The transition state **3** is nearly a pure biradical (ca. 90%, see Table II). The CC_1C_2C and HC_1C_2H torsion angles have decreased with respect to **1**; the C_1C_2 distance corresponds to a normal single bond. The other ring bonds in **3** show the relief of strain already achieved in the transition state.

Our results essentially confirm the predictions of Allinger and Sprague[6] and clearly indicate that *trans*-cyclohexene corresponds to a local minimum, although the activation energy for its isomerization is not very large. Thus, it might be possible to generate and observe it in an inert matrix. The stabilization of highly strained olefins by coordination to a transition metal has enabled the isolation of stable copper(I)–*trans*-cycloheptene complexes.[18] Similarly, we expect that coordination of **1** to a transition metal may result in a considerable stabilization, though probably not enough to produce isolable complexes of **1**. Nevertheless, coordinated **1** may well be an intermediate in metal-catalyzed photochemical reactions of **2**.[19]

Acknowledgment. This work was supported in part (P.J.J.A.T.) by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure research (ZWO).

Registry No. Cyclohexene, 110-83-8.

Supplementary Material Available: Complete geometry specifications (*Z* matrices, Cartesian coordinates, and important geometric parameters) of **1–3** (4 pages). Ordering information is given on any current masthead page.

(18) Evers, J. T. M.; Mackor, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 423. Evers, J. T. M. Ph.D. Thesis, Utrecht, 1979. Mackor, A., unpublished results.

(19) Timmermans, P. J. J. A.; et al., manuscript in preparation.

(20) Langhoff, S. R.; Davidson, E. R. *Int. J. Quantum Chem.* **1974**, *8*, 61.

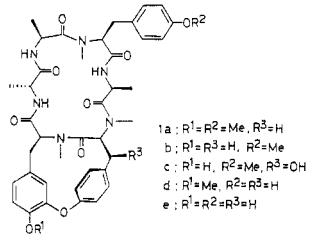
(21) Ahlrichs, R., private communication.

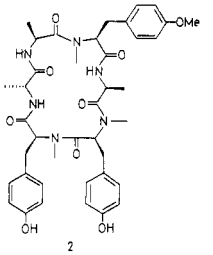
Communications

The First Total Synthesis of Deoxybouvardin and RA-VII, Novel Antitumor Cyclic Hexapeptides

Summary: Intramolecular oxidative coupling of two phenolic parts of protected (2,6-dibromotyrosyl)-2,6-dichlorotyrosine with thallium trinitrate afforded a highly strained 14-membered ring system, from which deoxybouvardin and RA-VII were synthesized.

Sir: Recently, unique hexapeptides, which show potent antitumor activity, were isolated from *Bouvardia termifolia*[2] (Rubiaceae) and *Rubia Coldifolia* L.[3] (Rubiaceae). They are represented by general formula **1** (**1a** = RA-VII; **1b** = deoxybouvardin or RA-V; **1c** = bouvardin; **1d** = RA-II). Their unusual structural feature is a highly strained 14-membered ring including a cis-peptide

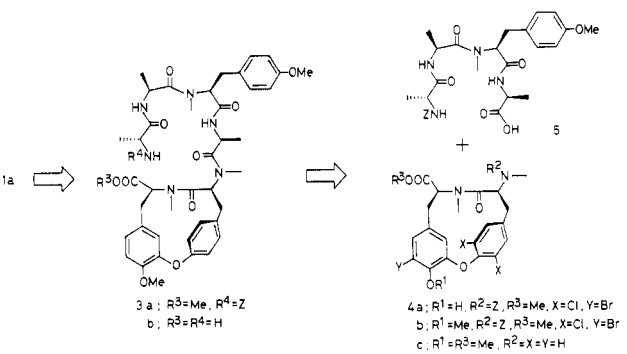




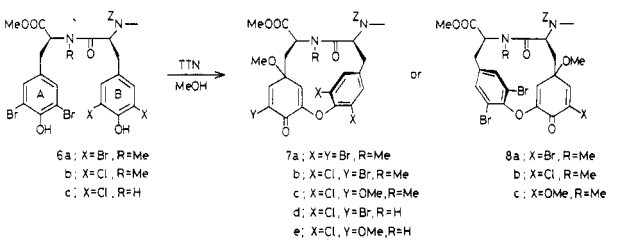
grouping as well as a paracyclophane and a metacyclophane ring system. The 14-membered ring, derived presumably by oxidative coupling of the phenolic parts of two adjacent tyrosines in plants, as shown to be indispensable to their antitumor activity since a ring-opened analogue (**2**) of deoxybouvardin (**1b**) lacks the activity.[4] In this paper we report the first total synthesis of RA-VII (**1a**) and deoxybouvardin (RA-V, **1b**).

Scheme I shows our strategy for the synthesis of **1a**, which comprises construction of the 14-membered ring unit

Scheme I



Scheme II



(1) (a) Tobishi Pharmaceutical Co., Ltd. (b) Tokyo College of Pharmacy. (c) Chiba University.

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

(3) (a) Itokawa, H.; Takeya, K.; Mihara, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Iitaka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1424. (b) Itokawa, H.; Takeya, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Mihara, K. *Ibid.* **1984**, *32*, 284. (c) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Serisawa, N.; Hamanaka, T.; Mihashi, S. *Ibid.* **1984**, *32*, 3216. (d) Itokawa, H.; Takeya, K.; Mori, N.; Kidokoro, S.; Yamamoto, H. *Planta Med.* **1984**, 313. (e) Itokawa, H.; Takeya, K.; Mori, N.; Takanashi, M.; Yamamoto, H.; Sonobe, T.; Kidokoro, S. *Gann* **1984**, *75*, 929. (f) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762.

(4) Bates, R. B.; Gin, S. L.; Hassen, M. A.; Hruby, V. J.; Janda, K. D.; Kriek, G. R.; Michaud, J. P.; Vine, D. B. *Heterocycles* **1984**, *22*, 785.

0022-3263/87/1952-2957$01.50/0

(4) and the subsequent coupling with a tetrapeptide (5), followed by ring closure leading to a cyclic hexapeptide. For the first step, which is crucial to the present strategy, we employed intramolecular oxidative coupling of two phenolic parts of a L-tyrosyl-L-tyrosine derivative (6) with thallium trinitrate (TTN). Yamamura and his co-workers succeeded in preparation of derivatives of 6-bromo-2-(2,6-dibromophenoxy)phenol by TTN oxidation of 2,6-dibromophenols followed by zinc reduction.[5] In our strategy, on oxidation of an asymmetrical tetrabromo derivative (**6a**),[6] there is a possibility of the undesired **8a** being formed besides the desired **7a**. When **6a**[7] (3×10^{-3} mol/L) was treated with TTN (3 equiv) in methanol at ambient temperature, unfortunately **7a** was not detected in the reaction mixture, but **8a**[8] (33%) and **8c** (49%) were obtained. The CPK molecular model suggests that the phenolic oxygen of the left tyrosine moiety (A) of the formula **6** approaches more easily to the ortho carbon of the right tyrosine moiety (B) than the phenolic oxygen of the B ring does to the ortho carbon of the A ring. The latter approach undergoes steric retardation of the methoxycarbonyl group. To our surprise, replacement of the bromine atoms of the B ring with chlorine atoms was found to induce ring closure in the opposite fashion. Thus, treatment of dichlorodibromo derivative **6b**[9] with TTN produced the desired **7b**[10] (5.2%) and a dimethoxy dienone (**7c**, 14.4%)[11] without contamination by **8b**. Although the present reversal of the ring closure is beyond our consideration, this method appears to be generally applicable because another derivative (**6c**) of L-tyrosyl-L-tyrosine gave the corresponding **7d** (9%) and **7e** (16%) (Scheme II).

Successive treatment of **7b** with zinc in 90% acetic acid at room temperature to yield **4a** and methylation of **4a** with diazomethane in diethyl ether–methanol gave **4b**. When **4b** was subjected to catalytic hydrogenolysis on 5% Pd–C in methanol in the presence of potassium acetate, **4c**[12] was produced in an overall yield of 43% from **7b**. Condensation of **4c** with the tetrapeptide **5**[13] to afford **3a** was achieved by action of DCC in dioxane–dichloromethane. Then **3b** was obtained by saponification of **3a** with a 0.2 N solution of sodium hydroxide in methanol–acetonitrile–water (2:2:1) followed by hydrogenolysis on 5% Pd–C. On treatment of **3b** with DCC in 1,4-dioxane (about 1×10^{-2} mol/L), the final intramolecular condenstion smoothly took place to give **1a** in 39% yield. The spectral data (^{1}H NMR,[14] IR, and EI-mass), optical rotation([α]$_D$ −209° (*c* 0.03, chloroform) [lit.[3a] [α]$_D$ −229° (*c* 0.1, chloroform)]) and TLC behavior of the thus obtained **1a** were in complete agreement with those of natural RA-VII.

Further we converted **1a** to deoxybouvardin (**1b**) and RA-II (**1d**). Reaction of **1a** with aluminum trichloride in dichloromethane induced selective demethylation to afford **1b**[2] in an excellent yield.[15] On the other hand, a dihydroxy derivative (**1e**) was quantitatively given on treatment of **1a** with aluminum trichloride in the presence of a large excess of ethanethiol. Monomethylation of **1e** with diazomethane in diethyl ether–ethyl acetate (1:10) afforded **1d**[3] in 56% yield along with **1b** (6%), **1a** (14%), and the unreacted **1e** (24%). The antitumor activity of unnatural **1e** is under investigation.

Acknowledgment. We are grateful to Professor Shosuke Yamamura, Keio University, and to Dr. Noboru Mori, chief director of Ohmori Research Laboratories, Tobishi Pharmaceutical Co., Ltd. for valuable discussion.

Supplementary Material Available: Spectral and analytical data on 15 new compounds as well as synthetic deoxybouvaldin, RA-VII, and RA-II (8 pages). Ordering information is given on any current masthead page.

(5) (a) Noda, H.; Niwa, M.; Yamamura, S. *Tetrahedron Lett.* **1981**, *22*, 3247. (b) Nishiyama, S.; Yamamura, S. *Ibid.* **1982**, *23*, 1281. (c) Nishiyama, S.; Suzuki, T.; Yamamura, S. *Ibid.* **1982**, *23*, 3699. (d) Nishiyama, S.; Suzuki, T.; Yamamura, S. *Chem. Lett.* **1982**, 1851.

(6) At the final stage of our investigation, Yamamura et al. reported the application of this method to intramolecular oxidative coupling of symmetrical 3,6-bis(3,5-dibromo-4-hydroxybenzyl)-2,5-piperazinedione, which took no notice of regioselectivity: Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481.

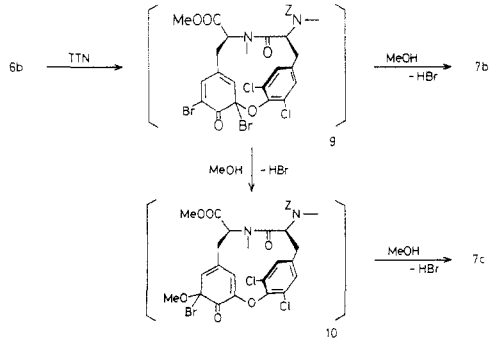
(7) **6a** was prepared in 58% yield from *N*-benzyloxycarbonyl-2,6-dibromo-*N*-methyltyrosine and 2,6-dibromo-*N*-methyltyrosine methyl ester by using DCC in 1,4-dioxane.

(8) (a) From its ^{1}H NMR ($CDCl_3$), **8a** was shown to consist of two conformers in the ratio of 4:1, which are in equilibrium at room temperature. (b) In a similar manner to the transformation of **7a** into RA-VII (**1a**) (vide infra), **8a** was derived to the corresponding bicyclic hexapeptide, the physical properties of which were not identical with those of RA-VII.

(9) **6b** was prepared in 76% yield from *N*-benzyloxycarbonyl-2,6-dichloro-*N*-methyltyrosine and 2,6-dibromo-*N*-methyltyrosine methyl ester by using DCC in 1,4-dioxane.

(10) The structure of **7b** was deduced from its IR, exact mass, and ^{1}H NMR spectra.

(11) **7b** and **7c** might be formed via a putative intermediate (**9**): Nucleophilic attack of methanol at the γ-position of **9** produces **7b**. When methanol attacks on the α-position, **7c** is formed through **10**.



(12) **4c** was shown by its ^{1}H NMR ($CDCl_3$) to consist of two conformers (5:4), which are in equilibrium at room temperature.

(13) **5** was prepared in 79% overall yield from *N*-benzyloxycarbonyl-*N*-methyltyrosine through eight steps.

(14) From its ^{1}H NMR, **1a** was shown to consist of two conformers (85:15), which were also observed in the ^{1}H NMR spectrum of natural **1a** (see ref 1b).

(15) A suspension involving **1a** and aluminum trichloride (38 equiv) in dichloromethane was stirred at room temperature for 14 h; **1b** was produced in 60% yield together with **1a** (40%).

Takashi Inaba,[1a] Isao Umezawa,[1a] Masayuki Yuasa[1a] Tsutomu Inoue,*[1a] Susumu Mihashi[1a] Hideji Itokawa,[1b] Katsuyuki Ogura[1c]

Ohmori Research Laboratories
Tobishi Pharmaceutical Co., Ltd.
16-18 Ohmori Nishi 1-chome
Ohtaku, Tokyo 143, Japan
Tokyo College of Pharmacy
Horinouch 1432-1, Hachioji, Tokyo 192-03, Japan
and Department of Synthetic Chemistry
Faculty of Engineering, Chiba University
Yayoicho 1-33, Chiba 260, Japan

Received April 10, 1987

β-Stannyl Enones as Radical Traps: A Very Direct Route to $PGF_{2\alpha}$

Summary: The reaction of β-stannyl enone **4** with carbon-centered radicals has been investigated. Reaction of iodo acetals **7** and **8** with **4**, under appropriate initiation conditions, afforded enones **9** and **10** via a cyclization–trapping sequence. A formal total synthesis of $PGF_{2\alpha}$ was accomplished starting from iodo acetal **6**.

0022-3263/87/1952-2958$01.50/0