Asymmetric Acetalization: A Simple Method for the Synthesis of Chiral α-Monosubstituted Cyclopentanones

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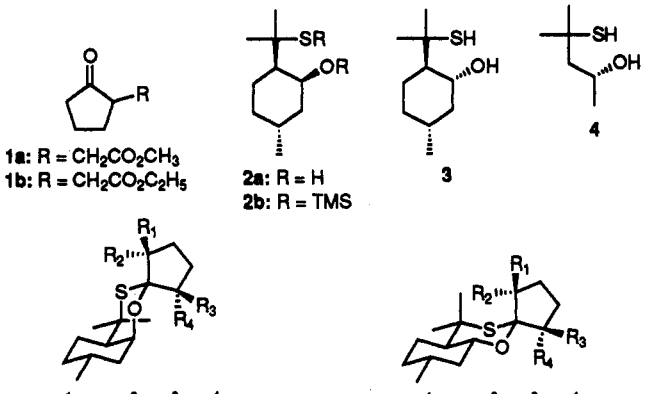
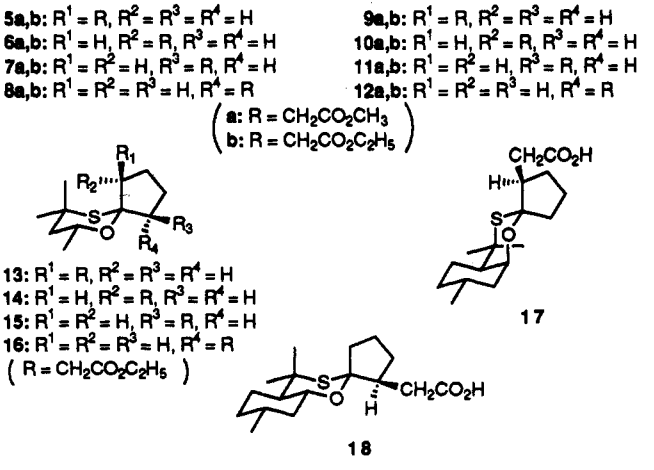
Summary: Acetalization of α-monosubstituted cyclopentanones with chiral hydroxy thiols under equilibrating conditions afforded a mixture of acetals in a highly diastereoselective manner, and deacetalization of the product affords optically active α-monosubstituted cyclopentanones.

Acetal formation of α-monosubstituted cyclopentanones proceeds with racemization under the standard acidic conditions.[4] If a chiral reagent is employed for the acetalization, a mixture of acetal diastereomers would be obtained and the diastereoselectivity should be governed by relative thermodynamic stabilities of the diastereomers. Therefore, a two-step procedure such as asymmetric acetalization using a chiral reagent followed by deacetalization without racemization might be a convenient method for the preparation of chiral α-substituted cyclopentanones (Scheme I). Here, we report that hydroxy thiols **2a** and **3**[5] are such reagents for asymmetric acetalization.





Acetalization of methyl (2-oxocyclopentyl)acetate, **1a**, with hydroxy thiol, **2a** under standard conditions (*p*-toluenesulfonic acid, benzene, reflux) afforded a separable mixture of two acetals among the four possible diastereomers **5a–8a** (Table I). Spectroscopic analysis showed the products to be **5a** and **6a** in a ratio of 9:1.[6] Ester hydrolysis of the products afforded a mixture of carboxylic acids which could be purified by recrystallization. The major diastereomer, **17**, was thus isolated in an optically pure form, and the structure was confirmed by X-ray analysis (Figure 1).[7]

Kinetic acetalization of **1a** using **2b** in the presence of trimethylsilyl trifluoromethanesulfonate[8] at room temperature afforded **5a** and **6a** in a ratio of 2:1. Acid-

Scheme I

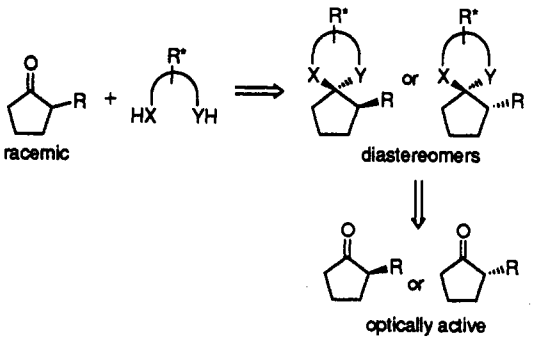


Table I. Diastereoselective Acetal Formation Using Chiral Hydroxy Thiols

run	substrate (1)	hydroxy thiol	condns[a]	time (h)	yield (%)	diast ratio
1	**1a**	**2a**	A	5.3	90	**5a:6a** = 9:1
2	**1b**	**2a**	A	5.3	90	**5b:6b** = 9:1
3	**1a**	**2b**	B	96	90	**5a:6a** = 2:1
4	**1a**	**3**	A	2.5	84	**11a:12a** = 7:1
5	**1b**	**3**	A	2.5	100	**11b:12b** = 7:1
6	**1b**	**4**	A	3	70	**15:16** = 5.8:1

[a] Conditions: (A) a benzene solution of 1 and hydroxy thiol was refluxed with a catalytic amount of *p*-toluenesulfonic acid; (B) a dichloromethane solution of **1b** and **2b** was stirred at room temperature with a catalytic amount of trimethylsilyl trifluoromethanesulfonate.

(1) Hokkaido University.
(2) Hokkaido Institute of Pharmaceutical Sciences.
(3) Kitasato University.
(4) Hashimoto, S.; Shinoda, T.; Shibata, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637.
(5) Both **2a** and **3** were prepared from (+)-pulegone: Eliel, E. L.; Lynch, J. E. *Tetrahedron Lett.* **1981**, *22*, 2855. Utilization of **2a** and **3** as a chiral auxiliary. See: Eliel, E. L. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press, New York, 1983; Vol. 2, Part A, p 125.
(6) All new compounds exhibited acceptable ^{1}H-NMR, ^{13}C-NMR, IR, MS, and HRMS spectral data.
(7) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
(8) Tsunoda, T.; Suzuki, M; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

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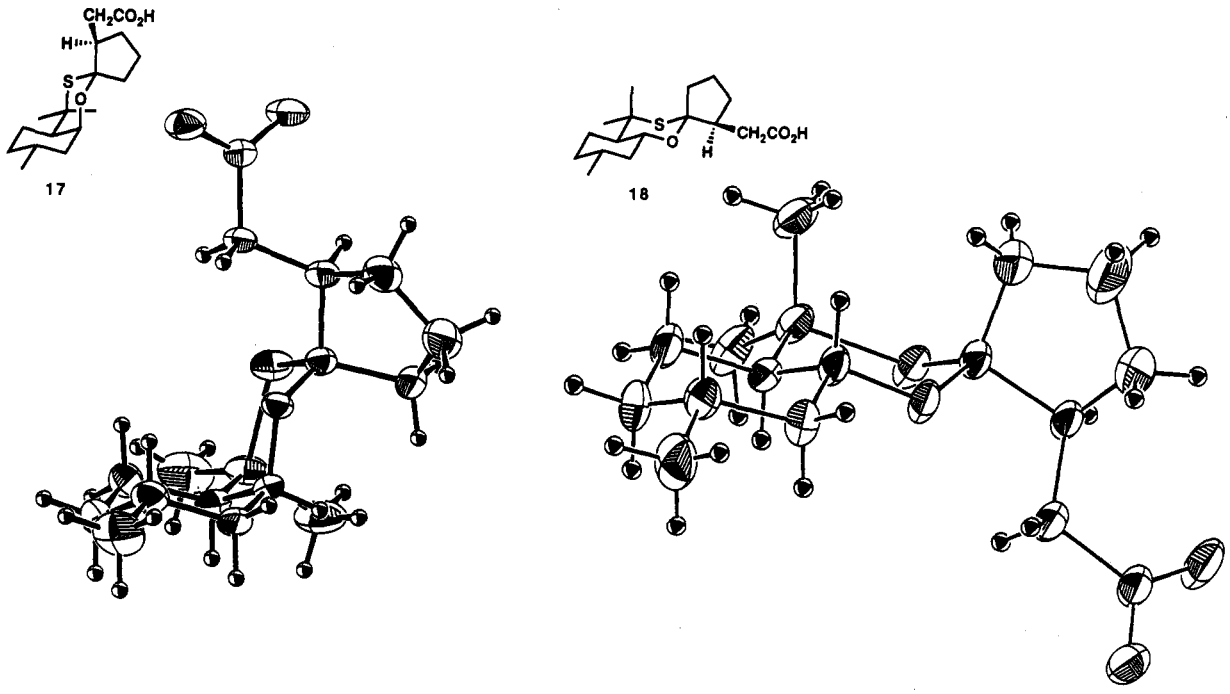
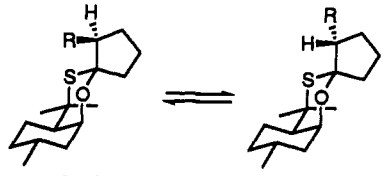


Figure 1. Molecular Structures of 17 and 18.

Table II. Effect of Side-Chain Structure on the Ratio of 5 and 6



5c-f 6c-f

	R	5:6
c	CH_3	6:1
d	CH_2OCH_2Ph	8:1
e	$CH_2CO_2(iPr)$	9:1
f	$CH_2CO_2(cHex)$	11:1

catalyzed equilibration of this mixture (0.2 equiv of trifluoromethanesulfonic acid, CH_2Cl_2, room temperature, 100% recovery) altered the diastereomeric ratio to 9:1 in favor of **5a**. The reaction of ethyl (2-oxocyclopentyl)-acetate, **1b**, also showed similar selectivity.

The reaction between hydroxy thiol **3** and **1a** afforded a mixture of **11a** and **12a** in a ratio of 7:1. The mixture, when treated with aqueous base, affords the acid **18** which is purified by recrystallization and characterized by spectroscopic and X-ray analysis (Figure 1).[7] The newly created asymmetric tertiary carbon center on the cyclopentane ring of **11a** was opposite to that of **5a**. Even the simpler chiral hydroxy thiol **4**[9] was nearly as effective as that for **3**. However, no asymmetric induction was observed using several chiral diols such as (*2R,3R*)-2,3-butanediol, (*R*)-1,3-butanediol, and (*2R,4R*)-2,4-pentanediol.

Table III. Computed Heat of Formation of Acetal Diastereomers

structure	ΔH_f (kcal/mol)	$\Delta\Delta H_f$[a]
5b	−148.0026	0*
6b	−147.6794	0.32*
7b	−145.9112	2.09
8b	−145.4484	2.55
9b	−144.9678	4.55
10b	−144.1562	5.36
11b	−149.5174	0*
12b	−149.0957	0.42*
13	−144.0769	2.51
14	−143.6759	2.91
15	−146.5888	0*
16	−146.1428	0.45*

[a] * indicated observed diastereomer.

Equilibration experiments between **5c–f** and **6c–f** revealed that the bulkiness of the side chain on the cyclopentane ring affects the ratio of the diastereomeric mixture (Table II).[10]

The observed tendency of the thermodynamic stabilities in a series of diastereomers was qualitatively simulated by comparison of their heats of formation calculated using the MNDO method[11] (Table III).

While the hydrolysis of dithianes or oxathianes may sometimes be difficult, in our hands, the best results were obtained using NCS and $AgNO_3$ in the presence of a large excess of 2,4,6-collidine in aqueous acetone at −20 °C.[12] Hydrolysis of **5a** and **11a** afforded (+)-(*R*)-**1a** (55%) and (−)-(*S*)-**1a** (75%), respectively, in an optically pure form.[13]

This procedure was successfully applied to the synthesis of optically active (*R*)-5-hexadecanolide, (*R*)-**19**, which has been reported to be a pheromone of the oriental hornet, *Vespa orientalis*[14] (Scheme II). When racemic 2-undecylcyclopentanone, racemic-**20**,[15] was treated with **3** (cat.

(9) Prepared from (*R*)-2-methyl-2,4-pentanediol: (1) trifluoroacetic acid, benzylmercaptan, (2) $NaBH_4$, (3) Na, liquid NH_3. Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1615.

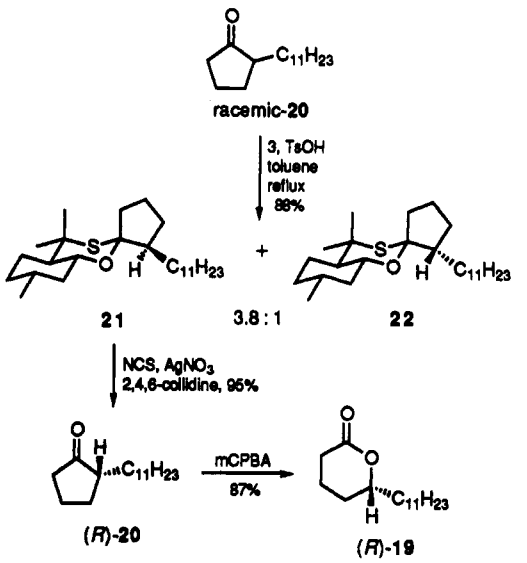
(10) Equilibrating conditions: a mixture of **5** and **6** was treated with 0.2 equiv of trifluoromethanesulfonic acid in CH_2Cl_2 at room temperature for 20 min, and the ratio was determined by ^{1}H-NMR. Mixtures of **5c,e,f** and **6c,e,f** were prepared by the acetalization of the corresponding cyclopentanones with **2**, and the mixtures were subjected to equilibration, respectively (**5c,6c**: 78%; **5e,6e**: 57%; **5f,6f**: 77%). A mixture of **5d** and **6d** was prepared from a mixture of **5a** and **6a** (LAH reduction followed by benzylation, 90%), and the mixture was equilibriated (100% recovery).

(11) Cooling, M. B.; Stewart, J. J. P. MOPAC version 6.0, QCPE 45. Neither the PM3 nor the AM1 method simulated the results correctly.

(12) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.

(13) Determined by ^{1}H-NMR analysis in the presence of Eu(hfc)$_3$ [tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium-(III) derivative]. Less than 2% of racemization was observed.

Scheme II



TsOH, toluene reflux), an easily separable mixture of two diastereomers was obtained in 88% yield (21:22 = 3.8:1). The major isomer, **21**, was converted to (*R*)-**20**[16] which was oxidized by *m*-CPBA to (*R*)-**19**, $[\alpha]^{18}_{D}$= +38.0° (*c* 0.79, THF) [lit.[14d] $[\alpha]^{21.5}_{D}$= +40.2° (*c* 1.76, THF)].[17]

In conclusion, the asymmetric acetalization–deacetalization method using chiral hydroxy thiols is a convenient method for the preparation of chiral α-monosubstituted cyclopentanones from racemic ketones.[18] Further studies on the origin of the diastereoselectivity and on applications toward other natural products synthesis are underway.

Acknowledgment. We wish to thank Drs. Kiyoshi Kondo and Takamasa Fuchikami of Sagami Chemical Research Center for their assistance of MNDO calculations and valuable discussions.

Supplementary Material Available: Experimental procedures for the synthesis of (*R*)-**19** and (*S*)-**19** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Previous synthesis of this pheromone: (a) Bund, J.; Gais, H.-J.; Erdelmeier, I. *J. Am. Chem. Soc.* **1991**, *113*, 1442. (b) Mori, K. *Tetrahedron* **1989**, *45*, 3233. (c) Mori, A.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 5444. (d) Mori, K.; Otsuka, T. *Tetrahedron* **1985**, *41*, 547.

(15) The synthetic procedure employed for (*R*)-**19**, except for the asymmetric acetalization step, was identical to the procedure in ref 14c.

(16) The reaction was carried out at 0 °C in aqueous acetonitrile.

(17) (*S*)-**19** was also prepared in three steps (40% overall); acetalization using **2a** (diastereomer ratio 4.8:1), deacetalization, and *m*-CPBA oxidation, $[\alpha]^{18}_{D}$ = −40.2° (*c* 0.76, THF).

(18) Much lower selectivity was observed when α-monosubstituted cyclohexanones were subjected to these acetalization conditions. The results will be published in a full description of this work.