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Synthetic Studies of Antitumor Natural Products Superstolides A and B. Construction of C20–C26 Fragment of Superstolide A

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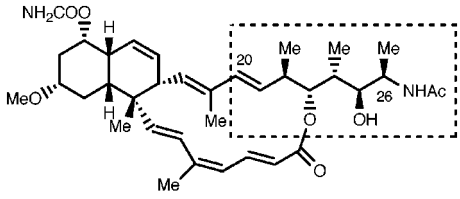
ABSTRACT

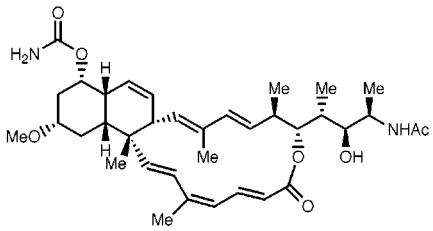


Superstolide A

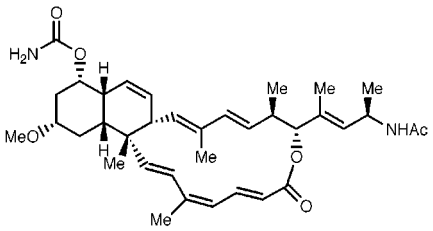
The C20–C26 portion of the antitumor macrolide superstolide A was synthesized by employing Brown's asymmetric crotylboronate methodology.

Superstolides A (**1**) and B (**2**) were isolated from the deep−water marine sponge *Neosiphonia superstes* collected off New Caledonia.[1] The structural novelty of these two molecules is characterized by a unique 16-membered macrolactone attached to a highly functionalized *cis*-decalin (Figure 1).

Superstolides A (**1**) and B (**2**) are highly cytotoxic against human bronchopulmunary non-small cell lung carcinoma NSCLC-N6-L16 cells with IC_{50} values of 0.04 and 0.039 μg/mL, respectively.[1] Both superstolides A (**1**) and B (**2**) exhibited potent cytotoxicity against murine leukemia P388 cells with an IC_{50} of 0.003 μg/mL and human nasopharyngeal carcinoma KB cells with IC_{50} values of 0.02 mg/mL and 0.005 μg/mL, respectively.[1] In addition, superstolide A (**1**) is also highly cytotoxic against human colon carcinoma HT29 cells with an IC_{50} of 0.04 μg/mL, and murine leukemia cells



1: Superstolide A



2: Superstolide B

Figure 1.

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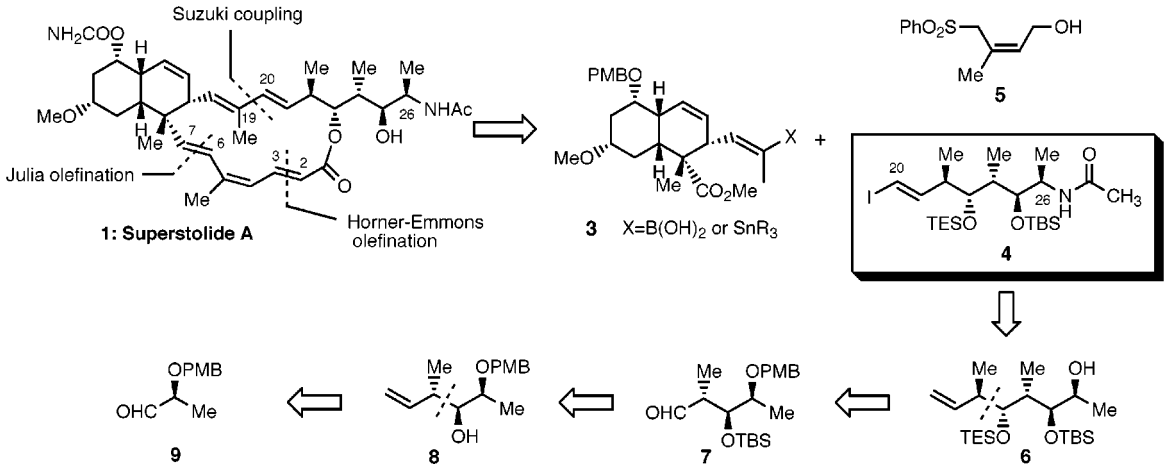
Scheme 1

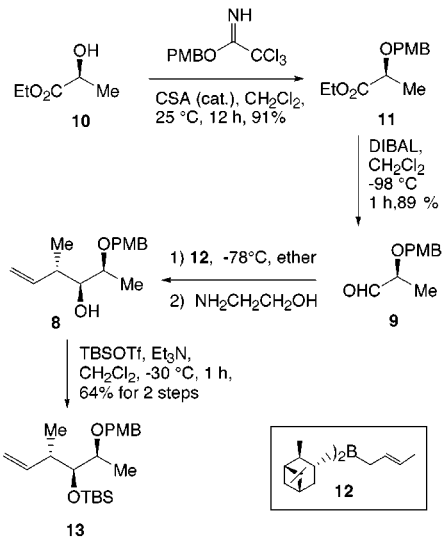


expressing resistance toward doxorubicine P388 Dox with an IC_{50} of 0.02 μg/mL.[1] Roush and co-workers published a diastereoselective synthesis of the *cis*-fused decalin using an intramolecular Diels−Alder reaction in 1996.[2] However, a complete total synthesis has not yet been reported.

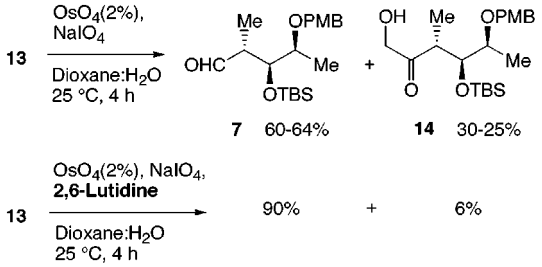
As part of our program studying the chemistry and biology of antitumor natural products, we recently initiated a project directed toward total synthesis of superstolides A and B. Our retrosynthetic analysis of superstolide A (**1**) is shown in Scheme 1. Disconnections at C2−C3, C6−C7, and C19−C20 reveals three key fragments, **3**, **4**, and **5**, with Horner−Emmons olefination, Julia olefination, and Suzuki (or Stille) coupling playing crucial roles in the synthetic strategy. Herein, we wish to report the asymmetric synthesis of fragment **4**, the linear polypropionate (C20−C26) portion of superstolide A.

(*S*)-(−)-Ethyl lactate **10** was the point of departure for the synthesis of the key fragment **4** (Scheme 2). Compound **10** reacted with *p*-methoxybenzyltrichloroacetimidate under acidic conditions to give compound **11** in 91% yield.[3] Reduction of ester **11** with DIBAL at −98 °C provided (*S*)-2-(4-methoxybenzyloxy)propionaldehyde **9** in 89% yield. Reaction of aldehyde **9** with (*d*)-(*E*)-crotyldiisopinocampheylborane **12** under Brown's conditions[4] afforded homoallylic alcohol **8** with complete diastereo- and enantioselectivity. Protection of the secondary alcohol **8** by TBSOTf afforded compound **13** in 64% yield from **9**. The oxidative cleavage of the double bond of compound **13** under the literature conditions[5] gave the desired aldehyde **7** in low yield (60−64%) due to the overoxidation of the diol intermediate leading to the formation of α-hydroxy ketone **14** (Scheme 3). We found the reaction solution to be acidic (pH = 2).

Scheme 2



Scheme 3



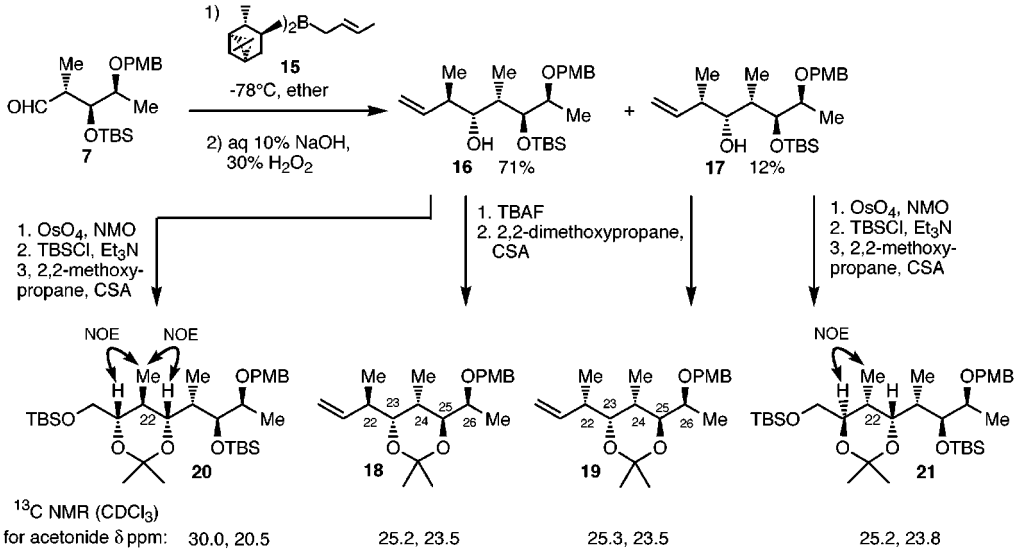
Addition of a base could suppress the formation of compound **14** and increase the yield of aldehyde **7**. After screening of a few bases, we found that 2,6-lutidine gave the best results without racemization of the α-methyl group. The desired aldehyde **7** was obtained in 90%.

(1) (a) D'Auria, M. V.; Debitus, C.; Paloma, L. G.; Minale, L.; Zampella, A. *J. Am. Chem. Soc.* **1994**, *116*, 6658. (b) D'Auria, M. V.; Debitus, C.; Paloma, L. G.; Minale, L.; Zampella, A. *J. Nat. Prod.* **1994**, *57*, 1595.

(2) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989.

(3) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

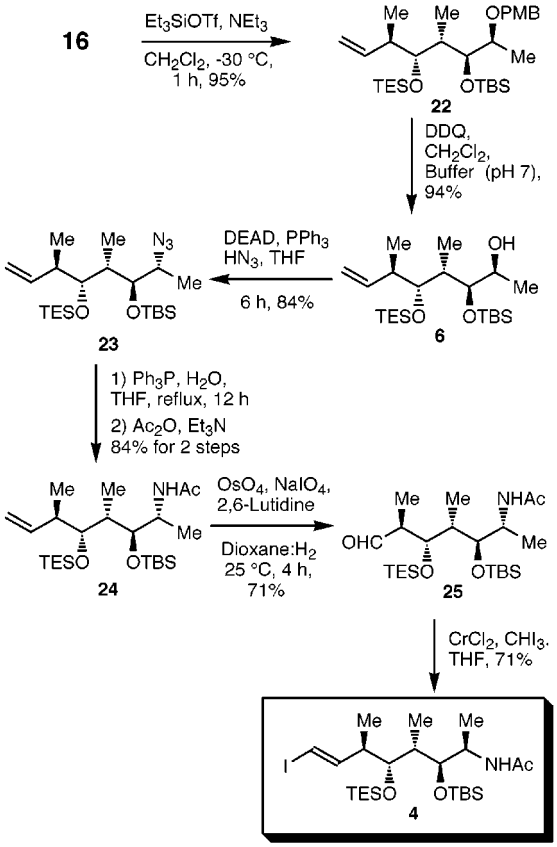
Scheme 4



Aldehyde **7** reacted with (*l*)-(*E*)-crotyldiisopinocampheylborane **15** under Brown's conditions[4] to provide homoallylic alcohol **16** along with minor diastereomer **17** (6:1) (Scheme 4). The stereochemistry of the secondary alcohols of compounds **16** and **17** was determined on the basis of the ^{13}C NMR analysis of 1,3-diol acetonides **18** and **19** derived from **16** and **17**, respectively.[6] It is surprising that the configuration of the secondary alcohols in both **16** and **17** is the requisite *R*. The absolute configuration of the methyl groups at C22 of compounds **16** and **17** was determined to be *R* and *S*, respectively, on the basis of proton homonuclear decoupling analysis, NOESY experiments, and ^{13}C NMR analysis of 1,3-diol acetonides of **20** and **21**.

After alcohol **16** was protected by a TES group, the *p*-methoxybenzyl group was removed by DDQ to give compound **6** in 94% yield (Scheme 5). The attempt to convert **6** to **23** under Mitsunobu conditions with diphenyl phosphorazidate[7] led to the exclusive formation of an intramolecular silyl transfer product. Our initial effort to employ HN_3[8] as the azide source gave either mainly intramolecular silyl transfer product or simply no reaction.[9] However, we found that by employing freshly prepared HN_3 which was further dried over 3 Å MS, the Mitsunobu reaction went smoothly and the desired azide **23** was obtained in 84% yield. Reduction of the azide **23** by Staudinger reaction[10] followed by acylation of the primary amine afforded amide **24** in 84% yield from **23**. Oxidative cleavage of the terminal double bond of **24** under our modified procedure gave aldehyde **25** in 71% yield. By employing Takai's reaction, aldehyde **25** was homologated to the requisite *trans*-vinyl iodide **4** in 71% yield with a ratio of 11:1 of *trans* to *cis* isomer.[11]

Scheme 5



(4) (a) Brown, H. C.; Ramachandran, P. V. *Adv. Asym. Synth.* **1995**, *1*, 147 and references therein. (b) Brown, H. C.; Singaram, B. *Acc. Chem. Res.* **1988**, *21*, 287 and references therein. (c) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570 and references therein.

(5) Schroder, M. *Chem. Rev.* **1980**, *80*, 187 and references therein.

(6) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(7) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.

(8) Fabiano, E.; Golding, B. T.; Sadeghi, M. M. *Synthesis* **1987**, *87*, 190.

(9) Other example of intramolecular silyl transfer product formation: Brandstetter, V. H.; Zbiral, E. *Helv. Chim. Acta* **1980**, 327.

In conclusion, fragment **4** was successfully synthesized in 12 steps using Brown's asymmetric crotylborane methodologies. By employing the enantiomer of starting material **10** and different crotylboranes, it will be possible to synthesize different diastereomers and enantiomers of fragment **4** which will be used in SAR studies. Currently, the asymmetric synthesis of fragment **3** is underway and will be reported in due course.

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Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763.

(11) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159.