Total Synthesis of Didemnins A, B, and C^{1,2}

Kenneth L. Rinehart,* Vimal Kishore, Srinivasan Nagarajan, Robin J. Lake, James B. Gloer, Frank A. Bozich, Kai-Ming Li, Robert E. Maleczka, Jr., William L. Todsen, Murray H. G. Munro, David W. Sullins, and Ryuichi Sakai

> Roger Adams Laboratory University of Illinois at Urbana-Champaign Urbana, Illinois 61801 Received February 3, 1987 Revised Manuscript Received July 30, 1987

The cyclic depsipeptide didemnin B (2),³ isolated from the tunicate *Trididemnum solidum*,⁴ is the first marine natural product to enter clinical trials as a potential anticancer agent.⁵ It has also been reported recently to be exceedingly active as an immunosuppressive agent in vitro and in vivo.⁶ The structure of didemnin B,^{3b} including absolute stereochemistry,^{1,2a,3c,7} was assigned earlier by us as the isomeric analogue containing (3S,4R)-statine instead of (3S,4R,5S)-isostatine.^{3b} Although amounts adequate for the scheduled phase II trials are available at present from the tunicate, a synthetic source is required for any larger scale testing. We describe here the total synthesis of didemnin B (2) as well as the syntheses of the more abundant didemnin A (1) and the less abundant didemnin C (3).

By far the most difficult part of the synthesis involved preparation of didemnin A, and we first synthesized the previously proposed isomer 1a. Major considerations were the unavailability of the two novel subunits, (2S,4S)-Hip^{2a} and (3S,4R)-statine (Sta),^{3c} and the proclivity of Hip to cyclization to the tetronic acid. The former consideration dictated that Sta and Hip be introduced at a late stage; the latter argued that Hip be protected by an amide (peptide) link at its introduction. The synthesis of statine has been reported,⁸ and routes employed previously^{8a,c} were followed in the present synthesis^{2b,c} to give the (3S, 4R)-isomer of Boc-Sta-OEt, after HPLC purification of the crude mixture of (3S, 4R)- and (3R,4R)-isomers, in 48% yield (based upon the aldehyde Boc-D-Leu-H). Boc-Sta-OEt was converted to Boc-Sta-OH, the starting material for the total synthesis, by hydrolysis with potassium hydroxide/dioxane. The other two uncommon amino acids, N-methyl-D-leucine⁹ and N,O-dimethyltyrosine,¹⁰ were employed

(2) Based in part on the following: (a) Nagarajan, S. Ph.D. Dissertation, University of Illinois at Urbana-Champaign, 1984. (b) Bozich, F. A. M.Sc. Dissertation, University of Illinois at Urbana-Champaign, 1984. (c) Maleczka, R. E., Jr. B.Sc. Thesis, University of Illinois at Urbana-Champaign, 1984. (d) Gloer, J. B. Ph.D. Dissertation, University of Illinois at Urbana-Champaign, 1983.

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(a) Rich, D. H.; Sun, E. T.; Boparai, A. S. J. Org. Chem. 1950, 42, 5863–5868); they were apparently unaware of our earlier reports.^{1a,b,2a}
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in the total synthesis as Z-D-MeLeu-OH and Me₂Tyr-ONb, respectively, prepared by reported methods for methylation⁹ of Z derivatives and *p*-nitrobenzyl esterification.¹⁰

Synthesis of ethyl α -(α -(benzyloxy)isovaleryl)propionate (Bzl-Hip-OEt) was achieved by coupling (2S)-2-(benzyloxy)-3methylbutanoyl chloride (prepared from L-valine) with the magnesium enolate of ethyl hydrogen methylmalonate to give a mixture of the ethyl (2R,4S)- and (2S,4S)-4-(benzyloxy)-2,5dimethylhexanoates and their common enolate (10:10:1).^{2a} The ester mixture was then hydrolyzed in 0.5 N potassium hydroxide to give Bzl-Hip-OH (a diastereomeric mixture of the 2R,4S- and 2S,4S-isomers) in 61% yield.

The remaining three units of didemnin A—Leu, Thr, and Pro—were converted to the derivatives H-Leu-OTMSe (Z-Leu-OTMSe¹¹ (H₂, Pd/C) \rightarrow H-Leu-OTMSe) and H-Thr-OTMSe (Z-Thr(*t*-Bu)-OTMSe¹¹ (TMS-I) \rightarrow H-Thr-OTMSe) and to Boc-Pro-OH,¹² respectively, for the start of the synthesis.

From these starting materials (protected amino and hydroxy acids) the synthesis proceeded as shown in Scheme I, involving

⁽¹⁾ Portions of this material have been presented elsewhere: (a) Presented at the International Symposium on Mass Spectrometry in the Health and Life Sciences, University of California, San Francisco, CA, September 9-13, 1984 (Rinehart, K. L., Jr. Anal. Chem. Symp. Ser. 1985, 24, 119-146). (b) Presented at the 1984 International Chemical Congress of Pacific Basin Societies, Honolulu, HI, December 16-21, 1984; Paper 10E01. (c) Presented at the 10th American Peptide Symposium, St. Louis, MO, May 23-28, 1987; Paper LTh 24. (d) Presented at the 28th Annual Meeting of the American Society of Pharmacognosy, Kingston, RI, July 19-22, 1987; paper 53.

⁽⁹⁾ Z-D-MeLeu-OH was prepared from D-Leu-OH by the method reported (McDermott, J. R.; Benoiton, N. L. Can. J. Chem. 1973, 51, 1915–1919) for Z-L-MeLeu-OH; the former has mp 71–72 °C, $[\alpha]^{22}_{D} + 25^{\circ}$ (c 2.3, EtOH); the latter was reported to have mp 73–74 °C, $[\alpha]^{2}_{D} - 23^{\circ}$ (c 1, EtOH). (10) N,O-Dimethyltyrosine (Marner, F.-J.; Moore, R. E.; Hirotsu, K.; Clardy, J. J. Org. Chem. 1977, 42, 2815–2819) was made by sodium/liquid ammonia reduction (Jošt, K.; Rudinger, J. Coll. Czech. Chem. Commun. 1961, 26, 2345–2354) of N,O-dimethyl-N-tosyltyrosine (Fischer, E.; Lipschitz, W. Ber. 1915, 48, 360–378) and converted to the p-nitrobenzyl ester salt [HMe₂Tyr-ONb-p-TsOH, mp 130 °C, $[\alpha]^{20}_{D}+19^{\circ}$ (c 2.06, CHCl₃)] by the method of Mazur et al. (Mazur, R. H.; Schlatter, J. M. J. Org. Chem. 1963, 28, 1025–1029).

⁽¹¹⁾ Sieber, P. Helv. Chim. Acta 1977, 60, 2711-2716.

⁽¹²⁾ Itoh, M.; Hagiwara, D.; Kamiya, T. Bull. Chem. Soc. Jpn. 1977, 50, 718-721.



Z, benzyloxycarbonyl; TBDMS, <u>t</u>-butyldimethylsilyl; HOBt, 1-hydroxybenzotriazole; DCC, dicyclohexylcarbodiimide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; NHS, N-hydroxysuccinimide; NMM, N-methylmorpholine; DMAP,

4-dimethylaminopyridine.

mainly standard peptide coupling, protection, and deprotection steps. Hip was introduced as a mixture of the (2R,4S)- and (2S,4S)-isomers, and a diastereomeric mixture was carried through the penultimate step yielding 4a. Purification by HPLC gave both 4a (N-Z-1a) and (2-epi-Hip)-4a.

Synthetic 4a and (2-epi-Hip)-4a both were identical in their FAB mass spectra and TLC behavior with authentic N-Z-didemnin A (4) and the more polar isomer coeluted with 4 on reversed phase (C-18) HPLC. However, both 4a isomers could be separated from 4 by normal phase (SiO₂) HPLC, as was true of the hydrogenation products 1a and (2-epi-Hip)-1a vis-a-vis authentic 1. Reinvestigation of the structure of didemnin A^{1c,13} revealed (mainly by ¹H NMR) the presence of an isostatine isomer, C₂H₅CH(CH₃)CHNH₂CHOHCH₂COOH, rather than statine, (CH₃)₂CHCH₂CHNH₂CHOHCH₂COOH, and the isostatine isomer was shown by synthesis from D-alloisoleucine^{1d,14} and ¹H NMR spectra of its lactam derivative C₂H₅CH(CH₃)-CHCH(OAc)CH₂CONH to have the stereochemistry 3S,4R,5S,

assigning the structure as 1.

Accordingly, the didemnin A synthesis was repeated as shown in Scheme I but by employing 3S,4R,5S-isostatine [in brackets], with the yields shown [also in brackets]. The product in this case also consisted of two isomers, 4 and (2-epi-Hip)-4. The former isomer moved faster on normal phase HPLC and coeluted with authentic 4. When (2-epi-Hip)-4 was isolated and rechromatographed by normal phase HPLC it appeared as two peaks, 4 and (2-epi-Hip)-4, showing that the latter is converted in solution to the former and that 4 is the more stable stereoisomer. ¹H NMR and FAB mass spectra of synthetic 4 were also identical with those of authentic N-Z-didemnin A. Removal of the Z group by hydrogenation gave 1, thus completing the synthesis of didemnin A. In an L1210 leukemia cell growth inhibition assay (Li, L. H.; Culp, J. W., The Upjohn Company) natural 1 had ID_{50} 0.021 μ g/mL; synthetic 1, 0.021; natural 4, 0.012; synthetic 4, 0.014; synthetic *epi-4*, 0.021. Synthetic 4a was ca. one-tenth as active as 4.

The conversion of didemnin A (1) to didemnin C (3) was effected in 37% yield (based on didemnin A) by coupling didemnin A with *O*-benzyl-L-lactic anhydride, prepared in three steps from

H-Lac-OEt
$$\xrightarrow{BzlBr}_{Ag_2O}$$
 Bzl-Lac-OEt $\xrightarrow{(1) \text{ NaOH}}_{(2) \text{ DCC}}$ 5 $\xrightarrow{H_2}_{Pd/C}$ 3

ethyl L-lactate, and then hydrogenolyzing the resulting O-(Lac)-benzyldidemnin C (5). The resulting synthetic and natural didemnin C (3) samples were essentially identical (mp, rotation, TLC and HPLC behavior, FAB mass spectra).

The conversion of A (1) to B (2) was carried out by the route shown, involving the coupling of *O*-benzyl-L-lactyl azide¹⁵ with L-Pro-OMe,¹⁶ followed by hydrolysis and conversion to the sym-

Bzl-Lac-OEt
$$\xrightarrow{(1) H_2NNH_2}$$
 (1) NaOH
(2) *i*-C₃H₁₁ONO
(3) H-Pro-OMe Bzl-Lac-Pro-OMe $\xrightarrow{(2) EDC}$
(3) 1
 $6 \xrightarrow{H_2} 2$

metrical anhydride (Bzl-Lac-Pro)₂O, which was coupled to didemnin A to give O-(Lac)-benzyldidemnin B (6). Hydrogenolysis then gave didemnin B (2), identical with the natural material by ¹H and ¹³C NMR and mass spectra, HPLC behavior, rotation, and bioactivity (L1210 leukemia cells). The conversion of didemnin A to didemnin B provides not only a conclusion to the

^{(13) (}a) Rinehart, K. L.; Gloer, J. B.; Nagarajan, S.; Sakai, R. to be submitted for publication. (b) A similar conclusion with regard to isostatine in didemnin from *T. cyanophorum* has been reached by Castro et al. (Castro, B.; Jouin, P.; Cové, A.; Dufour, M.; Banaigs, B.; Fransisco, C. 10th American Peptide Symposium, St. Louis, MO, May 23-28, 1987; Paper P-292).

⁽¹⁴⁾ Li, K.-M.; Sullins, D. W.; Kishore, V.; Sakai, R., to be submitted for publication.

 ⁽¹⁵⁾ A similar conversion, starting from D,L-lactic acid and employing HPLC for isolation, yielded (*epi*-Lac)didemnin B as well as didemnin B.
 (16) Guttmann, St. Helv. Chim. Acta 1961, 44, 721-744.

synthesis but also the bonus of immediately increasing the availability of didemnin B, since didemnin A was the major component in the T. solidum extract (A/B, ca. 3:1).

Note Added in Proof. Very recently, the structure of didemnin B was also assigned as 2 by X-ray crystallography (Hossain, M. B.; van der Helm, D.; Antel, J.; Sheldrick, G. M.; Sanduja, S. K.; Weinheimer, A. J. 14th Meeting International Union of Crystallography, Perth, Australia, August 12-20, 1987).

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Substitution Reactions of Sodium Tetracarbonylcobaltate(1-)

Ferenc Ungváry*[†] and Andrew Wojcicki*

Department of Chemistry, The Ohio State University Columbus, Ohio 43210 Received May 4, 1987

Salts of $[Co(CO)_4]^-$ have been extensively used in the synthesis of various cobalt(I) carbonyl derivatives via oxidative addition reactions^{1,2} and in catalytic carbonylation of aliphatic and aromatic halides, where an oxidative addition step is critical to the catalytic cycle.³ Recently, the possibility of ligand substitution in [Co-(CO)₄]⁻ upon irradiation was proposed based on the observation that alcoholic solutions of $[Co(CO)_4]^-$ catalyze the hydroformylation of olefins under photochemical conditions.⁴ However, salts of $[Co(CO)_4]^-$ have been regarded as inert to substitution of the carbonyl groups under thermal conditions.⁵

Herein we report the first⁶ direct evidence of the facile substitution of CO in Na[Co(CO)₄] by ¹³CO, phosphites, phosphines, and activated olefins which may provide new impetus for catalytic applications.

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Solutions of Na[Co(CO)₄] in THF under 1 atm of ¹³CO undergo rapid equilibration according to eq 1.7 The presence of

$$Na[Co(CO)_4] + x^{13}CO \rightleftharpoons Na[Co(^{13}CO)_x(CO)_{4-x}] + xCO$$
(1)

15-crown-5 ether dramatically slows down the exchange, and use of PPN⁺⁸ as the counterion affords no observable reaction at room temperature in 48 h. The lability of the Li⁺ and K⁺ salts of $[Co(CO)_4]^-$ is qualitatively similar to that of Na $[Co(CO)_4]$. These results indicate that ion-pairing phenomena9 play an important role in ligand replacement reactions of [Co(CO)₄]^{-. 13}CO exchange is inhibited by the presence of PPh₃¹⁰ to suggest that a 16-electron $[Co(CO)_3]^-$ may be involved in the reaction.

If a stream of Ar is used to remove CO, Na[Co(CO)₄] readily reacts with phosphites and phosphines according to eq 2, with the

$$Na[Co(CO)_4] + PR_3 \rightleftharpoons Na[Co(CO)_3PR_3] + CO \quad (2)$$

$$R = OPh, O-n-Bu, Ph, n-Bu$$

most facile substitution occurring for P(OPh)₃.¹¹ UV irradiation of the reaction mixtures accelerates these substitution processes. The reverse reaction proceeds readily; e.g., a 0.005 M solution of Na[Co(CO)₃PPh₃] in THF absorbs 1 mol of CO in less than 2 min at -10 °C.¹²⁻¹⁴ The uptake of CO is slower in the presence of PPh₃. The kinetics of this reaction, measured by following the initial rates of absorption of CO, show first-order dependence on the concentration of each of Na[Co(CO)₃PPh₃] and CO and an inverse first-order dependence on the concentration of PPh₃.^{15,16}

The PR_3 in $Na[Co(CO)_3PR_3]$ can be replaced not only by CO but also by a less basic ligand PR'₃. IR and ³¹P NMR spectra of a reaction mixture derived from a 1:1 molar ratio of Na[Co-(CO)₃PPh₃] and P(OPh)₃ at 25 °C under Ar showed that ligand exchange (eq 3) is essentially complete in 30 min. Similar ex-

$$Na[Co(CO)_{3}PPh_{3}] + P(OPh)_{3} \rightleftharpoons Na[Co(CO)_{3}P(OPh)_{3}] + PPh_{3} (3)$$

periments with different combinations of free and ligated $P(n-Bu)_3$, PPh_3 , $P(O-n-Bu)_3$, and $P(OPh)_3$ revealed that the more basic ligand can be replaced by a less basic one¹⁷ to establish equilibrium.

Activated olefins (L) react with $Na[Co(CO)_4]$ in THF solution to form mono- and disubstituted derivatives in equilibrium re-

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(10) No incorporation of ¹³CO could be detected after 10 min in the IR spectrum of a 0.03 M solution of $Na[Co(CO)_4]$ in THF at 28 °C in the presence of a 38-fold molar excess of PPh₃ under 1 atm of ¹³CO. After 60 min of reaction time, ν (¹³CO) bands appeared at 1862, 1851, and 1820 cm⁻¹, and the intensity of the original ν (¹²CO) band at 1888 cm⁻¹ decreased by about 20%. Essentially complete scrambling was observed after 20 h.

(11) Refluxing a 1:1 molar mixture of Na[Co(CO)₄] and P(OPh)₃ (0.06 M) in THF with a slow passage of Ar for 30 min gave virtually complete monosubstitution: IR (THF) 1959 (s), 1883 (vs), 1842 (s), 1594 (m) cm⁻¹; ³¹P NMR (THF, 100 MHz, 200 K) δ 175. These spectra are identical with those of the Na/Hg reduction product of Co₂(CO)₆[P(OPh)₃]₂: Hieber, W.; Lindner, E. Chem. Ber. 1961, 94, 1417–1425.

(12) It has been shown that PMe₃ in K[Co(PMe₃)₄]¹³ and P(OPh)₃ in Na[Co(P(OPh)₃)₄]¹⁴ can be successively replaced by CO.
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(15) $k_{obsd} = (4.5 \pm 0.3) \times 10^{-5} \text{ s}^{-1}$ at 0 °C for the initial concentration ranges 2.75 × 10⁻³ – 2.2 × 10⁻² M Na[Co(CO)₃PPh₃], 0.05–0.54 M PPh₃, and 2.9 × 10⁻³ – 9.5 × 10⁻³ M CO.¹⁶

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[†]On leave from the University of Veszprém, Hungary.

⁽⁷⁾ Complete scrambling was observed in 10 min at 25 °C for a 0.04 M (a) PPN⁺ = bis(triphenylphosphine)nitrogen(1+) ion.