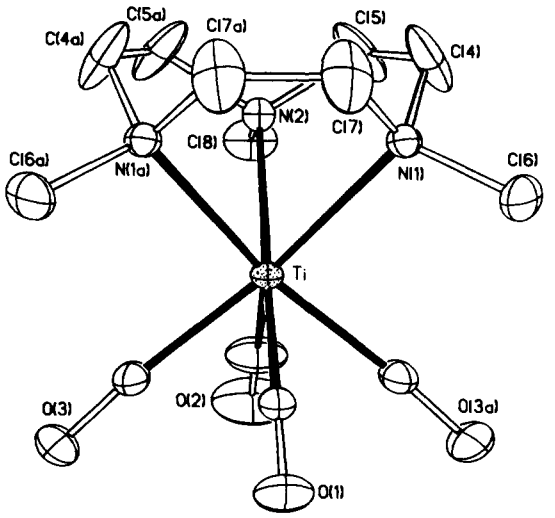


Figure 1. ORTEP drawing and labeling scheme for (1,4,7-trimethyl-1,4,7-triazacyclononane)tetracarbonyltitanium(0). Thermal ellipsoids are drawn with 35% probability boundaries, and hydrogen atoms are omitted for clarity. Selected interatomic distances (Å) and angles (deg): Ti–C(1) = 1.979 (6), Ti–C(2) = 2.009 (8), Ti–C(3) = 1.999 (5), Ti–N(1) = 2.378 (3), Ti–N(2) = 2.368 (4), C(1)–O(1) = 1.176 (7), C(2)–O(2) = 1.153 (10), C(3)–O(3) = 1.171 (6), C(1)–Ti–C(2) = 104.6 (3), C(1)–Ti–C(3) = 69.0 (2), C(2)–Ti–C(3) = 66.7 (2).

appear to have about the same donor ability to respective (tetracarbonyl)metal(0) units. By comparison, the tertiary amine products, **2** and **5**, have ν(CO) values closer to those of the corresponding $[(C_5H_5)M(CO)_4]^-$,[13] indicating that Me_3tacn is a somewhat weaker donor than tacn in these seven-coordinate complexes, perhaps for steric reasons. Interestingly, these vibrational data suggest that tacn is the strongest neutral donor ligand to zerovalent group 4 carbonyls presently known.

The molecular structure of **5** was determined by a single-crystal X-ray study and is shown in Figure 1, along with selected interatomic data. The metal–ligand coordination core is an unexceptional 4:3 piano stool, where the average Ti–C and C–O distances of 1.996 (6) and 1.167 (10) Å are in the range of corresponding values observed previously for the structurally related $[(C_5H_5)Ti(CO)_4]^-$: 1.994 (4) and 1.146 (6) Å, respectively.[13] A similar molecular structure has also been reported for $[t\text{-}BuSi(CH_2PMe_2)_3]Ti(CO)_4$.[15] As expected, the average Ti–N distance, 2.375 (4) Å, for this Ti(0) complex is longer than corresponding distances, 2.20–2.30 Å, recently reported for a series of Ti(III,IV) complexes containing Me_3tacn.[16] The coordinated Me_3tacn ligand in **5** has essentially the same interatomic distances and angles as those previously observed for other mononuclear complexes containing this ligand.[9,16,17]

In summary, labile phosphine carbonyls of zerovalent titanium, zirconium, and hafnium have been utilized as convenient synthetic equivalents of the corresponding unknown metal heptacarbonyls, $M(CO)_7$, in the synthesis of the first examples of amine complexes containing group 4 elements in their zero oxidation state. Extensions of this study are in progress.

Acknowledgment. We thank the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, for support of this research, and J.E.E. is grateful to Professor Karl Wieghardt for helpful discussions concerning this work.

Supplementary Material Available: Crystallographic details for $[Me_3tacn]Ti(CO)_4$ including tables of atomic coordinates, thermal parameters, bond angles, and bond lengths (5 pages); listing of observed and calculated structure factors for $[Me_3tacn]Ti(CO)_4$ (4 pages). Ordering information is given on any current masthead page.

(1) Highly Reduced Organometallics. 31. Part 30: Blackburn, D. W.; Britton, D.; Ellis, J. E.; *Angew. Chem., Int. Ed. Engl*, in press.
(2) Sikora, D. J.; Macomber, D. W.; Rausch, M. D. *Adv. Organomet. Chem.* **1986**, *25*, 317 and references cited therein.
(3) Abbreviations: dmpe = 1,2-bis(dimethylphosphino)ethane; trmpe = 1,1,1-tris(dimethylphosphinomethyl)ethane; tacn = 1,4,7-triazacyclononane; Me_3tacn = 1,4,7-trimethyl-1,4,7-triazacyclononane; THF = tetrahydrofuran; DME = 1,2-dimethoxyethane.
(4) Chi, K. M.; Frerichs, S. R.; Stein, B. K.; Blackburn, D. W.; Ellis, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 163.
(5) Blackburn, D. W.; Chi, K. M.; Frerichs, S. R.; Tinkham, M. L.; Ellis, J. E. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 437.
(6) Reactions of $M(CO)_4$(trmpe) with other Lewis bases are presently under investigation. Ellis, J. E. Unpublished research.
(7) (a) Wender, I.; Pino, P.; *Organic Synthesis via Metal Carbonyls*; Wiley-Interscience: New York, 1968. (b) Manuel, T. A. *Adv. Organomet. Chem.* **1965**, *3*, 181. (c) Abel, E. A.; Tyfield, S. P. *Adv. Organomet. Chem.* **1970**, *8*, 117. (d) Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds. *Comprehensive Organometallic Chemistry*; Pergamon: Oxford, 1982; Vols. 3–6.
(8) Chi, K. M.; DiMaio, A. J.; Ellis, J. E. Unpublished research.
(9) Chaudhiri, P.; Wieghardt, K. *Prog. Inorg. Chem.* **1988**, *35*, 329 and references cited therein.
(10) Satisfactory elemental analyses (C, H, N) have been obtained for compounds **1–5**.
(11) IR, ν(CO): (**1**) 1916 (m), 1769 (s) in DME; (**2**) 1923 (m), 1774 (s) in DME; (**3**) 1915 (m), 1774 (s) in DME; (**4**) 1916 (m), 1772 (s) in CH_3CN; (**5**) 1920 (m), 1776 (s) in CH_3CN, cm^{-1}.
(12) For example, for $[(C_5Me_5)Ti(CO)_4]^-$, ν(CO): 1914 (m), 1769 (s) cm^{-1} in DME. Kelsey, B. A.; Ellis, J. E. *J. Chem. Soc., Chem. Commun.* **1986**, 331.
(13) For example, for $[(C_5H_5)Ti(CO)_4]^-$, ν(CO): 1921 (m), 1777 (s) cm^{-1} in THF. Kelsey, B. A.; Ellis, J. E. *J. Am. Chem. Soc.* **1986**, *108*, 1344.
(14) Dark red single crystals of **5** were obtained from CH_3CN/Et_2O at 0 °C. Crystal data: orthorhombic, *Pnma*, a = 16.759 (3) Å, b = 11.769 (3) Å, c = 7.869 (2) Å, V = 1552.1 (6) Å^3, Z = 4, D(calcd) = 1.417 g cm^{-3}, μ(Mo Kα) = 11.62 cm^{-1}, T = 298 K; crystal dimensions, 0.51 × 0.48 × 0.39 mm^3. The intensities of 1941 reflections were measured ($4° \le 2\theta \le 55°$) on a Nicolet R3m diffractometer using Mo Kα radiation. The structure was solved by direct methods, and all non-hydrogen atoms were refined anisotropically (full matrix least squares). Hydrogen atoms were included as idealized isotropic contributions. For 1748 independent reflections, 1271 were observed ($5\sigma F$). At convergence $R(F)$ = 0.0611 and $R(wF)$ = 0.0669. SHELXTL software, Nicolet. Madison, WI. Further data are available as supplementary material.
(15) Gardner, T. G.; Girolami, G. S. *Organometallics* **1987**, *6*, 2551.
(16) Bodner, A.; Jeske, P.; Weyhermüller, T.; Wieghardt, K.; Dubler, E.; Schmalle, H.; Nuber, B. *Inorg. Chem.* **1992**, *31*, 3737.
(17) Backes-Dahmann, G.; Herrmann, W.; Wieghardt, K.; Weiss, J. *Inorg. Chem.* **1985**, *24*, 485.

Total Synthesis of Lactacystin

E. J. Corey* and Gregory A. Reichard

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

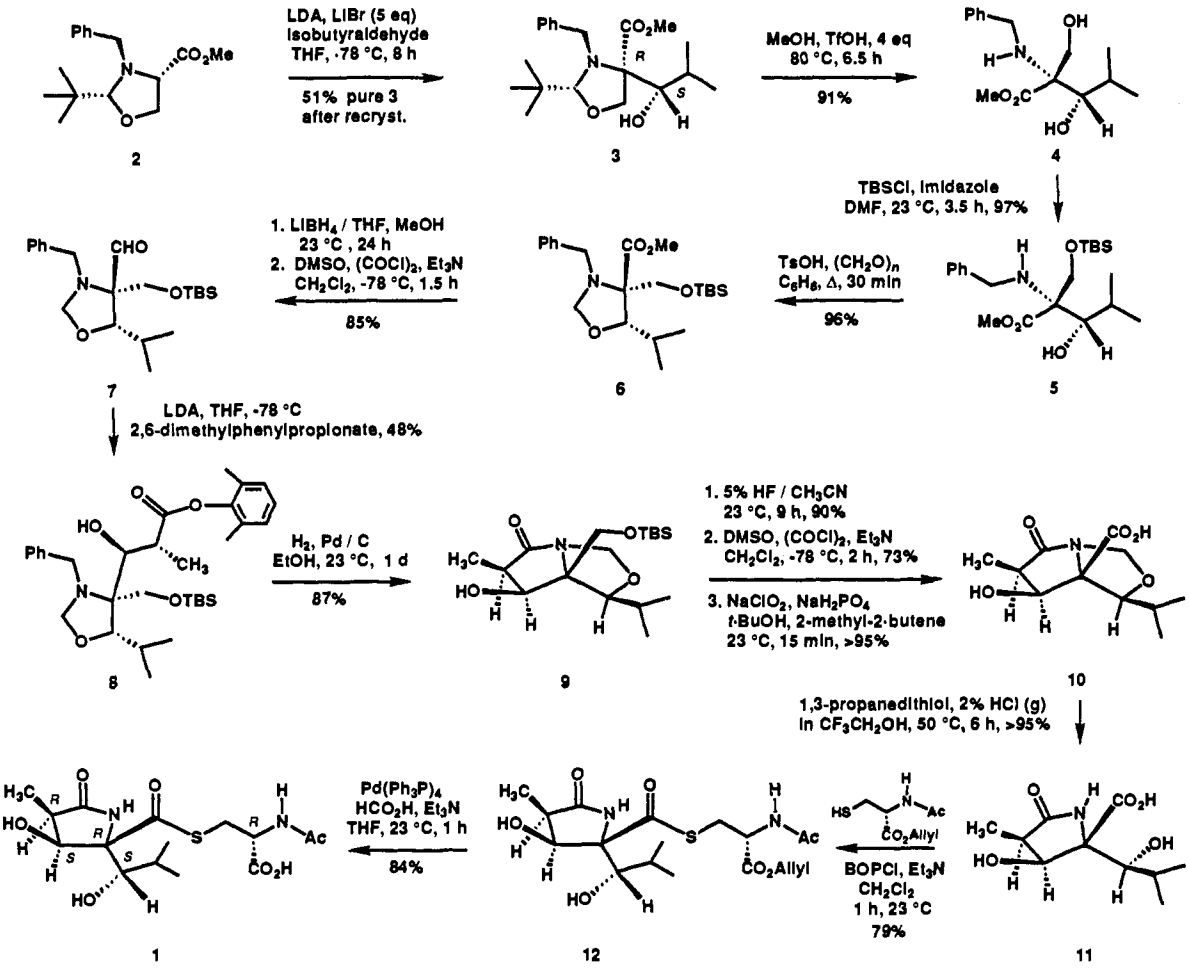
Received September 14, 1992

Lactacystin (**1**) is a novel microbial product which was identified by Ōmura et al. after screening several thousand culture samples for the capacity to induce differentiation in a neuroblastoma cell line.[1,2] The great current interest in neurotrophic proteins, e.g., nerve growth factor, as therapeutic agents and neuroscience research tools[3-6] and the scarcity of **1** encouraged us to undertake the synthesis which is described herein. The availability of synthetic **1** should help to establish whether it is the first non-protein to possess useful neurotrophic activity.

N-Benzylserine methyl ester[7a] was transformed into the *cis*-oxazolidine derivative **2**,[7b] whose structure was confirmed by a ^{1}H NMR NOE study, together with the C(2) diastereomer (ratio 9:1); see Scheme I. The 9:1 mixture was converted via the lithium enolate–lithium bromide complex with isobutyraldehyde into one principal aldol product (**3**), which was obtained in 77% yield and >98% diastereomeric purity by trituration of the crude aldol

0002-7863/92/1514-10677$03.00/0 © 1992 American Chemical Society

Scheme I



product with pentane; recrystallization from pentane afforded diastereo- and enantiomerically pure **3** (51%), mp 91–92 °C, the structure of which was confirmed by ^{1}H NMR NOE data. In the absence of lithium bromide, the aldol condensation proceeded with poor stereoselectivity and low yield. Aminal cleavage, silylation, and reaction with H_2CO cleanly effected transformation of **3** to the topologically different oxazolidine system **6** (via **4**, mp 66–67 °C, and **5**), after which COOMe → CHO conversion provided the key intermediate **7**. Aldol reaction of **7** under the Pirrung–Heathcock anti-aldol conditions[8] afforded the desired aldol stereoisomer **8** in 48% yield after silica gel chromatographic purification.[9] Catalytic hydrogenation of **8** gave the bicyclic lactam **9**, mp 83–85 °C, the stereochemistry of which was demonstrated by ^{1}H NMR NOE studies. Desilylation of **9** and selective oxidation of CH_2OH to COOH[10] afforded acid **10**, from which the *N/O* methylene bridge was removed by acid-catalyzed transfer of methylene to 1,3-propanedithiol to form **11** (mp 240 °C dec). The carboxylic acid function of **11** could be esterified selectively without hydroxyl protection by reaction with bis(2-oxo-3-oxazolidinyl)phosphinic chloride–Et_3N and *N*-acetylcysteine allyl ester to form the allyl ester of lactacystin **12** (mp 182–184 °C; $[\alpha]^{23}_D$ +34.4° (*c* 0.5, acetone)). Deallylation of **12** using triethylammonium formate–Pd(0), removal of volatiles in vacuo, trituration with HOAc–EtOAc, and addition of a small amount of water afforded pure synthetic lactacystin (**1**) as colorless needles (mp 233–235 °C dec; $[\alpha]^{23}_D$ +78.6° (*c* 0.5, methanol)). Chromatographic, ^{1}H and ^{13}C NMR, FTIR, and mass spectral comparison of synthetic **1** with an authentic sample, kindly provided by Dr. S. Ōmura, confirmed its identity.[11]

This first total synthesis of **1** includes a number of key steps which are of broader interest, including the aldol couplings to form **3** and **8** and the various functional group manipulations involving internal protection and group selectivity. The yields are generally good and very little chromatography is involved so that sizable amounts of synthetic **1** can be produced.[12]

Supplementary Material Available: Detailed experimental procedures for each step in the synthesis of **1** and listings of physical data for compounds **1–12**, including ^{1}H NMR NOE studies for assignment of stereochemistry to **2**, **3**, **9**, and the anti-aldol diastereomer of **9** (17 pages). Ordering information is given on any current masthead page.

(1) Ōmura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113–116.
(2) Ōmura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117–118.
(3) Levi-Montalcini, R. *Science* **1987**, *237*, 1154–1162.
(4) McDonald, N. Q.; Lapatto, R.; Murray-Rust, J.; Gunning, J.; Wlodawer, A.; Blundell, T. L. *Nature* **1991**, *354*, 411–414.
(5) Bothwell, M. *Cell* **1991**, *65*, 915–918.
(6) Rosenberg, S. *Annu. Rep. Med. Chem.* **1992**, *27*, 41–48.
(7) (a) Thompson, C. M.; Frick, J. A.; Green, D. L. C. *J. Org. Chem.* **1990**, *55*, 111–116. (b) See: Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194–1217.
(8) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727–1728.
(9) The alternative anti-aldol product derived from attack of the enolate at the opposite face of the formyl group of **7** which was also formed (ca. 30%) could be separated chromatographically from the more polar **8**. The optimization of this step is now under study.
(10) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574–5576.
(11) We are grateful to Dr. Omura for encouragement and assistance to this research.
(12) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.