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Synthetic Studies toward the Construction of the *cis*-Decalin Portion of Superstolides A and B. Application of a Sequential Double Michael Reaction and an Anionic Oxy-Cope Rearrangement

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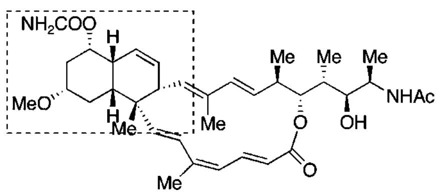
ABSTRACT



A highly convergent strategy for the asymmetric synthesis of the *cis*-decalin portion of the antitumor macrolide superstolide A was developed. The key reactions in our approach involve a sequential double Michael reaction and an anionic oxy-Cope rearrangement.

As part of our program studying the chemistry and biology of antitumor natural products, we initiated a project directed toward the total synthesis of Superstolides A (**1**) and B (**2**) that 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 NSCLC-N6-L16 cells, with IC_{50} values of 40 and 39 ng/mL, respectively.[1] They exhibited potent cytotoxicity against murine leukemia P388 cells, with an IC_{50} of 3 ng/mL, and human nasopharyngeal carcinoma KB cells, with IC_{50} values of 20 and 5 ng/mL, respectively.[1] In addition, superstolide A is also highly cytotoxic against HT29 cells, with an IC_{50} of 40 ng/mL, and murine leukemia cells expressing resistance toward doxorubicine P388 Dox, with an IC_{50} of 20 ng/mL.[1] These factors make both molecules

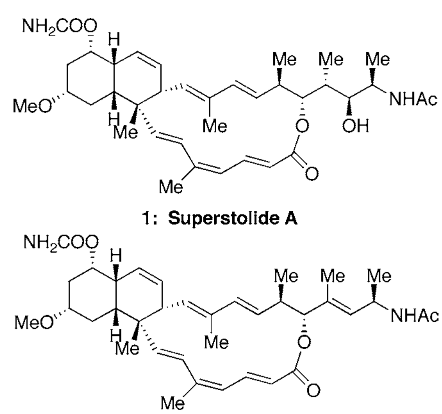


Figure 1. Antitumor marine macrolide superstolildes A and B.

(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.

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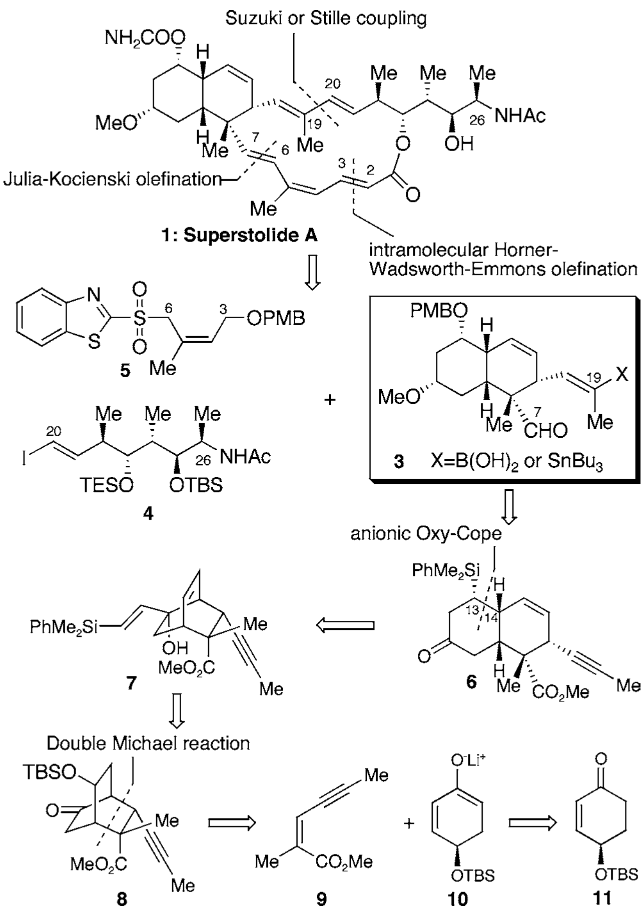
attractive synthetic targets.[2] However, a complete total synthesis has not yet been reported.

Our retrosynthetic analysis of superstolide A (**1**) is shown in Scheme 1. Disconnections at C2−C3, C6−C7, and C19−C20 reveal three key fragments **3**−**5** with intramolecular Horner−Wadsworth−Emmons olefination, Julia−Kocienski olefination, and Suzuki (or Stille) coupling playing crucial roles in the synthetic strategy. Fragment **4** (C20−C26) of superstolide A was successfully synthesized employing Brown's asymmetric crotylboronate methodology.[2b] Herein, we report our synthetic studies toward the construction of fragment **3**, the *cis*-decalin portion of the molecule.

Scheme 1. Retrosynthetic Analysis of Superstolide A

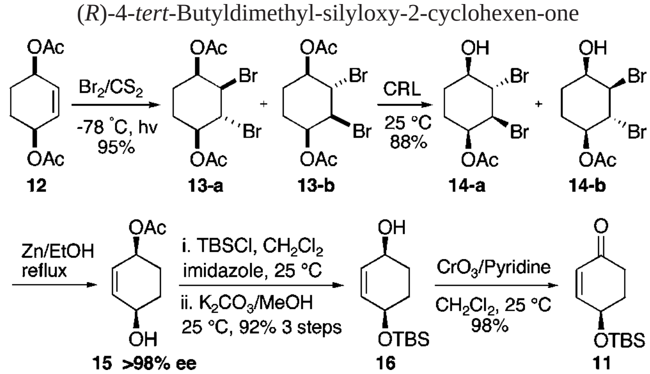


Fragment **3** is the core structure of the molecule. It is highly functionalized with six stereogenic carbons, including one quaternary carbon (Scheme 1). Disconnection at C13−C14 would be a crucial step. An anionic oxy-Cope rearrangement of **7** was expected to give the *cis*-fused bicyclic **6**, which after functional group manipulation would lead to fragment **3**. Compound **7** was envisaged to be formed via an asymmetric double Michael reaction between **9** and the cross-conjugated dienolate **10** derived from compound **11**. The major advantage of this double Michael approach might be that it could take place at low temperature and give a product with predominately *endo* selectivity as well as excellent diastereofacial selectivity.[3]

(*R*)-4-*tert*-Butyldimethyl-silyloxy-2-cyclohexen-one **11** is a very useful building block that has been used in organic synthesis on a number of occasions.[4] The advantage of using this compound as a starting material resides in the excellent diastereoselectivity often observed in its conjugate additions since all stereochemistry is introduced by communication from the stereogenic center at the C-4 position of compound **11**. However, to the best of our knowledge, asymmetric double Michael reactions employing cross-conjugated dienolate **10** derived from compound **11** have never been reported previously.

An enzymatic literature procedure was modified to prepare compound **11** (Scheme 2).[5] Bromination of *cis*-1,4-diacetoxy-2-cyclohex-ene **12**[6] gave the *trans*-dibromo compounds **13a** and **13b** in 95% yield. Asymmetric hydrolysis of **13** by

Scheme 2. Asymmetric Synthesis of (*R*)-4-*tert*-Butyldimethyl-silyloxy-2-cyclohexen-one



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(5) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia. L. A. *J. Org. Chem.* **1991**, *56*, 2656. For asymmetric synthesis of 4-hydroxy-2-cyclohexenone, see also: (a) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem*. **1989**, *54*, 3738. (b) Gebauer, O.; Bruckner, R. *Liebigs Ann*. **1996**, 1559. (c) Carreño, M. C.; García Ruano, J. L.; Garrido, M.; Ruiz, M. P.; Solladié, G. *Tetrahedron Lett*. **1990**, *31*, 6653. (d) Brunjes, R.; Tilstam, U.; Winterfeldt, E. *Chem. Ber*. **1991**, *124*, 1677. (e) Evarts, J. B, Jr.; Fuchs, P. L. *Tetrahedron Lett*. **2001**, *42*, 3673. (f) Demir, A. S.; Ozge, S. *Org. Lett*. **2002**, *4*, 2021. (g) Morgan, B. S.; Hoenner, D.; Evans, P.; Roberts, S. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2807.

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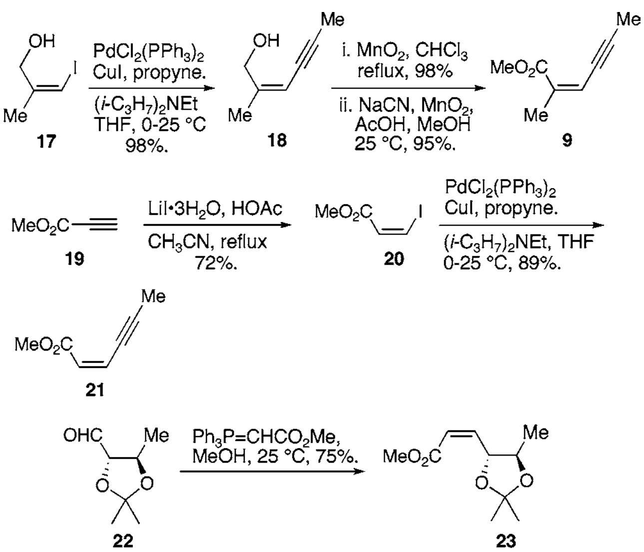
Candida rugosa lipase (CRL) provided **14a** and **14b** in 88% yield. Debromination followed by protection and hydrolysis gave compound **16** in 92% yield. Oxidation of compound **16** afforded enantiomerically pure **11** in 98% yield. This approach is highly reproducible and can easily be scaled up (100 g scale) to give excellent overall yield with >98% ee. Moreover, the approach can also be easily adapted to the synthesis of the (*S*)-isomer of compound **11** through protecting group manipulation.

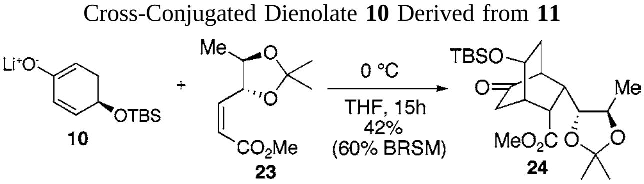
The key reaction in our approach is a highly controlled double Michael reaction for the asymmetric construction of bicyclo[2.2.2]octanone **8** employing the cross-conjugated dienolate **10** derived from compound **11**. A model study has been conducted to examine the feasibility of this key reaction. Several α,β-unsaturated esters have been prepared and carefully examined as partners in this double Michael reaction. Scheme 3 shows the preparation of three representative α,β-unsaturated esters.

Scheme 3. Preparation of α,β-Unsaturated Esters



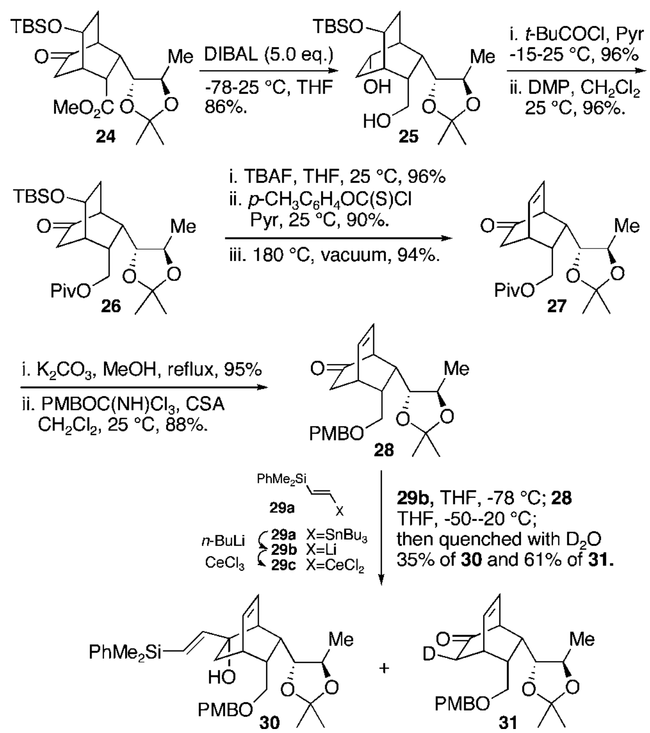
We found that both compounds **9** and **21** were poor partners in our double Michael reaction, and no desired reaction was observed. However, compound **23** underwent the requisite asymmetric double Michael reaction with **10** (Scheme 4).[7] The reaction was highly facial- and stereoselective and afforded only one of the eight possible diastereomers. An efficient double asymmetric induction process occurred during the double Michael reaction since two configurationally defined components reacted and four new stereogenic centers were created in a controlled manner. The stereochemical course was initially defined by the first Michael addition that occurred from the *endo* approach of the dienolate **10**, *anti* to the bulky OTBS substituent, to the *re*-face of the conjugate position of the Michael acceptor **23**. The following two stereogenic centers in the second Michael addition were imposed by the initial step. To the best of our knowledge, this is the first successful application of asymmetric double Michael reactions employing cross-conjugated dienolate **10** derived from compound **11**.

Scheme 4. Asymmetric Double Michael Reaction Employing Cross-Conjugated Dienolate **10** Derived from **11**



Treatment of compound **24** with an excess of DIBAL provided diol **25** in 86% yield (Scheme 5). Regioselective protection of the primary alcohol with a pivaloyl ester followed by Dess−Martin oxidation of the secondary alcohol gave compound **26** in 92% yield for two steps. Deprotection of the TBS group followed by the conversion of the resulting secondary alcohol to olefin afforded compound **27**, which underwent protecting group exchange to furnish ketone **28** in excellent yield. 1,2-Addition of vinyllithium reagent **29b**[8] to ketone **28** gave the tertiary alcohol **30** with complete stereoselectivity, but the yield was only 35%. The low yield was due to the extensive enolization of the ketone moiety of compound **28** by vinyllithium **29b**. Compound **31** was isolated in 61% yield after the reaction was quenched with

Scheme 5. Synthesis of Compound **30**



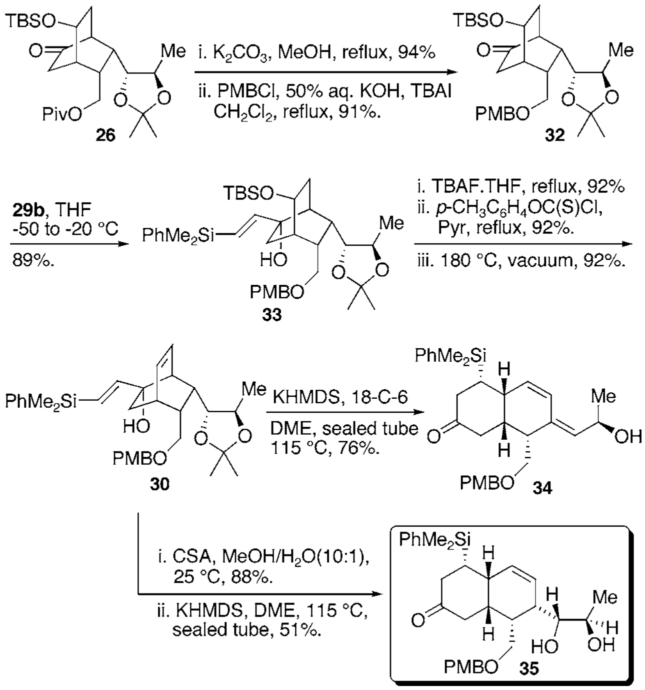
(7) Cross-conjugated dienolate **10** was prepared by the addition of a solution of **11** in THF to 1 equiv of LDA at −78 °C. The reaction mixture was warmed to −40 °C in 30 min.

(8) Kraihanzel, C. S.; Losee, M. L. *J. Orgnomet. Chem.* **1967**, *10*, 427.

D_2O. No improvement was observed when vinyl cerium reagent **29c** was employed in this reaction.

We speculated that increased steric hindrance might prevent the facile enolization of the ketone moiety of bicyclo[2.2.2]octanone. Therefore, we decided to investigate the requisite 1,2-addition on a different substrate such as compound **32** (Scheme 6). Hydrolysis of the pivaloyl ester

Scheme 6. Synthesis of *cis*-Decalin **35** via an Anionic Oxy-Cope Rearrangement



26 followed by the protection of the primary alcohol with a PMB group gave ketone **32**. As expected, 1,2-addition of vinyllithium reagent **29b** to ketone **32** provided tertiary alcohol **33** in 89% yield with complete stereoselectivity. Deprotection of the TBS group followed by the conversion of the resulting secondary alcohol to olefin afforded compound **30** in excellent yield.

Now the stage was set for the proposed anionic oxy-Cope rearrangement.[9] Treatment of compound **30** with excess KHMDS in DME at 115 °C in a sealed tube furnished the *cis*-decalin **34** in 76% yield. Unfortunately, the acetonide protecting group underwent a base-promoted β-elimination after the desired anionic oxy-Cope rearrangement. Limiting the amount of base KHMDS to 1 equiv did not prevent the β-elimination, and a large amount of starting material **30** was also recovered. To solve this problem, we decided to first remove the acetonide protecting group to give the free diol, which was subjected to the anionic oxy-Cope rearrangement to afford the requisite compound **35** in 51% yield (unoptimized).[10] It should be noted that four stereogenic centers in compound **35** have been set in their requisite forms and two more stereogenic centers can be easily installed late in the process. Currently, the conversion of compound **35** to fragment **3** is underway and will be reported in due course.

In conclusion, we have shown for the first time that cross-conjugated dienolate **10** derived from compound **11** can be employed in the double Michael reaction for the asymmetric synthesis of highly functionalized bicyclo[2.2.2]octanone. Furthermore, we have demonstrated that the combination of our asymmetric double Michael reaction and an anionic oxy-Cope rearrangement is a powerful approach for the synthesis of the *cis*-decalin portion of the antitumor marine natural products superstolides A and B.

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Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) All compounds were fully characterized. The stereochemistry was determined by extensive two-dimensional NMR analysis.