Enantioselective Total Synthesis of Lankacidin C

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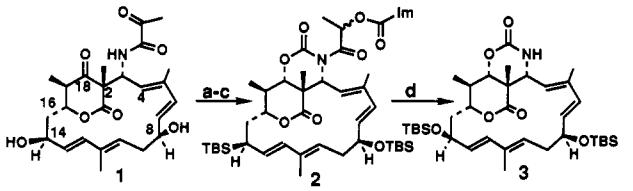
The lankacidins, represented by lankacidin C (**1**), comprise a group of structurally unique, orally active antibiotics with substantial *in vivo* antitumor activity.[1] Because of the lankacidins' instability to both acids and bases,[1c,2] chemical transformations of the intact antibiotics have been 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**.

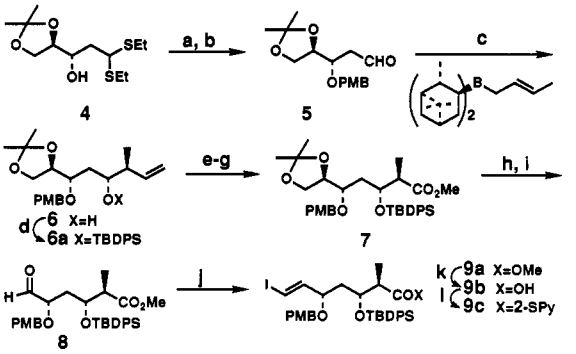
Lynchpin closure of **13** to relay **3** was achieved (Scheme IV) by Stille coupling of **13** with the stannane **14**[12] to give the tetraene **15a**. The chloride **15b** was reacted with TMSCN and then cyclized with LiHMDS at -78 °C to yield on hydrolysis the tetraenone **16**.[13] The stereospecific 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]



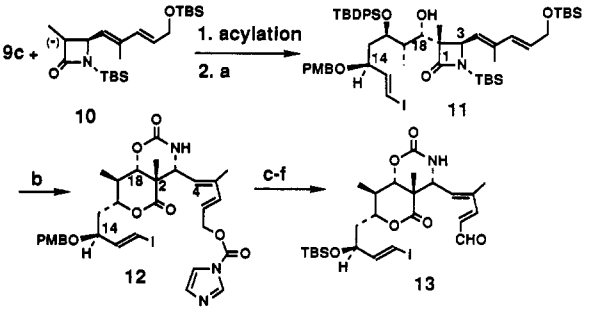
[a] (a) Imidazole, TBSCl, DMF, rt, 100%. (b) $NaBH_4$, MeOH, rt, 99%. (c) 1,1'-Carbonyldiimidazole, LiHMDS, THF, -78 °C, 92% (from the less polar isomer). (d) LiOOH, THF-H_2O (3:1), 98%.

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.

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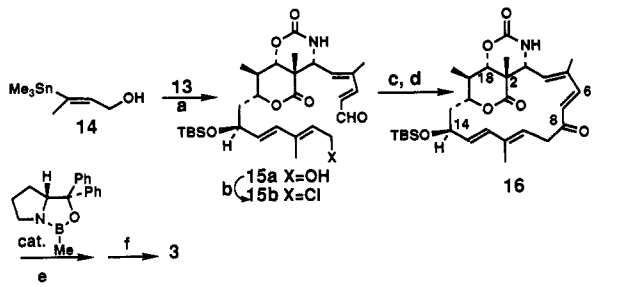
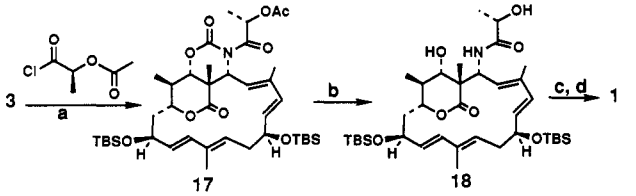
Scheme IV[a]



[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.

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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.