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Chiral Cyclobutane Synthesis by Exploiting a Heteroatom-Directed Conjugate Addition

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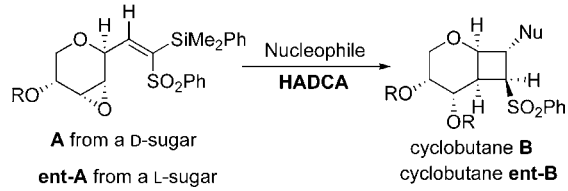
ABSTRACT



The syntheses of both enantiomers of cyclobutanes B and *ent*-B are achieved through heteroatom-directed conjugate addition (HADCA) of nucleophiles to the epoxyvinylsulfone-substituted carbohydrates A and *ent*-A, which provided carbanions that intramolecularly attacked the epoxide with concomitant formation of the cyclobutane ring.

Reactions to generate chiral cyclobutanes are important as four-membered carbocycles are substructures in many naturally occurring compounds, including solanoeclepin A,[1a] (−)-ampullicin,[1b] and (−)-copaene.[1c] Establishing new methods to synthesize diversified cyclobutane compounds in optically active forms would also provide strained intermediates, which can be further transformed into a variety of compounds via ring-opening and ring-expansion reactions.[2] However, the synthesis of enantiomerically pure cyclobutane derivatives is still a challenging task. Although the photochemical [2 + 2] cycloaddition is a popular method for constructing the cyclobutyl moiety,[2] the analogous reaction between two alkenes possessing chiral auxiliaries can be a synthetic problem when the preparation of optically active cyclobutanes is required on a large scale.[2a] Alternative strategies for constructing four-membered rings[3] have been reported by other researchers, including Paquette and co-workers,[4] while Taguchi and co-workers[5] reported a "Cp_2Zr"-mediated method for the preparation of optically pure cyclobutyl carbohydrate derivatives.

In 1974, Stork reported the first example of a cyclization to yield a four-membered ring through the nucleophilic attack of an epoxide by a carbanion stabilized by a nitrile group.[6] Krohn reported an alternative intramolecular epoxide opening by a 1,3-dithiane anion.[7] However, neither cyclization could accommodate many substituents in the substrate, which

(1) (a) Solanoeclepin A is the most active natural hatching agent of potato cyst nematodes. Its structure contains three-, four-, five-, six-, and seven-membered rings in which cyclobutane moiety of fully functional groups, see: Schenk, H.; Driessen, R. A. J.; Gelder, R. d.; Goubitz, K.; Nieboer, H.; Brüggemann-Rotgans, I. E. M.; Diepenhorst, P. *Croat. Chem. Acta* **1999**, *72*, 593. (b) (−)-Ampullicin shows remarkable growth-regulating properties, see: Kimura, Y.; Nakajima, H.; Hamasaki, T.; Matsumoto, T.; Matsuda, Y.; Tsuneda, A. *Agric. Biol. Chem.* **1990**, *54*, 813. (c) (−)-Copaene: Jacobson, M.; Uebel, E.; Lusby, W. R.; Waters, R. M. *J. Agric. Food Chem.* **1987**, *35*, 798.

(2) For recent reviews, see: (a) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (b) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485. (c) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539.

(3) (a) Wenkert, E.; Bakuzis, P.; Baumgarten, R. J.; Leicht, C. L.; Schenk, H. P. *J. Am. Chem. Soc.* **1971**, *93*, 3208. (b) Ihara, M.; Ohnishi, M.; Takano, M.; Makita, K.; Taniguchi, N.; Fukumotol, K. *J. Am. Chem. Soc.* **1992**, *114*, 4408. (c) Tanino, K.; Aoyagi, K.; Kirihara, Y.; Ito, Y.; Miyashita, M. *Tetrahedron Lett.* **2005**, *46*, 1169. (d) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (e) Meek, S. J.; Pradaux, F.; Demont, E. H.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 5597. (f) Redlich, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1345.

(4) (a) Paquette, L. A.; Cunière, N. *Org. Lett.* **2002**, *4*, 1927. (b) Paquette, L. A. *J. Organomet. Chem.* **2006**, *691*, 2083.

(5) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835.

(6) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270.

(7) Krohn, K.; Börner, G. *J. Org. Chem.* **1994**, *59*, 6063.

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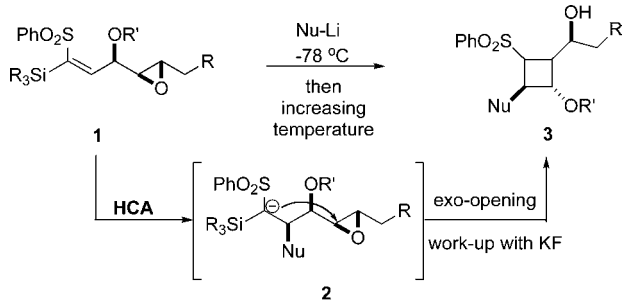
limited the wide applicability of these intramolecular opening processes for the synthesis of substituted cyclobutanes.

We have recently reported our first construction of polyfunctionalized cyclobutanes **3** from an acyclic precursor **1**, through intramolecular epoxide opening by carbanion intermediates **2** generated from conjugate addition (Scheme 1).[8] In this letter, enantiomerically pure fused

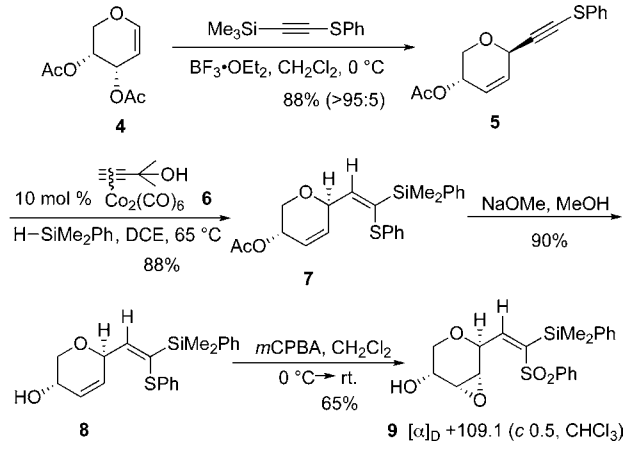
Scheme 1. Intramolecular Epoxide Opening in an Acyclic System by Carbanions Generated through Conjugate Addition



cyclobutanes are synthesized by exploiting the heteroatom-directed conjugate addition of carbanion nucleophiles to the epoxyvinylsulfone-substituted carbohydrates which produce carbanions that intramolecularly attack epoxides to form enantiomerically pure cyclobutanes.

Accordingly, we developed a four-step regio- and stereocontrolled synthesis of precursor **9** from D-arabinal (Scheme 2). Commercially available di-*O*-acetyl-D-arabinal **4** was

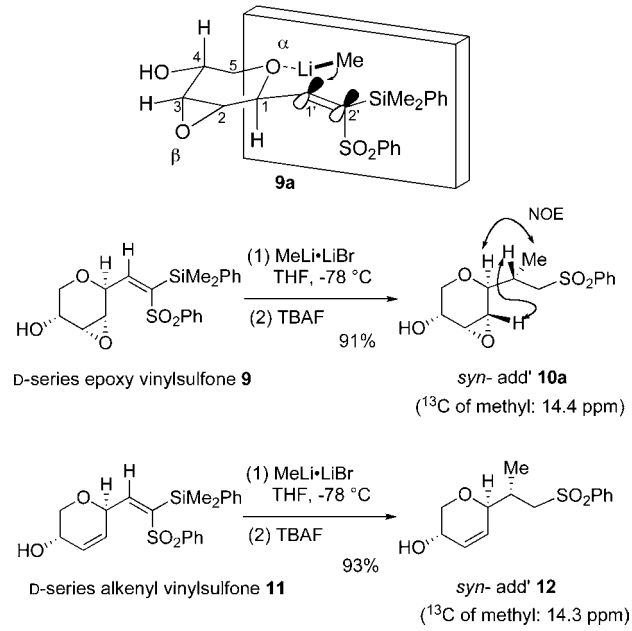
Scheme 2. Synthesis of Epoxy Vinylsulfone **9**



converted into C-alkynylated **5** in 88% yield with high 1,4-anti selectivity (de > 95:5).[9] Similarly, the enantiomer of **5** is available from L-arabinal or L-xylal derivatives. Alkyne **5** was subjected to hydrosilylation[10] with dimethylphenylsilane in the presence of 10 mol % of cobalt catalyst **6** to afford vinylsilane **7** in 88% yield, in which the olefin geometry was 100% regio- and stereoselective. Alcoholysis generated 4-hydroxyvinylsulfide **8**, which was bis-oxidized with *m*CPBA to give the epoxy vinylsulfone **9**. In this reaction, epoxidation was hydroxyl-directed according to Henbest's rule, to generate the desired epoxide stereochemistry for cyclobutane formation.

Next, the diastereoinduction in the conjugate addition was examined.[11] When treated with 2.5 equiv of methyllithium–lithium bromide complex, the D-series epoxy vinylsulfone **9** underwent conjugate addition on the *si*-face directed by α-chelation rather than *β*-chelation (Scheme 3). Desilylation

Scheme 3. Heteroatom-Directed Conjugate Addition of MeLi to Vinylsulfone-Substituted Pyrans **9** and **11** to Afford *syn*-Adducts **10a** and **12**



with TBAF yielded exclusively diastereomer **10a**. The stereochemistry of the product was deduced from the NOE correlations as shown. The stereochemistry of the methyl group of **10a** was further correlated with **12**, which was obtained from the reaction of D-series alkenyl vinylsulfone **11** without any epoxide that could competitively direct the conjugate addition. The ^{13}C methyl group of **10a** showed a peak at δ 14.4 ppm, while the methyl group of **12** showed a peak at δ 14.3 ppm, consistent with both methyl groups being in a similar stereochemical environment.

Other nucleophiles were examined for comparison, and the results are summarized in Table 1. In the case of both

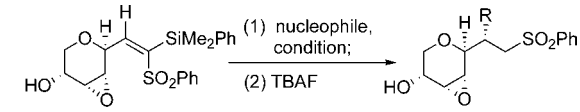
(8) Adachi, M.; Yamauchi, E.; Komada, T.; Isobe, M. *Synlett* **2009**, *7*, 1157. Formally we called it a hetero-conjugate addition, but recently, it has often been used for heteroatom nucleophiles. Now we propose HADCA instead to make it clearer.

(9) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917.

(10) Isobe, M.; Nishizawa, R.; Nishikawa, T.; Yoza, K. *Tetrahedron Lett.* **1999**, *40*, 6927.

(11) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1981**, *22*, 239.

Table 1. HADCA of Various Nucleophiles to D-Series Epoxy Vinylsulfone **9**



D-serise epoxy vinylsulfone **9** — *syn*-adduct **10**

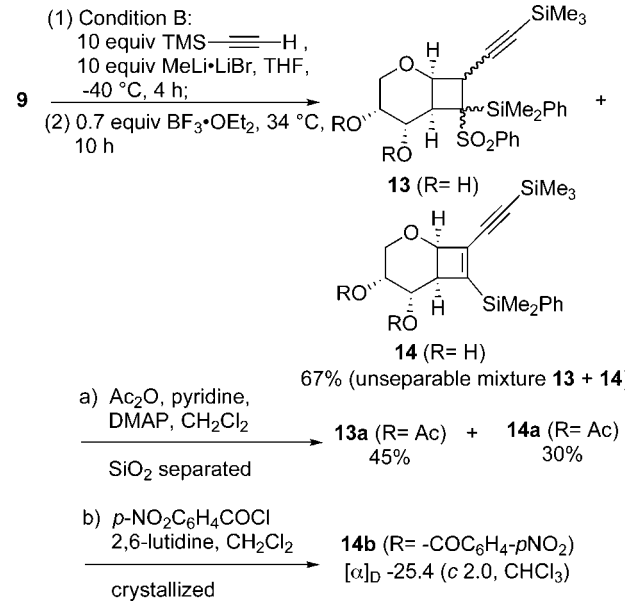
entry	nucleophile	condition[a]/ time	major product	yield[d] (*syn* : *anti*)	$[\alpha]_D$
1	2.5 equiv MeLi	A / 5 min	**10a**, R= Me	90% (>99:1)	+ 1.3
2	2.5 equiv MeLi•LiBr	A / 5 min	**10a**, R= Me	91% (>99:1)	+ 1.3
3	2.5 equiv *n*BuLi	A / 5 min	**10b**, R= *n*Bu	82% (83:17)	+ 6.6
4	2.5 equiv MgBr	B / 6 h	**10c**, R= vinyl	73% (>99:1)	+ 25.3
5[b]	5.0 equiv TMS—≡—Li	B / 4 h	**10d**, R= -≡	63% (85:15)	+ 52.7
6[b]	10.0 equiv TMS—≡—Li	B / 4 h	**10d**, R= -≡	55% (85:15)	-----
7[c]	5.0 equiv TMS—≡—Li	C / 2.5 h	**10d**, R= -≡	80% (>99:1)	+ 51.6

[a] Conditions: (A) THF, −78 °C; (B) THF, −40 °C; (C) hexane/ether, −40 °C. [b] The trimethylsilylacetylene was deprotonated with MeLi−LiBr at −20 °C for 1 h. [c] The trimethylsilylacetylene was deprotonated with MeLi at −20 °C for 1 h, then mixed with LiBr/NaBr (1:0.05) at −20 °C for 2 h. [d] Isolated yields after column chromatography; the ratios were determined by ^{1}H NMR.

methyllithium and the methyllithium−lithium bromide complex, the *syn*-adduct **10a** was obtained under Condition A (THF, −78 °C) in ≥90% yield with a high de ratio (entries 1 and 2).[12] The diastereoselectivity of the addition of *n*-butyllithium was somewhat lower (de = 83:17, entry 3). When **9** was treated with vinylmagnesium bromide (entry 4), no reaction took place at −78 °C. When the reaction temperature was raised to −40 °C (Condition B), adduct **10c** was formed in 73% yield with high de (>99:1). Similarly, the weaker nucleophile, lithium acetylide, did not undergo conjugate addition at −78 °C but reacted at −40 °C. When 5.0 equiv of lithium acetylide was employed (entry 5), **10d** was obtained in 63% with de = 85:15, but when 10 equiv of lithium acetylide was used, a lower yield of **10d** was obtained (55%, entry 6). However, we could enhance the nucleophilicity of lithium acetylide by adding 5 mol % of sodium bromide salt (Condition C). The acetylide thus prepared reacted to give *syn*-adduct **10d** in 80% yield and with high diastereoselectivity (de >99:1, entry 7). In a similar manner, the conjugate addition of nucleophiles to L-series epoxy vinylsulfone systems ***ent*-9** generated the enantiomeric *syn*-adducts ***ent*-10a−d** as major products (Table 2 in Supporting Information).

To study the application of this reaction toward the synthesis of the eastern hemisphere of solanoeclepin A, the addition of lithium acetylide was further investigated for the construction of the cyclobutane moiety. When precursor **9** was treated with an excess (10.0 equiv) of lithium acetylide and then addition of 0.7 equiv of BF_3•OEt_2 (Scheme 4), an

Scheme 4. Cyclobutane **13** and Cyclobutene **14** Formation under Condition B Followed by BF_3•OEt_2



inseparable mixture of cyclobutane **13** and cyclobutene **14**[13] was formed, which was subsequently acetylated and separated by silica gel chromatography to yield cyclobutane **13a** (45%) and cyclobutene **14a** (30%). The structures of cyclobutane **13a** and cyclobutene **14a** were identified by HMQC and HMBC NMR experiments. Fortunately the bis-PNB ester **14b** was crystallized, and the structure was established by X-ray crystallographic analysis.[14]

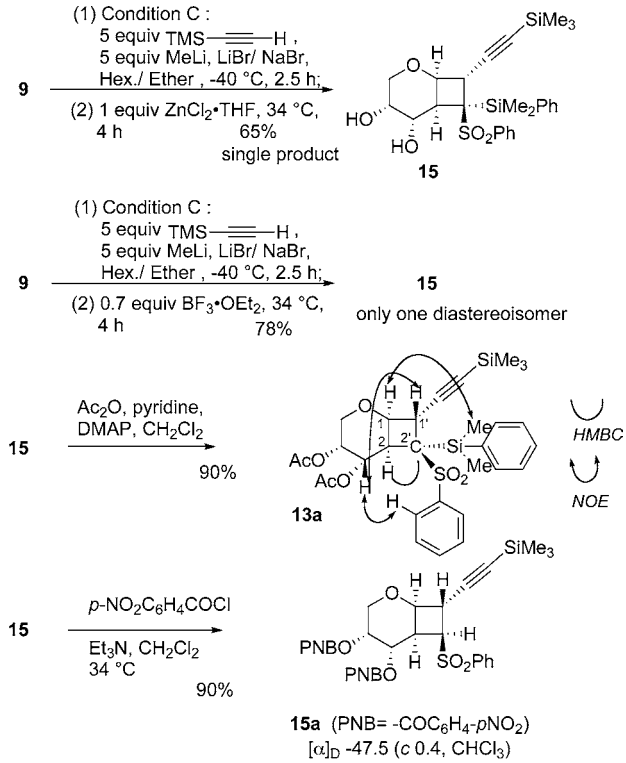
Gratifyingly, when the reaction was carried out using lithium acetylide•LiBr in the presence of NaBr (Condition C), cyclobutane **15** was procured as the only product (Scheme 5). Addition of the sodium salt and cosolvents to the reaction mixture of **9** and acetylide made the first heteroatom-directed conjugate addition at higher velocity and selectivity as the Condition C. To this anionic intermediate was further added 1 equiv of zinc chloride−THF at −40 °C, and the temperature was raised to 34 °C to result in the formation of epoxide opening product **15** to isolate as a single stereoisomer in 65% yield (Scheme 5). When we employed the same Condition C and changed the Lewis acid to BF_3•OEt_2 (0.7 equiv), the isolation yield of **15** was improved to 78% yield. The stereochemistry of this product was analyzed by NMR on

(12) In this case, the *syn*-isomer is defined as the same face of the incoming methyl group and neighboring oxygen atom, when drawn in zigzag main carbon chain according to S. Masamune's definition.

(13) This may have stereospecifically happened, after the cyclobutane formation, to one of the diastereomers, which posessed the stereochemistry orienting the sulfonyl group *trans* to the propargylic proton. An excess carbanion attacked the propargylic proton and eliminated the *trans*-sulfonyl group to give cyclobutene **14**.

(14) The ORTEPs of cyclobutene **14b** and the *p*-nitrobenzoate derivative of ***ent*-15a** are also included in the Supporting Information.

Scheme 5. HADCA Addition Followed by Cyclobutane Ring Formation with Assistance by Lewis Acid



its diacetate **13a**; thus, formation of the cyclobutane is shown by the correlation between H_2 and C_2' (HMBC), and the stereochemistry is shown as 1′*S*- and 2′*R*-configuration from NOE experiments (Scheme 5). Conversion to the crystalline di-*p*-nitrobenzoate derivative **15a** was achieved with loss of the phenyldimethylsilyl group. The crystal structure is shown in Figure 1.

The enantiomer of ***ent*-9** was also successfully converted to ***ent*-15a** by the same method starting from L-arabinal (Scheme 6). Furthermore, the absolute stereochemistry of both enantiomers has been established through X-ray crystallographic analysis of their *p*-nitrobenzoate derivatives cyclobutane ***ent*-15a**.[14]

In conclusion, we have accomplished the synthesis of both enantiomers of tetrasubstituted cyclobutanes in optically pure

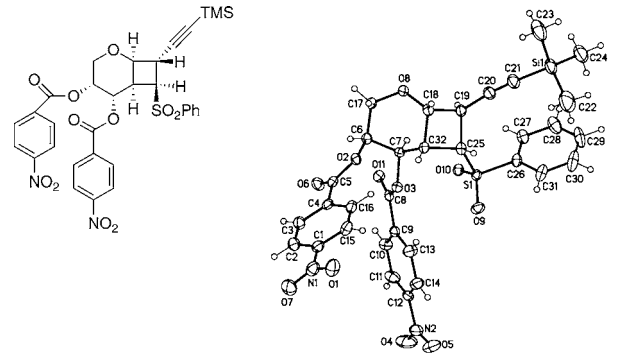
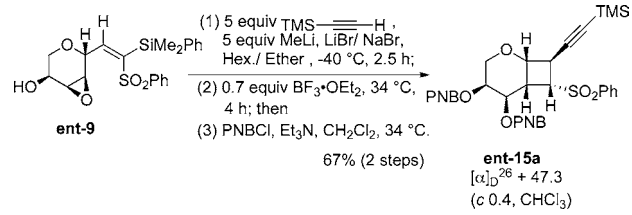


Figure 1. ORTEP of the crystal structure of cyclobutane **13b**.

forms in a stereocontrolled manner through intramolecular epoxide ring opening by trans-metalated carbanions, which

Scheme 6. Formation of Cyclobutane ***ent*-15a**



was generated in situ from an α-heteroatom directed conjugate addition followed by epoxide opening reactions by the assistance of a Lewis acid. Our studies to apply this synthetic method toward the asymmetric synthesis of natural products are in progress.

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Supporting Information Available: H NMR, C NMR, 2D NMR, and typical experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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