Asymmetric Reductive Cyclization Using the Intramolecular Conjugate Addition of Enolates onto α,β-Unsaturated Sulfoxides

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Abstract: Li(sec-Bu)$_3$BH-mediated reductive cyclization of optically pure 8-((S)-p-tolylsulfinyl)-(2E,7Z)-octadienoate **9** and 7-(p-tolylsulfinyl)-2,6-heptadienoate **16** afforded *trans*-2-((p-tolylsulfinyl)-methyl)cyclohexane-1-carboxylate and *trans*-2-((p-tolylsulfinyl)methyl)cyclopentane-1-carboxylate, respectively, as a single isomer.
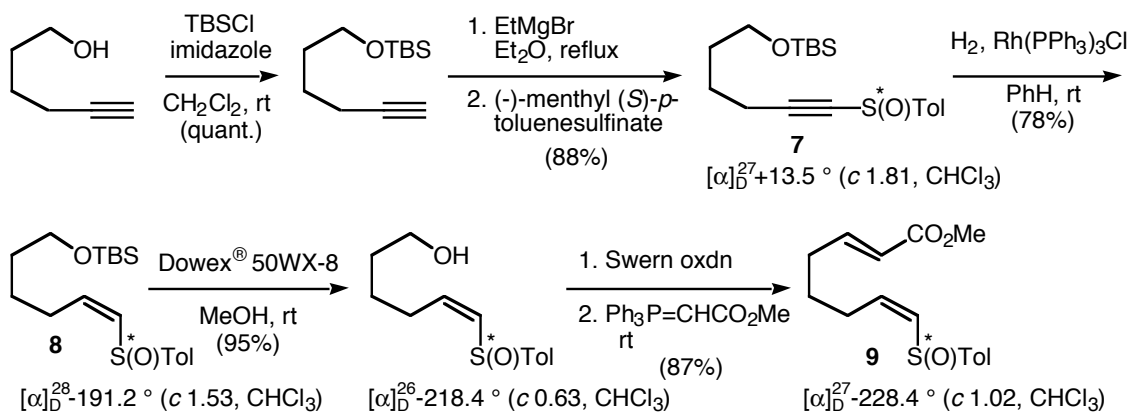
The asymmetric and stereospecific construction of functionalized six- and five-membered carbocycles continues to attract the attention of organic chemists. We have reported a new strategy for stereoselective synthesis of functionalized cyclohexane derivatives that uses intramolecular Michael reaction of ester enolate **2**, which is derived by lithium tri-*sec*-butylborohydride (L-Selectride®) reduction of bis enoate **1**.[1] The observed higher trans selectivity in the reaction of 2-methyl derivative **1b** in comparison to **1a** has been explained by steric repulsion between the methyl group and H-5 in the transition state **5** leading to **4b**. These results led us to consider the use of (Z)-vinyl sulfoxide[2] as a Michael acceptor[3,4] that would permit not only trans selective but also enantioselective construction of cyclohexane derivatives owing to its ready availability in geometrically and optically pure form in addition to the developing steric repulsion between the sterically demanding arylsulfinyl group and H-5 in the transition state **6** leading to the cis derivative.[5]

Scheme 1
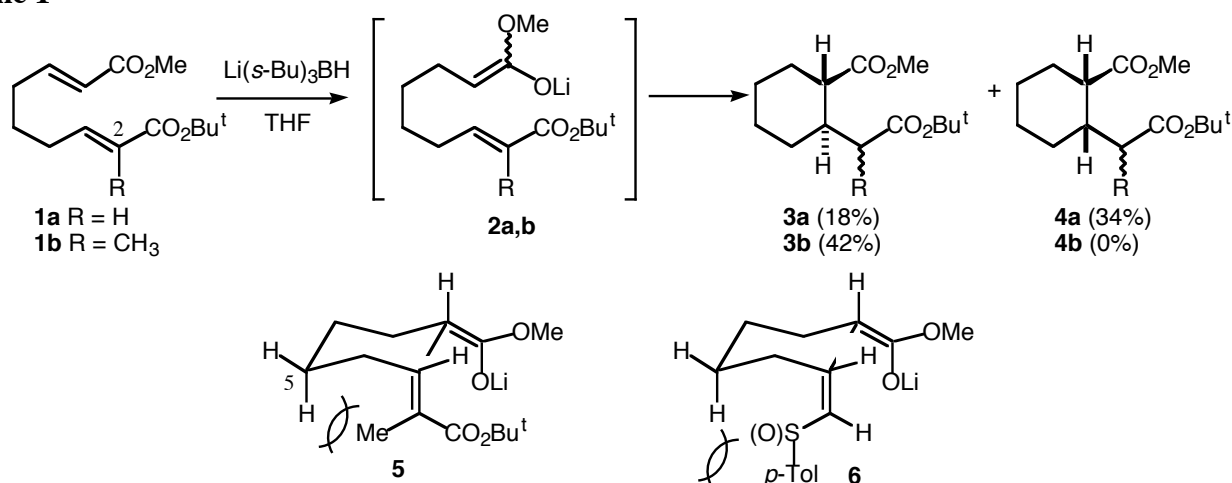
The cyclization precursor 8-((S)-p-tolylsulfinyl)-(2E,7Z)-octadienoate **9** was prepared by a five-step sequence starting with 5-hexyn-1-ol, which relied on the stereoselective formation of (Z)-α,β-unsaturated sulfoxide by hydrogenation of the triple bond with the Wilkinson catalyst (**7** →**8**).[6]

Scheme 2

7 $[\alpha]_D^{27}$ +13.5 ° (c 1.81, CHCl$_3$)

8 $[\alpha]_D^{28}$ -191.2 ° (c 1.53, CHCl$_3$)

$[\alpha]_D^{26}$ -218.4 ° (c 0.63, CHCl$_3$)
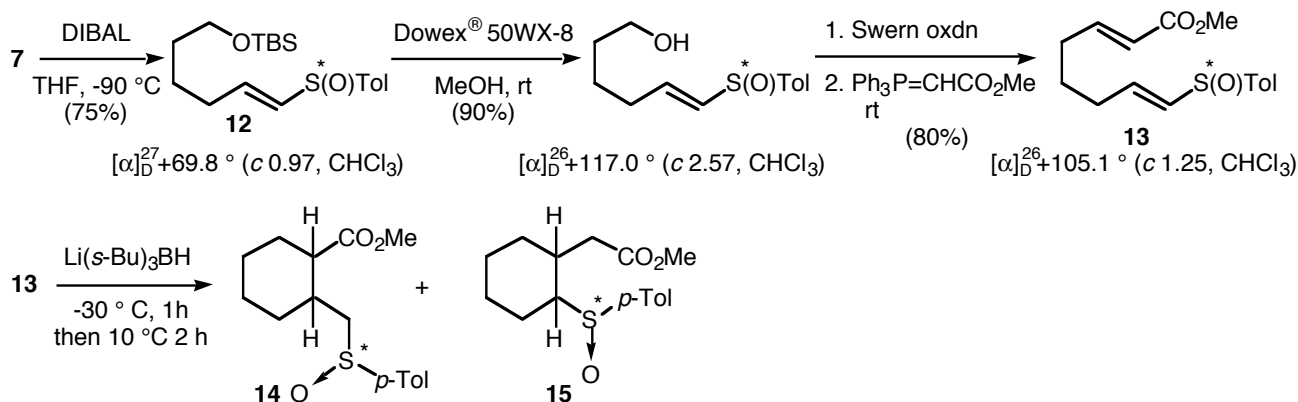
9 $[\alpha]_D^{27}$ -228.4 ° (c 1.02, CHCl$_3$)

When **9** was treated with L-Selectride® (1.1 equiv) in THF (0.01 M) at -30 °C for 1h and then 10 °C for 2 h, the intramolecular Michael addition proceeded with complete π-facial diastereoselectivity to afford *trans*-cyclohexanecarboxylate **10** as a single isomer in 50% yield, with the absolute structure determined by X-ray analysis[7]. Departing from this protocol led to a decrease in yield. The major side reactions were attributable to an intermolecular reductive dimerization and the formation of uncyclized 1,4-reduction compounds. The reaction in THF-HMPA (20:1) was much less stereoselective, affording both the trans and cis isomers in a ratio 39: 61 in 31% yield.[8]

Scheme 3

|		**10**	:	**11** (1,2-*cis*)
THF	50%	100	:	0
THF/HMPA (20:1)	31%	39	:	61
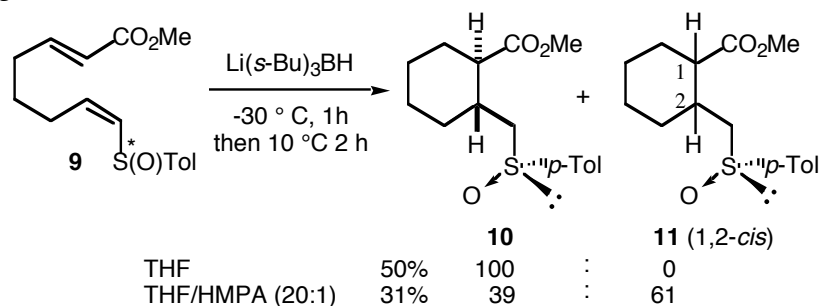
On the other hand, the same reaction using *E*-derivative **13**, prepared in a manner similar to **9** except that DIBAL was used for the hydrogenation step (**7** → **12**),[6] showed expectedly poor stereoselectivity, providing an inseparable mixture of cyclohexane derivatives whose ¹H NMR revealed the presence of three cyclohexanecarboxylates except **10**, and **15** (Scheme 4).

Scheme 4

12 $[\alpha]_D^{27}$ +69.8 ° (c 0.97, CHCl$_3$)

$[\alpha]_D^{26}$ +117.0 ° (c 2.57, CHCl$_3$)

**13** $[\alpha]_D^{26}$ +105.1 ° (c 1.25, CHCl$_3$)

Similar results were obtained with 7-(tolylsulfinyl)-2,6-heptadienoate **16**, derived from 4-pentyn-1-ol in a fashion similar to **9**, affording optically pure cyclopentane derivative **17**[9] in 60% yield. The relative stereochemistry was deduced from the combination of ¹H NMR and NOESY experiments and the absolute stereochemistry assigned by analogy with **10**. Use of THF-HMPA resulted in the decrease in the selectivity again, affording **17** and its isomer of undetermined stereochemistry in a ratio of 53:47 in 40% yield.

Scheme 5

$[\alpha]_D^{27}$ -218.1 ° (c 0.91, CHCl$_3$)
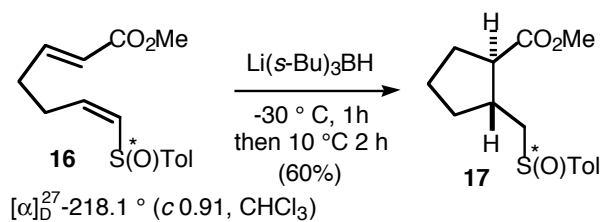
Initially, the observed trans selectivity in the reaction of **9** was attributed to the nonbonded repulsion between the sulfinyl group and the H-5 on the basis of the result with **1a,b**. The exclusive formation of the trans derivative **17** in the reaction of **16**, however, cannot be explained only by the interaction because of the absence of such repulsion in the transition state leading to the cis derivative in the case of **16**. Consequently, the origin of the trans selectivity is unknown at present but could be due to the eclipsing interaction of both the double bonds in **19** leading to the cis isomer relative to the transition state **18** leading to the trans one.

Figure 1
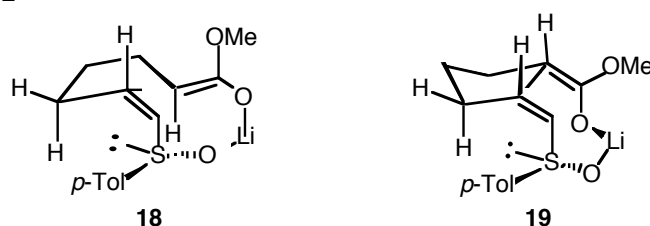
The facial selectivity can be accounted by preferential attack of the enolate from the less hindered side in the chelated structure involving the lithium atom, and the sulfinyl and the enolate oxygen atoms as shown in Scheme 6. This is supported by the results that the selectivity was significantly lowered upon addition of HMPA that can disrupt the chelated structure by solvating the lithium cation.

Scheme 6
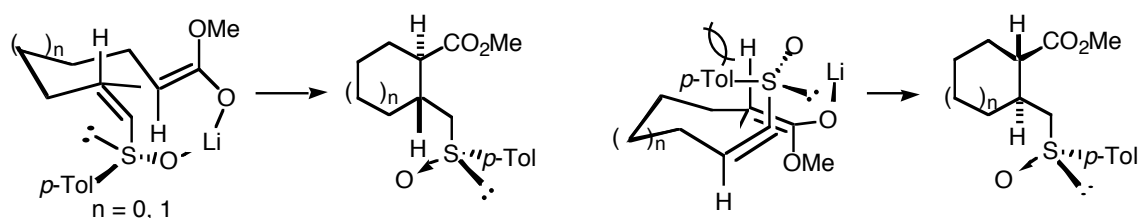
In summary, we have developed a new strategy for the asymmetric construction of the functionalized cyclohexane and cyclopentane derivatives using intramolecular Michael addition of ester enolate to vinyl sulfoxide. To the best of our knowledge, this is the first example of intramolecular Michael addition in which vinyl sulfoxide without any activation by electron-withdrawing groups can serve as a Michael acceptor. We are currently defining the scope and limitations of this methodology.

References and Notes

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7. To a cooled (-30 °C) solution of L-Selectride® (1.0 M in THF, 714 μL, 0.714 mmol) in THF (4.9 mL) was added dropwise a cooled (-30 °C) solution of **9** (190 mg, 0.649 mmol) in THF (60 mL). After stirring at -30 °C for 30 min, the solution was allowed to warm to 10 °C, and then stirred for 2 h at the same temperature before quenching by addition of a few drops of water at 0 °C. The solution was concentrated and partitioned between Et$_2$O and saturated brine. The aqueous phase was extracted with Et$_2$O, and then combined organic phases were washed with saturated brine, dried (MgSO$_4$), and concentrated under reduced pressure. The residual oil was subjected to column chromatography (silica gel, 20 g; hexane-AcOEt =1:1) to give **10** (95 mg, 50%). An analytical sample was obtained by recrystallization from hexane-CH$_2$Cl$_2$. mp 100-101 °C, colorless needles, R_f = 0.33 (hexane-AcOEt = 1:1).   IR (film) 1725 cm^{-1}. ^{1}H NMR (d$_6$-benzene, 500 MHz) δ (ppm) 0.88–1.09 (3H, m, H-4 and H-5), 1.35-1.47 (3H, m, H-2 and H-3), 1.76–1.83 (1H, m, H-2), 1.92-1.98 (1H, m, H-4), 2.00 (3H, s, Ar-Me), 2.20 (1H, ddd, *J* = 11.3, 11.3, 3.4 Hz, H-1), 2.24-2.32 (1H, m, H-6), 2.68 (1H. dd, *J* = 13.2, 6.2 Hz, H-1'), 2.71 (1H, dd, *J* = 13.2, 5.1 Hz, H-1'), 3.38 (3H, s, OMe), 6.93 (2H, d, *J* = 8.1 Hz, Ar-H), 7.56 (1H, d, *J* = 8.1 Hz, Ar-H). ^{13}C NMR (d$_6$-benzene, 125 MHz) δ (ppm) 21.6 (Ar-Me), 25.1 (C-3), 25.3 (C-5), 29.9 (C-2), 32.3 (C-4), 35.8 (C-6), 49.4 (C-1), 51.8 (OMe), 64.3 (C-1'), 124.3, 130.1, 141.3, and 141.7 (Ar), 175.3 (C=O). LRMS (EI, *m/z*) 294 (M$^+$), 278. 263 (M$^+$–CH$_3$O), 256, 234, 155, 123, 92. Anal. calcd for C$_{16}$H$_{22}$O$_3$S: C, 65.27; H, 7.53. Found: C, 65.47; H, 7.52. [α]$_D^{26}$ +92.6° (*c* 1.093, CHCl$_3$). X-ray: monoclinic P2$_1$ (#4), a = 10.791(4), b = 5.718(2), c = 13.285(3) Å, β = 100.53(2)°, V = 805.9(4) Å^3, Z = 2, D$_{calc}$ = 1.213 g/cm^3, R = 3.6 for 2144 reflections. Diffraction data were collected on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Ka radiation and 12 kW rotating generator. The structure was solved by the direct methods and expanded using Fourier techniques.

8. The characteristic data of **11**: colorless oil, R_f = 0.38 (hexane-AcOEt = 1:1). IR (film) 1730 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz) δ (ppm) 1.28-1.68 (6H, m, H-2, H-3, H-4 and H-5), 1.73 (1H, dddd, *J* = 13.0, 13.0, 9.2, 3.6 Hz, H-5), 1.82-1.93 (1H, m, H-3), 2.33-2.40 (1H, m, H-6), 2.40 (3H, s, Ar-Me), 2.79 (1H, dd, *J* = 13.3, 5.5 Hz, H-1'), 2.87-2.92 (1H, m, H-1), 2.92 (1H, dd, *J* = 13.3, 8.3 Hz, H-1'), 7.30 (2H, d, *J* = 8.4 Hz, Ar-H), 7.49 (2H, d, *J* = 8.4 Hz, Ar-H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ (ppm) 21.7 (Ar-Me), 23.2 and 23.9 (C-2 and C-4), 27.0 (C-3), 29.6 (C-5), 33.4 (C-6), 43.2 (C-1), 51.9 (C-1'), 124.1, 130.1, 141.3 and 141.6 (Ar), 174.5 (C=O). LRMS (EI, *m/z*) 295 (M$^+$+1), 278. 263 (M$^+$–CH$_3$O), 247, 155, 140, 123, 91. [α]$_D^{26}$ +141.5° (*c* 0.166, CHCl$_3$). The 1,2-*cis*-relationship was secured by NOESY experiments.

9. The characteristic data of **17**: colorless oil, R_f = 0.37 (hexane-AcOEt = 1:1). IR (film) 1730 cm^{-1}. ^{1}H NMR (CDCl$_3$, 500 MHz) δ (ppm) 1.52-1.65 (2H, m, H-3 and H-4), 1.78-1.98 (4H, m, H-2, H-3 and H-4), 2.40 (3H, s, Ar-Me), 2.51-2.60 (1H, m, H-5), 2.82 (1H, dd, *J* = 13.2, 6.2 Hz, H-1'), 2.93 (1H, dd, *J* = 13.2, 8.8 Hz, H-1'), 3.05 (1H, ddd, *J* = 7.7, 7.7, 5.6 Hz, H-1), 3.67 (3H, s, OMe), 7.31 (2H, dd, *J* = 8.1 Hz, Ar-H), 7.49 (2H, d, *J* = 8.1 Hz, Ar-H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ (ppm) 21.6 (Ar-Me), 23.7 (C-3), 29.1 (C-4), 31.9 (C-2), 37.8 (C-5), 46.6 (C-1), 51.7 (OMe), 60.6 (C-1'), 124.1, 130.1, 141.1 and 141.6 (Ar), 175.4 (C=O). Anal. calcd for C$_{15}$H$_{20}$O$_3$S: C, 64.26; H, 7.19. Found: C, 64.01; H, 7.11. [α]$_D^{27}$ +171.4° (*c* 1.157, CHCl$_3$).