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Total Synthesis and Stereochemical Assignment of the Salicylate Antitumor Macrolide Lobatamide C[1]

Ruichao Shen, Cheng Ting Lin, and John A. Porco, Jr.*

Department of Chemistry and Center for Streamlined Synthesis, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

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The salicylate enamide macrolides are an emerging class of antitumor natural products that have attracted considerable interest regarding both chemical synthesis[2] and biochemical mechanism of action studies.[3] Lobatamides A−F, unique members of this class containing a 15-membered ring macrodilactone, were isolated in 1998 by Boyd et. al. from southwestern Pacific tunicates.[4a] The absolute stereochemistry of the C15 divinylcarbinol of YM-75518A[4b] (identical to lobatamide A) was determined to be (*S*) using modified Mosher ester analysis.[4c] The stereogenic centers at C8 and C11 await confirmation by chemical synthesis. Like the salicylihalamides,[2a] the lobatamides display high potency against human tumor cell lines (mean panel GI_{50} values approximately 1.6 nM),[4a] which may be derived from their ability to inhibit vacuolar-type proton ATPase.[3] In light of the impressive biological activity and unique functionality of the lobatamides, including a *Z*-trisubstituted olefin, divinylcarbinol moiety, and *O*-methyloxime enamide side chain, we have targeted lobatamide C for synthesis. Herein, we report the first total synthesis and stereochemical assignment of lobatamide C.

Retrosynthetic analysis of lobatamide C reveals two principal fragments: the C11−26 salicylate subunit **3** and the C1−C10 enamide sector **4** (Figure 1). To construct the macrodilactone ring system, we planned to utilize macrolactonization of precursor **2**, which is derived from esterification of **3** and **4**. Although the configuration at C8 and C11 has not been determined, we first focused our attention on the preparation of the 8*S* enantiomer of **4** based on consideration of the absolute configuration of related natural products salicylihalamide A[2b] and the oximidines.[2g] Further disconnection of fragment **3** at the C18−C19 bond leads to benzylic bromide **5** and *Z*-vinyl stannane **6** via Stille cross-coupling.[5] Enamide subunit **4** was envisaged to be derived from Cu (I)-catalyzed amidation of vinyl iodide **7** with *E*-*O*-methyloxime amide **8**.[6]

The synthesis of the enamide segment **4** commenced with addition of the acetylenic alane[7] reagent derived from trimethylsilyl acetylene to (*R*)-ethyl-3,4-epoxybutanoate **9**[8] to afford **10** (Scheme 1). Hydroxyl protection using chlorodiethylisopropylsilane followed by treatment of the resulting silyl ether **11** with $AgNO_3$/NBS[9]/H_2O[10] afforded a bromoalkyne **12**, which was converted to (*E*)-stannylalkene **13** using Pattenden's method.[11] Iodine exchange of **13** furnished vinyl iodide **7** with full retention of olefin stereochemistry. After considerable experimentation, we found that copper(I) thiophenecarboxylate (CuTC)-mediated vinylic substitution of **7** with *E*-*O*-methyloxime amide **8**[6] (1.2 equiv), Cs_2CO_3 (1.2 equiv), 1,10-phenanthroline (0.5 equiv), and dba (0.2 equiv)[12] (DMA, 65 °C, 17 h) led to a 45% yield of enamide **14**, along with 10% of the easily separable *Z*-oxime stereoisomer. Desilylation of **14** using

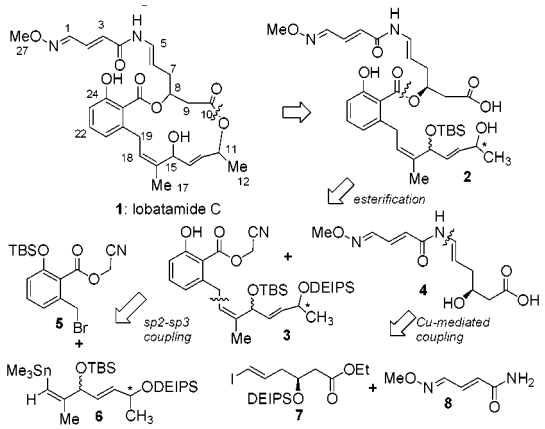
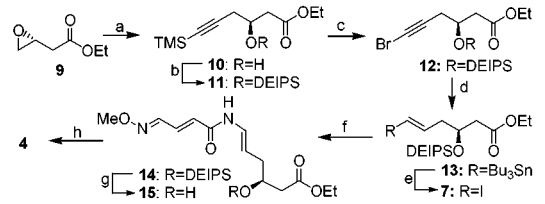


Figure 1. Retrosynthesis of lobatamide C

Scheme 1 [a]



[a] Conditions: (a) trimethylsilyl acetylene, *n*-BuLi, −35 °C, toluene; Et_2AlCl, 0 °C; then **9**, 0 °C, 72%; (b) DEIPSCl, imidazole, DMF, 97%; (c) NBS, $AgNO_3$, H_2O, 98%; (d) Bu_3SnH, $Pd(PPh_3)_4$, THF, −78 °C, 1 h, rt, 1 h, 86%; (e) I_2, THF, 0 °C, 93%; (f) **8**, CuTC (0.5 equiv), Cs_2CO_3, 1,10-phenanthroline, dba, DMA, 65 °C, 17 h, 45% (**14**), 10% (*Z*-oxime isomer); (g) TBAF, THF, rt, 99%; (h) aq LiOH, THF/MeOH, rt, 77%.

TBAF afforded enamide alcohol **15**, which was hydrolyzed with LiOH to provide the labile enamide acid fragment **4**.

Benzylic bromide **5** was prepared from readily available aryl triflate **16**[13] (Scheme 2). Treatment of **16** with lithium dimethylcuprate[14]/MeI[10] led to the production of 1,3-benzodioxan-4-one (**17**). Hydrolysis with KOH[13] provided 6-methylsalicylic acid, which was converted to cyanomethyl ester **18**.[15] Protection of **18** as a silyl ether, followed by benzylic bromination,[16] afforded **5**. Synthesis of the vinyl stannane **6** required for sp^2-sp^3 coupling with **5** began with hydrozirconation of protected alkyne **20**. Zirconocene−zinc transmetalation[17] followed by addition to configurationally stable enal **21**[18] afforded divinylcarbinol **23** as a 1:1 nonseparable mixture of diastereomers. Extensive studies were performed to establish the proposed *S* configuration of the divinylcarbinol at C15, including screening of various chiral amino alcohols. However, the best result was obtained with 2:1 (*S*:*R*) with Wipf's amino thiol ligand **22**.[17] Compound **23** (inseparable 2:1 mixture of diastereomers) was further advanced by silylation of the secondary alcohol followed by lithiation−trimethylstannylation to afford vinyl stannane **6**, which

* To whom correspondence may be sent. E-mail: porco@chem.bu.edu.

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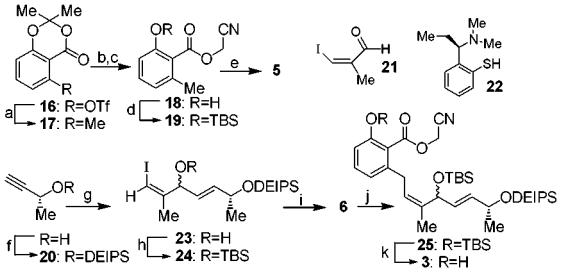
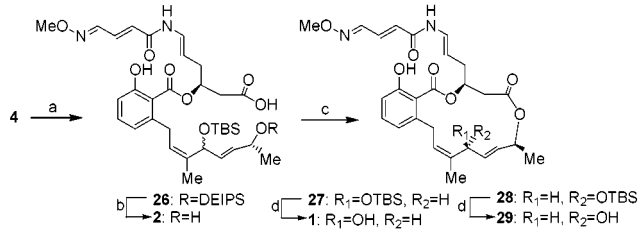
Scheme 2 [a]



[a] Conditions: (a) Me_2CuLi, THF, −78 °C; 0 °C, MeI, 85%; (b) aq KOH/THF, 100%; (c) $ClCH_2CN$, Et_3N, acetone, 80%; (d) TBSCl, imidazole, DMF, 99%; (e) NBS, AIBN, CCl_4, 72%; (f) DEIPSCl, imidazole, DMF, 91%; (g) Cp_2ZrHCl, CH_2Cl_2, rt; Et_2Zn, −78 °C, 10 min; **22**, −78→ −30 °C, 1 h; **21**, −30 °C, 20 h, 68% (*S*:*R* = 2:1); (h) TBSCl, imidazole, DMF, 93%; (i) *n*-BuLi, Et_2O; Me_3SnCl, 98%; (j) $Pd_2(dba)_3$−$CHCl_3$, $AsPh_3$, THF, rt; **5**, **6**, 70 °C, 3 h, 66%; (k) TBAF, 0 °C, 67%.

Scheme 3 [a]



[a] Conditions: (a) NBu_4OH, MeOH, rt; azeotropic removal of water; **3**, Na_2CO_3, DMF, 2-butanone, 80 °C, 2 h; (b) HF-pyridine/pyridine, THF, rt, 43% (2 steps); (c) PPh_3, DIAD, THF, rt; **2**, 0 °C, 3 h, 52% (**27**, 26%; **28**, 26%); (d) HF-pyridine/pyridine, THF, rt, 52% (**1**), 78% (**29**).

was coupled with benzylic bromide **5** using the conditions of Kamlage et al.[19] to furnish C11−C26 fragment **25**. Selective deprotection of **25** with TBAF at 0 °C afforded the target salicylate cyanomethyl ester **3**.

Initial base-catalyzed fragment couplings between salicylate cyanomethyl ester **3** and hydroxy ester **15** failed to effect esterification without extensive levels of elimination of the β-salicyloxy ester. However, after extensive optimization, we found that the tetrabutylammonium salt of enamide acid **4** participated in smooth esterification reactions with cyanomethyl ester **3** (Na_2CO_3, DMF/2-butanone, 80 °C) to provide the desired salicylate **26** (Scheme 3). The tetralkylammonium salt of **4** both increases solubility of the enamide alcohol fragment, and likely blocks an α-deprotonation/elimination pathway. Treatment of **26** with HF-pyridine afforded hydroxy acid **2** (43%, 2 steps). Both **26** and **2** are highly labile and could only be purified by using reverse phase (C18) silica. Gratifyingly, **2** was smoothly macrolactonized with use of Mitsunobu conditions[20] to afford the readily separable macrolactones **27** (26%) and **28** (26%). However, the formation of **27** and **28** in 1:1 ratio indicates influence of the protected divinylcarbinol stereocenter on the macrocyclization and thus necessitated independent confirmation of the C15 stereochemistry. Desilylation of **27** and **28** with HF-pyridine led to efficient production of **1** (52%) and its C15 epimer **29** (78%). The absolute configuration of **1** at C15 was determined to be *S* by using modified Mosher's ester analysis[21] according to Suzumura's procedure.[22] In addition, independent synthesis of the 11*R* diastereomers of **1** employing the same route from the enantiomer of **20** showed that these compounds did not match the natural product.[10] Synthetic **1** was confirmed to be identical with data reported for natural lobatamide C by ^1H and ^{13}C NMR, $[\alpha]_D$, and TLC R_f values in three solvent systems.

In summary, the first total synthesis of the antitumor natural product lobatamide C has been accomplished and its absolute configuration has been determined to be 8*S*, 11*S*, 15*S*. Further studies on the lobatamides and simplified analogues, as well as their biological evaluation, are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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