HETEROCYCLES, Vol. 100, No. 1, 2020, pp. 12 - 23. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2019, Accepted, 2nd September, 2019, Published online, 24th September, 2019
DOI: 10.3987/COM-19-14124

ALTERNATIVE CHIRAL PREPARATIONS OF A SWAMINATHAN KETONE *VIA* ASYMMETRIC ALDOL REACTIONS MEDIATED BY CHIRAL AMINES BEARING A PYRROLIDINE

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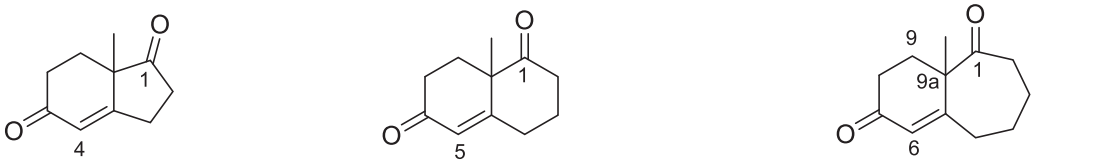
This paper is dedicated to the anniversary of achieving Volume 100 of HETEROCYCLES.

Abstract – We established a novel chiral route to provide a Swaminathan ketone (**3**) bearing a 7-membered ring *via* intramolecular aldol reaction of trione (**7**) mediated by chiral pyrrodinylmethylamine derivatives. Despite the moderate enantioselectivity of **3**, we succeeded in increasing optical purities by using a lipase-mediated asymmetric esterification of an alcohol (**16**) at a later synthetic stage. The absolute configuration was determined by Mosher's ester method, and relations between absolute configurations and optical rotations of **3** were clarified.

Hajos-Parrish (**1**) and Wieland-Miescher (**2**) ketones, which include carbobicyclic enediones, are highly useful synthons in the total synthesis of many natural products and pharmaceutically important compounds (Figure 1).[1-5]

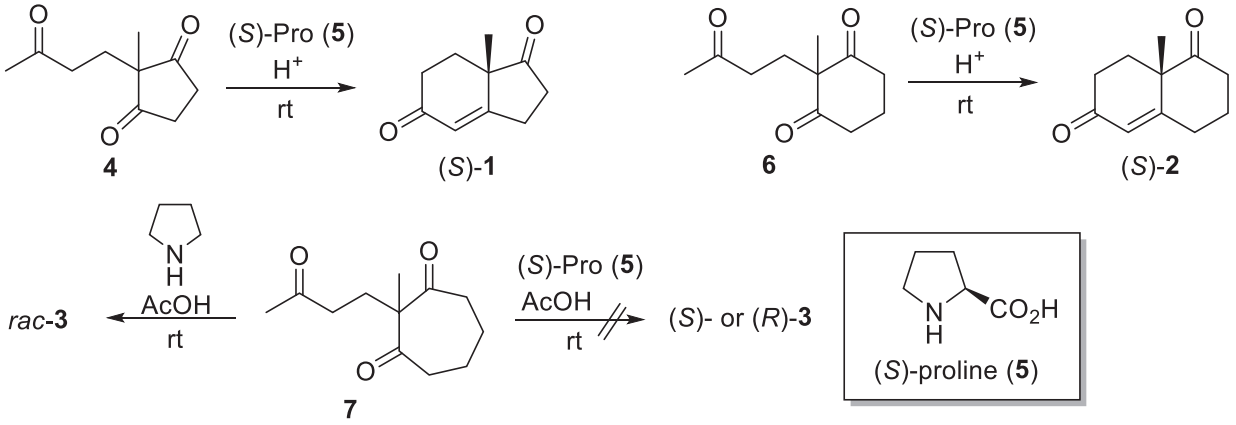


1: (Hajos-Parrish ketone) **2**: (Wieland-Miescher ketone) **3**: (Swaminathan ketone)

Figure 1

These useful enediones can be easily prepared by proline-mediated asymmetric intramolecular aldol reactions.[6] This asymmetric aldol reaction was first reported by Hajos *et al.* and is widely recognized to involve an enamine-based mechanism.[7-9] However, few reports regarding the preparation of **3** bearing a

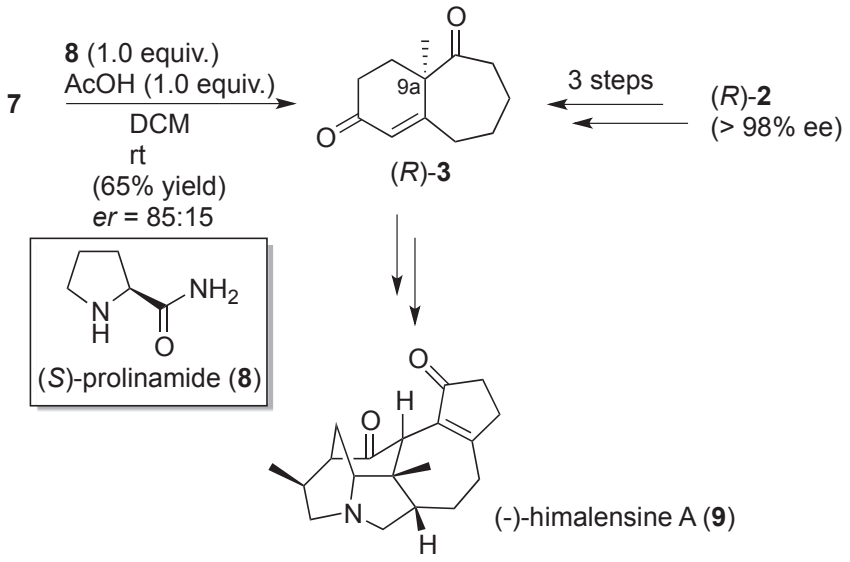
7-membered ring have been published.[10-12] Since many pharmaceutically important natural products containing 7-membered carbocycles have been published,[13] enedione (**3**) is an attractive potential chiral synthon to be used to achive total synthesis of these important products. The pioneering studies for obtaining **3** were reported by Swaminathan *et al.*,[10] synthesizing **3** as a racemic material *via* a pyrrolidine-mediated aldol reaction of trione (**7**) in the presence of acetic acid (AcOH). The authors also reported that similar reactions mediated by (*S*)-proline (**5**) did not yield the expected optically active **3** (Scheme 1).[10b]



Scheme 1

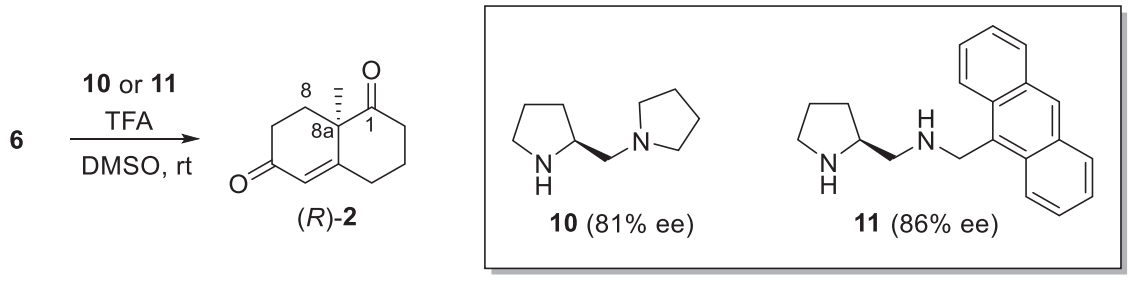
Uwai *et al*. first reported the lipase-mediated aldol reactions of **7** to afford (*S*)-(+)-**3** with a low enantioselectivity (8% ee) and retention times for both enantiomers of **3** on an HPLC instrument equipped with a chiral stationary phase column (Chiralcel OB). However, the authors did not provide any evidence for the determination of an absolute configuration of **3**.[12a] Although Pericàs *et al*. reported catalytic asymmetric aldol reactions of **7** mediated by a polymer-supported chiral amine, affording (*R*)-**3** with 53% ee, they did not discuss the details of its absolute configuration and optical rotation.[12b] Recently, Xu *et al*. reported the practical chiral preparation of (*R*)-**3** (70% ee) using aldol reactions of **7** mediated by (*S*)-prolinamide (**8**), elegantly achieving the total synthesis of (−)-himalensine A (**9**) starting from (*R*)-**3**.[12c] The authors determined an absolute configuration from single crystal X-ray analysis of (*R*)-**3** which was alternatively derived from commercially available (*R*)-**2** (> 98% ee). In their total synthesis, a chiral center at C-9a in (*R*)-**3** was directly reflected to natural (−)-himalensine A (**9**). This study indicated that the absolute configuration of (*R*)-**3** can be unambiguously identified (Scheme 2). However, both optical rotations and retention times of (*R*)- and (*S*)-**3** on the HPLC instrument equipped with a chiral stationary phase column have not been reported. Therefore, a method to determine the absolute configuration of **3** remains to be developed. Additionally, according to Xu's method, (*R*)-prolinamide (*ent*-**8**), which is derived from unnatural (*R*)-proline (*ent*-**5**), is necessary to form (*S*)-**3**. From these

reasons, novel and alternative chiral routes for **3** to clarify the relations among absolute configurations, optical rotations, and behaviors using HPLC of (*R*)- and (*S*)-**3** are required.



Scheme 2

We previously reported the asymmetric intramolecular aldol reaction of **6** mediated by chiral diamines (**10**) or (**11**) in the presence of trifluoroacetic acid (TFA).[1] These reactions afforded (*R*)-**2** in high yield and enantioselectivity (Scheme 3). According to this method, we attempted to use these chiral amines in the aldol reactions of **7**. Herein, we report the details of these reactions, chiral properties of (*R*)- and (*S*)-**3** including optical rotations and HPLC behaviors, and methods to increase optical purities through lipase-mediated asymmetric esterifications for **3** derived compounds.

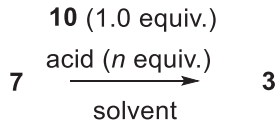


Scheme 3

First, we studied the aldol reactions of **7** mediated by a stoichiometric amount of **10**[14,15] in the presence of a Brønsted acid, and the results are summarized in Table 1. According to Xu's method,[12c] the reactions were performed in dichloromethane (DCM) at room temperature in the presence of AcOH or TFA. The reactions proceeded very slowly to afford **3** in low yields and low enantioselectivities (entries 1-4). Under

these conditions, the reactions did not proceed to completion. The reactions were then performed according to our previously developed method. A similar reaction in dimethyl sulfoxide (DMSO) at room temperature slightly improved the yield of **3** accompanied with a high enantioselectivity (entry 5). However, the reaction did not proceed to completion even after 93 h. The same reaction as entry 5 at 50 °C completed after a short time and greatly improved the yield of (*S*)-**3** with an acceptable enantioselectivity (entry 6). Details of the procedure used to determine the absolute configuration of **3** are described later (*vide infra*). The reaction conditions described in entry 6 were used for further studies.

Table 1. The aldol reaction of **7** mediated by **10**

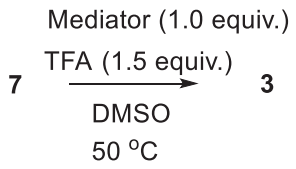


Entry[a]	Solvent	Acid (equiv.)	Temperature	Time (h)	Yield[b,c] (%)	Ee[d] (%)	Absolute configuration of **3**
1	DCM	TFA (1.0)	rt	44	trace	ND[e]	ND[e]
2	DCM	AcOH (1.0)	rt	44	15	14	*R*
3	DCM	TFA (0.5)	rt	90	9 (19)	2.9	*R*
4	DCM	AcOH (0.5)	rt	90	18 (31)	6.5	*S*
5	DMSO	TFA (1.5)	rt	93	47 (63)	64	*S*
6	DMSO	TFA (1.5)	50 °C	26	92	55	*S*

[a] 100 mg of **7** was used for all reactions.
[b] Isolated yield.
[c] Yields based on a recovery of starting **7** were shown in parentheses.
[d] Determined by HPLC equipped with a chiral stationary phase column.
[e] Not determined.

The reactions were studied in the presence of other chiral amines bearing a pyrrolidine and the obtained results are summarized in Table 2. The reaction mediated by (*S*)-proline (**5**) proceeded to afford (*R*)-**3** in a moderate yield and low enatioselectivity (entry 1). The reaction mediated by **8** was also performed to compare the Xu's method. However, lower yield and enantioselectivity were observed than the results reported in Ref. 12c (entry 2). The mediator (**11**),[1b] which exhibited high enantioselectivity in the aldol reaction of **6**, was unsuccessful in this reaction (entry 3), because of the lower yield and enantioselectivity compared to the reaction mediated by **10**. Although enantioselectivities under each conditions were not satisfactory, we planned to use enzymatic reactions focusing on two oxygen functionalities at C-1 and C-7 in (*S*)-**3** to increase the obtained optical purities.

Table 2. The aldol reaction of **7** mediated by chiral pyrrolidines



Entry[a]	Mediator	Time (h)	Yield[b,c] (%)	Ee[d] (%)	Absolute configuration of **3**
1	**5**	17.5	54	16	*R*
2	**8**	398[e]	36 (54)	56	*R*
3	**11**	48	27	33	*S*

[a] 100 mg of **7** was used for all reactions.

[b] Isolated yield.

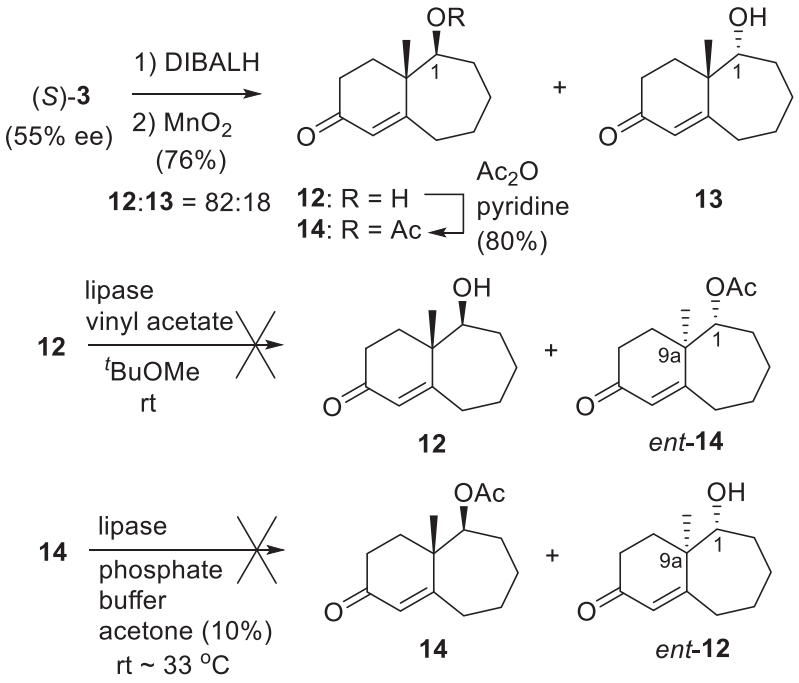
[c] Yields based on a recovery of starting **7** were shown in parentheses.

[d] Determined by HPLC equipped with a chiral stationary phase column.

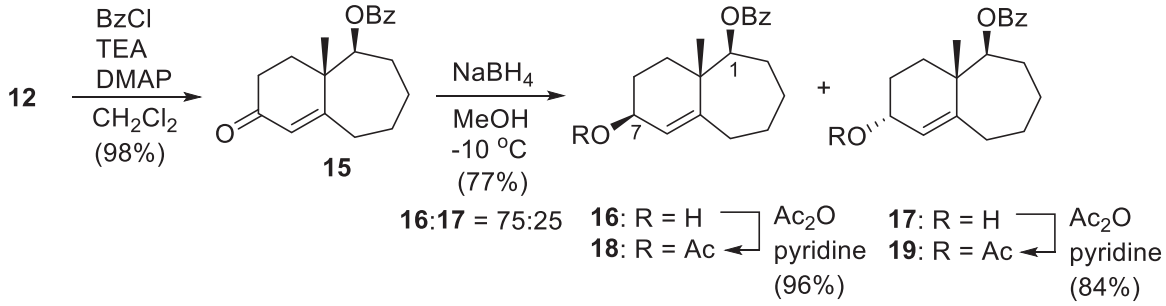
[e] The reaction was performed at rt.

The reduction of both carbonyl groups in (*S*)-**3** with diisobutylaluminum hydride (DIBALH) and following allylic oxidation in the presence of MnO_2 afforded known alcohols (**12**) and (**13**)[11c] with 82:18 diastereoselectivity. The major alcohol (**12**) was converted to acetate (**14**) using a common method. Unfortunately, both lipase-mediated asymmetric esterification[16] of **12** and asymmetric hydrolysis of **14** hardly proceeded to yield the expected alcohol (**12**) or acetate (**14**) with higher ee than the starting materials. In all cases, the starting **12** or **14** was completely recovered. These results indicated that **12** and **14** exist in the *cis*-orientation between the hydroxy group at C-1 and methyl group at C-9a and were unsuitable substrates for the lipases (Scheme 4).

We next focused on the oxygen functionality at C-7. The optical purities were determined using HPLC, so a benzoyl group was introduced to the major alcohol (**12**) as a UV chromophore. Sodium borohydride reduction of **15** in methanol afforded a diastereomeric mixture of **16** and **17** in a 75:25 ratio, which were readily separated by silica gel column chromatography. Acetylations of the obtained alcohols (**16**) and (**17**) using a typical method yielded the corresponding acetates (**18**) and (**19**), respectively (Scheme 5). NOE correlations of **19**, shown in Figure 2, indicated that the angular methyl at C-9a and the acetoxy group at C-7 existed in a *trans*-orientation. Therefore, the other diastereomeric acetate (**18**) must exist in the *cis*- configuration.



Scheme 4



Scheme 5

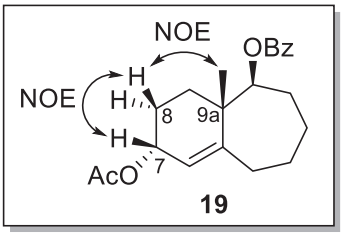
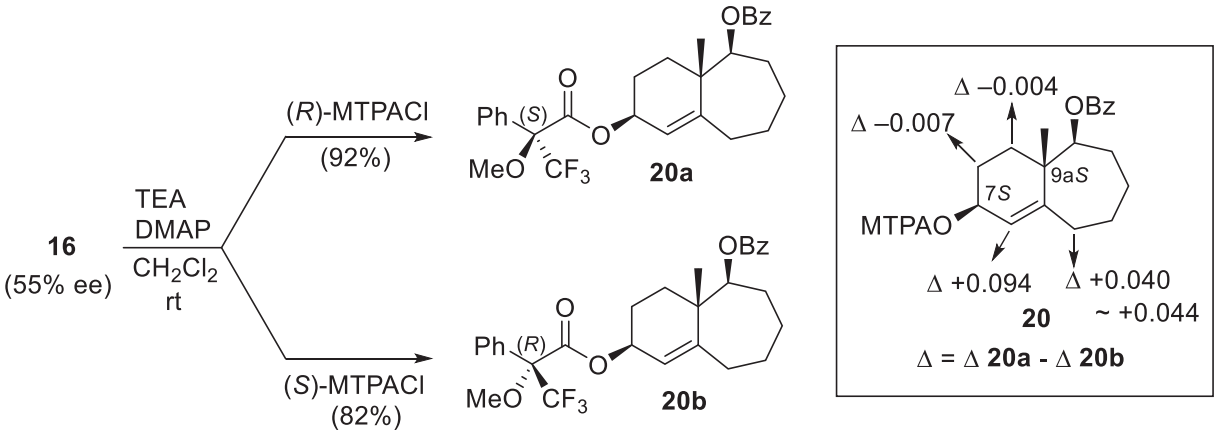


Figure 2

The absolute configuration of **16** was determined using Mosher's ester method.[17] Mosher's esters (**20a**) and (**20b**) were synthesized from **16** using (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride. The difference values (δ = δ**20a** - δ**20b**) of the chemical shifts in the ^{1}H-NMR spectra are shown in Scheme 6. We observed high field shifts of the protons on C-8 and C-9 and low field shifts

of the protons on C-5 and C-6. These results strongly indicated that the absolute configuration at C-7 was *S*. Because the relative configuration between the hydroxy group at C-7 and angular methyl at C-9a was *cis* (*vide supra*), the absolute configuration at C-9a must be *S*. This indicated that the aldol reaction of entry 6 in Table 1 afforded (*S*)-**3**.



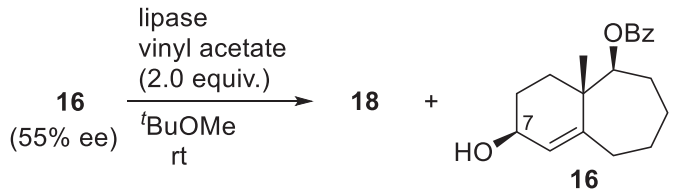
Scheme 6

The lipase-mediated asymmetric esterification of **16** was subsequently examined to increase the obtained optical purities. All reactions were performed in *tert*-butyl methyl ether (^{t}BuOMe) in the presence of 2.0 equiv. of vinyl acetate, and the obtained results are summarized in Table 3. All reactions afforded the acetate (**18**) with higher ee than the starting **16**. Especially, lipase AS was effective for increasing the optical purity and affording **18** with high ee (entry 4). In all reactions, the major enantiomer of the unreacted **16** remained in the same 7*S* configuration as the starting **16**, but with a lower ee. This indicated that enantioselectivity of lipase at C-7 was not high. However, these results revealed that the obtained (*S*)-**3** can be used a chiral synthon despite of its moderate ee, because it was possible to increase optical purity at a later synthetic stage.

Finally, we clarified the relationship between the absolute configurations, optical rotations, and HPLC retention times of both enantiomers of **3** and the obtained results are summarized in Table 4. It was observed that (*S*)-**3**, prepared from entry 6 in Table 1, exhibited similar optical rotations (*dextrorotatory*), and similar HPLC retention times on a OB-H column (entry 2) as entry 1, which was reported in Ref. 12a. However, the retention times of (*R*)- and (*S*)-**3** on the HPLC equipped with AS-H were different from those reported in Ref. 12b (entry 4 vs 5). Thus, we observed short retention time for (*R*)-**3** and long retention time for (*S*)-**3**, opposite to that of entry 5. Because the optical rotation data for (*R*)-**3** was not reported in Ref. 12b or 12c, we prepared (*R*)-**3** according to Xu's method. The obtained (*R*)-**3**, which exhibited slightly lower ee than that previously reported, exhibited similar retention times for (*R*)- and (*S*)-**3** as entry 4 (entry 6). Additionally, (*R*)-**3** was *levorotatory* and the absolute values of $[\alpha]_D$ between

(*R*)- and (*S*)-**3** were similar. Therefore, the behaviors of (*R*)- and (*S*)-**3** on HPLC with AS-H (entries 4 and 6), were reliable and it was clear that (*S*)-(+)-**3** was obtained from the asymmetric aldol reactions.

Table 3. Lipase-mediated asymmetric eaterifications of **16**



Entry[a]	Lipase[b]	Time (h)	18		16	
			Yield[g]	Ee[h i]	Yield[g]	Ee[h i]
1	AK[c]	61.5	19	75 (7*S*)	76	50 (7*S*)
2	PS-D[d]	7	53	73 (7*S*)	42	52 (7*S*)
3	AYS[e]	22.5	33	82 (7*S*)	54	39 (7*S*)
4	AS[f]	68	23	88 (7*S*)	76	45 (7*S*)

[a] 50 mg of **16** was used for all reactions.
[b] All lipases were commercially available from Amano Pharmaceutical Co., LTD.
[c] *Pseudomonas fluorescens*.
[d] *Pseudomonas cepacia* (immobilized on ceramic).
[e] *Candida rugosa*.
[f] *Aspergillus niger*.
[g] Isolated yield.
[h] Determined using an HPLC equipped with a chiral stationary phase column.
[i] Absolute configuration at C-7 of the major enantiomer was shown in parentheses.

Table 4. The relations of (*R*)- and (*S*)-**3** among absolute configurations, optical rotations, and HPLC retention times

Entry	Compound (ee)	$[\alpha]_D$[a] (in $CHCl_3$)	Column[b]	Eluent (v/v)	*Rt* (*R*, min)	*Rt* (*S*, min)
1[c]	(*S*)-**3** (8)	+7.9	OB	hexane: 2-propanol = 96:4[d]	27.7	23.7
2			OB-H	hexane: 2-propanol = 96:4[f]	40.7	27.8
3	(*S*)-**3**[e] (55)	+49.7	OJ-H	hexane: 2-propanol = 9:1[f]	15.2	17.3
4			AS-H	hexane: ethanol = 9:1[f]	37.0	42.5
5[g]	(*R*)-**3** (53)	NR[h]	AS-H	hexane: ethanol = 9:1[f]	37.0	34.4
6	(*R*)-**3**[i] (51)	−47.2	AS-H	hexane: ethanol = 9:1[f]	36.7	44.2

[a] The observed $[\alpha]_D$ accompanied with the corresponding enantiomeric excess.
[b] All of chiral stationary phase columns were commercially available as CHIRALCEL® or

CHIRALPAK® from Daicel Co., LTD.

[c] Data from Ref. 12a.

[d] Flow rate of 0.5 mL/min.

[e] Obtained *via* aldol reaction of entry 6 in Table 1.

[f] Flow rate of 1.0 mL/min.

[g] Data from Ref. 12b.

[h] Not reported.

[i] Obtained using the same method as in Ref. 12c.

In conclusion, we established a novel chiral route to provide a Swaminathan ketone (**3**) bearing a 7-membered ring *via* intramolecular aldol reaction of trione (**7**) mediated by chiral amines bearing a pyrrolidine. Although the enantioselectivity of **3** was moderate, we successfully increased the optical purities by using a lipase-mediated asymmetric esterification of alcohol (**16**) at a later synthetic stage. The absolute configuration was determined by Mosher's ester method, and the relationship between absolute configuration and optical rotation of **3** was determined. Further studies regarding the detailed reaction mechanism and development of a more efficient mediator for the reactions is currently in progress.

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