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SYNTHESIS OF (9*S*,12*S*)-CYCLOISODITYROSINE AND ITS UNNATURAL (9*R*,12*S*)-DIASTEREOMER

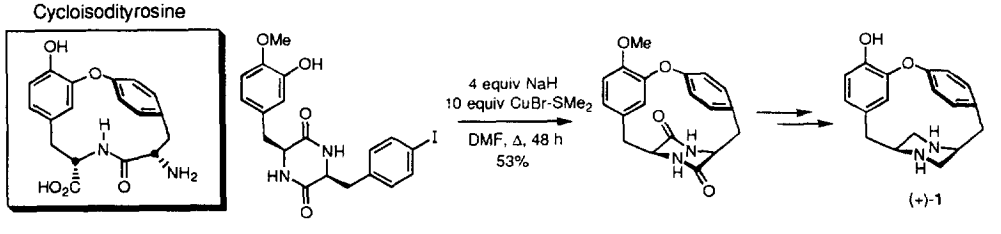
Dale L. Boger,* Jiacheng Zhou, Robert M. Borzilleri and Seiji Nukui

Department of Chemistry, The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037

Abstract. A synthesis of the (9*S*,12*S*)-cycloisodityrosine derivatives and their unnatural (9*R*,12*S*)-diastereomers are disclosed. The approach is based on an intramolecular aromatic nucleophilic substitution reaction for formation of the macrocyclic biaryl ether and includes the documentation of a remarkably facile base-catalyzed epimerization.

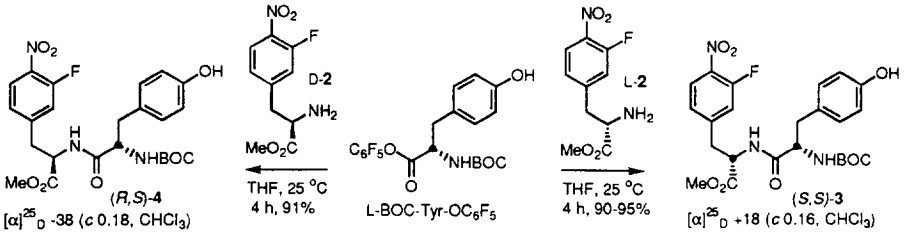
Piperazinomycin (**1**)[1] constitutes the simplest naturally occurring agent possessing a 14-membered biaryl ether core also found in bouvardin, deoxybouvardin, and the RA class of bicyclic hexapeptides.[2] Although related, the cycloisodityrosine subunit of **1** is further reduced and cyclized to provide the bicyclic core of the natural product while that of the latter agents is simply *N*-methylated. In recent studies, we disclosed the total synthesis of (+)-**1** based on an intramolecular Ullmann reaction for macrocyclization formation of the key biaryl ether (Chart 1).[3] In a recent communication,[4] we detailed a synthesis of the *N*-methylcycloisodityrosine subunit found in this latter class of agents and documented a facile epimerization of the C-9 carboxylate center to the unnatural (9*R*,12*S*)-diastereomer. Herein, we report our observations on the extension of these studies to the preparation of the (9*S*,12*S*)-cycloisodityrosine derivatives **8–10** potentially applicable in the synthesis of **1**, their unnatural (9*R*,12*S*)-cycloisodityrosine derivatives **12–14**, the documentation a facile epimerization in this series as well, and the resulting clarification of the analogous studies recently disclosed by Zhu and Beugelmans.[5]

Figure 1



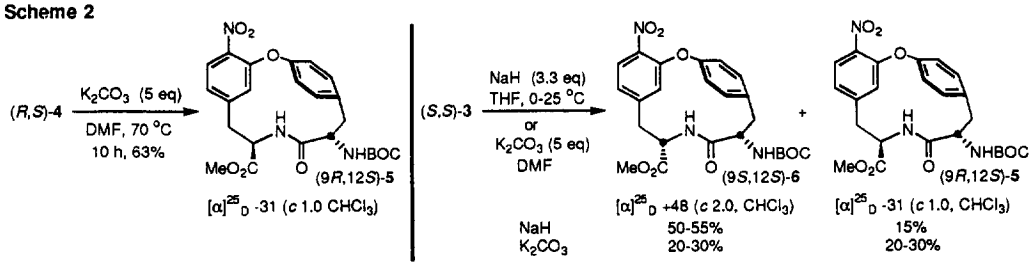
Both (*S*)- and (*R*)-3-fluoro-4-nitrophenylalanine methyl esters (**2**)[4,5] were prepared and coupled (THF, 25 °C, 4 h, 90–95%) with L-BOC-Tyr-OC_6F_5,[6] $[\alpha]_D^{25}$ –25 (*c* 0.4, $CHCl_3$), to provide (*S*,*S*)-**3**, $[\alpha]_D^{25}$ +18 (*c* 0.16, $CHCl_3$), and (*R*,*S*)-**4**, $[\alpha]_D^{25}$ –38 (*c* 0.18, $CHCl_3$). When this reaction was conducted with L-BOC-Tyr-OH activated for coupling by treatment with EDCI–HOBt, a 4:1 mixture of (*S*,*S*)-**3** and (*S*,*R*)-**4** was obtained and is facilitated by the kinetic preference for formation of the (*S*,*R*)- or (*R*,*S*)-diastereomer (Scheme 1).[7]

Scheme 1

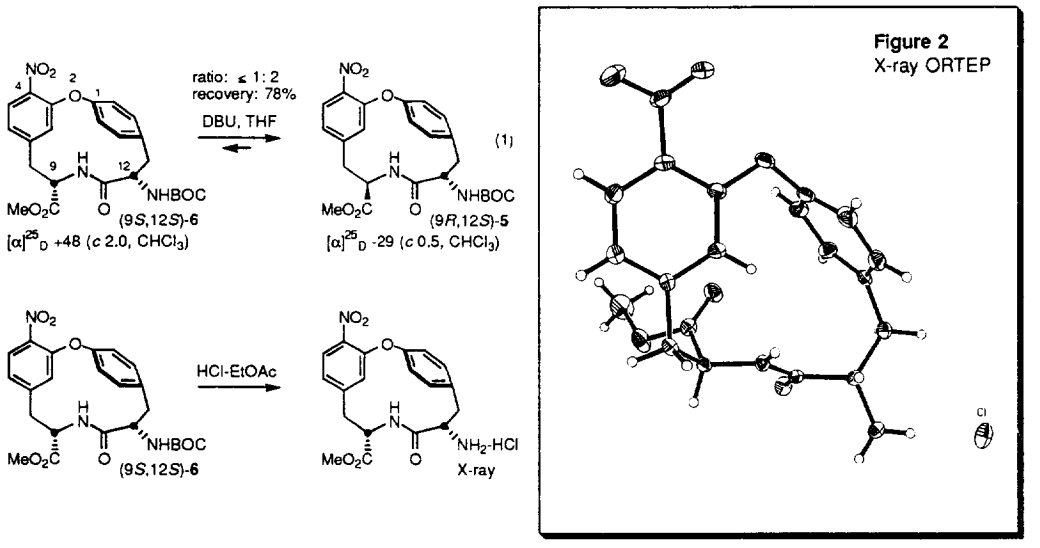


(*R,S*)-**4** underwent smooth macrocyclization upon treatment with K_2CO_3 (5 equiv, 0.005 M DMF, 70 °C, 10 h, 63%) to provide a single, stable diastereomer in excellent conversions (Scheme 2). In contrast, exposure of (*S,S*)-**3** to the same reaction conditions (70 °C) provided an approximate 1:1 mixture of the expected (9*S*,12*S*)-**6** and the epimerized diastereomer (9*R*,12*S*)-**5** in 50–60% combined yield (Scheme 2). Conducting this reaction at 25 °C (3 equiv, K_2CO_3, 0.01 M DMF, 20–24 h, 59%, 1:1 **5:6**) provided the same results but required a more extended reaction time for completion[8] and analogous but unrecognized observations have been disclosed in the independent efforts of Zhu and Beugelmans.[9] A detailed study of the macrocyclization reaction of **3** revealed that epimerization could be minimized by use of NaH (3.3 equiv, 0–25 °C, 6–12 h) or KF/18-c-6 (5 equiv, 0.1 equiv, DMF, 25 °C) but not completely eliminated. Optimal conversions (65–85%) albeit with 10–25% epimerization were obtained with NaH and the desired (9*S*,12*S*)-**6** was obtained pure by chromatographic separation of the resulting diastereomers.

Scheme 2

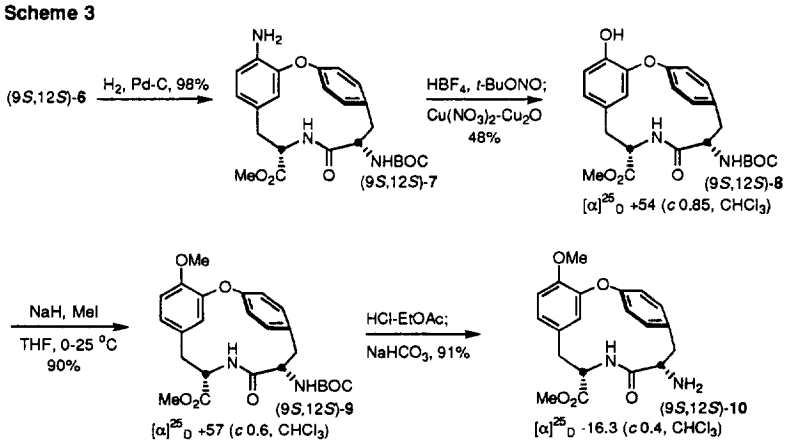


Characterization of **5** derived from the closure of (*S,S*)-**3** and its comparison with authentic (9*R*,12*S*)-**5** derived from (*R,S*)-**4** as well as deliberate epimerization of (9*S*,12*S*)-**6** established that isomerization occurs essentially exclusively at the C-9 ester center providing an equilibrium ratio of diastereomers of ≥2:1 (eq 1). The true equilibrium ratio was not able to be accurately assessed due to base-catalyzed decomposition of the products[3] through nucleophilic attack of the deprotonated central amide onto the C-12 N^{α}-BOC in a reaction that is not competitive upon C-12 *N*-methylation.[4] The structure of **6** was unambiguously established upon *N*-BOC deprotection (3.3 N HCl–THF, 25 °C, 3 h, 100%) and subsequent single-crystal X-ray structure determination of the resulting HCl salt (Figure 2).[10]

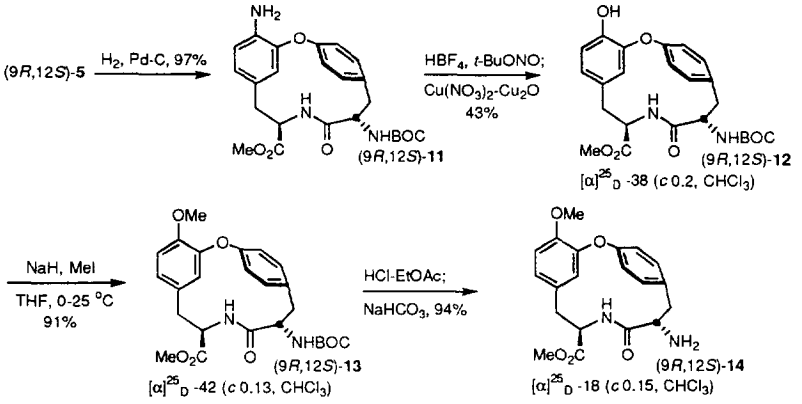


The conversions of (9*S*,12*S*)-**6** and (9*R*,12*S*)-**5** to the cycloisodityrosine derivatives **8–10** and **12–14**, respectively, are summarized in Schemes 3 and 4. Thus, nitro reduction (H_2, 10% Pd–C, CH_3OH, 25 °C, 2h, 97–98%), diazotization (2 equiv HBF_4, 2 equiv *t*-BuONO, THF, 0–25 °C, 1 h) and oxidative hydrolysis of the *in situ* generated diazonium salt (100 equiv $Cu(NO_3)_2$, 5 equiv Cu_2O, H_2O, 25 °C, 1–2 h, 40–55%), followed by selective *O*-methylation (1.5 equiv NaH, 5 equiv CH_3I, THF, 0–25 °C, 1 h, 90–91%) provided **9** and **13**, respectively. Subsequent *N*-BOC deprotection provided the free amines **10** and **14**.[10,11] With care, **6** could be taken through this sequence without epimerization. The conversion of the aryl nitro group into a hydroxy or methoxy substituent required of the cycloisodityrosine core structure suffers from competitive reduction of the diazonium salt, and requires the use of a nonprotic cosolvent (THF versus CH_3OH) for satisfactory conversions.

Scheme 3



Scheme 4



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6. Prepared by treatment of L-BOC-Tyr-OH with EDCI–C_6F_5OH (1.5/1.1 equiv, CH_2Cl_2, 25 °C, 3 h, 87%).
7. Similar, but unrecognized, observations with EDCI–HOBt were disclosed,[5,8] lit[5] $[\alpha]_D^{25}$ +12 (*c* 0.13, $CHCl_3$) versus $[\alpha]_D^{25}$ +18 (*c* 0.16, $CHCl_3$) for (*S,S*)-**3**.
8. Identical, but unrecognized, observations were disclosed[5] but represented as thermally stable, noninterconvertable atropisomers. The report that the starting materials and products are stable to base and the macrocyclization conditions are not accurate and our independent efforts establish that the two diastereomers are related by C9 epimerization.
9. The ^1H NMR reported in this work[5] for atropisomers match those of the diastereomers **5** and **6**. However, the specific rotations are not coincident with those disclosed herein: (9*S*,12*S*)-**6** $[\alpha]_D^{25}$ +48 (*c* 2.0, $CHCl_3$) versus +35 (*c* 0.28, $CHCl_3$)[5] and (9*R*,12*S*)-**5** $[\alpha]_D^{25}$ –31 (*c* 1.0, $CHCl_3$) versus –9 (*c* 0.1, $CHCl_3$).[5] This would seem to confirm the contamination of L,L-**3** with L,D-**4** in this work[5] which was derived from epimerization during coupling to provide **3**[7] (HOBt–EDCI, C12 center) in addition to that which occurs upon macrocyclization (C9 center).
10. The atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and may be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
11. The comparisons of **9–10** and **13–14** with our prior reported samples[12] requires their reassignment to the diastereomer **13–14** stereochemistry. The ramifications of these reassignments are under investigation and will be disclosed in due time.
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