Total Synthesis of (−)-Macrolactin A

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Received October 10, 1996

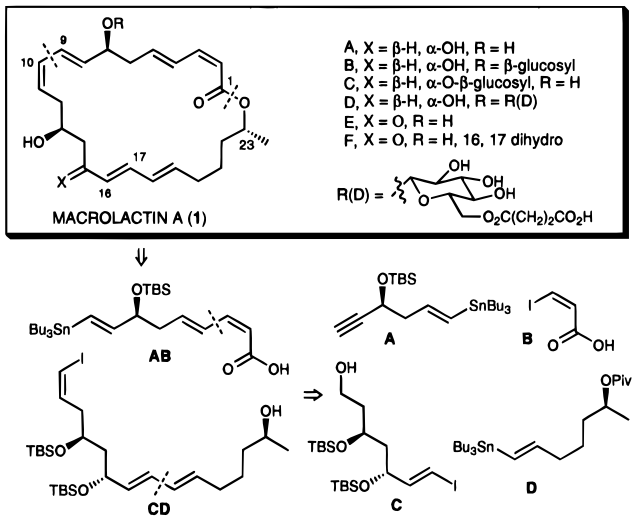
In 1989 Fenical et al. reported the isolation and planar structures of macrolactins A−F, highly unsaturated macrolides produced in culture by a taxonomically unclassifiable deep-sea bacterium.[1] The parent aglycon, (−)-macrolactin A (**1**), inhibits *Herpes simplex* type I and type II viruses with IC_{50} values of 5.0 and 8.3 μg/mL; comparison with its cytotoxicity against the carrier cell lines Hep-2 and MA-104 indicates a potential therapeutic index range of 10−100.[1] In addition, **1** blocks replication of B16-F10 murine tumor cells in vitro (IC_{50} 3.5 μg/mL). Most importantly, macrolactin A protects human T-lymphoblasts against the HIV-1 virus, with optimum effectiveness observed at 10 μg/mL.[1]

The relative and absolute stereochemistries of macrolactins B and F were subsequently assigned via a combination of ^{13}C-NMR analysis, degradation, and chemical correlation.[2] The extreme scarcity of the natural material has precluded elucidation of the three-dimensional architecture of macrolactin A, although it has reasonably been assumed that the identical configurations of congeners B and F are maintained throughout the macrolactin family (Scheme 1).[2]

The current unavailability of macrolactin A from fermentation,[3] juxtaposed with its potential importance in combating the AIDS epidemic, confronts the synthetic community with a challenge of considerable importance.[4,5] In this paper we report the first total synthesis of (−)-**1**. We note in advance that our approach is both concise and versatile, exploiting Stille cross-couplings[6] for stereospecific construction of the three diene moieties and closure of the 24-membered macrocyclic ring.[7]

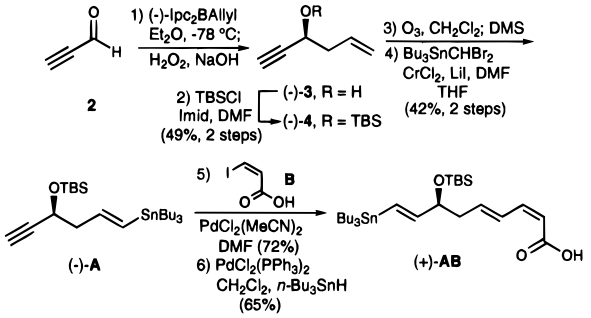
From the retrosynthetic perspective (Scheme 1), we envisioned cleavage at C(9,10) and at the lactone linkage to generate advanced subtargets **AB** and **CD**; assembly of the macrolide would then entail Mitsunobu[8] coupling and Stille macrocyclization. Similar σ-bond disconnections of the remaining diene units led to Stille coupling partners **A** plus **B** and **C** plus **D**.

Scheme 1



As our point of departure, asymmetric allylation of propargyl aldehyde (**2**, Scheme 2) with (−)-*B*-allyl(diisopinocampheyl)-borane[9] furnished known[10] alcohol (−)-**3** in 90% ee, as determined by optical rotation and Mosher ester analysis.[11] After protection as the TBS (*tert*-butyldimethylsilyl) ether (−)-**4**,[12a] selective ozonolysis[13] and chromium(II)-mediated one-carbon homologation[14] afforded *E* vinyl stannane (−)-**A**[12] as a single isomer in 20% overall yield from **2**. Palladium-catalyzed Stille cross-coupling with (*Z*)-3-iodopropenoic acid (**B**)[15] then installed the requisite *E*,*Z* diene (72% yield); palladium-catalyzed hydrostannylation[16] (65%) completed construction of the C(1−9) fragment (+)-**AB**.

Scheme 2



Preparation of the C(11−17) **C** fragment (Scheme 3) began with the ozonolysis of (+)-**4**.[17] Luche allylation[18] and Dess−Martin oxidation[19] of the resultant alcohols (ca. 1:1 mixture of diastereomers) furnished ketone (+)-**5**.[12] Desilylation and stereoselective reduction with $Me_4NBH(OAc)_3$[20] then gave the anti 1,3-diol (+)-**6**[12a] (ca. 15:1).[21] The *E* vinyl iodide (+)-**C**[12]

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(2) Rychnovsky, S. D.; Skalitzky, D. J.; Pathirana, C.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **1992**, *114*, 671.

(3) The original bacterial source no longer produces macrolactins A-E, only macrolactin F. Fenical, W. The Scripps Institution of Oceanography, University of California, San Diego, 1995. Personal communication.

(4) For a synthesis of 13,15-dimethoxymacrolactin A, which also exploits Stille cross-coupling chemistry for key bond constructions, see: Boyce, R. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 3501.

(5) For other synthetic approaches to macrolactin A and related derivatives, see: (a) Donaldson, W. A.; Bell, P. T.; Wang, Z. *Abstracts of Papers*, 207th National Meeting of the American Chemical Society, San Diego, CA, Fall 1994; American Chemical Society: Washington, DC, 1994; ORGN 43. (b) Rychnovsky, S. D.; Pickering, D. A. *Ibid.*; ORGN 209. (c) Benvegnu, T.; Scio, L.; Le Floc'h, Y.; Grée, R. *Synlett* **1994**, 505. (d) Donaldson, W. A.; Bell, P. T.; Wang, Z.; Bennett, D. W. *Tetrahedron Lett.* **1994**, *35*, 5829. Prahlad, V.; Donaldson, W. A. *Ibid*. **1996**. In press. (e) Tanimori, S.; Morita, Y.; Tsubobota, M.; Makayama, M. *Synth. Commun.* **1996**, *26*, 559. (f) Benvegnu, T. J.; Toupet, L. J.; Grée, R. L. *Tetrahedron* **1996**, *52*, 11811. Benvegnu, T. J.; Grée, R. L. *Ibid*. **1996**, *52*, 11821.

(6) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(7) To our knowledge, Stille was the first to employ his palladium-catalyzed cross-coupling for macrolide construction: Stille, J. K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 2785. Also see: Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883. Nicolaou elegantly extended this methodology by employing a Stille-type "stitching-cyclization" to install the C(19)−C(20) vinyl unit and close the macrocycle in rapamycin: Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419.

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(10) (*R*)- and (*S*)-5-Hexen-1-yn-3-ol have been resolved by lyophilized-yeast hydrolysis of the racemic acetate: Blänzer, B. I.; Faber, K.; Griengl, H. *Tetrahedron* **1987**, *43*, 5791.

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(12) (a) All synthetic compounds were purified by distillation or flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 500 MHz ^{1}H NMR, and 125 MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, this compound gave satisfactory combustion analysis.

(13) Joullié, M. M.; Chen, S.-Y. *Synth. Commun.* **1984**, *14*, 591.

(14) Hodgsen, D. M. *Tetrahedron Lett.* **1992**, *33*, 5603.

(15) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, *57*, 709.

(16) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(17) In analogous fashion, (+)-**4**[11a] was prepared with (+)-*B*-allyl-(diisopinocampheyl)borane.

(18) Pétrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910.

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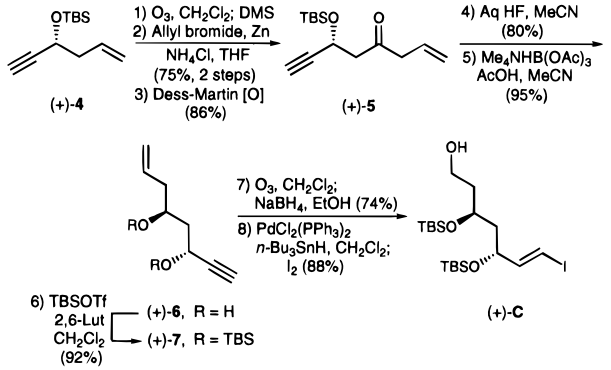
S0002-7863(96)03543-3 CCC: $12.00

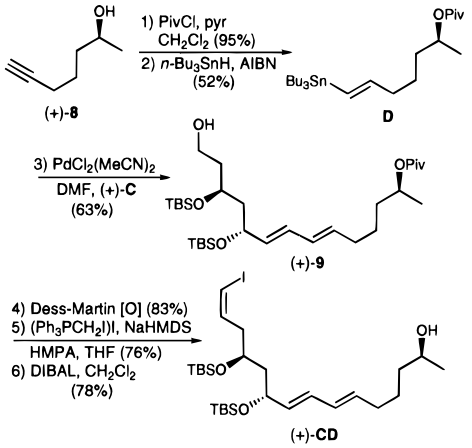
Scheme 3



was elaborated via hydroxyl protection (TBSOTf),[12] selective ozonolysis, reduction ($NaBH_4$), hydrostannylation [$PdCl_2(PPh_3)_2$, *n*-Bu_3SnH], and tin−halogen exchange (I_2, CH_2Cl_2). The overall yield for the eight-step sequence was 29%.

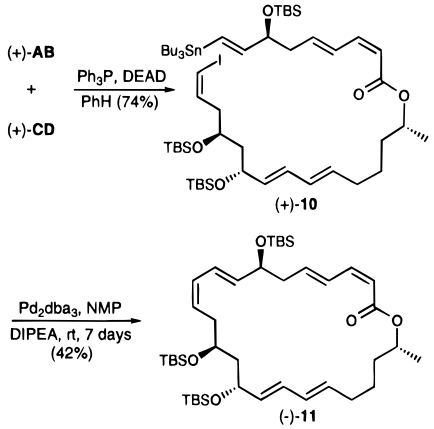
Subunit **D** derived from (*S*)-(+)-1-heptyn-6-ol (**8**).[22] Following protection of the hydroxyl (PivCl), hydrostannylation [*n*-Bu_3SnH, AIBN (2,2′-azobisisobutyronitrile)] generated the vinyl stannane **D**[12a] in 49% overall yield as an inseparable 4.1:1 mixture of *E* and *Z* isomers (Scheme 4). Stille coupling with (+)-**C** [$PdCl_2(MeCN)_2$, DMF] then furnished *E,E* diene (+)-**9**[12a] after flash chromatography (63%). Dess−Martin oxidation, Wittig olefination [$(Ph_3PCH_2I)I$, NaHMDS (sodium hexamethyldisilylazide), HMPA, THF],[23] and reductive removal of the pivalate (DIBAL) afforded the *Z* vinyl iodide (+)-**CD,**[12] the C(10−24) subtarget, in 49% yield for the three steps.

Scheme 4



With fragments **AB** and **CD** in hand, we turned to assembly of the macrolide (Scheme 5). Mitsunobu esterification (PPh_3, DEAD (diethyl azodicarboxylate), C_6H_6) smoothly yielded the Stille precursor (+)-**10**[12a] in 74% yield. Palladium-catalyzed ring closure[6] (Pd_2dba_3, NMP (*N*-methyl-2-pyrrolidinone), DIPEA) did generate (−)-**11,**[12a] but the reaction was plagued both by long reaction times (7 days) and modest efficiency (ca. 42% yields). At this juncture, we decided to interchange the C(9) and C(10) vinylic functionalities and also to replace the tributyltin moiety with a more reactive trimethylstannyl group (Scheme 6). Thus, tin−halogen exchange (I_2, CH_2Cl_2) converted (+)-**AB** to the vinyl iodide (+)-**12** in 77% yield, and iodide **CD** afforded the *Z* vinyl stannane (+)-**13**[12a] [$(Me_3Sn)_2$, Pd_2dba_3, NMP, 64%][24] with complete retention of stereochemistry. Mitsunobu esterification (74% yield) and palladium-

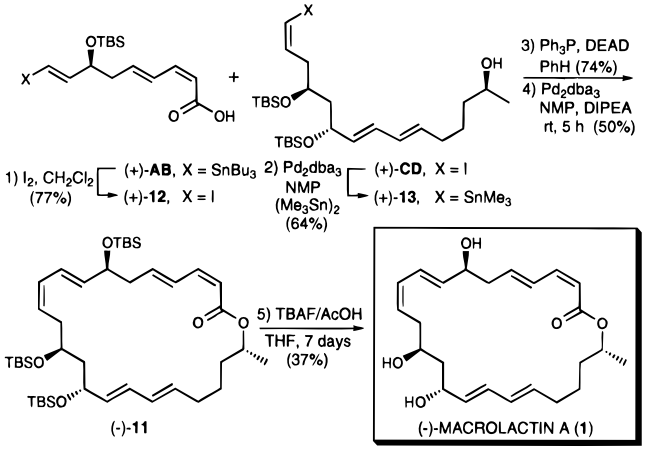
Scheme 5



catalyzed ring closure then provided (−)-**11** in only 5 h; the yield was 50%.

All that remained was unmasking of **1** by removal of the three silyl protecting groups; however, this proved to be no simple task! Exposure of (−)-**11** to a variety of acidic or strongly basic conditions led predominantly to decomposition. Eventually, desilylation was achieved with TBAF (tetrabutylammonium fluoride) in acetic acid[25] (7 days, Scheme 6), furnishing (−)-macrolactin A (**1**) in 37% yield after flash chromatography (silica, 10% $CHCl_3$/MeOH). The 500 MHz ^1H NMR and 125 MHz ^{13}C NMR spectra, high-resolution mass spectrum, and optical rotation of synthetic (−)-**1** were identical with the data reported for the natural product.[26]

Scheme 6



In summary, the first total synthesis of (−)-macrolactin A (**1**) has been designed and executed. The cornerstone of the successful strategy was the use of palladium-catalyzed Stille cross-couplings for stereocontrolled installation of the diene moieties and macrocyclization. The highly convergent route, with the longest linear sequence containing 17 steps, should offer access to a variety of potentially bioactive analogs. The synthesis also confirmed the relative and absolute stereochemistry of macrolactin A.[2]

Acknowledgment. We gratefully acknowledge financial support provided by the National Institutes of Health (National Cancer Institute) through grant CA-19033.

Supporting Information Available: Spectroscopic and analytical data for **1**, **4**−**7**, **9**−**13**, **A**, **AB**, **C**, **D**, and **CD**, as well as selected experimental procedures (8 pages). See any current masthead page for ordering and Internet access information.

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(26) We thank Professor Fenical for the ^1H and ^{13}C NMR spectra of **1**.