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Amino Acid Mediated Intramolecular Asymmetric Aldol Reaction to Construct a New Chiral Bicyclic Enedione Containing a Seven-Membered Ring: Remarkable Inversion of Enantioselectivity Compared to the Six-Membered Ring Example

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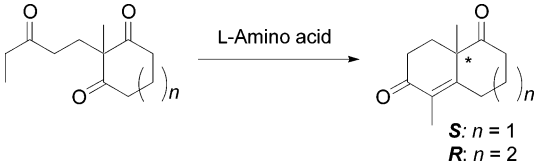

A detailed study to assess the enantioselectivity of the amino acid mediated intramolecular asymmetric aldol reaction of 1,3-cycloheptanedione bearing a C-2 methyl substituent has been undertaken. The cyclizations were mediated by a series of L-amino acids in the presence of an acid cocatalyst. Strikingly, the process is characterized by an inversion of enantioselectivity when compared to a similar reaction involving the 1,3-cyclohexanedione counterpart.

Introduction

In the early to mid 1970s, Hajos and Wiechert independently developed an asymmetric aldol reaction of trione **1** using a catalytic amount of L-proline (L-Pro, **2**) to provide the bicyclic enone **3** (Figure 1).[1−3] This process has become known as the Hajos−Parrish−Eder−Sauer−Wiechert reaction. In the intervening years, the bicyclic enone products **3** have often been used as choice chiral synthons for realizing the total syntheses of numerous natural products, especially in the area of steroids and terpenoids.[4,5] The reaction catalyzed by phenylalanine (Phe) to afford **3a** has also been reported and shown to be ac-

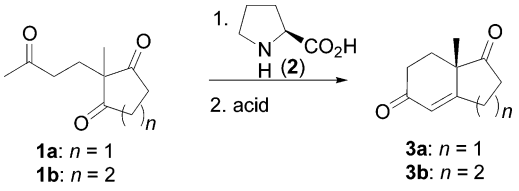

FIGURE 1. Hajos−Parrish−Eder−Sauer−Wiechert reaction.

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companied by a lower ee.[1c,6] The absolute configurations of the products were determined to be *S* when L-amino acids such as L-Pro or L-Phe were used to mediate the reaction. Quite recently, Davies disclosed that similar aldol reactions of **1** involving *cis*-pentacin, a cyclic β-amino acid, exhibited enantioselectivity opposite to those promoted by L-amino acids and afforded (*R*)-**3** in high ee.[7] This amino acid catalyzed asymmetric transformation has been widely recognized to consist of an enamine-based aldol reaction.[8,9] Successful extensions have included intermolecular asymmetric reactions such as cross-aldol couplings, Mannich condensations, and direct α-aminations.[10]

The Hajos−Parrish−Eder−Sauer−Wiechert reaction has been extended to prepare bicyclic ketones **5**[11,12] bearing a variety of substituents (R) such as methyl, ethyl, butenyl, and oxygenated alkyl and by the use of catalytic or stoichiometric amounts of L-amino acids, especially L-Phe (Figure 2).[13−16] Notwithstanding the variety of substituents, those reactions mediated by L-amino acids afforded the products **5** whose absolute configurations at the quaternary carbon were invariably *S*.

There has been little development of this reaction for the purpose of constructing new ring systems encompassing a seven-membered or larger carbocycle except for two studies reported independently by Swaminathan and our group.[17,18] Swaminathan et al. investigated attempts to bring about the L-Pro- or L-Phe-mediated asymmetric aldol reaction of trione **6** involving a seven-membered carbocycle, but no optically active product **7** was isolated under diverse reaction conditions. They also observed that the reaction of trione **6** involving pyrrolidine in acetic acid (AcOH) afforded racemic **7**[19] in 60−65% yield (Figure 3).[17b] This result demonstrates that the possibility exists for realizing enamine-based asymmetric aldol reactions of **6** when mediated by an amino acid to afford chiral **7**.

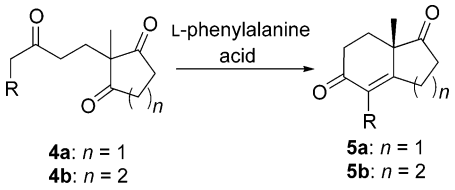

FIGURE 2. L-Phe-mediated intramolecular aldol reaction of **4**.

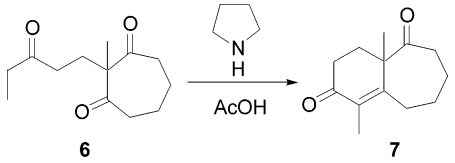

FIGURE 3. Example of an intramolecular aldol reaction to construct a 6-7 fused bicycle.

On the other hand, we reported that the amino acid mediated diastereomeric intramolecular aldol reaction of trione **8** bearing a chiral acetonide moiety afforded cyclized products **10** and **11**.[18] During these studies, we observed that the diastereoselectivity of this reaction did not depend on the stereostructure of the D- or L-amino acid because the same stereoselectivity was observed irrespective of the absolute configuration of the catalyst with the exception of Pro derivative **9**.[20] Although the reaction proceeded smoothly in the presence of various cyclic or acyclic amino acids, enone **11** was obtained as the major product in most cases, and diastereoselectivities observed for **10** and **11** gravitated around 40:60. Clearly, the chirality in the great majority of the amino acids was not reflected in the stereostructure of the products. Because we needed to synthesize **10** to develop an ongoing natural product synthesis, these results were inadequate. The best means for us to prepare the desired **10** was secured in the presence of a stoichiometric amount of **9** with only 16% diastereomeric excess (Figure 4). However, we achieved the inverted diastereoselectivity when using the enantiomer of **9** as a mediator.

Thus, application of the Hajos−Parrish−Eder−Sauer−Wiechert reaction for constructing 6-7 fused ring systems

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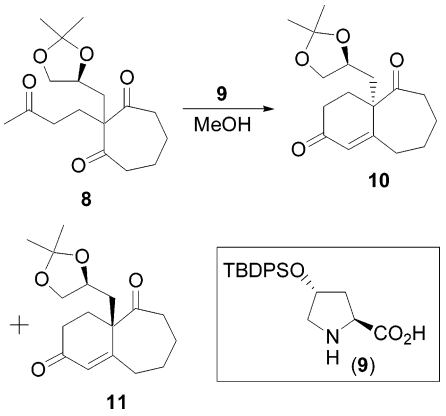
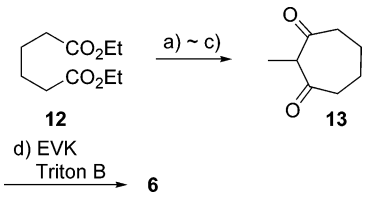


FIGURE 4. Diastereomeric intramolecular aldol reaction of **8** to construct 6-7 fused bicycles.

SCHEME 1[a]



[a] Reaction conditions: (a)~(c) See ref 21; (d) EVK (2.0 equiv), Triton B (0.1 equiv), methanol, reflux, 83%.

eventuates differently from those involved in construction of the 5-6 or 6-6 fused products in Figures 1 and 2. This fascinating divergence prompted us to scope out the features associated with construction of a 6-7 fused ring in a highly enantioselective fashion. Presently, we report our findings associated with intramolecular asymmetric aldol reactions of **6** to afford chiral **7** by the use of a series of amino acids. Also examined are the reactions of a substrate of differing ring size to allow direct comparisons of reactivity and enantioselectivity.

Results and Discussion

Dione **13** was prepared from diethyl adipate (**12**) according to a known method.[21] Following Michael addition of **13** to 1-penten-3-one (ethyl vinyl ketone, EVK) in the presence of a catalytic amount of benzyltrimethylammonium hydroxide (Triton B) in methanol, the trione **6**[17b] was isolated in 83% yield (Scheme 1).

In preliminary experiments, the aldol reaction of **6** in the presence of L-Pro or L-Phe at room temperature (rt) did not proceed to afford **7** in several solvents such as methanol, dimethylsulfoxide (DMSO), acetonitrile (MeCN), and *N*,*N*-dimethylformamide (DMF). When the same reaction mixtures were heated, very long times were needed to achieve completion, and complex mixtures of many products accompanied trace amounts of desired **7**. The reaction of **6** was greatly improved by adding 0.5 equiv of 1 N $HClO_4$ to stimulate the dehydration that follows the aldol reaction. There ensued the screening of several commercially available cyclic and acyclic L-amino acids for the aldol reaction. All of the reactions were carried out under the same conditions in the presence of a stoichiometric amount of L-amino acid and 0.5 equiv of 1 N $HClO_4$ in DMSO at 90 °C (Table 1). Enantiomeric excesses (ee's) of the resulting enone **7** were determined by HPLC equipped with a chiral stationary phase column (Chiralpak AS-H, Daicel Chemical Corporation, Ltd.). The results are compiled in Table 1.

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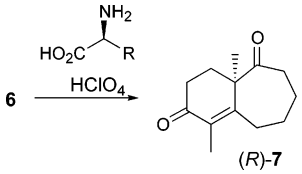
TABLE 1. Screening of Several L-Amino Acids for Asymmetric Aldol Reaction of 6[a]

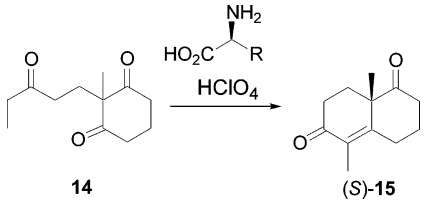


entry	amino acid	R	time, h	yield,[b] %	ee,[c,d] %
1	L-Pro (**2**)	−	114	7	6
2	L-Phe	CH_2Ph	100	86	48
3	L-Tyr	CH_2Ph-*p*-OH	95	24	6
4	L-Trp	CH_2-indol-3-yl	102	14	20
5	L-Val	$CH(CH_3)_2$	113	44	41
6	L-Leu	$CH_2CH(CH_3)_2$	144	34	32
7	L-Ser	CH_2OH	95	37	9
8	L-homo-Ser	$(CH_2)_2OH$	95	56	32
9	L-Cys	CH_2SH	120	23	1
10	L-Met	$(CH_2)_2SCH_3$	96	99	53
11	***S***-Me-L-Cys	CH_2SCH_3	120	47	11
12	L-Gln	$(CH_2)_2CONH_2$	120	18	2
13	L-Asn	CH_2CONH_2	137	40	47
14[e]	L-Asp	CH_2CO_2H	24	66	−0.5
15	L-Arg	$(CH_2)_3NHC(=NH)NH_2$	18	80	−13
16[e]	L-Lys (HCl)[f]	$(CH_2)_3NH_2HCl$	146	32	22

[a] Reaction conditions: L-amino acid (1.0 equiv), 1 N $HClO_4$ (0.5 equiv), DMSO, 90 °C. [b] Isolated yield. [c] Determined by HPLC with a chiral stationary phase. [d] Opposite enantioselection is denoted by a minus sign. [e] 1 N $HClO_4$ was not added. [f] Monohydrogen chloride salt was used.

Relevantly, most of the reactions involving L-amino acids afforded (*R*)-**7** as the major enantiomer. Because the reaction of **1** and **4** afforded (*S*)-**3** and (*S*)-**5**, respectively, in the presence of L-amino acids, inversion of enantioselectivity must be operative in those reactions of **6** that involve a seven-membered ring. The details relating to the determination of the absolute configuration of (*R*)-**7** are given below (vide infra). L-Pro (**2**) was not particularly effective in this reaction. Although a trace amount of **7** was isolated after 114 h, the ee value was only 6% (entry 1). Among several amino acids, L-Phe and L-methionine (L-Met) were particularly suitable, delivering (*R*)-**7** in 86% yield accompanied by 48% ee (entry 2) and in 99% yield accompanied by 53% ee, respectively (entry 10). Amino acids bearing other side chain aromatic substituents such as L-tyrosine (L-Tyr) and L-tryptophan (L-Trp) afforded **7** in lower yield and ee than L-Phe (entries 3 and 4). Both L-valine (L-Val) and L-leucine (L-Leu), which have a branched alkyl side chain, afforded **7** in moderate yield and ee (entries 5 and 6). In the case of L-serine (L-Ser) and L-homo-serine (L-homo-Ser) where the heteroatom is more remote, some beneficial effect on yield and ee was evident (entries 7 and 8). The same tendency was observed in relation to L-cysteine (L-Cys), L-Met, and *S*-methyl-L-cystein (*S*-Me-L-Cys, entries 9−11). An amide group on the side chain of the amino acid also gave rise to elevated levels of enantioselectivity. L-Asparagine (L-Asn), which has a nitrogen or an oxygen functionality at the position defined above as suitable, was more effective than L-glutamine (L-Gln), which has a longer carbon chain than L-Asn. However, the isolated yields of **7** in both cases were low or modest (entries 12 and 13). Both acidic and basic

TABLE 2. Screening of Several Amino Acids for Asymmetric Aldol Reaction of 14[a]



entry	amino acid	time, h	yield,[b] %	ee,[c] %
1	L-Pro	132	13	11
2	L-Phe	22	56	91
3	L-Tyr	22	70	79
4	L-Trp	22	51	90
5	L-Val	22	73	81
6	L-Leu	22	74	84
7	L-homo-Ser	22	71	80
8	L-Met	22	74	84
9[d]	L-Asp	22	41	31
10	L-His	22	69	19

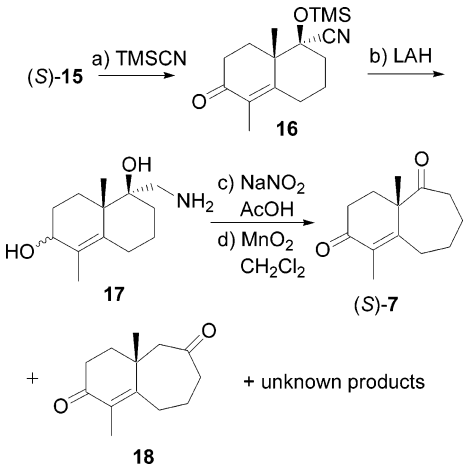
[a] Reaction conditions: L-amino acid (1.0 equiv), 1 N $HClO_4$ (0.5 equiv), DMSO, 90 °C. [b] Isolated yield. [c] Determined by HPLC equipped with a chiral stationary phase. [d] $HClO_4$ was not added.

amino acids were not suitable (entries 14−16). In the case of L-aspartic acid (L-Asp), the reaction was carried out without $HClO_4$ because of the existing carboxylic acid functionality and was completed in shorter time than the other amino acids, but no enantioselectivity was observed (entry 14). L-Arginine (L-Arg), with its existing basic guanidine functionality, revealed an opposite enantioselectivity to afford (*S*)-**7** as the major enantiomer accompanied by low ee, high chemical yield, and the shortest reaction time (entry 15). L-Lysine (L-Lys) monohydrogen chloride salt was also examined, but it was not effective (entry 16). Although the best ee value was moderate in our trials, we could obtain optically pure (*R*)-**7** by fractional recrystallization. In the final analysis, L-Met and L-Phe were selected as mediators to develop further experiments generating (*R*)-**7** via the asymmetric intramolecular aldol reaction.

To compare the reactivity offered by a differing ring size, we also studied the aldol reaction of **14** to provide **15** bearing a methyl substituent and a 6-6 fused bicyclic structure. Although many reports utilizing (*S*)- or (*R*)-**15** for syntheses of natural or unnatural products have been documented,[11,12] enantioselective syntheses of **15** via amino acid mediated aldol reactions of **14** have consisted of four methods as reported independently by Yamada, Pecher, Uda, and Swaminathan.[22] Pecher described a route to (*S*)-**15** via the L-Pro-catalyzed aldol reaction of **14** and obtained (*S*)-**15** in 44−60% yield with 24−41% ee after a reaction period of 20−34 days.[22b] This finding suggests that L-Pro is not a suitable promoter of the reaction. Recently, Shibasaki reported a catalytic asymmetric synthesis of (*S*)-**15** involving the use of L-Phe and *p*-toluenesulfonic acid pyridinium salt (PPTS) in 1.0 equiv of DMSO as solvent.[16] Here, (*S*)-**15** was always obtained as the major enantiomer when L-Pro, L-Phe, or L-Pro derivatives were used. However, there have been no reports describing reactions promoted by a variety of acyclic amino acids. For this reason, we next investigated the reaction of **14** with several acyclic amino acids under conditions similar to those utilized for **6** (Table 2).

Trione **14** was prepared from 2-methyl-1,3-cyclohexanedione by way of a known method.[16] In Table 2, the results of

SCHEME 2[a]



[a] Reaction conditions: (a) TMSCN (1.2 equiv), KCN (0.15 equiv), 18-crown-6 (0.04 equiv), CH_2Cl_2, 0 °C, 30 min, 92%; (b) LAH (4.0 equiv), THF, reflux, 13 h, 57%; (c) $NaNO_2$ (3.0 equiv), AcOH/H_2O = 1:1, 0 °C, 3 h; (d) MnO_2 (15.0 equiv), CH_2Cl_2, rt, 96 h, 25% (two steps) for **18**, 0.7% (two steps) for (*S*)-**7**.

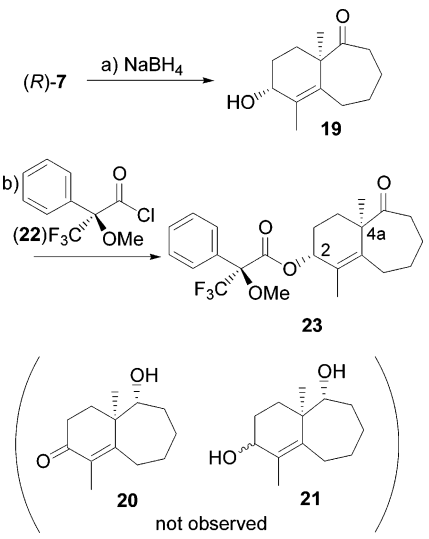
asymmetric aldol reactions involving **14** in the presence of several amino acids are compiled. All of these reactions were carried out in DMSO at 90 °C in the presence of 0.5 equiv of 1 N $HClO_4$ except for entry 9. The absolute configuration of **15** was assigned as *S* by comparison with the optical rotation of (*S*)-**15** reported previously.[16] More specifically, the optical rotation of product (*S*)-**15** displayed $[\alpha]_D$ +130.0 ($CHCl_3$, 86% ee) (lit.[16] $[\alpha]_D$ + 120.7 ($CHCl_3$, 80% ee)). The reaction using L-Pro (**2**) afforded (*S*)-**15** in low yield and low ee even after a reaction time of 132 h. This finding compares favorably with Pecher's result.[22b] Most of the L-amino acids were effective in this reaction and furnished (*S*)-**15** in the range of 51−74% yield and 80−91% ee (entries 2−8). The highest ee's were observed in the cases using L-Phe or L-Trp and were accompanied with modest yields. L-Met, which provided good results in the reaction of **6**, also afforded (*S*)-**15** with a little lower ee and higher yield than the examples involving L-Phe and L-Trp (entry 8). Both acidic and basic amino acids such as L-Asp and L-histidine (R = CH_2-imidazol-4-yl; L-His) were not effective and afforded (*S*)-**15** with quite low ee and moderate yield (entries 9 and 10). On the basis of these results, we came to the conclusion that asymmetric aldol reactions of **14** differ from those of **6** and that enantioselectivity is marginally, if at all, dependent on the nature of the amino acid side chain. A variety of L-amino acids could be used for highly enantioselective aldol reactions of **14** to afford (*S*)-**15**.

In a manner similar to that reported by us previously, we next synthesized (*S*)-**7** from (*S*)-**15** with 87% ee to determine the absolute configuration of the aldol product (*R*)-**7** (Scheme 2). To this end, chemo- and stereoselective cyanohydrin formation from ketone (*S*)-**15** was undertaken using trimethylsilyl cyanide[23] in the presence of a catalytic amount of

(22) (a) Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 1103. (b) Coisne, J.-M.; Pecher, J. *Bull. Soc. Chim. Belg.* **1981**, *90*, 481. (c) Tamai, Y.; Mizutani, Y.; Uda, H.; Harada, N. *J. Chem. Soc., Chem. Commun.* **1983**, 114. (d) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308.

(23) (a) Evans, D. A.; Truesdale, L. K.; Carroll, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, *55*.; *J. Org. Chem.* **1974**, *39*, 914. (b) Lidy, W.; Sundermeyer, W. *Chem. Ber.* **1973**, *106*, 587.

SCHEME 3[a]

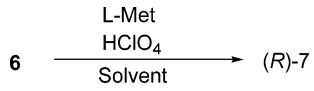


[a] Reaction conditions: (a) $NaBH_4$ (0.7 equiv), EtOH, 0 °C, 10 h, 80%; (b) (*R*)-MTPACl (**22**, 1.3 equiv), DMAP (0.05 equiv), pyridine-CH_2Cl_2, rt, 5 h, 90%.

18-crown-6 and potassium cyanide.[24] The single product **16** was obtained in 92% yield. Although the stereostructure of **16** has not been determined, we have anticipated that attack of cyanide occurs from the side opposite that occupied by the angular methyl substituent to afford the α-oriented isomer. When **16** was subsequently reduced with lithium aluminum hydride in refluxing tetrahydrofuran (THF), the amino diol was formed accompanied by 1,2-reduction of the enone moiety. The diastereoselectivity of allylic alcohol formation in **17** was determined to be 2.2:1 by integration of ^{1}H NMR spectra recorded on a $CDCl_3$ solution of unpurified products. The relevant signals of the amino methylene protons appear at δ 2.79 and δ 2.91, respectively. Diazotization of **17** with sodium nitrite in aqueous acetic acid[25] resulted in the generation of a number of products. Oxidation of the allylic alcohol functionality with manganese dioxide simplified matters to the four-component level. After chromatographic separation, two of these were identified as the desired enone (*S*)-**7** and the regioisomeric enone **18**[26] in 0.7% yield and 25% yield, respectively. We have not pursued identification of the other two components that were isolated in reasonable amounts. All of the spectral data for (*S*)-**7**, except for the optical rotation, were identical with those of enone (*R*)-**7** which was obtained as above from **6**. The optical purity of (*S*)-**7** was determined to be 91% ee by the same HPLC technique as that described above. Therefore, significant loss of optical purity had not occurred during the ring expansion process. The optical rotation of enone (*S*)-**7** was shown to be $[\alpha]_D$ +72.6 (*c* 0.66, $CHCl_3$, 91% ee). Because the optical rotation of the aldol product (*R*)-**7** consisted of $[\alpha]_D$ −83.4 (*c* 1.0, $CHCl_3$, >99% ee), the absolute configuration of the aldol product **7** must be *R*.

To provide added confirmation of the stereostructure of (*R*)-**7**, we also examined by X-ray diffraction the corresponding (*S*)-2-methoxy-2-(trifluoromethyl)phenylacetic acid [(*S*)-MTPA] ester **23** (Scheme 3). Sodium borohydride reduction of (*R*)-**7** of 57% ee in ethanol at 0 °C afforded allylic alcohol **19** stereoselectively in 85% yield as a single product. We did not observe the corresponding alcohol **20** or diol **21** in this reaction. This chemo- and stereoselective reduction differs intrinsically from a similar reaction of **3b** or **5** reported independently by Heathcock, Hagiwara, and Shibasaki.[16,22d,27] These works reported that reduction of **3b** or **5** with $NaBH_4$ afforded the product resulting from stereoselective reduction of the saturated ketone moiety and not the enone moiety. Alcohol **19** was in turn reacted with (*R*)-MTPA chloride [(*R*)-MTPACl] (**22**),[28] prepared from (*S*)-MTPA by a known method, in the presence of 4-dimethylaminopyridine (DMAP) in pyridine and dichloromethane to afford **23** accompanied by a small amount of a diastereomer at C-4a which originated from (*S*)-**7** contained in starting (*R*)-**7** with 57% ee. After fractional recrystallization, of major product **23** as single crystals, X-ray diffraction demonstrated the absolute configuration of **23** to be 2*R*,4a*R* by relating to the known (*S*)-configuration of the MTPA component. The absolute configuration of starting **7** had therefore been correctly assigned as *R*. Furthermore, it was demonstrated that hydride reduction of the enone functionality of (*R*)-**7** had occurred stereoselectively from the side opposite the angular methyl substituent.

TABLE 3. Solvent Effects of Asymmetric Aldol Reaction of 6 Mediated by L-Met[a]



entry	solvent	temp, °C	time, h	yield[b], %	ee[c], %
1	DMF	95	120	37	24
2	CH_3CN	75	120	61	40
3	dioxane	95	120	10	22
4	DME	75	120	5	37
5	^{n}BuOH	95	120	51	7
6	benzene	75	120	15	38

[a] Reaction and conditions: L-Met (1.0 equiv), 1 N $HClO_4$ (0.5 equiv). [b] Isolated yield. [c] Determined by HPLC with a chiral stationary phase.

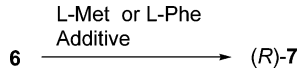
At this point, we returned to optimize the reaction conditions involving **6**. Table 3 summarizes those solvent effects involving the reaction mediated by L-Met. Nonprotic polar solvents such as DMF and MeCN prolonged the reaction time and afforded (*R*)-**7** in lower yield and ee than in the DMSO example (entries 1 and 2). Ethereal solvents such as 1,4-dioxane and 1,2-dimethoxyethane (DME) proved unsuitable (entries 3 and 4). When *n*-butanol was used as solvent, a modest yield accompanied by the lowest ee from among these trials was observed (entry 5). On this basis, DMSO was selected as the solvent for continued optimization.

The effect of additives was next probed. The reactions were carried out in DMSO at 90 °C in the presence of an L- or D-amino acid with or without an acid such as pyridinium *p*-toluenesulfonate (PPTS), *p*-toluenesulfonic acid (*p*-TsOH), and (+)- or (−)-camphorsulfonic acid (CSA) as the additive. The results are given in Table 4.

We first examined the effect of $HClO_4$. The opposite enantioselectivity to afford (*S*)-**7**, accompanied with a lower ee

(24) Greenlee, W. J.; Hangauer, D. G. *Tetrahedron Lett*. **1983**, *24*, 4559.
(25) Di Maio, G.; Tardella, P. A. *Tetrahedron* **1966**, *22*, 2069.
(26) Uma, R.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron* **1986**, *42*, 2757.
(27) Dutcher, J. S. D.; Macmillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663.
(28) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

TABLE 4. Effects of Additive in the Reaction of 6[a]



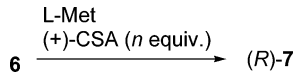
entry	amino acid	additive	time, h	yield,[b] %	ee,[c,d] %
1[e]	L-Met	$HClO_4$	96	99	53
2	L-Met	−	18	44	−14
3	L-Met	H_2O[f]	120	41	22
4	L-Met	PPTS	18	67	60
5	L-Met	*p*-TsOH	18	66	59
6	L-Met	(+)-CSA	15	82	53
7	L-Met	(−)-CSA	15	70	54
8[g]	−	(+)-CSA	120	52	−1
9	D-Met	$HClO_4$	114	40	−25
10	D-Met	PPTS	19	41	−55
11	D-Met	(+)-CSA	40	69	−57
12[e]	L-Phe	$HClO_4$	100	86	48
13	L-Phe	PPTS	13	80	50
14	L-Phe	(+)-CSA	21	81	52

[a] Reaction conditions: Met or L-Phe (1.0 equiv), additive (0.5 equiv), DMSO, 90 °C. [b] Isolated yield. [c] Determined by HPLC with a chiral stationary phase. [d] Opposite enantioselection was denoted by a minus sign. [e] The same result is shown in Table 1. [f] H_2O (0.23 mL) was added without any acids. [g] Amino acid was not added.

than that in entry 1 in Table 4, was observed in the presence of L-Met without $HClO_4$ (entry 2). Therefore, $HClO_4$ plays a very important role in this asymmetric process. Because 1 N $HClO_4$ contains water, the effect of water was next probed. Thus, the reaction was carried out with the same amount of water as in entry 1 without $HClO_4$ in the presence of L-Met. Entry 3 shows that (*R*)-**7** was obtained in moderate yield and lower ee than in entry 1. In comparison with entries 2 and 3, it was seen that a proton source, especially an acid, affected the enantioselection. Next, acidic additives were screened to optimize the reaction. The addition of PPTS or *p*-TsOH led to a slight increase in ee with accompanying shortened reaction times (entries 4 and 5). When (+)-CSA was used, (*R*)-**7** was obtained in 82% yield and 53% ee (entry 6). Although the addition of (−)-CSA afforded almost the same result as that in entry 1, the yield was a bit lower than the example involving (+)-CSA (entry 7). Subsequently, reaction was carried out in the presence of D-Met instead of L-Met to invert the enantioselectivity (entry 9). We observed the production of (*S*)-**7** under these conditions, but both yield and ee were lower than those in the case involving L-Met. Thus, complete inversion of enantioselectivity could not be realized by the combination of D-Met and $HClO_4$. In the case of D-Met with PPTS or (+)-CSA, complete inversion of enantioselectivity was observed with modest yield (entries 10 and 11). To elucidate the effect of CSA on asymmetric induction, we tried the reaction without amino acid. Aldolization of **6** by adding only (+)-CSA proceeded slowly to afford **7** after 120 h in 52% yield with no enantioselectivity (entry 8). Consequently, enantioselection must be due to the chirality of the amino acid and not to CSA. We also examined the combination of L-Phe and PPTS or (+)-CSA, but no drastic effect was observed, except for the shortening of reaction times (entries 12−14).

We next examined the effect of quantities of (+)-CSA on the yield and ee of (*R*)-**7**. All reactions were carried out with 1.0 equiv of L-Met in DMSO at 90 °C for 21 h in the presence of (+)-CSA over the range of 0 to 1.2 equiv (see Table 5 and Figure 5). Higher yields and ee's than those for the reaction without any acids were observed upon increasing the amount

TABLE 5. Effects of the Amount of (+)-CSA for Asymmetric Intramolecular Aldol Reaction of 6[a]



entry	(+)-CSA, equiv	yield[b] of **7**, %	ee[c,d] of **7**, %	recovery[b] of **6**, %
1[e,f]	0	44	−14	0
2	0.2	66	26	0
3	0.4	82	55	0
4[g]	0.5	87	53	0
5	0.6	85	54	0
6	0.8	91	56	0
7	1.0	27	58	70
8	1.2	15	10	69

[a] Reaction and conditions: L-Met (1.0 equiv), (+)-CSA (*n* equiv), DMSO, 90 °C, 21 h. [b] Isolated yield. [c] Determined by HPLC with a chiral stationary phase. [d] Opposite enantioselection was denoted by a minus sign. [e] The same result is shown in Table 4. [f] Reaction was complete after 18 h. [g] Reaction was complete after 15 h.

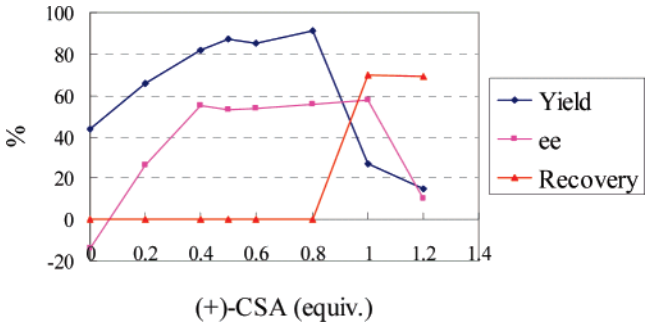


FIGURE 5. Effects of the level of (+)-CSA on the asymmetric intramolecular aldol reaction of **6**.

of (+)-CSA, and both parameters reached a plateau at around 85% yield and 55% ee in the range of 0.4−0.8 equiv of CSA (entries 3−6). Reactivity in the presence of more than 1.0 equiv of CSA decreased drastically, and starting **6** was recovered even after 21 h. However, the ee of (*R*)-**7** continued to be around 55% (entry 7). With more than 1.2 equiv of CSA, the ee decreased sharply. Therefore, the optimal amount of CSA is in the range from 0.4 to 0.8 equiv.

Finally, we tried to extend this process to a catalytic version. When the reaction was carried out in the presence of 0.3 equiv of L-Met and 0.15 equiv of (+)-CSA or PPTS in DMSO at 90 °C, the results compiled in Table 6 were noted. Both reactions using CSA or PPTS afforded (*R*)-**7** in moderate yield with lower ee, accompanied by recovery of **6** even after 120 h (entries 1 and 3). Shortened reaction times were a good improvement. Thus, when the reaction was arrested after 24 h, (*R*)-**7** was obtained in moderate yield with almost the same ee as that in the stoichiometric reaction, and the chemical yield based on the recovery of starting **6** in both cases was improved to 75−77% (entries 2 and 4). However, the catalytic version of the reaction was difficult to achieve because of the low turn-over numbers (TONs) in the attempted reactions. This low TON meant that L-Met would lose the activity as a reaction mediator or decompose under these conditions.

In the aldol reaction of **6** to afford a 6-7 fused bicycle, there exists the possibility of producing eight stereoisomers as a result of three newly generated stereogenic centers. Because we could not isolate the initially formed β-hydroxy ketones, dehydration to afford **7** must occur rapidly. The transition states predicted

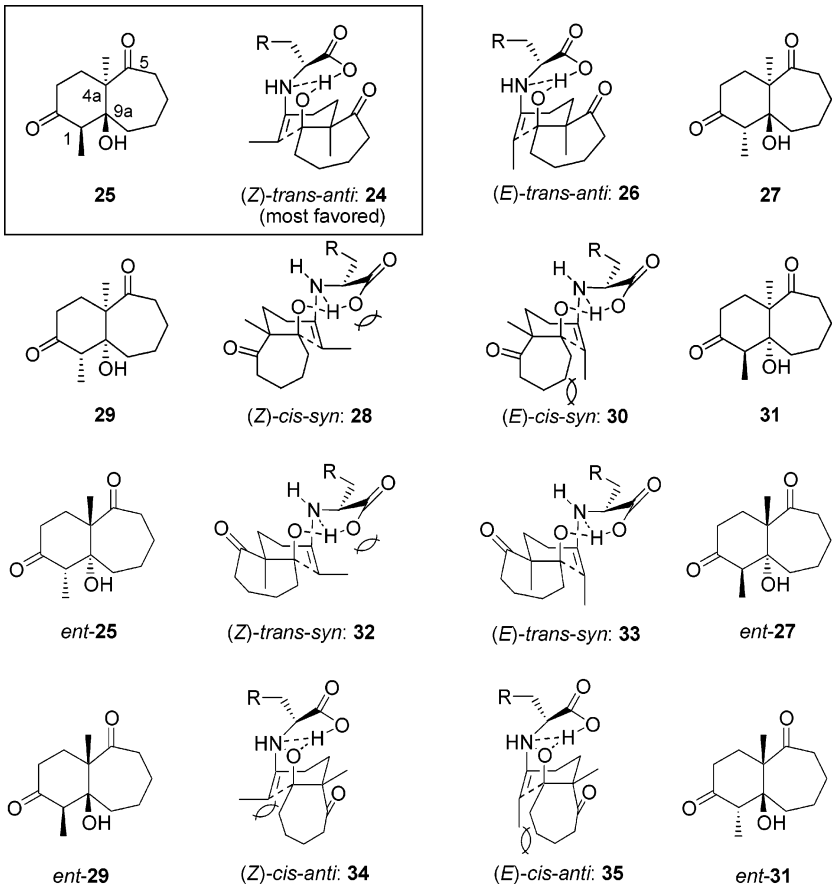
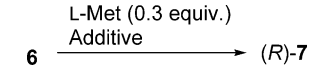


FIGURE 6. Proposed transition states for the aldol reaction of **6** to afford all stereoisomers of aldol products.

TABLE 6. Asymmetric Aldol Reaction of 6 in the Presence of a Catalytic Amount of L-Met[a]



entry	additive	time, h	yield[b,c] of **7**, %	ee[d] of **7**, %	recovery[b] of **6**, %
1	(+)-CSA	120	40 (48)	35	17
2	(+)-CSA	24	43 (77)	55	44
3	PPTS	120	41 (40)	33	33
4	PPTS	24	43 (75)	56	43

[a] Reaction conditions: L-Met (0.3 equiv), (+)-CSA or PPTS (0.15 equiv), DMSO, 90 °C. [b] Isolated yield. [c] Yields in parentheses were based on the recovery of starting **6**. [d] Determined by HPLC with a chiral stationary phase.

to reach each of the stereoisomers, which are based on Houk's transition model from the reaction of **4a** (R = CH_3, $n = 1$), are shown in Figure 6.[9g] Among these models, all of the *syn* (*syn*, *anti*: conformation between olefinic and carboxylic acid moieties) transition states, **28**, **30**, **32**, and **33**, are considered to be significantly higher in energy because of the steric hindrance caused by repulsion between the methyl enamine and carboxylic acid moieties in **28** and **32**, the seven-membered carbocycle in **30**, and the angular methyl substituent in **33**. The *trans-anti* (*cis*, *trans*: *cis*- or *trans*-fused carbocycles) transition state **26** appears to be disfavored because of 1,3-diaxial repulsion between two methyl substituents. The (*Z*)- or (*E*)-*cis-anti* (*Z*,*E*: geometry of the enamine moiety) transition states **34** and **35** also feature steric repulsion between the methyl enamine and the seven-membered carbocycle. From expectations based on these considerations, the (*Z*)-*trans-anti* transition states **24** should be most favored and afford the 1*R*,4a*R*,9a*S*-aldol product **25**, which would give rise to (*R*)-**7** after dehydration. The existence of hetero atoms at key positions on the side chain of the amino acid can help to stabilize the transition state by engaging in a new coordination to the hydrogen-bonded proton. When no Brønsted acid was used, inversion of enantioselectivity was noted with lower ee (Table 4, entry 2). This result means that the reaction without an acid might proceed through an acyclic transition state and result in lower ee. A Brønsted acid cocatalyst, such as $HClO_4$, CSA, and PPTS, may suppress dissociation of the proton from the carboxylic acid moiety and help to maintain or stabilize the cyclic transition states. Further investigations into the effects of an acid cocatalyst and calculations involving the energy differentiation of our proposed transition states are currently underway.

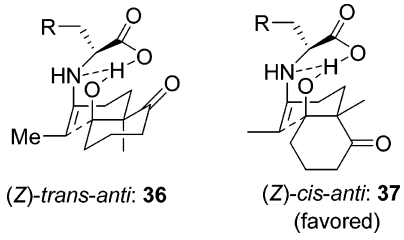


FIGURE 7. Proposed transition states for the aldol reaction of **14**.

The favored predicted transition states leading to (*S*)- or (*R*)-**15** existing in a 6-6 fused bicycle are shown in Figure 7. All of the *syn*- and (*E*)-*trans-anti* transition states are expected to be disfavored as per the reasons described above. On direct

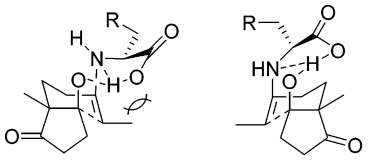


FIGURE 8. Transition states for the aldol reaction of **3a** as proposed by Houk.

comparison of (*Z*)-*trans-anti*-**36** with (*Z*)-*cis-anti*-**37**, **37** should be more favored because of the lack of steric repulsion due to the axial methyl substituent in **36**. Also, there is no serious steric hindrance as observed in **34** between the methyl enamine moiety and the six-membered carbocycle because of the smaller six-membered ring. The reaction should therefore proceed through transition state **37** to afford (*S*)-**15** preferentially after dehydration.

In regards to the aldol reaction of **3a** to afford a 5-6 fused bicycle in the presence of L-Phe, Houk reported the calculated most favored transition states leading to (*S*)- and (*R*)-**5a** to be **39** and **38**, respectively (Figure 8).[9g] Because the energy of transition state **39** was 5.6 kcal/mol lower than that of **38**, the reaction of **3a** afforded (*S*)-**5a** preferentially.

Conclusion

In conclusion, we have developed a new intramolecular asymmetric aldol reaction involving the use of amino acids to obtain both enantiomers of the 6-7 fused bicyclic enone **7**. During these studies, a crossover in enantioselectivity was uncovered as a function of the differing ring size. The inducement of more elevated levels of enantioselectivity is anticipated. The use of **7** as a new chiral synthon to achieve total syntheses of selected pharmaceutically important natural products is currently being probed.

Experimental Section

2-Methyl-2-(3-oxopentyl)cycloheptane-1,3-dione (6). To a stirred solution of 1-penten-3-one (1 mL, 10 mmol) and Triton B (0.21 mL, 0.5 mmol) in methanol (4 mL) was added 2-methylcycloheptane-1,3-dione (**13**)[21] (700 mg, 5 mmol) as a small portion over 5 min at rt. The mixture was heated to reflux for 1 h. After cooling, the solvent was removed under reduced pressure and the residue was dissolved in ether. The ether layer was washed with saturated $NaHCO_3$ solution and brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexanes/ethyl acetate, 10:1) to afford **6** (932 mg, 83%) as a pale yellow oil: IR (film, cm^{-1}) 1715, 1694; ^1H NMR (270 MHz, $CDCl_3$) δ 2.54−2.40 (m, 4 H), 2.39 (q, J = 7.4 Hz, 2 H), 2.33−2.27 (m, 2 H), 2.11−2.05 (m, 2 H), 1.93−1.83 (m, 4 H), 1.18 (s, 3 H), 1.03 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 212.2, 209.7, 63.4, 41.2, 36.1, 35.8, 27.8, 26.6, 17.5, 7.5; EIMS m/z 224 (M^+), 125 (100%); HRMS calcd for $C_{13}H_{20}O_3$ 224.1412, obsd 224.1431.

Typical Procedure for Amino Acid Mediated Aldol Reaction of 6. A mixture of **6** (400 mg, 1.78 mmol), L-methionine (266 mg, 1.78 mmol), and (+)-CSA (207 mg, 0.89 mmol) in DMSO (4 mL) was stirred at 90 °C for 15 h. After cooling, the mixture was poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate (AcOEt). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was chromatographed on silica gel (hexanes/AcOEt, 7:1) to afford (*R*)-**7** (300 mg, 82%) as pale yellow crystals. The optical purity of (*R*)-**7** was determined to be 53% ee by HPLC equipped with a chiral stationary phase. HPLC conditions: Chiralpak AS-H, ethanol/hexanes = 10:90, flow rate 1.0 mL/min, detected at 254 nM, t_R = 9.5 min for (*R*)-**7**, 10.5 min for (*S*)-**7**. Optically pure material was obtained by fractional recrystallization as follows: compound (*R*)-**7** (1.33 g, 53% ee) was recrystallized from hexanes/ether (4:1) to afford racemic **7** (0.445 g, 0.27% ee) as colorless prisms, and the filtrate was concentrated under reduced pressure to afford (*R*)-**7** (0.885 g, 80% ee), which was recrystallyzed twice from hexanes/ether (4:1) to afford optically pure (*R*)-**7** (0.134 g, >99% ee) as colorless prisms. For (*R*)-**7**: mp 98 °C (hexanes/ether); $[\alpha]^{23}_D$ −83.4 (*c* 1.01, $CHCl_3$, >99% ee); IR (KBr, cm^{-1}) 1710, 1664, 1616; ^1H NMR (270 MHz, $CDCl_3$) δ 2.78−2.65 (m, 2 H), 2.62−2.46 (m, 2 H), 2.35−2.28 (m, 1 H), 2.16 (dt, J = 6.0 Hz, 13.4 Hz, 1 H), 2.05−1.95 (m, 2 H), 1.86 (s, 3 H), 1.76−1.46 (m, 4 H), 1.34 (s, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 213.7, 197.0, 158.9, 132.7, 53.4, 39.9, 32.7, 32.2, 31.2, 28.3, 28.2, 18.2, 10.4; EIMS m/z 206 (M^+), 121 (100%); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, obsd 206.1308.

Typical Procedure for Amino Acid Mediated Aldol Reaction of 14. A mixture of **14** (100 mg, 0.48 mmol), L-methionine (71 mg, 0.48 mmol), and 1 N $HClO_4$ (0.24 mL, 0.24 mmol) in DMSO (1 mL) was stirred at 90 °C for 22 h. After cooling, the mixture was poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate (AcOEt). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was chromatographed on silica gel (hexanes/AcOEt, 5:1) to afford (*S*)-**15** (68 mg, 74%) as a pale yellow oil. The optical purity of (*S*)-**15** was determined to be 84% ee by HPLC equipped with a chiral stationary phase. HPLC conditions: Chiralpak AS-H, ethanol/hexanes = 10:90, flow rate 1.0 mL/min, detected at 254 nM, t_R = 10.9 min for (*S*)-**15**, 12.3 min for (*R*)-**15**. For (*S*)-**15**: $[\alpha]^{24}_D$ +130.0 (*c* 1.0, $CHCl_3$, 86% ee), lit.[16] $[\alpha]^{22}_D$ + 120.7 ($CHCl_3$, 80% ee); IR (KBr, cm^{-1}) 1708, 1660, 1609; ^1H NMR (270 MHz, $CDCl_3$,) δ 2.88 (dtd, J = 1.2 Hz, 5.0 Hz, 15.9 Hz, 1 H), 2.69 (ddd, J = 5.8 Hz, 10.3 Hz, 15.9 Hz, 1 H), 2.57−2.38 (m, 4 H), 2.21−2.02 (m, 3 H), 1.85−1.67 (m, 1 H), 1.81 (d, J = 1.4 Hz, 3 H), 1.42 (s, 3 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 212.0, 197.5, 158.1, 130.6, 50.5, 37.2, 33.2, 29.5, 27.2, 23.3, 21.4, 11.2; EIMS m/z 192 (M^+), 136 (100%); HRMS calcd for $C_{12}H_{16}O_2$ 192.1150, obsd 192.1149.

Silylated Cyanohydrin (16). To a stirred solution of (*S*)-**15** (10 g, 5.2 mmol, 87% ee) in CH_2Cl_2 (10 mL) was added KCN (50 mg, 0.78 mmol), 18-crown-6 (55 mg, 0.21 mmol), and trimethylsilyl cyanide (0.83 mL, 6.2 mmol) at 0 °C. After being stirred for 30 min at the same temperature, the mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution and brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was chromatographed on silica gel (hexanes/ethyl acetate, 20:1 to 5:1) to afford **16** (1.389 g, 92%) as a colorless solid: mp 67−69 °C (hexanes); $[\alpha]^{22}_D$ +67.9 (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) 1657, 1609; ^1H NMR (400 MHz, $CDCl_3$) δ 2.76 (ddd, J = 2.2 Hz, 4.6 Hz, 15.3 Hz, 1 H), 2.55 (dt, J = 3.8 Hz, 16.4 Hz, 1 H), 2.41 (dt, J = 5.1 Hz, 15.4 Hz, 1 H), 2.29 (dt, J = 4.4 Hz, 13.7 Hz, 1 H), 2.16−1.92 (m, 5 H), 1.87−1.74 (m, 1 H), 1.82 (s, 3 H), 1.23 (s, 3 H), 0.26 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 155.7, 132.3, 120.5, 79.2, 45.2, 33.8, 33.5, 30.9, 25.6, 21.2, 16.7, 11.6, 1.2; EIMS m/z 291 (M^+), 291 (100%); HRMS calcd for $C_{16}H_{25}NO_2Si$ 291.1655, obsd 291.1659. Anal. calcd for $C_{16}H_{25}NO_2Si$: C, 65.93; H, 8.65; N, 4.81. Found: C, 66.10; H, 8.77; N, 4.81.

Hydride Reduction of 16. To a stirred suspension of lithium aluminum hydride (6.345 g, 167.2 mmol) in THF (240 mL) was added a solution of **16** (12.169 g, 41.8 mmol) in tetrahydrofuran (120 mL) at 0 °C, and the mixture was heated to reflux for 13 h. After cooling, water was carefully introduced, and stirring was resumed for 2 h at rt. The mixture was filtered through a Celite pad, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was chromatographed on basic

Al_2O_3 (ethyl acetate/methanol/NH_4OH, 10:1:0.1) to afford a diastereomeric mixture of amino alcohol (5.311 g, 57%) as a pale yellow oil. Product **17** was used in subsequent reactions without further purification of diastereomers.

Ring Expansion of 17. To a stirred solution of **17** (5.311 g, 23.6 mmol) in acetic acid (25 mL) and water (25 mL) was added sodium nitrite (4.885 g, 70.8 mmol) at 0 °C. After being stirred for 3 h at the same temperature, the mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), and manganese dioxide (20 g, 230 mmol) was added to the solution at rt. After 48 h of stirring at rt, more manganese dioxide (10 g, 115 mmol) was added. The mixture was stirred at rt for a further 48 h and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was chromatographed on basic alumina (hexanes/ethyl acetate, 100:1 to 10:1) to afford pure **18** (1.224 g, 25%) and (*S*)-**7** with a trace amount of impurity. The latter was chromatographed again on silica gel (CH_2Cl_2/ethyl acetate, 100:1) to afford (*S*)-**7** (35 mg, 0.7%).

For **18**: colorless oil; $[\alpha]^{23}_D$ +261.2 (*c* 1.01, $CHCl_3$); IR (film, cm^{-1}) 1697, 1666, 1620; ^1H NMR (400 MHz, $CDCl_3$) δ 2.91 (d, J = 12.4 Hz, 1 H), 2.82 (dt, J = 4.8 Hz, 13.5 Hz, 1 H), 2.62−2.35 (m, 5 H), 2.24 (d, J = 12.4 Hz, 1 H), 2.24−2.08 (m, 2 H), 1.78 (s, 3 H), 1.72−1.59 (m, 2 H), 1.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 197.7, 161.7, 131.7, 54.0, 43.6, 37.5, 33.9, 33.8, 27.9, 25.3, 22.8, 11.0; EIMS *m*/*z* 206 (M^+), 91 (100%); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, obsd 206.1277.

For (*S*)-**7**: colorless crystals; mp 98 °C (hexanes/ether); $[\alpha]_D^{24}$ +72.6 (*c* 0.66, $CHCl_3$, 91% ee). The spectroscopic data were identical to those of authentic (*R*)-**7**.

Sodium Borohydride Reduction of (*R*)-7. To a stirred suspension of (*R*)-**7** (1.892 g, 9.18 mmol, 57% ee) in ethanol (20 mL) was added $NaBH_4$ (121 mg, 3.21 mmol) in small portions over 5 min at 0 °C. After 3 h of stirring at the same temperature, $NaBH_4$ (121 mg, 3.21 mmol) was added to the mixture again and stirring was maintained for a further 7 h. The reaction mixture was quenched by adding acetone (20 mL), and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated $NaHCO_3$ solution and brine, and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was chromatographed on silica gel (hexanes/Et_2O, 2:1) to afford **19** (1.53 g, 80%) as a pale yellow oil: $[\alpha]^{23}_D$ −5.3 (*c* 1.01, $CHCl_3$); IR (film, cm^{-1}) 3409, 1705, 1653; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (t, J = 7.5 Hz, 1 H), 2.72−2.65 (m, 1 H), 2.58 (dd, J = 5.3 Hz, 11.7 Hz, 1 H), 2.21 (dd, J = 6.7 Hz, 10.7 Hz, 1 H), 2.14−2.05 (m, 1 H), 1.97−1.90 (m, 1 H), 1.90−1.78 (m, 1 H), 1.81 (s, 3 H), 1.73−1.62 (m, 3 H), 1.57−1.37 (m, 4 H), 1.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.0, 135.4, 132.6, 70.2, 52.7, 40.0, 31.0, 30.3, 28.5, 28.4, 27.9, 20.6, 13.8; EIMS *m*/*z* 208 (M^+), 107 (100%); HRMS calcd for $C_{13}H_{20}O_2$ 208.1463, obsd 208.1469.

(*S*)-MTPA Ester (23). To a stirred solution of **19** (678 mg, 3.26 mmol) and (*R*)-MTPACl[28] (1.068 g, 4.24 mmol), which was freshly prepared from (*S*)-MTPA, in CH_2Cl_2 (4 mL) was added pyridine (4 mL) and DMAP (20 mg, 0.16 mmol) at 0 °C. After being stirred for 5 h at rt, the mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried (Na_2SO_4). After solvent removal under reduced pressure, the residue was chromatographed on silica gel (hexanes/ethyl acetate, 5:1) to afford **23** as a diastereomeric mixture at C-4a (1.25 g, 90%, dr 4:1). Pure **23** was obtained as colorless prisms after recrystallization from hexanes/CH_2Cl_2 (5:2).

For **23**: mp 123 °C (hexanes/CH_2Cl_2); $[\alpha]^{24}_D$ −27.2 (*c* 1.01, $CHCl_3$); IR (KBr, cm^{-1}) 1741, 1710, 1656; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.55 (m, 2 H), 7.43−7.39 (m, 3 H), 5.60 (t, J = 7.2 Hz, 1 H), 3.65−3.55 (m, 3 H), 2.68−2.62 (m, 1 H), 2.54 (dd, J = 5.4 Hz, 11.8 Hz, 1 H), 2.28−2.18 (m, 2 H), 1.94−1.72 (m, 4 H), 1.54−1.37 (m, 4 H), 1.48 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 166.4, 138.9, 132.3, 129.5, 128.3, 127.6, 127.1, 123.3 (q, J_{C-F} = 290 Hz, *C*F_3), 84.3 (q, J_{C-F} = 28 Hz, *C*CF_3), 75.5, 55.4, 52.4, 40.1, 30.6, 30.4, 28.5, 27.9, 24.4, 20.5, 13.8; EIMS *m*/*z* 424 (M^+), 190 (100%); HRMS calcd for $C_{23}H_{27}F_3O_4$ 424.1861, obsd 424.1869. Anal. calcd for $C_{23}H_{27}F_3O_4$: C, 65.08; H, 6.41. Found: C, 65.10; H, 6.42.

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Supporting Information Available: General procedures; the ORTEP structure and the crystallographic data for compound **23** in CIF format; and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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