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COMMUNICATIONS

Published on Web 07/17/2003

Macrolactonization via Ti(IV)-Mediated Epoxy-Acid Coupling: A Total Synthesis of (−)-Dactylolide [and Zampanolide]

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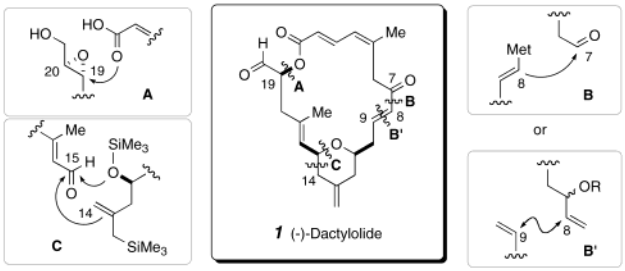
Dactylolide (**1**) is a naturally occurring, cytotoxic, 20-membered macrolactone isolated by Riccio and co-workers from the Vanuatu Sponge *Dactylospongia* sp. (off the coast of the Vanuatu Islands).[1] The relative configuration of the dactylolide stereocenters was fully established by the Smith group through their recent studies culminating in the first total synthesis of **1**.[2] Dactylolide has a highly unsaturated macrocycle skeleton and a very unusual α-acyloxyaldehyde functionality. Here, we report a total synthesis of dactylolide (**1**) that features two distinct macrocyclization strategies: a novel Ti(IV)-mediated macrolactonization of an epoxy-acid and a complementary RCM macrocyclization.

The strategic dissection of dactylolide (**1**) we have explored is outlined in Scheme 1. A key event was the formation of bond A by a Lewis acid-catalyzed opening of the C(19)/C(20) epoxide by a carboxylic acid (box A), as was originally disclosed by Sharpless.[3] This reaction could either precede or follow formation of bond B [C(8)-vinyl anion to a C(7)-aldehyde] or B′ [ring-closing metathesis]. In either event, bond A construction was destined for a sophisticated and, thereby, unprecedented acid−epoxide substrate pair. The remaining challenge, construction of the *cis*-2,6-disubstituted-4-methylene tetrahydropyran, was addressed by an intramolecular Sakurai cyclization reaction between a C(15)-enal and an allylic silane (box C).

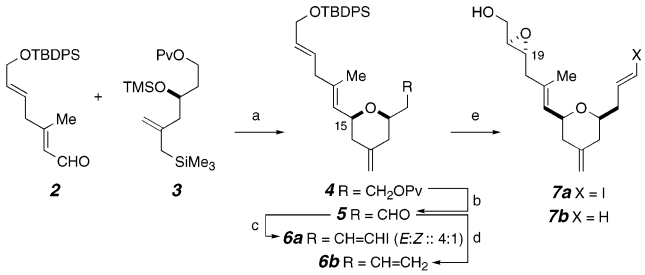
Synthesis of the two important pyran-containing building blocks **7a** and **7b** is presented in Scheme 2. The critical union[4] of enal **2**[5] and allylic silane (−)-**3**[6] was initially investigated with non-Brønsted acids (BF_3·OEt_2 or TMSOTf). While the yield of the 4-methylene pyran unit **4** was good, the cis/trans stereoselectivity was unacceptable (∼2:1, cis:trans). Fortunately, the protic acid, camphorsulfonic acid (CSA), provided only *cis*-**4**.[5,7] Pivalate removal and Dess−Martin oxidation furnished the common intermediate aldehyde **5**, from which iodoalkene **6a** or simple alkene **6b** were readily produced. TBDPS removal from **6b** with TBAF was uneventful and, from **6a**, beneficial. That is, the minor *Z*-isomer of **6a** underwent facile E2-elimination to give a more polar (and separable) alkyne. This suggests the potential utility of TBAF treatment as a convenient and general protocol for improving the *E*/*Z*-ratio of many 1-iodo-1-alkenes. Finally, Sharpless asymmetric epoxidation set the important C(19) stereocenter in each of **7a** and **7b** (∼25:1 dr in each case).

The final stages of our initial dactylolide synthesis are described in Scheme 3. The vinyllithium species derived from the TBS ether of vinyliodide **7a** was added to the C(1)−C(7) aldehyde **8**[5] to form the C(7)−C(8) bond and carbinol **9** as a nearly 1:1 mixture of epimers. Protection of the new C(7) secondary alcohol, removal of the C(1) pivalate ester, oxidation to the C(1) carboxylic acid, and removal of the C(21) primary TBS ether gave epoxy-acid **12**, the substrate for the focal macrocyclization. Exposure of a solution of **12** in methylene chloride (∼2 mM) to titanium tetraisopropoxide at 75 °C resulted in closure to the macrolactone **13**. Initial experiments provided evidence for side reactions that limit the ultimate efficiency of this cyclization. A macrocyclic lactone engaged at C(20) [H(20): m at δ 4.9 ppm in the ^{1}H NMR spectrum] and a C(1) isopropyl ester, both derived from initially formed **13**

Scheme 1

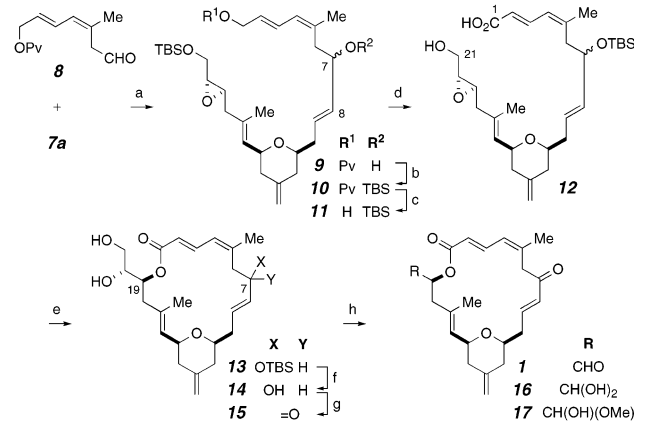


Scheme 2 [a]



[a] (a) CSA (5 mol %), Et_2O, 78%. (b) (i) DIBALH, CH_2Cl_2, 80%; (ii) DMP, CH_2Cl_2, 82%. (c) $CrCl_2$, CHI_3, THF, 76%. (d) $Ph_3P{=}CH_2$, THF, 90%. (e) (i) TBAF, THF, 72% (for **6a**), 95% (for **6b**); (ii) SAE, −25 °C, 89%.

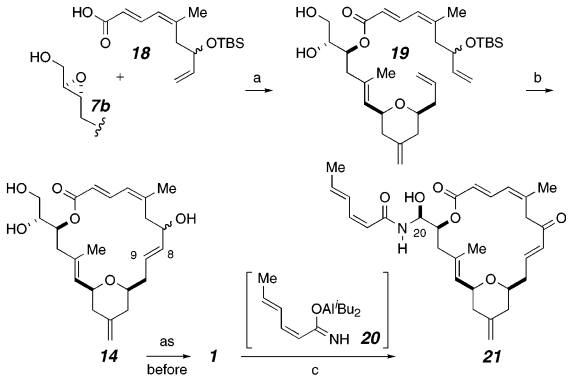
Scheme 3 [a]



[a] (a) (i) TBSCl, ImH, CH_2Cl_2, 98%; (ii) *n*-BuLi, Et_2O, −78 °C; then **8**,[5] Et_2O, 58%. (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 90%. (c) DIBALH, CH_2Cl_2, 97%. (d) (i) MnO_2, CH_2Cl_2, 98%; (ii) $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O, $Me_2C{=}CHMe$, 85%; (iii) TBAF, THF, 52%. (e) $Ti(O^iPr)_4$, CH_2Cl_2, 75 °C, 40% **13** with 30% **12**. (f) TBAF, THF, 85%. (g) 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, SiO_2, CH_2Cl_2, 80%. (h) $Pb(OAc)_4$, PhH, 90%.

10.1021/ja035579q CCC: $25.00

Scheme 4 [a]



[a] (a) Ti(O^{t}Bu)$_4$, CH_2Cl_2, 75 °C, 67%. (b) (i) BSA, PhH; (ii) RuCHPhCl$_2$(PCy$_3$)(H$_2$IMes), PhH, 60 °C, 77%; (iii) TBAF, THF, 89%. (c) (*Z*,*E*)-MeCH═CHCH═CHCONH$_2$, THF, DIBALH/hexanes; **1**, THF, room temperature.

(TLC and ^{1}H NMR evidence), accumulated at longer reaction times. Limiting the reaction time to ∼12 h (∼50% conversion) minimized byproduct formation (<5%) and permitted the isolation of **13** and unreacted **12** as the only components. Importantly, **13** is produced as an ∼1:1 mixture of C(7) epimers, demonstrating that the two diastereomers of **12** are comparably competent substrates for the key closure. Removal of the C(7) TBS ether gave the triol **14**. The chemoselective oxidation of the allylic alcohol in **14** using a stoichiometric amount of 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate[8] to give the diol enone **15** is noteworthy. Final cleavage of the C(20)−C(21) diol with lead tetraacetate provided (−)-dactylolide [**1**, spectral data (^{1}H and ^{13}C NMR, IR, and HRMS) match those reported for natural and synthetic (+)-dactylolide[9]].

A more convergent construction of dactylolide (**1**) as well as its subsequent conversion to the naturally occurring, acyclic carbinolamide zampanolide (**21**) is outlined in Scheme 4. Epoxide **7b** and the trienoic acid **18**[5] were coupled by the action of Ti(O^{t}Bu)$_4$ to provide the ring-closing metathesis substrate **19** (∼1:1 dr). The vicinal diol was protected in situ with excess bis-trimethylsilylacetamide (BSA)[5] in benzene, and RuCHPhCl$_2$(PCy$_3$)(H$_2$IMes)[10] was directly added. Each diastereoisomer smoothly cyclized at 60 °C, and each gave rise to only a single C(8)−C(9) alkene of *E*-geometry. All three silyl ethers were removed to provide triol **14** (68% from **19**). Finally, (−)-dactylolide (**1**) was converted to the related natural product, zampanolide (**21**),[11] and its C(20) epimer (∼1:1 ratio) by the aza-aldol addition of the species derived from titration of (*Z*,*E*)-sorbamide with 1 equiv of DIBALH (cf., **20**). Studies to further delineate the stereochemical aspects of this transformation are continuing.[5]

In conclusion, our synthesis shows that the Ti(IV)-promoted ring opening of "Sharpless epoxides" by carboxylic acids, even in settings where both components are structurally complex, is sufficiently versatile to serve as a key coupling strategy. Both the convergent bimolecular union between **7b** and **18** (Scheme 4) and the intramolecular macrolactonization within **12** (Scheme 3) demonstrate this point. Other notable features include the proton-catalyzed, *cis*-selective construction of pyran **4** from enal **2** and allylic silane **3**; the selective oxidation of triol **14** by an oxoammonium ion; the efficient RCM reaction of the in situ (TMS)-protected α,ω-dienediol **19**; and the aluminum aza-aldol addition reaction of "**20**" to **1** to construct the acyclic carbinolamide in zampanolide (**21**).

Acknowledgment. This investigation was supported by a grant awarded by the DHHS (GM-65597). We thank Professors Amos B. Smith, III, for sharing relevant information prior to publication and James M. Bobbitt for providing a sample of oxoammonium salt.[8a]

Supporting Information Available: Spectroscopic characterization data for compounds **1**−**15**, **18**, **19**, and **21** and procedures for preparation of **1** and **21** and copies of their NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) It is more than a curiosity that we have observed varying amounts of the hydrate **16** in the proton NMR spectra ($CDCl_3$) of different samples of dactylolide. The propensity of the aldehyde to hydrate, presumably heightened by both the electronic effect and the hydrogen-bonding network (cf., ref 12) afforded by the α-acyloxy substituent, is quite likely related to the stability of the unusual acyclic carbinolamide in zampanolide (**21**). It is also relevant that an initial oxidative cleavage of **15** with *n*-Bu$_4$N$^+$-IO$_4^-$ in methanol/CH_2Cl_2 provided **1** along with a portion of the methyl hemiacetal **17**. Moreover, **17** (both epimers) survived silica gel chromatography, again attesting to the predisposition of the free aldehyde in **1** to form stable adducts with protic nucleophiles. The existence of methanol adduct(s) was first detected for methanol solutions of **1** by both mass spectrometry and NMR analyses during the isolation/characterization work.[1] We observed that the ^{1}H NMR spectrum of a solution of **1** in CD_3OD gave no evidence of any free aldehyde; a mixture of diastereomeric hemiacetals was present instead. The value of the specific rotation we obtained for our synthetic sample of **1** ($[\alpha]^{RT}_D = -128°/-129°$, c = 0.39/0.26, MeOH) differed from values previously reported for both natural[1] ($[\alpha]^{RT}_D = +30°$, c = 1.0, MeOH) and synthetic[2] ($[\alpha]^{RT}_D = +235°$, c = 0.52, MeOH; recently remeasured at a second concentration as +240°, c = 0.2, MeOH; private communication with A. B. Smith, III) dactylolide (**1**). (+)-Dactylolide synthesized in the Smith laboratory[2] was the opposite antipode of that described here. The question of the absolute configuration of natural dactylolide is still open, because the specific rotation of the natural sample differs so greatly from that of each synthetic antipode.
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JA035579Q