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Enzymatic kinetic resolution studies of racemic 4-hydroxycyclopent-2-en-1-one using Lipozyme IM®

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Abstract

Enzymatic kinetic resolution studies of (±)-4-hydroxycyclopent-2-en-1-one **2** were taken up in organic solvents by transesterification with vinyl acetate and alcoholysis of its acetate **3** as an alternative to the desymmetrization of *meso*-cyclopentenediol to provide faster and economic access to enantiomerically pure 4-(*R*)-*tert*-butyldimethylsilyloxycyclopent-2-en-1-one **1**. Parameters were screened using Lipozyme IM® as catalyst. Although enantioselectivity observed was moderate (E=24, by alcoholysis of **3** with 2-butanol), trends in the effect of solvent, water content and alcohol structure showed useful directions for screening of other enzymes for optimization of the method to useful levels of efficiency.

1. Introduction

The importance of 4-(*R*)-*tert*-butyldimethylsilyloxycyclopent-2-en-1-one **1** in the synthesis of cyclopentanoid natural products (prostaglandins, prostacyclins, thromboxane and nucleosides)[1–4] has attracted the attention of chemists and has resulted in development of various methods for its preparation, viz.: (i) desymmetrization of *meso*-cyclopentenediol or *meso*-cyclopent-2-endiacetate using lipases and followed by chemical conversion;[5–7] (ii) classical resolution of racemic 4-hydroxycyclopent-2-en-1-one **2** by forming diastereomers with enantiomerically pure caronaldehyde followed by separation;[8] (iii) kinetic resolution of **2** using lipases[9] and chiral catalyst;[10] and (iv) synthesis from D-tartaric acid.[11] Even though a substantial amount of literature is available on the subject, since there is increasing demand for prostaglandins and their intermediates due to their varied biological activities, development of cost effective methods for their large-scale preparation has been the major goal for our group.

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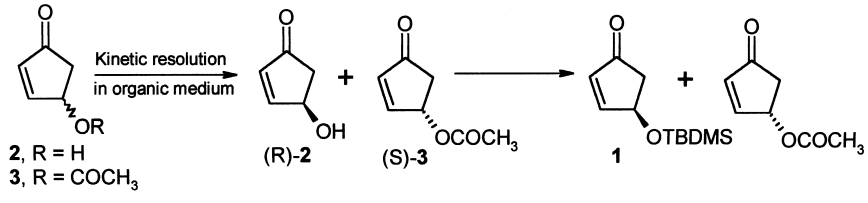
Desymmetrization methods are an attractive and extensively studied (including two methods developed by our group[5b,6j]) approach for the production of **1** since a 100% yield of one of the enantiomers can be obtained theoretically whereas kinetic resolution suffers from the drawback of throwing away half of the material, i.e. the unwanted isomer. But for the large-scale production, the desymmetrization method becomes costly because preparation of the required *meso*-cyclopentene derivatives involves either expensive and sensitive Pd(0) complexes as catalysts[12] or photochemical reactions[13] wherein yields are low and scale-up is difficult. In addition, the method involves three to five additional chemical steps wherein *tert*-butyldimethylsilyl chloride, which is a major cost component, is used at an early stage of the synthesis.[7] Comparatively, direct resolution of racemic 4-hydroxycyclopentenone **2** would be an attractive alternative as the large-scale preparation of **2** is easier.[14] We have already scaled up the process using furfuryl alcohol to 3 kg scale. Also, there are literature reports wherein (*S*)-**2** has been inverted to (*R*)-**2** by simple chemical steps.[15] This resolved (*R*)-**2** can then be directly converted to **1** using expensive *tert*-butyldimethylsilyl chloride as the silylating agent at the last step, saving on the cost. The classical resolution approach involving caronaldehyde as the resolving agent is discouraging on the large scale due to the exorbitant high cost of caronaldehyde. Another successful approach involves kinetic resolution by enantioselective hydrogenation using chiral catalyst developed by Noyori et al.[10] Although lipase-catalyzed resolution of (±)-**2** would be an economical approach, very few reports are available on the lipase-catalyzed kinetic resolution by hydrolysis of (±)-**3** in aqueous media. The limiting factors of the approach are mainly: (i) high solubility of **2** in aqueous medium makes its isolation tedious, and requires continuous extraction with ethyl acetate for 3 days; and (ii) possibility of racemization in aqueous media which would deteriorate enantiopurity at least to some extent. Winterfeldt et al. have overcome the problem of racemization by derivatizing (±)-**2** to a cyclic ketal prior to resolution.[9b] But this protection step is very tricky and low yielding, hence not suitable to scale-up. These problems can be circumvented by the judicious use of organic solvents for the conversion. But to our knowledge such an attempt is not reported. Therefore, we decided to study the lipase-catalyzed kinetic resolution of **2** and **3** in organic solvents. Herein we report our preliminary results on: (i) Lipozyme IM®-catalyzed irreversible transesterification of (±)-**2** in organic solvents; and (ii) Lipozyme IM®-catalyzed alcoholysis of (±)-**3** in organic solvents.



2. Results and discussions

2.1. Transesterification of (±)-2 with vinyl acetate catalyzed by Lipozyme IM®

Transesterification of (±)-**2** was attempted using vinyl acetate as acyl donor and lipozyme IM® as catalyst (Table 1). Since the enantioselectivity of the enzyme is higher at lower temperatures, reactions were carried out at 12°C. The initial experiment in dry diisopropyl ether (DIPE) exhibited high reaction rates (80% conversion (c) in 4 h) but the enantioselectivity of the reaction was rather poor (E=4, entry no. 1, Table 1).

Since an intrinsic water content (more precisely, the water activity, a_w) as low as 1% is reported to

Table 1
Transesterification of (±)-4-hydroxycyclopentenone **2** with vinyl acetate catalyzed by Lipozyme IM® in various solvents at 12°C[a]

No	Acyl donor	Solvent	Water content %	Time hr	c %	$[\alpha]_D$ of **1**[b]	ee of **1** ee_s %	$[\alpha]_D$ of **3**[c] %	ee of **3** % ee_p	E
1.	Vinyl acetate	DIPE	-	4	80.0	+59.4	89.2	-22.2	22.2	4
2.	,,	DIPE	1	19	28.0	+20.5	30.8	-78.2	78.2	11
3.	,,	TBME	1	11	46.5	+33.0	49.5	-56.9	56.9	6
4.	,,	Dibutyl ether	1	11	17.0	+0.9	1.3	-75.0	75.0	7
5.	,,	Toluene	1	16	22.9	+11.2	16.9	-56.8	56.8	4
6.	Isopropenyl acetate	DIPE	-	7	39.2	+30.0	45.0	-29.0	29.0	3
7.	,,	DIPE	1	7	only	traces	of	product	-	-
8.	,,	-	-	7	,,	,,	,,	,,	-	-
9.	Ethyl acetate	-	-	7	No	reaction	-	-	-	-
10.	Isopropyl acetate	-	-	7	No	reaction	-	-	-	-
11.	Trichloro-ethyl acetate	DIPE	-	7	No	reaction	-	-	-	-

a: 2 mmol of **2** were reacted with 5 equi. of acyl donor in 10 mL solvent b: rotations in methanol Lit[10] (R)-enantiomer, $[\alpha]_D$ = +66.3 (c 1, methanol), c: rotations in methanol, Lit[9] (R)-enantiomer $[\alpha]_D$ = +100 (c 2.9, methanol)

be beneficial for enzyme selectivity in several cases,[16] the conversion was attempted in diisopropyl ether containing 1% water. Now the reaction rate was much slower (c=28% in 19 h, entry no. 2, Table 1), the enantioselectivity improved significantly (E=11) by 2.8 times. Such kinds of beneficial effects of water content were reported previously in a few cases; the reason, though not very clear, was attributed to an increase in enzyme flexibility by added water in a dry system. The reaction was attempted in a few other solvents containing 1% water (entry nos. 3–5, Table 1), but an E value of more than 11 could not be achieved.

The effect of an acyl donor on the enantioselectivity of lipase-catalyzed transesterification reaction has been well demonstrated by Ema et al.[17] Therefore, we tested a few other acyl donors for the conversion. With isopropenyl acetate the enantioselectivity as well as rate of reaction were poor (c=39.2% in 1 week, E=3, entry 6, Table 1). Addition of 1% water did not prove to be beneficial, but rather inhibited reaction. Reaction did not proceed with acyl donors such as isopropyl acetate, ethyl acetate, etc. (Table 1).

Thus, the enantiodiscrimination in kinetic resolution of (±)-**2** with vinyl acetate using Lipozyme IM® as catalyst was not satisfactory. The highest value of enantiomeric ratio obtained was 11 which is not

Table 2
Preliminary screening of various alcohols in different solvents at 12°C for the alcoholysis of (±)-4-oxocyclopenten-2-yl acetate **3**

No	Alcohol	Solvent	Time hr	c %	$[\alpha]_D$ of **1**	ee of **1** % ee_p	$[\alpha]_D$ of **3**	ee of **3** % ee_s	E
1.	1-Butanol	Toluene	10	51.2	-25.0	37.7	+39.6	39.6	3
2.	Isobutyl alcohol	Toluene	17	45.0	-32.4	48.8	+40.0	40.0	4
3.	t-Butyl alcohol	Toluene	14	42.6	-31.1	54.6	+40.5	40.5	5
4.	Methanol	Toluene	19	20.5	-30.3	45.7	+11.8	11.8	3
5.	2-propanol	Toluene	45	29.3	-30.8	46.3	+19.2	19.2	3
6.	2-propanol	DIPE	15	31.5	-35.5	53.5	+22.5	22.5	6
7.	2-propanol	MIBK	15	42.5	-32.6	49.0	+36.2	36.2	4
8.	Isoamyl alcohol	Toluene	16	50.8	-25.0	37.7	+39.0	39.0	3
9.	Benzyl alcohol	Toluene	6	46.0	-35.0	52.8	+45.0	45.0	5
10.	Cyclohexanol	Toluene	6	35.2	-25.0	37.7	+20.5	20.5	3

good enough for practical purposes. Therefore, the resolution of (±)-**3** was planned by alcoholysis with different alcohols in organic solvents using Lipozyme IM®.

*2.2. Alcoholysis of (±)-4-oxocyclopenten-2-yl acetate **3***

Alcoholysis of **3** was attempted initially in toluene using various alcohols (Table 2).

The rates of the alcoholysis reactions were good enough, but the enantioselectivity was not satisfactory (E=3–5). Among all alcohols investigated, 2-propanol, which is a moderately hindered secondary alcohol, reacted much more slowly (c=29.3% in 45 h, entry 5, Table 2) in toluene, but when DIPE and methyl isobutyl ketone (MIBK) were used as solvents, reaction rates improved considerably (c=31.5% in 15 h and c=42.5% in 15 h, resp., entries 6 and 7, Table 2) with some improvement in enantioselectivity (E=6 and 4, resp.).

We observed that when 2-propanol containing some water was used for alcoholysis, the rate improved considerably with some improvement in the E ratio as compared to the anhydrous reaction. Subsequently, the effect of water content was studied in DIPE using 2-propanol for alcoholysis (Table 3). A water content of 1% was found to enhance the reaction rates as well as the enantioselectivity considerably. Thus, 37.3% conversion was achieved with an E value of 17 (entry 3, Table 3), i.e. a 3-fold increase in enantioselectivity at 1% water content. To study further the water effect, several reactions were conducted using different alcohols in different solvents containing 1% water (Table 4). For 2-propanol reaction (entries 5 and 7, Table 4), enantioselectivity was maximum in DIPE (E=17) and dibutyl ether (DBE) (E=19). Beneficial effects of water were observed with most other alcohols.

Enantioselectivity is found to be associated with the alcohol structure. Thus, an E value of >10 was

Table 3
Effect of water content on the alcoholysis of (±)-4-oxocyclopenten-2-yl acetate **3** by 2-propanol catalyzed by Lipozyme IM® in diisopropyl ether at 12°C

No	Water content (%)	Time (hr)	C (%)	$[\alpha]_D$ of **1**	ee of **1** (%) ee_p	$[\alpha]_D$ of **3**	ee of **3** (%) ee_s	E
1	-	12	25.0	-34.1	51.3	+17.3	17.3	4
2	0.80	12	41.4	-46.1	69.2	+48.9	48.9	9
3	1	12	37.3	-55.1	82.7	+49.5	49.5	17
4	1.25	12	39.4	-43.9	65.9	+42.9	42.8	7
5	1.43	12	39.4	-47.2	70.9	+46.1	46.1	9

Table 4
Alcoholysis of (±)-4-oxocyclopenten-2-yl acetate **3** with various alcohols in different organic solvents containing 1% water at 12°C

No	Alcohol	Solvent	Time (hr)	C (%)	$[\alpha]_D$ of **1**	ee of **1** ee_p (%)	$[\alpha]_D$ of **3**	ee of **3** ee_s (%)	E
1.	Isobutyl alcohol	DIPE	12	49.2	-44.3	66.7	+64.5	64.5	9
2.	t-Butyl alcohol	DIPE	12	45.1	-45.6	68.6	+56.4	56.4	9
3.	Methanol	Toluene	24	very	slow	reacn	-	-	-
4.	2-Propanol	Toluene	24	33.0	-42.1	63.2	+31.3	31.3	6
5.	2-Propanol	DIPE	12	37.0	-55.1	82.7	+49.5	49.3	17
6.	2-Propanol	TBME	16	35.0	46.2	69.4	+37.4	37.0	10
7.	2-Propanol	DBE	12	39.8	-55.5	83.3	+55.0	55.0	19
8.	2-Propanol	Ether	18	18.6	-51.0	76.6	+17.5	17.5	9
9.	2-Butanol	DIPE	12	43.3	-56.8	85.2	+65.0	65.0	24
10.	4-Methyl-2-pentanol	DIPE	12	46.5	-50.6	76.0	+66.1	66.0	14
11.	2-Pentanol	DIPE	12	43.0	-50.4	75.7	+5.7	57.0	13
12.	3-Pentanol	DIPE	18	47.6	51.8	77.8	+70.6	70.0	17

observed with all secondary alcohols, 2-butanol (entry 9, Table 4) showing the best results (E=24). Such kinds of influence of alcohol structure on the enantioselectivity of enzymes during alcoholysis are somewhat analogous to the effect of the structure of the acyl donor on enzyme enantioselectivity in transesterification reactions studied by Ema et al.[17] Thus, moderate steric hindrance provided by 2-butanol is most suitable for the enzyme active site during the reaction, giving the highest enantiodiscrimination. Further decrease or increase in the hindrance by addition or deletion of -CH_3 groups deteriorates the enantiodiscrimination in the case studied. With an E value of approx. 25 substrate of >95% ee can be obtained at 60% conversion whereas product of 85% ee can be obtained near 40% conversion (vide infra Eq. 1 and Adachi et al.[18]).

3. Conclusion

We could resolve (±)-**2** in moderate enantioselectivity (E=24) by alcoholysis of its acetate (±)-**3** in organic solvents using commercially available enzyme Lipozyme IM®. Our study demonstrates strong effects of solvent, alcohol structure and water content on the enzymatic alcoholysis reaction in organic media. Even though the enantioselectivity obtained is not very high, this study has set the guidelines for further optimization work. Currently we are investigating some other commercial lipases and in-house cultures from the National Collection of Industrial Microorganisms, NCL, Pune for the conversion to achieve high enantioselectivity and to get the (*R*)-enantiomer **1** in high enantiomeric excess. We hope that this methodology would provide a more economic alternative to the desymmetrization method for the large-scale production of **1**.

4. Experimental

4.1. General

Optical rotations were recorded on a Jasco Dip-181 digital polarimeter using sodium vapor lamp. Enantiomeric excesses (ee) were determined by comparing the specific rotation value $[\alpha]_D$ with the literature value. All reagents were purchased from Aldrich and were used without further purification. Solvents used were of LR quality and were dried before use by standard methods. Lipozyme IM® was obtained as a gift sample from Arun & Co., Mumbai. Enantiomeric ratio E was calculated using the following formula (Eq. 1),[18] where c, ee_s and ee_p are conversion, enantiomeric excess of substrate and enantiomeric excess of product, respectively.

$$E = \frac{(1 - c)(1 - ee_s)}{(1 - c)(1 + ee_s)} \tag{1}$$

$$\text{conversion}: \; c = \frac{ee_s}{ee_s + ee_p}$$

4.2. Typical laboratory procedure for preparation of (±)-4-hydroxycyclopent-2-en-1-one **2**

A 3 L three-necked round bottomed flask, equipped with long air condenser, thermometer pocket and a bubbler, was charged with furfuryl alcohol (25 g, 0.255 mol), potassium dihydrogen orthophosphate (6.3 g, 0.022 mol) and distilled water (1.5 L). The reaction mixture was purged with a slow stream of nitrogen along with magnetic stirring. It was heated to 95°C for 48 h while maintaining effective stirring and

nitrogen purge. The solution developed brownish insoluble impurities during reaction. It was cooled to room temperature and then washed twice with ethyl acetate. The aqueous layer was concentrated almost to dryness under reduced pressure. The residue was then thoroughly extracted with ethyl acetate. The combined organic extracts were then dried on anhydrous sodium sulfate and concentrated under vacuum. The residue was distilled under high vacuum using a fractionating column. Product **2** was obtained as a lemon yellow colored liquid distilling at 95–100°C at 0.5 mm vacuum. Yield=10 g (40%). Compound **2** was stored in a refrigerator (ca. −5°C).

*4.3. Typical laboratory procedure for preparation of (±)-4-oxocyclopenten-2-yl acetate **3***

Into a 100 mL two-necked round bottomed flask equipped with a two-way stopcock and a dropping funnel (±)-**2** (5 g, 51 mmol) was placed. The assembly was evacuated and flushed with argon. Dry dichloromethane (50 mL) was added and the solution was cooled below 0°C using an ice-salt bath along with magnetic stirring. To the cold solution dry pyridine (7.9 g, 0.1 mol) was added and stirred at 0°C for 10 min. To the stirred solution, acetic anhydride (7.8 g, 76.5 mmol) was added dropwise while maintaining the temperature below 0°C. The reaction mixture was stirred at room temperature for 15 h, then quenched by adding cold, dilute hydrochloric acid. The organic layer was washed four times with a 1:4 mixture of brine and dilute hydrochloric acid, followed by washing with cold water, 10% sodium bicarbonate solution and finally with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was distilled under high vacuum. Product **3** was obtained as a colorless liquid (b.p. 59–61°C at 0.2 mm vacuum) which solidified as colorless crystals on cooling. Yield=5.71 g (80%).

4.4. General procedure for enzymatic transesterification of (±)-2

Compound (±)-**2** (1.5 mmol, 0.150 g) was stirred with 5 equiv. acyl donor and Lipozyme IM® (0.3 g) in 10 mL organic solvent at 12°C. The reaction was monitored by TLC. At sufficient conversion the reaction mixture was filtered, dried on anhydrous sodium sulfate and the solvent was removed under vacuum. The residue was treated with *tert*-butyldimethylsilyl chloride (1.5 mmol, 0.225 g), *p*-dimethylaminopyridine (0.15 mmol, 0.018 g) and triethylamine (2 mmol, 0.2 g, 0.28 mL) under an argon atmosphere in dry dichloromethane at 0°C. The reaction mixture was stirred at room temperature for a further 3 h. It was then washed with cold dil. hydrochloric acid followed by a water wash, bicarbonate wash and finally a brine wash. Organic layer was dried on sodium sulfate and solvent was removed under vacuum. This derivatized residue contained OTBDMS derivative **1** and acetate **3**. These were separated on a silica gel column using pet. ether and ethyl acetate (gradient elution).

4.5. General procedure for enzymatic alcoholysis of (±)-3

Compound (±)-**3** (1.5 mmol, 0.2 g) was stirred with 5 equiv. alcohol and Lipozyme IM® (0.3 g) in 10 mL organic solvent at 12°C. The progress of reaction was monitored by TLC. At sufficient conversion the reaction mixture was filtered, the solvent was removed under vacuum and the residue was treated as described in Section 4.4.

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References

1. Harre, M.; Raddatz, P.; Walenta, R.; Winterfeld, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *94*, 480.
2. Noyori, R.; Suzuki, M. *Angew. Chem*. **1984**, *96*, 854.
3. Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 847.
4. Nokami, J.; Matsuura, H.; Nakasima, K.; Shibata, S. *Chem. Lett*. **1994**, 1071.
5. (a) Theil, F. *Catal. Today* **1994**, *22*, 517. (b) Ghorpade, S. R.; Kharul, R. K.; Joshi, R. R.; Kalkote, U. R.; Ravindranathan, T. *Tetrahedron: Asymmetry* **1999**, *10*, 891.
6. (a) Miura, S.; Kurozumi, S.; Toru, T.; Tanaka, T.; Kobayashi, M.; Matsubara, S.; Ishimoto, S. *Tetrahedron* **1976**, *32*, 1893. (b) Takano, S.; Tanigawa, K.; Ogasawaara, K. *Chem. Lett*. **1976**, 189. (c) Wang, Y.-F.; Chen, C.-S.; Gidaukas, G.; Sih, C. J. *J. Am. Chem. Soc*. **1984**, *106*, 3695. (d) Laumen, K.; Schneider, M. *Tetrahedron Lett*. **1984**, *25*, 5875. (e) Laumen, K.; Reimerdes, E. H.; Schneider, M. *Tetrahedron Lett*. **1985**, *26*, 407. (f) Laumen, K.; Schneider, M. *J. Chem. Soc., Chem. Commun*. **1986**, 1298. (g) Deardorff, D. R.; Matthews, A. J.; MacMeeken, D. S.; Cranely, C. L. *Tetrahedron Lett*. **1986**, *27*, 1255. (h) Sugai, T.; Mori, K. *Synthesis* **1988**, 19. (i) Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Org. Synth*. **1995**, *73*, 25. (j) Kalkote, U. R.; Joshi, R. R.; Joshi, R. A.; Ravindranathan, T.; Bastawade, K. B.; Patil, S. G.; Gokhale, D. V. *Biotech. Lett*. **1992**, *14*, 785.
7. (a) Paquett, L. A.; Earle, M. J.; Smith, G. F. *Org. Synth.* **1995**, *73*, 36. (b) Biadatt, T.; Esker, J. L.; Johnson, C. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2313. (c) Curran, T. T.; Hay, D. A. *Tetrahedron: Asymmetry* **1996**, *7*, 2791. (d) Nokami, J.; Matsuura, H.; Nakasima, K.; Shibata, S. *Chem. Lett*. **1994**, 1071. (e) Myers, A. G.; Hammond, M.; Wu, Y. *Tetrahedron Lett*. **1996**, *37*, 3083.
8. Suzuki, M.; Kawagishi, T.; Suziki, T.; Noyori, R. *Tetrahedron Lett*. **1982**, *23*, 405.
9. (a) Masura, M.; Yasumitsu, A.; Fumitaka K. (Sumitomo Chem. Co. Ltd) Japanese patents: JP 62,244,394, Chem. Abs., 1988, Vol. 109, p. 5298g; JP 62,244,396, Chem. Abs., 1988, Vol. 108, p. 130062f. (b) Washausen, P.; Grebe, H.; Kieslich, K.; Winterfeldt, E. *Tetrahedron Lett*. **1989**, *30*, 3777, German patent: DE 3724721 A1, 1990, Vol. 112, p. 156738p. (c) Masayoshi, M.; Yuji, U. (Sumitomo Chem. Co. Ltd.) Japanese patent: JP 60,256,389, Chem. Abs., 1986, Vol. 105, p. 170645t.
10. (a) Kitamura, M.; Manabe K.; Noyori, R. *Tetrahedron Lett*. **1987**, *28*, 4719. (b) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R. *J. Org. Chem*. **1988**, *53*, 708.
11. Rubin, L. J.; Lardy, H. A.; Fischer, H. O. L. *J. Am. Chem. Soc*. **1952**, *74*, 425
12. Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett*. **1985**, *26*, 5615.
13. Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876.
14. (a) Minai, M. Japanese patents: JP 55138502, Jpn Kokai 5762236, 1983, Vol. 98, p. 106860u. (b) Watson, T. J.; Curran, T. T.; Hay, A. D.; Shah, R. S.; Wenstrup, D. L.; Webster, M. E. *Org. Proc. Res. and Devp.* **1998**, *2*, 357.
15. Masayashi, M.; Yuji, U. (Sumitomo Chemicals Co., Ltd.) Japanese patent: EP 170,506, Chem. Abs., 1986, Vol. 105, p. 78566.
16. (a) Kvittingen, L. *Tetrahedron* **1994**, *50*, 8253. (b) Kitaguchi, H.; Itoh, I.; Ono, M. *Chem. Lett*. **1990**, 1203.
17. Ema, T.; Maeno, S.; Takaya, Y.; Sakai, T.; Utaka, M. *Tetrahedron: Asymmetry* **1996**, *7*, 625.
18. Adachi, K.; Kobayashi, S.; Ohno, M. *Chimia* **1986**, *4*, 311.