Total Synthesis of Didemnins A, B, and C[1,2]

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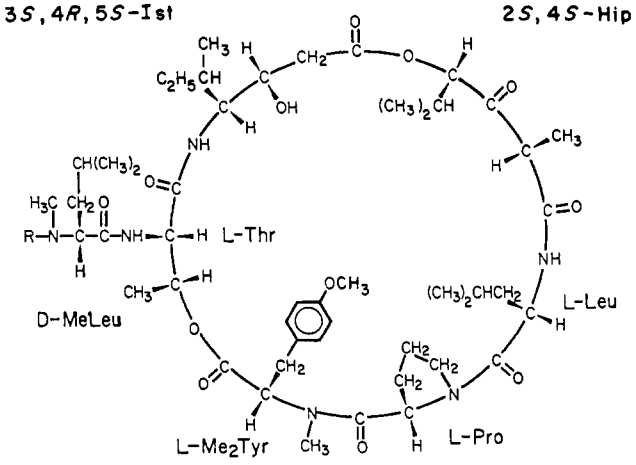
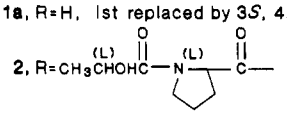
The cyclic depsipeptide didemnin B (**2**),[3] isolated from the tunicate *Tridemnum solidum*,[4] is the first marine natural product to enter clinical trials as a potential anticancer agent.[5] It has also been reported recently to be exceedingly active as an immunosuppressive agent in vitro and in 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 (3*S*,4*R*)-statine instead of (3*S*,4*R*,5*S*)-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**).

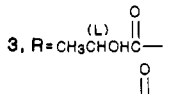
By far the most difficult part of the synthesis involved preparation of didemnin A, and we first synthesized the previously proposed isomer **1a**. Major considerations were the unavailability of the two novel subunits, (2*S*,4*S*)-Hip[2a] and (3*S*,4*R*)-statine (Sta),[3c] and the proclivity of Hip 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 (3*S*,4*R*)-isomer of Boc-Sta-OEt, after HPLC purification of the crude mixture of (3*S*,4*R*)- and (3*R*,4*R*)-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-leucine[9] and *N*,*O*-dimethyltyrosine,[10] were employed



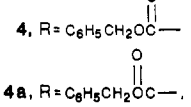
1, R=H
1a, R=H, Ist replaced by 3*S*, 4*R*-Sta



2, R=CH3CHOHC(L)—N(L)—C

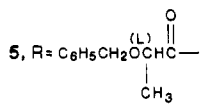


3, R=CH3CHOHC(L)—

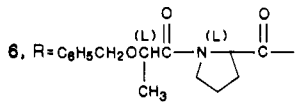


4, R=C6H5CH2OC—

4a, R=C6H5CH2OC—, Ist replaced by 3*S*, 4*R*-Sta



5, R=C6H5CH2OCHC(L)—



6, R=C6H5CH2OCHC(L)—N(L)—C

in the total synthesis as Z-D-MeLeu-OH and Me_2Tyr-ONb, respectively, prepared by reported methods for methylation[9] of Z derivatives and *p*-nitrobenzyl esterification.[10]

Synthesis of ethyl α-(α-(benzyloxy)isovaleryl)propionate (Bzl-Hip-OEt) was achieved by coupling (2*S*)-2-(benzyloxy)-3-methylbutanoyl chloride (prepared from L-valine) with the magnesium enolate of ethyl hydrogen methylmalonate to give a mixture of the ethyl (2*R*,4*S*)- and (2*S*,4*S*)-4-(benzyloxy)-2,5-dimethylhexanoates 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 2*R*,4*S*- and 2*S*,4*S*-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-OTMSe[11] (H_2, Pd/C) → H-Leu-OTMSe) and H-Thr-OTMSe (Z-Thr(*t*-Bu)-OTMSe[11] (TMS-I) → 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.

(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.

(3) (a) Rinehart, K. L., Jr.; Gloer, J. B.; Hughes, R. G., Jr.; Renis, H. E.; McGovren, J. P.; Swynenberg, E. B.; Stringfellow, D. A.; Kuentzel, S. L.; Li, L. H. *Science (Washington, D.C.)* **1981**, *212*, 933-935. (b) Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857-1859. (c) Rinehart, K. L., Jr.; Cook, J. C., Jr.; Pandey, R. C.; Gaudioso, L. A.; Meng, H.; Moore, M. L.; Gloer, J. B.; Wilson, G. R.; Gutowsky, R. E.; Zierath, P. D.; Shield, L. S.; Li, L. H.; Renis, H. E.; McGovern, J. P.; Canonico, P. G. *Pure Appl. Chem.* **1982**, *54*, 2409-2424.

(4) Demattè, N.; Guerriero, A.; De Clauser, R.; De Stanchina, G.; Lafargue, F.; Cuomo, V.; Pietra, F. *Comp. Biochem. Physiol.* **1985**, *81B*, 479-484. *T. solidum*, *T. cyanophorum*, and *T. palmae* all contain didemnins A and B (Monniot, F.; Bible, K. C.; Rinehart, K. L., unpublished observation).

(5) Chun, H. G.; Davies, B.; Hogh, D.; Suffness, M.; Plowman, J.; Flora, K.; Grieshaber, C.; Leyland-Jones, B. *Invest. New Drugs* **1986**, *4*, 279-284.

(6) Montgomery, D. W.; Zukoski, C. F. *Transplantation* **1985**, *40*, 49-56.

(7) The assignment of 2*S*,4*S* stereochemistry to the hydroxyisovaleryl-propionic acid (Hip) residue of the didemnins was very recently confirmed by others (Ewing, W. R.; Bhat, K. L.; Joullie, M. M. *Tetrahedron* **1986**, *42*, 5863-5868); they were apparently unaware of our earlier reports.[1a,b,2a]

(8) (a) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624-3626. (b) Liu, W.-S.; Smith, S. C.; Glover, G. I. *J. Med. Chem.* **1979**, *22*, 577-579. (c) Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016-3018.

(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° (*c* 2.3, EtOH); the latter was reported to have mp 73-74 °C, $[\alpha]^{25}_D$ -23° (*c* 1, EtOH).

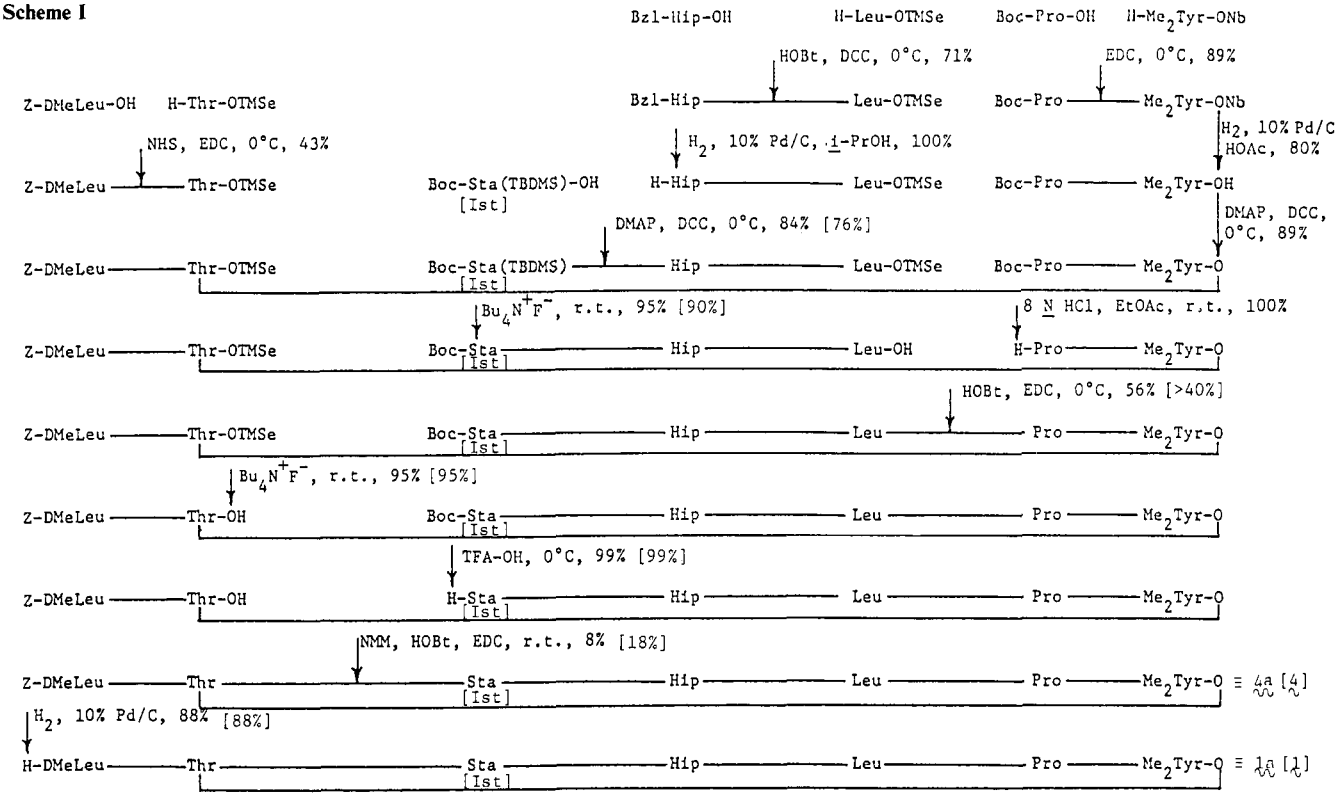
(10) *N*,*O*-Dimethyltyrosine (Marner, F.-J.; Moore, R. E.; Hirotsu, K.; Clardy, J. *J. Org. Chem.* **1977**, *42*, 2815-2819) was made by sodium/liquid ammonia reduction (Jošt, K.; Rudinger, J. *Coll. Czech. Chem. Commun.* **1961**, *26*, 2345-2354) of *N*,*O*-dimethyl-*N*-tosyltyrosine (Fischer, E.; Lipschitz, W. *Ber.* **1915**, *48*, 360-378) and converted to the *p*-nitrobenzyl ester salt [HMe_2Tyr-ONb-*p*-TsOH, mp 130 °C, $[\alpha]^{20}_D$ +19° (*c* 2.06, $CHCl_3$)] 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.

0002-7863/87/1509-6846$01.50/0

Scheme I



Abbreviations: Bzl, benzyl; TMSe, β-trimethylsilylethyl; Boc, t-butyloxycarbonyl; nB, p-nitrobenzyl; Z, benzyloxycarbonyl; TBDMS, t-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 (2*R*,4*S*)- and (2*S*,4*S*)-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 (SiO_2) 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, $C_2H_5CH(CH_3)CHNH_2CHOHCH_2COOH$, rather than statine, $(CH_3)_2CHCH_2CHNH_2CHOHCH_2COOH$, and the isostatine isomer was shown by synthesis from D-alloisoleucine[1d,14] and ^1H NMR spectra of its lactam derivative $C_2H_5CH(CH_3)$-CHCH(OAc)CH_2CONH to have the stereochemistry 3*S*,4*R*,5*S*, assigning the structure as **1**.

Accordingly, the didemnin A synthesis was repeated as shown in Scheme I but by employing 3*S*,4*R*,5*S*-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 μg/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

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

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 azide[15] with L-Pro-OMe,[16] followed by hydrolysis and conversion to the symmetrical anhydride $(Bzl\text{-}Lac\text{-}Pro)_2O$, 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 ^{13}C 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

$$\text{Bzl-Lac-OEt} \xrightarrow[(2)\ i\text{-}C_5H_{11}ONO\ (3)\ \text{H-Pro-OMe}]{(1)\ H_2NNH_2} \text{Bzl-Lac-Pro-OMe} \xrightarrow[(2)\ EDC\ (3)\ \mathbf{1}]{(1)\ NaOH} \mathbf{6} \xrightarrow[Pd/C]{H_2} \mathbf{2}$$

(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.; Covê, 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).

Acknowledgment. This work was supported in part by research grants from the National Institute of Allergy and Infectious Diseases (AI01278, AI04769) and the National Institute of General Medical Sciences (GM27029). We thank Drs. Françoise Monniot, Museum National d'Histoire Naturelle, Paris, France, and Françoise Lafargue, Laboratoire Arago, Banyuls-sur-Mer, France, for tunicate identification and Mark D. Prairie, The Upjohn Co., for CD data.

Substitution Reactions of Sodium Tetracarbonylcobaltate(1-)

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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 first[6] direct evidence of the facile substitution of CO in $Na[Co(CO)_4]$ by ^{13}CO, phosphites, phosphines, and activated olefins which may provide new impetus for catalytic applications.

Solutions of $Na[Co(CO)_4]$ in THF under 1 atm of ^{13}CO undergo rapid equilibration according to eq 1.[7] The presence of

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

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 phenomena[9] play an important role in ligand replacement reactions of $[Co(CO)_4]^-$. ^{13}CO exchange is inhibited by the presence of PPh_3[10] 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

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

$$R = OPh, O\text{-}n\text{-}Bu, Ph, n\text{-}Bu$$

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 $Na[Co(CO)_3PPh_3]$ 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 PPh_3. 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 $Na[Co(CO)_3PPh_3]$ and CO and an inverse first-order dependence on the concentration of PPh_3.[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 ^{31}P NMR spectra of a reaction mixture derived from a 1:1 molar ratio of $Na[Co(CO)_3PPh_3]$ and $P(OPh)_3$ at 25 °C under Ar showed that ligand exchange (eq 3) is essentially complete in 30 min. Similar ex-

$$Na[Co(CO)_3PPh_3] + P(OPh)_3 \rightleftharpoons Na[Co(CO)_3P(OPh)_3] + PPh_3 \quad (3)$$

periments with different combinations of free and ligated $P(n\text{-}Bu)_3$, PPh_3, $P(O\text{-}n\text{-}Bu)_3$, and $P(OPh)_3$ revealed that the more basic ligand can be replaced by a less basic one[17] to establish equilibrium.

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

† On leave from the University of Veszprēm, Hungary.

(1) Review: Kemmitt, R. D. W.; Russell, D. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abels, E. W., Eds.; Pergamon Press: Oxford, U.K., 1982; Vol. 5, pp 1-276.

(2) Some recent examples: (a) Donaldson, W. A.; Hughes, R. P. *J. Am. Chem. Soc.* **1982**, *104*, 4846-4859. (b) Milstein, D.; Huckaby, J. *Ibid.* **1982**, *104*, 6150-6152. (c) Gusbeth, P.; Vahrenkamp, H. *J. Organomet. Chem.* **1983**, *247*, C53-C55. (d) Braunstein, P.; Schubert, U.; Burgard, M. *Inorg. Chem.* **1984**, *23*, 4057-4064. (e) Doyle, G.; Eriksen, K. A. *Organometallics* **1985**, *4*, 877-881. (f) Schulze, W.; Hartl, H.; Seppelt, K. *Angew. Chem.* **1986**, *98*, 189-190. (g) Röper, M.; Schieren, M.; Heaton, B. T. *J. Organomet. Chem.* **1986**, *299*, 131-136.

(3) (a) Heck, R. F.; Breslow, D. S. *J. Am. Chem. Soc.* **1963**, *85*, 2779-2782. (b) Alper, H.; des Abbayes, H. *J. Organomet. Chem.* **1977**, *134*, C11-C14. (c) Cassar, L.; Foa, M. *Ibid.* **1977**, *134*, C15-C16. (d) Francalanci, F.; Foa, M. *Ibid.* **1982**, *232*, 59-70. (e) des Abbayes, H.; Buloup, A.; Tanguy, G. *Organometallics* **1983**, *2*, 1730-1736. (f) Francalanci, F.; Gardano, A.; Abis, L.; Fiorani, T.; Foa, M. *J. Organomet. Chem.* **1983**, *243*, 87-89. (g) Foa, M.; Francalanci, F.; Gardano, A.; Cainelli, G.; Umani-Ronchi, A. *Ibid.* **1983**, *248*, 225-231. (h) Foa, M.; Francalanci, F.; Bencini, E.; Gardano, A. *Ibid.* **1985**, *285*, 293-303. (i) Francalanci, F.; Bencini, E.; Gardano, A.; Vincenti, M.; Foa, M. *Ibid.* **1986**, *301*, C27-C30.

(4) Mirbach, M. J.; Mirbach, M. F.; Saus, A.; Topalsavoglou, N.; Phu, T. N. *J. Am. Chem. Soc.* **1981**, *103*, 7594-7601.

(5) (a) For example, in a recent review the following is stated: "Ionic $[Co(CO)_4]^-$ salts do not undergo substitution reactions"; see ref 1, p 14. (b) Howell, J. A.; Burkinshaw, P. M. *Chem. Rev.* **1983**, *83*, 557-599.

(6) After this paper was submitted for publication, we have learned that thermal and photochemical substitution reactions of $[Co(CO)_4]^-$ were studied by Ellis and Winzenburg who isolated salts of several $[Co(CO)_3PR_3]^-$: Winzenburg, M. L. Ph.D. Thesis, University of Minnesota, 1979. We thank Professor J. E. Ellis for making this information available to us.

(7) Complete scrambling was observed in 10 min at 25 °C for a 0.04 M solution: $Na[Co(^{13}CO)_4]$ IR (THF) 1845 (vs br), 1814 (s) cm^{-1}.

(8) PPN^+ = bis(triphenylphosphine)nitrogen(1+) ion.

(9) (a) Schussler, D. P.; Robinson, W. R.; Edgell, W. F. *Inorg. Chem.* **1974**, *13*, 153-158. (b) Recent review: Darensbourg, M. Y. *Prog. Inorg. Chem.* **1985**, *33*, 221-274.

(10) No incorporation of ^{13}CO 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 PPh_3 under 1 atm of ^{13}CO. After 60 min of reaction time, ν (^{13}CO) bands appeared at 1862, 1851, and 1820 cm^{-1}, and the intensity of the original ν (^{12}CO) 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}; ^{31}P NMR (THF, 100 MHz, 200 K) δ 175. These spectra are identical with those of the Na/Hg reduction product of $Co_2(CO)_6[P(OPh)_3]_2$: Hieber, W.; Lindner, E. *Chem. Ber.* **1961**, *94*, 1417-1425.

(12) It has been shown that PMe_3 in $K[Co(PMe_3)_4]$[13] and $P(OPh)_3$ in $Na[Co(P(OPh)_3)_4]$[14] can be successively replaced by CO.

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