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# Controlling the Facial Selectivity of Asymmetric [4 + 2] Cyclo-additions: A Concise Synthesis of the *cis*-Decalin Core Structure of Superstolides A and B

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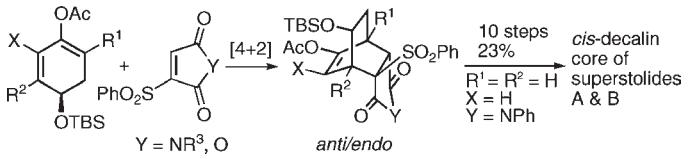
## ABSTRACT




**Regio-, stereo-, and facial selective [4 + 2] cycloadditions between highly activated vinyl sulfones and 1,3-dienes derived from (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclohexen-1-one provide a powerful approach for the asymmetric synthesis of compounds containing the bicyclo[2.2.2]octanone carbon skeleton. This new methodology has been successfully applied to the asymmetric synthesis of the *cis*-decalin core structure of the potent anticancer marine natural products superstolides A and B.**

Bicyclo[2.2.2]octanone derivatives have attracted considerable interest from organic chemists because the unique molecular architecture can be found in natural products[1] and can serve as scaffolds in the design of therapeutic agents.[2] In addition, the rigid bicyclo[2.2.2]-octanone structure can undergo versatile transformations to other molecular structures that are difficult to be constructed.[3] Although a number of methods have been developed for the synthesis of racemic bicyclo[2.2.2]-octanone derivatives,[4] asymmetric synthesis of highly functionalized bicyclo[2.2.2]octanone derivatives still poses a formidable synthetic challenge.[5]

We have recently reported for the first time that 1,3-dienes derived from (*R*)-4-*tert*-butyldimethyl-silyloxy-2-cyclohexen-1-one can undergo stereo- and facial selective asymmetric [4 + 2] cycloadditions with various activated

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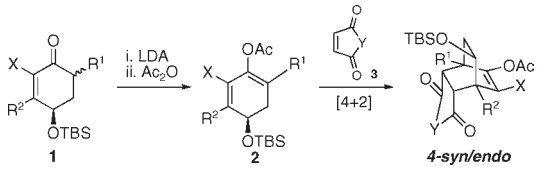
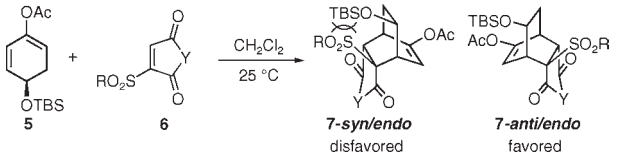
symmetric dienophiles (Scheme 1).[6] These reactions are exclusively *endo* selective and occur at the face *syn* to the bulky TBSO group to afford predominantly (or sometimes exclusively) *syn*/*endo* products. These controlled [4 + 2] cycloadditions increase the asymmetric complexity from one asymmetric center in the starting material to five asymmetric centers in the products in a single step and provide a powerful approach for the asymmetric synthesis of compounds containing the bicyclo[2.2.2]octanone carbon skeleton.

**Scheme 1.** [4 + 2] Cycloadditions with *Syn* Facial Selectivity




To expand the scope of these new asymmetric [4 + 2] cycloadditions, we decided to investigate the possibility of employing unsymmetric dienophiles. We were particularly interested in highly activated unsymmetric dienophiles such as vinyl sulfone **6** (Scheme 2).[7] Because of the steric hindrance between the alkyl (or aryl) sulfone moiety and TBSO group, **7-*anti*/*endo*** should be formed predominantly.

**Scheme 2.** [4 + 2] Cycloadditions with *Anti* Facial Selectivity




In the event, 1,3-diene **5** reacted with dienophile **6a**[8] to provide **7a** in 92% yield (entry 1, Table 1). The reaction was highly regioselective and completely stereo- and facial selective. As expected, the [4 + 2] cycloaddition occurred at the face *anti* to the bulky TBSO group, and **7-*syn*/*endo*** was not detected. The facial selectivity observed in this reaction is opposite to that of those reactions employing symmetric dienophiles shown in Scheme 1.

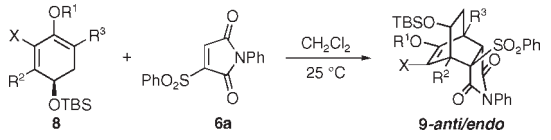
Several highly reactive vinyl sulfones (**6b**−**e**) were chosen to study the scope and limitation of this asymmetric [4 + 2] cycloaddition, and the results are summarized in Table 1. All reactions provided exclusive **7-*anti*/*endo*** products in very good yields (entries 2−5, Table 1). These experiments showed that the N-substituent on the maleimide moiety of the dienophile had no effect on the stereo- and facial selectivity of the [4 + 2] cycloadditions (entries 1−3, Table 1). In addition, α-(phenylsulfonyl)maleic anhydride **6d** reacted with 1,3-diene **5** in the same fashion. The relatively low yield of **7d** was due to the decomposition of the anhydride moiety of the product on the silica gel during flash column chromatography.[9] Furthermore, it was found that the phenylsulfonyl group could be replaced by the *tert*-butylsulfonyl group, and there was no change in the facial selectivity of the reaction (entry 5, Table 1).

**Table 1.** [4 + 2] Cycloadditions with *Anti* Facial Selectivity[a]

| entry | 1,3-diene **5** | dienophile **6** | **7**-*anti*/*endo* yield[b] (%) |
|---|---|---|---|
| 1 | **5** | **6a**, R = Ph, Y = NPh | **7a**, 92 |
| 2 | **5** | **6b**, R = Ph, Y = NBn | **7b**, 93 |
| 3 | **5** | **6c**, R = Ph, Y = NEt | **7c**, 79 |
| 4 | **5** | **6d**, R = Ph, Y = O | **7d**, 58 |
| 5 | **5** | **6e**, R = *t*-Bu, Y = NPh | **7e**, 83 |

[a] All reactions were run in $CH_2Cl_2$ at 25 °C for 1 day under argon. [b] These were isolated yields. All compounds were fully characterized.

**Scheme 3.** [4 + 2] Cycloadditions with *Anti* Facial Selectivity




We then turned our attention to the scope of chiral 1,3-dienes (Scheme 3). The results of asymmetric [4 + 2] cycloadditions between various chiral 1,3-dienes (**8a**−**e**) and vinyl sulfone **6a** are summarized in Table 2.[10]

Compound **9-*anti*/*endo*** was the only product that was isolated from the reaction, and the yields (**9a**−**e**) were uniformly excellent. Experimental results show that introducing an alkyl group at the 1 and/or 4 position of the 1,3-diene had no effect on the stereochemical outcome of the reaction (entries 1 and 2, Table 2). It should be noted that among four newly created stereogenic centers in **9b** three of them are quaternary carbons and two of them are bridgehead quaternary carbons, which are difficult to construct. In addition, the reactions were relatively faster when 1,3-diene **8c** with a vinyl carbonate moiety and 1,3-dienes **8d** and **8e** with silyl enol ether moiety were employed (entries

(5) (a) Tzvetkov, N. T.; Schmoldt, P.; Neumann, B.; Stammler, H.-G.; Mattay, J. *Tetrahedron: Asymmetry* **2006**, *17*, 993. (b) Friberg, A.; Johanson, T.; Franzen, J.; Gorwa-Grauslund, M. F.; Frejd, T. *Org. Biomol. Chem.* **2006**, *4*, 2304. (c) Luo, Y.; Carnell, A. J. *J. Org. Chem.* **2010**, *75*, 2057. (d) Dong, S.; Zhu, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2738. (e) Fisher, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (f) Almqvist, F.; Ekman, N.; Frejd, T. *J. Org. Chem.* **1996**, *61*, 3794. (g) Paquette, L. A.; Tsui, H.-C. *J. Org. Chem.* **1996**, *61*, 142. (h) Hua, Z; Yu, W.; Su, M.; Jin, Z. *Org. Lett.* **2005**, *7*, 1939. (i) Kitahara, T.; Miyake, M.; Kido, M.; Mori, K. *Tetrahedron: Asymmetry* **1990**, *1*, 775.

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(7) (a) El-Awa, A.; Noshi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315. (b) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951.

(8) Compounds **6a**−**e** were prepared using the procedure for the preparation of **6d** from the following article: Ramezanian, M.; Abdelkader, M.; Padias, A. B.; Hall, H. K., Jr.; Brois, S. J. *J. Org. Chem.* **1989**, *54*, 2852.

(9) The actual yield was much higher based on the analysis of the $^1$H NMR spectrum of the crude product.

(10) Compounds **8a**−**e** were prepared using the procedures published in ref 6.

3−5, Table 2). Furthermore, entry 5 indicates that an iodo group at the 3 position of the 1,3-diene had no effect on the facial selectivity (entry 5, Table 2).

**Table 2.** [4 + 2] Cycloadditions with *Anti* Facial Selectivity[a]

| entry | 1,3-diene | dienophile | **9**-*anti*/*endo* yield[b] (%) |
|---|---|---|---|
| 1 | **8a**: $R^1$ = Ac, $R^2$ = Me, $R^3$ = X = H | **6a** | **9a**, 83 |
| 2 | **8b**: $R^1$ = Ac, $R^2$ = *n*-Bu, $R^3$ = Me, X = H | **6a** | **9b**, 97 |
| 3 | **8c**: $R^1$ = $CO_2$Me, $R^2$ = H, $R^3$ = X = H | **6a** | **9c**, 87 |
| 4 | **8d**: $R^1$ = TIPS, $R^2$ = H, $R^3$ = Me, X = H | **6a** | **9d**, 90 |
| 5 | **8e**: $R^1$ = TIPS, $R^2$ = H, $R^3$ = Me, X = I | **6a** | **9e**, 91 |

[a] All reactions were run in $CH_2Cl_2$ at 25 °C for 1 day under argon unless other stated. [b] These were isolated yields. All compounds were fully characterized.

The enantiopure products of these highly controlled [4 + 2] cycloadditions contain the rigid bicyclo[2.2.2]octanone carbon skeletons that are rich in both functionality and stereochemical complexity. These compounds are excellent scaffolds for further synthetic manipulations. To demonstrate the synthetic utility we decided to design a concise approach for the conversion of compound **7a** to the *cis*-decalin core structure present in the highly potent anticancer marine natural products superstolides A (**10**) and B (**11**) that were isolated from the deep-water marine sponge *Neosiphonia superstes* collected off New Caledonia (Figure 1).[11,12]

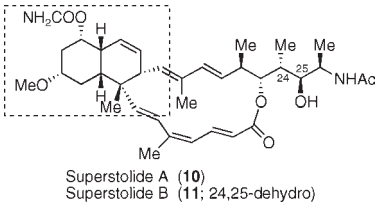
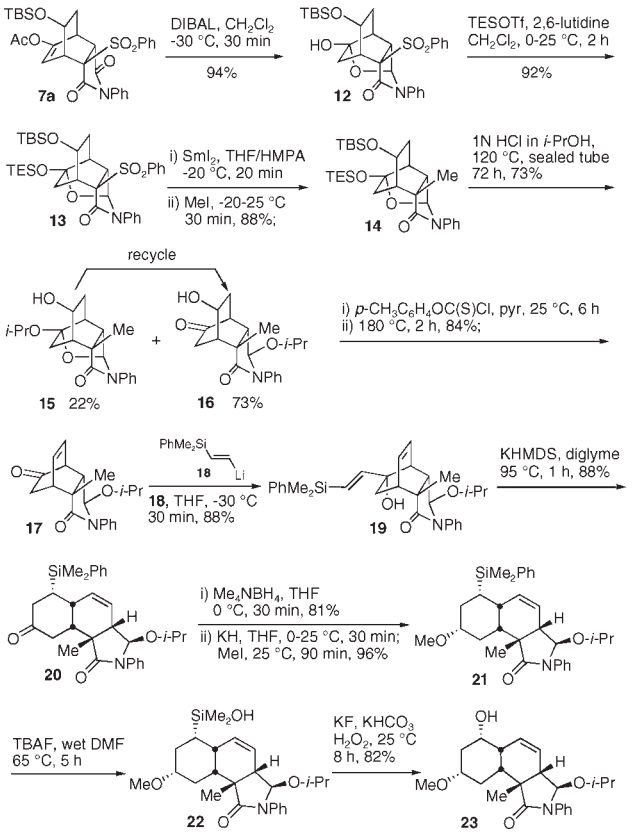



**Figure 1.** Anticancer marine natural products superstolides A and B.

Compound **7a** was chemo- and regioselectively reduced to give compound **12** in 94% yield (Scheme 4). Hemiacetal **12** was protected by a TES group to afford compound **13**,

**Scheme 4.** Synthesis of the Core Structure of Superstolides A and B




which was converted to a samarium enolate followed by the addition of MeI to provide compound **14** with the requisite stereochemistry of the quaternary carbon in 88% yield. Compound **14** was treated with 1 N HCl in *i*-PrOH at 120 °C in a sealed tube to reach an equilibrium to give a mixture of **15** and **16** in an approximately 1:3 ratio with a combined yield of 95% (compound **15** could be recycled to **16** under the same reaction conditions). Compound **16** was converted to olefin **17** in 84% yield under the standard conditions. Vinyllithium **18**, prepared from the corresponding vinylstannane,[13] underwent a stereospecific 1,2-addition to ketone **17** to afford *tert*-alcohol **19**, which underwent an anionic oxy-Cope rearrangement to provide *cis*-decalin **20** with the five requisite stereogenic centers and the double bond at the desired positions. Stereoselective reduction of ketone **20** by $Me_4NBH_4$ followed by the methylation of the resulting alcohol gave compound **21** in 78% yield.

The conversion of compound **21** to **23** failed under various Tamao−Fleming oxidation conditions because of the quick cleavage of the isopropyl group of the hemiaminal ether moiety of compound **21** in the presence of typical strong acidic conditions of the Tamao−Fleming oxidation and the labile olefin moiety toward various electrophilic reagents such as $Hg(OAc)_2$ and $Br_2$.[14]

(11) For the isolation of superstolides A and B: (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.; Paloma, L. G.; Minale, L.; Zampella, A.; Debitus, C. *J. Nat. Prod.* **1994**, *57*, 1595.

(12) Synthetic efforts toward the synthesis of the *cis*-decalin core structure of superstolide A: (a) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989. (b) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 2722. (c) Tortosa, M.; Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 9657. (d) Reference 5h.

(13) Cunico, R. F.; Clayton, F. J. *J. Org. Chem.* **1976**, *41*, 1480.

To solve these common problems in Tamao–Fleming oxidation it was imperative to develop a mild procedure that avoids the strong acidic conditions as well as those electrophilic reagents. We were delighted to observe that the phenyl group of the dimethylphenylsilyl moiety could be cleaved by TBAF in wet DMF at 65 °C to give compound **22**, which was easily oxidized to alcohol **23** in 82% yield. It was discovered that the reaction temperature of 65 °C was critical. If the temperature was too low, the reaction was very slow. If the temperature was too high, then compound **22** further reacted with TBAF resulting in protiodesilylation.[15,16] In 10 operations the [4 + 2] cycloaddition adduct **7a** was converted to the *cis*-decalin core structure present in superstolides A (**10**) and B (**11**), and two fused rings, six stereogenic centers (including one quaternary carbon), and a double bond were established.

In conclusion, we have demonstrated for the first time that 1,3-dienes derived from (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclohexen-1-one react with highly activated vinyl sulfones in a highly regio-, stereo-, and facial-selective fashion. The facial selectivity of these cycloadditions is opposite to that of those [4 + 2] cycloadditions employing symmetric dienophiles. In addition, this new methodology has been successfully applied to the asymmetric synthesis of the *cis*-decalin core structure of the potent anticancer marine natural products superstolides A and B. Furthermore, a mild procedure was developed to solve a long-standing problem in the Tamao–Fleming oxidation of the dimethylphenylsilyl group. The scope and limitations of this protocol are currently under investigation and will be reported in due course.

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**Supporting Information Available.** Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun*. **1984**, 29. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599 and references cited therein.

(15) During the preparation of this manuscript, we learned that a very similar protocol for the Tamao–Fleming oxidation of methyldiphenylsilyl and triphenylsilyl groups to alcohols was reported (one example): Knölker, H.-J.; Wanzi, G. *Synlett* **1995**, 378.

(16) Protiodesilylation by TBAF was reported by Roush. See: Heitzman, C.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett*. **2005**, *7*, 2405.