Alternative Synthesis of the Cycloisodityrosine Subunit of Deoxybouvardin, RA-VII, and Related Agents: Reassignment of the Stereochemistry of Prior Intermediates

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Deoxybouvardin and RA-VII constitute representative members of a growing class of naturally occurring antitumor agents (Chart 1).[1−3] In the course of our and Inoue's efforts on their total synthesis,[4,5] a discrepancy in the properties of an intermediate cycloisodityrosine derivative was observed. Given that both efforts provided synthetic materials identical to the natural products, investigations into its origin were initiated. Independent of these efforts, we were investigating[6] an alternative synthesis of the cycloisodityrosine subunit of the natural products based on an intramolecular aromatic nucleophilic substitution reaction[7] for formation of the key biaryl ether and considered this an opportunity to address the structural assignments of past intermediates. Herein, we report this alternative synthesis of the cycloisodityrosine subunit of deoxybouvardin and related agents, the extension of the studies to the preparation of its unnatural diastereomer, the comparison with prior synthetic intermediates, and the resulting reassignment of their stereochemistry. The studies also led to documentation of a remarkably facile epimerization that went undetected in our prior efforts.

Both (*S*)- and (*R*)-3-fluoro-4-nitrophenylalanine methyl ester, $[\alpha]^{25}_D$ +12 (*c* 1.2, $CHCl_3$) and −11.6 (*c* 1.2, $CHCl_3$), were prepared[7,8] and coupled with L- and D-BOC-NMe-Tyr-OC_6F_5,[9] $[\alpha]^{25}_D$ −93 (*c* 1.0, $CHCl_3$) and $[\alpha]^{25}_D$ +93 (*c* 1.0, $CHCl_3$), in THF (25 °C, 4 h, 80−90%). This coupling reaction exhibits a kinetic preference for formation of the

Chart 1

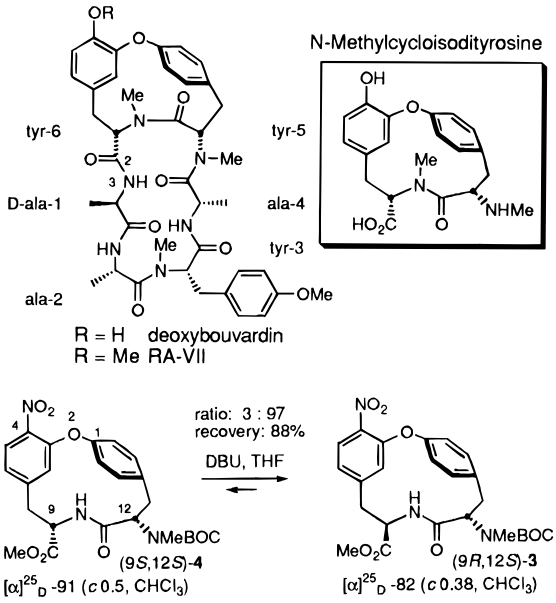

Figure 1.

(*S*,*R*)- or (*R*,*S*)-diastereomer and the use of excess amounts of optically enriched but impure active ester[10] preferentially provided the mixed (*S*,*R*)- or (*R*,*S*)-diastereomer. Consistent with prior observations,[6,7] treatment of the dipeptides with K_2CO_3 (5 equiv, 0.008 M DMF, 45−50 °C, 2−4 h) or NaH (2.2 equiv, 0.004 M THF, 2−6 h) led to smooth 14-membered ring closure (Scheme 1). In the case of **2**, both conditions provided a single product **3** in superb conversions (76−78%), and the relative stereochemistry was unambiguously established upon *N*-BOC deprotection (2.2 N HCl−EtOAc, 25 °C, 30 min, 100%) and subsequent X-ray analysis (Figure 1).[11]

In contrast, **1** only provided the expected diastereomer **4** under carefully defined reaction conditions where potential epimerization is minimized (2.2 equiv of NaH, 0.004 M THF, 0−25 °C, 2−6 h, 50−61%). Moreover, increasing amounts of the diastereomer **3** were obtained if this reaction was extended to longer reaction times or conducted with excess NaH. Conducting this reaction under the apparently milder conditions of K_2CO_3−DMF (5.0 equiv, 45−50 °C, 0.008 M, 3−4 h) provided the epimerized diastereomer **3** nearly exclusively (45−55%) with only a trace of the expected product **4** (5−10%) being detected at any time during the reaction. Equilibration studies conducted on (9*S*,12*S*)-**4** confirmed the unusually facile epimerization that could be effected by treatment with K_2CO_3, K_2CO_3/18-crown-6, or KF in DMF as well as DBU or Et_3N in THF. The studies also established an equilibrium ratio of ≥97:3 in favor of the unnatural diastereomer **3** and that this epimerization occurs at the C9 center adjacent to the methyl ester (Figure 1). The

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(8) Prepared by coupling 4-(bromomethyl)-2-fluoronitrobenzene with the higher order cuprate of (2*R*)-(−)- and (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine, respectively, followed by hydrolysis (0.25 N HCl, 25 °C, 8 h; saturated aqueous $NaHCO_3$, 91−92%) of the intermediate alkylated dihydropyrazines, $[\alpha]^{25}_D$ +41 (*c* 0.9, $CHCl_3$) and −39 (*c* 0.5, $CHCl_3$).

(9) Prepared by *N*-methylation of L- and D-BOC-Tyr(OBn)-OH (2.2 equiv of NaH, 5.0 equiv of CH_3I, 20:1 THF−DMF, 0−25 °C, 10 h, 82−90%), hydrogenolysis of the benzyl ether (H_2, 10% Pd−C, CH_3OH, 25 °C, 91−97%), and active ester formation (1.1 equiv of C_6F_5OH, 1.5 equiv of EDCI, CH_2Cl_2, 25 °C, 74−83%).

(10) Extensive racemization is observed if the *N*-methylation of BOC-Tyr(OBn)-OH is conducted on a corresponding ester or under conditions where the methyl ester is formed directly especially if excess NaH is employed.

(11) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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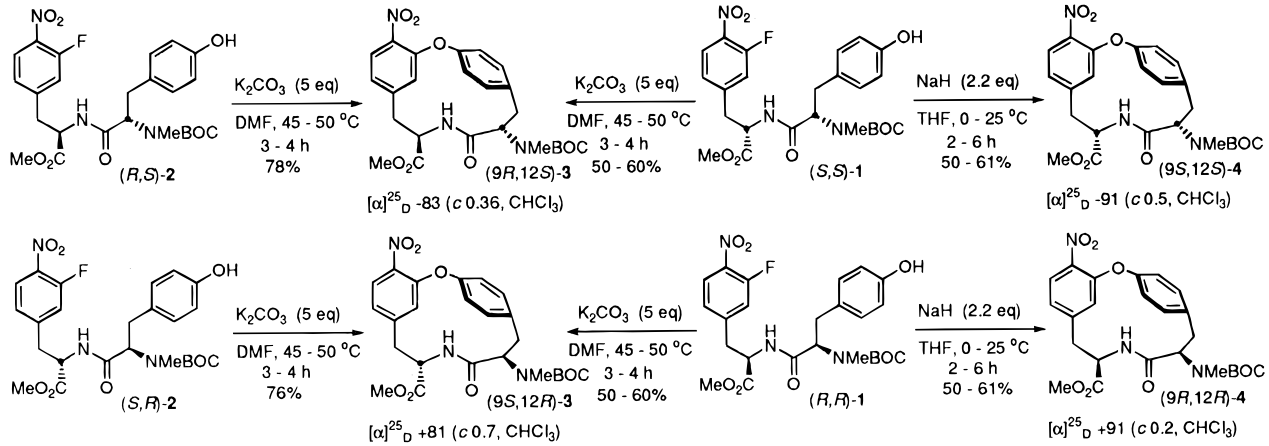
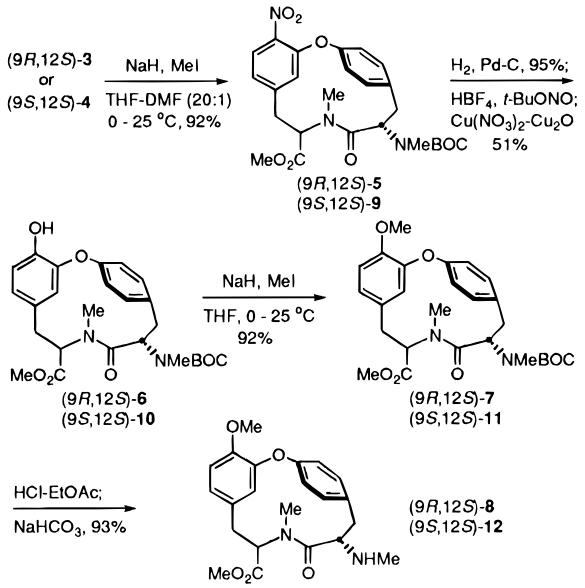
Scheme 1



Scheme 2



facile epimerization of **4** is in sharp contrast to the observations made in related systems, which do not embody the cycloisodityrosine 14-membered ring, where epimerization is minimal under comparable[7] or more vigorous reaction conditions.[12,13]

Conversions of (9*S*,12*S*)-**4** and (9*R*,12*S*)-**3** to L,L-*N*-methylcycloisodityrosine methyl ester ((9*S*,12*S*)-**12**) and its unnatural diastereomer, (9*R*,12*S*)-**8**, were accomplished as outlined in Scheme 2. N^{10}-Methylation (1.2 equiv of NaH, 10 equiv of CH_3I, 20:1 THF−DMF, 0−25 °C, 3 h, 84−92%) of **3** and **4** provided **5** and **9**, respectively. No epimerization of **3** was detected, and the more sensitive **4** suffered trace detectable epimerization (≤3%) under the conditions. Nitro reduction to the aryl amine (H_2, 10% Pd−C, CH_3OH, 25 °C, 1 h, 95%) followed by diazotization (2 equiv of *t*-BuONO, 2 equiv of HBF_4, THF−H_2O, 0 °C, 1 h) and subsequent oxidative hydrolysis of the diazonium salt using $Cu(NO_3)_2$−Cu_2O (0−25 °C, 1 h) afforded the phenols **6** and **10**. *O*-Methylation (1.2 equiv of NaH, 10 equiv of CH_3I, THF, 0−25 °C, 1−1.5 h, 84−92%) provided **7** and **11**, respectively, and acid-catalyzed *N*-BOC deprotection (2.2 N HCl−EtOAc, 25 °C, 1 h, 91−93%) followed by liberation of the free amines provided **8** and **12**.

The comparison of the samples with those previously reported[4,5,14] revealed that our past intermediates possessed the unnatural (*R*,*S*)-stereochemistry of **6**−**8** and that their conversion to deoxybouvardin and RA-VII requires reepimerization of the C9 center to the natural (*S*)-configuration. Although undetected in our efforts, this occurs at the stage of the hexapeptide macrocyclization with formation of the C^2−N^3 amide. As noted in our efforts, the macrocyclization of selected hexapeptides has been shown to improve remarkably with the incorporation of a D-amino acid at the cyclization site amine terminus (57−76% versus 2−3%).[15] This preference for cyclization at a site containing a D-amine/L-carboxylate termini and the facile epimerization of the C9 cycloisodityrosine center suggests that it is at the stage of the hexapeptide closure with *in situ* generation of the intermediate acyl azide ($(PhO)_2P(O)N_3$, 0.004 M DMF, Et_3N, or K_2CO_3) that this reepimerization occurs and is driven by its preferential cyclization. As such, the macrocyclization conducted with formation of the C^2−N^3 amide employing a D-amino acid amine terminus proved more strategic to our efforts than previously recognized. These and related issues[16] are under investigation and will be disclosed in due course.

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Supporting Information Available: Full experimental details and characterization of **1**−**12** are provided (14 pages).

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