $J=2.2$, 8.4 Hz), 7.44–7.32 (m, 13H), 7.00–6.88 (m, 4H), 6.81 (d, 1H, $J=9.7$ Hz), 5.25–5.16 (m, 2H), 5.12–4.93 (m, 5H), 4.87–4.77 (m, 2H), 4.63–4.57 (m, 1H), 5.54–4.47 (m, 1H), 4.24 (bs, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.65–3.52 (m, 4H), 2.69–2.46 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 171.2, 155.6, 154.4, 150.0, 145.0, 144.9, 144.6, 138.0, 136.3, 135.8, 135.5, 134.8, 132.7, 132.3, 128.9, 128.7, 128.5, 128.2, 128.1, 127.7, 126.1, 118.3, 118.0, 114.6, 67.8, 67.5, 61.5, 61.2, 53.5, 52.9, 52.6, 37.8, 32.8, 29.6; IR (film) ν_{max} 3350, 2942, 1738, 1682, 1532, 1494, 1353, 1279, 1223,

997, 910, 733 cm^{-1}; MALDIFTMS (DHB) m/z 650.0737 (M^++Na, $C_{28}H_{26}BrN_3O_9$ requires 650.0745).

14. For **9**: $[\alpha]_D^{25}$ +128 (*c* 0.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (dd, 1H, $J=2.1$, 8.2 Hz), 7.39 (m, 5H), 7.18 (dd, 1H, $J=2.3$, 8.2 Hz), 7.93–6.76 (m, 3H), 6.53 (d, 1H, $J=10.3$ Hz), 5.16 (d, 1H, $J=12.0$ Hz), 5.08 (d, 1H, $J=11.7$ Hz), 5.03–4.96 (m, 1H), 4.73 (d, 1H, $J=1.2$ Hz), 4.55–4.50 (m, 1H), 4.28 (d, 1H, $J=9.7$ Hz), 4.03 (s, 3H), 3.80 (s, 3H), 3.63–3.52 (m, 2H), 2.62–2.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 170.4, 157.5, 156.8, 144.6, 134.7, 133.5, 131.9, 130.2, 128.8, 128.7, 127.2, 125.2, 123.0, 117.8, 116.2, 67.9, 61.1, 53.2, 52.7, 38.1; IR (film) ν_{max} 3354, 3007, 2949, 1735, 1669, 1489, 1434, 1278, 1216, 997, 751 cm^{-1}; MALDIFTMS (DHB) m/z 605.0893 (M^++Na, $C_{28}H_{27}BrN_2O_7$ requires 605.0894).
15. Crystallographic data (excluding structure factors) for **9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 174086. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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