Enantioselective Total Synthesis of Lankacidin C

Andrew S. Kende,* Kevin Koch, Gilbert Dorey, István Kaldor, and Kun Liu

Department of Chemistry, University of Rochester Rochester, New York 14627-0216

Received July 12, 1993

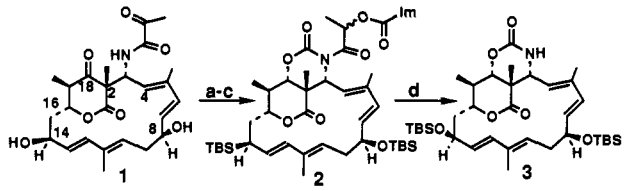
The lankacidins, represented by lankacidin C (**1**), comprise a group of structurally unique, orally active antibiotics with substantial *in vivo* antitumor activity.[1] Because of the lankacidins' instability to both acids and bases,[1c,2] chemical transformations of the intact antibiotics have been limited, and only a few approaches to their total synthesis have been reported.[3] We now describe the first total synthesis of natural (-)-lankacidin C (**1**) by a convergent, enantioselective sequence starting from D-arabinose and L-aspartic acid, proceeding through the tricyclic carbamate **3** as an advanced relay intermediate. Structure **3** was chosen because it precluded the known degradative chemistry of this system.[1c,2] To this end, natural **1** was silylated and reduced (Scheme I) to give a 1:1 mixture of C(2′)-diol epimers, of which the less-polar isomer[4] was reacted with Im_2CO to yield **2**. Selective deacylation of **2** with LiOOH[5] gave a 98% yield of the stable relay **3**, mp 186–187 °C, $[\alpha]^{22}_D = -68.3°$.

The enantiopure C(12)–C(18) segment was prepared (Scheme II) from the known dithioacetal **4**, derived in 43% yield from D-arabinose.[6] The aldehyde **5** reacted with the crotylborane shown to give 58% of the adduct **6**,[7] which was smoothly transformed to the ester **7**. Oxidative cleavage produced the unstable noraldehyde **8**, which was directly converted by the Takai method[8] to the iodoalkene **9a** and then to the acid **9b**.

Stereoselective acylation by **9c** of the Li enolate **10**[9] gave a β-ketolactam, reduced by KEt_3BH to the single carbinol **11** (Scheme III).[10] As explored earlier by Koch, **11** was desilylated and subjected to $MeSO_3H$-catalyzed N → O acyl migration and then Im_2CO trapping to yield **12**.[3c,9] Hydrolysis, Dess–Martin oxidation,[11] and PMB scission gave the stable iodoaldehyde **13**.

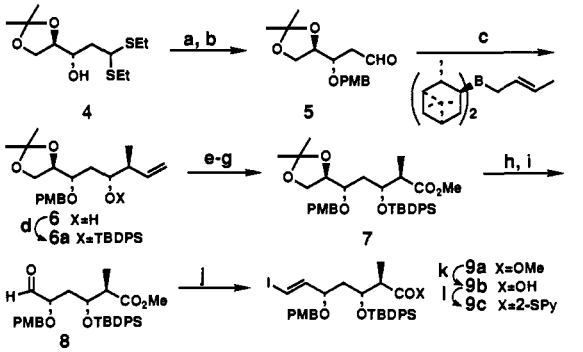
Lynchpin closure of **13** to relay **3** was achieved (Scheme IV) by Stille coupling of **13** with the stannane **14**[12] to give the tetraene **15a**. The chloride **15b** was reacted with TMSCN and then cyclized with LiHMDS at -78 °C to yield on hydrolysis the tetraenone **16**.[13] The stereospecific reduction at C(8) was achieved by the (*R*)-CBS method[14] to give 89% of the 8β-ol, which on silylation gave crystalline **3**, mp 187–188 °C, $[\alpha]^{22}_D = -69.9°$, indistinguishable by mmp, TLC, ^1H NMR, ^{13}C NMR, IR, and FAB HRMS from **3** made from natural **1**.

Scheme I[a]



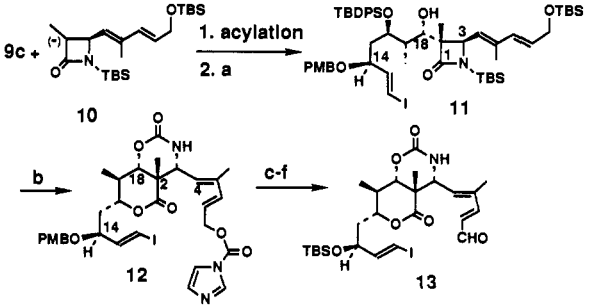
[a] (a) Imidazole, TBSCl, DMF, rt, 100%. (b) $NaBH_4$, MeOH, rt, 99%. (c) 1,1′-Carbonyldiimidazole, LiHMDS, THF, -78 °C, 92% (from the less polar isomer). (d) LiOOH, THF–H_2O (3:1), 98%.

Scheme II[a]



[a] (a) NaH, PMBCl, DMF, rt, 91%. (b) $HgCl_2$, $CaCO_3$, MeCN–H_2O, 77%. (c) Chiral borane reagent, NaOH, H_2O_2, THF, 55%. (d) TBDPSCl, imidazole, DMF, rt, 48 h, 84%. (e) O_3, Sudan III, Me_2S, CH_2Cl_2–CH_3OH (1:1), -78 °C. (f) $NaClO_2$, rt, 78% (two steps). (g) CH_2N_2, 87%. (h) $CuCl_2$, MeOH, reflux for 1 h, 97%. (i) $Pb(OAc)_4$, THF, 0–5 °C. (j) $CrCl_2$, CHI_3, THF, 62% (two steps). (k) LiOH, THF–H_2O–MeOH (6:3:2), rt, 12 h. (l) PySSPy, Ph_3P, THF, rt, 15 h, 79% (two steps).

Scheme III[a]



[a] (a) KEt_3BH, Et_2O, -78 °C. (b) Bu_4NF, THF, rt, 2 h; MsOH, rt, 2 h; 1,1′-carbonyldiimidazole, NEt_3, rt, 12 h, 75% (two steps). (c) HCl (0.14 M), H_2O–dioxane (1:1), rt, 8 h, 70%. (d) Dess–Martin periodinane, CH_2Cl_2, 85%. (e) CAN, MeCN–H_2O, 97%. (f) TBSCl, imidazole, 79%.

(1) (a) Uramoto, M.; Ōtake, H.; Ogawa, Y.; Yonehara, H.; Marumo, F.; Saito, Y. *Tetrahedron Lett.* **1969**, *27*, 2249. (b) Harada, S.; Kishi, T. *Chem. Pharm. Bull.* **1974**, *22*, 99. (c) Harada, S. *Chem. Pharm. Bull.* **1975**, *23*, 2201 and earlier citations in the above references. (d) Ootsu, K.; Matsumoto, T.; Harada, S.; Kishi, T. *Cancer Chemother. Rep., Part 1* **1975**, *59*, 919.

(2) For an illustration of this instability, see: McFarland, J. W.; Pirie, D. K.; Retsema, J. A.; English, A. R. *Antimicrob. Agents Chemother.* **1984**, *25*, 226.

(3) (a) Fray, M. J.; Thomas, E. J. *Tetrahedron* **1984**, *40*, 673. (b) Thomas, E. J.; Williams, A. C. *J. Chem. Soc., Chem. Commun.* **1987**, 992. (c) Kende, A. S.; Luzzio, M. J.; Koch, K. In *Chemistry and Biotechnology of Biologically Active Natural Products, Proceedings of the Fourth International Conference*; Szántay, C., Ed.; Budapest, Hungary, Aug 10–15, 1987; Akad Kiado: Budapest, 1988; p 93, *Chem. Abstr.* **1989**, *111*, 214771m. (d) Rieger, D. L. Ph.D. Thesis, Department of Chemistry, Indiana University, 1989, *Chem. Abstr.* **1990**, *113*, 58758w. (e) Roe, J. M.; Thomas, E. J. *Syn. Lett.* **1990**, 727.

(4) Formation of both C(2′)-carbinols on controlled reduction of **1** has been reported in ref 1b. The C(2′) stereochemistry of the less polar carbinol was subsequently found to be *S* by showing its identity with the synthetic diol **18** made from relay **3** (Scheme V).

(5) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(6) (a) Wong, M. Y. H.; Gray, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 3548. (b) Maehr, H.; Perrotta, A.; Smallheer, J. *J. Org. Chem.* **1988**, *53*, 832.

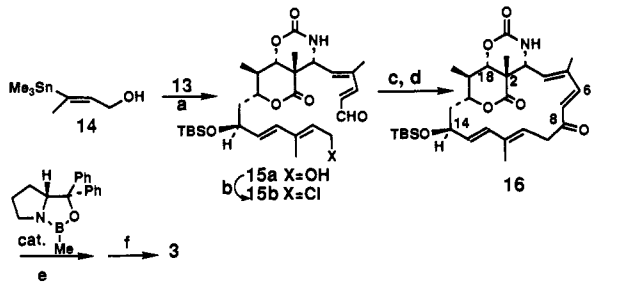
(7) Cf.: Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

(8) Takai, K.; Natta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. This reaction was performed under sonication.

(9) Koch, K. Ph.D. Thesis, Department of Chemistry, University of Rochester, New York, 1988; *Diss. Abstr. Int. B* **1989**, *50*(4), 1416. An account of our β-lactam rearrangement strategy toward lankacidin C, describing a successful prototype rearrangement to form a hydroxypyranone, was reported in August 1987 in Budapest, as cited in ref 3c. For an analogous and independently conceived approach, see refs 3b and 3e. The β-ketolactam corresponding to **10** was synthesized by an efficient sequence from the known 1-(TBS)-4-formylazetidin-2-one, itself derived from L-aspartic acid (Labia, R.; Morin, C. *Chem. Lett.* **1984**, 1007. Salzmann, T. H.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161). Reaction of the above aldehyde with the Li salt of *t*-BuN=CHCH($SiEt_3$)-CH_3 (Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *26*, 2391), followed by $(PhS)_2$/AIBN equilibration of the resulting crude enals, produced the pure (*E*)-α,β-unsaturated aldehyde. A second Schlessinger–Peterson condensation with the Li salt of *t*-BuN=$CHCH_2SiEt_3$ gave on workup the (*E*,*E*)-dienal, which was reduced with $LiBH_4$ (THF, -30 °C), O-silylated (TBSCl, Im, DMF), and C-methylated (LDA, MeI, -78 °C) to give the neutral form of **10** in 30% yield over six steps.

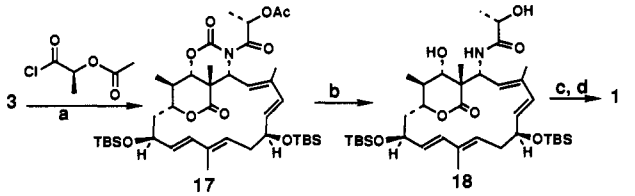
0002-7863/93/1515-9842$04.00/0

Scheme IV[a]



[a] (a) Catalytic $PdCl_2(CH_3CN)_2$, DMF, rt, 90%. (b) 2,6-Lutidine, LiCl, MsCl, DMF, 0 °C. (c) Catalytic KCN/18-crown-6, TMSCN. (d) LiHMDS, THF, −78 °C; AcOH, THF–H_2O, rt, 20 h; 1% aqueous NaOH, 61% from **15a**. (e) Oxazaborole catalyst, BH_3–THF, THF, −10 °C, 89%. (f) TBSCl, imidazole, DMF, rt, 95%.

Scheme V[a]



[a] (a) LiHMDS, THF, −78 °C, 85%. (b) LiOH, THF–H_2O (3:1), 0 °C, 82%. (c) Dess–Martin periodinane, CH_2Cl_2, rt, 96%. (d) HCOOH–THF–H_2O (3:6:1), rt, 3 h, 82%.

The final relay conversion of **3** to **1** by direct alkaline hydrolysis failed. However, when relay **3** (from natural **1**) was acylated as in Scheme V, the *N*-acylcarbamate **17** was formed. Aqueous LiOH at 0 °C gave 82% of the bicyclic amide **18**, which on Dess–Martin oxidation and careful desilylation (aqueous HCO_2H-THF) gave 80% of the target molecule **1**, identical in all respects with the natural antibiotic. This first total synthesis of (−)-**1** proceeds in 30 steps from D-arabinose to relay **3** and proceeds from **3** to **1** over four steps in 55% yield.

Acknowledgment. Partial support of this work by Grant CA-18846, awarded by the National Cancer Institute (NIH), by grants from the French Ministry of Foreign Affairs and l'Institut de Recherches Servier (to G.D.), and by Sherman Clarke Fellowships (to K.K. and K.L.) is gratefully acknowledged. We thank Takeda Chemical Industries for providing us with a sample of Lankacidin C, Dr. Tom Jackson (Kodak Research Laboratories) for the FAB mass spectra, and Mr. Fujii for the resynthesis of β-lactam intermediates.

Supplementary Material Available: Physical and analytical data for **1**, **3**, **6**, **9a**, **10**, **12**, **13**, **15a**, **16**, and **17** (14 pages). Ordering information is given on any current masthead page.

(10) The C(18)-*S* stereochemistry of **11** is assigned from NOE studies on the derived carbamate **12**. Irradiation of the C(2)-Me in **12** gave an NOE of 7% on the *cis*-C(18)–H and one of 9% on the *cis*-C(3)–H. Together with the observed vicinal $J_{17,18}$ = 9.4 Hz, these data suggest a half-chair lactone conformation in **12**, with a H(17)–H(18) dihedral angle of ca. 160° (cf. Fray, M. J.; Thomas, E. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2763). This C(18)–*S* assignment would imply that KEt_3BH–Et_2O reduction of the β-ketolactam derived from acylation of **10** gives a configuration opposite that observed for a structurally related thienamycin precursor lacking the angular methyl substituent (Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208).

(11) For the preparation, use, and possible hazards of the Dess–Martin periodinane, see: Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(12) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263.

(13) Takahashi, T.; Nagashima, T.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 1359.

(14) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. *J. Am. Chem. Soc.* **1987**, *109*, 7925. A 10:1 ratio of chromatographically separable 8β/8α epimers was obtained using the (*R*)-CBS reagent.