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Total synthesis of (+)-spiculoic acid A

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ABSTRACT

The total synthesis of natural (+)-spiculoic acid A, a new cytotoxic marine natural product of polyketide origin, has been accomplished for the first time. The key step of the total synthesis was a stereoselective and high-yielding intramolecular Diels–Alder reaction of a highly functionalized (*E*,*E*,*E*)-2,7,9-dodecanal derivative for the construction of the core tetrahydroindan-2-one skeleton.

(+)-Spiculoic acid A (**1**) (Fig. 1) is a secondary metabolite of polyketide origin, which was isolated in 2004 from the methanol-extracts of the Caribbean marine sponge *Plakortis angulospiculatus* (Carter) by Andersen et al.[1] This natural product **1** showed in vitro cytotoxicity against the human breast cancer MCF-7 cells. The relative stereochemistry of **1** was determined by the Andersen group on the basis of thorough NMR analysis. At the same time, the Andersen group isolated and characterized a closely related spiculane-type compound, (−)-spiculoic acid B (**2**), which showed no in vitro cytotoxicity against the human breast cancer MCF-7 cells. Later, a number of structurally related spiculane-type natural products have been isolated from another marine sponge, *Plakortis zyggompha*, and their interesting biological activities have been reported.[2,3] Some of them are (+)-isospiculoic acid A (**3**), (+)-*nor*-spiculoic acid A (**4**), and (+)-*dinor*-spiculoic acid A (**5**).[2] These spiculane-type natural products also showed cytotoxicity against several tumor cell lines. Andersen et al. have proposed that **1** might be produced biosynthetically through an enzyme-catalyzed intramolecular Diels–Alder (IMDA) reaction of a linear triene equipped with all the functionalities in **1**, including a conjugated diene (4π) and a terminal unsaturated ester (2π).

The synthetic studies on these natural products have been extensively explored by several groups.[4–6] In 2006, Baldwin, Lee et al. reported the total synthesis of unnatural (−)-spiculoic acid A, thereby establishing the absolute stereochemistry of **1** as depicted.[5a,7] Inspired by Andersen's proposal, their total synthesis of (−)-spiculoic acid A has been achieved by using the IMDA reaction of a linear conjugate diene with a terminal unsaturated ester functionality for the stereoselective construction of the bicyclic core structure.[8] Herein, we describe the total synthesis of natural (+)-spiculoic acid A (**1**) for the first time.

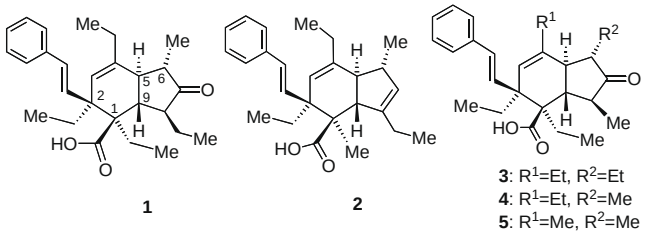

Figure 1. (+)-Spiculoic acid A (**1**) and related natural products (**2**–**5**).

Our total synthesis of **1** relied on the IMDA reaction of a linear (*E*)-unsaturated aldehyde **6** installing an (*E*,*E*)-conjugate diene unit, which possessed all requisite functionalities except the styryl side chain attached to the cyclohexene ring (Scheme 1).[9,10] As described later, the IMDA reaction of substrate **23** (**6**:R^1 = TBS; R^2 = MOM) underwent with complete *endo*- and π-facial selectivities, providing a bicyclic precursor **24** for the total synthesis of **1** quite efficiently. The substrate **23** would be in turn synthesized stereoselectively from known enantiomerically homogeneous branched five-carbon diol **7**.[11]

The synthesis and IMDA reaction of substrate **23** are summarized in Scheme 2. Swern oxidation of the monoprotected diol **7** provided aldehyde **8**. The Wittig olefination of **8** with $Ph_3P{=}C(Et)$-CO_2Et in refluxing toluene provided the (*E*)-unsaturated ester **9** stereoselectively (*E*/*Z* > 20:1 on the basis of ^1H NMR analysis).

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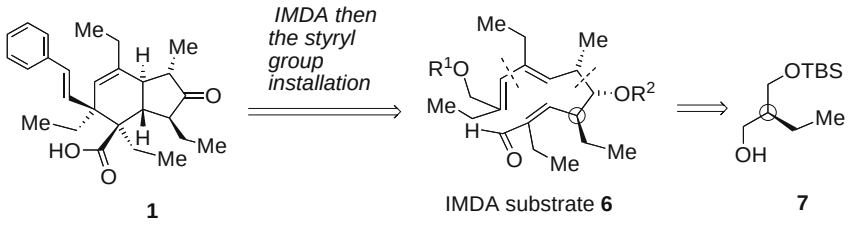
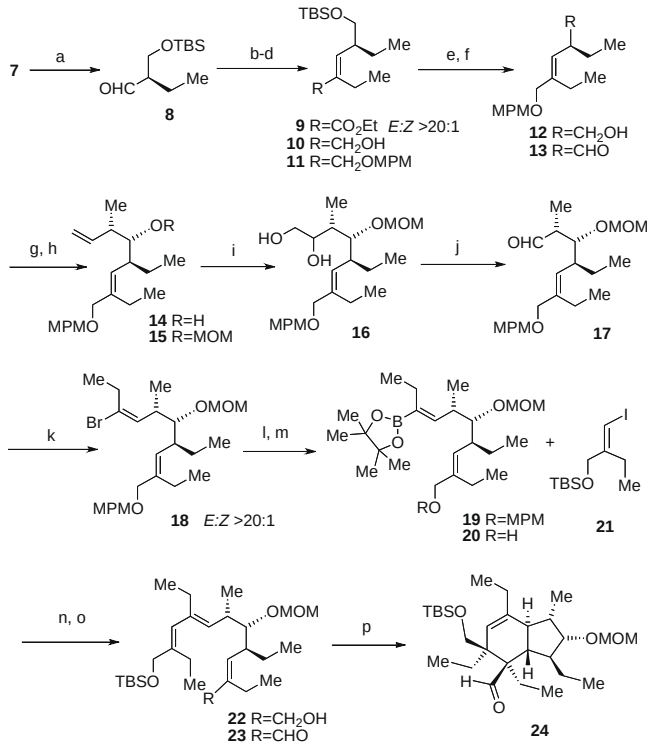


Scheme 1. Our IMDA approach for the total synthesis of **1**. TBS = *tert*-butyldimethylsilyl.

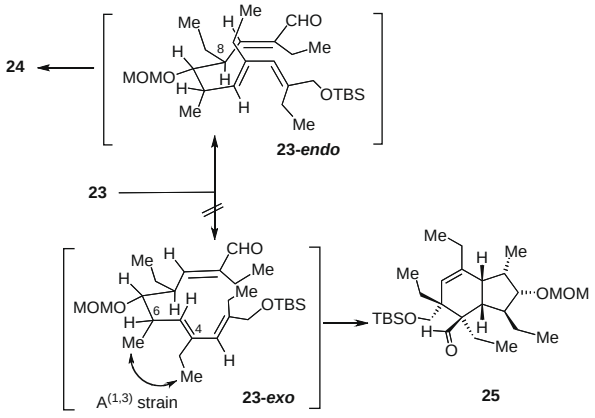


Scheme 2. Synthesis of substrate **23** and the IMDA reaction. Reagents and conditions: (a) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, rt; (b) $Ph_3P{=}C(Et)CO_2Et$, toluene, reflux, 85% over two steps; (c) DIBAL-H, CH_2Cl_2, −78 °C, 95%; (d) MPMCl, NaH, Bu_4NI, DMF, rt, 94%; (e) AcOH/THF/H_2O = 3:2:1, rt, 87%; (f) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, rt, 95%; (g) *tert*-BuOK, *n*BuLi, THF, *trans*-2-butene, −100 °C to −50 °C then (−)-*B*-methoxy-diisopinocampheylborane, $BF_3{\cdot}Et_2O$, **13**, −78 °C then 3 M aq NaOH, 35% H_2O_2, reflux; (h) MOMCl, iPr_2NEt, CH_2Cl_2, reflux 65% over two steps: (i) OsO_4 in *tert*-BuOH, NMO, acetone/H_2O = 6:1, rt, 92%; (j) $NaIO_4$, acetone/H_2O = 4:1, rt; (k) 1,1-(dibromopropyl)triphenylphosphonium bromide, *n*BuLi, Et_2O, −78 °C, 77% over two steps; (l) bis(pinacolato)diboron, $PdCl_2(PPh_3)_2$, PPh_3, PhOK, toluene, 50 °C, 78%; (m) DDQ, CH_2Cl_2, aq phosphate buffer, rt, 79%; (n) $PdCl_2$(dppf) (cat.), 3 M aq NaOH, degassed THF, reflux, 71%; (o) MnO_2, CH_2Cl_2, rt, 97%; (p) degassed toluene, BHT (cat.), 70 °C, 5 d, 97%.

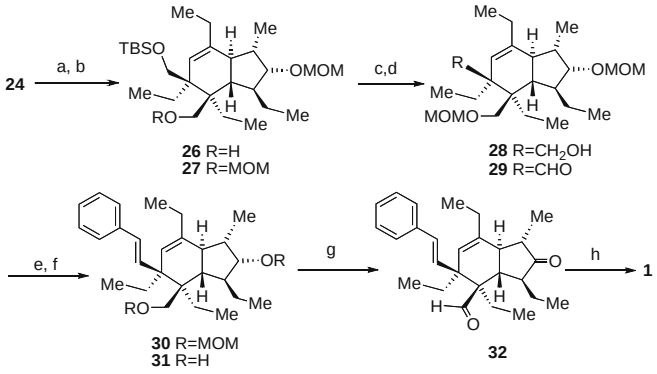
Hydride reduction of **9** followed by protection of the resulting allylic alcohol **10** as the (4-methoxyphenyl)methyl (MPM) ether provided **11**. Deprotection of the TBS group in **11** under acidic conditions provided **12**. Swern oxidation of **12** provided aldehyde **13** efficiently. The stereoselective introduction of an *anti*-β-methylhomoallylic alcohol unit was next explored. We eventually found that the Brown crotylboration protocol applied to **13** provided the most satisfactory result for our expectations. Thus, exposure of (*E*)-crotyldiisopinocampheylborane,[12] prepared by mixing the potassium salt of *trans*-2-butene and (-)-*B*-methoxydiisopinocampheylborane, to **13** in the presence of $BF_3{\cdot}Et_2O$, followed by treatment with alkaline H_2O_2, provided the desired *anti*-β-methylhomoallylic alcohol **14** with high stereoselectivity.[13,14] Protection of the homoallylic alcohol **14** as the methoxymethyl (MOM) ether provided **15**, which was converted into aldehyde **17** by a two-step carbon-carbon bond cleavage via diol **16**. The Wittig olefination of **17** with 1,1-(dibromopropyl)triphenylphosphonium bromide[15] in the presence of base (*n*BuLi) at −78 °C provided stereoselectively the (*E*)-trisubstituted bromoolefin **18** (*E*/*Z* > 20:1 on the basis of ^1H NMR analysis). Treatment of **18** with bis(pinacolato)diboron[16] in the presence of $PdCl_2(PPh_3)_2$, PPh_3, and PhOK in toluene at 50 °C provided vinylboronate **19** in a good yield of 78%. The DDQ-mediated deprotection of the MPM group in **19** provided allylic alcohol **20**. The Suzuki–Miyaura cross-coupling of **20** and (*E*)-vinyl iodide **21**[17] under the standard Pd-catalyzed conditions provided the desired coupling product **22** uneventfully. Oxidation of the allylic alcohol **22** with MnO_2 provided α,β-unsaturated aldehyde **23**, the substrate for the IMDA reaction.[18] To our satisfaction, prolonged (5 days) heating of **23** at 70 °C in toluene provided the desired *endo*-adduct **24** as a sole product in an excellent yield of 97%.[19]

As depicted in Scheme 3, the observed exclusive *endo*- and π-facial selectivity in the IMDA reaction of **23** was reasonably explainable using two transition states, **23**-*endo* leading to **24** and **23**-*exo* leading to undesired *cis*-fused *exo*-adduct **25**.[20] Regarding the depicted two transition states, **23**-*exo* suffers significantly as a result of a severe allylic interaction ($A^{(1,3)}$ strain) between the ethyl substituent at C-4 and the methyl group at C-6. In the case of **23**-*endo*, this interaction can be avoided; thus, the IMDA reaction proceeded via the **23**-*endo* transition state, leading to **24** exclusively.[21]

The transformation of the cycloadduct **24** into **1** is summarized in Scheme 4. $NaBH_4$ reduction of **24**[22] and protection of the resulting primary alcohol **26** with MOMCl provided **27**. Deprotection of the TBS group in **27** and successive Swern oxidation of the resulting primary alcohol **28** provided the aldehyde **29**. Introduction of the styryl group into **29** was accomplished by a Horner–Wadsworth–Emmons olefination with the excess amount of the anion generated from diethyl (benzyl)phosphonate with *n*BuLi at 0 °C. As a result, the styryl derivative **30** was obtained in a good yield of 88%. Deprotection of both MOM groups in **30** and Dess–Martin oxidation[23] of the resulting diol **31** provided the aldehyde-keto intermediate **32**. Finally, Kraus–Pinnick oxidation[24] of **32** provided (+)-spiculoic acid A (**1**). The spectral data (^1H and ^{13}C NMR) of the



Scheme 3. The *endo*-and *exo*-transition states for the IMDA reaction of **23**.



Scheme 4. Conversion of the IMDA adduct **24** into **1**. Reagents and conditions: (a) $NaBH_4$, MeOH/THF = 1:1, rt, 91%; (b) MOMCl, iPr$_2$NEt, CH_2Cl_2, reflux; (c) nBu$_4$NF, THF, 50 °C, 99% over two steps; (d) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, rt, 90%; (e) diethyl (benzyl)phosphonate, nBuLi, THF, −78 °C then **29**, 0 °C, 88%; (f) CSA, MeOH, 40 °C, 6 d; (g) Dess–Martin periodinane, CH_2Cl_2, rt, 85% over two steps; (h) $NaClO_2$, 2-methyl-2-butene, phosphate buffer, *tert*-BuOH/H_2O = 5:1, rt, 82%.

synthetic **1** were identical with those reported for the natural product **1**.[1] Furthermore, $[\alpha]_D$ of the synthetic **1** [$[\alpha]_D^{25}$ +102 (*c* 0.38, CH_2Cl_2)] coincided with that reported for the natural sample [$[\alpha]_D$ +110 (*c* 0.1, CH_2Cl_2)], including its sign.[25]

In summary, we have achieved the first total synthesis of natural (+)-spiculoic acid A (**1**), which featured the IMDA reaction of the trienic aldehyde **23** for the highly stereoselective and expeditious construction of a core bicyclic structure with correct stereochemistry for the total synthesis of **1**. The highly stereoselective outcome of the IMDA reaction can be explained by the presence or by the absence of the steric hindrance in the two possible transition states. Relying on the mentioned transition state argument, we have also accomplished the synthesis of a cis-fused spiculoic acid A congener.

Acknowledgments

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Supplementary data

The experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.101.

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7. The absolute stereochemistries of **2**–**5** are still unknown, and the structural drawings for **2**–**5** in Figure 1 are arbitrary.
8. Although the IMDA approach to the total synthesis of (−)-spiculoic acid A disclosed by the Baldwin/Lee group was straightforward for the construction of the bicyclic structure possessing all the requisite functionalities, the desired cycloadduct was obtained in a less satisfactory yield of 25% (100 °C in toluene).
9. A recent review on the IMDA reactions applied to natural product synthesis, see: Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779–4807.
10. We expected that the attempted IMDA reaction would be effectively accelerated in the presence of the unsaturated aldehyde moiety as the dienophile part in place of the unsaturated ester used in the Baldwin/Lee's total synthesis. And we also expected higher reactivity and higher stereoselectivity in the IMDA reaction for construction of the core bicyclic structure of **1** by using substrate **6**, which possesses a sterically bulky substituent such as a (*tert*-butyldimethylsilyloxy)methyl group in the diene part. On the other hand, the Baldwin/Lee substrate for their IMDA approach incorporated a linear styryl group in the diene part, which may deactivate in the diene part to some extent.
11. According to the Fukumoto's precedent, the starting material **7**, that is, (2*S*)-2-[(*tert*-butyldimethylsilyloxy)methyl]butan-1-ol, was synthesized using an Evans' aldol approach with the (*S*)-phenylalanine-derived chiral auxiliary, see: Ihara, M.; Setsu, F.; Shoda, M.; Taniguchi, N.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 5317–5323.
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13. The diastereomeric ratio of this asymmetric crotylboration products was approximately 3 to 1 in favor of **14** based on ^1H NMR analysis of the crude mixture. The monor *anti*-adduct, produced as a result of opposite π-facial selection, was clearly separated from **15** by chromatography on silica gel after converting into the corresponding MOM ethers through the MOM ether formation of the adducts mixture.
14. The *anti*-configuration of the β-methylhomoallylic alcohol part in **14** was confirmed using advanced intermediates by examination of their ^1H NMR analysis.
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17. The vinyl iodide **21** was synthesized starting from commercially available diethyl ethylmalonate as follows: (1) diethyl ethylmalonate, NaH, Et_2O, reflux, 1 h, then CHI_3, reflux, 24 h; (2) KOH, EtOH/H_2O = 3:1, reflux, 60 h: (3) $LiAlH_4$, THF, rt, 3 h, 30% over 3 steps; (4) TBSCl, DMAP, Et_3N, CH_2Cl_2, rt, 1 h, 83%. For an analogous procedure, see: Baker, R.; Castro, J. L. *J. Chem. Soc. Perkin Trans.1* **1990**, 47–65.
18. The direct formation of the IMDA substrate **23** was also observed in the Suzuki–Miyaura coupling of **20** and **21** when the cross-coupling was executed with an excess amount of the Pd-catalyst in DMF in the presence of Cs_2CO_3 at 70 °C for a prolonged reaction time (more than 3 days). Under these conditions, the formation of **23** and a spontaneous IMDA reaction occurred. $NaBH_4$ reduction of the crude reaction mixture and purification of crude product on silica gel provided **26** in a less effective overall yield of 33% from **20**. For an example of the palladium-catalyzed oxidation of primary (allylic) alcohols, See: Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286–1292.
19. As the spontaneous IMDA reaction started at 70 °C under the Suzuki–Miyaura coupling conditions, we kept continuing the IMDA reaction at 70 °C. The IMDA reaction of **23** proceeded at 70 °C rather slowly but cleanly. For completion of the IMDA reaction, it required 5 days. After heating for 1 or 2 days at 70 °C, substantial amount of **23** remained intact. We did not execute the IMDA reaction at other temperatures.
20. It is apparently obvious that the C-8 substituent (an ethyl group) cooperates in realizing the high stereoselectivity of the IMDA reaction. In the two transition states **23**-*endo* and **23**-*exo*, π-facial selectivities are the same as depicted in Scheme 3. On the other hand, opposite π-facial attack in the *endo*-mode is significantly unfavorable owing to a severe allylic interaction ($A^{(1,3)}$ strain) generated between the ethyl group at C-8 and the ethyl group in the dienophile part.
21. We obtained further evidence for this steric disadvantage generated by the allylic strain in the IMDA reaction. Thus, we synthesized another IMDA substrate, in which the configuration of methyl substituent at C-6 was opposite to that in **23**. The IMDA reaction of this substrate provided an *exo*-adduct predominantly. In this case, a severe $A^{(1,3)}$ strain was most likely in an *endo*-mode transition state. This *exo*-adduct was eventually converted into a diastereomer of spiculoic acid A, namely, 2,5,6-tri-*epi*-spiculoic acid A, by the analogous reaction sequence used for the synthesis of **1**.
22. In another approach, we obtained the following result: $NaClO_2$ oxidation of the aldehyde functionality in an *endo*-cycloadduct similar to **24**, which possesses a (4-methoxyphenyl)methyl (MPM) group in place of the TBS group, provided the corresponding carboxylic acid. After methyl esterification, the removal of the MPM group in the resulting ester with DDQ was investigated. As a result, only γ-lactonization occurred exclusively after deprotection of the MPM group. It was, thus, obvious that the facile γ-lactone formation occurred spontaneously owing to the vicinal cis-relationship of the carboxylic acid and the primary hydroxyl group. Furthermore, we could not find efficient conditions to open this γ-lactone for further functionalization. From this result, we concluded that the synthetic route involving direct oxidation of the aldehyde **24** to the corresponding carboxylic acid could not evade the above-mentioned synthetic dead end.
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25. The reported $[\alpha]_D$ for unnatural (−)-spiculoic acid A: $[\alpha]_D^{22}$ −97 (*c* 0.16, CH_2Cl_2), see Ref. 5a.