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Toward a Total Synthesis of the Novel Polyketide Natural Product Spiculoic Acid A

Goverdhan Mehta* and Uday Kumar Kundu

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

gm@orgchem.iisc.ernet.in

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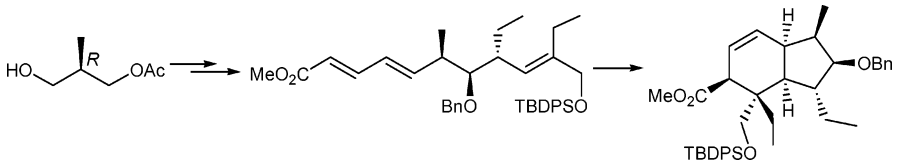
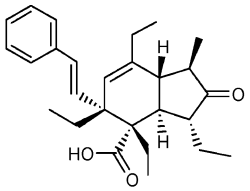
ABSTRACT

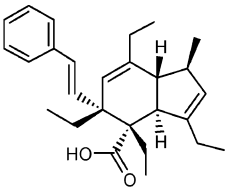


An enantioselective approach toward the recently isolated marine natural product, spiculoic acid A, conceptualized along the proposed biogenetic hypothesis, involving an intramolecular Diels–Alder reaction as the pivotal step, is delineated. Access to a structurally embellished bicyclic core of the natural product has been accomplished.

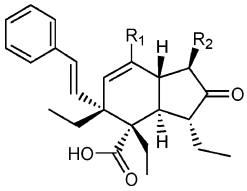
In 2004, Andersen and co-workers[1] reported the isolation of novel polyketide natural products spiculoic acids A (**1**) and B (**2**) from the extracts of the Caribbean marine sponge *Plakortis angulospiculatus* (Carter) collected from the reefs off the coast of Dominica. Bicyclic hydrindane-based structures **1** and **2** for these natural products were arrived at on the basis of incisive high-field 2D NMR studies. It was further shown that spiculoic acid A **1** exhibited in vitro cytotoxicity against the human breast cancer MCF cell line with an IC_{50} of 8 μg/mL. More recently, three more natural products based on the spiculane skeleton, *iso*-**3**, *nor*-**4**, and *dinor*-spiculoic acids A **5**, have been isolated from sponge *Plakortis zyggompha*, and **3** and **4** were shown to display weak cytotoxicity against both tumor cell lines A549 (lung carcinoma) and HT 29 (colon carcinoma).[2] Absolute configuration of these spiculane natural products **1**−**5** has not been determined and remains unknown. From biogenetic considerations, spiculoic acid A **1** is an unusual and rare construct, putatively incorporating four butyrate and a propionate unit and involving a Diels−Alderase-mediated intramolecular [4 + 2]-cycloaddition in a precursor such as **6** to generate its highly embellished bicyclic structure (Scheme 1).[1]



Spiculoic acid A (**1**)



Spiculoic acid B (**2**)



Isospiculoic acid A (**3**) R_1 = Et, R_2 = Et
Nor-spiculoic acid A (**4**) R_1 = Et, R_2 = Me
Dinor-spiculoic acid A (**5**) R_1 = Me, R_2 = Me

The presence of six stereogenic centers, two vicinal quaternary carbons, and a network of diverse and distributed functionalities on its novel framework, together with its bioactivity profile, makes spiculoic acid A **1** a challenging and enticing synthetic objective that immediately engaged our attention. In formulating a synthetic strategy toward **1**,

(1) Huang, X. H.; Soest, R. V.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2004**, *6*, 75.
(2) Berrué, F.; Thomas, O. P.; Fernández, R.; Amade P. *J. Nat. Prod.* **2005**, *68*, 547.

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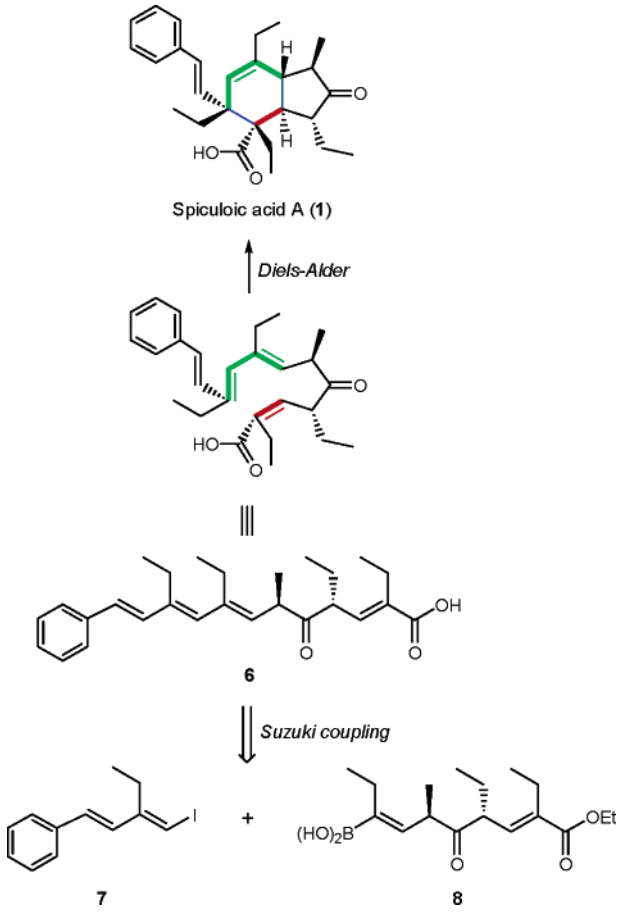
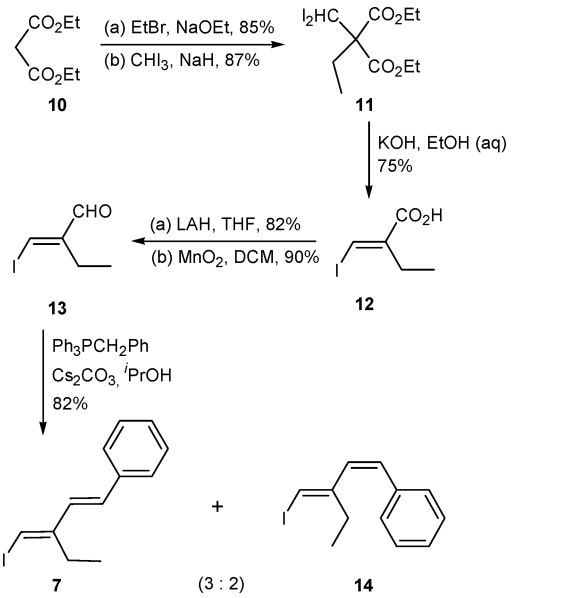
Scheme 1



Scheme 2



recourse to the putative biogenetic pathway involving an intramolecular Diels−Alder reaction as the pivotal step in precursor **6** appeared to be most appealing. From a retrosynthetic point of view, it was further reasoned that **6** could be assembled from two building blocks **7** and **8** involving a Suzuki or equivalent cross-coupling reaction (Scheme 1). In this letter, we detail the travails toward speculoic acid A **1** that have so far led to the bicyclic hydrindane **9** (vide infra), incorporating much of the framework and several key stereochemical features present in the natural product.

Preparation of fragment **7** was fairly straightforward and accomplished from diethyl malonate **10** (Scheme 2). Sequential alkylation in **10** with ethyl bromide and diiodocarbene furnished **11**.[3,4] Base-mediated decarboxylative elimination gave (*E*)-3-iodo-2-methyl-2-propenoic acid **12**, and further LAH reduction and oxidation of the resulting allylic alcohol led to aldehyde **13**. Wittig styrenylation on **13** delivered the desired **7** (3:2) along with the (*Z*)-isomer **14** from which it was easily separable (Scheme 2).[4]

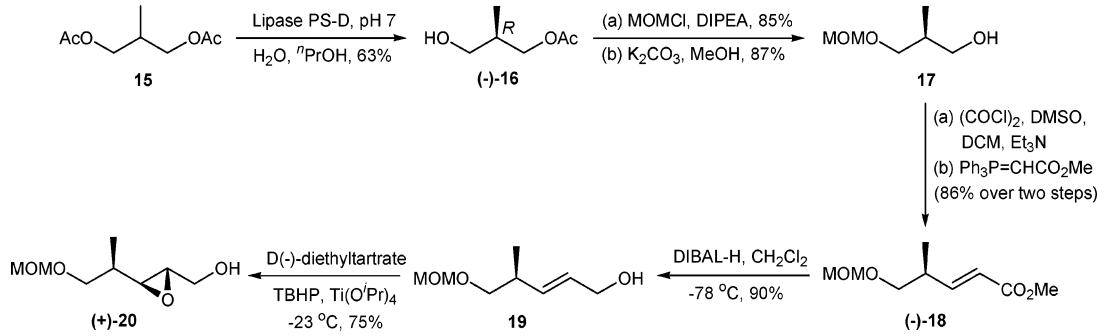
For an enantioselective approach toward the synthesis of the more challenging fragment **8**, we selected (*R*)-monoacetate **16** (98% ee), readily prepared from the enzymatic desymmetrization of the diacetate of the *meso*-2-methyl-1,3-propanediol **15** (Scheme 3).[5] Hydroxyl protection in **16** as MOM ether and acetate hydrolysis yielded **17**.[4] Swern oxidation in **17** and Horner−Wittig olefination furnished the α,β-unsaturated ester **18**.[4] DIBAL-H reduction in **18** led to the allylic alcohol **19** (Scheme 3). Sharpless epoxidation[6] of allylic alcohol **19** in the presence of the D-tartaric acid diethyl ester was stereoselective (9:1) and afforded the epoxide **20** in a predictable manner with ample precedence.[7]

Regioselective epoxide opening in **20** with Et_2CuLi led[8] to the diol **21**, and the primary hydroxyl group was chemoselectively oxidized to the hydroxyl aldehyde **22** (Scheme 4). Horner−Wittig olefination in **22** with ethyl 2-(triphenylphosphoranylidene)butyrate introduced the elements of the second butyrate moiety in a stereoselective manner to furnish **23**.[4] The free hydroxyl group in **23** was now protected as the benzyl ether derivative **24**. DIBAL-H reduction in **24** gave the allylic alcohol **25**, and the primary hydroxyl group was now protected as the TBDPS derivative **26**, in which the three hydroxyl groups were chemodifferentiable through protective group manoeuvres (Scheme 4). Removal of the MOM protection in **26** led to **27**, and further PDC oxidation furnished the key aldehyde **28**.

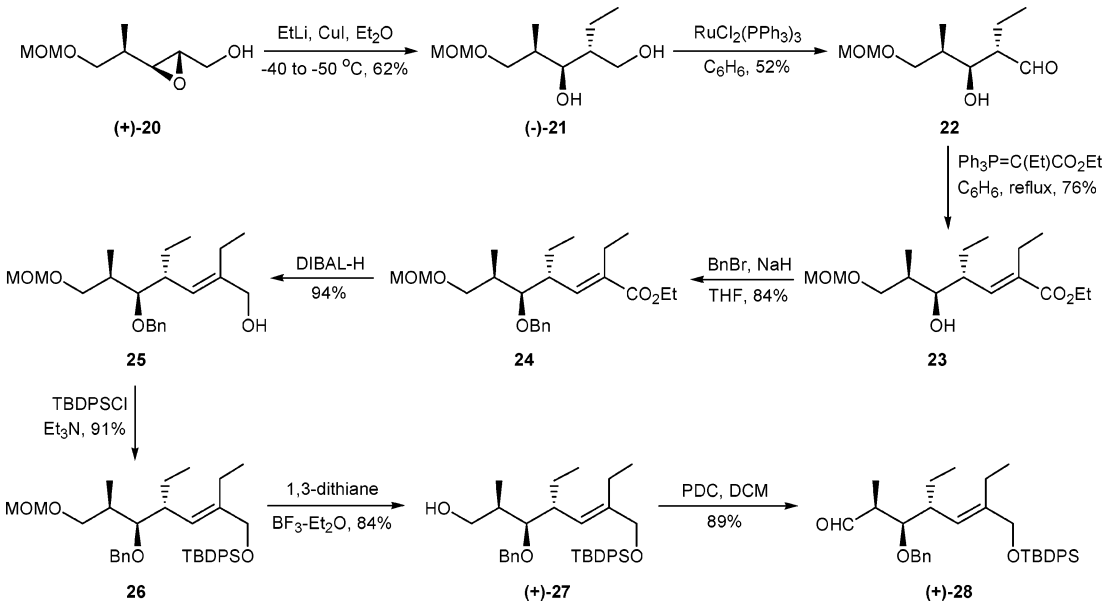
Our original plan was to elaborate the aldehyde **28** to *gem*-dibromoalkene **29** and further to the alkyne **30** en route to the pivotal fragment **8** (Scheme 5). However, several tactical operations on **28** using PPh_3-CBr_4 reagent[9] failed to deliver the desired **29** and only led to the elimination of the OBn

(3) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 47.
(4) All new compounds reported here were characterized on the basis of their spectral data (IR, ^1H and ^{13}C NMR, and HRMS).
(5) For a related example, see: Grisenti, P.; Ferraboschi, P.; Manzocchi, A.; Santaniello, E. *Tetrahedron* **1992**, *48*, 3827.
(6) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(7) (a) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(8) For examples of cuprate-mediated epoxide opening, see: (a) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830. (b) Horita, K.; Tanaka, K.; Yonemitsu, O. *Chem. Pharm. Bull.* **1993**, *41*, 2044.

Scheme 3

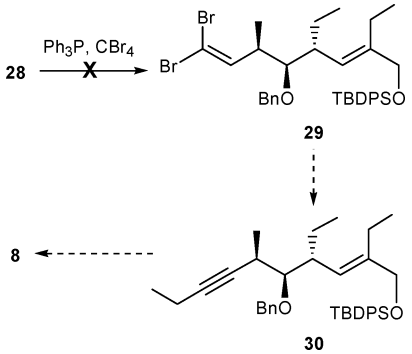


Scheme 4



protection and formation of an α,*β*-unsaturated aldehyde. Frustrated in the efforts to access **8**, we decided to settle for a lesser objective and ventured to demonstrate the viability of the IMDA reaction[10] to access the basic carbocyclic framework and some of the stereochemical features present in spiculoic acid A. For this purpose, the aldehyde group in **28** needed to be elaborated to a (*E*,*E*)-1,3-diene to setup the Diels−Alder reaction, keeping in mind the stereochemical imprint of the target structure. Toward this end, aldehyde **28** was subjected to Horner−Wittig olefination to deliver the α,*β*-unsaturated (*E*)-ester **31** and further reduced with DIBAL-H to the allylic alcohol **32** (Scheme 6). Dess−Martin oxidation[11] of **32** led to the unsaturated aldehyde **33**, and repeat of the Horner−Wittig olefination delivered the (*E*,*E*)-1,3-diene ester **34** (Scheme 6). In **34**, the elements for an IMDA reaction were in place, albeit in an inverse electron demand sense and in a complex stereochemical environment. When **34** was heated in *o*-dichlorobenzene in the presence of BHT,[12] a smooth [4 + 2]-cycloaddition occurred and a single bicyclic product **9** was obtained.[4] The stereostructure of **9** was delineated on the basis of incisive analyses of its spectral characteristics, particularly the COSY and nOe data.

Scheme 5

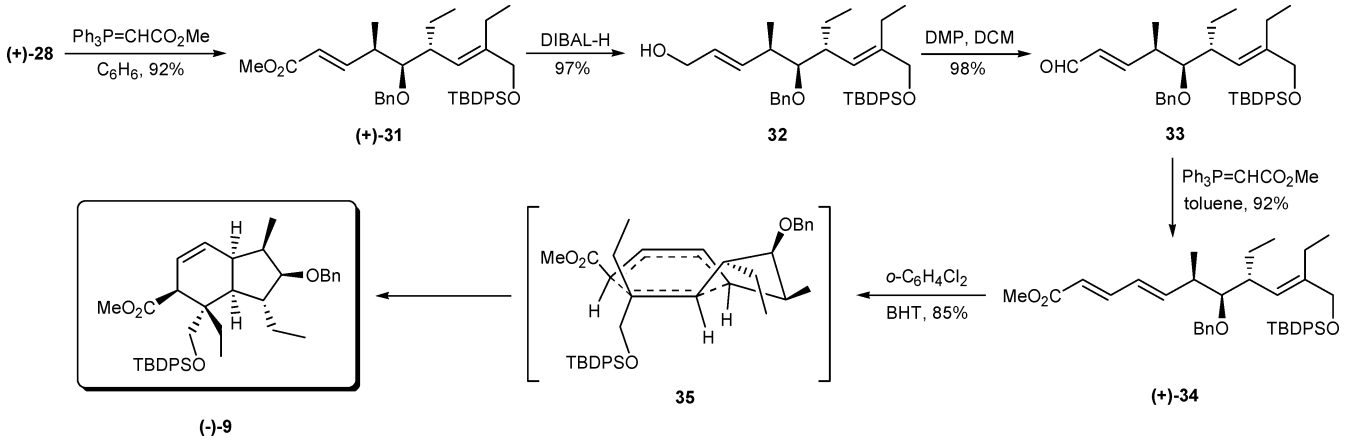


(9) (a) Kobayashi, S.; Mori, K.; Wakabayashi, T.; Yasuda, S.; Handa, K. *J. Org. Chem.* **2001**, *66*, 5580. (b) Mandal, A. K. *Org. Lett.* **2002**, *4*, 2043.

(10) For a recent review, see: Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

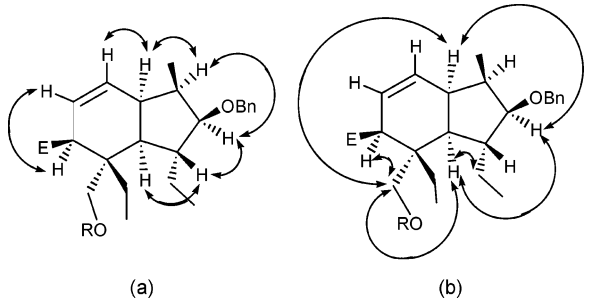
(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

Scheme 6



The stereochemical outcome of the IMDA reaction in **34**, leading to a *cis*-hydrindane derivative, was not completely along the anticipated lines but can be reconciled in terms of the preferred *exo* transition state depicted in **35** (Scheme 6). The important consequence of the key IMDA reaction in **34** was the establishment of five (as in **9**) of the six stereogenic centers of the target natural product **1** and this was a very encouraging sign. Thus, the stage is now set for the stereoelectronic retuning of the diene and dienophilic components for a normal electron demand IMDA reaction to generate the desired stereochemistry. In summary, we have delineated an enantioselective approach toward the novel polyketide natural product spiculoic acid A **1**, which is patterned along the proposed biogenetic hypothesis. Retrosynthesis on **1** identified two key fragments **7** and **8**, and while the former was assembled quite uneventfully, the latter presented considerable problems necessitating a deviation to a model study. These endeavors have culminated in the synthesis of a much embellished hydrindane, endowed with much of the stereochemical features of the natural product, and have laid the foundation for further efforts toward the total synthesis of spiculoic acids **1**−**5**.

Chart 1. ^{1}H−^{1}H COSY (a) and nOe (b) Correlations in (−)-**9**



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Supporting Information Available: Spectroscopic data as well as copies of the spectra of the key compounds are provided. This material is available free of charge via the Internet at http://pub.acs.org.

OL0521329

(12) Motozaki, T.; Sawamura, K.; Suzaki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.-i.; Tadano, K.-i. *Org. Lett.* **2005**, *7*, 2261.