Asymmetric Michael Addition of Malonate Anions to Prochiral Acceptors Catalyzed by L-Proline Rubidium Salt

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Received February 1, 1996[⊗]

L-Proline rubidium salt catalyzes the asymmetric Michael addition of malonate anions to prochiral enones and enals. This method can be applied to a wide range of substrates to give adducts with a predictable absolute configuration: (*S*)-adducts from (*E*)-enones/enals and (*R*)-adducts from cyclic (*Z*)-enones. Both the secondary amine moiety and the carboxylate moiety are critical for the catalytic activity and asymmetric induction. Varying the countercation also affects the reaction course. High enantiomeric excesses were attained when di(*tert*-butyl) malonate was added to (*E*)-enones in the presence of CsF. The stereochemistry of the Michael reaction indicates that asymmetric induction takes place via enantioface discrimination involving the acceptor α-carbon atom rather than the *β*-carbon atom.

The Michael addition reactions of enolates are some of the most fundamental C−C bond-forming reactions. Therefore, their catalytic asymmetric versions have been studied extensively.[1] The asymmetric reactions can be categorized into two groups: (i) enantioselective addition of prochiral enolates (donors) to acceptors; and (ii) enantioselective addition of enolates (donors) to prochiral acceptors (Figure 1). The former reactions discriminate the enantiofaces of the donors, and asymmetric centers are formed on the donors. Considerable progress has been made for this group of reactions, and oxyindancarboxylates, phenylacetates, cyanoacetates, *etc.* have been added to activated olefins to achieve more than 90% ee.[2] Chiral environments constructed by crown ethers or phosphines can effectively differentiate the donor enantiofaces. However, this method inherently limits the substrates that can be used. Acrylates, acroleins, and vinyl ketones are typical acceptors. In contrast to prochiral donor reactions, prochiral acceptor reactions proceed via enantioface differentiation of Michael acceptors to generate chiral centers on the acceptors. This method has the potential to produce various chiral centers by simply changing the acceptors, although it has met with less success than the former method. The reported optical yields have been generally moderate at best,[3] and their applicability is quite limited. Very often, previous reports have described only one or two combinations of substrates, and acceptable results were obtained usually with chalcone and related compounds. Reactions with aliphatic acyclic enones, for example, have been rare.

We previously described the asymmetric Michael addition of a simple malonate anion to prochiral enones and

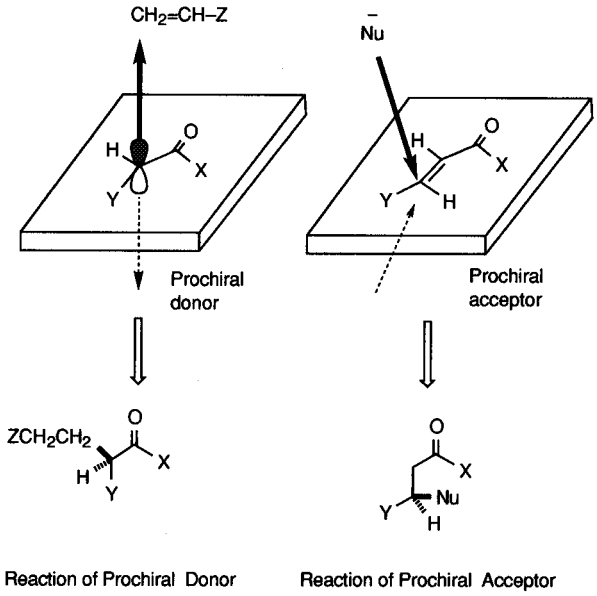


Figure 1. Asymmetric Michael addition reactions.

enals catalyzed by L-proline rubidium salt (Scheme 1), which was the first catalytic asymmetric version of this reaction.[4] This method can be applied to a wide range of substrates to give adducts with predictable absolute configurations and enantiomeric excesses of close to 80%. After our preliminary report, Sasai and Shibasaki reported the lanthanide-catalyzed asymmetric addition of malonates to cyclic (*Z*)-enones and chalcone, which gave very high stereoselectivities (>90% ee).[5] Taguchi used pyrrolidylalkyl ammonium hydroxide derived from L-

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

(1) A review: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford. 1992.

(2) For recent examples, see: Desimoni, G.; Quadrelli, P.; Righetti, P. P. *Tetrahedron* **1990**, *46*, 2927. Brunner, H.; Zintl, H. *Monatsh. Chem.* **1991**, *122*, 841. Dehmlow, E. W.; Knufinke, V. *Liebigs Ann. Chem.* **1992**, 283. Sawamura, H.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295; *Tetrahedron* **1994**, *50*, 4439. Crosby J.; Stoddart, J. F.; Sun, X.; Venner, M. R. W. *Synthesis* **1993**, 141. Bonadies, F.; Lattanzi, A.; Orelli, L. R.; Pesci, S.; Scettri, A. *Tetrahedron Lett.* **1993**, *34*, 7649. Riant, O.; Kagan, H. B.; Ricard, L. *Tetrahedron* **1994**, *50*, 4543. Kumamoto, T.; Aoki, S.; Nakajima, M.; Koga, K. *Tetrahedron: Asymmetry* **1994**, *5*, 1431. Brunet, E.; Poveda, A. M. Rabasco, D.; Oreja, E.; Font, L. M.; Batra, M. S.; Rodríguez-Ubis, J. C. *Tetrahedron: Asymmetry* **1994**, *5*, 935. Töke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* **1995**, *36*, 5951.

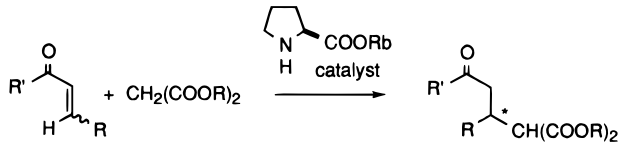
(3) See the following for the recent examples.; also see references cited therein: Takasu, M.; Wakabayashi, H.; Furuta, K.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 6943. Sera, A.; Takagi, K.; Katayama, H.; Yamada, H.; Matsumoto, K. *J. Org. Chem.* **1988**, *53*, 1157. Iwasawa, N.; Yura, T.; Mukaiyama, T. *Tetrahedron* **1989**, *45*, 1197. Loupy, A.; Sansoulet, J.; Zaparucha, A.; Merienne, C. *Tetrahedron Lett.* **1989**, *30*, 333. Botteghi, C.; Paganelli, S.; Schionato, A.; Boga, C.; Fava, A. *J. Mol. Catal.* **1991**, *66*, 7. Hayashi, Y.; Otaka, K.; Saito, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2122. Hirai, Y.; Terada, T.; Katoh, H.; Sonohara, S.; Momose, T. *Heterocycles* **1991**, *32*, 7. Aoki, S.; Sasaki, S.; Koga, K. *Heterocycles* **1992**, *33*, 493.

(4) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176.

(5) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571. Sasai, H.; Arai, T.; Satow, Y. Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194.

S0022-3263(96)00216-2 CCC: $12.00

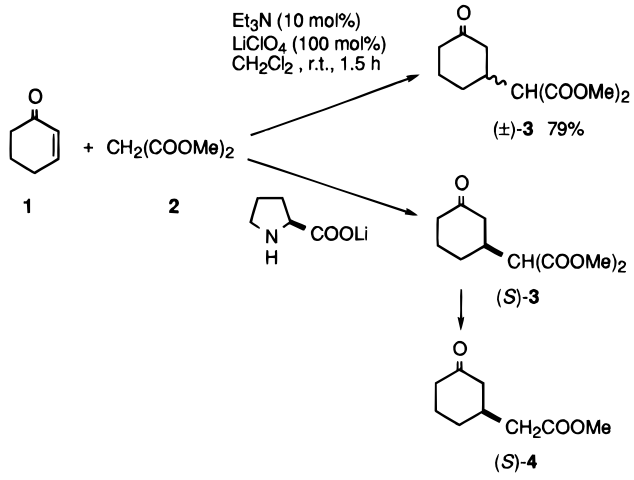
Scheme 1



proline and obtained optically active adducts from cyclic (*Z*)-enones and 4-phenyl-3-propen-2-one.[6] These are still exceptional enolate addition reactions which can be applied to several prochiral acceptors.[7] Apparently, further study is required to develop effective methods, particularly for (*E*)-enones. We describe here recent advances in the asymmetric malonate addition catalyzed by L-proline salts.

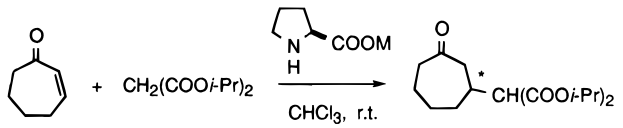
We began work on the asymmetric reaction using a novel catalyst system. Our initial idea was to use combination of a lithium salt and an amine.[8] While no reaction took place by treating 2-cyclohexenone (**1**) and dimethyl malonate (**2**) with triethylamine (10 mol %) at room temperature, the addition of lithium perchlorate (100 mol %) dramatically promoted the reaction to give the racemic adduct (±)-**3** in 79% yield after 1.5 h (Scheme 2). However, we were disappointed to find that asymmetric induction did not occur when optically active amines such as (*S*)-1-phenylethylamine, (*S*)-nicotine, (−)-sparteine, (−)-strychnine, L-prolinol, (−)-brucine, *etc*., were used in place of triethylamine.

Scheme 2



We next tested an amino acid lithium salt, which possesses an amine group and lithium cation.[9] L-Proline lithium salt was prepared from the amino acid and lithium hydroxide in methanol. The salt efficiently promoted the Michael addition of **2** to enones and enals in methanol, but the products were again racemic.[10] After various trials, we observed an appreciable asymmetric induction when **1** and **2** were reacted *in chloroform* to give (*S*)-**3** in 47% ee (Scheme 2). The absolute configuration was determined by converting to a known keto ester (*S*)-**4**.[11] However, the catalytic activity was very low, and the yield was only 13% after 112 h, even when using 100 mol % of the salt. Addition of a small amount (30 mol %) of water promoted the reaction, but it was not enough to be useful with other less-reactive acceptors.

Table 1. Use of Metal L-Prolinate in the Asymmetric Michael Addition



5 **6** **7**

M	mol %	time, h	yield, %[a]	ee, %[b]	config
Li	100	48	23	28	*S*
	100	72	15	17	*S*[c]
Na	5	48	72	29	*R*
K	5	48	72	51	*R*
Rb	5	48	91	59	*R*
	10	30	64	53	*R*[c]
	10	48	78	26	*S*[d]
Cs	5	31	73	56	*R*
$Mg_{1/2}$	200	96	8	31	*S*
$Ca_{1/2}$	20	58	41	22	*S*
$Sr_{1/2}$	20	58	39	12	*S*
$Ba_{1/2}$	20	58	48	1	*S*

[a] Isolated yields are shown. [b] Enantiomeric excesses were determined by optical rotations. [c] Reaction in THF. [d] 18-Crown-6 (10 mol %) was added.

Other L-proline metal salts were examined for higher catalytic activity using the reaction of 2-cycloheptenone (**5**) and diisopropyl malonate (**6**) (Table 1). Sodium and potassium L-prolinate were more effective than the lithium salt. Rubidium and cesium salts enhanced the stereoselectivity. Interestingly, the absolute configuration of the adduct **7** differed between the lithium reaction and the rubidium reaction. Alkaline earth metal salts showed somewhat similar trends. A small amount of water promotes the rubidium salt reaction, since addition of MS 4 Å completely inhibited the reaction.

L-Proline tetraalkylammonium salts were also used as catalysts (Table 2). When the number of carbons in (n-$C_nH_{2n+1})_4N$ increased, the absolute configuration of the adduct **7** changed from (*R*) to (*S*). Asymmetric inductions of $BnNMe_3$ salt, (1-phenylethyl)trimethylammonium salts, and 1-(hydroxymethyl)-5-azoniaspiro[4.4]nonane salts

(6) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805.

(7) Silyl thioketene acetals were added to cyclic (*Z*)-enones and chalcones. As high as 90% ee was attained in the reaction of 2-cyclopentenone. Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97.

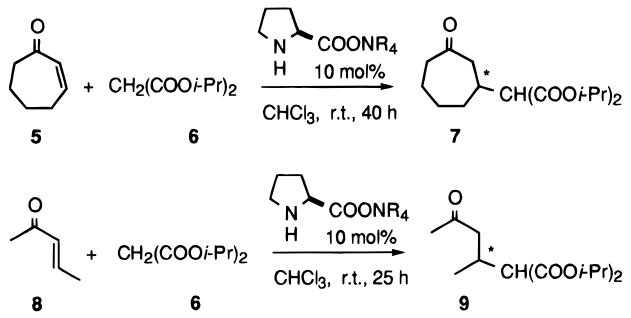
(8) Combinatory use of amine and LiX in the Horner−Wadsworth−Emmons reaction was reported: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624.

(9) Use of proline in the asymmetric Michael addition reactions of thiolate anion: Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick,W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210. Use of proline in the intramolecular Michael addition: Kozikowski, A. P.; Mugrage, B. B. *J. Org. Chem.* **1989**, *54*, 2274.

(10) Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1088.

(11) Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Asirvatham, E.; Cun-Heng, H.; Clardy, J. *Tetrahedron* **1986**, *42*, 2919.

Table 2. Use of Tetraalkylammonium L-Prolinate in the Asymmetric Michael Addition



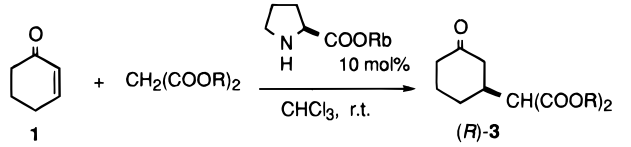
NR_4	yield, %[a]	ee, %[b]	config
Me_4N	33	41	*R*
$BnNMe_3$	34	39	*R*
(*R*)-PhCHMeNMe$_3$	51	23	*R*
(*S*)-PhCHMeNMe$_3$	43	22	*R*
(*R*)-1-(hydroxymethyl)-5-azoniaspiro[4.4]nonane	33	17	*R*
(*S*)-1-(hydroxymethyl)-5-azoniaspiro[4.4]nonane	33	17	*R*
Et_4N	41	8	*S*
(n-Pr)$_4$N	26	10	*S*
(n-Bu)$_4$N	41	38	*S*
(n-C_6H_{13})$_4$N	44	44	*S*
(n-$C_{10}H_{21}$)$_4$N	41	41	*S*
(n-$C_{12}H_{25}$)$_4$N	45	40	*S*
$BnNMe_3$	48[c]	10	*S*
Et_4N	66[c]	10	*R*
(n-Bu)$_4$N	69[c]	28	*R*

[a] Isolated yields are shown. [b] Enantiomeric excesses were determined by optical rotations. [c] Reaction was carried out with (*E*)-3-penten-2-one (**8**).

were intermediate between those of Et_4N salt and Me_4N salt. The chirality of the ammonium salts does not affect the stereochemical outcome. Apparently, the size of the ammonium cation governs stereoselectivity, and its shape is unimportant. Virtually the same relationship between the cation structure and the product configuration was obtained with (*E*)-3-penten-2-one (**8**) (Table 2), where larger ammonium salts predominantly gave adduct (*R*)-**9**. Ammonium cations may be associated with the substrates and prolinate in the transition state. The aggregation of malonate anion and tetraalkylammonium salt has been reported in nonpolar aprotic solvents.[12] Inversion of the absolute configuration by simply changing the size of the cation implies the involvement of more than two competitive reaction pathways.[13]

By analogy to the ammonium cation reactions, metal cations may also play a role in the transition state. Sodiomalonate alkylation in THF, DME, or DMF has been reported to proceed via solvated ion pairs.[14] However, the stereochemistry of the L-proline metal salt reactions and the tetraalkylammonium salt reactions at first appeared to differ. In the case of metal cations, salts with a larger crystal radii gave (*R*)-**7** (Table 1), while larger tetraalkylammonium salts gave (*S*)-**7** (Table 2). This discrepancy may be explained if one considers solvation. The numbers of coordinating solvents in

Table 3. Effect of Ester Group on Asymmetric Induction



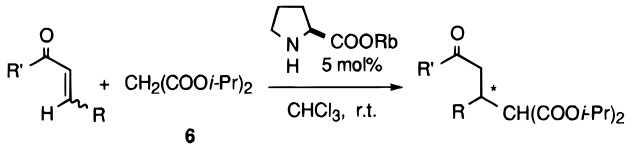
R	time, h	yield, %[a]	ee, %[b]
Me	15	88	40
Et	24	87	43
$PhCH_2$	17	99	39
i-Pr	59	88	53
t-Bu	63	39	65

[a] Isolated yields are shown. [b] Enantiomeric excesses were determined by 400 or 600 MHz ^{1}H-NMR of ketals synthesized from the adducts and (2*R*,3*R*)-2,3-butanediol.

organic solvents as well as in water are generally in the order of $Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$ and $Mg^{2+} > Ca^{2+} > Sr^{2+} > Ba^{2+}$.[15] Solvation of tetraalkylammonium salt other than tetramethyl derivative is believed to be negligible.[16] Thus, the cation effect shown in Tables 1 and 2 may be related to the effective size of the cation in the solvent: L-Proline salts with large cations show (*S*)-selectivity, and small cations show (*R*)-selectivity. Addition of 18-crown-6 to the L-proline rubidium salt reaction altered the product configuration to give (*S*)-**7** (Table 1). This inversion may be due to the strong coordination of the polydentated ligand to the rubidium cation, which increases the effective cation size. The oxygenated ligand must be polydentated, since reactions in THF gave results similar to those in chloroform (Table 1).

The ester group of malonate also affected asymmetric induction (Table 3). Higher optical yields were attained with diisopropyl ester **6** than with dimethyl ester **2**. Use of di(*tert*-butyl) ester further enhanced the selectivity, although the yield decreased.

Table 4. Asymmetric Michael Addition of Diisopropyl Malonate to Enone and Enal



enone/enal	time, h	yield, %[a]	ee, %	config
(*E*)-CH_3CH=$CHCOCH_3$	21	71	76	*S*
(*E*)-CH_3CH=$CHCO$*n*-C_3H_7	46	73[b]	74	S
(*E*)-*n*-$C_5H_{11}CH$=$CHCOCH_3$	7 d	62	77	
(*E*)-$PhCH$=$CHCOCH_3$	9 d	79[b]	53	*S*
2-cycloheptenone	59	91	59	*R*
2-cyclohexenone	46	87	49	*R*
(*E*)-*n*-C_3H_7CH=$CHCHO$	17	58	41	
(*E*)-CH_3CH=$CHCHO$	3	63	35	*S*

[a] Isolated yields are shown. [b] 20 mol % of rubidium L-prolinate was used.

With use of the resulting optimized conditions, **6** was added to several enones and enals in the presence of L-proline rubidium salt (Table 4). The catalyst (5 mol %) gave satisfactory results for relatively reactive substrates. The applicability of this method to a wide range

(12) Reetz, M. T.; Hütte, S.; Goddard, R. *J. Am. Chem. Soc.* **1993**, *115*, 9339.

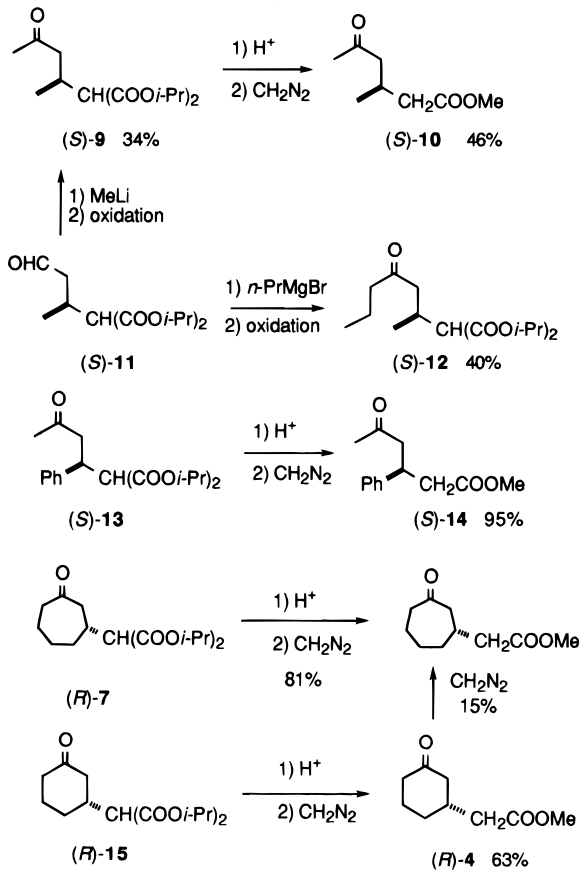
(13) See for example: Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* **1992**, *57*, 1332. Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793.

(14) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. Barlow, G. H.; Zaugg, H. E. *J. Org. Chem.* **1972**, *37*, 2246. Zaugg, H. E.; Ratajczyk, J. F.; Leonard, J. E.; Schaefer, A. D. *J. Org. Chem.* **1972**, *37*, 2249.

(15) Hinton, J. F.; Amis, E. S. *Chem. Rev.* **1971**, *71*, 627.

(16) For examples: Bhattacharyya, D. N.; Lee, C. L.; Smid, J.; Szwaec, M. *J. Phys. Chem.* **1956**, *69*, 608. Krumgalz, *J. Chem. Soc., Faraday Trans. 1* **1980**, *76*, 1887; **1982**, *78*, 437.

Scheme 3

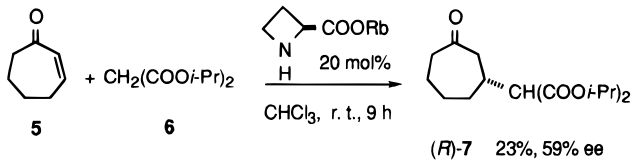


of unhindered acceptors including aliphatic acyclic enone, aromatic acyclic enone, cyclic enone, and enal is notable, when compared to previous methods.[3] However, multiple substitution on the enone double bond inhibited the reaction. Treatment with β,β-disubstituted enones or α,β-disubstituted enones gave low yields of the product under these reaction conditions.

The absolute configurations were determined by chemical correlations to known compounds using a decarboxylation reaction (Scheme 3). (*S*)-**9**, (*S*)-**11**, and (*S*)-**12** were correlated to (*S*)-**10**.[17] Similarly, (*S*)-**13** was converted to (*S*)-**14**.[18] A ring-expansion reaction[19] was used to relate (*R*)-**7** and (*R*)-**15** to (*R*)-**4**.[11] These studies revealed that the acyclic (*E*)-enones and (*E*)-enals gave (*S*)-adducts, while cyclic (*Z*)-enones gave (*R*)-adducts, when L-proline rubidium salt was used (Table 4). These asymmetric inductions are under kinetic control, since the treatment of (*R*)-**7** (58% ee) with D-proline rubidium salt did not change the optical purity. (*Z*)-4-Phenyl-3-buten-2-one was prepared by photoisomerization of the (*E*)-isomer, and was subjected to the asymmetric reaction. However, double-bond isomerization was more rapid than C−C bond formation, and the above observations were not confirmed for the acyclic (*Z*)-enone.[20]

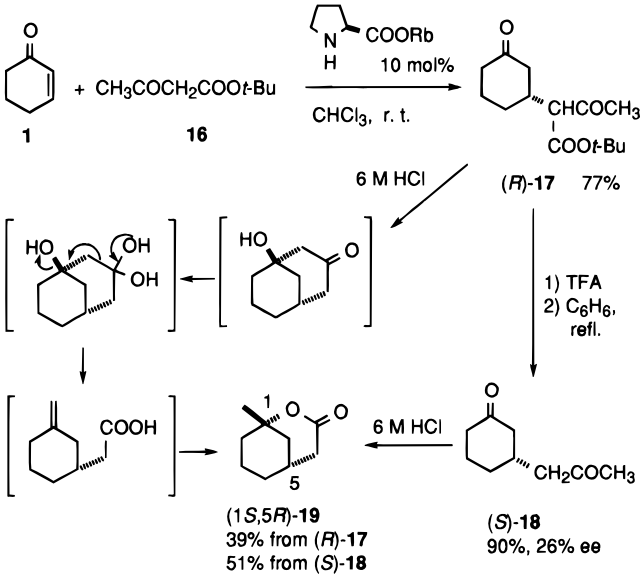
The effect of the catalyst structure was examined. Rubidium L-azetidinecarboxylate showed asymmetric induction comparable to that of the L-prolinate (Scheme 4). Rubidium *N*-benzyl-L-prolinate and triethylamine did not catalyze the reaction, indicating the need for the secondary amine moiety. Since L-proline, L-prolinol, and pyrrolidine were not effective, the carboxylate moiety is also critical. Recently, optically active pyrrolidylalkylammonium hydroxide was used for asymmetric malonate addition.[6] Thus, the carboxylate moiety can be replaced with a tetraalkylammonium group. However, the absolute configurations were opposite those in the carboxylate reactions. Steric congestion around the secondary amino group inhibited the Michael addition, as indicated by the inertness of rubidium L-piperidinecarboxylate, 2-methyl-L-prolinate, *N*-methyl-L-leucinate, *N*-methyl-L-alaninate, and *N*-benzyl-L-leucinate. Rubidium L-homoprolinate, L-thiazoline-4-carboxylate, and 2-methyl-L-thiazoline-4-carboxylate were also not effective catalysts.

Scheme 4



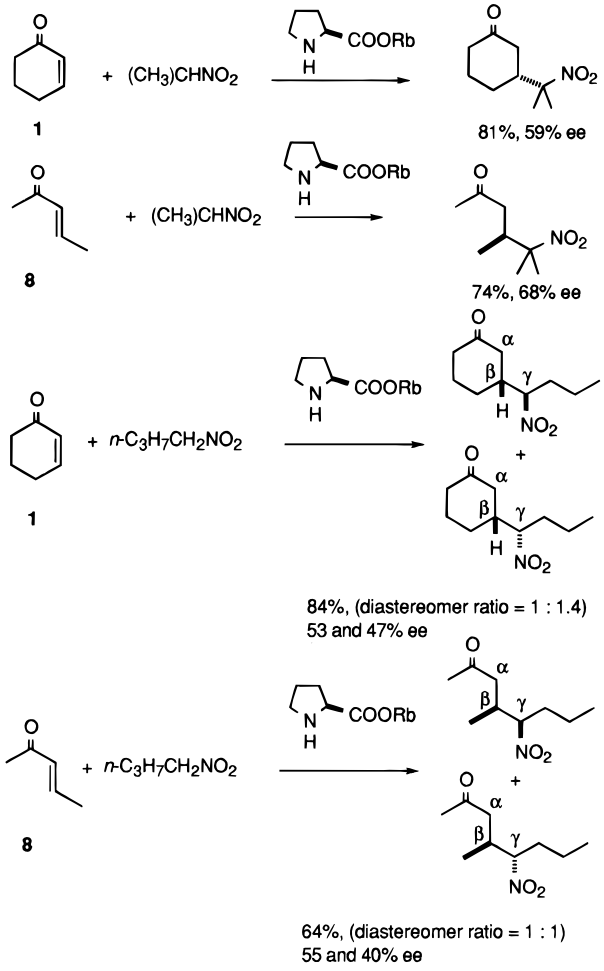
Reaction of **1** and *tert*-butyl acetoacetate (**16**) in the presence of L-proline rubidium salt gave (*R*)-adduct **17**, the absolute configuration of which was determined by converting to a known (*S*)-diketone **18**[21] (Scheme 5). Although the enantiomeric excess was not high, the stereochemistry in the acetoacetate addition is the same as that in the malonate addition. (*R*)-**17** was decarboxylated by a two-step procedure. When (*R*)-**17** was heated in 6 M HCl, a novel rearrangement took place to give optically active (1*S*,5*R*)-2-oxabicyclo[3.3.1]nonan-3-one [(1*S*,5*R*)-**19**]. This transformation involves decarboxylation, intramolecular aldol reaction, fragmentation, and addition of a carboxyl group to olefin.[22] In fact, heating (*S*)-**18** in 6 M HCl gave (1*S*,5*R*)-**19** in 51% yield.

Scheme 5



(17) Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967.
(18) Tomioka, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 4611.
(19) de Boer, T. J.; Backer, H. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 225.
(20) Amine-catalyzed isomerization of (*Z*)-unsaturated carbonyl compounds is known. See for example: Southwick, P. L.; Shozda, R. J. *J. Am. Chem. Soc.* **1959**, *81*, 3298. Rappoport, Z.; Degani, C.; Patai, S. *J. Chem. Soc.* **1963**, 4513.
(21) Yamamoto, K.; Iijima, M.; Ogimura, Y. *Tetrahedron Lett.* **1982**, *23*, 3711.

Scheme 6

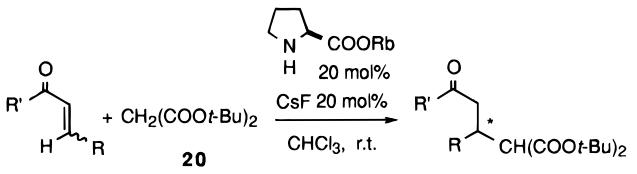


We previously reported the asymmetric nitroalkane addition to enones using a catalyst.[23] The asymmetric induction mode was the same as in the malonate reaction: (*R*)-Adducts were obtained from cyclic (*Z*)-enones, and (*S*)-adducts were obtained from acyclic (*E*)-enones. Examples are shown in Scheme 6. Essentially the same mechanism may be involved in the malonate, acetoacetate, and nitroalkane reactions.

To attain higher asymmetric induction in the malonate reaction, the use of di(*tert*-butyl) malonate (**20**) was reexamined. To our delight, addition of CsF improved the chemical yield without affecting the stereoselectivity (Table 5). Enantiomeric excesses close to 90% were attained with aliphatic (*E*)-enones. At present, this is the best method for conducting the asymmetric malonate addition to (*E*)-enones. Optical yields of adducts were slightly decreased with cyclic (*Z*)-enones. The absolute configurations were the same as in the diisopropyl malonate reaction. CsF probably enolizes the malonate, although CsF itself does not promote conjugate addition.

The *tert*-butyl ester **20** reacted with macrocyclic (*E*)-enones to give adducts in more than 80% ee (Table 5). The absolute configuration of adduct **22** derived from (*E*)-2-pentadecenone (**21**)[24] was determined by converting it

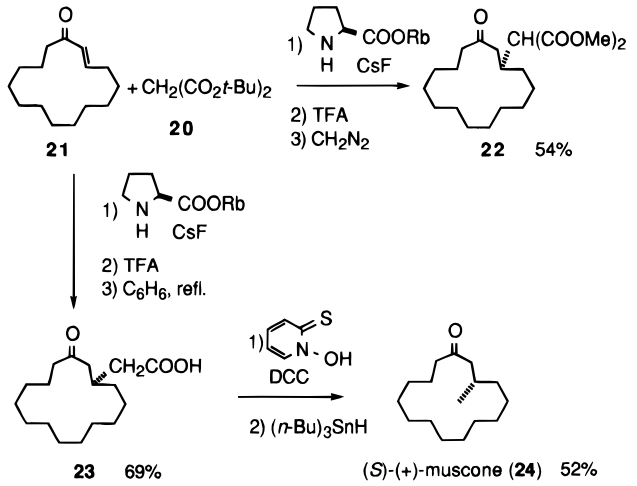
Table 5. Asymmetric Michael Addition of Di(*tert*-butyl) Malonate to Enone



enone	time, h	yield, %[a]	ee, %	config
(*E*)-$CH_3CH{=}CHCOCH_3$	48	65	88	*S*
(*E*)-*n*-$C_5H_{11}CH{=}CHCOCH_3$	96	92[b]	86	
(*E*)-$Ph(CH_2)_2CH{=}CHCOCH_3$	96	73	60	*S*
(*E*)-$PhCH{=}CHCOCH_3$	96	52	76	
(*E*)-$CH_3CH{=}CHCOC_2H_5$	96	84	76	
2-cyclohexenone	48	84	65	*R*
2-cycloheptenone	48	75	74	*R*
(*E*)-2-cyclododecenone	96	45[b]	81	
(*E*)-2-cyclopentadecenone	96	54[b,c]	82	*S*

[a] Isolated yields are shown. [b] Three equivalents of the malonate were used. c) Isolated as dimethyl ester.

Scheme 7



to optically active muscone (**24**) (Scheme 7).[24,25] The Michael adduct without isolation was thermally decarboxylated to give keto acid **23**, which was transformed to (*S*)-**24** by decarboxylation under radical conditions.[26] To synthesize the active ester in the second decarboxylation reaction, the acid anhydride method using carbodiimide was more effective than the acid chloride method using oxallyl chloride. A considerable amount of enol lactone was formed in the latter method.

Figure 2 shows how we defined *re*- and *si*-enantiofaces of enones, where the first priority is given to the C= group. This definition is relatively insensitive to changes in the substituents compared with the conventional *re*/*si*-face definition, and is useful for mechanistic discus-

Figure 2. *re*-Face and *si*-face definition of enantiofaces.

(22) Related reactions were reported using ethylene glycol and $BF_3{\cdot}OEt_2$: Suemune, H.; Oda, K.; Sakai, K. *Tetrahedron Lett.* **1987**, *28*, 3373.

(23) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233.

(24) Tanaka, K.; Ushio, H.; Kawabata, Y.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1445.

(25) Branca, Q.; Fischli, A. *Helv. Chim. Acta* **1977**, *60*, 925.

(26) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

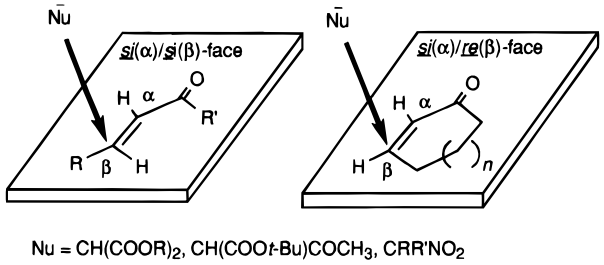


Figure 3. *si*(α)-Attack in the L-proline rubidium salt-catalyzed Michael addition.

sions. Since enones possess two prochiral centers, the α-carbon and *β*-carbon, an enantioface can be described as, for example, *re*(α), *si*(*β*), *si*(α)/*si*(*β*), or *re*(α)/*si*(*β*).

All of the donors that have been examined thus far in the present asymmetric addition attack (*E*)-enones at the *si*(α)/*si*(*β*)-face and (*Z*)-enones at the *si*(α)/*re*(*β*)-face, using L-proline rubidium salt (Figure 3). Both cases involve *si*(α)-attack. Similar observations were made for L-proline tetraalkylammonium salts; *si*(α)-attack for $BnMe_3N$ salt and *re*(α)-attack for $(n\text{-Bu})_4N$ salt (Table 2). The involvement of separate mechanisms for cyclic enones and acyclic enones is unlikely, since their behaviors are similar in many respects, such as the reaction rate, the effect of the catalyst structure, the extent of the asymmetric induction, *etc.* Most likely, the reaction takes place via *s-trans*-conformation of the acceptors.[27] Thus, in these Michael additions, the arrangement of the substituents at the acceptor α-carbon is recognized (α-enantioface discriminating mechanism) rather than the *β*-substituents, although the *β*-carbon is the C-C bond-forming center (Figure 4). In the transition state, L-prolinate should be located in the vicinity of the α-carbon, which generates chiral environments for effective asymmetric induction. Interactions between the carbonyl group and the catalyst are conceivable. Addition of 1-nitrobutane to **1** and **8** gave the *si*(α)-attack products as approximately 1:1 mixtures of diastereomers with regard to the *γ*-carbon atom (Scheme 6).[23] This is consistent with the above view in that the chiral catalyst affects the stereochemistry at the *β*-carbon atom, but not at the remote *γ*-carbon atom.

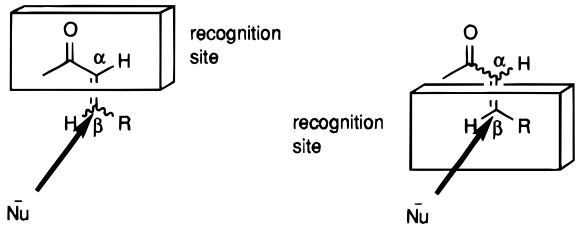


Figure 4. Asymmetric induction mechanisms in Michael addition reactions.

A similar relationship between the acceptor olefin stereochemistry and enantioface selection can be found in the literature. Typical examples are the conjugate addition reactions to chiral enoates.[28] For example, Oppolzer reported the addition of organocopper to chiral enoates derived from (−)-8-phenylmenthol to give *re*(α)-attack adducts for both (*E*)-enoate and (*Z*)-enoate. The chiral auxiliary attached to the acceptors differentiated their α-enantiofaces.[29]

The other asymmetric induction mode involves recognition of the substituent arrangement at the *β*-carbon atom (*β*-enantioface discriminating mechanism in Figure 4), and explicit examples are relatively rare.[30] Kretchmer reported the Grignard conjugate addition to 2-cyclohexenone (**2**) and (*E*)-3-penten-2-one (**8**) in the presence of (−)-sparteine. Both acceptors gave *re*(*β*)-attack products in low optical yields.[31] It may be reasonable to assume that the chiral catalyst in this reaction is located in the vicinity of the *β*-carbon atom in the transition state, and controls the stereochemical approach of the nucleophilic donor carbon atom to the acceptor *β*-carbon atom. However, this asymmetric induction mechanism in principle requires appropriate combinations of donor and acceptor and should therefore be sensitive to the structure of the substrates. The preferred use of chalcones in many catalytic asymmetric Michael additions in the literature[1−3] suggests the involvement of this mechanism. Phenyl group and hydrogen atom differ both sterically and electronically and are relatively easy to discriminate.[32] The wide applicability of the present Michael addition catalyzed by L-proline salts may be due to the involvement of the α-enantioface discriminating mechanism, which recognizes the arrangement of the carbonyl group and the hydrogen atom. This reaction should be less sensitive to the structure of donors and acceptors.

The transition state in the present reaction involves a quaternary complex of donor, acceptor, L-prolinate, and countercation. Although our understanding of the detailed structure is premature, we propose that it includes the formation of an iminium salt between the catalyst and the acceptor.[33] Nakanishi reported the formation of L-proline iminium salts from enals.[34] Unsaturated iminium salt is more reactive than the corresponding enone toward the malonate addition.[35] When iminium salt, prepared from (*E*)-4-phenyl-3-buten-2-one and pyrrolidine,[36] was treated with dimethyl malonate in the presence of triethylamine (10 mol %), the starting material was consumed at room temperature over several hours to give the 1,4-adduct in 16% yield after aqueous workup.

(27) Some conjugate addition reactions rigorously require *s-cis* configuration of acceptors and are not applicable to cyclic enones. Hooz, J.; Layton, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 7320. Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954.

(28) Oppolzer, W.; Löher, H. J. *Helv. Chim. Acta,* **1981**, *64*, 2808; Oppolzer, W.; Poli, G. *Tetrahedron Lett.* **1986**, *27*, 4717. For other example: Takaki, K.; Maeda, T.; Ishikawa, M. *J. Org. Chem.* **1989**, *54*, 58. Pyne, S. G.; Griffith, R.; Edwards, M. *Tetrahedron Lett.* **1988**, *29*, 2089. Corey, E. J.; Hannon, F. J.; Boaz, N. W. *Tetrahedron* **1989**, *45*, 545.

(29) Such stereochemical outcome was also found in addition reactions of chiral cuprate reagents: Leyendecker, F.; Jesser, F.; Ruhland, B. *Tetrahedron Lett.* **1981**, 3601. Andersson, S.; Jagner, S.; Nilsson, M.; Urso, F. *J. Organomet. Chem.* **1986**, *301*, 257. Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040.

(30) The Sasai−Shibasaki Michael addition showed *re*(*β*)-attack to 2-cycloalkenone and chalcone.[5] Discussion, however, is not simple here, since chalcones are unusual substrates in the asymmetric Michael addition as shown by many examples.

(31) Kretchmer, R. A. *J. Org. Chem.* **1972**, *37*, 2744.

(32) Importance of *π*−*π* attractive interaction between the catalyst and chalcone was indicated in the Michael addition reaction: Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993**, *34*, 473.

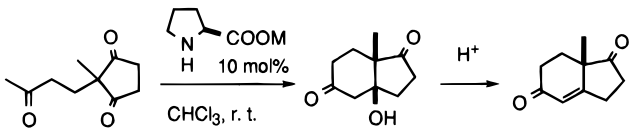
(33) Example of iminium salt used in the asymmetric synthresis: Takano, S.; Iwata, H.; Ogasawara, K. *Heterocycles* **1978**, *9*, 845.

(34) Sheves, M.; Nakanishi, K. *J. Am. Chem. Soc.* **1983**, *105*, 4033.

(35) Conjugate addition reactions to unsaturated iminium salts: Pandit, U. K.; Cabré, F. R. M.; Gase, R. A.; de Nie-Sarink, M. J. *J. Chem. Soc., Chem. Commun.* **1974**, 627. de Nie-Sarink, M. J.; Pandit, U. K. *Tetrahedron Lett.* **1979**, 2449.

(36) Compare: Leonard, N. J.; Paukstelis, J. V. *J. Org. Chem.* **1963**, *28*, 3021.

Scheme 8



M = Li: 93 h, 43% (two steps), 54% ee
M = Rb: 54 h, 43% (two steps), 43% ee
M = H: 44 h, 13% (two steps), 80% ee

1,2-Adduct was not detected. The low yield was due to polymerization of the iminium salt. In contrast, essentially no reaction took place with the enone itself under these conditions. The following observations are also consistent with a mechanism involving iminium salt: (i) the requirement of an unhindered secondary amine moiety in the catalyst; (ii) the requirement of a small amount of water for promotion of the reaction; and (iii) the lack of asymmetric induction in the malonate addition to ethyl 2-cyano-2-octenoate, which cannot form iminium salt. However, other noncovalent bond interactions cannot be excluded at present.

Finally, the present Michael addition reaction was compared with the Hajos−Wiechert reaction, which is the intramolecular asymmetric aldol reaction catalyzed by L-proline.[37] An enamine nucleophile intermediate has been suggested in the latter reaction.[38] There are similarities in the catalyst structure−activity relationship, although the former uses amino acid salts and the latter uses amino acids. L-Proline and L-azetidine-2-carboxylic acid derivatives are effective catalysts in both reactions, while *N*-alkyl-L-proline and (±)-piperidinecarboxylic acid derivatives are ineffective. These observations appear to indicate the involvement of similar reaction intermediates. However, there are several differences. The Hajos−Wiechert reaction showed a negative nonlinear effect, which supports the notion that two molecules of the catalyst are involved in the transition state.[39] In contrast, the effect was not observed in the Michael addition of **6** to **5**. The transition-state structure probably contains one molecule of the prolinate. The effect of the countercation also differs between the aldol reaction and the Michael reaction. The absolute configuration of the adducts gradually changed depending on the size of cations in L-proline salts in the Michael addition (Tables 1 and 2). In contrast, this only had a small effect in the aldol reaction. L-Proline rubidium salt and lithium salt promoted the aldol reaction equally well to give the enones with the same absolute configuration (Scheme 8). The stereochemistry is the same as that in the reaction promoted by L-proline itself. Prolinate anion appears to be the crucial species in the aldol reaction. Use of L-proline $BnNMe_3$ salt, $(n\text{-}Bu)_4N$ salt, or Et_4N salt gave aldol products with very low enantiomeric excesses, although the reactions were much faster. Further studies are required to understand the precise role of this useful amino acid in these catalytic asymmetric reactions.

In summary, L-proline rubidium salt promotes the catalytic asymmetric Michael addition of malonate anions to enones and enals. This reaction can be applied to a wide range of acceptors and gives adducts with a predictable absolute configuration. Especially high asymmetric inductions were attained with (*E*)-enones. This reaction is noteworthy because of the use of a simple and readily available catalyst in a highly stereoselective reaction. The stability of the catalyst with respect to oxygen and moisture is another advantage of this method. It should also be noted that the present Michael reactions involve a new asymmetric carbonyl activation mechanism which may find use in other enantioselective reactions.

Experimental Section

^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian Gemini 200 (200 MHz), a Varian XL-200 (200 MHz), a JEOL GX-400 (400 MHz), or a Brucker AM-600 (600 MHz). Chemical shift values are given in parts per million (ppm) relative to internal Me_4Si. In some cases, $CHCl_3$ (δ 7.24 for ^{1}H-NMR and δ 77.0 for ^{13}C-NMR) or D_2O (δ 4.80 for ^{1}H-NMR) was also used for the internal standard. IR spectra were recorded on a JASCO FT/IR-7000. MS spectra were taken with a HITACHI M-52 or a JEOL HX-110. Optical rotations were obtained with a JASCO DIP-370 polarimeter. Elemental analysis was conducted with a YANACO CHN Corder MT-5. Chloroform was purified by passing it through a basic alumina column just prior to use. Methanol was distilled from magnesium metal and stored over molecular sieves 3 Å. L-Proline, D-proline, L-prolinol, and L-piperidinecarboxylic acid were purchased from Aldrich, Fluka, or Wako and used as received. *N*-Benzyl-L-proline,[40] 2-methyl-L-proline,[41] *N*-benzyl-L-leucine,[42] *N*-methyl-L-alanine,[42] L-homoproline,[43] L-thiazoline-4-carboxylic acid,[44] and 2-methyl-L-thiazoline-4-carboxylic acid[44] were prepared according to the literature. Teraalkylammonium halides were purchased from Aldrich or Wako. (*R*)- and (*S*)-(1-phenylethyl)trimethylammonium iodide were prepared according to the literature.[45]

Amino Acid Salts. Amino acid salts were prepared by adding 1 equiv of alkali metal hydroxide or tetraalkylammonium hydroxide to the amino acid in methanol at 0 °C and stirring at 25 °C for 1−3 h. After the solvent was evaporated, the salts were dried at 25 °C *in vacuo*. The amino acid salts thus obtained were used without further purification. Methanol solutions of tetraalkylammonium hydroxides which were not commercially available were prepared from tetraalkylammonium halides and 2 equiv of Ag_2O at room temperature.[46] Alkaline earth metal salts were prepared by treating the amino acid with equimolar amounts of metal methoxides in methanol.

L-Proline Lithium Salt. Mp: >250 °C. $[\alpha]^{25}_D$: −101 (*c* 1.0, MeOH). Anal. Calcd for $C_5H_8NO_2Li$: C, 49.61; H, 6.66; N, 11.57. Found: C, 50.02; H, 6.62; N, 11.52.

L-Proline Sodium Salt. Mp: 234−237 °C. $[\alpha]^{22}_D$: −90 (*c* 1.0, MeOH).

L-Proline Potassium Salt. Mp: >250 °C. $[\alpha]^{24}_D$: −81 (*c* 1.0, MeOH).

L-Proline Rubidium Salt. Mp: >250 °C. $[\alpha]^{23}_D$:−61 (*c* 1.0, MeOH). ^{1}H-NMR (D_2O): δ 1.60−1.78 (3H, m), 2.00−2.14 (1H, m), 2.62−2.80 (1H, m), 2.92−3.06 (1H, m), 3.45 (1H, dd, J = 8.0, 6.0 Hz). Anal. Calcd for $C_5H_8NO_2Rb\cdot{}^1/_2H_2O$: C, 28.79; H, 4.35; N, 6.71. Found: C, 28.90; H, 4.58; N, 6.44.

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L-Proline Cesium Salt. Mp: >250 °C. $[\alpha]^{26}_D$: −50 (*c* 1.0, MeOH). Anal. Calcd for $C_5H_8NO_2Cs\cdot H_2O$: C, 22.66; H, 3.80; N, 5.28. Found: C, 22.74; H, 3.55; N, 5.17.

L-Proline Magnesium Salt. Mp: >250 °C. $[\alpha]^{25}_D$: −54 (*c* 1.0, MeOH).

L-Proline Calcium Salt. Mp: 152−162 °C dec. $[\alpha]^{23}_D$: −42 (*c* 1.0, MeOH). Anal. Calcd for $C_{10}H_{16}N_2O_4Ca$: C, 44.76; H, 6.01; N, 10.44. Found: C, 45.01; H, 6.30; N, 10.41.

L-Proline Strontium Salt. Mp: 190−205 °C dec. $[\alpha]^{25}_D$: −39 (*c* 1.0, MeOH). Anal. Calcd for $C_{10}H_{16}N_2O_4Sr\cdot{}^1/_2H_2O$: C, 36.97; H, 5.27; N, 8.62. Found: C, 37.31; H, 5.07; N, 8.65.

L-Proline Barium Salt. Mp: 167−177 °C dec. $[\alpha]^{23}_D$: −48 (*c* 1.0, MeOH). Anal. Calcd for $C_{10}H_{16}N_2O_4Ba\cdot H_2O$: C, 32.06; H, 4.57; N, 7.48. Found: C, 32.08; H, 4.40; N, 7.57.

L-Azetidinecarboxylic Acid Rubidium Salt. Mp: >250 °C. $[\alpha]^{26}_D$: −78 (*c* 1.1, H_2O). ^{11}H-NMR (D_2O): δ 1.15−2.32 (1H, m), 2.49−2.68 (1H, m), 3.41 (2H, t, J = 7.8 Hz), 4.10 (1H, dd, J = 9.3, 6.8 Hz). IR (KBr): 3406, 1591 cm^{-1}. Anal. Calcd for $C_4H_6NO_2Rb\cdot{}^1/_2H_2O$: C, 24.69; H, 3.63; N, 7.20. Found: C, 24.85; H, 3.63; N, 6.94.

***N*-Benzyl-L-proline Rubidium Salt.** Mp: 196−199 °C. $[\alpha]^{27}_D$: −60 (*c* 1.0, MeOH). Anal. Calcd for $C_{12}H_{14}NO_2Rb\cdot H_2O$: C, 46.84; H, 5.57; N, 4.55. Found: C, 47.40; H, 5.09; N, 4.61.

2-Methyl-L-proline Rubidium Salt. Mp: >250 °C. $[\alpha]^{22}_D$: −52 (*c* 1.0, MeOH). ^{11}H-NMR (D_2O): δ 1.31 (3H, s), 1.60−1.90 (3H, m), 2.02−2.18 (1H, m), 2.78−3.06 (2H, m). IR (KBr): 3398, 1580 cm^{-1}. Anal. Calcd for $C_6H_{10}NO_2Rb\cdot H_2O$: C, 31.11; H, 5.22; N, 6.05. Found: C, 31.71; H, 4.99; N, 6.08.

L-Piperidinecarboxylic Acid Rubidium Salt. Mp: >250 °C. $[\alpha]^{24}_D$: −5.8 (*c* 1.1, H_2O). ^{11}H-NMR (D_2O): δ 1.30−1.68 (4H, m), 1.71−1.84 (1H, m), 1.86−2.00 (1H, m), 2.55−2.71 (1H, m), 3.00−3.22 (2H, m). Anal. Calcd for $C_6H_{10}NO_2Rb\cdot{}^1/_2H_2O$: C, 32.37; H, 4.53; N, 6.29. Found: C, 32.92; H, 4.91; N, 6.12.

***N*-Benzyl-L-leucine Rubidium Salt.** Mp: >250 °C. $[\alpha]^{23}_D$: −2.4 (*c* 1.0, H_2O). ^{11}H-NMR (D_2O): δ 0.83 (3H, d, J = 6.8 Hz), 0.87 (3H, d, J = 6.6 Hz), 1.35−1.62 (3H, m), 3.12 (1H, t, J = 6.5 Hz), 3.56 (1H, d, J = 12.5 Hz), 3.76 (1H, d, J = 12.4 Hz), 7.30−7.45 (5H, m). IR (KBr): 3298, 1575 cm^{-1}. Anal. Calcd for $C_{13}H_{18}NO_2Rb\cdot H_2O$: C, 48.22; H, 6.23; N, 4.33. Found: C, 48.58; H, 5.77; N, 4.33.

***N*-Methyl-L-alanine Rubidium Salt.** Mp: 196−197 °C dec. $[\alpha]^{27}_D$: +1.1 (*c* 1.0, MeOH). ^{11}H-NMR (D_2O): δ 1.19 (3H, d, J = 7.0 Hz), 2.26 (3H, s), 3.02 (1H, q, J = 7.0 Hz). IR (KBr): 3404, 1589 cm^{-1}. Anal. Calcd for $C_4H_8NO_2Rb\cdot H_2O$: C, 23.37; H, 4.90; N, 6.81. Found: C, 23.57; H, 4.40; N, 6.90.

L-Homoproline Rubidium Salt. Mp: >250 °C. $[\alpha]^{23}_D$: −5.7 (*c* 1.0, MeOH). ^{11}H-NMR (D_2O): δ 1.22−1.44 (1H, m), 1.64−2.00 (3H, m), 2.27 (1H, dd, J = 14.2, 7.4 Hz), 2.40 (1H, dd, J = 14.2, 7.0 Hz), 2.70−2.98 (2H, m), 3.28 (1H, quintet, J = 7.2 Hz). IR (KBr): 3406, 1576, 1396 cm^{-1}. Anal. Calcd for $C_6H_{10}NO_2Rb\cdot{}^1/_2H_2O$: C, 32.37; H, 4.98; N, 6.29. Found: C, 32.24; H, 4.71; N, 6.21.

L-Thiazoline-4-carboxylic Acid Rubidium Salt. Mp: 232−235 °C dec. $[\alpha]^{23}_D$: −127 (*c* 1.50, H_2O). ^{11}H-NMR (D_2O): δ 2.75 (1H, dd, J = 10.4, 8.8 Hz), 3.24 (1H, dd, J = 10.3, 7.2 Hz), 3.57 (1H, dd, J = 8.6, 7.2 Hz), 3.95 (1H, d, J = 9.5 Hz), 4.32 (1H, d, J = 9.5 Hz). IR (KBr): 3480, 1584 cm^{-1}. Anal. Calcd for $C_4H_8NO_2SRb\cdot H_2O$: C, 20.39; H, 3.42; N, 5.94. Found: C, 20.70; H, 3.11; N, 5.74.

2-Methyl-L-thiazoline-4-carboxylic Acid Rubidium Salt. Obtained as 2:1 mixture of diastereomers. Mp: 164−168 °C dec. $[\alpha]^{24}_D$: −119 (*c* 1.2, H_2O). ^{11}H-NMR (D_2O): δ 1.40 (1H, d, J = 6.6 Hz), 1.54 (2H, d, J = 6.2 Hz), 2.82−3.00 (1H, m), 3.25−3.40 (1H, m), 3.62 (0.6H, dd, J = 7.3, 7.1 Hz), 3.89 (0.3H, t, J = 7.1 Hz), 4.49 (0.6H, q, J = 6.4 Hz), 4.82 (0.3H, q, J = 6.0 Hz). IR (KBr): 3366, 1586 cm^{-1}. Anal. Calcd for $C_5H_8NO_2SRb\cdot H_2O$: C, 24.05; H, 4.04; N, 5.61. Found: C, 23.26; H, 3.61; N, 4.89.

(*S*)-(−)-1-(Hydroxymethyl)-5-azoniaspiro[4.4]nonane Bromide. Under an argon atmosphere, a mixture of L-prolinol (2.27 g, 22.5 mmol), 1,4-dibromobutane (2.7 mL, 22.6 mmol), and $NaHCO_3$ (3.78 g, 45 mmol) in methanol (25 mL) was heated at reflux for 3 days. After the mixture was cooled to room temperature, the solvents were removed *in vacuo*, and the residue was crystallized by adding ether. Recrystallization from ethanol/ether (3:1) gave the salt (1.01 g, 19%). Mp: >250 °C. $[\alpha]^{24}_D$: −20 (*c* 1.0, MeOH). Anal. Calcd for $C_9H_{18}NOBr$: C, 45.78; H, 7.68; N, 5.93. Found: C, 45.12; H, 7.66; N, 5.86.

The Michael Addition Reaction of Diisopropyl Malonate (6) to Enone and Enal. Diisopropyl (*R*)-(+)-(3-Oxocycloheptyl)malonate [(*R*)-(+)-7]. Under an argon atmosphere, a mixture of diisopropyl malonate (**6**, 1.30 mL, 6.72 mmol), 2-cycloheptenone (**5**, 0.50 mL, 4.48 mmol), and L-proline rubidium salt (46 mg, 0.22 mmol) in chloroform (5 mL) was stirred for 59 h at 25 °C. The reaction was quenched by adding 2 M HCl, and organic materials were extracted twice with ethyl acetate. Combined extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated, and flash chromatographed over silica gel, giving (*R*)-(+)-**7** (1.21 g, 91%). $[\alpha]^{23}_D$: +22 (*c* 1.0, $CHCl_3$, 59% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.24 (12H, d, J = 6.2 Hz), 1.3−1.7 (3H, m), 1.7−2.1 (3H, m), 2.3−2.7 (5H, m), 3.23 (1H, d, J = 7.1 Hz), 5.058 (1H, septet, J = 6.2 Hz), 5.062 (1H, septet, J = 6.2 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 21.5, 21.6, 24.4, 28.8, 34.1, 35.5, 43.5, 47.2, 57.8, 69.0, 167.6, 212.6. IR (neat): 1729 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_5$: C; 64.41, H; 8.78. Found: C; 64.39, H; 8.77. The enantiomeric excess was determined as follows: A mixture of (*R*)-(+)-**7** (44 mg, 0.15 mmol), (2*R*,3*R*)-2,3-butanediol (0.2 mL, 0.23 mmol), and a catalytic amount of *p*-toluenesulfonic acid in dry benzene (2 mL) was stirred for 24 h at rt (or at reflux for 1 h). The reaction was quenched by adding saturated aqueous $NaHCO_3$, and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with water, dried over Na_2SO_4, filtered, concentrated, and flash chromatographed over silica gel, giving ketal (50 mg, 92%). The enantiomeric excess was determined by ^{1}H-NMR (400 MHz, $CDCl_3$) and observing the resonance signals at δ 3.22 (d, J = 7.5 Hz) and δ 3.26 (d, J = 7.8 Hz). Essentially the same results were obtained by ketalization reaction with (2*S*,3*S*)-2,3-butanediol.

Diisopropyl (*S*)-(+)-(1-Methyl-3-oxobutyl)malonate [(*S*)-(+)-9]. (*E*)-3-Penten-2-one (**8**) (Aldrich) was used after distillation, which contained 17% of 4-methyl-3-penten-2-one. $[\alpha]^{26}_D$: +13 (*c* 1.0, $CHCl_3$, 76% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.02 (3H, d, J = 6.8 Hz), 1.25 (12H, d, J = 6.3 Hz), 2.14 (3H, s), 2.3−2.5 (1H, m), 2.6−2.9 (2H, m), 3.27 (1H, d, J = 6.6 Hz), 5.05 (2H, septet, J = 6.3 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.5, 21.4, 21.5, 28.6, 30.1, 47.5, 56.4, 68.6, 167.9, 206.9. IR (neat): 1725 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_5$: C; 61.74, H; 8.88. Found: C; 61.68, H; 8.76. The enantiomeric excess was determined by ^{1}H-NMR (600 MHz, $CDCl_3$) of the ketal with (2*R*,3*R*)-2,3-butanediol by observing at δ 3.37 (d, J = 6.4 Hz) and δ 3.52 (d, J = 5.6 Hz). Treatment with (2*S*,3*S*)-2,3-butanediol gave essentially the same results.

Diisopropyl (*S*)-(+)-(1-Methyl-3-oxohexyl)malonate [(*S*)-(+)-12]. $[\alpha]^{22}_D$: +11 (*c* 1.0, $CHCl_3$, 74% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.2 Hz), 1.02 (3H, d, J = 6.7 Hz), 1.24 (12H, d, J = 6.3 Hz), 1.60 (2H, q, J = 7.2 Hz), 2.3−2.5 (3H, m), 2.6−2.8 (2H, m), 3.28 (1H, d, J = 6.6 Hz), 5.05 (2H, septet, J = 6.3 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.5, 17.1, 17.5, 21.46, 21.54, 28.7, 44.9, 46.7, 56.5, 68.6, 168.0, 209.3. IR (neat): 1729 cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_5$: C; 63.98, H; 9.39. Found: C; 63.68, H; 9.40. The enantiomeric excess was determined by ^{1}H-NMR (600 MHz, $CDCl_3$) and observing the absorptions of the ketal with (2*R*,3*R*)-2,3-butanediol at δ 3.37 (d, J = 6.3 Hz) and δ 3.54 (d, J = 5.2 Hz).

Diisopropyl (+)-(1-Pentyl-3-oxobutyl)malonate. $[\alpha]^{24}_D$: +8.0 (*c* 1.0, $CHCl_3$, 77% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.87 (3H, t, J = 6.4 Hz), 1.24 (6H, d, J = 6.3 Hz), 1.25 (6H, d, J = 6.3 Hz), 1.2−1.5 (8H, m), 2.14 (3H, s), 2.4−2.8 (3H, m), 3.46 (1H, d, J = 5.4 Hz), 5.04 (2H, septet, 6.3 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.8, 21.4, 22.3, 26.4, 30.0, 31.6, 31.9, 33.2, 45.2, 54.2, 68.5, 168.0, 168.2, 207.1. IR (neat): 1727 cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_5$: C; 65.82, H; 9.82. Found: C; 65.53, H; 9.67. The enantiomeric excess was determined by ^{1}H-NMR (600 MHz, $CDCl_3$) of the ketal with (2*R*,3*R*)-2,3-butanediol by observing at δ 3.70 (d, J = 5.0 Hz) and δ 3.81 (d, J = 4.3 Hz).

Diisopropyl (*S*)-(+)-(1-Phenyl-3-oxobutyl)malonate [(*S*)-(+)-13]. $[\alpha]^{24}_D$: +11 (*c* 1.0, $CHCl_3$, 53% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.96 (3H, d, J = 6.3 Hz), 1.04 (3H, d, J = 6.3

Hz), 1.23 (3H, d, J = 6.3 Hz), 1.24 (3H, d, J = 6.3 Hz), 2.01 (3H, s), 2.8−3.1 (2H, m), 3.63 (1H, d, J = 10.1 Hz), 3.94 (1H, ddd, J = 10.1, 8.4, 5.4 Hz), 4.77 (1H, septet, J = 6.3 Hz), 5.05 (1H, septet, J = 6.3 Hz), 7.2−7.3 (5H, m). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 21.2, 21.4, 21.5, 30.1, 40.3, 47.6, 57.6, 68.6, 69.1, 127.0, 128.17, 128.24, 140.4, 167.0, 167.6, 205.8. IR (neat): 1725, 758, 700 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_5$: C; 68.24, H; 7.84. Found: C; 68.52, H; 7.78. The enantiomeric excess was determined by ^{1}H-NMR (600 MHz, $CDCl_3$) of the ketal with (2*R*,3*R*)-2,3-butanediol by observing at δ 1.13 (s) and δ 1.19 (s).

Diisopropyl (*R*)-(+)-(3-Oxocyclohexyl)malonate [(*R*)-(+)-15]. $[\alpha]^{24}_D$: +2.3 (*c* 1.0, $CHCl_3$, 49% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.25 (12H, d, J = 6.3 Hz), 1.4−2.7 (9H, m), 3.23 (1H, d, J = 7.5 Hz), 5.06 (1H, septet, J = 6.3 Hz), 5.07 (1H, septet, J = 6.3 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 21.25, 21.34, 24.3, 28.4, 37.6, 40.7, 44.8, 56.8, 68.7, 167.0, 167.1, 209.2. IR (neat): 1725 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_5$: C; 63.36, H; 8.51. Found: C; 63.27, H; 8.48. The enantiomeric excess was determined by ^{1}H-NMR (600 MHz, DMSO-d_6) of the ketal with (2*R*,3*R*)-2,3-butanediol by observing at δ 3.19 (d, J = 8.9 Hz) and δ 3.21 (d, J = 8.6 Hz).

Diisopropyl (+)-(1-Propyl-3-oxopropyl)malonate. $[\alpha]^{24}_D$: +4.6 (*c* 1.0, $CHCl_3$, 41% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.0 Hz), 1.24 (6H, d, J = 6.3 Hz), 1.25 (6H, d, J = 6.3 Hz), 1.3−1.5 (4H, m), 2.48 (1H, ddd, J = 18.5, 8.2, 2.0 Hz), 2.6−2.8 (2H, m), 3.44 (1H, d, J = 5.9 Hz), 5.05 (2H, septet, J = 6.3 Hz), 9.76 (1H, dd, J = 2.0, 1.3 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.6, 19.6, 21.16, 21.22, 31.8, 34.3, 45.6, 54.5, 68.5, 167.5, 167.8, 200.7. IR (neat): 1727 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O_5$: C; 62.91, H; 9.15. Found: C; 62.41, H; 8.92. The enantiomeric excess was determined by ^{1}H-NMR (600 MHz, CD_3CN) of the ketal with (2*R*,3*R*)-2,3-butanediol by observing at δ 3.46 (d, J = 6.7 Hz) and δ 3.49 (d, J = 6.6 Hz).

Diisopropyl (*S*)-(+)-(1-Methyl-3-oxopropyl)malonate [(*S*)-(+)-11]. $[\alpha]^{22}_D$: +5.6 (*c* 1.0, $CHCl_3$, 35% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.07 (3H, d, J = 6.8 Hz), 1.25 (12H, d, J = 6.3 Hz), 2.41 (1H, ddd, J = 17.2, 8.6, 2.2 Hz), 2.70 (1H, dd, J = 17.2, 4.3 Hz), 2.7−3.0 (1H, m), 3.28 (1H, d, J = 7.1 Hz), 5.059 (1H, septet, J = 6.3 Hz), 5.065 (1H, septet, J = 6.3 Hz), 9.75 (1H, dd, J = 2.2, 1.1 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.9, 21.6, 27.7, 48.1, 56.8, 68.9, 167.8, 200.8. IR (neat): 1727 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_5$: C; 60.45, H; 8.58. Found: C; 60.40, H; 8.72. The enantiomeric excess was determined by ^{1}H-NMR (600 MHz, $CDCl_3$) of the ketal with (2*R*,3*R*)-2,3-butanediol by observing at δ 3.30 (d, J = 7.2 Hz) and δ 3.32 (d, J = 7.2 Hz).

***tert*-Butyl (*R*)-(+)-3-Oxo-2-(3-oxocyclohexyl)butanoate [(*R*)-(+)-17].** Reaction of *tert*-butyl acetoacetate (**16**) and **1** in the presence of 10 mol % of L-proline rubidium salt gave (*R*)-(+)-**17** in 77% yield as a 1:1 mixture of diastereomers. $[\alpha]^{22}_D$: +3 (*c* 1.1, $CHCl_3$, 26% ee, mixture of diastereomers). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.2−2.6 (9H, m), 1.47 (4.5H, s), 1.48 (4.5H, s), 2.21 (1.5H, s), 2.23 (1.5H, s), 3.27 (0.5H, d, J = 8.8 Hz), 3.28 (0.5H, d, J = 8.8 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 25.0, 28.3, 28.9, 29.5, 29.8, 38.1, 41.5, 41.6, 45.4, 45.9, 66.2, 66.6, 82.9, 167.6, 167.8, 202.2, 202.3, 210.0, 210.1. IR (neat): 1715 cm^{-1}. MS (EI): *m*/*e* 254 (M, 0.6), 198 (M − C_4H_8, 100), 181 (M − C_4H_9O, 38). HRMS: Calcd for $C_{14}H_{22}O_4$ 254.1518; found 254.1519. The enantiomeric excess was determined by converting to (*S*)-(+)-**18**.

Decarboxylation and Esterification Procedures. Methyl (*R*)-(+)-3-Oxocycloheptaneacetate. (*R*)-(+)-**7** (54% ee, 500 mg, 1.67 mmol) in 6 M HCl (10 mL) was refluxed for 9 h. On cooling, organic materials were extracted with chloroform, dried over Na_2SO_4, and concentrated. The residue was dissolved in methanol (2 mL), and an excess diazomethane in ether was added at 0 °C. After removing the solvents *in vacuo*, the product (264 mg, 86%) was obtained by flash chromatography on silica gel. $[\alpha]^{25}_D$: +32 (*c* 1.9, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.20−1.74 (3H, m), 1.78−2.04 (3H, m), 2.16−2.40 (3H, m), 2.42−2.65 (4H, m), 3.68 (3H, s). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 23.9, 28.1, 32.4, 36.2, 41.1, 43.5, 49.1, 51.2, 172.1, 212.6. IR (neat): 1738, 1702 cm^{-1}.

Methyl (*R*)-(+)-3-Oxocyclohexaneacetate [(*R*)-(+)-4]. Synthesized from (*R*)-(+)-**15** (49% ee). $[\alpha]^{27}_D$: +4.4 (*c* 0.82, $CHCl_3$). Lit.[11] (*S*)-isomer. $[\alpha]^{20}_D$: −10.0 (*c* 1.50, $CHCl_3$, 95% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.36−1.50 (1H, m), 1.60−1.82 (1H, m), 1.88−2.52 (9H, m), 3.69 (3H, s). IR (neat): 1738, 1715 cm^{-1}.

Methyl (*S*)-(+)-3-Methyl-5-oxohexanoate [(*S*)-(+)-10]. Synthesized from (*S*)-(+)-**9** (76% ee). $[\alpha]^{25}_D$: +1.8 (*c* 30, ether). Lit.[17] (*R*)-isomer. $[\alpha]^{22}_D$: −2.7° (*c* 30.7, ether). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.98 (3H, d, J = 6.4 Hz), 2.13 (3H, s), 2.20−2.60 (5H, m), 3.67 (3H, s). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 19.9, 26.2, 30.2, 40.6, 49.8, 51.3, 172.8, 207.5.

Methyl (*S*)-(−)-5-Oxo-3-phenylhexanoate [(*S*)-(−)-14]. Synthesized from (*S*)-(+)-**13** (53% ee). $[\alpha]^{23}_D$: −13 (*c* 1.0, C_6H_6). Lit.[18] (*S*)-isomer. $[\alpha]^{20}_D$: −20.7 (C_6H_6, 93% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.06 (3H, s), 2.59 (1H, dd, J = 15.4, 7.6 Hz), 2.70 (1H, dd, J = 15.4, 7.5 Hz), 2.78−2.88 (2H, m), 3.58 (3H, s), 3.68 (1H, quintet, J = 7.4 Hz), 7.15−7.35 (5H, m). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 30.3, 37.2, 40.5, 49.3, 51.5, 126.8, 127.1, 128.6, 143.0, 172.1, 206.7.

(1*S*,5*R*)-(+)-1-Methyl-2-oxabicyclo[3.3.1]nonan-3-one [(+)-19]. Treatment of (*R*)-(+)-**17** (26% ee) with 6 M HCl gave (+)-**19** in 39% yield instead of diketone **18**. Refluxing (*S*)-(+)-**18** in 6 M HCl also gave (+)-**19** in 51% yield. $[\alpha]^{26}_D$: +5 (*c* 0.8, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, s), 1.38−1.49 (1H, m), 1.50−1.60 (2H, m), 1.60−1.72 (3H, m), 1.82 (1H, dq, J = 13.8, 2.5 Hz), 1.92 (1H, brd, J = 12.8 Hz), 2.3−2.4 (1H, m), 2.42 (1H, d, J = 18.0 Hz), 2.65 (1H, ddd, J = 18.0, 7.0, 0.8 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.3, 26.6, 28.9, 30.3, 35.1, 36.4, 37.2, 80.7, 172.4. IR (neat): 1721 cm^{-1}. MS (EI): *m*/*e* 154 (M, 83), 139 (M − CH_3, 10), 111 (M − C_3H_7, 84), 110 (M − CO_2, 20), 97 (M − C_3H_5O, 100). HRMS: Calcd for $C_9H_{14}O_2$ 154.0994; found 154.0987.

(*S*)-(+)-3-(2-Oxopropyl)cyclohexanone [(*S*)-(+)-18]. Under an argon atmosphere, a mixture of (*R*)-(+)-**17** (351 mg, 1.38 mmol) and trifluoroacetic acid (1 mL) was stirred at room temperature for 1 h. Volatile materials were removed by repeated addition and evaporation of benzene. Benzene (5 mL) was then added to the residue, and the mixture was heated at reflux for 1 h. Removal of the solvent and flash chromatography on silica gel gave (*S*)-(+)-**18** (191 mg, 90%). $[\alpha]^{22}_D$: +3.9 (*c* 3.1, C_6H_6, 26% ee). Lit.[21] $[\alpha]^{25}_D$: +14.6 (C_6H_6). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.14 (3H, s), 1.2−2.6 (11H, m). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 24.7, 30.2, 30.7, 34.1, 41.0, 47.3, 49.5, 206.7, 210.4. IR (neat): 1711 cm^{-1}. Optical purity was determined by ^{13}C-NMR (50 MHz, $CDCl_3$) of bisketal with (2*R*,3*R*)-2,3-butanediol by observing at δ 23.4/23.8, 31.5/32.1, and 36.4/37.4.

Ring Enlargement of (*R*)-(+)-4 to Methyl (*R*)-(+)-3-Oxocycloheptaneacetate by Diazomethane.[19] A solution of KOH (0.5 g) in H_2O−MeOH (1:1, 1.5 mL) was slowly added to a methanol (3 mL) solution of (*R*)-(+)-**4** (49% ee, 130 mg, 0.77 mmol) and *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (199 mg, 0.93 mmol) at 0 °C. The mixture was stirred for 15 min at the temperature and was acidified by adding 1 M HCl. Organic materials were extracted with chloroform, dried over Na_2SO_4, and concentrated *in vacuo*. The resulted carboxylic acid was treated with diazomethane in ether at 0 °C, giving an isomeric mixture of methyl 3-oxo- and 4-oxocycloheptaneacetate (99 mg, 70%). Methyl (*R*)-(+)-3-Oxocycloheptaneacetate (16% yield) was obtained by repeated flash chromatography on silica gel. $[\alpha]^{24}_D$: +21 (*c* 1.27, $CHCl_3$). ^{1}H-NMR, ^{13}C-NMR, IR, and the sign of the optical rotation coincided with the compound synthesized by decarboxylation of (*R*)-(+)-**7**.

Organometal Addition to Diisopropyl (*S*)-(+)-(1-Methyl-3-oxopropyl)malonate [(*S*)-(+)-11] Followed by Oxidation. Under an argon atmosphere, (*S*)-(+)-**11** (35% ee, 174 mg, 0.67 mmol) in THF (3 mL) was added at −40 °C to *n*-propylmagnesium bromide in THF (2 mL), prepared from magnesium (100 mg, 4.11 mmol) and *n*-propyl bromide (0.4 mL). After stirring for 30 min at the temperature the mixture was warmed to 0 °C. The reaction was quenched by adding 1 M HCl, and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with water and brine, dried over Na_2SO_4, filtered, concentrated, and flash chromatographed over silica gel giving a diastereomeric mixture of diisopropyl (1-methyl-3-hydroxyhexyl)malonate (99

mg, 49%). The hydroxy ester (99 mg, 0.33 mmol) was oxidized according to the Swern's method (ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, −60 °C), giving (*S*)-(+)-**12** (81 mg, 82%). $[\alpha]^{22}_D$: +5.6 (*c* 1.0, $CHCl_3$). ^{1}H-NMR, IR, and the sign of the optical rotation coincided with (*S*)-(+)-**12** obtained by the Michael addition.

Similarly, reaction of (*S*)-(+)-**11** and methyllithium at −78 °C followed by PDC oxidation gave (*S*)-(+)-**9**. $[\alpha]^{23}_D$: +4.8 (*c* 0.79, $CHCl_3$).

The Michael Addition Reaction of Di(*tert*-butyl) Malonate (20) to Enones and Enals. Di(*tert*-butyl) (*R*)-(+)-(3-Oxocyclohexyl)malonate. Under an argon atmosphere, a mixture of di(*tert*-butyl) malonate (**20**, 0.88 mL, 4.5 mmol), **1** (0.25 mL, 2.5 mmol), L-proline rubidium salt (100 mg, 0.50 mmol), and CsF (70 mg, 0.50 mmol) in $CHCl_3$ (2 mL) was stirred vigorously at rt for 35 h. The reaction was quenched by adding 2 M HCl, and organic materials were extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated, and flash chromatographed over silica gel, giving the (*R*)-(+)-adduct (658 mg, 84%). Mp: 37−38 °C. $[\alpha]^{26}_D$: +4.2 ($CHCl_3$, *c* 1.02, 65% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.18−1.82 (2H, m), 1.47 (18H, s), 1.92−2.58 (7H, m), 3.10 (1H, d, J = 7.7 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 24.3, 27.5, 28.4, 37.5, 40.7, 44.7, 58.3, 81.3, 166.7, 209.3. IR (neat): 1725 cm^{-1}. MS (EI): *m/e* 256 (M, 31), 241 (M − CH_3, 22), 200 (M − C_4H_8, 100). HRMS: Calcd for $C_{17}H_{28}O_5$ 312.1937; found 312.1937. Anal. Calcd for $C_{17}H_{28}O_5$: C; 65.36, H; 9.03. Found: C; 65.06, H; 8.87. The enantiomeric excess was determined by converting to dimethyl ester (trifluoroacetic acid (TFA) and diazomethane at rt) followed by ketalization with (2*R*,3*R*)-2,3-butanediol under toluene reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid. The crude product was analyzed to avoid kinetic resolution during the ketalization procedures. ^{13}C-NMR (50 MHz, $CDCl_3$) peaks at δ 41.4/40.4 and 23.1/22.8 were compared. An authentic sample was prepared by ketalization of the racemic adduct, and these chemical shifts were confirmed to be those of the diastereomers. The absolute configuration was determined by decarboxylation in 6 M HCl and esterification with diazomethane giving (*S*)-(+)-**4**. $[\alpha]^{22}_D$: +12 ($CHCl_3$, *c* 2.9).

Di(*tert*-butyl) (*S*)-(+)-(1′-Methyl-3-oxobutyl)malonate. 3-Penten-2-one (Aldrich) was used after distillation, which contained 17% of 4-methyl-3-penten-2-one. Mp: 60−61 °C (hexane). $[\alpha]^{30}_D$: +15 ($CHCl_3$, *c* 2.0, 88% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.01 (3H, d, J = 7.0 Hz), 1.46 (18H, s), 2.14 (3H, s), 2.36 (1H, dd, J = 17.6, 9.9 Hz), 2.60−2.80 (2H, m), 3.13 (1H, d, J = 6.9 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.5, 27.8, 28.7, 30.1, 47.8, 58.2, 81.4, 167.9, 207.3. IR (neat): 1721 cm^{-1}. MS (EI): *m/e* 300 (M, 0.08), 244 (M − C_4H_8, 21), 188 (M − C_8H_{16}, 100). HRMS: Calcd for $C_{16}H_{28}O_5$ 300.1937; found 300.1920. Anal. Calcd for $C_{16}H_{28}O_5$: C; 63.98, H; 9.39. Found: C; 63.93, H; 9.50. The enantiomeric excess was determined by converting to methyl ester (TFA and diazomethane) followed by ketalization with (2*R*,3*R*)-2,3-butanediol. ^{1}H-NMR (600 MHz, C_6D_6) peaks at δ 3.89 (d, J = 5.5 Hz) and δ 3.74 (d, J = 6.1 Hz) were compared. The absolute configuration was determined by decarboxylation in 6 M HCl and esterification with diazomethane giving (*S*)-(+)-**10**. $[\alpha]^{22}_D$: +1.5 (*c* 5.5, ether).

Di(*tert*-butyl) (+)-(1-Pentyl-3-oxobutyl)malonate. $[\alpha]_D$ +7.5 ($CHCl_3$, *c* 1.0, 88% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.87 (3H, t, J = 6.5 Hz), 1.16−1.40 (8H, m), 1.46 (18H, s), 2.15 (3H, s), 2.47 (1H, dd, J = 15.7, 6.6 Hz), 2.52−2.68 (1H, m), 2.73 (1H, dd, J = 15.7, 3.4 Hz), 3.33 (1H, d, J = 5.4 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.8, 22.3, 26.4, 27.8, 30.1, 31.7, 32.0, 32.2, 45.4, 55.7, 81.2, 81.3, 167.9, 168.2, 207.4. IR (neat): 1725 cm^{-1}. Anal. Calcd for $C_{20}H_{36}O_5$: C; 67.38, H; 10.18. Found: C; 67.26, H; 10.20. The enantiomeric excess was determined by converting to methyl ester (TFA and diazomethane) followed by ketalization with (2*R*,3*R*)-2,3-butanediol. ^{1}H-NMR (600 MHz, $CDCl_3$) peaks at δ 3.81 (d, J = 4.3 Hz) and δ 3.91 (d, J = 5.0 Hz) were compared.

Di(*tert*-butyl) (+)-(1-Phenylethyl-3-oxobutyl)malonate. $[\alpha]_D$ +1.6 ($CHCl_3$, *c* 1.0, 86% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.45 (9H, s), 1.47 (9H, s), 1.62−1.81 (2H, m), 2.12 (3H, s), 2.42−2.86 (5H, m), 3.41 (1H, d, J = 5.4 Hz), 7.10−7.33 (5H, m). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 27.8, 27.9, 30.1, 33.2, 33.3, 34.1, 45.4, 55.6, 81.5, 81.6, 125.7, 128.2, 128.3, 141.7, 167.9, 168.1, 207.3. IR (neat): 1723 cm^{-1}. MS (EI): *m/e* 390 (M, 0.7), 334 (M − C_4H_8, 16), 278 (M − C_8H_{16}, 58), 261 (M − $C_8H_{17}O$, 33), 242 (M − $C_8H_{20}O_2$, 24), 234 (M − $C_9H_{16}O_2$, 100). HRMS: Calcd for $C_{23}H_{34}O_5$ 390.2412; found 390.2406. The enantiomeric excess was determined by converting to methyl ester (TFA and diazomethane) followed by ketalization with (2*R*,3*R*)-2,3-butanediol. ^{1}H-NMR (200 MHz, $CDCl_3$) peaks at δ 3.86 (d, J = 4.8 Hz) and 3.96 (d, J = 4.6 Hz) were compared.

Di(*tert*-butyl) (+)-(1-Phenyl-3-oxobutyl)malonate. Mp: 92−94°C (hexane). $[\alpha]^{22}_D$: +18 ($CHCl_3$, *c* 1.1, 60% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.19 (9H, s), 1.46 (9H, s), 2.00 (3H, s), 2.84 (1H, dd, J = 16.2, 9.3 Hz), 2.95 (1H, dd, J = 16.2, 4.7 Hz), 3.50 (1H, d, J = 10.2 Hz), 3.85 (1H, ddd, J = 10.2, 9.3, 4.7 Hz), 7.10−7.28 (5H, m). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 27.4, 27.8, 30.2, 40.5, 48.0, 59.0, 81.3, 81.9, 126.9, 128.2, 128.3, 140.6, 166.8, 167.5, 206.2. IR (neat): 1744, 1715 cm^{-1}. MS (EI): *m/e* 362 (M, 1), 306 (M − C_4H_8, 21), 289 (M − C_4H_9, 3), 250 (M − C_8H_{16}, 100). HRMS: Calcd for $C_{21}H_{30}O_5$ 362.2094; found 3962.2089. The enantiomeric excess was determined by converting to methyl ester (TFA and diazomethane) followed by ketalization with (2*R*,3*R*)-2,3-butanediol. ^{1}H-NMR (200 MHz, $CDCl_3$) peaks at δ 1.22 (s)/1.24 (s) and 3.85 (d, J = 9.7 Hz)/3.89 (d, J = 9.3 Hz) were compared. The absolute configuration was determined by decarboxylation in 6 M HCl and esterification with diazomethane giving (*S*)-(+)-**14**. $[\alpha]^{22}_D$: −12 (C_6H_6, *c* 0.5).

Di(*tert*-butyl) (+)-(1-Methyl-3-oxopentyl)malonate. Mp: 44−45 °C (hexane). $[\alpha]^{23}_D$: +14 ($CHCl_3$, *c* 1.3, 76% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.01 (3H, d, J = 6.6 Hz), 1.05 (3H, t, J = 7.3 Hz), 1.46 (18H, s), 2.26−2.54 (3H, m), 2.58−2.80 (2H, m), 3.12 (1H, d, J = 6.8 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 7.6, 17.5, 27.8, 28.7, 36.2, 46.5, 58.1, 81.3, 167.8, 210.0. IR (neat): 1723 cm^{-1}. Anal. Calcd for $C_{17}H_{30}O_5$: C; 65.94, H; 9.62. Found: C; 65.17, H; 9.62. The enantiomeric excess was determined by converting to methyl ester (TFA and diazomethane) followed by ketalization with (2*R*,3*R*)-2,3-butanediol. ^{1}H-NMR (600 MHz, C_6D_6) peaks at δ 3.75 (d, J = 6.3 Hz) and δ 3.91 (d, J = 5.5 Hz) were compared.

Di(*tert*-butyl) (*R*)-(+)-(3-Oxocycloheptyl)malonate. $[\alpha]^{23}_D$: +29 ($CHCl_3$, *c* 1.02, 76% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.20−1.70 (2H, m), 1.46 (18H, s), 1.74−2.04 (4H, m), 2.32−2.68 (5H, m), 3.10 (1H, d, J = 6.7 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 24.3, 27.7, 28.7, 34.0, 35.3, 43.4, 47.1, 59.1, 81.6, 167.3, 167.4, 212.7. IR (neat): 1729 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_5$: C; 66.23, H; 9.26. Found: C; 66.93, H; 9.56. The enantiomeric excess was determined by converting to methyl ester (TFA and diazomethane) followed by ketalization with (2*R*,3*R*)-2,3-butanediol. ^{1}H-NMR (600 MHz, $CDCl_3$) peaks at δ 3.36 (d, J = 7.4 Hz) and δ 3.38 (d, J = 7.9 Hz) were compared. The absolute configuration was determined by decarboxylation in 6 M HCl and esterification with diazomethane giving methyl (*R*)-(+)-3-oxocycloheptaneacetate. $[\alpha]^{18}_D$: +49 ($CHCl_3$, *c* 1.12).

Di(*t*-buytl) (+)-(3-Oxocyclododecyl)malonate. (*E*)-2-Cyclododecenone was synthesized from cyclododecanone via silyl enol ether by using Tsuji method.[47] Mp: 96.5−97.5 °C (hexane). $[\alpha]^{21}_D$: +4 ($CHCl_3$, *c* 0.6, 81% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.20−1.72 (15H, m), 1.45 (9H, s), 1.47 (9H, s), 1.74−1.92 (1H, m), 2.36 (1H, ddd, J = 15.2, 6.8, 1.8 Hz), 2.52−2.82 (4H, m), 3.32 (1H, d, J = 7.4 Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 22.6, 22.8, 23.1, 24.7, 25.1, 25.2, 25.5, 28.5, 33.3, 41.1, 44.3, 56.9, 82.0, 82.1, 168.4, 168.7, 211.6 (one peak overlapped). IR (KBr): 1738, 1705 cm^{-1}. MS (EI): *m/z* 396 (M, 3), 340 (M − C_4H_8, 10), 284 (M − C_8H_{16}, 100). HRMS: Calcd for $C_{23}H_{40}O_5$ 396.2876; found 396.2878. The enantiomeric excess was determined by converting to methyl ester (TFA and diazomethane) followed by ketalization with (2*R*,3*R*)-2,3-butanediol. ^{1}H-NMR (600 MHz, $CDCl_3$) peaks at δ 4.17 (d, J = 3.5 Hz) and 4.30 (d, J = 3.5 Hz) were compared.

Dimethyl (*S*)-(+)-(3-Oxocyclopentadecyl)malonate [(*S*)-(+)-22]. Reaction of di(*tert*-butyl) malonate (**20**, 0.84 mL, 3.75 mmol) and (*E*)-2-cyclopentadecenone[24] (**21**, 277 mg, 1.25 mmol)

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gave crude product (985 mg). A part of the adduct (351 mg) was treated with TFA and diazomethane. Flash chromatography on silica gel gave dimethyl ester (*S*)-(+)-**22** (86 mg, corresponding to 54% yield from **21**). $[\alpha]^{21}_D$: +17 ($CHCl_3$, *c* 1.0, 82% ee). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.10−1.78 (22H, m), 2.24−2.78 (5H, m), 3.51 (1H, d, J = 6.2 Hz), 3.67 (3H, s), 3.68 (3H, s). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 23.5, 25.9, 26.3, 26.7, 27.0 (3 carbons), 27.3, 27.6, 28.1, 32.4, 33.9, 42.5, 44.9, 52.7, 52.8, 55.4, 169.5, 169.7, 210.5. IR (neat): 1738 cm^{-1}. MS (EI): *m*/*z* 354 (M, 60), 323 (M − CH_3O, 26), 263 (M − $C_3H_7O_3$, 21), 223 (M − $C_5H_7O_4$, 100). HRMS: Calcd for $C_{20}H_{34}O_5$ 354.2406; found 354.2404. The enantiomeric excess was determined by ketalization with (2*R*,3*R*)-2,3-butanediol. ^{1}H-NMR (600 MHz, C_6D_6) peaks at δ 3.32 (s) and 3.33 (s) were compared.

***(S)*-(+)-Muscone, (*S*)-(+)-24.** To a crude product obtained from **21** (447 mg, 2.0 mmol) and **20** (1.0 mL, 4.5 mmol) was added trifluoroacetic acid (1 mL). After standing for 1 h at room temperature the solvent was evaporated *in vacuo*. A trace amount of trifluoroacetic acid was removed azeotropically with benzene. Then, toluene (3 mL) was added, and the mixture was stirred at reflux for 10 h. After the solvent was removed, (*S*)-(+)-(3-oxocyclopentadecyl)acetic acid (*S*)-(+)-**23** (389 mg, 69%) was obtained by flash chromatography on silica gel. Mp: 86.5−88.0 °C (hexane). $[\alpha]^{22}_D$: +12 ($CHCl_3$, *c* 1.9). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.20−1.45 (20H, m), 1.45−1.75 (2H, m), 2.29−2.52 (7H, m), 10.7 (1H, br). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 23.5, 25.4, 26.4, 26.6, 27.0 (two carbons overlapped), 27.1, 27.2, 27.5, 28.1, 31.1, 33.7, 39.8, 42.7, 47.1, 179.3, 211.6. IR (KBr): 3600−2400, 1700 cm^{-1}. Under a nitrogen atmosphere, a mixture of (*S*)-(+)-**23** (148 mg, 0.52 mmol), 1-hydroxy-2-mercaptopyridine (75 mg, 0.59 mmol), dicyclohexylcarbodiimide (186 mg, 0.90 mmol), 4-(*N*,*N*-dimethylamino)pyridine (111 mg, 0.90 mmol), and benzene (4 mL) was stirred at reflux for 0.25 h. A benzene (1 mL) solution of Bu_3SnH (0.54 mL, 2.0 mmol) and a catalytic amount of AIBN were then added at the temperature. Stirring was continued for 0.5 h at reflux, when CCl_4 (10 mL) was added. After another 1 h of heating, the solvents were removed *in vacuo*. Iodine (2.0 g, 7.9 mmol), CH_2Cl_2 (5 mL), and saturated aqueous KF (1 mL) were added, and the mixture was stirred vigorously at rt overnight. Insoluble materials were removed by filtration through celite. Organic materials were extracted twice with CH_2Cl_2, washed with aqueous $NaHSO_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography on silica gel gave (*S*)-(+)-**24** (65 mg, 52%). $[\alpha]^{22}_D$: +9.4 (MeOH, *c* 1.12). Lit.[24] $[\alpha]_D$ −11.7 (MeOH, *c* 0.8, (*R*)-muscone). ^{1}H-NMR and IR spectra coincided with the reported data.[25] ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 21.6, 23.5, 25.5, 26.6, 26.7, 27.0, 27.0, 27.1, 27.2, 27.6, 28.0, 29.5, 36.0, 42.5, 50.9, 212.5.

1-(4-Phenyl-3-buten-2-ylidene)pyrrolidine Perchlorate (25).[36] Triethylamine (80 μL, 0.58 mmol) was added to a solution of pyrrolidine perchlorate (1.00 g, 5.83 mmol) and 4-phenyl-3-buten-2-one (1.63 g, 11.2 mmol) in ethanol (5 mL). After stirring for 40 min, the precipitate was filtered and washed with ethanol, giving **25** (1.12 g, 68%). ^{1}H-NMR (200 MHz, CD_3CN-$CDCl_3$): δ 2.17−2.28 (4H, m), 2.64 (3H, s), 3.94−4.18 (4H, m), 7.13 (1H, d, J = 15.6 Hz), 7.25−7.62 (3H, m), 7.68−7.81 (2H, m), 7.89 (1H, d, J = 15.6 Hz). IR (neat): 1626 cm^{-1}. Anal. Calcd for $C_{14}H_{18}NO_4Cl$. C; 56.10, H; 6.05; N, 4.67. Found. C; 55.84, H; 6.04; N, 4.66.

The Hajos−Wiechert Reaction with L-Proline Rubidium Salt. Under an argon atmosphere, a mixture of 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (100 mg, 0.55 mmol) and L-proline rubidium salt (11 mg, 0.055 mmol) in $CHCl_3$ was stirred at rt for 54 h. The reaction was quenched by adding 2 M HCl, and organic materials were extracted five times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography on silica gel gave (+)-(3a*S*,7a*S*)-3a,4,7,7a-tetrahydro-3a-hydroxy-7a-methyl-1,5(6*H*)-indandione (45 mg, 45%). $[\alpha]^{22}_D$: +28 (*c* 0.90, $CHCl_3$). Under an argon atmosphere a mixture of the aldol (45 mg, 0.25 mmol) and a catalytic amount of *p*-toluenesulfonic acid in benzene (10 mL) was heated at reflux for 2 h. After the mixture was cooled to rt, saturated aqueous $NaHCO_3$ was added, and organic materials were extracted four times with CH_2Cl_2. After the resulting mixture was dried over Na_2SO_4, the solvents were removed *in vacuo*, and flash chromatography on silica gel gave (7a*S*)-(+)-7,7a-dihydro-7a-methyl-1,5(6*H*)-indandione, (39 mg, 95%). $[\alpha]^{22}_D$: +158 (*c* 1.1, benzene). It corresponds to 43% ee. Lit.[37] $[\alpha]^{25}_D$: +369 (*c* 1.0, benzene).

Acknowledgment. We thank Professor T. Minami, Mr. K. Yokota, and Mr. M. Okuma (Kyushu Institute of Technology) for encouragement and assistance at the early stage of the present work. This work was supported by a grant from the Ministry of Education, Science and Culture, Japan (No. 06225203).

JO960216C