Communications

A Synthesis of D,L-*N*,*N*-Dimethylcycloisodityrosines: A Comment on the Stereochemistry of Previously Reported Intermediates Related to the Synthesis of RA-VII and Deoxybouvardin

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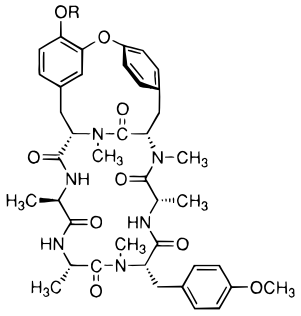
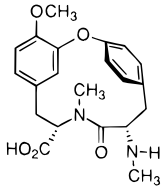
A number of bicyclic hexapeptides (bouvardin[1] and RA-I−XIV[2]), which have an L,L-*N*,*N*-dimethylcycloisodityrosine subunit, have been isolated from Rubiaceae plants (*Rubia akane* in Japan, *Rubia cordifolia* in China, and *Bouvardia ternifolia*). Previously,[3] we reported the first total synthesis of RA-VII (**1**) and deoxybouvardin (**2**) (Figure 1) starting from L,L-*N*,*N*-dimethylcycloisodityrosine (**6**), which was synthesized by thallium trinitrate (TTN) oxidation of the L,L-dibromo dichloro amide **3** followed by the sequential reaction sequences of aromatization, *O*-methylation, and catalytic hydrogenolysis. Independently, Boger and co-workers[4] have reported a total synthesis of **1** and **2** *via* L,L-*N*,*N*-dimethylcycloisodityrosine (**10**), which was obtained by means of an Ullmann reaction of the amide **8** followed by *N*-Boc deprotection (Chart 1). In addition, they have also reported the synthesis of *N*-desmethyl derivatives of RA-VII and deoxybouvardin by the same method.[5]

As part of our continuing examination of the stereostructure of this key intermediate,[6] we found that the



R = CH_3 : RA-VII (**1**)
R = H : Deoxybouvardin (**2**)



L,L-*N*,*N*-Dimethylcycloisodityrosine **6**

Figure 1.

^{1}H NMR spectral data for the free amine **6** and the *N*-Boc derivative **7** were not in agreement with those for the compounds **10** and **9** reported by Boger and co-workers.[4−6] This finding provided the incentive to address the discrepancy by the synthesis of the diastereomer **20** of **6**. The present paper details the synthesis of the title compounds **20** and **21** for direct comparison with the stereostructure of **9** and **10** and the X-ray crystallographic analysis of the *N*-Boc derivative **21**.

N-Methyl-D-tyrosine (**11**)[7] was converted quantitatively into *N*-Cbz-*N*-methyl-D-tyrosine (**12**), $[\alpha]^{25}_D$ +45.7 (*c* 2.38, $CHCl_3$) in a usual manner (2 equiv of CbzCl, K_2CO_3, aqueous acetone, 25 °C, 1 h). Coupling (1.1 equiv of DCC, dioxane, 25 °C, 3 h) of **12** with methyl 3,5-dibromo-*N*-methyl-L-tyrosinate (**13**)[3] gave methyl *N*-methyl-D-tyrosyl-3,5-dibromo-L-tyrosinate (**14**, pale yellow foam, 48%), $[\alpha]^{23}_D$ +8.9 (*c* 0.51, $CHCl_3$).

Chlorination (3.3 equiv of Cl_2, $CHCl_3$, 15−20 °C, 1 h)[3] of **14** afforded the dibromo dichloro amide **15** (pale yellow amorphous solid, 74%), $[\alpha]_D^{25}$ +24 (*c* 0.7, $CHCl_3$) (Chart 2).

With the dibromo dichloro amide **15** in hand, conversion into D,L-*N*,*N*-dimethylcycloisodityrosine (**20**) was carried out in a manner similar to that reported previously.[3] TTN oxidation (3 equiv of TTN, MeOH, 4 °C, 18 h, then pyridine) of **15** gave **16** (pale yellow foam, 11%), $[\alpha]^{25}_D$ +70 (*c* 0.5, $CHCl_3$) and **17** (yellow oil, 34%), $[\alpha]^{25}_D$ +113 (*c* 0.7, $CHCl_3$), respectively, each structure of which was supported on the basis of the spectral evidence. Interestingly, the oxidation of **15** was found to proceed more readily than that of **3**. Aromatization (Zn, AcOH, 25 °C, 18 h) of the former **16** gave the phenol **18** (colorless foam, 73%), $[\alpha]^{25}_D$ +79.8 (*c* 0.87, $CHCl_3$), followed by *O*-methylation (CH_2N_2−Et_2O, MeOH) and catalytic hydrogenolysis (5% Pd−C/H_2, AcOK, MeOH, 25 °C) produced D,L-*N*,*N*-dimethylcycloisodityrosine (**20**), $[\alpha]^{21}_D$ +17 (*c* 0.21, MeOH) in 50% overall yield from **18**. The ^{1}H NMR spectral data of **20** were in agreement with those for **10**.[8]

Finally, *tert*-butoxycarbonylation [5.4 equiv of $(Boc)_2O$, THF, 25 °C, 2.5 h, 99%] of **20** furnished D,L-*N*-Boc-*N*-methylcycloisodityrosine (**21**) (mp 137−138 °C), $[\alpha]^{21}_D$ +168 (*c* 0.21, MeOH), the ^{1}H NMR spectral data of which were also in agreement with those for **9**.[8] In contrast to

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(1) (a) Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040. (b) Bates, R. B.; Cole, J. R.; Hoffmann, J. J.; Kriek, G. R.; Linz, G. S.; Torrance, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 1343.

(2) (a) For a review on oligopeptides related to RA: Itokawa, H.; Takeya, K. *Heterocycles* **1993**, *35*, 1482−1501 and references cited therein. (b) Itokawa, H.; Saitou, K.; Morita, H.; Takeya, K.; Yamada, K. *Chem. Pharm. Bull.* **1992**, *40*, 2984. (c) Hitotsuyanagi, Y.; Suzuki, J.; Takeya, K.; Itokawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1633. (d) Itokawa, H.; Kondo, K.; Hitotsuyanagi, Y.; Isomura, M.; Takeya, K. *Chem. Pharm. Bull.* **1993**, *42*, 1402.

(3) (a) Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957. (b) Inoue, T.; Inaba, T.; Umezawa, I.; Yuasa, M.; Komatsu, K.; Itokawa, H.; Ogura, K.; Hara, H.; Hoshino, O. *Chem. Pharm. Bull.* **1995**, *43*, 1325.

(4) (a) Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 14. (b) Boger, D. L.; Yohannes, D.; Zhou, J.; Patane, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 3420.

(5) Boger, D. L.; Zhou, J. *J. Am. Chem. Soc.* **1995**, *117*, 7364.

(6) The observation that the spectral data of **9** are not identical with those for our synthetic compound **7**[3] has been described in the literature.[5] However, the origin of this discrepancy in the spectral properties had not been addressed.

(7) Izumiya, N.; Nagamatsu, A. *Bull. Chem. Soc. Jpn.* **1952**, *25*, 265.

(8) Specific rotation and mp are not coincident with those for **10** described in the literature.[5]

S0022-3263(96)00381-7 CCC: $12.00

Chart 1

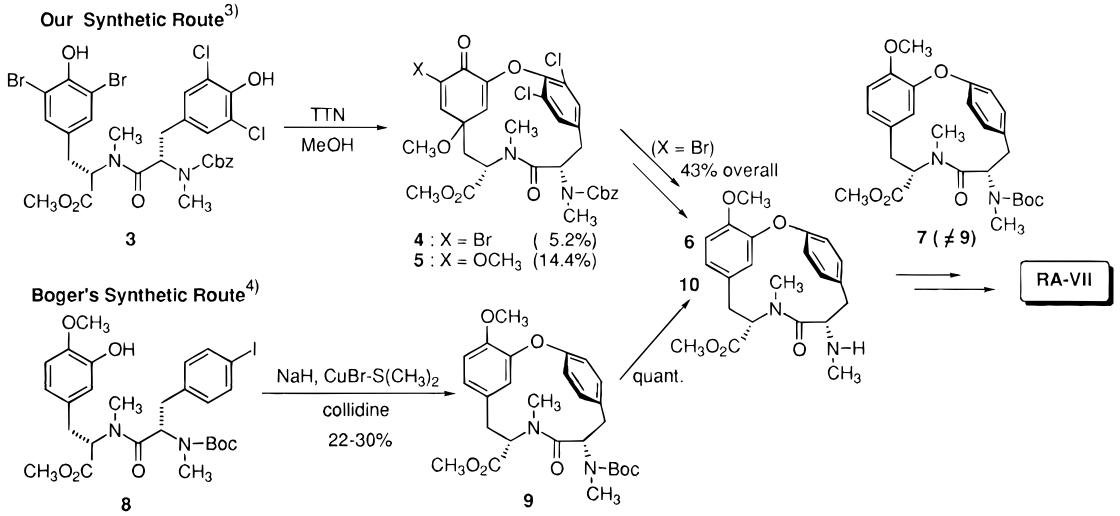


Chart 2

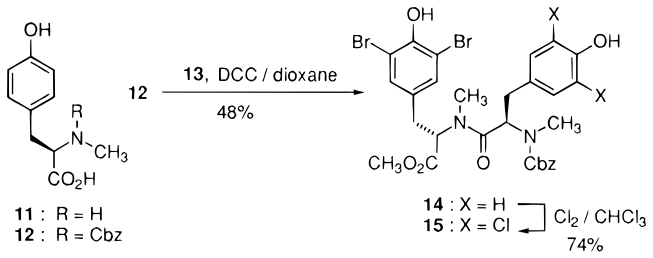
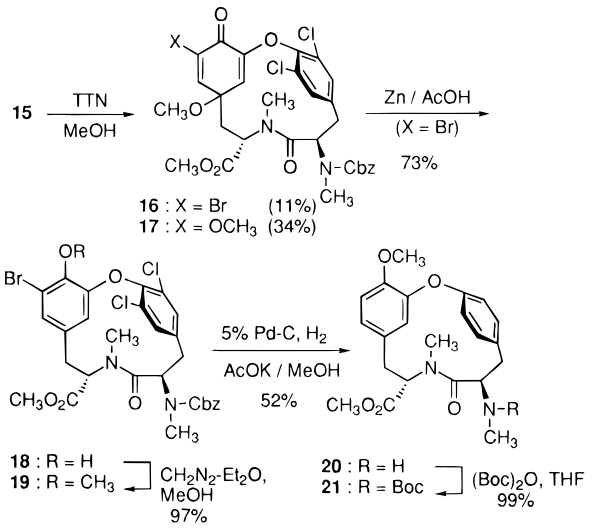


Chart 3



L,L-*N*,*N*-dimethylcycloisodityrosines,[3,9] all cyclized products (**16**−**21**) were found to be single conformational isomers (Chart 3).

The stereostructure of **21** was confirmed by X-ray crystallographic analysis of crystals grown from ether−hexane. An ORTEP drawing of **21** is shown in Figure 2.[10]

In conclusion, D,L-*N*,*N*-dimethylcycloisodityrosines **20** and **21** were synthesized, proving the stereostructure of

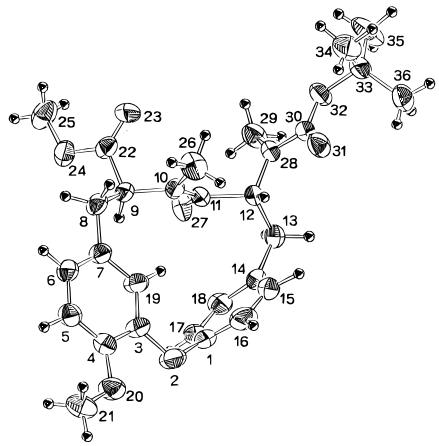


Figure 2. ORTEP drawing.

9 and **10**[11] described in the literature.[4,5] to be **21** and **20** or their enantiomers.

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Supporting Information Available: ^{1}H NMR spectra of **15**−**21** and their full experimental data and X-ray crystallographic data of **21** are provided (13 pages).

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(9) The conformational isomers are separable. However, when each separated compound was allowed to stand in $CHCl_3$, it reverted to an equilibrium mixture.[3]

(10) Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

(11) For RA-VII (**1**) and deoxybouvardin (**2**) to be synthesized from the enantiomer of D,L-*N*,*N*-dimethylcycloisodityrosine (**20**), epimerization of **20** or its enantiomer to **10** must occur. Boger and Zhou address this in an accompanying paper.[12]

(12) Boger, D. L.; Zhou, J. *J. Org. Chem.* **1996**, *61*, XXXX.