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Asymmetric Michael–aldol tandem cyclization of ω-oxo-α,β-unsaturated esters with 10-mercaptoisoborneol methyl ether

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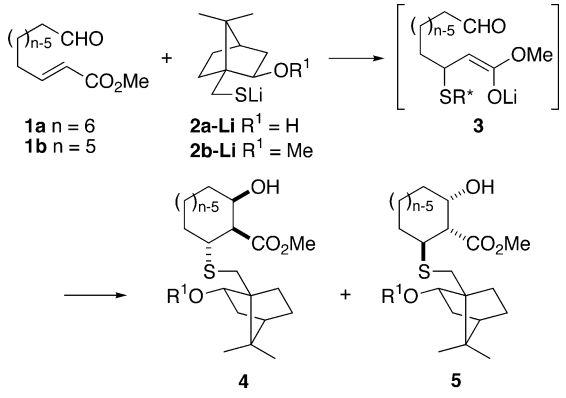
Abstract—The asymmetric reaction of ω-oxo-α,β-unsaturated esters with lithium chiral thiolates afforded the Michael–aldol tandem cyclization products in high yield and good stereoselectivity. Reductive desulfurization gave the corresponding optically pure 2-hydroxycycloalkanecarboxylates.

An asymmetric carbon–carbon bond forming cyclization methodology is of importance in the synthetic chemistry of chiral carbocycles.[1,2] Especially, an aldol-type reaction of a lithium ester enolate with an aldehyde is one of the most powerful process for a carbon–carbon bond formation. For the constriction of chiral carbocycles by intramolecular aldol reaction, it is highly desirable to establish an asymmetric methodology for selective generation of lithium enolate of a chiral ester bearing an enolizable aldehyde in the same molecule.[3,4] Such selective generation of a lithium chiral ester enolate is possible through the Michael addition reaction of a lithium chiral thiolate with an enoate bearing an ω-formyl group.[5,6] As part of our projects on an asymmetric reaction of a thiolate,[7] we have recently reported the lithium benzylthiolate-initiated Michael addition–intramolecular aldol tandem cyclization of ω-oxo-enoates.[8,9] We describe herein the extension of the process into the asymmetric cyclization of ω-oxo-α,β-unsaturated esters **1** with use of **2-Li** as an initiating chiral thiolate, providing a new methodology for asymmetric construction of chiral carbocycles (Scheme 1). Furthermore, the cyclization using lithium thiolate **2-Li** gave **4** and **5** in a perfect *syn*-aldol stereoselectivity.

Treatment of **1a**[10] ($n=6$) with 1.2 equiv. of a lithium thiolate of 10-mercaptoisoborneol **2a-Li** ($R^1=H$)[11,12] in THF at 0°C for 0.5 h gave **4aa**[13] and **5aa** ($n=6$, $R^1=H$) as a mixture of two separable diastereomers in 38 and 9% yields, respectively.[14,15] The same reaction in THF at lower temperature, −78°C for 1 h and then −40°C for 0.5 h, gave the Michael addition products only in 77% combined yield without formation of the tandem aldol cyclization products, **4**, **5** and other stereoisomers. The reaction in toluene at 0°C for 2 h gave **4aa** and **5aa** in 17 and 4% yields, together with the Michael addition products in 19% yield.

Since intra- or intermolecular protonation of **3** by a free hydroxyl group in **2a** may be responsible for the failure in tandem aldol-cyclization, an alcohol **2a** was converted to a methyl ether **2b** ($R^1=Me$) (Scheme 2). A



Scheme 1. The Asymmetric Michael–aldol tandem cyclization of **1** with **2**.

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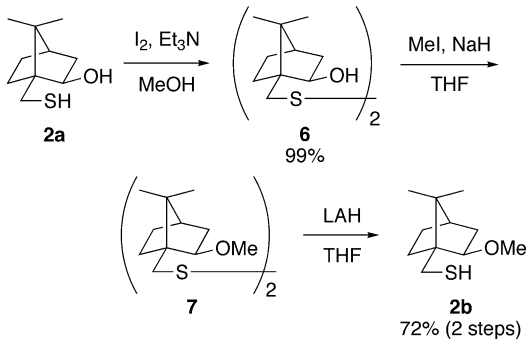
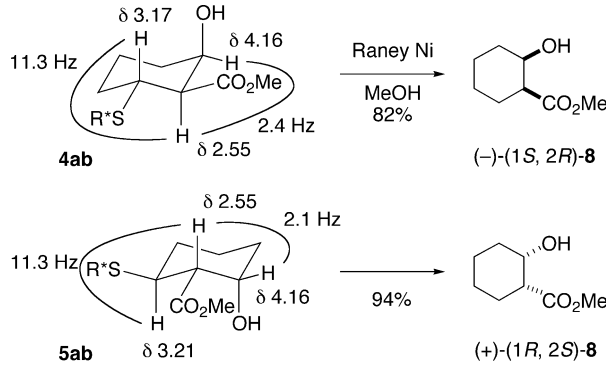
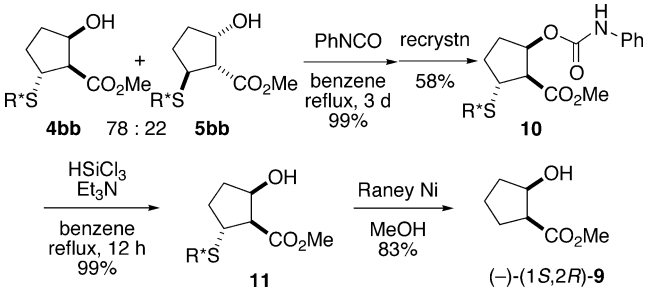


Scheme 2. Synthesis of chiral thiol **2b** from **2a**.



Scheme 3. ^{1}H NMR and conversion of **4ab** and **5ab** to **8**.



Scheme 4. Synthesis of an optically pure five-membered carbocycle **9**.

hydroxythiol **2a** was initially converted to a disulfide **6** and then methylated to **7**, and finally reduced back with lithium aluminum hydride to **2b** in 71% overall yield from **2a**.

The reaction of **1a** ($n=6$) with **2b-Li** ($R^1=Me$), prepared by treating **2b** with butyllithium, in THF at 0°C for 0.5 h gave chromatographically separable two isomers **4ab** and **5ab** ($n=6$, $R^1=Me$) in 77 and 18% yields (81:19 dr), respectively. It is important to note that only *syn*-aldol cyclization products were obtained without formation of *anti*-aldol products. The diastereomer ratio was improved by lowering reaction temperature at –40°C, giving **4ab** and **5ab** in 77 and 13% yields (86:14 dr).

The reaction efficiency highly depends on the solvent used to give **4ab** and **5ab** in 69 and 26% in DME at 0°C, 23 and 14% in ether, 46 and 17% in acetonitrile (Table 1). In methylene chloride, **4ab** was an only isolable product although in 30% yield. Additives, HMPA, Dabco, and trimethylaluminium in a THF solvent were not factors improving efficiency to afford **4ab** and **5ab** in 75 and 19%, 65 and 21%, 46 and 11%, respectively.

The stereochemical structures of **4ab** and **5ab** were determined based on ^{1}H NMR and conversion to *cis*-**8** and its enantiomer of the established absolute configuration. Coupling constants, 2.4 Hz and 11.3 Hz between methine protons at 4.16, 3.17 and 2.55 ppm of **4ab** indicate the chair stereostructure, where SR* and CO_2Me are equatorial, OH is axial, as shown in Scheme 3. Reductive removal of a sulfanyl group SR* with Raney-nickel in methanol afforded optically pure (–)-(1*S*,2*R*)-**8**[16] of $[\alpha]_D^{20}$ –32.8 (*c* 4.6, ether) in 82% yield,

Table 1. Solvent dependency of the reaction of **1a** with **2b-Li** giving **4ab** and **5ab**

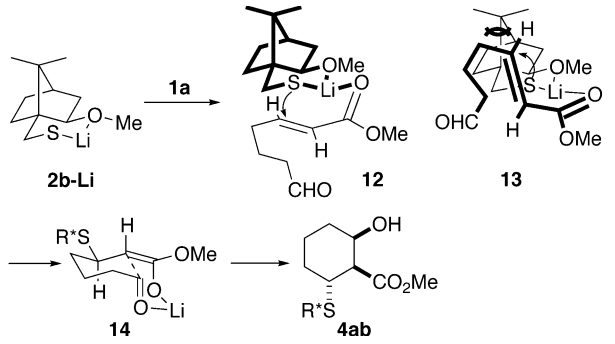
Entry	Solvent	Temp. (°C)	Yield (%)	Dr
1	THF	−40	90	86:14
2	THF	0	95	81:19
3	DME	0	95	73:27
4	Ether	0	37	62:38
5	CH_3CN	0	63	73:27
6	CH_2Cl_2	0	30	99:1

thus established the absolute stereostructure of **4ab**. Similarly, **5ab** was also determined by converting to (+)-**8** as shown. The structures of **4aa** and **5aa** were also determined by the same way.

Five-membered carbocycle is also a good target. The reaction of **1b** ($n=5$) with 1.2 equiv. of **2b-Li** in THF at –20°C for 0.5 h gave **4bb** and **5bb** ($n=5$, $R^1=Me$) in 78:22 dr and 96% combined yield. Direct Raney-nickel reduction of a mixture gave (–)-(1*S*,2*R*)-methyl 2-hydroxycyclopentanecarboxylate **9**[17] of $[\alpha]_D^{23}$ –8.2 (*c* 1.2, $CHCl_3$) with 49% ee in 73% yield, establishing the stereochemistry of a major product **4bb** (Scheme 4). A 78:22 mixture was converted to their carbamates and fractionally recrystallized from ether–hexane to give pure **10**, which was then reduced via **11** to optically pure **9** in 45% overall yield from **1b**.[18]

The stereochemistry of the tandem reaction is rationalized by the model **12**, which is sterically favorable much more than **13** (Scheme 5). The oxo-ester **1a** reacts in *s-cis* form to generate *cis*-enolate **3**,[19,20] which then reacts intramolecularly with lithium-coordinated carbonyl group shown in **14** to result in the observed major *syn*-only aldol product **4ab**. In this context it is interesting to examine the reaction of **2b** without activation by lithium.

The reaction of **1a** with **2b** in THF was catalyzed by 0.1 equiv. of Triton B at rt for 0.5 h to give a mixture of possibly all four cyclization products, *syn*-aldols **4ab** (48%) and **5ab** (22%), *anti*-aldols **15** and **16** (ca 1:1, 26%) in 96% combined yield (Fig. 1). It is also impor-



Scheme 5. Plausible stereochemical pathway to **4ab** starting from **1a** with **2b-Li**.

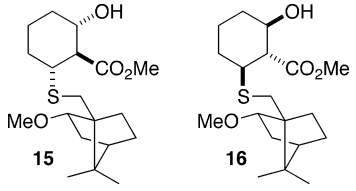


Figure 1. Structures of **15** and **16**.

tant to note that treatment of **4ab** with 1 equiv. of butyllithium to generate lithium alkoxide of **4ab** in THF at −20°C for 1 h recovered **4ab** unchanged, suggesting absence of retro-aldol–re-aldol equilibrium. Thus, inter- and intramolecular coordination of lithium to carbonyl groups is one of the critical factors determining kinetic stereochemical pathway starting from **2b-Li** and **1a** to **4ab**.

In summary, a new methodology has been developed for the construction of chiral carbocycles by employing an asymmetric Michael–aldol tandem cyclization of ω-oxo-α,β-unsaturated esters with a lithium chiral thiolate.

Acknowledgements

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13. The expression of **1aa** means that the first **a** is derived from **1** ($n=6$) and the second **a** is derived from **2** ($R^1=$ H).
14. The ratio of **4** and **5** was alternatively determined by NMR of the crude product. Other possible isomers were not detected.

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20. The *cis*-enolate refers the *syn* orientation of OLi and side chain.