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A Formal Total Synthesis of Deoxybouvardin

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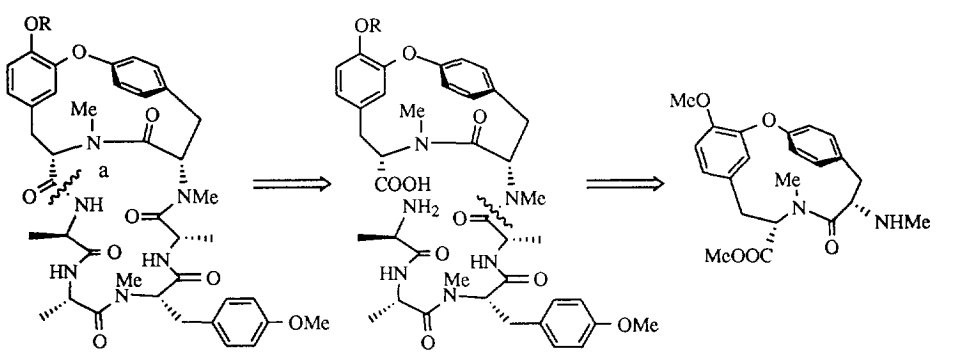
Abstract: A synthesis of (L, L)-*N*, *N*-dimethylcycloisodityrosine **4** based on intramolecular S_NAr reaction is reported. A possible explanation was proposed to account for the facile epimerization encountered in the cycloetherification of dipeptide (L,L)-**10** and a solution to this problem led to a formal total synthesis of deoxybouvardin. © 1997 Elsevier Science Ltd.

Deoxybouvardin (**1**)[1] and RA-VII (**2**)[2] (Figure 1) are two prominent representatives of an important family of naturally occurring antitumor agents. These bicyclic hexapeptides act by inhibiting protein synthesis through an interaction with eukaryotic 80S ribosomes.[3] RA-VII is currently undergoing clinical trial in Japan.[4]

Top-down approach, retrosynthetic analysis



1 Deoxybouvardin R = H
2 RA-VII R = Me

3

4 *N*, *N*-dimethylcycloisodityrosine

Figure 1

The molecular architecture and interesting biological activity made these compounds attractive synthetic targets.[5] Although several synthetic strategies could be envisaged, only three primary routes have been exploited, namely: 1) transannulation;[6] 2) bottom-up[7] and 3) top-down[6,8,9]. While the first two strategies failed

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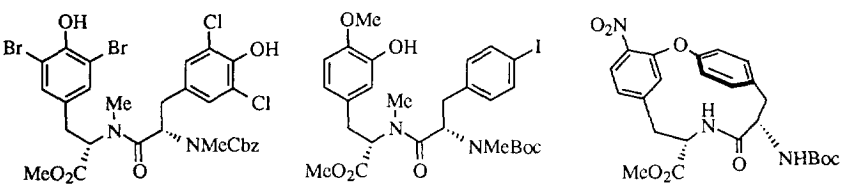
to give the target molecules, the "top-down" approach was found to be more rewarding. Realizing that ring closure of bottom 18-membered macrocycle from seco-acid **3** (bond disconnection a) was relatively easy,[10] all synthetic efforts have thus far concentrated on synthesis of the key subunit, L,L-*N*,*N*-dimethylcycloisodityrosine **4**. Nevertheless, difficulties have been encountered in the construction of this structurally simple cyclophane and untill now, only Inoue *et al.*[8] and Boger *et al.*[6,9] have achieved the synthesis of **4** and ultimately, of compounds **1** and **2**.

Both of these syntheses were accomplished by formation of the biaryl ether bond as the key ring closure step, since macrolactamization was shown to be ineffective in the construction of the ring structure of compound **4**.[11] The strategy employed by Inoue and co-workers[8] involved thallium trinitrate[12] promoted oxidative coupling of the L,L-dichloro dibromo dipeptide **5** (Figure 2) followed by aromatization, *O*-methylation and reductive dehalogenation to give *N*,*N*-dimethylcycloisodityrosine (**4**) in 5% overall yield. A more direct approach by Boger and co-workers[6,9] used the intramolecular Ullmann reaction to give compound **4** in a single step from the L, L-dipeptide **6** (Figure 2) under carefully controlled conditions (NaH, collidine, CuBr, 20%). While both groups have accomplished the total synthesis of deoxybouvardin, the key intermediate **4** reported by these two groups had different physical properties. This unusual discrepancy has posed the question of stereostructure of these synthetic materials and recent literature reports by Inoue[13] and Boger[14] shed light on this irregularity by explaining that under Ullmann cyclization conditions, epimerization occurred to give *epi*-**4**.

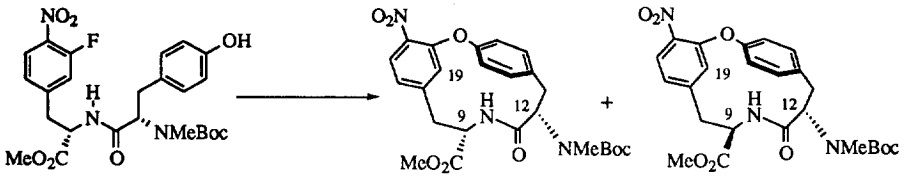


5 **6** **7**

Figure 2

Recent work in this laboratory has demonstrated the power of an intramolecular nucleophilic aromatic substitution (S_NAr) reaction for synthesizing macrocycles containing a biaryl ether bridge.[15,16] Biaryl ether formation with concomitant ring closure under extremely mild conditions (K_2CO_3 or CsF, DMF, room temperature) constitutes the basic strategy of our approach.[17] As a continuation of our research programme, we have synthesized the 14-membered *m*,*m*-cyclophane,[18] fragment of teicoplanine, and recently the *m*,*p*-cyclophane (**7**, Figure 2)[19], fragment of bouvardin, by means of this cycloetherification reaction. Employing this same methodology, an elegant and detailed study along this line has also been carried out by Boger and co-workers.[14, 20] We now report, in full detail, our own results concerning the synthesis of *N*,*N*-dimethylcycloisodityrosine **4**.

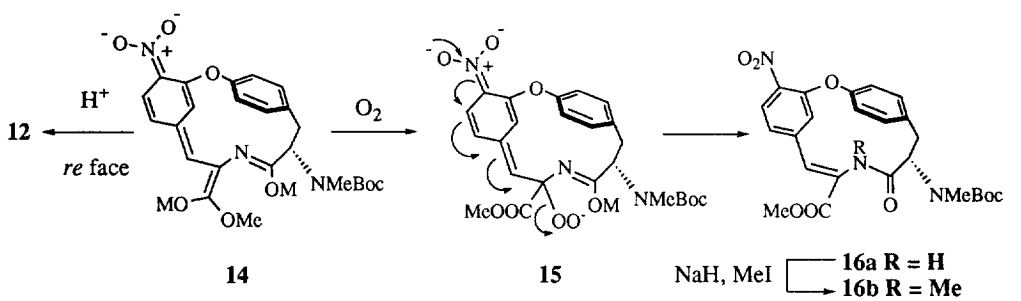
Coupling (EDC, HOBt) of the known compound L-3-fluoro-4-nitro phenylalanine methyl ester (**8**)[15c,21] with L-*N*-Boc-*N*-methyl tyrosine (**9a**), obtained in three steps from L-tyrosine, gave the dipeptide (**10**) in 78% yield. The reaction conditions had to be carefully controlled in order to avoid any epimerization in this coupling process. A similar result was obtained from the reaction between L-(**8**) and the L-*N*-Boc-*N*-methyl tyrosine pentafluorophenyl ester (**9b**).



10	11	12
K_2CO_3-DMF, rt, 24 h	---	65%
KH-THF, 0°C, 1 h	30%	30%
LiH-THF, rt, 6 days	---	---
Na_2CO_3-DMF, 3 days	---	---
NaH-THF, 0°C, 1h, then 3h at rt	54%	19%
CsF, 0°C, 15 days	---	30%

Scheme 1

Cyclization of compound (L,L)-**10** proceeded readily under our standard conditions (K_2CO_3, DMF, room temperature)[15] to give the constrained *m,p*-cyclophane **12** in 65% yield (Scheme 1). While the cyclic structure of **12** is easily recognized by the characteristic high field shift of the H-19 proton in the ^1H NMR spectrum, it appeared that epimerization at the C-9 chiral centre had occurred under the above cyclization conditions and that the product was, in fact (9*R*, 12*S*)-**12**, the epimer of the desired compound (9*S*, 12*S*) **11** as observed by Boger *et al.*[14] The stereochemistry of **12** was confirmed by comparison with an authentic sample resulting from the cyclization of (D,L)-**13** (*vide supra*). Although no clear-cut experiment has been carried out to determine whether epimerization occurred before or after cyclization (or both), we have nevertheless found that cyclo (L,L)-**11** is more configurationally labile than its acyclic counterpart (L,L)-**10**.[22]

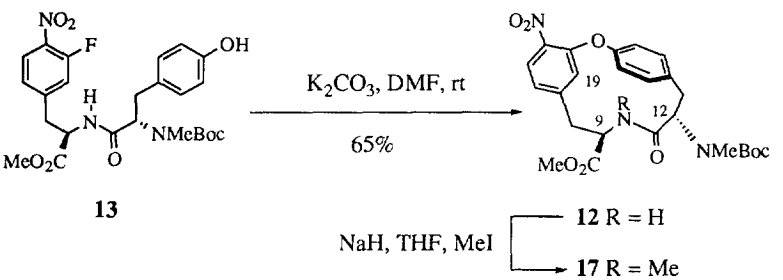


Scheme 2

While the mechanism of epimerization could be explained by enolization followed by diastereoselective protonation leading to the thermodynamically more stable cyclo (D,L) isomer, it was, at first glance, surprising that chiral centre at C-9 was epimerized in preference to that of C-12, as it is known that *N*-methylamino acid is more prone to racemization.[23] However, taking into account the work of Seebach[24] on nitroalkanes, specifically

on the double deprotonation of β-nitro-propionate,[24b] we hypothesized that formation of the intermediate **14** with a fully conjugated polyanion system would be thermodynamically favored thus accounting for the observed results (Scheme 2).

To avoid undesired epimerization during the cyclization of (L,L)-**10**, the effects of changing the solvent, the base and the temperature were investigated (Scheme 1). Sodium carbonate and lithium hydride were found to be ineffective for promoting the cyclization while CsF (DMF, room temperature) afforded the epimerized product (D,L)-**12** after prolonged period (15 days) at 0°C. Surprisingly, epimerization was minimized under the more basic conditions but relatively shorter reaction time. Thus, with potassium hydride, compounds (L,L)-**11** and (D,L)-**12** were isolated in a 1 to 1 ratio in 60% overall yield, whilst with sodium hydride under optimized conditions, the two cyclic compounds **11** and **12** were obtained in 54% and 19% yield, respectively. Under these conditions, a small amount of the oxidized product **16a** (Scheme 2) was also isolated (*vide supra*). It seemed to us that there is a counter cation effect and that the degree of racemization increased on moving from sodium to cesium.



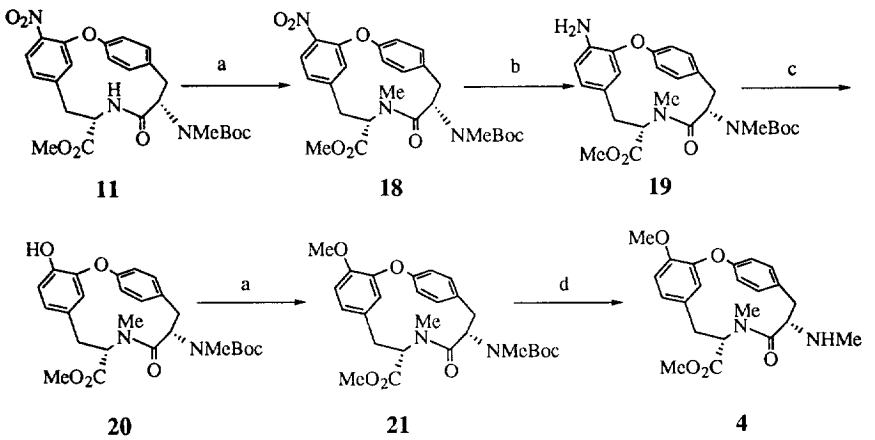
13

NaH, THF, MeI → **12** R = H; **17** R = Me

Scheme 3

The aforementionned cyclization conditions have also been applied to linear dipeptide (D,L)-**13** (Scheme 3). In contrast to its (L,L) counterpart **10**, cyclization of (D,L)-**13** proceeded smoothly under all conditions tested (K_2CO_3, CsF, KH, NaH as bases) to afford cyclo (D,L)-**12** in good yield. However, care should be taken when the cyclization of (D,L)-**13** was carried out using NaH as base. In fact, when sodium hydride was used in conjuction with freshly redistilled but non-degassed THF, up to 50% of previously unknown compound **16a** (Scheme 2) was isolated along with the desired cyclic compound (9*R*, 12*S*) **12**. These two compounds have a very similar behaviour on TLC and were difficult to purify at this stage. However after methylation (NaH, MeI, THF), two new compounds, namely **16b** and **17**, were easily separated and characterized. The structure of product **16b** (Scheme 2) was determined from detailed spectroscopic studies. The presence of an upfield shifted proton H-19 (δ = 5.47 ppm) indicated that this compound had a cyclic structure. However, the disappearance of the three aliphatic proton signals and the observation of an extra singlet (δ = 7.16 ppm) at low field relative to compound **12** in ^1H NMR spectra indicated a degree of unsaturation in the cyclic framework. This assumption was confirmed by ^{13}C and 2D (COSY, HMBC) NMR spectra. The position of the double bond was deduced from the IR spectrum. The ester function of all compounds studied in this work absorbed around 1740 cm^{-1}. However, the IR spectrum of compound **16b** had a sharp peak at 1728 cm^{-1} indicating the presence of an α, β-conjugated ester function. Thus, the structure of **16b** and consequently that of **16a** was determined as shown in Scheme 2. The mass spectra and HRMS of **16b** correspond to the formula

$C_{26}H_{30}N_3O_8$ (M + 1) which also matched the proposed structure. Mechanistically, the formation of compound **16a** is in accord with the observation that the chiral centre at C-9 is more prone to racemization than that at C-12. We speculated that both the epimerization and the oxidation processes went through a common enolate intermediate. Formation of oxidized compound **16a** could occur via peroxidation[25] of the enolate **14** (Schema 2) followed by β-elimination. Experimental evidence to support this hypothesis is that formation of **16** was largely supressed when the reaction was carried out in degassed THF. It is of interest to note that this side reaction is more pronounced in the cyclization of (D,L)-**13** than in that of (L,L)-**10**. This may indicate that (D,L)-**13** and/or cyclo (D,L)-**12** are more prone to enolization than their (L,L) counterparts leading to the intermediate **14**. However, in the case of (D,L)-**13**, protonation of enolate from *re* face regenerated the *R* configuration at C-9 affording cyclo (D,L)-**12**.



Reagents and Conditions: a) NaH, THF, MeI, 88%; b) H_2, Pd/C, MeOH; c) (i) HBF_4, ^tBuONO; (ii) $Cu(NO_3)_2$, $Cu(NO_3)_2$, Cu_2O, 48% ; d) TFA, 92%.

Scheme 4

With compound (L,L)-**11** in hand, the synthesis of *N*,*N*-dimethylcycloisodityrosine (**4**) was accomplished as shown in Scheme 4. *N*-methylation of **11** in degassed THF (NaH, MeI) gave the dimethylated compound **18** in 88% yield. A small amount of the *N*, *N*-dimethylated derivative of compound **16b** was isolated. It is appropriate to point out that a large excess of freshly distilled MeI should be used in order to increase the reaction rate and thus avoid the degradation of compound **11**. In fact, a control experiment showed that treatment of compound **11** with NaH in the absence of MeI led not only to the formation of cyclo (D,L)-**12** but also to other unidentified polar compounds, indicating the instability of compound **11** under methylation conditions. Hydrogenation of **18** (Pd/C, degassed MeOH) gave a quantitative yield of the amino compound (**19**) which was submitted directly to the hydroxylation conditions[15c,26] to provide **20** in 48% yield. Methylation of the phenol founction followed by removal of the *N*-Boc group gave the target compound *N*,*N*-dimethyl cycloisodityrosine **4** in 92% yield with physical data identical in all respects to the literature values.[8,14] While (L,L)-**11** has a single solution conformation in $CDCl_3$ and CD_3OD, all other *N*,*N*-dimethylated

cycloisodityrosine derivatives (**18, 19, 20, 21** and **4**) reported in this paper exist in two rigid solution conformations. In the case of **4**, the two conformers were even detectable by TLC.[8,14]

In summary, a synthesis of *N,N*-dimethylcycloisodityrosine **4** based on our cycloetherification methodology was described. A combination of inherent ring strain and the presence of *para*-nitrosubstituted phenylalanine unit in 14-membered cyclophane may be responsible for the facile epimerization encountered in this work.[27] As compound **4** has been converted into natural products deoxybouvardin and RA-VII by Inoue *et al.*,[8] the work described in this letter represents a formal total synthesis of these natural products.

Experimental Section

Melting points were determined with a Kofler apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Nicolet-205 spectrometer. ^{1}H NMR spectra were measured on Brucker AC-200 (200MHz), Bruker AC-250 (250MHz), Bruker (300 MHz) and Bruker WM-400 (400MHz) spectrometers with tetramethylsilane as internal standard (d ppm). Flash chromatography was performed using Kieselgel 60 (230-400 mesh, E. Merk) and usually employed a stepwise solvent polarity gradient, correlated with TLC mobility. Solvents and reagents were purified according to standard laboratory techniques. Optical rotation were determined on a Perkin-Elmer automatic polarimeter at room temperature. Mass spectra were run on AEI MS-50 (EI), AEI MS-9 (CI) and Kratos MS-80 (FAB), respectively. All reactions requiring anhydrous conditions or in an inert atmosphere were conducted under an atmosphere of Argon.

L-*N*-Boc-N-methyl tyrosine 9a: Compound **9a** was prepared from L-tyrosine in three steps via *O*-benzylation, *N*-methylation and hydrogenolysis. $[\alpha]_D$ = -62.7° (MeOH, *c* 2.1); IR ($CHCl_3$) 3600, 3344, 2975, 1719, 1688, 1606 cm^{-1}; ^{1}H NMR (200 MHz, CD_3COCD_3, mixture of two rotamers) δ 1.34 and 1.40 (2 s, 9H), 2.68 (s, 3H), 2.8-3.1 (m, 1H), 3.1-3.2 (m, 1H), 4.60 (dd, *J* = 4.1, 10.7 Hz) and 4.85 (dd, *J* = 4.9, 10.2 Hz, 1H), 6.7 (m, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 8.1 (br. s, 2H); ^{13}C NMR (75 MHz, CD_3COCD_3, mixture of two rotamers) δ 28.3, 32.3 and 32.5, 34.5 and 35, 60.3 and 61.9, 79.8 and 80.1, 115.8 and 115.9, 116.3, 129.2 and 129.4, 130.5 and 130.6, 131.6, 156.6, 172.6 and 172.8; MS *m/z* 295 (M), 195.

L-*N*-Boc-N-methyl tyrosine pentafluorophenyl ester 9b: To a solution of L-*N*-Boc-N-methyl tyrosine **9a** (255 mg, 0.86 mmol) in CH_2Cl_2 (10 mL) were added pentafluorophenol (175 mg, 0.95 mmol) and EDC (183 mg, 0.95 mmol). The reaction mixture was stirred at ambient temperature for 15 hours. After evaporation of the solvent, the crude mixture was submitted to purification by flash chromatography (SiO_2, AcOEt / Heptane = 1/3) to give product **9b** (318 mg, 80%) as a colorless oil which crystallized upon standing: mp 147-148°; $[\alpha]_D$ = -90° ($CHCl_3$, *c* 1.2); IR ($CHCl_3$) 3600, 3119, 2988, 2938, 1788, 1694, 1525, 1398, 1163, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of two rotamers) δ 1.41 and 1.42 (2 s, 9H) 2.82 and 2.85 (2 s, 3H) 3.10 (m, 1H) 3.32 (m, 1H), 4.85 (m, 1H), 5.2 (dd, *J* = 5.4, 9.8 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of two rotamers) δ 28.2 and 28.3, 32.2 and 32.9, 34.2 and 34.6, 59.8 and 61.7, 81.8 and 82.3, 115.7 and 115.8, 127.9, 130.2, 137.4 (m), 138.5 (m), 139.5 (m), 140.7 (m), 141.6 (m), 155.2 and 155.4, 167.4 and 167.6; MS *m/z* 461 (M), 361.

L-3-fluoro-4-nitro-*N*-[*N*-Boc-*N*-methyl-L-tyrosyl] phenylalanine methyl ester 10. Method A : A solution of L-*N*-methyl-*N*-Boc tyrosine pentafluorophenyl ester (52.4 mg, 0.11 mmol, 1.1 eq) and L-3-fluoro-4-nitro phenylalanine methyl ester (24 mg, 0.1 mmol) in anhydrous THF (10 mL) was stirred at room temperature for 6 hrs. The volatile was evaporated under reduced pressure and the crude product was purified by flash chromatography (SiO_2, AcOEt/Heptane = 1/3 then 1/1) to give dipeptide **10** as a white foam (37 mg, 70 %); $[\alpha]_D$ = -44.9° ($CHCl_3$, *c* 1.2); IR ($CHCl_3$) 3599, 3409, 2981, 1743, 1687, 1616, 1609, 1532, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of two rotamers) δ 1.33 and 1.41 (2 br. s, 9H), 2.67 and 2.75 (2 br. s, 3H), 2.8-2.9 (m, 1H), 3.0-3.2 (m, 2H), 3.27 (dd, *J* = 5.6, 13.9 Hz, 1H), 3.71 and 3.72 (2 br. s, 3H), 4.74 (dd, *J* = 6.9, 8.8 Hz, 1H), 4.7-4.8 (m, 1H), 5.43 (br s, 1H), 6.7-6.8 (m, 3H), 7.0-7.1 (m, 4H), 7.97 (br. t, *J* = 8.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$, mixture of two rotamers) δ 28.2, 30.8 and 31, 33.3 and 33.3, 37.6, 52.8, 59.8, 81.2, 115.5, 119.1 (d, *J* = 21 Hz), 125.5 (d, *J* = 3.6 Hz), 126.2, 128.3, 130, 135.9 (d, *J* = 20 Hz), 145.5 and 145.9, 155.1, 155.3 (d, *J* = 264 Hz), 156.7, 170.7 and 170.8; MS *m/z* 520 (M + H). Anal. Calcd for $C_{25}H_{30}FN_3O_8$: C, 57.79; H, 5.82; N, 8.09. Found: C, 57.61; H, 6.16; N, 7.47.

Method B : To a solution of L-*N*-methyl-*N*-Boc tyrosine (428 mg, 1.45 mmol) and L-3-fluoro-4-nitrophenylalanine methyl ester (350 mg, 1.45 mmol) in distilled CH_2Cl_2 (40 mL) were added HOBt (196 mg, 1.45 mmol), and EDC (334 mg, 1.74 mmol). After being stirred for 22 hours at room temperature, 10 ml of 1N HCl and 50 ml of water were added, and the aqueous solution was extracted CH_2Cl_2. The combined organic extracts were washed with brine, dried and evaporated under the reduced pressure. The residue was purified by flash column chromatography (SiO_2, AcOEt/Heptane = 1/1.5) to give dipeptide **10** as a white foam (600 mg, 80 %) and the epimerized D,L-Dipeptide **13** (75 mg, 10%).

D-3-fluoro-4-nitro-*N*-[*N*-Boc-*N*-methyl-L-tyrosyl] phenylalanine methyl ester 13: Following the procedure A described for the synthesis of (L,L)-**10**, the coupling reaction between L-*N*-methyl-*N*-Boc tyrosine pentafluorophenyl ester and D-3-fluoro-4-nitrophenylalanine methyl ester in anhydrous THF (10 mL) gave dipeptide **13** (70%) as a yellow oil: $[\alpha]_D$ = -50° ($CHCl_3$, *c* 0.7); IR ($CHCl_3$) 3954, 3406, 3219, 3025, 2950, 1744, 1688, 1613, 1606, 1531, 1519, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of two rotamers) δ 1.39 (br. s, 9H) 2.75 (br. s, 3H) 3.0-3.3 (m, 4H) 3.72 (br. s, 3H), 4.7-4.9 (m, 2H), 5.83 (br. s, 1H) 6.46 (br. s, 1H), 6.71 (br. d, *J* = 7.6 Hz, 2H), 6.8-6,9 (m, 2H), 7.01-7.07 (m, 2H), 7.88 (br. t, *J* = 8.5 Hz, 1H); ^{13}C NMR (50,05 MHz, $CDCl_3$, mixture of two rotamers) δ 28.3, 30.8, 33.3, 37.3 and 37.5, 52.6 and 52.8, 59.8, 81.2 and 82.4, 115.4, 119 (d, *J* = 20.7 Hz), 125.5 (d, *J* = 3,6 Hz), 126.3, 128.3 and 128.5, 130.3, 145.5 and 145.7, 154.7 (d, *J* = 230 Hz), 155.6, 170.5 and 170.7; MS *m/z* 390 [(M + H)-NMeBoc]$^+$.

Cyclic dipeptide 11 (9*S*, 12*S*): To a solution of 100 mg of **10** (0.19 mmole) in freshly distilled THF (20 mL, 0.01 M) was added NaH (17 mg, 0.42 mmol, 60 % dispersion in paraffin) and the resulting slurry was stirred at 0° C for 10 min and then at room temperature for 3 hrs . The reaction was quenched by addition of aqueous NH_4Cl solution. The aqueous solution was then extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, AcOEt/Heptane = 1/2) to give cyclic dipeptide **11** and **12** in the yields of 54% and 19%, respectively. Compound **11**: mp 109-111° C (dec.); $[\alpha]_D$ = - 90° ($CHCl_3$, *c* 0.6); IR ($CHCl_3$) 3031, 3013, 2925, 2856, 1738, 1675, 1600, 1531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.96 (t, *J* = 16.8 Hz ,1H), 3.09 (s, 3H), 3.3-3.1 (m, 3H), 3.57 (s, 3H), 4.29 (m, 1H), 4.56 (dd, *J* = 5.1, 11.8 Hz, 1H), 5.36 (br. s, 1H), 5.58 (br. s, 1H), 6.69 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.15 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.16 (dd, *J*

= 2.3, 8.2 Hz, 1H), 7.5 (m, 2H), 7.87 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 31.1, 35.1, 36.7, 52.3, 53.1, 62, 80.7, 119.8, 122, 124.2, 125.8, 126, 130.9, 133.9, 135.9, 143, 150.9, 156, 156.6, 159.5, 168.5, 171.3; MS *m/z* 500 (M+H); HRMS *m/z* 500.2036 ($C_{25}H_{30}N_3O_8$ (M + 1) requires 500.2033).

Cyclic dipeptide 12 (9*R*, 12*S*): To a solution of dipeptide **13** (16 mg, 0.031 mmoles) in DMF (3 mL, 0.01 M) was added K_2CO_3 (13 mg, 0.093 mmoles) and the resulting reaction mixture was stirred at room temperature for 22 hours. The solvent was removed and the residue was directly purified by flash chromatography (SiO_2, AcOEt/Heptane = 1/3) to give product **12** (10 mg, 65 %) as a white solid: mp 119-120°; $[\alpha]_D$ = -79.4° ($CHCl_3$, *c* 1.4); IR ($CHCl_3$) 3050, 2956, 2931, 2856, 1750, 1688, 1675, 1588, 1525, 1500 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.76 (dd, *J* = 11.3, 17 Hz, 1H), 3 (s, 3H), 3.0-3.1 (m, 2H), 3.29 (t, *J* = 11.9 Hz, 1H), 3.68 (s, 3H), 4.25 (t, *J* = 9.8 Hz, 1H), 4.58 (m, 1H), 5.43 (br. s, 1H), 5.9 (d, *J* = 7.2 Hz, 1H), 6.75 (dd, *J* = 1.4, 8.4 Hz, 1H), 7.02 (dd, *J* = 1.3, 8.1 Hz, 1H), 7.1 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.34 (dd, *J* = 2.1, 8.3 Hz, 1H), 7.49 (dd, *J* = 2.1, 8.3 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (50,05 MHz, $CDCl_3$) δ 28.5, 30.2, 35, 35.3, 52.2, 52.8, 61.3, 80.9, 116.6, 121.7, 123.9, 124, 125.7, 131.8, 133.9, 135.9, 145.3, 155.7, 156.5, 169.9, 171.1; MS *m/z* 499 (M).

***N*,*N*-dimethylated cyclic dipeptide (9*S*, 12*S*)-18**: To a solution of cyclic dipeptide (9S, 12S)-**11** (53.4 mg, 0.11 mmol) in degassed THF (10 mL) and DMF (500 µL) were added distilled MeI (670 µL, 10.7 mmol) followed by NaH (5 mg, 0.13 mmole, 60 % dispersion in parafin) at 0°C. The resulting reaction mixture was stirred at 0°C for 10 min. and then at room temperature for 1.5 h. The reaction was quenched by addition of water (1 mL) and saturated aqueous NH_4Cl solution (10 mL). The aqueous solution was extracted with AcOEt and the combined organic extracts were washed with brine, dried and evaporated under the reduced pressure. The residue was purified by preparative TLC (Toluene/AcOEt / 4/1) to give **18** (47 mg, 85 %) as a colorless oil: $[\alpha]_D$ = - 143° ($CHCl_3$, *c* 0.7); IR ($CHCl_3$) 3025, 1744, 1675, 1650, 1613, 1588, 1525, 1500 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, mixture of two conformers A and B (4/1)) **Conformer A** δ 1.47 (s, 9H), 2.54 (s, 3H), 2.74 (m, 1H), 2.95 (s, 3H), 3.03 (m, 1H), 3.42 (m, 1H), 3.67 (m, 1H), 3.7 (s, 3H), 4.64 (s, 1H), 4.73 (dd, *J* = 3.6, 12.1 Hz, 1H), 4.90 (dd, *J* = 3.1, 11.3 Hz, 1H), 6.75 (d, *J* = 8.5 Hz, 1H), 6.92 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.19 (dd, *J* = 2.5, 8.4 Hz, 1H), 7.31 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.51 (m, *J* = 2.2, 8.5 Hz, 1H), 7.89 (d, *J* = 8.5 Hz, 1H); **Conformer B** δ 1.5 (s, 9H), 2.78 (s, 3H), 2.93 (s, 3H), 2.92-3.11 (m, 2H), 3.16-3.26 (m, 2H), 3.65 (s, 3H), 4.62 (m, 1H), 5.11 (s, 1H), 5.53 (dd, *J* = 5.5, 12 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 7.03 (dd, *J* = 2.4, 8.5 Hz, 2H), 7.39 (m, 1H), 7.58 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of two conformers, not assignable) δ 28.4, 28.5, 28.6, 29.8, 29.9, 30.4, 31.1, 31.5, 33.7, 34.3, 35, 37.6, 40.1, 52.5, 52.9, 54.8, 55.4, 56.9, 65.5, 80.5, 115.1, 115.2, 121.1, 121.3, 121.4, 121.9, 123, 123.2, 123.5, 124.2, 125.4, 125.6, 125.8, 126.8, 131.6, 131.7, 132, 132.2, 132.9, 136.2, 137.3, 143.5, 144.8, 157.2, 170.7, 171.2; MS *m/z* 514 (M+H); HRMS *m/z* 514.2209 ($C_{26}H_{32}N_3O_8$ (M + 1) requires 514.2189).

Depending on the reaction conditions, a variable amount of an oxidized compound **16a** was formed which was fully caracterized after *N*-methylation. Compound **16b**: mp 182-183°; $[\alpha]_D$ = -110.2° ($CHCl_3$, *c* 0.6); IR ($CHCl_3$) 2981, 2956, 2931, 2856, 1728, 1675, 1659, 1581, 1525 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.92 (s, 3H), 2.96 (s, 3H), 3.07 (dd, *J* = 4.9, 11.7 Hz, 1H), 3.24 (t, *J* = 12 Hz, 1H), 3.72 (s, 3H), 5.47 (d, *J* = 1.5 Hz, 1H), 5.51 (dd, *J* = 4.9, 11.9 Hz, 1H), 6.9 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.08 (dd, *J* = 2.4, 8.3 Hz, 1H), 7.16 (s, 1H), 7.2 (dd, *J* = 2.4, 8.6 Hz, 1H), 7.36 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.66 (dd, *J* =

1.3, 8.7 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H); ^{13}C NMR (50,05 MHz, $CDCl_3$) δ 28.6, 29.8, 30, 35.4, 38, 52.8, 54.8, 80.6, 116.9, 123.1, 123.7, 125.3, 126.1, 128.7, 130.9, 131.4, 132.3, 133.5, 136.3, 137.8, 138.4, 155.3, 155.3, 156.3, 164.1; MS *m/z* 512 (M + H); HRMS *m/z* 512.2043 ($C_{25}H_{30}N_3O_8$ (M + 1) requires 512.2033.

***N,N*-dimethylated cyclic dipeptide (9*R*, 12*S*)-17**: Compound **17** was prepared from (9*R*, 12*S*)-**12** following the same procedure detailed for the preparation of compound **18**. Compound **17**: $[\alpha]_D$ = -95.4° ($CHCl_3$, *c* 0.1); IR ($CHCl_3$) 3698, 3064, 2931, 2854, 1743, 1673, 1652, 1588, 1525, 1349 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.51 (br. s, 9H), 2.8 (s, 3H), 2.93 (s, 3H), 2.89-3.3 (m, 4H), 3.69 (s, 3H), 4.82 (m, 1H), 5.02 (br. s, 1H), 5.37 (m, 1H), 6.78 (dd, J = 1.7, 8.5 Hz, 1H), 7.04 (dd, J = 2.3, 8.5 Hz, 1H), 7.06 (m, 1H), 7.35 (dd, J = 1.8, 8.5 Hz, 1H), 7.53 (br. d, J = 7.3 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 28.5, 28.8, 30.2, 31.6, 35.8, 52.7, 55.4, 56.9, 80.6, 115.2, 121.4, 123.1, 124.2, 125.6, 131.6, 134, 136.2, 146, 155.1, 156, 170.6; MS *m/z* 514 (M + H).

***N,N*-dimethylated amino cyclic dipeptide (9*S*, 12*S*)-19**: A suspension of **18** (18 mg, 0.035 mmol) and 10% Pd/C in 3 ml of degassed MeOH was vigorously stirred under 1 atm hydrogen atmosphere. After 45 minutes, the reaction mixture was filtrated through a short pad of celite, and washed thoroughly with MeOH. The filtrate was evaporated under reduced pressure to give **19** (17 mg, quantitative) as a pink oil: $[\alpha]_D$ = - 54.3° ($CHCl_3$, *c* 0.4); IR ($CHCl_3$) 3624, 3014, 2979, 2938, 2897, 1743, 1690, 1679, 1649, 1520, 1503, 1444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of two conformers), **Major conformer** δ 1.48 (s, 9H), 2.57 (s, 3H), 2.93 (s, 3H), 2.6-3.3 (m, 4H), 3.67 (s, 3H), 3.92 (br. s, 2H), 4.36 (s, 1H), 4.68 (dd, J = 4, 12 Hz, 1H), 4.90 (dd, J = 2.9, 11.2 Hz, 1H), 6.47 (m, 1H), 6.85 (dd, J = 2.3, 8.4 Hz, 1H), 7.01 (m, 1H), 7.17 (dd, J = 2.3, 8.3 Hz, 1H), 7.28 (m, 1H), 7.46 (dd, J = 1.9, 8.3 Hz, 1H); MS *m/z* 482 (M+H).

(9*S*, 12*S*)-*N,N*-Dimethyl cycloisodityrosine 20: To a solution of **19** (17 mg, 0.035 mmol) in MeOH (3 mL) were added, at 0°C, HBF_4 (5 μL, 0.11 mmol, 54% in diethylether) and ^tBuONO (10 μL, 0.071 mmol). The reaction mixture was stirred at 0°C for 30 minutes and then at room temperature for 1 hour. After being cooled again to 0° C, a solution of $Cu(NO_3)_2.3H_2O$ (5.12 grammes, 21.2 mmole) and Cu_2O (15 mg, 0.035 mmol) in distilled water (10 mL) were introduced. After being stirred for another 30 minutes, the reaction mixture is filtered through a short pad of celite, and washed thoroughly with CH_2Cl_2. The aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product is purified by preparative TLC (SiO_2, toluene/AcOEt 4/1) to give product **20** (8 mg, 47 %) as colorless oil: $[\alpha]_D$ = - 134° ($CHCl_3$, *c* 0.4); IR ($CHCl_3$) 3694, 3556, 3025, 2931, 1744, 1675, 1650, 1606, 1519, 1500, 1444 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of two conformers A and B (4/1)) **Conformer A** δ 1.47 (s, 9H), 2.55 (s, 3H), 2.91 (s, 3H), 2.59-3.44 (m, 3H), 3.63 (m, 1H), 3.67 (s, 3H), 4.41 (s, 1H), 4.68 (dd, J = 4/J_2 = 12 Hz, 1H), 4.88 (dd, J = 2.9/J_2 = 11.2 Hz, 1H), 5.6 (br. s, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.71-6.87 (m, 1H), 7.17 (dd, J = 1.9/J_2 = 8.6 Hz, 1H), 7.26 (m, 1H), 7.47 (dd, J = 1.9, 8.6 Hz, 1H); **Conformer B** δ 1.50 (s, 9H), 2.54 (s, 3H), 2.68 (s, 3H), 2.59-3.44 (m, 4H), 3.64 (s, 3H), 4.39 (m, 1H), 4.71 (s, 1H), 5.48 (dd, J = 4.9/J_2 = 12.2 Hz, 1H), 5.6 (br. s, 1H), 6.59 (d, J = 8.3 Hz, 1H), 6.77 (m, 1H), 6.88 (m, 1H), 7.00 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H); MS(FAB) *m/z* 507 (M+Na), 485 (M + H).

(9*S*, 12*S*)-*N,N,O*-Trimethyl cycloisodityrosine 21: To a solution of **20** (4 mg, 8.3 μmole) in dry THF (500 μL) was added, at 0° C, freshly redistilled CH_3I (30 μL, 0.50 mmol, 60 eq) and NaH (1 mg,

0.018 mmol, 60% dispersion in paraffin). After being stirred at room temperature for 1 hour, the reaction was quenched by addition of saturated aqueous NH_4Cl. The aqueous solution was extracted with AcOEt. The combined organic extracts were washed, dried and evaporated under reduced pressure. The crude product was purified by preparative TLC (toluene/AcOEt 5/1) to give **21** (3.8 mg, 93 %) as a colorless oil: $[\alpha]_D$ = - 160° ($CHCl_3$, *c* 0.4); IR ($CHCl_3$) 3033; 2930; 2859; 1744; 1673; 1648; 1519; 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of two conformers A and B (4/1)) **Conformer A** δ 1.47 (s, 9H), 2.56 (s, 3H), 2.93 (s, 3H), 2.60-3.35 (m, 3H), 3.65 (m, 1H), 3.67 (s, 3H), 3.94 (s, 3H), 4.42 (br. s, 1H), 4.70 (dd, *J* = 3.6, 12 Hz, 1H), 4.90 (dd, *J* = 2.8, 11.3 Hz, 1H), 6.60 (m, 1H), 6.81 (br. d, *J* = 8.3 Hz, 1H), 6.89 (dd, *J* = 2.5, 8.2 Hz, 1H), 7.17 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.33 (m, 1H), 7.46 (dd, *J* = 1.8, 8.4 Hz, 1H); **Conformer B** δ 1.50 (s, 9H), 2.76 (s, 3H), 2.87 (s, 3H), 2.60-3.35 (m, 4H), 3.65 (s, 3H), 3.93 (s, 3H), 4.38 (m, 1H), 4.81 (s, 1H), 5.53 (dd, *J* = 4.8, 11.9 Hz, 1H), 6.63 (m, 1H), 6.75 (br. d, *J* = 8.1 Hz, 1H), 6.90 (m, 1H), 7.04 (m, 1H), 7.24 (m, 1H), 7.53 (d, *J* = 8.3 Hz, 1H); MS *m/z* 499 (M + H).

Cycloisodityrosine 4: A solution of compound **21** (3.8 mg, 7.7 μmole) in CH_2Cl_2 (1.5 mL) and CF_3COOH (150 μL) was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O and extracted with Et_2O to remove the neutral species. The aqueous solution was then carefully basified and extracted with AcOEt. The combined organic extracts were washed with brine, dried and concentrated under reduced pressure to give pure compound **4** (2.9 mg, 96 %) as a colorless oil. Compound **4** was found to existe as a mixture of two distinct conformers and was readily detected by TLC (R_f = 0.41 and 0.48 in CH_2Cl_2 / MeOH 10/1): IR ($CHCl_3$) 3682, 2985, 1748, 1642, 1522, 1501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, mixture of two conformers A and B (1/1) not assignable) δ 2.59 (s, 3H), 2.62 (s, 3H), 2.66 (s, 3H), 2.75 (s, 3H), 2.79-3.25 (m, 6H), 3.56 (dd, *J* = 4.2, 10.1 Hz, 1H), 3.69 (s, 3H), 3.75 (s, 3H), 3.86 (m, 1H), 3.94 (s, 3H), 3.95 (s, 3H), 4.27 (d, *J* = 2 Hz, 1H), 4.41 (dd, *J* = 3.7, 12.1 Hz, 1H), 4.67 (d, *J* = 2 Hz, 1H), 6.62 (br. d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.93 (dd, *J* = 2.5, 8.4 Hz, 1H), 7.07 (dd, *J* = 2.3, 8.3 Hz, 1H), 7.22-7.29 (m, 1H), 7.3 (m, 1H), 7.4 (dd, *J* = 2.1, 8.3 Hz, 1H), 7.48 (dd, *J* = 2.1, 8.3 Hz, 1H); MS *m/z* 399 (M + H).

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