The Journal of
Organic
Chemistry

VOLUME 57, NUMBER 5 FEBRUARY 28, 1992

Communications

Synthesis of N^{29}-Desmethyl RA-VII. Identification of the Pharmacophore of RA-I–VII and Deoxybouvardin and Reassignment of the Subunit Functional Roles

Dale L. Boger,* Daniel Yohannes, and James B. Myers, Jr.

Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907

Received August 30, 1991 (Revised Manuscript Received December 9, 1991)

Summary: N^{29}-Desmethyl RA-VII was prepared in efforts that address the key structural and conformational features of the agent that contribute to its antitumor activity.

Bouvardin (**8**) and deoxybouvardin (**2**) constitute the initial members of a growing class of potent antitumor antibiotics now including RA-I to RA-VII (**1–7**).[1-7] Bouvardin has been shown to inhibit protein synthesis through eukaryotic 80S ribosomal binding resulting in inhibition of aminoacyl-*t*RNA binding and peptidyl-*t*RNA translocation, and this is presently thought to be the site of action for the agent antitumor activity.[8] Early studies have supported the proposal that the unusual 14-membered *N*-methyl cycloisodityrosine subunit of the agents may serve to induce a rigid, normally inaccessible conformation within the 18-membered cyclic hexapeptide that in turn constrains the biologically relevant D-Ala-Ala-*N*HMe-Tyr(OMe)-Ala tetrapeptide to a biologically active conformation.[9-11] Thus, the functional role of the unusual 14-membered *N*-methyl cycloisodityrosine subunit of **1–8** has been suggested to be that of the scaffolding role of maintenance of an active, normally inaccessible conformation within the 18-membered ring and the agent tetrapeptide. Herein, we detail the synthesis of N^{29}-desmethyl RA-VII[12,13] based on the implementation of an Ullmann diaryl ether macrocyclization reaction[13,14] conducted in efforts to assess the relative conformational and biological importance of the key cis N^{29}–C^{30} *N*-methylamide bond central to the 14-membered ring. As detailed herein, the evaluation of **9** along with that of **10** and **11** proved more revealing than anticipated, permitted the pharmacophore assignment for **1–9**, and suggests a reversal of the assigned functional roles of the agent subunits.

O-Methylation of *N*-CBZ-3-acetyl-L-tyrosine methyl ester[15] followed by Baeyer–Villiger oxidation and subsequent methanolysis of the resulting acetate provided **12**, Scheme I. Catalytic hydrogenolysis of **12** and coupling of the resultant amine **13** with *N*-BOC-*N*-methyl-4-iodo-L-phenylalanine[13] provided **14**. Subjection of **14** to intramolecular Ullmann macrocyclization conditions[14] provided **10** (36%), and optimal results were obtained employing methyl copper to stoichiometrically generate the initial cuprous phenoxide.[16] Similar to *N*-methyl cycloisodi-

(1) 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.

(2) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762.

(3) Itokawa, H.; Takeya, K.; Mihara, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Iitaka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1424.

(4) Itokawa, H.; Takeya, K.; Mori, N.; Kidokoro, S.; Yamamoto, H. *Planta Med.* **1984**, *51*, 313.

(5) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Serisawa, N.; Hamanaka, T.; Mihashi, S. *Chem. Pharm. Bull.* **1984**, *32*, 3216.

(6) Itokawa, H.; Takeya, K.; Mori, N.; Takanashi, M.; Yamamoto, H.; Sonobe, T.; Kidokoro, S. *Gann.* **1984**, *75*, 929.

(7) Itokawa, H.; Takeya, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Mihara, K. *Chem. Pharm. Bull.* **1984**, *32*, 284.

(8) Zalacain, M.; Zaera, E.; Vazquez, D.; Jimenez, A. *FEBS Lett.* **1982**, *148*, 95.

(9) Bates, R. B.; Cole, J. R.; Hoffmann, J. J.; Kriek, G. R.; Linz, G. S.; Torrance, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 1343.

(10) 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.

(11) Morita, H.; Kondo, K.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H.; Tomioka, N.; Itai, A.; Iitaka, Y. *Tetrahedron* **1991**, *47*, 2757.

(12) Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957.

(13) Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 1427.

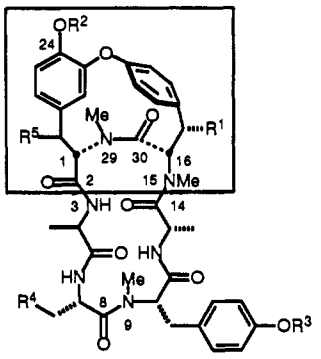
(14) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 1763.

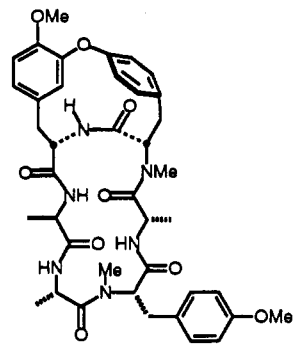
(15) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1987**, *52*, 5283.

(16) Boger, D. L.; Yohannes, D.; Sakya, S. M. *J. Org. Chem.* **1991**, *56*, 4204.

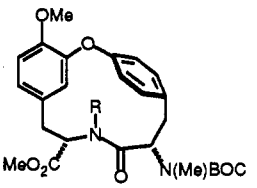
0022-3263/92/1957-1319$03.00/0

Pharmacophore





9



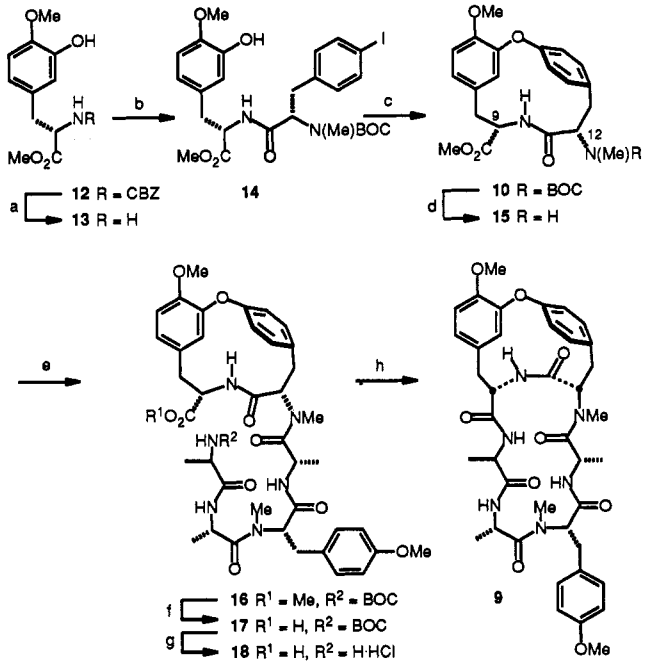
10 R = H
11 R = Me

	R^1	R^2	R^3	R^4	R^5	
1	H	Me	Me	H	H	RA-VII
2	H	H	Me	H	H	RA-V
						deoxybouvardin
3	H	H	Me	OH	H	RA-I
4	H	Me	H	H	H	RA-II
5	H	Me	Me	OH	H	RA-III
6	H	Me	Me	H	OH	RA-IV
7	OH	Me	Me	H	H	RA-VI
8	OH	H	Me	H	H	bouvardin

tyrosine derivatives,[13,14] **10** was found to possess a rigid solution conformation possessing a trans C^{11}–N^{10} amide bond.[17] Amine deprotection and coupling of **15** with *N*-BOC-D-Ala-L-Ala-L-*N*Me-Tyr(OMe)-L-Ala-CO_2H[18] provided **16**. Sequential methyl ester hydrolysis, *N*-BOC deprotection and macrocyclization with C^2–N^3 amide bond formation strategically conducted at a secondary amide site possessing a D-amino acid amine terminus[18-20] provided **9** $[\alpha]^{22}_D$ −202° (*c* 0.5, $CHCl_3$).

The near-identical ^1H NMR and ^{13}C NMR spectroscopic properties of **1** and **9** and an intense and diagnostic C1-H/C16-H crosspeak in the 2D ^1H–^1H NOESY NMR spectrum of **1** unambiguously established that they adopt a predominant solution conformation possessing a cis N^{29}–C^{30} amide bond,[21] Figure 1. Thus, in marked contrast to the cycloisodityrosine **10** and *N*-methyl cycloisodityrosine **11** which possess trans C^{11}–N^{10} amides central to the 14-membered ring, the 14-membered ring of **9** has adopted a conformation possessing the inherently disfavored cis C^{30}–N^{29} secondary amide. Consequently, *the experimental observations illustrate that it is the tetrapeptide housed within the 18-membered ring that induces a rigid, normally inaccessible conformation within the 14-membered cycloisodityrosine ring.* Consistent with this reinterpretation of the origin of the conformational properties of the agents, **9** was found to possess potent cytotoxic activity 2× greater than that of the natural products, Table I. Moreover, in contrast to the suppositions to date, the simple 14-membered cycloisodityrosine derivatives **10**–**11** exhibited potent in vitro cytotoxic activity and were found to be only 15-30× less potent than the natural products. As such, the experimental studies detailed herein in conjunction with the results of related studies[22] suggest that it is the tetrapeptide housed within the 18-membered ring that alters the conformational properties and potentiates the biological properties of cycloisodityrosine. Studies to

Scheme I[a]



[a] Key: (a) 0.1 wt equiv of 10% Pd–C, 1 atm of H_2, CH_3OH, 25 °C, 6 h, 99%; (b) 1.0 equiv of *N*-BOC-L-*N*Me-Phe(I), 1.0 equiv of EDCI, 1.0 equiv of HOBt, DMF, 25 °C, 12 h, 92%; (c) 2.0 equiv of CH_3Cu, collidine, 130 °C, 9 h, 36%; (d) 3.0 M HCl/EtOAc, 25 °C, 1 h, 100%; (e) 2.0 equiv of *N*-BOC-D-Ala-L-Ala-L-*N*Me-Tyr-(OMe)-L-Ala,[18] 2.0 equiv of EDCI, 2.0 equiv of HOBt, 5.0 equiv of $NaHCO_3$, DMF, 25 °C, 16 h, 59%; (f) 3.0 equiv of LiOH, 11 equiv of H_2O_2, THF/H_2O (3:1), 25 °C, 6 h, 91%; (g) 3.0 M HCl/EtOAc, 25 °C, 1.5 h, 97%; (h) 1.5 equiv of DPPA, 5.0 equiv of $NaHCO_3$, DMF, 0 °C, 72 h.

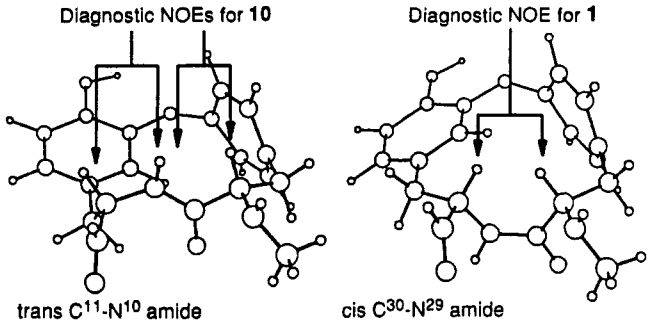


Figure 1.

Table I

agent	IC_{50} (μg/mL, L1210)	agent	IC_{50} (μg/mL, L1210)
1, RA-VII	0.002	10	0.06
2, deoxybouvardin	0.002	11	0.03
9	0.001		

(17) Diagnostic of the trans C^{11}–N^{10} amide bond, characteristic NOE crosspeaks were observed for C12-H/N^{10}-R and C9-H/N^{10}-R in the 2D ^1H-^1H NOESY NMR spectrum of **10** and **11** and the NOE crosspeaks between C12-H/C9-H expected of the cis C^{11}–N^{10} amide bond were not observed.

(18) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487.

(19) Rich, D. H.; Bhatnagar, P.; Mathiaparanam, P.; Grant, J. A.; Tam, J. P. *J. Org. Chem.* **1978**, *43*, 296.

(20) Brady, S. F.; Freidinger, R. M.; Paleveda, W. J.; Colton, C. D.; Homnick, C. F.; Whitter, W. L.; Curley, P.; Nutt, R. R.; Veber, D. F. *J. Org. Chem.* **1987**, *52*, 764. Brady, S. F.; Varga, S. L.; Freidinger, R. M.; Schwenk, D. A.; Mendlowski, M.; Holly, F. W.; Veber, D. F. *J. Org. Chem.* **1979**, *44*, 3101.

(21) Diagnostic of the cis C^{30}–N^{29} amide bond, an intense NOE crosspeak between C1-H and C16-H is observed in the 2D ^1H–^1H NOESY NMR spectrum of RA-VII and deoxybouvardin in solution ($CDCl_3$) and the NOE crosspeaks between C1-H/N^{29}-R or C16-H/N^{29}-R expected of a trans C^{30}–N^{29} amide bond are not observed. The agent **9**, like **1**,[1,9,11] adopts a major (85–90%) and minor (10–15%) spectroscopically detectable solution conformation both of which possess the cis N^{29}–C^{30} amide, cf. ref 11 for a detailed discussion of **1**.

(22) Boger, D. L.; Myers, J. B., Jr. *J. Org. Chem.* **1991**, *56*, 5385. Boger, D. L.; Myers, J. B., Jr.; Yohannes, D.; Kitos, P. A.; Suntornwat, O.; Kitos, J. C. *BioMed. Chem. Lett.* **1991**, *1*, 313.

determine whether the tetrapeptide potentiation of the properties of cycloisodityrosine is conformationally or structurally based is in progress and will be reported in due course.

Acknowledgment. This work was assisted through the financial support of the National Institutes of Health (CA41101, D.L.B.; CA08883, J.B.M). We wish to thank Professor P. A. Kitos and O. Suntornwat for conducting the in vitro cytotoxic evaluations (L1210).

Registry No. 9, 138571-36-5; 10, 138571-37-6; 11, 138605-22-8; 12, 132513-32-7; 13, 37466-41-4; 14, 138571-38-7; 15, 138571-39-8; 16, 138605-23-9; 17, 138571-40-1; 18, 138571-41-2; Cbz-Tyr(3-Ac)-OMe, 79677-60-4; Boc-NMe-Phe(I), 138571-42-3; Boc-D-Ala-Ala-NMe-Tyr(Me)-Ala, 112196-84-6.

Supplementary Material Available: Full physical and spectroscopic characterization of 14, 16, 9, and 10 and tables comparing the spectroscopic properties (^1H and ^{13}C) of 1 and 9 (6 pages). Ordering information is given on any current masthead page.

A New Iterative Route to Optically Active Polyols Using α-Alkoxy Silanes as Key Intermediates

Jun-ichi Yoshida,* Tsuyoshi Maekawa, Yuko Morita, and Sachihiko Isoe*

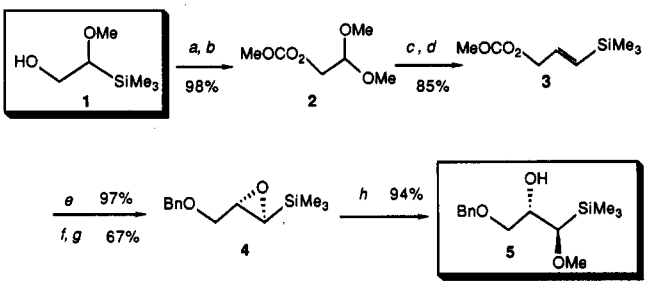
Institute of Organic Chemistry, Faculty of Science, Osaka City University, Sugimoto 3-3-138, Sumiyoshi, Osaka 558, Japan

Received November 21, 1991

Summary: A new iterative and modular strategy which is applicable to the synthesis of any enantiomers and diastereomers of straight chain 1,*n*-polyols has been developed utilizing electrochemical oxidation of α-alkoxy silanes.

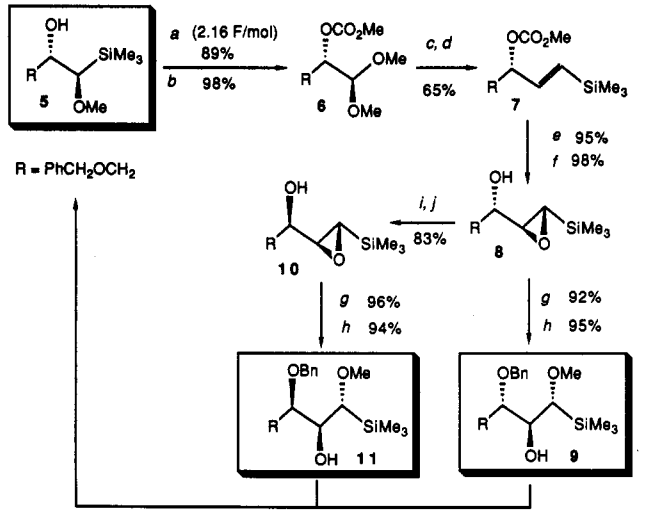
Strategies which allow synthesis of a variety of target molecules by repetition of simple procedures are needed for the development of robot synthesis.[1] As part of a program aimed at new methods for such strategies, we have developed a new iterative route[2] to optically active polyols which is applicable to the synthesis of many biologically interesting polyhydroxylated natural products.[3] Our approach is designed around a new carbonyl synthon[4] which is based upon silicon β effects in electron-transfer reactions.[5] The reaction sequences consist of several simple modules and can be applied to the synthesis of all enantiomers and diastereomers of straight-chain 1,*n*-polyols and amino polyols.[6]

Scheme I[a]



[a] Key: (a) anodic oxidation Et_4NOTs/MeOH; (b) $ClCO_2Me$, pyridine; (c) H^+; (d) $Br_2CHSiMe_3$, $CrCl_2$; (e) $LiAlH_4$; (f) L-(+)-DIPT, $Ti(OPr^i)_4$, TBHP; (g) NaH, $PhCH_2Br$; (h) $BF_3{\cdot}OEt_2$/MeOH.

Scheme II[a]



[a] Key: (a) anodic oxidation Et_4NOTs/MeOH; (b) $ClCO_2Me$, pyridine; (c) H^+; (d) $Br_2CHSiMe_3$, $CrCl_2$; (e) $LiAlH_4$; (f) L-(+)-DIPT, $Ti(OPr^i)_4$, TBHP; (g) NaH, $PhCH_2Br$; (h) $BF_3{\cdot}OEt_2$/MeOH; (i) Ph_3P, diethyl azodicarboxylate, $PhCO_2H$; (j) NaOH/MeOH.

As key intermediates for the iterative route to polyols, α-hydroxy aldehydes or their protected forms seemed attractive because the formyl group can be readily utilized for carbon extension reactions. Recently, we have found

(1) For example: (a) Frisbee, A. R.; Nantz, M. H.; Kramer, G. W.; Fuchs, P. L. *J. Am. Chem. Soc.* **1984**, *106*, 7143–7145. (b) Takuma, Y.; Imaki, N. *J. Syn. Org. Chem. Jpn.* **1990**, *48*, 587–592.

(2) Iterative strategy. For example: (a) Watt, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 271–273. (b) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564–1565. (c) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666. See also refs 3a,h,k,q.

(3) 1,2-Polyols. For example: (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949–951. (b) Lee, A. W. M.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Walker, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 3515–3516. (c) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373–1378. (d) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–76. (e) Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3712–3714. (f) Matteson, D. S.; Peterson, M. L. *J. Org. Chem.* **1987**, *52*, 5116–5121. (g) Solladie, G.; Hutt, J.; Frechou, C. *Tetrahedron Lett.* **1987**, *28*, 61–64. (h) Donddoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. 1,3-Polyols. For example: (i) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378–1380. (j) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292–1293. (k) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. (l) Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982–4984. (m) Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525–6532. (n) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4383–4386. (o) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090–6093. (p) Harada, T.; Matsuda, Y.; Wada, I.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21–22. (q) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147–1149. (r) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495–4499.

(4) (a) Yoshida, J.; Murata, T.; Isoe, S. *J. Organomet. Chem.* **1988**, *345*, C23–C27. (b) Yoshida, J.; Matsunaga, S.; Isoe, S. *Tetrahedron Lett.*, **1989**, *30*, 219–222. (c) Yoshida, J.; Matsunaga, S.; Murata, T.; Isoe, S. *Tetrahedron* **1991**, *47*, 615–624.

(5) Yoshida, J.; Maekawa, T.; Murata, T.; Matsunaga, S.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962–1970.

(6) For example: Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. *Helv. Chim. Acta* **1985**, *68*, 1217–1225.

0022-3263/92/1957-1321$03.00/0