Regioselective Synthesis of 14-Membered Biaryl Ethers: Total Synthesis of RA-VII and Deoxybouvardin

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In order to obtain a key compound (22a″) for synthesis of RA-VII (1) and deoxybouvardin (2), construction of the 14-membered ring system was performed by means of thallium trinitrate-mediated oxidation of the tetrahalogeno amides 5—7. The dibromo dichloro amide 6 or the bromo trichloro amide 7 gave a natural type of 14-membered ring dienone (23a or 23c), whereas the tetrabromo amide 5 gave an unnatural type of product, 19a. The formation of the latter product 19a could be understood on the basis of energy calculations on plausible intermediates 26a—c and 27a—c in the transition state in the oxidaive coupling reaction. Compound 23a was further converted to 22a″ through conventional procedures (aromatization; methylation; catalytic hydrogenation). This intermediate was readily converted to 1 and 2. Thus, total synthesis of RA-VII (1) and deoxybouvardin (2) was achieved for the first time.

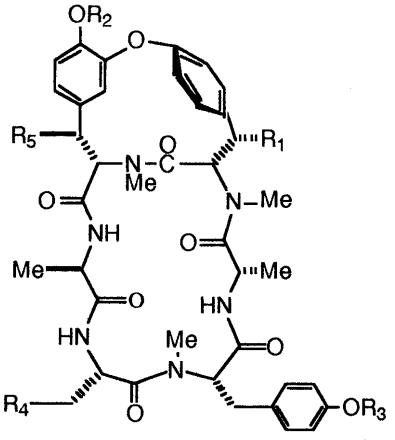
Key words tetrahalogeno-L-tyrosyl-L-tyrosine; regioselective oxidation; cycloisodityrosine (14-membered); RA-VII total synthesis; deoxybouvardin synthesis; energy calculation

A number of bicyclic hexapeptides [RA-I,[1)] II,[1)] III,[1,2)] IV,[1,2)] V,[2)] VI,[3)] and VII,[2)] and bouvardin[4)]], which have a 14-membered cycloisodityrosine moiety, have been isolated from *Rubiaceae* plants (*Rubia akane* in Japan, *Rubia cordifolia* in China and *Bouvardia ternifolia*).[5)]

Among the bicyclic hexapeptides, RA-VII (**1**) and its derivatives possess potent cytotoxic activity against KB cells, P388 lymphocytic leukemia cells and MM2 mammary carcinoma cells, and also exhibit antitumor activity *in vivo*.[1,6)] Extensive investigation on the site of action of **1** and deoxybouvardin (**2**) has revealed that they act as protein synthesis inhibitors through binding to eukaryotic 80 s ribosomes.[7)] The unique bicyclic hexapeptide structure and potent biological activity have stimulated our interest in the synthesis of **1** and **2**.

For total synthesis of these compounds, construction of the 14-membered ring system seems to be the most important step. Two methods can be considered; 1) intramolecular amide formation and 2) intramolecular biaryl ether formation. As regards the former method, all attempts in our laboratory to convert the biaryl ether **3** derived from **4**[8)] to a 14-membered-ring cyclophane under usual conditions (*N,N*-dicyclohexylcarbodiimide (DCC), DCC–*N*-hydroxybenzotriazole (HOBt)) resulted in failure.[9,10)] Hence, the latter method[11,12)] was examined. Although there are several approaches[13)] for formation of biaryl ethers, we chose the oxidative coupling reaction, because it should be closely related to the biogenetic formation of bicyclic hexapeptides.

Yamamura and co-workers have reported effective inter- and intra-molecular formation of biaryl ethers by use of thallium(III) trinitrate (TTN) and they employed this method to synthesize bastadins[14)] and piperadinomycin.[15)] Therefore, we selected TTN as an oxidant for construction of the 14-membered ring system. In order to confirm the direction of cyclization in the formation of the biaryl ether, we examined TTN-mediated oxidative coupling reaction of three kinds of tetrahalogeno-L-



R^1	R^2	R^3	R^4	R^5	
H	Me	Me	H	H	RA-VII (1)
H	H	Me	H	H	RA-V, deoxybouvardin (2)
H	H	Me	OH	H	RA-I
H	Me	H	H	H	RA-II
H	Me	Me	OH	H	RA-III
H	Me	Me	H	OH	RA-IV
OH	Me	Me	H	H	RA-VI
OH	H	Me	H	H	bouvardin

Chart 1

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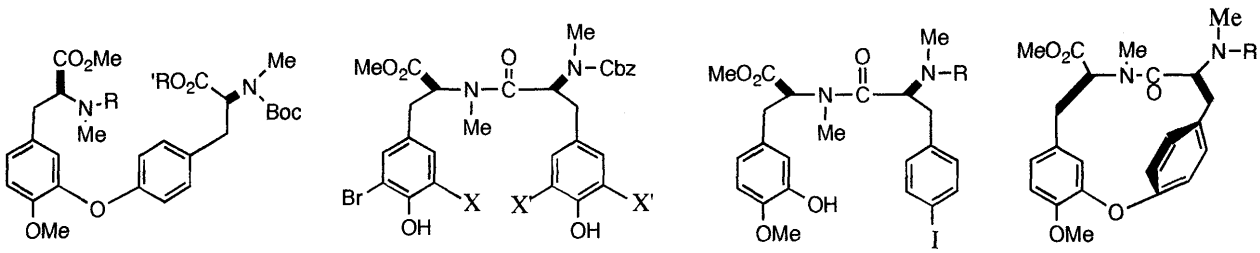


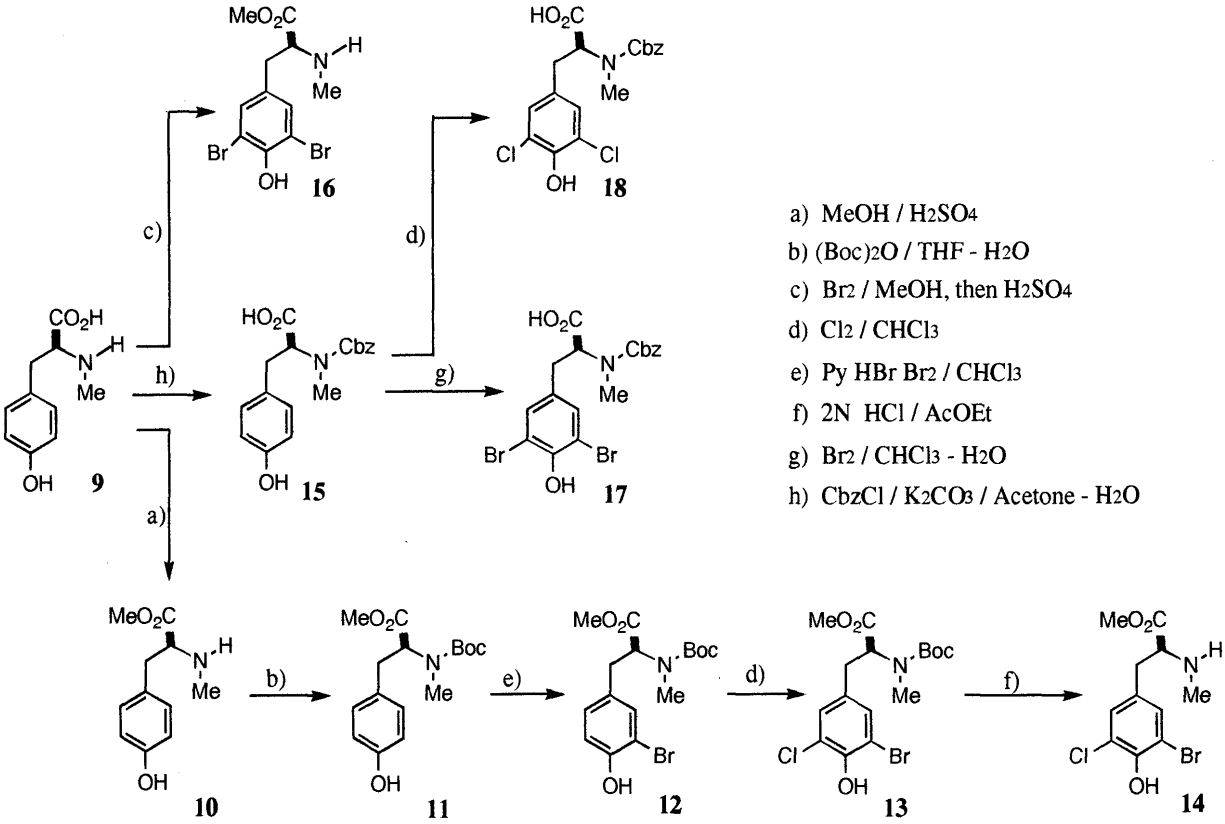
3: R = Cbz, R' = Bn
4: R = H, R' = H

5: X = Br, X' = Br
6: X = Br, X' = Cl
7: X = X' = Cl

8a: R = Cbz
8b: R = Boc

22a'': R = H
22c: R = Cbz
22d: R = Boc

Chart 2



a) MeOH / H_2SO_4
b) $(Boc)_2O$ / THF - H_2O
c) Br_2 / MeOH, then H_2SO_4
d) Cl_2 / $CHCl_3$
e) Py HBr Br_2 / $CHCl_3$
f) 2N HCl / AcOEt
g) Br_2 / $CHCl_3$ - H_2O
h) CbzCl / K_2CO_3 / Acetone - H_2O

Chart 3

tyrosyl-L-tyrosine **5**—**7** (Chart 2). As expected, we obtained the biaryl ether **22a''** having the natural type of 14-membered ring system and subsequently succeeded in total synthesis of RA-VII (**1**) and deoxybouvardin (**2**) for the first time, from this key compound.[16] More recently, Boger and co-workers[17] have also achieved a total synthesis of **1** and **2** through the same intermediate **22a''**,[18] prepared by intramolecular Ullmann reaction of the amides **8a, b**.

In this paper we present details of the construction of the 14-membered ring with a isodityrosine moiety, the total synthesis of RA-VII (**1**) and deoxybouvardin (**2**), and the results of energy calculations on the expected intermediates **26a**—**d** and **27a**—**d** in the transition state of the oxidative coupling reaction of **5**.

Results and Discussion

Preparation of Tetrahalogeno-L-tyrosyl-L-tyrosines 5, 6, and 7 Starting materials for synthesis of tetrahalogeno-L-tyrosyl-L-tyrosines, 3,5-dihalogeno-L-tyrosine derivatives, were prepared as follows (Chart 3). The 3-bromo-5-chloro compound **14** was prepared from *N-tert*-butoxycarbonyl (Boc)-*N*-methyl-L-tyrosine methyl ester (**11**) by mono-bromination followed by chlorination and subsequent deprotection of the resulting dihalogeno ester **13**. *N*-Benzyloxycarbonyl (Cbz)-3,5-dibromo or 3,5-dichloro-*N*-methyl-L-tyrosine (**17** or **18**) was synthesized by *N*-benzyloxycarbonylation followed by dibromination or dichlorination of *N*-Cbz-*N*-methyl-L-tyrosine (**15**). 3,5-Dibromo-*N*-methyl-L-tyrosine methyl ester (**16**) was prepared by dibromination of *N*-methyl-L-tyrosine in methanol (MeOH) followed by esterification. Furthermore, condensation of the dibromo-*N*-methyl ester **16** with the *N*-Cbz-dibromotyrosine **17** in the presence of DCC gave the dipeptide **5**. Similarly, the amide **6** or **7** was prepared from the dibromo ester **16** and *N*-Cbz-

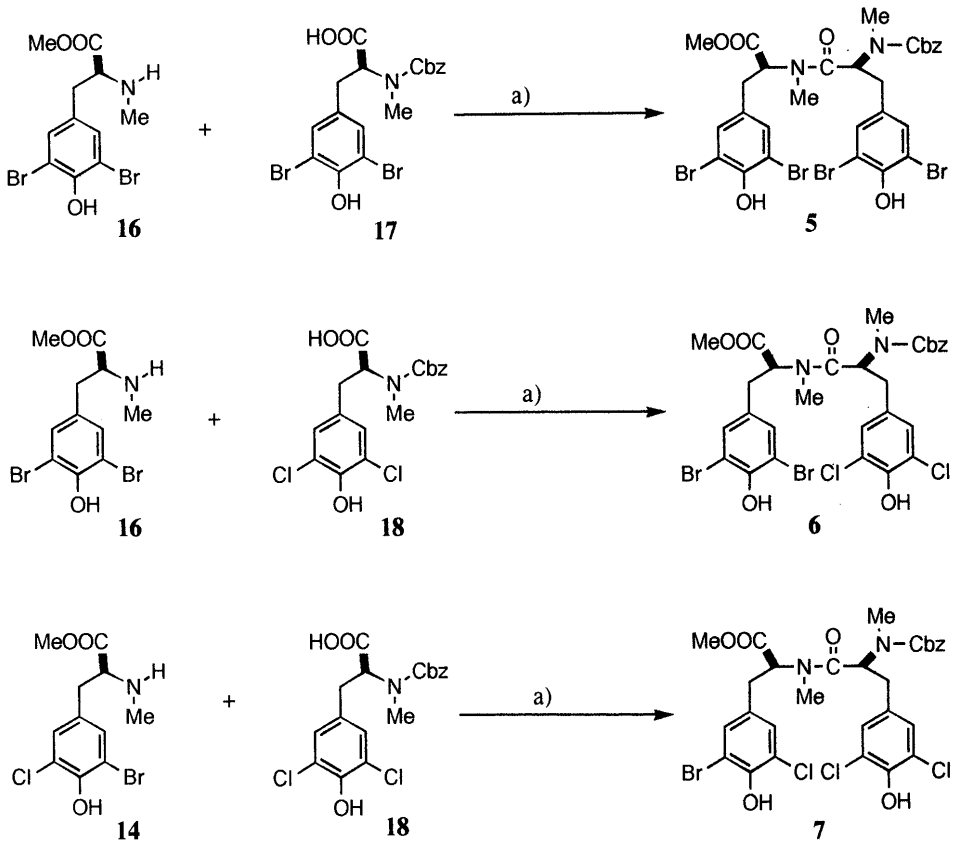
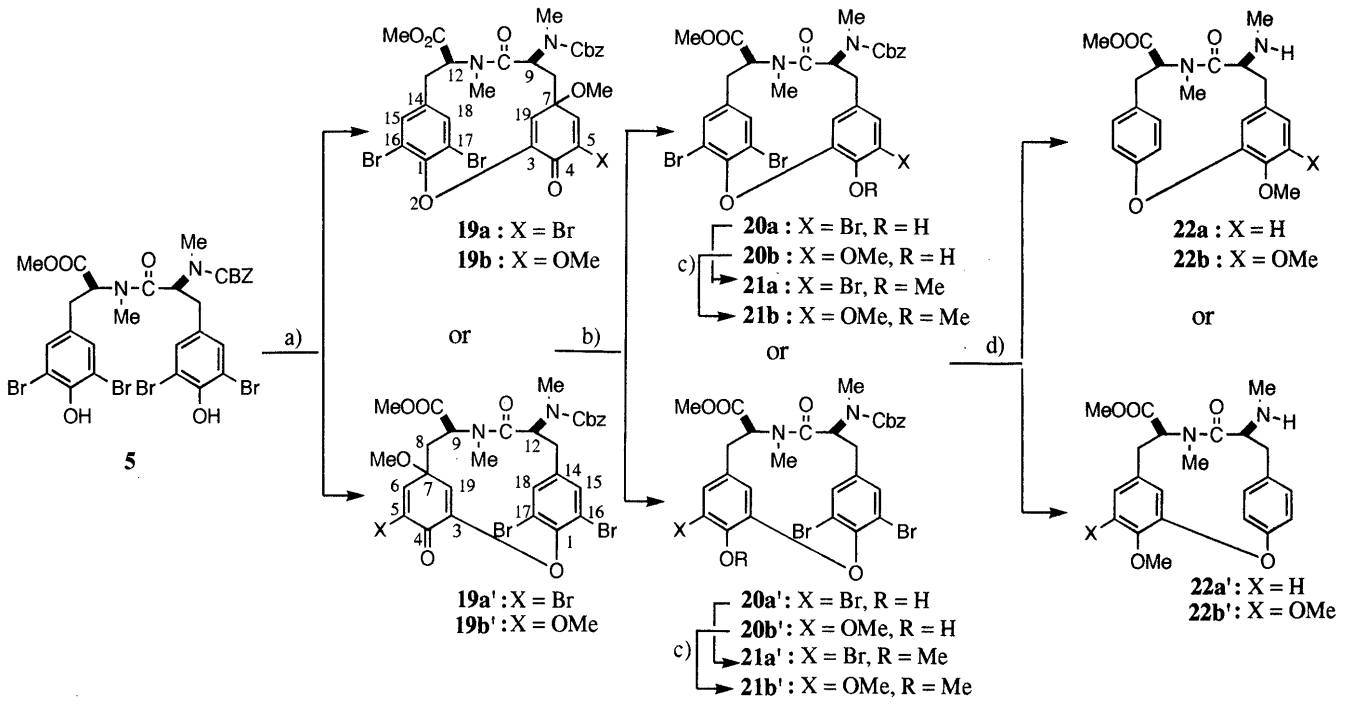


Chart 4

dichloro-*N*-methyl-L-tyrosine **18** or **18** and the bromo chloro ester **14**, respectively. The structures of the dipeptides **5**, **6**, and **7** were confirmed by spectral (^{1}H-NMR and MS) measurements (Chart 4).

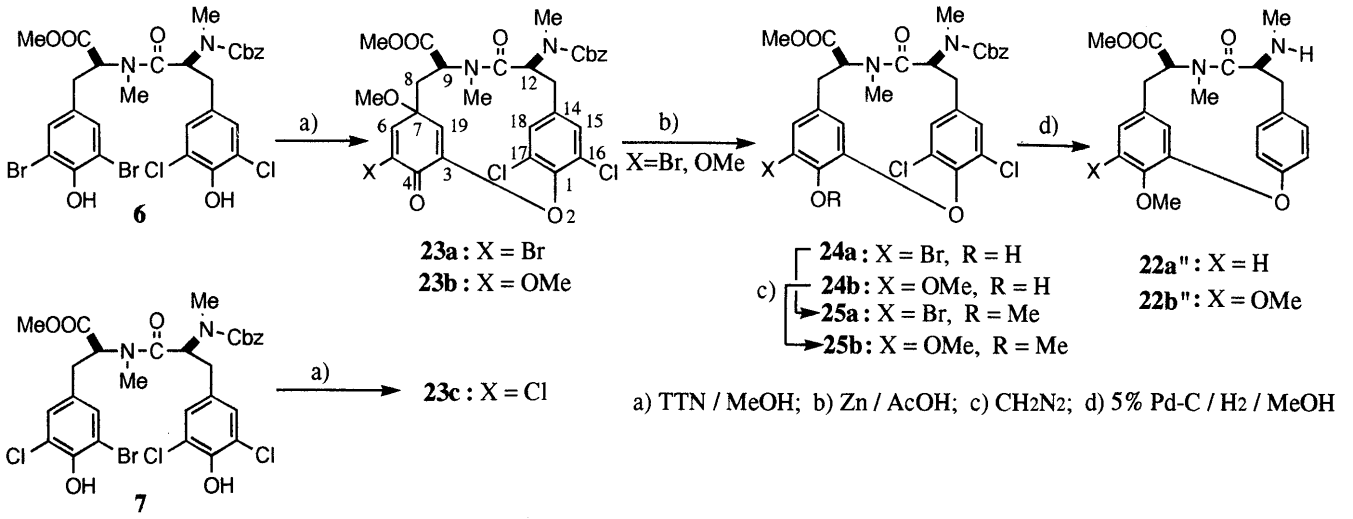
Oxidative Coupling of Tetrahalogeno Amides (5—7) by TTN With the diphenolic amides **5**—**7** in hand, we conducted oxidative cyclization with TTN in order to confirm the direction of cyclization. First, we tried oxidation of **5**. Namely, a solution (3×10^{-3} mol) of **5** in MeOH was treated with TTN (3 eq) at 4 °C for 18 h to give two products, isolated by column chromatography on silica gel. The ^{1}H-NMR spectrum of the less polar product exhibited characteristic signals due to two β-protons of a dienone at δ 6.37 and 7.14 (each 1H, d, J=2.7 Hz), suggesting formation of a cyclized product, which was also supported by MS. Therefore, the less polar product was deduced to be a separable equilibrium mixture[19] of **19a** (or **19a'**). For the purpose of conversion of the dienone to biaryl ether, **19a** (or **19a'**) was treated with zinc (Zn) in acetic acid (AcOH) at room temperature to give a phenoxyphenol **20a** (or **20a'**), which was methylated with diazomethane (CH_2N_2) to afford the methoxyaryl aryl ether **21a** (or **21a'**). Debromination of **21a** (or **21a'**) was carried out with hydrogen over 5% palladium on carbon (Pd–C) in MeOH containing potassium acetate to afford a debrominated 14-membered ring compound as a colorless oil, the structure of which was deduced to be **22a** (or **22a'**) on the basis of ^{1}H-NMR and MS. However, the direction of cyclization remained unclear. The more polar product was deduced to be **19b** (or **19b'**) on the basis of the ^{1}H-NMR spectrum, which showed characteristic high field-shifted signals at δ 5.58 and 6.32 (each 1H, d, J=2.7 Hz) due to two β-protons of the dienone and signals due to three methoxyl groups at δ 2.89, 3.63 and 3.68 (each 3H, s). The MS indicated three peaks of 1 : 2 : 1 ratio at m/z 734 (M^+), 736 ($M^+ + 2$) and 738 ($M^+ + 4$), clearly showing the presence of two bromine atoms. Compound **19b** (or **19b'**) was treated with Zn in AcOH to give the phenol **20b** (or **20b'**), which has two methoxyl groups and two bromine atoms. From the above findings, one of the two methoxyl groups in **20b** (or **20b'**) was assumed to be located at the C-5 position. Compound **20b** (or **20b'**) was transformed to the debrominated biaryl ether **22b** (or **22b'**) *via* **21b** (or **21b'**) through procedures similar to those noted for **22a** (or **22a'**). However, the structure of **19b** (or **19b'**) could not be determined by inspection of the spectral data (H–H correlation spectroscopy (COSY) and nuclear Overhauser and exchange spectroscopy (NOESY)).

Although the foregoing results showed formation of a 14-membered ring system by oxidation with TTN, the direction of cyclization could not be determined. Hence, the dibromo dichloro amide **6** was employed as a starting material for oxidation with TTN, because the different reactivity of bromine from chlorine atoms was expected to give a natural type of cyclized product, and the structure of products can be easily judged by MS. TTN oxidation of **6** was carried out in a manner similar to that noted for **5** to give two products **23a** (less polar) and **23b** (more polar) after column chromatography. The ^{1}H-NMR



a) TTN / MeOH ; b) Zn / AcOH; c) CH_2N_2; d) 5% Pd-C / H_2 / MeOH

Chart 5



a) TTN / MeOH; b) Zn / AcOH; c) CH_2N_2; d) 5% Pd-C / H_2 / MeOH

Chart 6

spectrum of **23a** showed high field-shifted signals at δ 4.63 and 6.98 (each 1H, d, J=2.7 Hz) due to two β-protons of the dienone. The MS exhibited the presence of one bromine and two chlorine atoms, supporting the formation of the desired cyclized product. Thus, the cyclization was proved to take place in the expected manner.

To confirm the structure of **22a** (or **22a'**) obtained from **5**, **23a** was converted to the biaryl ether **22a''** *via* **25a** through reaction sequences similar to those noted for **22a** (or **22a'**). The ^{1}H-NMR spectrum of **22a''** thus obtained was clearly different from that of **22a** (or **22a'**). Namely, a peak due to a methine proton (C<u>H</u>CO$_2$Me) of **22a''** appeared at δ 5.73, while that of **22a** (or **22a'**) was observed at δ 4.35. From the spectral data, the structure **22a'** was excluded and the product formed by oxidation of **5** with TTN was proved to be the undesired compound **19a**. The structure of **23b** was also determined on the basis of spectral evidence (^{1}H-NMR and MS), which showed the presence of two methoxyl groups (^{1}H-NMR) and the absence of a bromine atom (MS). Furthermore, the findings were confirmed by conversion of **23b** to **22b''** through reaction sequences (**24b**→**25b**) similar to those noted for **19b**. The ^{1}H-NMR (δ 4.32, C<u>H</u>CO$_2$Me) of **22b''** was also different from that (δ 5.70, C<u>H</u>CO$_2$Me) of **22b**.

With the findings mentioned above in mind, we sought to avoid formation of **23b** by oxidizing the bromo trichloro amide **7** under conditions similar to those noted for **5**, to give a sole cyclized product **23c** (5.6% yield, which could not be improved).

Formation of **19a** and **19b** was considered to occur as follows. Phenoxy radicals formed by oxidation of **5** with TTN would be coupled at the C-3 position to generate an

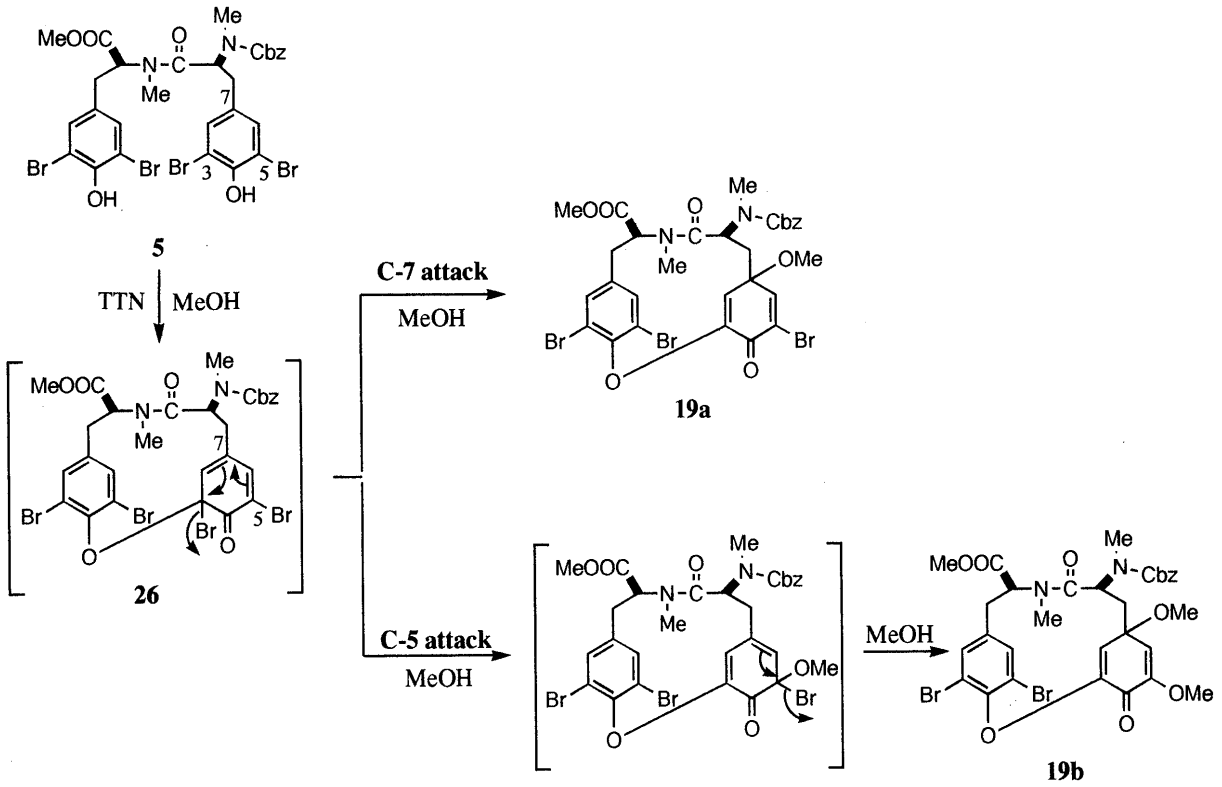


Chart 7

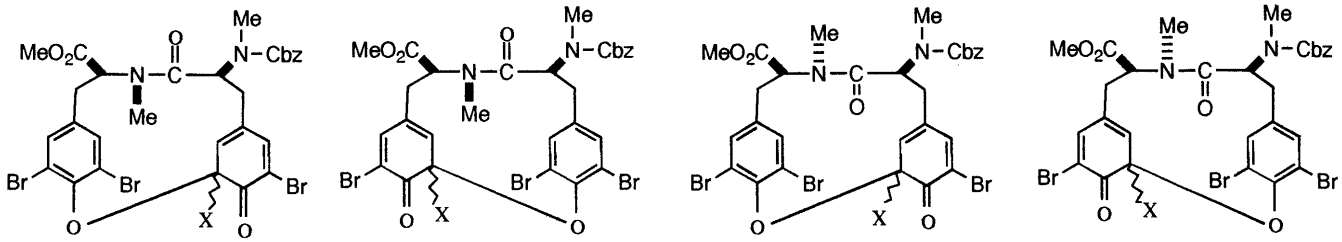


Chart 8

Table 1. Total Energies for Conformers **26a—d** and **27a—d** Calculated by the MOPAC AMI Method

Conformer	Total energy (eV)[a]
26a	−8137.322 (0.038)
26b	−8137.534 (0.026)
26c	−8137.233 (0.056)
26d	−8137.415 (0.065)
27a	−8137.224 (0.078)
27b	−8137.351 (0.052)
27c	−8137.526 (0.010)
27d	−8137.413 (0.010)

a) The average of five optimized geometries was noted for each conformer. The values in parentheses are the standard deviations.

intermediate **26**, though the reason why **26** is formed exclusively is unclear. When the bromine atom at the C-3 position in **26** is eliminated, conjugate addition of MeOH may take place at the C-7 and C-5 positions. The conjugate addition at the C-7 position would lead to **19a**, while that at the C-5 position could produce **19b** by elimination of the bromine atom, followed by concerted addition of MeOH at the C-7 position.

These results implied that the direction of cyclization might depend on the reactivity of the halogen atom. However, it was surprising that TTN oxidation of the tetrabromo amide **5** gave exclusively the unnatural type of cyclized products (**19a** and **19b**). We therefore calculated the lowest energy of the eight plausible conformers **26a—d** and **27a—d** in the transition state using a Kubota TITAN 750 computer.[20] The operations were: 1) energy minimization by molecular mechanics; 2) relaxation of molecular structure by molecular dynamics; 3) optimization of geometries by AM1[21] molecular orbital calculation. The results are listed in Table 1. The results showed that conformer **26b** is the most favorable intermediate (having the lowest energy), and it can be transformed to **19a** and **19b**.

Thus a new methodology for regioselective cyclization of isodityrosine derivatives was developed and a key compound **22a**" for total synthesis of bicyclic hexapeptides was prepared.

Synthesis of the Tetrapeptide Acid 34 The tetrapeptide acid segment for synthesis of RA-VII (**1**) and deoxy-

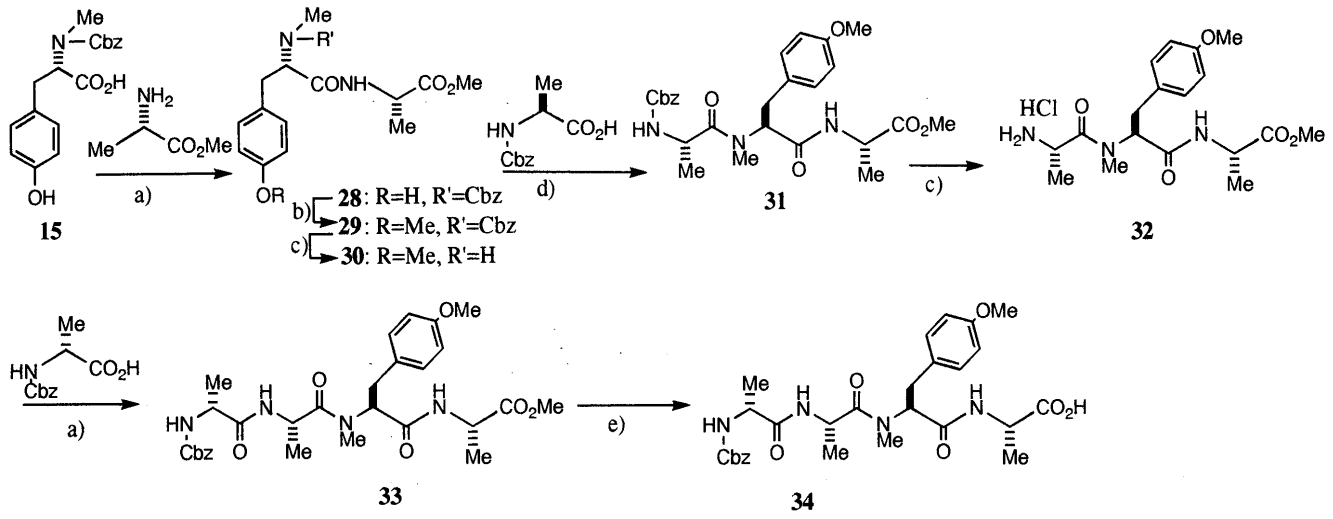


Chart 9

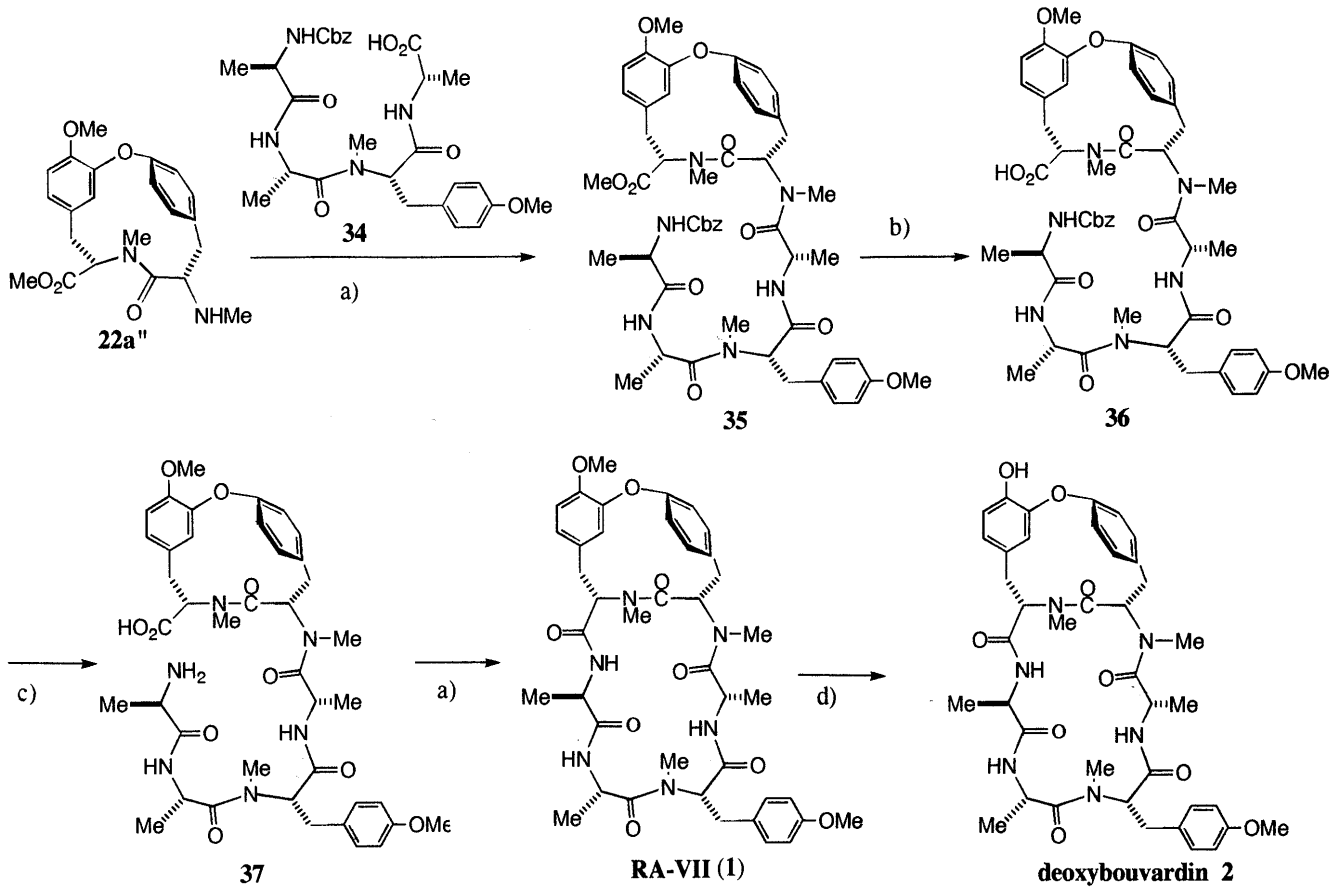


Chart 10

bouvardin (**2**) was prepared as follows (Chart 9). Reaction of *N*-Cbz-*N*-methyl-L-tyrosine (**15**) with L-alanine methyl ester in the presence of DCC and HOBt in dioxane gave a dipeptide, *N*-Cbz-*N*-methyl-L-tyrosyl-L-alanine methyl ester (**28**), in good yield. Treatment of **28** with excess CH_2N_2 afforded the methylated product **29** in quantitative yield. Removal of the *N*-protecting group in **29** was performed by hydrogenation over 5% Pd–C in MeOH containing hydrochloric acid to give a hydrochloride salt of **30** in high yield. Condensation of free **30** with *N*-Cbz-L-alanine by using DCC afforded the tripeptide **31**, the *N*-protecting group of which was removed in a manner similar to that noted for **30**, to give **32**. Condensation of **32** with D-alanine gave the desired tetrapeptide **33** (79% overall yield from

15), which was hydrolyzed with 1 N NaOH in aqueous MeOH–acetonitrile solution to afford the tetrapeptide acid **34**.

Synthesis of RA-VII (1) and Deoxybouvardin (2) Coupling of the tetrapeptide acid **34** with the 14-membered ring amide **22a''** in the presence of DCC in dioxane for 4 h readily proceeded to produce the seco compound **35** in 63% yield. Partial hydrolysis of **35** with 1 N NaOH in aqueous MeOH–acetonitrile solution at room temperature for 2 h gave an acid **36** in 24% yield, deprotection of which with hydrogen over 5% Pd–C in MeOH gave the amino acid **37**. The final macro lactamization was accomplished by slowly adding a solution of DCC in dioxane to a solution (*ca.* 1×10^{-2} mol) of **37** in dioxane at room temperature to produce RA-VII (**1**) in 39% yield. Its spectral data (^{1}H-NMR, MS) and sign of specific rotation ($[\alpha]_D$) were identical with those[2] of natural RA-VII. Furthermore, selective demethylation of **1** with $AlCl_3$ in dichloromethane afforded deoxybouvardin (**2**) in good yield. Again, the spectral data of **2** were identical with those[2,4] of natural deoxybouvardin.

Thus, a total synthesis of RA-VII (**1**) and deoxybouvardin (**2**) was achieved through the 14-membered ring compound **22a''** derived from **23a**, which was obtained by TTN-mediated oxidation of the dibromo dichloro amide **6**.

Experimental

Melting points were determined on a Ishii melting point apparatus and are uncorrected. Optical rotations were determined with a JASCO DIP-360. EI-MS and HRMS were taken on a JEOL JMS-SX-102 spectrometer. IR spectra were taken with a Shimadzu DR-8000 spectrometer in $CHCl_3$ solution unless otherwise noted. NMR spectra were measured with Hitachi R-24B and JEOL EX-270 spectrometers for one dimensional (1D) NMR and a JEOL GSX-500 spectrometer for two dimensional (2D) NMR in $CDCl_3$ solution using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) and coupling constants (J values) are given in hertz (Hz). The following abbreviations are used: s=singlet, br=broad, d=doublet, t=triplet, and m=multiplet . For column chromatography, BW-820MH (Fuji silicia) was used. Thin layer chromatography (TLC) was conducted on precoated Kieselgel 60 F_{254} plates (Merck).

Methyl *N*-Boc-*N*-methyl-L-tyrosinate (11) A solution of di-*tert*-butyl dicarbonate [$(Boc)_2O$] (10.9 g, 50 mmol) in tetrahydrofuran (THF) (30 ml) was added dropwise to a stirred solution of *N*-methyl-L-tyrosine methyl ester (10.4 g, 50 mmol) in THF (500 ml) and H_2O (50 ml). The mixture was stirred for 3 h at room temperature, then concentrated *in vacuo* to a volume of *ca.* 100 ml, and the product was extracted with AcOEt (150 ml × 2). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give **11** (29.4 g, 95.1%) as a white solid, mp 151—153 °C (benzene), $[\alpha]_D$ −80.34° (c=1, $CHCl_3$ at 25 °C). *Anal.* Calcd for $C_{16}H_{23}NO_5$: C, 62.18; H, 7.5; N, 4.53. Found: C, 62.47; H, 7.37; N, 4.17. IR (KBr) cm^{-1}: 3320, 1740, 1665. ^{1}H-NMR δ: 1.35, 1.40 [9H, each s, $(Me)_3C$], 2.74 (3H, s, NMe), 2.93—3.20 (2H, m, CH_2), 3.72, 3.75 [3H (2:3), each s, CO_2Me], 4.44, 4.96 [1H (3:2), each br dd, CH), 5.70—5.85, 6.2—6.35 [1H (2:3), m, OH], 6.6—6.8, 6.95—7.1 [4H (1:1), arom.-H × 4].

***N*-Cbz-*N*-methyl-L-tyrosine (15)** A solution of benzyloxycarbonyl chloride (Cbz-Cl) (154 g, 0.90 mol) in acetone (300 ml) was added dropwise to a stirred solution of *N*-methyl-L-tyrosine (80.0 g, 0.41 mol) and K_2CO_3 (165 g, 1.2 mol) in acetone (700 ml) and H_2O (620 ml). The mixture was stirred for 0.5 h at room temperature, then H_2O (1000 ml) was added and the solution was adjusted to pH 3 with 6 N HCl. The product was extracted with benzene (1000 ml × 2). The organic layer was washed with brine and dried over MgSO4. The solvent was evaporated *in vacuo* and the residue was dissolved in CH_3CN (450 ml) and MeOH (450 ml). Then 2 N NaOH (615 ml) was added to the solution and the whole was stirred for 2.5 h. The mixture was diluted with H_2O (1000 ml) and the aqueous layer was washed with benzene (2000 ml). The aqueous layer was acidified to pH 3 with 6 N HCl and extracted with AcOEt (1000 ml × 2). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evapolated *in vacuo* to give a solid, which was triturated in hexane–AcOEt (2:1) to afford **15** as colorless crystals (122 g, 100%), $[\alpha]_D$ −40.8° (c=0.48, $CHCl_3$ at 25 °C). HRMS m/z Calcd for $C_{18}H_{19}NO_5$ (M^+): 329.1262. Found: 329.1269. IR cm^{-1}: 2950, 1710, 1685. ^{1}H-NMR δ: 2.82, 2.85 [3H (2:1), s, NMe], 2.90—3.1, 3.15—3.35 [2H (1:1), m, 1'-CH_2], 4.75—4.85, 4.9—5.0 [1H (1:2), m, 2'-CH], 5.0, 5.1 [2H (1:2), s, CH_2 of Cbz], 6.69 (2H, d, J=8.3 Hz, arom.-H × 2), 6.94, 7.03 [2H (1:2), d, J=8.3 Hz, arom.-H × 2], 7.31 (5H, br s, arom.-H × 5).

Methyl 3,5-Dibromo-*N*-methyl-L-tyrosinate (16) Br_2 (52 g, 0.325 mol) was added dropwise to an ice-cold, stirred solution of **9** (30.1 g, 0.154 mol) in MeOH (500 ml) over a period of 20 min. The mixture was stirred at room temperature until the color of bromine disappeared. Concentrated H_2SO_4 (10 ml) was added to the mixture and the whole was refluxed for 46 h. It was concentrated *in vacuo* to a volume of *ca.* 100 ml and the residue was diluted with H_2O (300 ml). This solution was neutralized with $NaHCO_3$ powder and then extracted with $CHCl_3$. The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to leave **16** as colorless crystals, mp 133—134.5 °C (benzene). *Anal.* Calcd for $C_{11}H_{13}Br_2NO_4$: C, 35.99; H, 3.57; N, 3.81. Found: C, 36.03; H, 3.37; N, 3.35. $[\alpha]_D$ +48.6° (c=1, $CHCl_3$ at 26 °C). IR cm^{-1}: 3510, 2920, 1725, 1160. ^{1}H-NMR δ: 2.38 (3H, s, NMe), 2.81 (1H, d, J=5.6 Hz, 1'-H), 2.83 (1H, d, J=6.1 Hz, 1'-H), 3.37, 3.40 [1H (1:1), d, 2'-H], 3.71 (3H, s, CO_2Me), 7.26 (2H, s, arom.-H × 2).

***N*-Cbz-3,5-dibromo-*N*-methyl-L-tyrosine (17)** Br_2 (105 g, 0.66 mol) was added dropwise to an ice-cold, stirred solution of **15** (111 g, 0.337 mol) in $CHCl_3$ (300 ml) and H_2O (500 ml) over a period of 20 min. The mixture was stirred for 10 min at room temperature, Then diluted with $CHCl_3$ (1000 ml). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give **17** (159 g, 100%) as a colorless oil, $[\alpha]_D$ −47.5° (c=1.0, $CHCl_3$ at 26 °C). HRMS m/z Calcd for $C_{18}H_{17}Br_2NO_5$ (M^+): 484.9473. Found: 484.9468. IR cm^{-1}: 3500, 2900, 1740, 1320, 1160. ^{1}H-NMR δ: 2.82, 2.84 [3H (2:1), each s, NMe], 2.8—3.0, 3.1—3.3 [2H (1:2), each m, 1'-CH_2], 3.67, 3.73 [3H (1:2), each s, NMe], 4.70, 4.85 [1H (1:2), each br d, 2'-CH], 5.1 (2H, br d, OCH_2Ph), 7.2—7.55 (7H, m, arom.-H × 7).

***N*-Cbz-3,5-dichloro-*N*-methyl-L-tyrosine (18)** A solution of Cl_2 (1.8 g, 25.35 mmol) in $CHCl_3$ (30 ml) was added dropwise to an ice-cold, stirred solution of **15** (3.5 g, 10.6 mmol) in $CHCl_3$ (100 ml). The mixture was stirred for 1 h at the same temperature, then a saturated aqueous $NaHSO_3$ solution was added and the organic layer was separated. The organic layer was washed with brine and dried over $MgSO_4$. Usual work-up of the extract gave a residue, which was purified by column chromatography with $CHCl_3$–MeOH (100:2—100:4) as the eluent to leave **18** (2.58 g, 61%) as a colorless amorphous mass. The product was treated with CH_2N_2 in ether to give the methyl ester, $[\alpha]_D$ −48.8° (c=1.0, $CHCl_3$ at 26 °C). IR cm^{-1}: 3400, 1720, 1680. ^{1}H-NMR δ: 2.82, 2.84 [3H (3:2), each s, NMe], 2.8—3.0, 3.15—3.3 [2H (2:3), each m, 1'-CH_2], 3.67, 3.74 (3H, each s, CO_2Me), 4.65—4.75, 4.8—4.9 [1H (1:2), each m, 2'-H], 5.0—5.2 [2H (1:2), m, OCH_2Ph], 7.0, 7.1 [2H (2:3), each s, arom.-H × 2], 7.3 (5H, s, arom.-H × 5).

Methyl *N*-Boc-3-bromo-*N*-methyl-L-tyrosinate (12) Pyridinium·bromide·perbromide (4.45 g, 13.9 mmol) was added in one portion to an ice-cold, stirred solution of **11** (4.3 g, 13.9 mmol) in $CHCl_3$ (150 ml) and the whole was stirred at the same temperature until the reagent was dissolved. Saturated aqueous $NaHCO_3$ solution was added to the reaction mixture and the organic layer was separated. Usual work-up of the organic layer gave a residue, which was purified by column chromatography with hexane–AcOEt (4:1) to afford **12** (4.8 g, 89%) as a colorless oil, $[\alpha]_D$ −67.08° (c=1.0, $CHCl_3$ at 26 °C). HRMS m/z Calcd for $C_{16}H_{23}BrNO_5$ (M^+): 387.0681. Found: 387.0688. IR cm^{-1}: 3500, 1745, 1680, 1500. ^{1}H-NMR δ: 1.35, 1.40 [9H (1:1), each s, $(Me)_3C$], 2.70, 2.73 [3H (1:1), each s, NMe], 2.8—3.0, 3.1—3.2 [2H (2:3), each m, 1'-CH_2], 3.75 (3H, br s, CO_2Me), 4.48—4.53, 4.81—4.86 [1H (1:1), each m, 2'-CH), 5.46 (1H, br d, OH), 6.93 (1H, d, J=8.24 Hz, 5-CH), 6.95—7.1 (1H, m, 6-CH), 7.29 (1H, br s, 2-CH × 2).

Methyl *N*-Boc-3-bromo-5-chloro-*N*-methyl-L-tyrosinate (13) A solution of Cl_2 (852 mg, 12 mol) in $CHCl_3$ (20 ml) was added dropwise to an ice-cold, stirred solution of **12** (3.87 g, 10 mmol) in $CHCl_3$ (100 ml). The mixture was stirred for 30 min at the same temperature, then saturated aqueous $NaHSO_3$ solution was added and the organic layer was separated. The organic layer was successively washed with saturated

aqueous $NaHCO_3$ solution and brine, then dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by column chromatography with hexane–AcOEt (3 : 1) to afford **13** (3.6 g, 85.2%) as a colorless oil, $[\alpha]_D$ −56.5° (c=1, $CHCl_3$ at 26 °C). HRMS m/z Calcd for $C_{16}H_{21}BrCl\,NO_5$ (M^+): 421.0291. Found: 421.0310. IR (KBr) cm^{-1}: 3420, 1740, 1685. ^{1}H-NMR δ: 1.37, 1.41 [9H (1 : 1), each s, $(Me)_3C$], 2.71, 2.74 [3H (1 : 1), each s, CO_2Me], 2.8—3.0 (1H, m, 1′-H), 3.2 (1H, dd, J=5.2, 14.52 Hz, 1′-H), 3.75 (3H, br s, CO_2Me), 4.5—4.6, 4.75—4.85 [1H (1 : 1), each m, 2′-H], 7.13, 7.25 [2H (1 : 1), each br d, arom.-H × 2].

Methyl 3-Bromo-5-chloro-*N*-methyl-L-tyrosinate (14) The *N*-Boc-bromo methyl ester **13** (3 g, 7.1 mmol) was added to a stirred solution of 2 N HCl–AcOEt (30 ml) and the whole was stirred for 1 h at room temperature. It was neutralized with $NaHCO_3$ (powder) and the organic layer was separated. Usual work-up of the organic layer gave a residue, which was purified by column chromatography with hexane–AcOEt (5 : 1—4 : 1) to afford **14** (2.60 g, 80.0%) as a colorless oil, $[\alpha]_D$ +16.8° (c=0.5, $CHCl_3$ at 23 °C). EIMS m/z for $C_{11}H_{13}BrClNO_3$: 321 (M^+), 323 (M^++2), 325 (M^++4). IR (KBr) cm^{-1}: 3440, 1740, 1725. ^{1}H-NMR δ: 2.39 (3H, s, NMe), 2.77 (1H, dd, J=7.5, 13.9 Hz, 1′-H), 2.89 (1H, dd, J=6.1, 13.9 Hz, 1′-H), 3.47 (1H, dd, J=6.1, 7.3 Hz, 2′-H), 3.72 (3H, s, CO_2Me), 3.95 (2H, br s, NH and OH), 7.10, 7.20 (2H, each d, J=2.2 Hz, 2 and 6-H).

Methyl *N*-Cbz-3,5-dibromo-*N*-methyl-L-tyrosyl-3,5-dibromo-*N*-methyl-L-tyrosinate (5) A solution of DCC (14.4 g, 69.7 mmol) in dioxane (50 ml) was added dropwise to a stirred solution of **17** (33.9 g, 69.7 mmol) and **16** (25.6 g, 69.7 mmol) in dioxane (200 ml) at room temperature. The mixture was stirred for 1 h at the same temperature, and the resulting white solid was filtered off. The filtrate was evaporated *in vacuo* to give a residue, which was dissolved in AcOEt (300 ml). The organic layer was washed with 0.5 N HCl, saturated aqueous $NaHCO_3$ solution and brine, then dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a residue, which was dissolved in hot $CHCl_3$. A mixture of hexane–AcOEt (2 : 1) was added to the solution to give **5** (33.5 g, 57.5%) as white crystals, mp 149—150 °C (benzene), $[\alpha]_D$ −103.3° (c=1.0, $CHCl_3$ at 24 °C). EIMS m/z for $C_{29}H_{28}Br_4N_2O_7$: 835 (M^++3). IR cm^{-1}: 3500, 1735, 1685, 1650, 1600, 1320. ^{1}H-NMR δ: 2.59, 2.62, 2.65 [3H (4.7 : 1.5 : 1.5), each s, NMe], 2.72, 2.74, 2.86 [3H (1 : 2 : 1), each s, NMe), 2.70—3.0, 3.1—3.4 [4H, m, C$\underline{H}_2$–CH), 3.55, 3.71, 3.78 [3H (2 : 7 : 1.5), each s, CO_2Me], 4.65—5.25 (2H, m), 5.78 (2H, m), 7.07, 7.14, 7.16 [2H (1 : 6.5 : 2), each s, arom.-H], 7.23—7.35 (7H, m, arom.-H).

Methyl *N*-Cbz-3,5-dichloro-*N*-methyl-L-tyrosyl-3,5-dibromo-*N*-methyl-L-tyrosinate (6) A solution of DCC (3.78 g, 18.3 mmol) in dioxane (50 ml) was added dropwise to a solution of **18** (6.92 g, 17.38 mmol) and **16** (4.25 g, 11.68 mmol) in dioxane (50 ml) at room temperature with stirring. Stirring was continued for 20 h at the same temperature and the resulting white solid was filtered off. The filtrate was evaporated *in vacuo* to afford a residue, which was purified by column chromatography with hexane–AcOEt (1 : 1) to give **6** (6.53 g, 76%) as colorless crystals, mp 68—72 °C, $[\alpha]_D$ −108° (c=1, $CHCl_3$ at 24 °C). HRMS m/z Calcd for $C_{29}H_{28}Br_2Cl_2N_2O_7$ (M^+): 743.9639. Found: 743.9657. IR (KBr) cm^{-1}: 3400, 1740, 1685, 1645. ^{1}H-NMR δ: 2.60, 2.62, 2.65, 2.74, 2.85, 2.86 [6H (1.4 : 1 : 4 : 1 : 1 : 2.7), each s, NMe], 2.6—3.35 (4H, m, C$\underline{H}_2$–CH), 3.55, 3.71, 3.78 [3H (1.5 : 4.5 : 1), each s, OMe), 4.75—5.3 (4H, m, chiral-H × 2, C$\underline{H}_2$O), 5.9 (2H, br s, OH × 2), 6.73, 6.87, 6.96, 7.03, 7.15, 7.16 [4H (1 : 1 : 1 : 1 : 7 : 6), each s, arom.-H), 7.3 (5H, m, arom.-H).

Methyl *N*-Cbz-3,5-dichloro-*N*-methyl-L-tyrosyl-3-bromo-5-chloro-*N*-methyl-L-tyrosinate (7) A solution of DCC (18 g, 87.3 mmol) was added dropwise to a solution of **18** (30 g, 75 mmol) and **14** (20 g, 65 mmol) in dioxane (500 ml) at room temperature. The mixture was stirred for 15 h at the same temperature. Work-up similar to that noted for **6** gave **7** (26.4 g, 61.0%) as a colorless amorphous mass, $[\alpha]_D$ −41.3° (c=0.97, $CHCl_3$ at 29 °C). HRMS m/z Calcd for $C_{29}H_{28}BrCl_3N_2O_7$ (M^+): 700.0120. Found: 700.0132. IR (KBr) cm^{-1}: 3400, 1740, 1690, 1645. ^{1}H-NMR δ: 2.60, 2.61, 2.65, 2.74, 2.85, 2.86 (6H, each s), 2.60—3.35 (4H, m), 3.55, 3.71, 3.79 (3H, each s), 4.7—5.3 (4H, m), 5.9 (2H, br s), 6.80, 7.16 (4H, m), 7.35 (5H, m).

General Procedure for Oxidation of Methyl *N*-Cbz-3,5-dihalogeno-*N*-methyl-L-tyrosyl-3,5-dihalogeno-*N*-methyl-L-tyrosinates (5—7) with TTN TTN was added to an ice-cold, stirred solution of a tetrahalogeno amide (**5**—**7**) in MeOH. The mixture was stirred for 18 h at 4 °C, then pyridine was added. Removal of the solvent *in vacuo* gave a residue, which was diluted with brine and the product was extracted with AcOEt. The organic layer was successively washed with saturated aqueous $Na_2S_2O_3$ solution and brine, then dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give a residue, which was purified by column chromatography.

From **5**: **5** (7.65 g, 9.15 mmol), TTN (12 g, 27 mmol), MeOH (3000 ml) and pyridine (12 ml) were used. The fraction eluted with hexane–AcOEt (3 : 1) gave **19a** (2.43 g, 38.3%) as a pale yellow oil and the fraction eluted with hexane–AcOEt (3 : 2—1 : 1) gave **19b** (3.40 g, 50.5%) as a pale yellow amorphous mass. **19a** [TLC in $CHCl_3$–AcOEt (10 : 3) showed two spots[19]]. EIMS m/z for $C_{30}H_{29}Br_3N_2O_8$: 782 (M^+), 784 (M^++2), 786 (M^++4), 788 (M^++6) (1 : 2 : 2 : 1). IR cm^{-1}: 1735, 1680, 1650. ^{1}H-NMR δ: 1.17 (1H, d, J=16.5 Hz, C8-H), 2.38 (1H, dd, J=11.2, 16.5 Hz, C8-H), 2.64, 2.70 [3H (4 : 1), each s, NMe], 2.79, 2.83 [3H (1 : 4), each s, NMe or OMe], 2.88, 3.10 [3H (4 : 1), each s, NMe or OMe], 2.91 (1H, dd, J=10.5, 3.0 Hz, C13-H), 3.24 (1H, d, J=12.2 Hz, C13-H), 3.55 (1H, d, J=11.2 Hz, C9-H), 3.64 (3H, s, CO_2Me), 4.25 (1H, d, J=10.2 Hz, C12-H), 5.12 (2H, s, CH_2Ph), 5.35, 6.37 [1H (1 : 4), each d, J=2.6 Hz, C6-H], 7.14, 7.2 [1H (4 : 1), each d, J=2.6 Hz, C6-H], 7.0, 7.68 (2H, each d, J=2 Hz, C15, C18-H), 7.34 (5H, s, arom.-H × 5). **19b** [TLC in hexane–AcOEt (3 : 2) showed two spots[19]]. HRMS m/z Calcd for $C_{31}H_{32}Br_2N_2O_9$ (M^+): 734.0473. Found: 734.0464. IR cm^{-1}: 2950, 1730, 1680, 1645, 1605, 1395. ^{1}H-NMR δ: 1.17 (1H, d, J=16.5 Hz, C8-H), 2.37 (1H, dd, J=11.2, 14.5 Hz, C8-H), 2.64, 2.70 [3H (4 : 1), each s, NMe], 2.79, 2.82, 3.06 [6H (1 : 8 : 1), each s, NMe and OMe], 2.88 (1H, dd, J=11, 14.5 Hz, C13-H), 3.21, 3.60 (2H, each d, J=11 Hz, C9 and C13-H), 3.62, 3.68, 3.70, 3.75 [3H (4 : 4 : 1 : 1), OMe × 2] , 4.32 (1H, d, J=9.6 Hz, C12-H), 5.12 (2H, s, CH_2Ph), 5.55, 5.56 [1H (4 : 1), d, J=2.3 Hz, C19-H], 5.81, 6.3 [1H (1 : 4), d, J=2.3 Hz, C6-H], 6.99, 7.69 (2H, each d, J=2.0 Hz, C15 and C18-H), 7.34 (5H, br s, arom.-H × 5).

From **6**: **6** (8.0 g, 10.72 mmol), TTN (14.3 g, 32.16 mmol), MeOH (5.5 l), and pyridine (15 ml) were used. The fraction eluted with hexane–AcOEt (3 : 1) gave **23a** (380 mg, 5.2%) and the fraction eluted with hexane–AcOEt (3 : 2—1 : 1) gave **23b** (1.0 g, 14.4%), each as a colorless amorphous mass. They each showed a single spot on TLC with hexane–AcOEt (3 : 1). **23a**: $[\alpha]_D$ −120.6° (c=0.45, $CHCl_3$ at 29 °C). HRMS m/z Calcd for $C_{30}H_{29}BrCl_2N_2O_8$ (M^+): 694.0482. Found: 694.0484. IR cm^{-1}: 1740, 1685, 1645. ^{1}H-NMR δ: 1.48 (1H, dd, J=6.6, 15.2 Hz, C8-H), 1.88 (1H, dd, J=11.6, 15.1 Hz, C13-H), 2.55 (1H, dd, J=2.3, 15.1 Hz, C13-H), 2.65 (1H, d, J=15.2 Hz, C8-H), 2.75, 2.91 [3H (1 : 5), each s, NMe], 2.96, 3.07 [3H (1 : 2), each s, NMe or OMe], 3.14, 3.17 [3H (2 : 3), each s, NMe or OMe], 3.55, 3.59 [3H (2 : 1), each s, OMe], 3.95 (1H, dd, J=2.3, 11.6 Hz, C12-H), 4.50, 4.63 (1H, br d, J=2.6 Hz, C19-H), 5.20 (2H, br s, CH_2Ph), 5.50 (1H, br d, J=6.5 Hz, C9-H), 6.72, 6.80 [1H (1 : 2), br d, J=2.6 Hz, C6-H], 7.3—7.5 (7H, arom.-H × 7). **23b**: $[\alpha]_D$ −170.81° (c=0.69, $CHCl_3$ at 29 °C). HRMS m/z Calcd for $C_{31}H_{32}Cl_2N_2O_9$ (M^+): 646.1482. Found: 646.1463. IR cm^{-1}: 1740, 1685, 1645. ^{1}H-NMR δ: 1.53 (1H, m, C7-H), 1.87 (1H, dd, J=11.2, 1.18 Hz, C13-H), 2.83 (1H, m, C8-H), 2.92, 3.09, 3.14 [9H (1 : 1 : 1), each s, NMe × 2, OMe], 3.54, 3.72 [6H (1 : 1), each s, OMe × 2], 4.01 (1H, dd, J=2.3, 11.2 Hz, C12-H), 4.65, 5.39 [2H (1 : 1), each d, J=2.6 Hz, C19 and C6-H], 5.21 (2H, s, CH_2Ph), 5.25, 5.35 (1H, m, C9-H), 7.28 (1H, d, J=1.98 Hz, C15-H), 7.38 (5H, br s, arom.-H × 5).

From **7**: **7** (1.75 g, 2.5 mmol), TTN (3.32 g, 7.5 mmol), MeOH (1.25 l) and pyridine (3.5 ml) were used. The fraction eluted with hexane–AcOEt (3 : 1) gave **23c** (90 mg, 5.6%) as a colorless amorphous mass, HRMS m/z Calcd for $C_{30}H_{29}Cl_3N_2O_3$ (M^+): 650.0985. Found: 650.0998. IR (KBr) cm^{-1}: 1740, 1695, 1645. ^{1}H-NMR δ: 1.46 (1H, dd, J=6.6, 14.8 Hz, C8-H), 1.84 (1H, dd, J=10.8, 15.5 Hz, C13-H), 2.55 (1H, br d, J=15.7 Hz, C13-H), 2.65 (1H, d, J=15.2 Hz, C8-H), 2.75, 2.91 [3H (1 : 2), each s, NMe], 2.97, 3.07 [3H (3 : 2), each s, NMe or OMe], 3.16, 3.19 [3H (2 : 1), each s, NMe or OMe], 3.55, 3.59 [3H (2 : 3), each s, CO_2Me], 3.96 (1H, dd, J=2.3, 11.2 Hz, C12-H), 4.50, 4.63 [1H (2 : 1), each d, J=2.6 Hz, C19-H], 6.72, 6.80 [1H (1 : 2), each d, J=2.6 Hz, C6-H], 5.20 (2H, br s, CH_2Ph), 5.50 (1H, br d, C9-H), 7.37—7.5 (7H, br s, arom.-H × 7).

General Procedure for Reduction of the Dienones 19a, b and 23a, b with Zn in AcOH Zn (powder) was added in one portion to a stirred solution of a dienones (**19a, b** or **23a, b**) in 90% aqueous AcOH at room temperature. Stirring was continued for 1 h at the same temperature, brine was added to the reaction mixture and the product was taken up in $CHCl_3$. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a residue, which was purified by column chromatography.

From **19a**: **19a** (400 mg, 0.575 mmol), Zn (800 mg, 12.3 mmol) and 90% aqueous AcOH (15 ml) were used. The fraction with hexane–AcOEt (3 : 1—2 : 1) gave the biaryl ether **20a** (327 mg, 85.0%) [TLC in $CHCl_3$–AcOEt (5 : 1) showed two spots[19]] as a colorless amorphous

mass, $[\alpha]_D$ −81.17° (c=1.2, $CHCl_3$ at 25 °C). HRMS m/z Calcd for $C_{29}H_{27}Br_3N_2O_7$ (M^+): 751.9367. Found: 751.9361. IR cm^{-1}: 3530, 1742, 1700, 1683, 1643, 1505. ^{1}H-NMR δ: 2.0—2.4 (1H, m, C8-H), 2.09, 2.70 [3H (5:4), each s, NMe], 2.83, 2.87, 2.94 [3H (3:5:4), each s, NMe], 2.7—3.1, 3.3—3.8, 4.0—4.2, 4.3—4.5, 4.6—4.9, 5.8—6.0 (5H, each m, C8-H, C9-H, C12-H, C13-H×2), 3.55, 3.72, 3.81 [3H (3:5:2), each s, OMe), 4.11, 4.31 [1H (1:1), each s, C19-H], 5.0—5.3 (2H, m, CH_2Ph), 6.90, 6.95 [1H (1:2), each br s, C6-H), 6.50, 7.20 [1H (1:1), each d, J=2.0 Hz, C15-H], 7.72, 8.08 [1H (1:1), each d, J=2.0 Hz, C18-H], 7.2—7.5 (5H, br s, arom.-H×5).

From **19b**: **19b** (423 mg, 0.576 mmol), Zn (800 mg) and 90% AcOH (15 ml) were used. **20b** (340.8 mg, 84.0%) was obtained as a colorless oil from the fraction eluted with $CHCl_3$–AcOEt (5:1), $[\alpha]_D$ −85.54° (c=1, $CHCl_3$ at 24 °C). HRMS m/z Calcd for $C_{30}H_{30}Br_2N_2O_8$ (M^+): 704.0368. Found: 704.0372. IR cm^{-1}: 1748, 1700, 1650, 1520, 1450, 1240, 1080. ^{1}H-NMR δ: 2.0—2.2, 2.25—2.4 (1H, each m, C8-H), 2.70, 2.73 [3H (2:1), each s, NMe], 2.81, 2.87, 2.94 [3H (1:2:1), each s, NMe], 2.7—3.1, 3.35—3.8, 4.4—4.9, 5.4—5.6 (5H, m, C8-H, C9-H, C12-H, C13-H×2), 3.55, 3.71 [3H (1:1), each s, CO_2Me], 3.85, 3.86 [3H (3:2), each s, OMe], 4.04 (1H, br s, C19-H), 5.0—5.25 (2H, m, CH_2Ph), 6.31, 6.34 [1H (1:4), br s, C6-H], 6.48, 7.16 [1H (1:1), each d, J=2.0 Hz, C18-H], 7.69, 8.03 [1H (1:1), each d, J=2.0 Hz, C15-H].

From **23a**: **23a** (400 mg, 0.576 mmol), Zn (800 mg) and 90% AcOH (15 ml) were used. The fraction eluted with $CHCl_3$–AcOEt (20:1) provided **24a** (150 mg, 38.0%) [TLC in $CHCl_3$–AcOEt (10:1.5) showed two spots[19]] as a colorless amorphous mass, $[\alpha]_D$ −181.91° (c=0.153, $CHCl_3$ at 29 °C). HRMS m/z Calcd for $C_{29}H_{27}BrCl_2N_2O_7$ (M^+): 664.0378. Found: 664.0393. IR cm^{-1}: 1748, 1690, 1650, 1450, 1380. ^{1}H-NMR δ: 2.55, 2.72 [3H (3:1), each s, NMe], 2.70 (1H, dd, J=2.93, 11.35 Hz, C8-H), 2.78—2.96 (1H, m, C13-H), 2.98, 3.02 [3H (1:3), each s, NMe], 3.35—3.41 (1H, m, C13-H), 3.49, 3.54 [3H (3:1), each s, CO_2Me], 3.57, 3.67 (1H, m, C13-H), 4.61, 4.92 [1H (2:1), each d, J=1.71 Hz, C19-H], 4.72 (1H, dd, J=4.15, 12.2 Hz, C9-H), 4.92 (1H, dd, J=2.93, 11.35 Hz, C12-H), 5.11, 5.20 [2H (2:1), br d and s, CH_2Ph], 5.95 (1H, br s, OH), 6.95, 6.98 [1H (3.5:1), each d, J=1.71 Hz, C6-H], 7.13—7.48 (7H, br s, C15-H, C18-H, arom.-H×5).

From **23b**: **23b** (360 mg, 0.557 mmol), Zn (750 mg, 11.5 mmol) and 90% AcOH (15 ml) were used. The fraction eluted with $CHCl_3$–AcOEt (2:1) afforded **24b** (192 mg, 56.0%) [TLC in $CHCl_3$–AcOEt (10:1) showed two spots[19]] as a colorless amorphous mass, $[\alpha]_D$ −60.77° (c=0.87, $CHCl_3$ at 29 °C). IR cm^{-1}: 1748, 1680, 1650, 1450. ^{1}H-NMR δ: 2.57, 2.70 [3H (6:1), each s, NMe], 2.69 (1H, dd, J=3.0, 11.5 Hz, C8-H), 2.8—3.2 (1H, m, C13-H), 2.91—3.02 [3H (1:6), each s, NMe], 3.3—3.65 (2H, m, C8-H and C13-H), 3.45, 3.48 [3H (1:6), each s, OMe], 3.87 (3H, s, CO_2Me), 4.22, 4.29 [1H (1:6), each d, J=1.6 Hz, C19-H], 4.72 (1H, dd, J=3.2, 12.2 Hz), 4.92 (1H, dd, J=3.0, 11.5 Hz, C9-H), 5.10, 5.13 [2H (1:1), each d, J=14.8 Hz, CH_2Ph], 6.31, 6.38 [1H (6:1), each d, C6-H], 7.23 (1H, d, J=2.3 Hz, C15-H), 7.36 (6H, br s, C18-H, arom.-H×5).

General Procedure for Methylation of the Phenols 20a, b and 24a, b with CH_2N_2 An ice-cold solution of a phenol (**20a, b** or **24a, b**) in MeOH was treated with an excess of CH_2N_2–ether for 1 h at room temperature. The solvent was removed *in vacuo* to afford a residue, which was purified by column chromatography.

From **20a**: **20a** (150 mg, 0.2 mmol) and MeOH (3 ml) were used. The fraction eluted with $CHCl_3$–AcOEt (5:1) produced the ether **21a** (120 mg, 78.4%) [TLC in $CHCl_3$–AcOEt (5:1) showed two spots[19]] as a colorless amorphous mass, $[\alpha]_D$ −177.5° (c=1.42, $CHCl_3$ at 24 °C). HRMS m/z Calcd for $C_{30}H_{29}Br_3N_2O_7$ (M^+): 765.9525. Found: 765.9538. IR cm^{-1}: 1749, 1700, 1650, 1498, 1450. ^{1}H-NMR δ: 2.0—2.4 (1H, m, C8-H), 2.68, 2.69, 2.72 [3H (2:3:1.7), each s, NMe], 2.7—3.1, 3.3—3.8, 4.4—4.82 (4H, m, C8-H, C9-H, C13-H×2), 3.55, 3.71, 3.80 [3H (3:4:2), each s, NMe], 3.55, 3.71, 3.80 [3H (3:4:2), each s, CO_2Me], 4.05, 4.07, 4.08 [3H (3:4:2), each s, OMe], 4.88 (1H, d, J=1.98 Hz, C19-H), 5.0—5.2 (2H, m, CH_2Ph), 5.1—5.25 (1H, m, C12-H), 6.50, 7.20 (1H, each d, J=2.0 Hz, C15-H), 6.92, 6.98 [1H (1:2), each d, J=2.0 Hz, C6-H], 7.73, 8.06 [1H (1:1), each d, J=2.0 Hz, C18-H].

From **20b**: **20b** (65 mg, 0.092 mmol) and MeOH (2 ml) were used. The fraction eluted with $CHCl_3$–AcOEt (10:1.5) afforded **21b** (58.1 mg, 86.5%) as a colorless oil, $[\alpha]_D$ −130.42° (c=1.2, $CHCl_3$ at 24 °C). HRMS m/z Calcd for $C_{31}H_{32}Br_2N_2O_4$ (M^+): 718.0525. Found: 718.0537. IR cm^{-1}: 1749, 1700, 1650, 1450, 1100. ^{1}H-NMR δ: 2.0—2.15, 2.2—2.35 (1H, m, C8-H), 2.63, 2.66 [3H (2:1), each s, NMe], 2.76, 2.81, 2.90 [3H (2:3:1), each s, NMe], 2.7—3.1, 3.35—3.8, 4.4—4.9, 5.4—5.6 (5H, m, C8-H, C9-H, C12-H, C13-H), 3.48, 3.64 [3H (1:1), each s, CO_2Me], 3.73, 3.75, 3.76 [3H (5:6:4), each s, OMe], 3.94, 3.96, 3.97 [3H (3:4:2), each s, OMe], 4.44, 4.50 [1H (4:1), each br s, C19-H], 5.0—5.2 (2H, m, CH_2Ph), 6.18, 6.23, 6.29 [1H (1:2:5), each br s, C6-H], 6.42, 7.12 [1H (1:1), each d, J=2.0 Hz, C15-H], 7.2—7.5 (5H, m, arom.-H×5), 7.64, 7.90 [1H (1:1), each d, J=2.0 Hz, C18-H].

From **24a**: **24a** (150 mg, 0.226 mmol) and MeOH (2 ml) were used. The fraction eluted with $CHCl_3$–AcOEt (20:1) produced the ether **25a** (120 mg, 78.4%) [TLC in $CHCl_3$–AcOEt (10:1.5) showed two spots[19]] as a colorless amorphous mass, $[\alpha]_D$ −87.64° (c=0.326, $CHCl_3$ at 29 °C). HRMS m/z Calcd for $C_{30}H_{29}BrCl_2N_2O_7$ (M^+): 678.0535. Found: 678.0524. IR cm^{-1}: 1749, 1680, 1650, 1490, 1450. ^{1}H-NMR δ: 2.57, 2.82 [3H (5:1), each s, NMe], 2.72 (1H, dd, J=2.80, 10.49 Hz, C8-H), 2.86—2.96 (1H, m, C13-H), 3.00, 3.03 [3H (1:4), each s, NMe], 3.36—3.7 (2H, m, C8-H and C13-H), 3.48, 3.54 [3H (4:1) each s, CO_2Me], 4.09 (3H, s, OMe), 4.50 (1H, d, J=1.89 Hz, C19-H), 4.71 (1H, dd, J=3.91, 11.97 Hz, C9-H), 4.93 (1H, dd, J=2.69, 11.48 Hz, C12-H), 5.08, 5.14, 5.20 [2H (4:4:1), d (J=12.6 Hz), d (J=12.6 Hz), s, CH_2Ph], 6.98, 7.00 [1H (4:1), each d, J=1.9 Hz, C6-H], 7.25—7.50 (7H, br s, C15-H, C18-H, arom.-H×5).

From **24b**: **24b** (140 mg, 0.227 mmol) and MeOH (2 ml) were used. The fraction eluted with $CHCl_3$–AcOEt (10:1) provided **25b** (107.0 mg, 75.2%) [TLC in $CHCl_3$–AcOEt (10:1) showed two spots[19]] as a colorless amorphous mass, $[\alpha]_D$ −102.39° (c=0.45, $CHCl_3$ at 29 °C). HRMS m/z Calcd for $C_{31}H_{32}Cl_2N_2O_8$ (M^+): 630.1534. Found: 630.1548. IR cm^{-1}: 1745, 1680, 1650, 1450, 1250, 1100. ^{1}H-NMR δ: 2.59, 2.80 [3H (8:1), each s, NMe], 3.01, 3.03 [3H (1:6), each s, NMe], 3.48, 3.72 [3H (6:1), each s, OMe], 3.83 (3H, s, CO_2Me), 4.04 (3H, s, OMe), 2.65—3.75 (1H, m, C8-H), 2.85—4.45, 3.35—3.55 (2H, each m, C13-H), 3.50—3.70 (1H, m, C8-H), 4.18 (1H, br s, C19-H), 4.72 (1H, dd, J=3.2, 12.2 Hz, C12-H), 4.92 (1H, dd, J=2.7, 11.3 Hz, C9-H), 5.11, 5.14 [2H (1:1), each d, J=14.6 Hz, CH_2Ph], 6.32, 6.34 [1H (6:1), each br s, C6-H], 7.2—7.4 (2H, m, C15-H and C18-H), 7.36 (5H, s, arom.-H×5).

General Procedure for Hydrogenation of Halogeno Methyl Ethers 21a, b and 25a, b over 5% Pd–C A mixture of a halogeno methyl ether (**21a, b** or **25a, b**), 5% Pd–C and AcOK in MeOH was shaken with H_2 at room temperature until H_2 absorption ceased. The catalyst was filtered off and the solvent was removed *in vacuo* to give a residue. Saturated aqueous $NaHCO_3$ was added to the residue and the product was taken up in $CHCl_3$. Usual work-up of the extract afforded a residue, which was purified by preparative TLC to afford the corresponding methyl ether (**22a, b** or **22a″, b″**).

From **21a**: **21a** (110 mg, 0.143 mmol), 5% Pd–C (110 mg), AcOK (110 mg, 1.12 mmol) and MeOH (3 ml) were used. Development with $CHCl_3$–MeOH (10:1) afforded **22a** (46 mg, 71.4%) [TLC in $CHCl_3$–MeOH (10:1) showed two spots[19]] as a colorless amorphous mass, $[\alpha]_D$ −64.48° (c=0.63, $CHCl_3$ at 25 °C). HRMS m/z Calcd for $C_{22}H_{26}N_2O_5$ (M^+): 398.1840. Found: 398.1857. IR cm^{-1}: 3460, 1740, 1650, 1520, 1500, 1260, 1130. ^{1}H-NMR δ: 2.09, 2.28 [3H (4:1), each s, NMe], 2.76 (1H, dd, J=6.6, 15.5 Hz, C8-H), 2.89 (1H, t, J=12.5 Hz, C13-H), 2.95, 3.14 [3H (1:4), each s, NMe], 3.3—3.6 (3H, m, C8-H, C9-H, C13-H), 3.77, 3.83 [3H (4:1), each s, CO_2Me], 3.91, 3.94 [3H (1:3), each s, OMe], 4.75, 4.85 [1H (1:5), each d, J=1.65 Hz, C19-H], 4.52, 5.73 [1H (1:5), each dd, J=3.63, 12.21 Hz, C12-H], 6.64 (1H, dd, J=1.65, 8.24 Hz, C6-H), 6.76, 7.18 [1H (2:1), each d, J=8.24 Hz, C5-H], 7.05—7.25 (2H, m, C16-H and C17-H), 7.20 (1H, dd, J=2.3, 8.58 Hz, C15-H), 7.42 (1H, dd, J=2.3, 8.25 Hz, C18-H).

From **21b**: **21b** (40 mg, 0.056 mmol), 5% Pd–C (40 mg), AcOK (40 mg, 0.4 mmol) and MeOH (2 ml) were used. Development with $CHCl_3$–AcOEt (10:1.5) gave **22b** (19.2 mg, 61.3%) as a colorless oil, $[\alpha]_D$ −54.37° (c=1.26, $CHCl_3$ at 25 °C). HRMS m/z Calcd for $C_{23}H_{28}N_2O_6$ (M^+): 428.1965. Found: 428.1955. IR cm^{-1}: 1740, 1650, 1640, 1500, 1100. ^{1}H-NMR δ: 2.13, 2.24 [3H (4:1), each s, NMe], 2.75 (1H, dd, J=6.6, 15.5 Hz, C8-H), 2.90 (1H, br t, J=13.5 Hz, C13-H), 2.96, 3.13 [3H (2:3), each s, NMe], 3.3—3.6 (3H, m, C8-H, C9-H, C13-H), 3.76, 3.86 [3H (4:5), each s, CO_2Me], 3.83, 3.96, 4.0 [3H (1:1:2), each s, OMe], 4.48 (1H, d, J=1.8 Hz, C19-H), 5.70 (1H, dd, J=3.63, 12.5 Hz, C12-H), 6.29 (1H, d, J=1.8 Hz, C6-H), 6.80 (1H, dd, J=2.63, 8.25 Hz, C16-H), 7.14 (1H, dd, J=2.3, 8.25 Hz, C17-H), 7.17 (1H, dd, J=2.31, 8.25 Hz, C18-H), 7.41 (1H, dd, J=2.63, 8.25 Hz, C15-H).

From **25a**: **25a** (95 mg, 0.15 mmol), 5% Pd–C (90 mg), AcOK (130 mg, 0.13 mmol) and MeOH (3 ml) were used. Development with $CHCl_3$–MeOH (10:1) produced **22a″** (39.7 mg, 71.4%) [TLC in $CHCl_3$–MeOH

(10:1) showed two spots[19)]] as a colorless amorphous mass, $[\alpha]_D$ −17.59° (c=0.25, $CHCl_3$ at 23 °C); HRMS m/z Calcd for $C_{22}H_{26}N_2O_5$ (M^+): 398.1839. Found: 398.1836. IR cm^{-1}: 1745, 1640, 1520, 1500, 1265, 1200, 1030. ^{1}H-NMR δ: 2.35, 2.46 [3H (5:4), each s, NMe], 2.71, 2.73 [3H (5:4), each s, NMe], 2.9—3.25 (4H, m, C8-H×2, C13-H×2), 3.40, 3.53 [1H (5:4), m, dd, J=3.90, 10.23 Hz, C12-H], 3.67, 3.70 [3H (4:5), each s, OMe], 3.93, 3.94 [3H (4:5), each s, CO_2Me], 3.86, 4.35 [1H (4:5), dd (J=5.3, 11.54 Hz), dd (J=3.6, 11.2 Hz), C9-H], 4.29, 4.73 [1H (4:5), d (J=2.3 Hz), d (J=2.0 Hz), C19-H], 6.61 (1H, d, J=2.0 Hz, C6-H), 6.75, 6.82 [1H (4:5), d (J=7.92 Hz), d, J=8.0 Hz), C5-H], 6.92 (dd, J=2.4, 8.57 Hz), 7.05 (dd, J=2.0, 8.3 Hz), 7.14 (dd, J=2.44, 8.3 Hz), 7.21—7.28 (m), 7.34 (dd, J=2.2, 8.3 Hz), 7.43 (dd, J=1.95, 8.3 Hz), 6.92—7.43 (not assignable).

From **25b**: **25b** (63 mg, 0.1 mmol), 5% Pd–C (60 mg), AcOK (65 mg, 0.66 mmol) and MeOH (2 ml) were used. Development with $CHCl_3$–MeOH (10:1) afforded **22b″** (15.9 mg, 37.4%) [TLC in $CHCl_3$–MeOH (10:1) showed two spots[19)]] as a colorless amorphous mass, $[\alpha]_D$ +15.35° (c=0.45, $CHCl_3$ at 29 °C). HRMS m/z Calcd for $C_{23}H_{28}N_2O_6$ (M^+): 428.1948. Found: 428.1946. IR cm^{-1}: 1748, 1650, 1600, 1500, 1460, 1450, 1100. ^{1}H-NMR δ: 2.34, 2.46 [3H (2:1), each s, NMe], 2.70, 2.73 [3H (1:2), each s, NMe], 2.8—3.25 (2H, m, C8-H), 3.38, 3.53 [1H (2:1), dd (J=3.6, 11.2 Hz), dd (J=3.96, 10.23 Hz), C12-H], 3.68, 3.69 [3H (1:2), each s, CO_2Me], 3.81 (3H, s, OMe), 3.93, 4.46 [1H (3:2), d (J=1.65 Hz), d (J=2.0 Hz), C19-H], 4.0 (3H, s, OMe), 4.32 (1H, dd, J=3.3, 11.2 Hz, C9-H), 6.21, 6.26 [1H (3:2), d (J=1.65 Hz), d (J=2.0 Hz), C6-H], 6.90 (1H, dd, J=2.3, 8.3 Hz, C16-H), 6.97 (dd, J=2.0, 8.23 Hz), 7.11 (dd, J=2.3, 8.25 Hz), 7.23 (dd, J=2.14, 8.3 Hz), 7.32 (dd, J=2.14, 8.25 Hz), 6.97—7.32 (not assignable).

Energy Calculation on Eight Plausible Intermediates 26a—d and 27a—d The 3D structures of **26a—d** and **27a—d** were simulated using a molecular simulation package, POLYGRAF, on a Kubota TITAN 750 computer, in which the Dreiding II force field parameter was used. Initial 3D molecular models were obtained by 1) drawing the structure by two dimensionally on the screen, 2) energy minimization using molecular mechanics. Molecular dynamics calculations on the initial models were run for 40 pico seconds (40000 steps) at 600 K. Annealed dynamics calculations on the last conformer, which was almost in the equilibrium state energetically and conformationally, were run at a starting temperture at 600 K with a final run at 0 K for five cycles (*i.e.*, 60 ps). The five conformers with the lowest energy from each annealing cycle were extracted and the geometries were optimized by AM1 molecular orbital calculations using MOPAC 6. The results are listed in Table 1.

Methyl *N*-Cbz-*N*-methyl-L-tyrosyl-L-alaninate 28 A solution of DCC (30 g, 0.145 mol) in CH_2Cl_2 (500 ml) was added dropwise to a stirred solution of **15** (39.5 g, 0.12 mol), L-alanine methyl ester HCl (30 g, 0.215 mol), HOBt (23 g, 0.17 mol) and triethylamine (30 ml) in CH_2Cl_2 (500 ml) at room temperature. The mixture was stirred for 12 h at the same temperature and the resulting white solid was filtered off. The filtrate was successively washed with 1 N HCl, brine, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give a residue, which was purified by column chromatography with hexane–AcOEt (1:1) to give **28** (48.1 g, 97.0%) as a colorless oil, $[\alpha]_D$ −57.26° (c=1, $CHCl_3$ at 24 °C). HRMS m/z Calcd for $C_{22}H_{26}N_2O_6$ (M^+): 414.1789. Found: 414.1797. IR cm^{-1}: 3600, 3410, 1740. ^{1}H-NMR δ: 1.34 (3H, d, J=7.0 Hz, CMe), 2.85 (3H, s, NMe), 2.8—3.0, 3.15—3.3 [total 2H (1:1), m, C<u>H</u>$_2$–CH), 3.71 (3H, br s, CO_2Me), 4.51 (1H, quintet, J=7.3 Hz, Me-C<u>H</u>), 4.7—5.1 (1H, m, CH_2–C<u>H</u>), 5.1 (2H, br s, CH_2 of Cbz), 6.5—6.7, 6.85—7.1 [4H (3:1), m, arom.-H], 7.26—7.37 (5H, m, arom.-H of Cbz).

Methyl *N*-Cbz-*N*,*O*-dimethyl-L-tyrosyl-L-alaninate 29 A solution of CH_2N_2 in ether was added to an ice-cold solution of **28** (40.6 g, 98.1 mmol) in MeOH (120 ml) and the mixture was allowed to stand for 5 h at room temperature. The solvent was evaporated *in vacuo* to give a residue, which was purified by column chromatography with hexane–AcOEt (2:1) to give **29** (42.0 g, 100%) as a colorless amorphous mass, $[\alpha]_D$ −53.48° (c=1, $CHCl_3$ at 24 °C). HRMS m/z Calcd for $C_{23}H_{28}N_2O_6$ (M^+): 428.1945. Found: 428.1950. IR cm^{-1}: 3410, 1740, 1680. ^{1}H-NMR δ: 1.34 (3H, br d, CMe), 2.84 (3H, s, NMe), 2.8—3.0, 3.2—3.35 [2H (1:1), m, C<u>H</u>$_2$–CH], 3.72, 3.77 [6H (1:1), s, OMe], 4.52 (1H, quintet, J=7.1 Hz, Me–C<u>H</u>), 4.65—5.1 (1H, m, Me–C<u>H</u>), 5.10 (2H, br s, CH_2 of Cbz), 6.57, 6.78, 7.0, 7.1 [4H (0.5:2:0.5:1), br d, arom.-H], 7.26—7.36 (5H, m, arom.-H of Cbz).

Methyl *N*-Cbz-L-alanyl-*N*,*O*-Dimethyl-L-tyrosyl-L-alaninate 31 A mixture of **29** (42.5 g, 99.3 mmol), 5% Pd–C (5 g) and concentrated HCl (9.5 ml) in MeOH (300 ml) was shaken with H_2 at room temperature until hydrogen absorption ceased. The catalyst was filtered off and the solvent was evaporated *in vacuo* to give methyl *N*,*O*-dimethyl-L-tyrosyl-L-alaninate HCl (**30**, 29.9 g, 91.2%) as a colorless solid. This compound was used for the next reaction without further purification. A mixture of **30** (29.64 g, 89.7 mmol), *N*-Cbz-L-alanine (25 g, 112 mmol), triethylamine (14 ml) and DCC (23.1 g, 112 mmol) was reacted according to the procedure for the synthesis of **28**. Compound **31** (42.4 g, 94.7%) was obtained as a colorless amorphous mass, $[\alpha]_D$ −101.7° (c=1, $CHCl_3$ at 24 °C). HRMS m/z Calcd for $C_{26}H_{33}N_3O_7$ (M^+): 499.2316. Found: 499.2315. IR cm^{-1}: 3420, 3310, 1740, 1705, 1675, 1640. ^{1}H-NMR δ: 0.41, 1.27, 1.33, 1.37 [total 6H (1:0.5:0.5:1), each d, J=7.3 Hz, CMe×2], 2.91, 2.96 [total 3H (2:1), each s, NMe], 2.9—3.3 [total 2H, m, CH_2–C<u>H</u>], 3.70, 3.74, 3.75 [total 9H (1:1:1), s, OMe], 4.2—4.3, 4.45—4.6 [3H (1:2), m, Me–C<u>H</u>], 4.85 (1H, dd, J=3.3, 10.85 Hz, CH_2–C<u>H</u>), 4.9—5.2 (total 2H, m, CH_2 of Cbz), 6.80, 6.81 [total 2H (1:2), d, J=8.0 Hz, arom.-H], 7.04, 7.10 [total 2H (3:2), d, J=8.0 Hz, arom.-H], 7.25—7.4 (5H, m, arom.-H of Cbz), 5.21, 5.56, 6.55, 8.1 [total 2H (2:1:1:2), each broad, NH].

Methyl *N*-Cbz-D-alanyl-L-alanyl-*N*,*O*-dimethyl-L-tyrosyl-L-alaninate 33 A mixture of **31** (42.1 g, 84.4 mmol), 5% Pd–C (5 g), concentrated HCl (8.5 ml) and MeOH (500 ml) was hydrogenated according to the procedure for the synthesis of **30**. L-Alanyl-*N*,*O*-dimethyl-L-tyrosyl-L-alanine methyl ester HCl (**32**, 33.2 g, 97.9%) was obtained as colorless crystals, $[\alpha]_D$ −81.58° (c=1, $CHCl_3$ at 24 °C). HRMS m/z Calcd for $C_{18}H_{27}N_3O_5$ (M^+): 365.1948. Found: 365.1930. A mixture of **32** (13.16 g, 32.8 mmol), *N*-Cbz-D-alanine (11.0 g, 49.3 mmol), HOBt (7.55 g, 49.3 mmol), triethylamine (6 ml) and DCC (10.17 g, 49.3 mmol) was reacted according to the procedure for the synthesis of **28**. The title compound **33** was obtained as a colorless amorphous mass (18.2 g, 97.8%). This compound afforded crystals on standing, mp 126—128 °C (MeOH), $[\alpha]_D$ −90.99° (c=1, $CHCl_3$ at 24 °C). *Anal.* Calcd for $C_{29}H_{38}N_4O_8$: C, 61.04; H, 6.71; N, 9.82. Found: C, 60.82; H, 6.64; N, 9.83. IR cm^{-1}: 3420, 3300, 1720, 1660. ^{1}H-NMR δ: 0.43, 1.2—1.4 [total 9H (1:5), m, CMe×3], 2.87, 2.95 [total 3H (2:1), each s, NMe], 2.9—3.35 (total 2H, m, C<u>H</u>$_2$–CH), 3.67, 3.71, 3.75, 3.76 [total 6H (1:2:2:3), s, OMe], 4.2—4.35, 4.52, 4.75 [total 3H (8:8:1), m, quintet, quintet, Me-C<u>H</u>], 4.95 (1H, br dd, CH_2–C<u>H</u>) 5.07 (2H, br s, CH_2 of Cbz), 6.80, 6.83 [total 2H (2:3), d, J=7.5, 8.6 Hz, arom.-H], 7.02, 7.10 [total 2H (3:2), each d, J=8.6 Hz, arom.-H], 4.95, 5.4, 5.63, 6.60, 8.15 [total 3H (3:1:3:2:3), each broad, NH×3], 7.2—7.4 (5H, m, arom.-H).

***N*-Cbz-D-alanyl-L-alanyl-*N*,*O*-dimethyl-L-tyrosyl-L-alanine 34** A 1 N NaOH solution (8.5 ml, 8.5 mmol) was added to a stirred solution of **33** (4.0 g, 7.02 mmol) in MeOH (25 ml) and the solution was stirred for 1 h at room temperature. It was acidified with diluted HCl, and the product was extracted with $CHCl_3$. The organic extract was washed with brine then dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give **34** as a colorless amorphous mass (3.88 g, 99.4%), IR cm^{-1}: 3420, 3300, 1720, 1660. ^{1}H-NMR δ: 0.49, 1.23—1.45 (total 9H, m , CMe×3), 2.83, 2.87, 2.90, 2.92 (total 3H, each s, NMe), 2.90, 3.23 (total 2H, each m, C<u>H</u>$_2$–CH), 3.72, 3.74, 3.75, 3.79 (total 3H, each s, OMe), 4.20, 4.37, 4.49, 4.71, 4.89, 5.00 (total 4H, each m, Me–C<u>H</u>), 5.04—5.11 (2H, m, CH_2 of Cbz), 5.53, 5.93, 8.00 (total 3H, br s, NH), 6.82, 7.06 (4H, d, J=8.3 Hz, arom.-H), 7.23—7.34 (5H, m, arom.-H of Cbz).

Reaction of Tetrapeptide Acid 34 with 14-Membered Ring Cyclophane 22a″ A solution of DCC (50 mg, 0.242 mmol) in dioxane (2 ml) was added dropwise to a stirred solution of **22a″** (40 mg, 0.101 mmol) and **34** (120 mg, 0.216 mmol) in dioxane (3 ml) at room temperature. Stirring was continued for 4 h and then the resulting white solid was filtered off. The solvent was evaporated *in vacuo* to afford a residue, which was purified by columm chromatography with AcOEt to give **35** (60 mg, 63%) as a colorless amorphous mass, IR (KBr) cm^{-1}: 3420, 3320, 1740, 1720, 1640. ^{1}H-NMR δ: 0.48—0.60, 1.22—1.37 (total 9H, m, CMe×3), 2.54 (3H, s, NMe), 2.72—3.28 (6H, m), 2.87, 2.89, 2.95 (total 3H, s, NMe), 3.12, 3.17, 3.24 (total 3H, each s, NMe), 3.58, 3.62, 3.63 (total 3H, each s, OMe), 3.79 (3H, s, OMe), 3.94, 3.96 (total 3H, each s, OMe), 4.16—4.37 (total 2H, m), 4.37 (1H, br s), 4.58—4.82 (3H, m), 4.88—5.17 (2H, m, CH_2 of Cbz), 5.29 (1H, m), 5.80 (1H, m, NH), 6.58 (1H, br, NH), 6.59 (1H, m, NH), 7.79 (1H, br, NH), 6.74—7.38 (14H, m, arom.-H×14).

Synthesis of RA-VII (1) and Deoxybouvardin 2 RA-VII (**1**): A solution of **35** (40 mg, 0.043 mmol) and 1 N NaOH (0.5 ml) in MeOH–CH_3CN (1:1) (2 ml) was stirred for 0.5 h at room temperature. The reaction

mixture was acidified with saturated aqueous citric acid, then diluted with brine (20 ml). The product was extracted with $CHCl_3$ (20 ml × 3). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give a residue, which was purified by preparative TLC with $CHCl_3$–MeOH (10 : 1) to afford **36** (9.5 mg, 24.0%) as a colorless amorphous mass, IR (KBr) cm^{-1}: 3420, 3320, 1725, 1640. ^{1}H-NMR δ: 0.44—0.56, 1.06—1.37 (9H, m, CMe × 3), 2.68—3.72 (6H, m), 2.61, 2.78, 2.95, 3.11, 3.21 (total 9H, s, NMe × 3), 3.77, 3.78 (total 3H, each s, OMe), 3.94, 3.95 (total 3H, each s, OMe), 4.12—5.12 (total 5H, m, chiral H × 5), 4.39 (1H, br s), 5.05, 5.08 (total 2H, each s, CH_2 of Cbz), 5.50 (total 2H, m, chiral H and NH), 6.32 (1H, br, NH), 6.60 (1H, br), 6.76—7.43 (total 15H, m, arom.-H × 14 and CO_2H), 8.27 (1H, br, NH). A mixture of **36** (9.5 mg, 0.010 mmol) and 5% Pd–C (5 mg) in MeOH (1 ml) was shaken with H_2 at room temperature for 3 h. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to give the amino acid **37** (6.1 mg). This compound was used for the next reaction without further purification. A solution of DCC (5 mg, 0.024 mmol) in dioxane (3 ml) was added dropwise to a solution of **37** (6.1 mg) in dioxane (3 ml) over a period of 20 min. The mixture was stirred at the same temperature for 15 h and concentrated *in vacuo* to give a residue. AcOEt (2 ml) was added to this residue and the white precipitate was filtered off. The filtrate was evaporated *in vacuo* to give a residue, which was purified by preparative TLC (AcOEt) followed by column chromatography [$CHCl_3$–MeOH (10 : 1)] to afford RA-VII (**1**) (3.0 mg, 39.0%) as a colorless amorphous mass, $[\alpha]_D$ −209° (c = 0.39, $CHCl_3$) [lit.[2] $[\alpha]_D$ −229° (c = 0.1, $CHCl_3$)]. The spectral data (^{1}H-NMR, IR, and EIMS) and TLC behavior of synthetic RA-VII (**1**) were in complete agreement with those[2] of natural RA-VII.

Deoxybouvardin (**2**): $AlCl_3$ (20 mg, 0.15 mmol) was added to a stirred solution of RA-VII (**1**) (31 mg, 0.04 mmol) in CH_2Cl_2 (10 ml) at room temperature. The mixture was stirred for 2 h at the same temperature, then brine was added. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give a residue, which was purified by column chromatography [$CHCl_3$–MeOH (10 : 1)] gave deoxybouvardin (**2**, 15.3 mg, 60%) as a colorless amorphous mass, the spectral data (^{1}H-NMR, IR, and EIMS) and TLC behavior of which were in complete agreement with those[2,4] of natural deoxybouvardin.

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