Total Synthesis of (+)-Calyculin A and (−)-Calyculin B

Amos B. Smith, III,* Gregory K. Friestad, James J.-W. Duan, Joseph Barbosa, Kenneth G. Hull, Makoto Iwashima, Yuping Qiu, P. Grant Spoors, Emmanuel Bertounesque, and Brian A. Salvatore

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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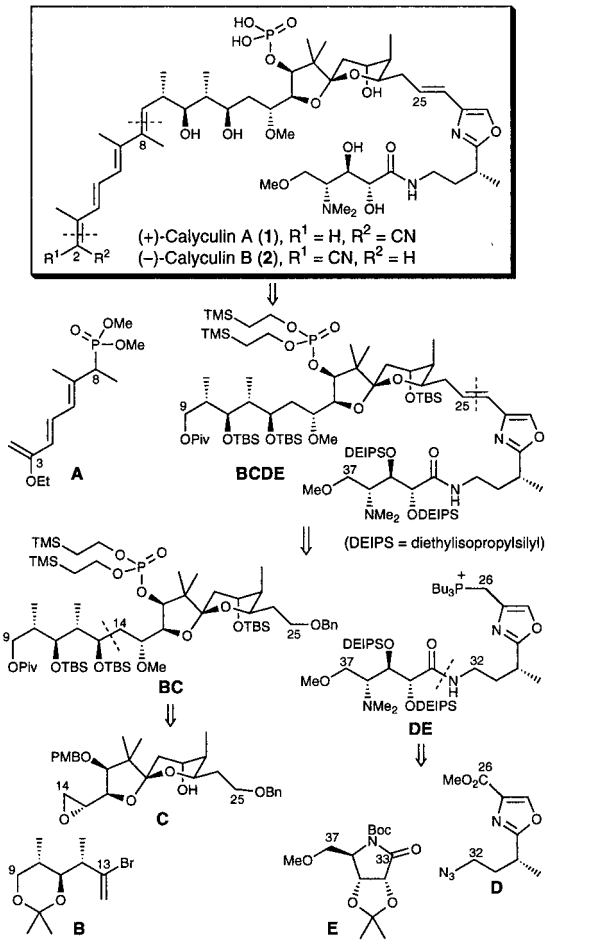
In the late 1980s, Fusetani and co-workers reported the isolation and structural elucidation of calyculins A and B,[1] potent serine-threonine protein phosphatase (PP1 and PP2A) inhibitors[2] endowed with remarkable cell membrane permeability.[3] The striking array of stereochemical and functional elements, in conjunction with the increasing use of (−)-**1** to explore intracellular phosphorylation,[4] has engendered considerable interest by the synthetic community, with notable total syntheses of the unnatural and natural antipodes of calyculin A [i.e., (+)-**1** and (−)-**1**] by Evans[5] and Masamune,[6] respectively.[7] Our interest in the calyculins emanated from the novel [5.6]spiroketal moiety, a central feature in our phyllanthostatin−breynolide synthetic ventures.[8] Herein we disclose an efficient, convergent total synthesis of (+)-**1** and the first total synthesis of (−)-calyculin B (**2**).[9]

From the outset, we envisioned an approach that would provide both **1** and **2** from a common advanced intermediate, avoid extensive manipulations of the light-sensitive[10] C(1−9) cyanotetraene, and permit flexibility in fragment coupling. Accordingly, disconnections at the C(2) and C(8) olefins led to phosphonate **A** (Scheme 1), possessing a latent C(3) carbonyl for penultimate Peterson olefination to access both **1** and **2**. Disconnection of **BCDE** at the C(25) olefin revealed subtargets **BC**, envisioned to arise via coupling acyl anion equivalent **B** with epoxide **C**, and **DE**, available from oxazole **D** and lactam **E**. Efficient stereoselective routes to (+)-**C**, (−)-**D**, and (−)-**E**,[11] in conjunction with a highly diastereoselective IBr-induced iodocarbonate cyclization[12] and a dithiane-epoxide coupling tactic[13] to construct a

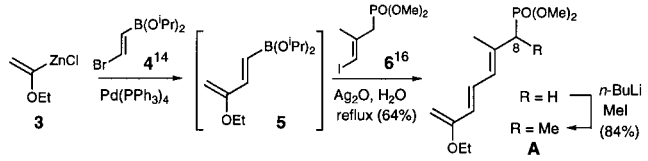
Scheme 1



C(16−25) masked aldol en route to spiroketal **C**,[11a] were disclosed previously.

Phosphonate **A** presented the intriguing possibility of olefin σ-bond construction[13] via a Suzuki[14] one-pot three-component triene synthesis (Scheme 2). In the event, Pd-catalyzed coupling of organozinc **3**, (*E*)-bromovinyl boronate **4**,[14] and vinyl iodide **6**[15,16] furnished the desired triene. Methylation at C(8) completed the preparation of **A**.

Scheme 2



To set the stage for assembly of **BCDE**, we required subtargets **B** and **DE**. For **B**, desilylation of the Roush crotylboration product (+)-**7**[17] (Scheme 3), 1,3-acetonide

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(9) At the start of our work, the absolute stereochemistry was unknown.

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(15) The structure assigned to each new pure compound is in accord with its IR, ^{1}H and ^{13}C NMR, and high-resolution mass spectra.

(16) Phosphonate **6** was prepared from the corresponding alcohol (Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E.-I. *J. Org. Chem.* **1981**, *46*, 4093) in two steps [MsCl, DMAP; $P(OMe)_3$, NaI, neat; 70% yield].

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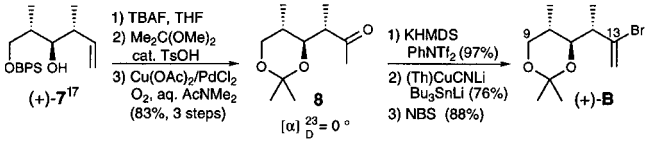
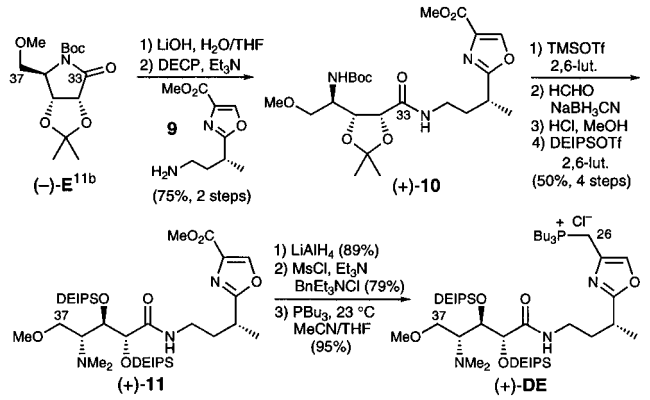
formation, and execution of a modified Wacker oxidation protocol[18] furnished ketone **8**.[15] Generation of the kinetic enol triflate,[19] reaction with a mixed stannylcuprate,[20] and bromodestannylation led efficiently to acyl anion equivalent (+)-**B**[15] (ca. 54%; six steps).

Scheme 3



We next addressed preparation of the **DE** Wittig reagent (Scheme 4). Hydrolysis of lactam (−)-**E**,[11b] followed by coupling with amine **9**, obtained via Lindlar reduction of azide (−)-**D**,[11c] afforded amide (+)-**10**.[15] Deprotection, reductive methylation of the C(36) amine, and interchange of C(34,35) diol protecting groups gave bis-diethylisopropylsilyl[21] ether (+)-**11**.[15] Completion of (+)-**DE**[15] was achieved by ester reduction, conversion to the primary chloride, and displacement with tri-*n*-butylphosphine.

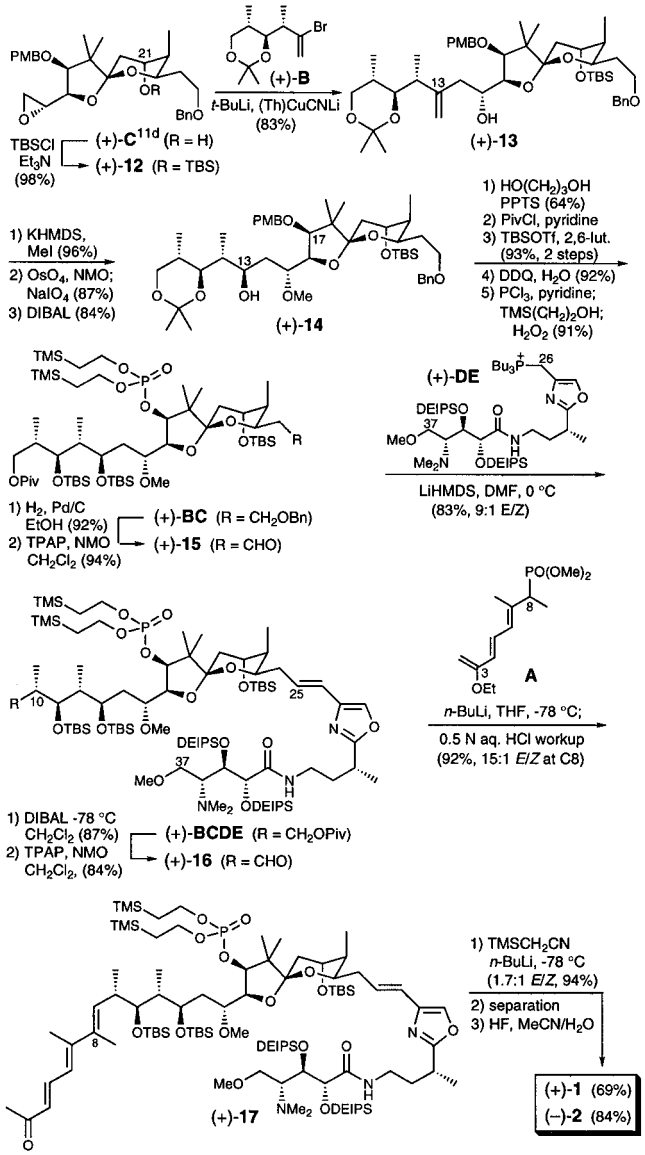
Scheme 4



With the requisite subtargets in hand, we embarked upon their union (Scheme 5). To link (+)-**B** with the C(14−25) spiroketal, (+)-**C**[11d] was converted to TBS ether (+)-**12**[15] and exposed to the vinyl thienylcuprate[22] derived from (+)-**B** (1.5 equiv) to furnish exclusively alcohol (+)-**13** in 83% yield. O-Methylation, olefin cleavage, and selective DIBAL reduction (β/α >12:1) afforded β alcohol (+)-**14**.[15] Arrival at (+)-**BC**[15] entailed protecting group interchange, PMB removal and phosphorylation employing the Evans protocol.[5]

Final assembly of the calyculin framework began with hydrogenolysis of (+)-**BC** (Scheme 5), TPAP oxidation,[23] and Wittig olefination[24] with (+)-**DE** (1.7 equiv) to provide (+)-**BCDE**[15] (E/Z = 9:1; 83% yield). Removal of the pivaloate moiety, TPAP oxidation,[23] and Horner−Emmons olefination with phosphonate **A** (*n*-BuLi, −78 °C), followed by brief exposure to acid (0.5 N HCl), furnished trienone (+)-**17**[15] with excellent selectivity (E/Z = 15:1) and good overall efficiency (67% yield). Peterson olefination (Me_3SiCH_2CN, *n*-BuLi, −78 °C)[25] then afforded protected calyculins A and

Scheme 5



B (1:1.7, 94% yield). Careful radial chromatographic separation (1 mm silica, 5:1 hexanes/EtOAc) and global deprotection with aqueous HF in CH_3CN furnished pure (+)-calyculin A (69% yield) and (−)-calyculin B (84% yield), identical in all respects (^{1}H and ^{13}C NMR, IR, UV, HRMS, TLC, and HPLC) except for chiroptic properties to authentic **1** and **2**.[26]

In summary, an efficient, convergent total synthesis of (+)-calyculin A and (−)-calyculin B has been achieved. The synthesis of (−)-**2** also confirms the structure of calyculin B, previously based only on spectral comparison with calyculin A.

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Supporting Information Available: Spectroscopic and analytical data for **A**, **B**, **BC**, **DE**, **BCDE**, **1**, **2**, **6**, **8**, and **10**−**17** and selected experimental procedures (13 pages).

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(26) We thank Professors Nobuhiro Fusetani and Shigeki Matsunaga (University of Tokyo) for authentic samples of both natural (−)-**1** and (+)-**2** and for confirming that the correct $[\alpha]_D$ for natural **2** is +15° (*c* 0.07, EtOH). We also thank Professor David Evans (Harvard University) for an authentic sample of synthetic (+)-**1**.