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ENZYMATIC RESOLUTION OF BUTANOIC ESTERS OF 1-PHENYLMETHYL AND 1-[2-PHENYLETHYL] ETHERS OF 3-CHLORO-1,2-PROPANEDIOL

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Abstract: The enzymatic hydrolysis of butanoic esters of 1-phenylmethyl- and 1-[2-phenylethyl] ethers of 3-chloro-1,2-propanediol has been studied by using lipases. Highest enantiomeric ratio was obtained with PPL for the phenylmethyl ether and with Amano SAM II for the phenylethyl ether. The absolute configurations of the products were verified in two ways. Both the produced alcohols and the remaining esters were converted into the corresponding glycidyl ethers which also were synthesised in homochiral forms starting from *(S)*- epichlorohydrin. The produced alcohols and the remaining esters were prepared independently from *(S)*-epichlorohydrin.

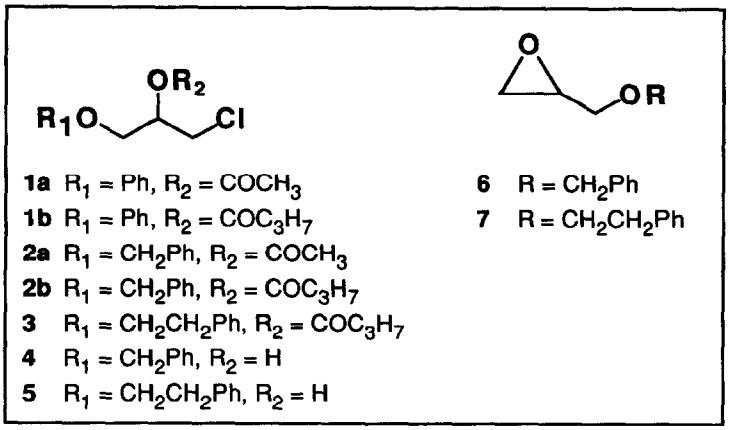
INTRODUCTION

We have continued our efforts, by biocatalytic methods, to resolve racemic mixtures of C-3 esters. Previously we have reported results with various enzymes that catalyse the hydrolysis of primary esters of 1,2-ketals of glycerol. Variations of the acyl part, the ketal group or the enzyme gave only moderate enantiomeric ratios.[1]

Encouraged by the results of other workers who have obtained high *E*-values from the hydrolysis of 1-phenyl-2-acetyl (**1a**) and butanoyl (**1b**)-3-chloro-1,2-propanediol[2] and 1-phenylmethyl-2-acetyl-3-chloro-1,2-propanediol (**2a**)[3], we have also undertaken studies on the hydrolysis of secondary esters of derivatives of 3-chloro-1,2-propanediol. This compound should be an important chiral building block for various biologically active compounds.

Due to the ease with which the phenylmethyl group may be removed, we were particularly interested in homochiral **2b** and **4**. Another interesting feature of our studies was to observe the

way the lipases respond to minor variations in the structure of the substrate on going through the homologous series phenyl, phenylmethyl, 2-phenylethyl.



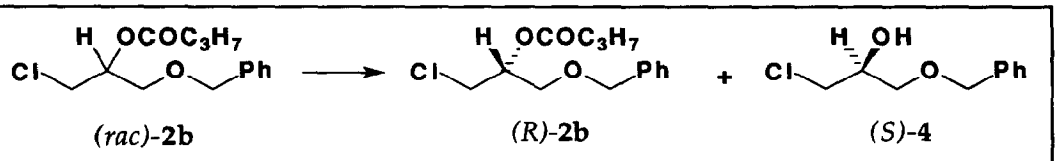
1a R_1 = Ph, R_2 = $COCH_3$
1b R_1 = Ph, R_2 = COC_3H_7
2a R_1 = CH_2Ph, R_2 = $COCH_3$
2b R_1 = CH_2Ph, R_2 = COC_3H_7
3 R_1 = CH_2CH_2Ph, R_2 = COC_3H_7
4 R_1 = CH_2Ph, R_2 = H
5 R_1 = CH_2CH_2Ph, R_2 = H

6 R = CH_2Ph
7 R = CH_2CH_2Ph

RESULTS AND DISCUSSION

The phenylmethyl ether **4** and the 2-phenylethyl ether **5** were synthesised from epichlorohydrin and the appropriate alcohol with boron trifluoride diethyl etherate as catalyst. Addition of epichlorohydrin was accompanied by the evolution of heat and the product contained considerable amounts of dibenzyl ether. Adequate cooling is therefore necessary. Esterification of **4** and **5** with butanoic anhydride gave the esters **2b** and **3** respectively.

We have used five lipases for the hydrolysis of **2b** (Scheme 1) and **3** (Scheme 2) and the results are presented in Tables 1 and 2 respectively. In both cases the *S*-alcohols were formed in excess. We have measured the conversion using a pH-stat and analysed enantiomeric excess of both the alcohol (ee_p) and the unreacted ester (ee_s) using a chiral HPLC-column. The calculated values for the enantiomeric ratio on the basis of the product value (*E*p) and the remaining ester (*E*s) should of course be the same. The *E*-values should also be independent on the conversion.[4] Nevertheless, we found relatively large deviation in the *E*-values calculated by the two methods. However, when we used the values for conversion calculated from $c = ee_s/ee_s + ee_p$ (Table 1 in brackets) we



(rac)-**2b** *(R)*-**2b** *(S)*-**4**

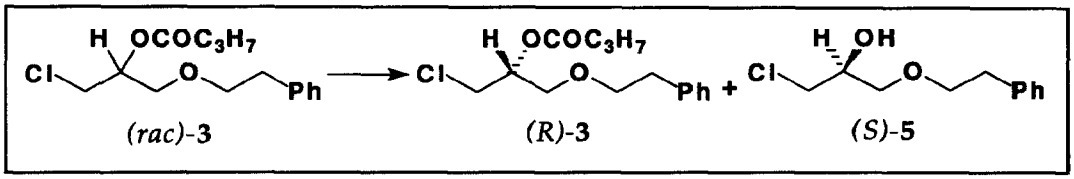
Scheme 1

got more consistent *E*-values (Table 1 in brackets). As is evident from Table 1 the *E*-values range from low to moderate, the highest being $E \approx 15$ for PPL. It is remarkable that, at low conversion, PPL gives a much lower enantiomeric ratio. We assume that this is due to the action of different enzymes in the rather crude PPL-preparation that was used.

Enzyme	Conver -sion,%	React. time (h)	ee_p	ee_s	E_p	E_s
P P L	23 (19)	4.8	62	15	5.0(4.9)	3.5(5.2)
	51	17.6	-	88	-	34(15.5)
	64 (66)	41	50	99	8.3 (11.5)	>17 (14.6)
SAM II	48(51)	24	48	49	4.3(4.5)	5.2(4.4)
Amano PS	25 (29)	1.1	61	25	5.0(5.2)	8.9 (5.3)
Mucor miehei	43(45)	22	39	32	2.9(3.1)	3.3 (3.1)
Candida antarctica B	65 (65)	2.6	47	89	7.4	7.9

Table 1. Enzymatic hydrolysis of the butanoate of 1-phenylmethyl-3-chloro-1,2-propanediol (**2b**). The conversion was measured with pH-stat and values corrected according to $c = ee_s/ee_s + ee_p$ are given in brackets. The ee-values were analysed by HPLC on chiral column. The *E*-values calculated on the bases of corrected conversion is shown in brackets.

The results with the 2-phenylethyl ether are shown in Table 2. It is remarkable that the introduction of one CH_2-group reduced the enantioselectivity of PPL to almost nothing while the Amano-lipase SAM II showed a relatively high $E \approx 25$. Also the immobilised Novo-Nordisk lipase B from *Candida antarctica* showed a reasonable high $E \approx 21$. It is worth noting that only minor variations in the value for the conversion have, in some cases, a dramatic effect on the enantiomeric ratio.



Scheme 2

Enzyme	Conver -sion,%	React. time (h)	ee_p	ee_s	E_p	E_s
P P L	64 (68)	19	10	21	1.0(1.5)	1.5 (1.5)
SAM II	40(45)	9.7	84	70	20.0 (23.5)	86.5 (26.8)
Amano PS	25 (32)	2.2	80	37	12.0 (12.9)	27.6 (11.9)
Mucor miehei	61	43	59	93	12.2	12.7
Candida antarctica B	36 (35)	3.6	87	46	23.3 (22.8)	15.7 (20.0)

Table 2. Enzymatic hydrolysis of the butanoate of 1-[2-phenylethyl]-3-chloro-1,2-propanediol (**3**). The conversion was measured with pH-stat and values corrected according to $c = ee_s/ee_s + ee_p$ are given in brackets. The ee-values were analysed by HPLC on chiral column. The *E*-values calculated on the bases of corrected conversion is shown in brackets.

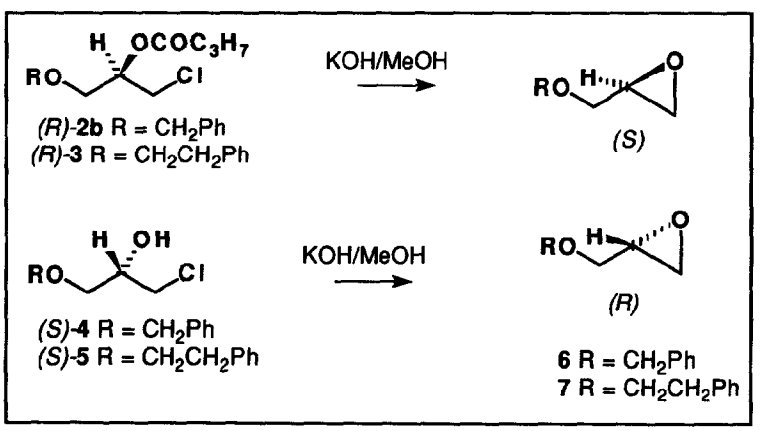
As mentioned above, hydrolysis of the phenyl ethers **1a** and **1b** has shown excellent enantiomeric ratios ($E > 100$)[2] using lipase from Pseudomonas sp. possibly the same as the present SAM II. We notice that there seems to be a trend for this enzyme and also the Mucor lipase, that phenyl ethers give high *E*, phenylmethyl low and phenylethyl reasonably good *E*-values. We have also observed a similar trend when chlorine is substituted with methoxy in similar C-3 compounds.[5] These observations cannot be explained on the basis of the relatively crude mechanisms for lipase

catalysis that have been suggested previously.[6] In some cases *E*-values of more than one hundred were observed for the methoxy derivatives.[5]

In all cases the *S*-alcohols were formed in excess during the hydrolysis. The configuration was confirmed by conversion of both of the *S*-alcohols *S*-**4** and *S*-**5** into the glycidyl ethers *R*-**6** and *R*-**7** respectively. Moreover, the remaining esters *R*-**2b** and *R*-**3** were converted into the corresponding *S*-glycidyl ethers (Scheme 3).

We have also synthesised homochiral *(S)*-enantiomers of **2b**, **3**, **4** and **5** starting with *(S)*-epichlorohydrin. The conversions were performed either by base or acid catalysis (Scheme 4). We have investigated acid catalysed ring opening of some epoxides and find no racemisation with epichlorohydrin. With other substrates and catalysts however, racemisation may occur to various extents, in one case ee = 0.[7]

The borontrifluoride diethyl etherate catalysed formation of **4** and **5** takes place with retention of configuration, while the formation of the glycidyl ethers give inversion (Scheme 4). Similar results have been obtained by others.[3,9,10,11,12] In one report the *R,S*-nomenclature seems to be incorrectly used for benzyl glycidyl ethers.[8]



Scheme 3

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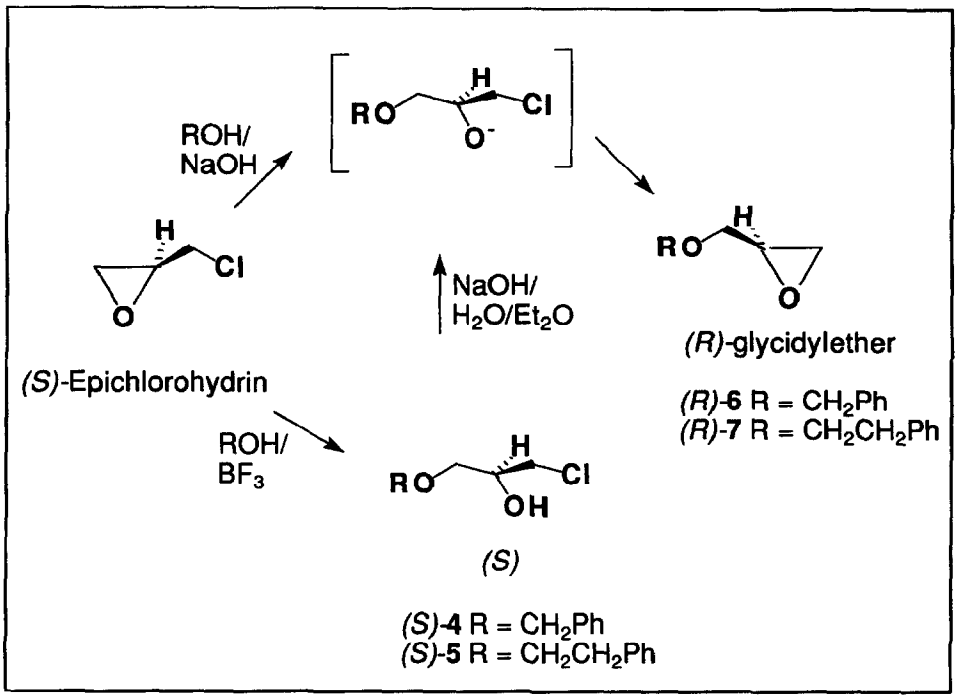

Scheme 4

EXPERIMENTAL

Enzymes. Amano PS and SAM-II (Pseudomonas sp.) were gifts from Amano Pharmaceutical Co., PPL type II (Sigma L-3126) was purchased from Sigma. The immobilised lipases from *Mucor miehei* and *Candida antarctica* B were gifts from Novo-Nordisk A/S, Bagsværd, Denmark.

Chemicals. Pure enantiomers of epichlorohydrin were purchased from Daiso. Co., Ltd., Osaka, Japan.

Analytical methods. Enantiomeric excess (ee) of both the alcohols and esters was determined by HPLC using a Varian 9000 system equipped with UV/VIS detector(2550) and a chiral column, Chiralcel OB, deliverd by J.T. Baker, Deventer, Holland. Solvents: **2b**, hexane : isopropanol = 90 : 10, 0.2 mL/min., **3**, hexane : isopropanol = 90 : 10, 0.3 mL/min. **4**, hexane : ethanol = 90 : 10, 0.2 mL/min., **5**, hexane : ethanol = 90 : 10, 0.3 mL/min. The ee-values were also determined by optical rotation using Optical Activity Ltd. AA-10 Automatic polarimeter, concentrations (c) are given in g/100mL. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions using TMS as

internal reference, shift values are in ppm. The instrument was JEOL EX-400 operating at 400 MHz for ^1H and 100.4 MHz for ^{13}C. All asignements are confirmed by ^1H-^{13}C correlation and DEPT. Mass spectral measurements were performed using an AEI MS-902 instrument.

General experimental procedure for enzymatic hydrolysis. The butanoates **2b** and **3** (8 mmol) were suspended in 300 mL of 0.05M phosphate buffer (pH 7.0). The lipases PPL (400 mg), SAM-II (20 mg), PS (500 mg), Mucor lipase (1.5 g) and Candida lipase (160 mg) were added and the reaction mixture stirred at room temp. The enzymatic hydrolysis was monitored by a pH-stat consisting of a Radiometer PHM 64 pH meter and a Metrohm Herisau Dosimat pump. Addition of N NaOH solution was controlled by a Copam PC. The hydrolysis was stopped by repeated extraction with Et_2O and the reaction mixture was either analysed directly by HPLC or after separation by column chromatography (silica gel, hexane : acetone 4:1).

Conversion of alcohols and esters into epoxides was performed by stirring them with KOH in EtOH at 0 °C overnight.

1-Phenylmethyl-3-chloro-1,2-propanediol [*(rac)*-**4**) and *(S)*-**4**] was prepared by dropwise addition of epichlorohydrin (0.4 mole) to a mixture of phenylmethanol (0.32 mole) and BF_3-Et_2O (5 mL) . The mixture was heated at 85-90 °C for 2 h. Distillation gave **4**, $bp_{0.5}$: 110-112 °C, yield 28%. ^1H NMR ABMXY-syst. for -O-CH_2-CH(OH)-CH_2-Cl, $\nu_A = \nu_B = 3.60$, $\nu_M = 4.01$, $\nu_X = 3.66$, $\nu_Y = 3.61$, J_{AM}, J_{BM}, J_{MX}, J_{YM}, = 5.2 ± 0.4 Hz, J_{XY} = 11.10 Hz, ν_{Bn} = 4.57(s), ^{13}C NMR 46.0(t), 70.3(d), 70.7(t), 73.5(t), 127.6(2d), 127.9(d), 128.5(2d), 137.6(s). *(S)*-**4** was synthesised in the same way from *(S)*-epichlorohydrin, ee > 99%, $[\alpha]_D^{20}$ = +4.5 (c 2.15 EtOH).

1-[2-Phenylethyl]-3-chloro-1,2-propanediol [*(rac)*-**5**) and *(S)*-**5**] was prepared from epichlorohydrin, 2-phenylethanol and BF_3-Et_2O as described for **4**. Distillation gave **5**, $bp_{0.1}$: 108-116 °C, yield 22%. ^1H NMR ABMXY-syst. for -O-CH_2-CH(OH)-CH_2-Cl, $\nu_A = \nu_B = 3.56$, ν_M=3.94, J_{AM}, J_{BM}, J_{MX}, J_{YM}, = 5.2 ± 0.4 Hz, ν_X = 3.58, ν_Y= 3.53, $J_{XY} \approx 12$ Hz, CH_2CH_2, 2.90(t, 2H), 3.72(t, 2H), ^{13}C NMR 36.1(t), 45.9(t), 70.2(d), 71.3(t), 72.3(t), 126.3(2d), 128.3(d), 129.0(2d), 138.7(s). *(S)*-**5** was synthesised in the same way from *(S)*-epichlorohydrin, ee > 99%, $[\alpha]_D^{20}$ = +6.5 (c 1.29 EtOH). $[M-18]^{\cdot+}$ 196. 0656, calc. for $C_{11}H_{13}OCl$ 196.0655.

2-Butanoyl-1-phenylmethyl-3-chloro-1,2-propanediol [*(rac)*-**2b**) and *(S)*-**2b**] was prepared by stirring at room temp 4 with butanoic anhydride (0.023 mole) in pyridine (5 mL) and 4-dimethylaminopyridine as catalyst. Distillation gave **2b** $bp_{0.1}$: 200 °C yield 80%.^1H NMR ABMXY-syst. for -O-CH_2-CH(OR)-CH_2-Cl, $\nu_A = 3.62$, $\nu_B = 3.66$, $J_{AB} \approx 10.0$ Hz, ν_M= 5.18, J_{AM}, J_{BM}, J_{MX}, J_{YM}, = 5.2 ± 0.4 Hz, ν_X= 3.76, ν_Y= 3.68, J_{XY} = 12.0 Hz, ν_{Bn} = 4.54 and 4.57(AB-syst.), R = $CH_3CH_2CH_2CO$ 0.96, 1.67, 2.33. ^{13}C NMR 13.6(q), 18.4(t), 36.1(t), 42.90(t), 68.3(t), 71.4(d), 73.4(t) 127.7(2d), 127.8(d), 128.4(2d), 137.6(s), 172.9(s). *(S)*-**2b** was synthesised from *(S)*-**4**, ee > 99%, $[\alpha]_D^{20}$ = +10.3 (c 2.03 EtOH), $M^{\cdot+}$ 270. 1027, calc. for $C_{14}H_{19}O_3Cl$ 270.1023.

2-Butanoyl-1-(2-phenylethyl)-3-chloro-2-propanediol [*(rac)*-**3**) and *(S)*-**3**] was prepared from **5** as for **2b**. Distillation gave **3**, $bp_{0.1}$: 220 °C, yield 85%. ^1H NMR ABMXY-syst. for -O-CH_2-CH(OR)-CH_2-Cl, $\nu_A \approx \nu_B = 3.6$, $\nu_M = 5.12$, J_{AM}, J_{BM}, J_{MX}, J_{YM}, = 5.2 ± 0.4 Hz, $\nu_X \approx \nu_Y = 3.7$, CH_2CH_2, 2.86(2H,t), 3.6-3.7(2H,m), R = $CH_3CH_2CH_2CO$ 0.95, 1.66, 2.32. ^{13}C NMR 13.6(q), 18.4(t), 36.1(2t), 42.9(t), 68.9(t), 71.3(d), 72.4(t) 126.3(d), 128.3(2d), 128.9(2d), 138.7(s), 172.9(s). *(S)*-**3** was synthesised from *(S)*-**5** , ee > 99%, $[\alpha]_D^{20}$ = +7. 1(c 2.25, EtOH), $M^{\cdot+}$ 284. 1182, calc. for $C_{15}H_{21}O_3Cl$ 284. 1179.

(R)-(-)-Phenylmethyl glycidyl ether (*R*-**6**). To a stirred mixture of *(S)*-epichlorohydrin (0.0217 mole), phenylmethanol (0.02 mol) and Bu_4NHSO_4 (0.3 g) was added 50% aqueous NaOH (10 mL) dropwise at 0 °C and the stirring is continued for 30 min. at the same temp and for 4 h at room temp. Extraction with Et_2O and distillation gave *(R)*-**6**, $bp_{0.1}$: 130 °C, 80%, $[\alpha]_D^{20}$ = -6.2 (c 1.58 benzene), lit.[9] $[\alpha]_D^{20}$: -5.4 (c 5 benzene), $[\alpha]_D^{20}$ = -6.5 (c 1.69 EtOH). ^1H NMR 2.62, 2.80, 3.19 (oxirane), J_{gem}= 4.5 Hz, J_{vic}= 4.5 and 3.6 Hz, 3.43, 3.77, (CH_2) J_{gem}= 11.2 Hz, J_{vic}= 3.1 and 5.7 Hz, ν_{Bn} = 4.56 and 4.61, J_{AB} = 11.5 Hz. ^{13}C NMR 44.3(t) and 50.9(d) (oxirane), 70.8(t), 73.3(t), 127.4(d), 127.8(2d), 128.4(2d) and 137.9(s)

(R)-(-)-2-Phenyletyl glycidyl ether (*R*-**7**) was prepared from *(S)*-epichlorohydrin(0.0326 mole), 2-phenylethanol (0.031 mole) and BF_3-Et_2O(1.2 mL) as for **6**. Distillation gave *(R)*-**7**, $bp_{0.1}$: 150 °C 78%, $[\alpha]_D^{20}$ = -16.7 (c 1.44 , benzene), $[\alpha]_D^{20}$ = -10.5 (c 1,71 EtOH). ^1H NMR 2.59, 2.78, 3.13 (oxirane), J_{gem}= 4.5 Hz, J_{vic}= 4.5 and 3.6 Hz, 3.40, 3.69, (CH_2), J_{gem}= 11.2 Hz, J_{vic}= 3.1 and 5.7 Hz, 2.90 (2H) 3.73 (2H), (CH_2CH_2), ν_{Bn} = 4.56 and 4.61, J_{AB} = 11.5 Hz. ^{13}C NMR 44.3(t) and 50.9(d) (oxirane), 36.3(t), 71.5(t), 72.4(t), 126.2(d), 128.4(2d), 128.9(2d) and 138.7(s), $M^{\cdot+}$ 178. 0992, calc. for $C_{11}H_{14}O_2$ 178. 0994.

REFERENCES

1. Partali, V.; Melbye, A. G.; Alvik, T.; Anthonsen, T. *Tetrahedron: Asymmetry*, **1992**, *3*, 65 - 72.
2. Ader, U.; Schneider, M.P. *Tetrahedron Assymetry* ,**1992**, *3*, 201 - 204 and 205 - 208.
3 Pederson, R.L.; Lin, K.K.; Rutan, J.F.; Chen, L.; Wong, C.-H.J. *Org. Chem.* **1990**, *55*, 4897 - 4901.
4. Sih, C.J. and Wu, S.-H. *Topics in Stereochemistry* **1990**, *19*, 63-125.
5. Waagen, V.; Hollingsæter, I.; Partali, V.; Anthonsen, T. To be published.
6. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656 - 2665.
7. Waagen, V.; Fylkesnes, A.; Anthonsen, T. To be published.
8 Takano, S.; Sekiguchi, Y.; Setoh, M.; Yoshimitsu, T.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Heterocycles* ,**1990**, *31*, 1715 - 1719.
9. Byun, H. S.; Bittman, R., *Tetrahedron Lett.* **1989**, 2751 - 2754.
10. Kobayashi, Y.; Ito, T.; Yamakawa, I.; Urabe, H.; Sato, F. *Synlett*, **1991**, 811.
11. Anisuzzaman, A. K. M.; Own, L. N. *J. Chem. Soc.* **1967**, 1021 - 1026.
12. Hirth, G.; Barner, R. *Helv. Chim. Acta*, **1982**, *65*, 1059.