Facile and Stereoselective Access to Nonracemic Tricyclic Cyclobutanes by Asymmetric Intramolecular Michael−Aldol Reaction: Thermodynamic Equilibrium and Activation by Iodonium Ion

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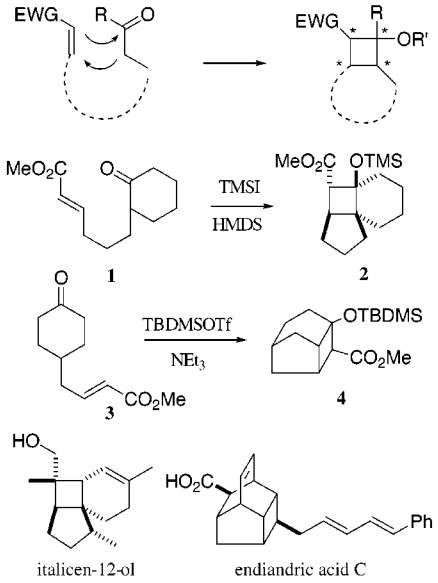
Intramolecular Michael−aldol reactions of (−)-phenylmenthyl enoates tethered to cycloalkanone affords tricyclic cyclobutanes with high degrees of diastereochemical control. Kinetic and thermodynamic studies revealed that the Michael−aldol reaction is reversible under conditions in which trimethylsilyl iodide is used in the presence of hexamethyldisilazane at ambient temperature. Different levels of diastereoselectivity are observed when this cyclization process is carried out under kinetic vs thermodynamic conditions. Finally, an influence of added iodonium donors on the reaction rate has been noted.

Introduction

Substances containing fused polycyclic cyclobutane ring systems are found often in nature,[1] and they serve as key intermediates[2] in routes to biologically and medicinally important synthetic targets. Despite this, stereocontrolled construction of the fused cyclobutanes remains a difficult task in preparative organic chemistry.[3] In recent studies, we have shown that intramolecular Michael−aldol reactions can serve as powerful and efficient methods to construct polycyclic cyclobutanes. In addition, the ability to control relative stereochemistry at four or five stereogenic centers in this process enhances its synthetic power.[4] Specifically, keto-α,β-unsaturated esters undergo Lewis acid−base co-mediated sequential Michael addition and aldol reaction to afford cyclobutane derivatives. For example, treatment of keto-enoate **1** with trimethylsilyl iodide−hexamethyldisilazane (TMSI−HMDS)[5] produces the tricyclo[5.4.0.0^{3,7}]undecane **2**, which possesses the italicen skeleton.[6] Also, reaction of keto-enoate **3** using TBDMSOTf−NEt$_3$[7] gives tricyclo[4.2.1.0^{3,8}]-nonane **4**, which contains the partial framework of endiandric acids[8] (Scheme 1).

Scheme 1



The asymmetric version of this cyclization reaction would be an extremely potent methodology to access enantiomerically enriched, fused polycyclic cyclobutanes.

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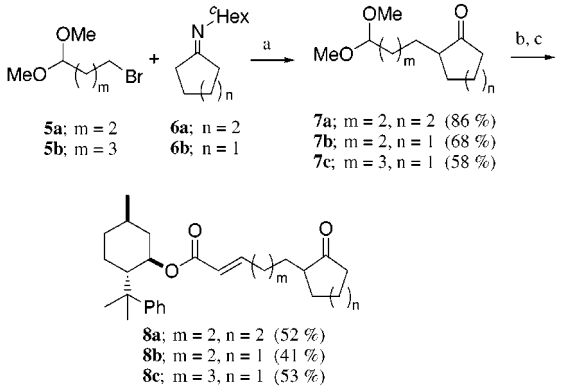
Scheme 2[a]



[a] Key: (a) LDA, HMPA, THF; (b) $(CO_2H)_2 \cdot H_2O$, THF−H_2O; (c) $PhMenO_2CCH{=}PPh_3$, MeCN.

We recently described asymmetric Michael−aldol reactions of **3** by using silyl triflate and C_2 chiral amines.[9] Asymmetric induction in theses processes is based on initial enantioselective enol silylation. However, this strategy cannot be applied to α-substituted ketones, such as **1**, since reaction of **1** with silyl triflate and amines does not afford the desired Michael−aldol adduct, but instead, it produces a kinetically stable silyl enol ether.[4b,7] In the current investigation, we observed that Michael−aldol reactions of α-substituted ketones can be promoted by using TMSI−HMDS and related conditions. Importantly, by using 8-arylmenthol ester[10] derivatives of α-substituted ketones, asymmetric Michael−aldol reactions can be achieved.[11]

Results and Discussion

Asymmetric Michael−Aldol Reaction. The 8-phenylmenthyl esters **8a**−**c** are synthesized by use of minor modifications of reported procedures[4b] (Scheme 2). For example, α-alkylation of *N*-(cycloalkylidene)cyclohexylamine (**5**) with 1-bromo-4,4-dimethoxyalkane (**6**) followed by aqueous workup affords the α-substituted ketones **7**. Acetal cleavage followed by Wittig olefination[12] transforms **7** into the 8-phenylmenthyl enoates **8**. The relative configuration of the α-ketone position in **5** was not determined. In any event, the chirality at this center is lost during Michael−aldol reaction.

On the basis of the results of our previous studies,[4] intramolecular Michael−aldol reaction of the α-substituted substrates (**8**) were performed by using TMSI−HMDS conditions (Scheme 3). It is known that the treatment of ketones with this mixed reagent system predominantly gives thermodynamic silyl enol ethers.[5] At ambient temperature, reaction of **8a** with TMSI−HMDS in CH_2Cl_2 affords tricyclo[5.3.0.$0^{3,7}$]undecanes, **9a** and **10a**, as separable diastereomers. When the reaction is quenched by the addition of water after 1 h, **9a**, **10a**, and silyl enol ether **11a** are obtained in 44, 6, and 38% yield, respectively (Table 1, entry 1), and the diastereomeric excess of **9a** over **10a** is 76% de. Reaction for an 11 h period gives significantly lower levels (33% de, entry 2) of diastereoselectivity. The de is also low for reactions in $ClCH_2CH_2Cl$ (18% de, entry 3). Reactions run at the lower temperatures in CH_2Cl_2 are highly diastereoselective, and the yields of the silyl enol ether byproducts **11** are decreased (entries 4−6). For example, when the reaction of **8a** is carried out at −78 °C, **9a** is obtained in 85% yield as the sole diastereomer. Reaction of **8a** promoted by using TMSOTf−HMDS, although showing the same levels of diastereoselectivity, occurs at a remarkably lower temperature (entries 7 and 8). The cyclopentanone **8b** also furnishes Michael−aldol adducts **9b** and **10b** under these conditions, and excellent diastereoselectivities are achieved at −78 °C (entries 9 and 10).

To assign relative stereochemistry, **9a** and **10a** are transformed into the corresponding tricyclic diols by the reductive removal of the auxiliary, followed by desilylation. The diols **12** (Scheme 4) obtained from **9a** and **10a** have known[4b] relative stereochemistry. Their specific rotations ($[\alpha]^{26}_D$ (*c* 1.0 $CHCl_3$)) are −26.6 and +26.1, respectively. The absolute configuration of **9a** is determined by use of circular dichroism analysis of the derived spirocyclohexanone acid **13**, obtained by the treatment of **9a** with TBAF, followed by hydrolysis with NaOMe (Scheme 5). The keto-acid **13** shows a weak positive Cotton effect ($[\theta] = +886$, $\lambda_{ext} = 308.6$ nm). Application of the octant rule[13] suggests that the spiro carbon has the (*R*)-configuration. On the basis of these findings, **9a** and **10a** are assigned the (1*S*,2*R*,3*R*,7*R*)- and (1*R*,2*S*,-3*S*,7*S*)-tricyclo[5.4.0.$0^{3,7}$]undecane stereochemistry, respectively. The relative stereochemistries of **9b** and **10b** are determined by using similar procedures, and the absolute configurations of these substances is assumed to be the same as those for **9a** and **10a**.

Michael−aldol reaction of **8c**, which has a longer side chain, by using TMSI−HMDS at room temperature gives (1*R*,2*R*,3*S*,7*S*)-tricyclo[5.4.0.$0^{3,7}$]undecane **14** in 15% yield along with the spiro compound **15** in 76% yield (4:1 pseudo-enantiomeric mixture) (Scheme 6). In this process, **15** is produced by Michael addition of **8c**, followed by enol silylation of the keto-carbonyl group. This reaction, although inefficiently producing **14**, does not generate the pseudo-antipode. Also, reaction of **8c** at −78 °C only gives silyl enol ether **16**. The relative and absolute configuration of **14** is assumed to be the same as for **9a**. The absolute configuration of **15** is assigned by the comparison of the circular dichroism spectrum of its derived keto-acid with that of **13**. Independent desilylation of **14** and **15**, followed by hydrolysis, furnishes different spiro keto-acids **17** and **18**, respectively. Thus, **17** and **18** must have opposite relative configurations at C(5) and C(6). Because of the flexibility of the longer tether in **8c**, the transition state for initial Michael addition is not conformationally fixed; therefore, two different products, **14** and **15**, are formed.

Mechanistic Insights of Intramolecular Michael−Aldol Reaction. The results presented above suggest that an equilibrium is established between **9a**, **10a**, and **11a** when **8a** is treated with TMSI−HMDS at rt. This proposal is supported by the observed variations seen in

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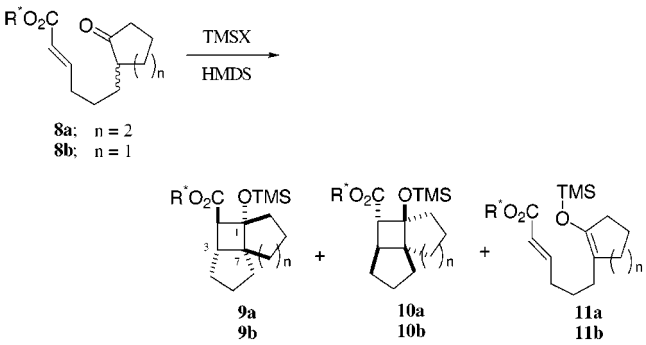
Table 1. Asymmetric Michael−Aldol Reactions of 8a and 8b

entry	substrate	reagent	solvent	temp (°C)	time (h)	yield (%) 9	10	11	de (%)[f]
1[a]	**8a**	TMSI−HMDS	CH_2Cl_2	rt	1	44	6	38	76
2[a]	**8a**	TMSI−HMDS	CH_2Cl_2	rt	11	30	15	33	33
3[a]	**8a**	TMSI−HMDS	$ClCH_2CH_2Cl$	rt	11	36	25	25	18
4[a]	**8a**	TMSI−HMDS	CH_2Cl_2	0	9	55	6	23	80
5[a]	**8a**	TMSI−HMDS	CH_2Cl_2	−30	9	76	3	15	92
6[a]	**8a**	TMSI−HMDS	CH_2Cl_2	−78	11	85	0	0	100
7[b]	**8a**	TMSOTf−HMDS	CH_2Cl_2	rt	14	29	15	30	32
8[c]	**8a**	TMSOTf−HMDS	CH_2Cl_2	−30	15	35	trace	7	∼95
9[d]	**8b**	TMSI−HMDS	CH_2Cl_2	rt	8	70[e]	∼5[e]	0	∼90
10[d]	**8b**	TMSI−HMDS	CH_2Cl_2	−78	20	73[e]	0	0	100

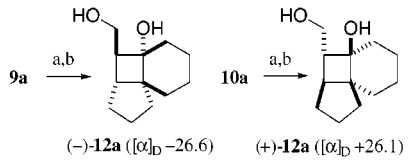
[a] TMSI (1.2)−HMDS (1.5 equiv). [b] TMSOTf (1.2)−HMDS (1.5 equiv). [c] TMSOTf (3.0)−HMDS (3.0 equiv). [d] TMSI (1.5)−HMDS (1.5 equiv). [e] The configuration was determined based on the reaction mechanism. [f] The diastereomeric excess (de) was determined based on isolated yield. de = (**9** − **10**)/(**9** + **10**).

Scheme 3[a]



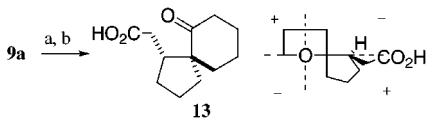
[a] R* = (−)-8-phenylmethyl.

Scheme 4[a]



[a] Key: (a) DIBAL−H, CH_2Cl_2; (b)TBAF, TF.

Scheme 5[a]



[a] Key: (a) TBAF, THF; (b) NaOMe, H_2O.

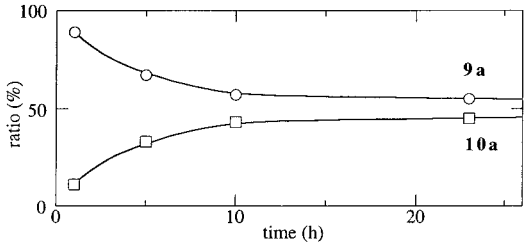


Figure 1. Time course of the reaction of **8a** to produce two diastereomers with proportions of **9a** (○) and **10a** (□).

the product ratios as a function of reaction time (Figure 1, product ratios calculated by use of ^{1}H NMR). After a 1 h reaction time, the amount of **9a** is ca. 7× that of **10a**, and as the reaction time increases, the **9a**:**10a** ratio increases, reaching a final ratio of ca. 11:9. The relative

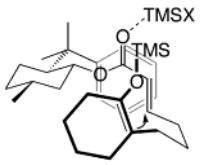


Figure 2. Diastereofacial selection of **8a**.

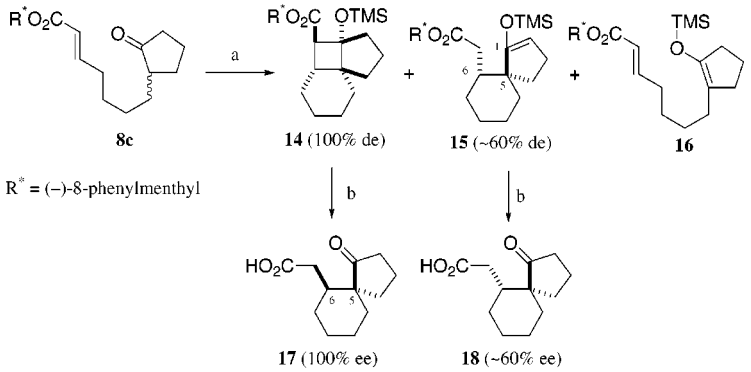
ratio of **11a** to the sum of **9a** and **10a** remains constant throughout this period. In addition, exposure of **9a** to TMSI−HMDS at rt affords **10a**, **11a**, and unreacted **9a**.

The stereochemical course of the Michael−aldol reactions of **8a** and **8b** can be explained in the following manner. Initially, the thermodynamically stable silyl enol ether **11a** and **11b** is generated by reaction of **8a** and **8b**, respectively, with TMSI−HMDS. Mukaiyama-type Michael addition and aldol reaction ensues to give **9** and/or **10**. A preference for the s-trans conformation of the enoate moiety, caused by $\pi-\pi$ attractive interactions, appears to exist. This is indicated in the ^{1}H NMR spectrum of **8a** by the downfield shifts of the vinyl protons ($\Delta\delta = -0.56$ and -0.45 ppm for α- and β- protons, respectively) and comparisons to related methyl ester analogues.[4b] At low temperature, the diastereofacial selection favoring **9** is controlled by π-stacking interaction of the aromatic ring of the phenylmenthol moiety (Figure 2). Even at room temperature, the kinetic product **9** is formed initially. However, at this temperature, reversible Michael−aldol reaction promoted by TMSI−HMDS results in isomerization of the adducts via the silyl enol ether.

In contrast, a rather complex pathway is involved in reaction of **8c**. The products vs reaction time profile for this process (Figure 3) shows that regioselective enolsilylation occurs initially to form **16**. At longer reaction times, the amount of **15** increases at the expense of **16**, which decreases. Finally, at the end of the process, **16** has nearly disappeared, and **15** becomes the main product. Simultaneously, **14** forms quickly in this mixture, but it gradually disappears after ca. 10 h. The behavior summarized above is consistent with the simultaneous operation of (1) a reversible Michael−aldol reaction, which equilibrates **14** and **16** and (2) a nonreversible Michael addition enol silylation sequence to produce the stable **15**. Actually, **15** is found to be unreactive under the conditions used in this process.

Effect of Iodine on the Michael−Aldol Reaction. In the course of these studies, we observed that the rate of the Michael−aldol reaction is dependent on the purity

Scheme 6[a]



[a] Key: (a) TMSI, HMDS, CH_2Cl_2; (b) TBAF, THF; (c) NaOMe, H_2O.

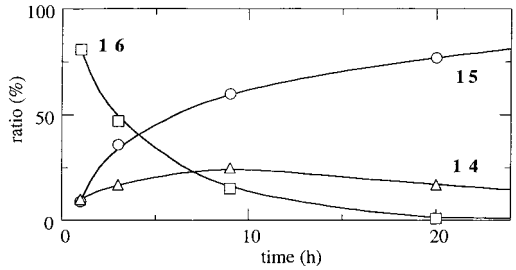


Figure 3. Time course of the reaction of **8c** to produce **14** (△), **15** (○), and **16** (□).

Table 2. Influence of Iodide/Iodine Additive

entry[a]	color of TMSI	additive	yield (%) **9a**
1	red-brown		85
2	colorless		24
3	colorless	*n*Bu4NI (4 mol %)	15
4	colorless	NIS (4 mol %)	46

[a] All reactions were carried out in the presence of 1.2 equiv of TMSI and 1.5 equiv of HMDS in CH_2Cl_2 at −78 °C for 8−11 h.

of TMSI. For example, reaction of **8a** with nonpurified TMSI (red-brown color) resulted in high yielding generation of **9a** (Table 2, entry 1). In contrast, when purified TMSI (colorless) is used under otherwise identical reaction conditions, **9a** is produced in only low yield (entry 2). We believe that small amounts of iodide/iodine, present in unpurified TMSI, enhances the rate of the Micheal−aldol reaction. To test this proposal, the influence of iodide/iodine additives was investigated.[15] Treatment of **8a** with purified TMSI and HMDS in the presence of a catalytic amount of tetrabutylammonium iodide led to the formation of **9a** in a 15% yield (entry 3). On the other hand, addition of a catalytic amount of *N*-iodosuccinimide (NIS) markedly increased the production of **9a** (46% yield, entry 4). From these observations, we conclude that the Michael−aldol reaction is activated by iodonium cation (I^+) donors rather than by iodide (I^-). Although the mechanistic reasons for this are not clear at this time, we believe that interaction of the iodonium cation donor with the electron-negative iodine atom of TMSI might catalyze the initial enolsilylation step in the overall process.

(14) For a review of π-stacking effects in asymmetric synthesis, see: Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475−497.

(15) When Michael−aldol reaction of **5a** with a catalytic amount of iodine (I_2) was tested, rate enhancement was observed. Because of the difficult handling of a small amount of I_2, precise results could not be obtained.

Conclusion. In summary, we have developed an effective asymmetric Michael−aldol methodology for the construction of enantiomerically enriched, tricyclic cyclobutanes. In addition, the observations we have made clearly show that the TMSI−HMDS promoted Michael−aldol reaction is reversible at room temperature and, as a result, that the stereoselectivity of the process is dependent on the reaction temperature and time. Finally, it is noteworthy that stereochemistry at the four stereogenic centers generated in these reactions is controlled by 8-phenylmenthol chiral auxiliary.

Experimental Section

General. All reactions were carried out under an inert atmosphere. Anhyd THF, MeCN, and CH_2Cl_2 were purchased from the Kanto Chemical Co., Inc. Dichloroethane, HMPA, and HMDS were distilled from CaH_2 under atmospheric or reduced pressure. Unless otherwise described, pale red TMSI was used for the Michael−aldol reaction. Unless otherwise described, the materials were obtained from commercial suppliers and used without further purification. Organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure using an evaporator. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and were reported in ppm downfield from TMS ($\delta = 0$) for the ^1H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.00$) for the ^{13}C NMR.

General Procedure for Preparation of Acetals 7b,c. To a solution of *i*-$PrNH_2$ (1.4 equiv) in THF (0.65 M) at 0 °C was added BuLi (1.53 M in hexane; 1.2 equiv). To this was added a solution of *N*-(cyclopentylidene)cyclohexylamine (**6b**; 1.0 equiv) in THF (0.33 M) dropwise at −78 °C, and the solution was stirred for 1 h at 0 °C. To the resulting mixture were added HMPA (1.2 equiv) and then a solution of bromoacetal **5** (1.3 equiv) in THF (0.45 M) at 0 °C, and the resulting solution was stirred for 1 h at the same temperature. After dilution with Et_2O, the mixture was washed with saturated NH_4Cl and brine. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel with 25% AcOEt/hexane.

2-(4,4-Dimethoxybutyl)cyclopentan-1-one (7b). 7b was prepared from 1-bromo-4,4-dimethoxybutane (**5a**; 1.61 g, 8.2 mmol) and **6b** (1.06 g, 6.4 mmol) in 68% yield (0.88 g) as a colorless oil. IR (neat) ν: 2946, 1735, 1452, 1125, 1060 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.37 (t, 1H, $J = 5.6$ Hz), 3.32 (s, 6H), 2.37−1.93 (m, 5H), 1.88−1.68 (m, 2H), 1.66−1.20 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 221.5, 104.4, 52.7, 52.6, 49.0, 38.0, 32.4, 29.4, 22.5, 20.6. LRMS (*m*/*z*): 199 ($M^+ - 1$). HRMS (*m*/*z*): calcd for $C_{11}H_{19}O_3$, 199.1334; found, 199.1336.

2-(4,4-Dimethoxypentyl)cyclopentan-1-one (7c). 7c was prepared from 1-bromo-5,5-dimethoxypentane (**5b**; 2.60 g, 12.3 mmol) and **6b** (1.67 g, 10.1 mmol) in 58% yield (1.25 g) as a colorless oil. IR (neat) ν: 2940, 1739, 1452, 1125, 1053 cm^{-1}.

^{1}H NMR (MHz, $CDCl_3$): δ 4.35 (t, 1H, J = 5.8 Hz), 3.31 (s, 6H), 2.36−1.94 (m, 5H), 1.89−1.69 (m, 2H), 1.66−1.43 (m, 3H), 1.42−1.19 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 221.6, 104.4, 52.5, 48.9, 38.0, 32.2, 29.4, 27.2, 24.4, 20.6. LRMS (*m*/*z*): 213 (M^+ − 1). HRMS (*m*/*z*): calcd for $C_{12}H_{21}O_3$, 213.1491; found, 213.1448.

General Procedure for Preparation of Phenylmenthyl Enoate 8a−c. A solution of **7** (1.0 equiv) and $(CO_2H)_2\cdot 2H_2O$ (5.0 equiv) in THF−H_2O (1:1 v/v; 0.25 M) was stirred at rt for 4 h. The reaction mixture was diluted with Et_2O, neutralized with saturated $NaHCO_3$ while being cooled, and then extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated to give the crude aldehyde, which was used in the following reaction without further purification. A solution of the above aldehyde and $Ph_3P{=}CHCO_2PhMen$[12] in MeCN was stirred at rt for 13 h. The mixture was concentrated and purified by column chromatography on silica gel with 20% AcOEt/hexane.

2-{[(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]-(4*E*)-4-pentenyl}cyclohexanone (8a). 8a was prepared from **7a**[4b] (3.29 g, 15.3 mmol) in 52% overall yield (3.36 g) in two steps as a colorless oil. $[\alpha]^{22}_D$ +1.4 (*c* 1.0, $CHCl_3$). IR (neat) ν: 2925, 2850, 1710, 1650, 1265, 1130, 760, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.31−7.19 (m, 4H), 7.15−7.05 (m, 1H), 6.51 (dt, 1H, J = 15.5, 6.7 Hz), 5.27 (dt, 1H, J = 15.5, 0.9 Hz), 4.82 (ddd, 1H, J = 10.7, 10.7, 4.3 Hz), 2.37 (tt, 1H, J = 12.9, 3.3 Hz), 2.32−1.19 (m, 2H), 2.15−1.57 (m, 13H), 1.54−0.78 (m, 7H), 1.29 (s, 3H), 1.20 (s, 3H), 0.85 (d, 3H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 213.2, 165.9, 151.7, 148.3, 128.0, 125.5, 124.9, 121.8, 74.0, 50.5, 41.9, 41.6, 39.6, 34.5, 33.82, 33.78, 32.0, 31.1, 28.9, 27.9, 27.4, 16.5, 25.4, 25.3, 25.2, 24.8, 21.5. LRMS (*m*/*z*): 424 (M^+). Anal. Calcd for $C_{28}H_{40}O_3$: C, 79.20; H, 9.50. Found: C, 79.25; H, 9.25.

2-{[(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]-(4*E*)-4-pentenyl}cyclopentanone (8b). 8b was prepared from **7b** (0.31 g, 1.5 mmol) in 41% overall yield (0.26 g) in two steps as a colorless oil. IR (neat) ν: 2940, 1730, 1700, 1260, 1165, 1150, 1120, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.28−7.21 (m, 4H), 7.13−7.07 (m, 1H), 6.50 (dt, 1H, J = 15.7, 6.9 Hz), 5.27 (d, 1H, J = 15.7 Hz), 4.83 (ddd, 1H, J = 15.1, 10.7, 4.4 Hz), 2.37−1.38 (m, 18H), 1.32−0.79 (m, 3H), 1.30 (s, 3H), 1.21 (s, 3H), 0.86 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 221.3, 165.9, 151.8, 148.0, 128.0, 125.5, 124.6, 121.9, 74.1, 50.4, 48.9, 41.6, 39.6, 38.0, 34.5, 31.9, 31.2, 29.4, 29.2, 27.5, 26.5, 25.8, 25.8, 25.1, 21.6, 20.6. LRMS (*m*/*z*): 410 (M^+). Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.94; H, 9.48.

2-{[(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]-(5*E*)-5-hexenyl}cyclopentanone (8c). 8c was prepared from **7c** (0.46 g, 2.1 mmol) in 53% overall yield (0.48 g) in two steps as a colorless oil. IR (neat) ν: 2925, 1735, 1705, 1645, 1260, 760, 795 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.32−7.18 (m, 4H), 7.15−7.07 (m, 1H), 6.51 (dddd, 1H, J = 15.7, 6.9, 6.9, 1.9 Hz), 5.26 (d, 1H, J = 15.7 Hz), 4.83 (ddd, 1H, J = 10.4, 10.4, 4.4 Hz), 2.35−0.90 (m, 23H), 1.30 (s, 3H), 1.21 (s, 3H), 0.86 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 221.5, 165.9, 151.7, 148.4, 127.9, 125.5, 124.9, 121.8, 74.0, 50.5, 48.9, 41.6, 39.6, 38.0, 34.5, 31.7, 31.2, 29.5, 29.3, 27.7, 27.4, 27.0, 26.5, 25.2, 21.6, 20.6. LRMS (*m*/*z*): 424 (M^+). Anal. Calcd for $C_{28}H_{40}O_3$: C, 79.20; H, 9.50. Found: C, 79.16; H, 9.52.

General Procedure for Asymmetric Michael−Aldol Reaction of 8a and 8b. To a solution of **8** and HMDS (1.5 equiv) in CH_2Cl_2 was added TMSI (1.2 or 1.5 equiv) at the reaction temperature. After being stirred for several hours, the mixture was diluted with Et_2O and washed with saturated $NaHCO_3$ and brine. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel with 4% Et_2O/hexane.

(1*S*,2*R*,3*R*,7*R*)-2-[(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]-1-(trimethylsiloxy)-tricyclo[5.4.0.0^{3,7}]undecane (9a). Colorless oil, $[\alpha]^{27}_D$ −23.4 (*c* 1.1, $CHCl_3$). IR (neat) ν: 2950, 1715, 1250, 1200, 840, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.30−7.23 (m, 4H), 7.19−7.12 (m, 1H), 4.85 (ddd, 1H, J = 10.8, 10.8, 4.4 Hz), 2.36 (d, 1H, J = 7.7 Hz), 2.26 (dd, 1H, J = 8.0, 4.0 Hz), 2.22 (m, 1H), 2.00−1.85 (m, 3H), 1.78−0.72 (m, 18H), 1.33 (s, 3H), 1.23 (s, 3H), 0.86 (d, 3H, J = 6.6 Hz), 0.16 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 171.9, 151.1, 128.0, 125.6, 125.3, 75.1, 74.2, 52.7, 52.6, 50.3, 41.9, 40.1, 39.4, 34.7, 34.5, 34.3, 31.7, 31.3, 30.3, 28.5, 27.0, 25.1, 25.0, 22.5, 21.7, 19.8, 1.68. LRMS (*m*/*z*): 496 (M^+). HRMS (*m*/*z*): calcd for $C_{31}H_{48}O_3S$, 496.3370; found, 496.3369.

(1*R*,2*S*,3*S*,7*S*)-2-[(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]-1-(trimethylsiloxy)-tricyclo[5.4.0.0^{3,7}]undecane (10a). Colorless oil, $[\alpha]^{27}_D$ +32.0 (*c* 1.4, $CHCl_3$). IR (neat) ν: 2950, 1715, 1245, 1215, 840, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.30−7.21 (m, 4H), 7.18−7.10 (m, 1H), 4.89 (ddd, 1H, J = 10.8, 10.8, 4.4 Hz), 2.30 (dd, 1H, J = 7.3, 4.8 Hz), 2.17 (m, 1H), 1.99 (m, 1H), 1.93 (d, 1H, J = 7.4 Hz), 1.86 (m, 1H), 1.76−0.76 (m, 19H), 1.31 (s, 3H), 1.21 (s, 3H), 0.87 (d, 3H, J = 6.6 Hz), 0.10 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 172.6, 151.5, 128.1, 125.5, 125.1, 75.3, 74.1, 53.4, 52.6, 50.2, 42.2, 39.7, 38.0, 35.0, 34.4, 33.6, 32.0, 31.3, 30.6, 27.3, 36.7, 25.8, 25.1, 22.0, 21.7, 19.6, 2.02. LRMS (*m*/*z*): 496 (M^+). HRMS (*m*/*z*): calcd for $C_{31}H_{48}O_3Si$, 496.3370; found, 496.3382.

1-(Trimethylsiloxy)-2-{[(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexylcarbonyl]-(4*E*)-4-pentenyl}cyclohexene (11a).[16] Colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.30−7.20 (m, 4H), 7.15−7.05 (m, 1H), 6.56 (dt, 1H, J = 15.9, 6.9 Hz), 5.28 (dt, 1H, J = 15.6, 1.5 Hz), 4.83 (ddd, 1H, J = 10.8, 10.8, 4.5 Hz), 2.08−1.86 (m, 9H), 1.69−0.78 (m, 3H), 1.30 (s, 3H), 1.21 (s, 3H), 0.86 (d, 3H, J = 6.6 Hz), 0.17 (s, 9H).

(1*S*,2*R*,3*R*,7*S*)-2-[(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]-1-(trimethylsiloxy)-tricyclo[5.3.0.0^{3,7}]decane (9b). Colorless oil, $[\alpha]^{25}_D$ −10.6 (*c* 0.9, $CHCl_3$). IR (neat) ν: 2940, 1705, 1250, 880, 840, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.32−7.22 (m, 4H), 7.19−7.10 (m, 1H), 4.86 (ddd, 1H, J = 10.7, 10.7, 4.4 Hz), 2.39 (d, 1H, J = 6.6 Hz), 2.27 (m, 1H), 2.02−1.80 (m, 4H), 1.76−0.71 (m, 16H), 1.30 (s, 3H), 1.23 (s, 3H), 0.86 (d, 3H, J = 6.6 Hz), 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 171.7, 151.1, 128.1, 125.6, 125.3, 99.2, 82.6, 74.4, 57.9, 53.0, 50.3, 41.9, 40.1, 38.8, 37.4, 35.5, 34.5, 32.1, 31.3, 30.1, 28.4, 27.0, 25.5, 25.2, 24.1, 21.7, 1.5. LRMS (*m*/*z*): 482 (M^+). Anal. Calcd for $C_{30}H_{46}O_3Si$: C, 74.64; H, 9.60. Found: C, 74.52; H, 9.48.

Transformation into Diol (−)-12 from 9a. (1*S*,2*R*,3*R*,7*R*)-1-Hydroxy-2-(hydroxymethyl)tricyclo[5.4.0.0^{3,7}]undecane ((−)-12). To a solution of **9a** (45 mg, 0.090 mmol) in CH_2Cl_2 (0.7 mL) was added 0.94 M DIBALH−hexane (0.22 mL, 0.31 mmol) at −78 °C and stirred for 3 h. The resulting mixture was poured onto Et_2O/H_2O and then stirred for 1.5 h at rt. After addition of $MgSO_4$, the mixture was filtered through Celite and evaporated to give the corresponding crude alcohol. To a solution of the above alcohol in THF (0.7 mL) was added 1.0 M TBAF−THF (0.14 mL, 0.14 mmol), and it was stirred for 30 min at rt. The resulting mixture was diluted with AcOEt, washed with H_2O and brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel with AcOEt to give (−)-**12** (13 mg, 73% for two steps) as colorless needles, mp 108−110 °C, whose spectral data were identical with the reported racemate.[4b] $[\alpha]^{26}_D$ −26.6 (*c* 1.0, $CHCl_3$).

Transformation into Diol (+)-12 from 10a. The transformation into (+)-**12** from **10a** was carried out by the same procedure as above. (+)-**12** colorless needles, mp 109−111 °C, whose spectral data were identical with the reported racemate.[4b] $[\alpha]^{26}_D$ +26.1 (*c* 0.9, $CHCl_3$).

[(1*R*,5*R*)-Spiro[4.5]decan-6-one-1-yl]acetic Acid (13). To a solution of **9a** (117 mg, 0.24 mmol) in THF (1.9 mL) was added 1M TBAF−THF (0.35 mL, 0.35 mmol) and stirred for 12 h at rt. The mixture was diluted with AcOEt, washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was purified on silica gel with 8% Et_2O/hexane to give the corresponding spiro ketone as a colorless oil (38 mg, 32%). IR (neat) ν: 2940, 2850, 1715, 1695, 1175, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.34−7.21 (m, 4H), 7.20−7.18 (m, 1H), 4.79 (ddd,

(16) Silyl enol ethers **11a** and **16** were unstable against the atmosphere. All analytical spectra except for ^{1}H NMR could not be obtained.

1H, J = 10.8, 10.8, 4.5 Hz), 2.47−2.34 (m, 1H), 2.26−2.16 (m, 1H), 2.16−0.76 (m, 23H), 1.29 (s, 3H), 1.20 (s, 3H), 0.86 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 213.9, 173.1, 151.5, 128.0, 125.4, 125.2, 74.1, 59.3, 50.2, 43.9, 41.8, 40.4, 39.6, 38.0, 35.5, 35.1, 34.4, 31.2, 29.9, 27.4, 26.52, 26.49, 25.4, 22.3, 21.7, 21.1. HRMS (m/z): (M^+) calcd for $C_{28}H_{40}O_3$, 424.2975; found, 424.2962.

A solution of the above ketone (38 mg, 0.089 mmol) and NaOMe (48 mg, 0.89 mmol) in MeOH (2.0 mL) was refluxed for 5 h. The mixture was quenched with H_2O, evaporated, and extracted with AcOEt. The aqueous layer was turned acidic with 10% HCl and extracted with AcOEt. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give **13** as a colorless oil (12 mg, 64%). CD (MeOH) λ_{ext}, nm [θ]: 309 [+886]. UV (MeOH) λ_{max}, nm (ϵ): 284 (34). IR (neat) ν: 3400 (br), 2925, 1695, 1440, 945 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.65−2.52 (m, 1H), 2.52−2.38 (m, 1H), 2.36−1.96 (m, 5H), 1.96−1.20 (m, 10H), 0.86 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 214.3, 179.4, 59.2, 44.2, 40.2, 38.0, 36.1, 34.8, 30.2, 26.4, 22.4, 21.3. HRMS (m/z): (M^+) calcd for $C_{12}H_{18}O_3$, 210.1255; found, 210.1260.

Asymmetric Michael−Aldol Reaction of 8c. To a solution of **8c** (55 mg, 0.13 mmol) and HMDS (44 μL, 0.19 mmol) in CH_2Cl_2 (0.9 mL) was added TMSI (28 μL, 0.20 mmol) at rt. After being stirred for 20 h, the mixture was extracted with Et_2O and washed with saturated $NaHCO_3$ and brine. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel with 2% Et_2O/hexane to give **14** (9.3 mg, 15%) and **15** (48.8 mg, 76%).

(1*R*,2*R*,3*S*,7*S*)-2-[(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonyl]-3-(trimethylsiloxy)-tricyclo[5.4.0.0^{3,7}]decane (14). Colorless oil, $[\alpha]^{25}_D$ −10.2 (c 0.9, $CHCl_3$). IR (neat) ν: 2920, 1710, 1245, 840, 755 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.32−7.21 (m, 4H), 7.20−7.10 (m, 1H), 4.85 (ddd, 1H, J = 10.7, 10.7, 6.6 Hz), 2.61 (d, 1H, J = 10.4 Hz), 2.37−2.24 (m, 1H), 2.00−0.68 (m, 22H), 1.33 (s, 3H), 1.23 (s, 3H), 0.85 (d, 3H, J = 6.3 Hz), 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 172.6, 151.2, 128.1, 125.7, 125.4, 84.4, 74.3, 51.3, 50.5, 49.3, 42.2, 40.2, 38.3, 36.8, 34.5, 31.9, 31.4, 28.6, 27.1, 25.2, 24.6, 23.7, 21.8, 21.2, 20.9, 1.7. LRMS (m/z): 482 (M^+). HRMS (m/z): calcd for $C_{31}H_{48}O_3Si$, 496.3370; found, 496.3411.

(5*R,6*R**)-6-[(1*R*,2*S*,5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohexyloxycarbonylmethyl]-1-(trimethylsiloxy)-spiro[4.5]dec-1-ene (15) (4:1 Mixture of (5*R*,6*R*)/(5*S*,6*S*)).** Colorless oil, $[\alpha]^{23}_D$ −11.4 (c 1.3, $CHCl_3$). IR (neat) ν: 2920, 1720, 1640, 1245, 870, 840, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.33−7.20 (m, 4H), 7.19−7.02 (m, 1H), 4.77 (ddd, 1H, J = 10.7, 10.7, 4.4 Hz), 4.55 (t, 0.8H, J = 2.3 Hz), 4.78 (t, 0.2H, J = 2.3 Hz), 2.21−2.08 (m, 1H), 2.26−1.78 (m, 5H), 1.70−0.75 (m, 17H), 1.29 (s, 3H), 1.21 (s, 3H), 0.85 (d, 3H, J = 6.6 Hz), 0.23 (s, 7.2H), 0.17 (s, 1.8H). ^{13}C NMR ($CDCl_3$): δ 211.1, 173.5, 158.0, 151.8, 128.1, 128.0, 125.4, 125.1, 122.4, 99.3, 74.1, 50.8, 50.4, 41.9, 39.7, 37.6, 36.2, 36.0, 34.5, 31.2, 28.4, 27.1, 26.6, 25.83, 25.79, 25.6, 22.6, 21.7, −0.14. LRMS (m/z): 496 (M^+). Anal. Calcd for $C_{31}H_{48}O_3Si$: C, 74.95; H, 9.74. Found: C, 74.80; H, 9.48.

Trimethylsiloxy-2-{[(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexycarbonyl]-(5*E*)-5-hexenyl}-1-cyclopentene (16).[16] Colorless oil, ^{1}H NMR ($CDCl_3$): δ 7.31−7.20 (m, 4H), 7.15−7.05 (m, 1H), 6.53 (ddd, 1H, J = 15.7, 6.9, 6.9 Hz), 5.27 (d, 1H, J = 15.7 Hz), 4.84 (ddd, 1H, J = 10.4, 10.4, 4.4 Hz), 2.30 (t, 1H, J = 7.3 Hz), 2.18 (t, 1H, J = 7.3 Hz), 2.14−0.77 (m, 20H), 1.30 (s, 3H), 1.21 (s, 3H), 0.85 (d, 3H, J = 6.6 Hz), 0.16 (s, 9H).

[(5*R*,6*S*)-Spiro[4.5]decan-1-one-6-yl]acetic Acid (17). 17 was prepared from **14** (7.4 mg, 15 μmol) in 39% overall yield (6.5 mg) in two steps, according to the same procedure as described in the preparation of **13**. Colorless plates, mp 121−124 °C, $[\alpha]^{24}_D$ +12.3 (c 0.94, $CHCl_3$). IR (neat) ν: 3100 (br), 2950, 2885, 1735, 1710, 1450, 1405, 945, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (dd, 1H, J = 16.3, 4.8 Hz), 2.35−1.13 (m, 16H), 0.90 (m, 1H). HRMS (m/z): (M^+) calcd for $C_{12}H_{18}O_3$, 210.1255; found, 210.1234.

[(5*R*,6*R*)-Spiro[4.5]decan-1-one-6-yl]acetic Acid (18). 18 was prepared from **15** (23 mg, 46 μmol) in 20% overall yield (9.6 mg) in two steps, according to the similar procedure as described in the preparation of **13**. Colorless crystals, $[\alpha]^{24}_D$ +34.0 (c 0.67, $CHCl_3$; ∼60% ee). IR (neat) ν: 3000 (br), 2920, 2850, 1725, 1700, 1440, 1180, 1160 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56−1.15 (m, 17H), 1.05 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 223.5, 178.1, 53.2, 38.4, 37.5, 37.0, 33.0, 28.6, 27.3, 25.4, 21.4, 18.7. HRMS (m/z): (M^+) calcd for $C_{12}H_{18}O_3$, 210.1255; found, 210.1271.

Time Course of the Reaction of 8a under TMSI−HMDS. To a solution of **8a** (105 mg, 0.247 mmol) in CH_2Cl_2 (1.7 mL) was added HMDS (85 μL, 0.0.371 mmol) and TMSI (42 μL, 0.295 mmol) at rt. After the mixture was stirred for 1 h, a part of the mixture (about 0.3 mL) was taken out by a syringe, diluted with Et_2O, washed with a saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. After the mixture was stirred for 5, 10, and 23 h, the same handling as above was done. The ratio of **9a**, **10a**, and **11a** was determined by the integration from ^{1}H NMR.

Michael−Aldol Reaction in the Presence of Iodide/Iodine Additive. To a solution of **8a** (0.10 mmol) and the iodide/iodine additive (4.0 μmol) in CH_2Cl_2 (0.9 mL) was added HMDS (0.15 mmol) and purified colorless TMSI (16 μL, 0.11 mmol) at −78 °C. After being stirred for 8 h, the mixture was worked-up and purified according to the general procedure that gave **8a**.

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Supporting Information Available: ^{1}H NMR spectra (300 MHz) for compounds **7b**,**c**; **9a**; **10a**; **11a**; **13**; **14**; and **16**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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