Pergamon

Tetrahedron Vol. 51, No. 12, pp. 3617-3626, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00077-1

Stereoselective Synthesis of β-Alkoxy- and β-Alkylthio-Acrylic Esters and Amides from β-Tosylacrylic Derivatives

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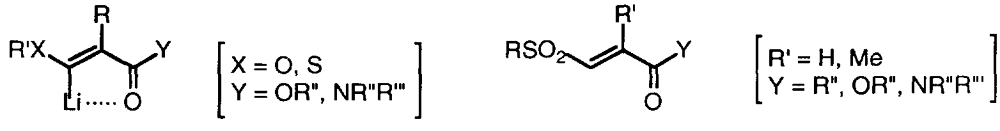
Abstract: A simple and stereoselective synthesis of β-alkoxy- and β-alkylthio-acrylic esters and amides (**8**) by nucleophilic vinylic substitution of the tosyl group by sodium alcoholates and thiolates of *(E)*-β-tosylacrylic derivatives (**7**), prepared by iodosulfonylation-dehydroiodination of acrylic compounds, is described. This methodology is applied to the synthesis of sinharine (**8eh**) a natural antifungal isolated from *glycosmis cyanocarpa*.

INTRODUCTION

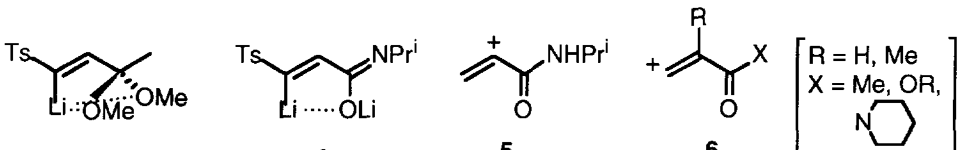
β-Alkoxy- and β-alkylthio-acrylic derivatives are an important class of compounds in synthetic organic chemistry, specially as precursors of β-acylvinyl anions **1**[1] in the preparation, for instance, of γ- and δ-lactones, butenolides, tetronates and 13-crown-4 derivatives[2]. In the case of β-alkoxyacrylates derived from scalemic alcohols, they have also been used as β-lithiated β-alkoxyacrylates in the enantioselective synthesis of butenolides[3], tetronic acid derivatives[4] and functionalized cyclopentenones[5]. More recently, β-alkoxyacrylates derived from homochiral diols have been diastereoselectively transformed into α-hydroxy-β-ketoesters by oxidation with MCPBA[6]. On the other hand, β-alkoxyacrylates are also very efficient radical acceptors in intramolecular cyclizations to give oxacycles[7] stereoselectively. Also, β-alkoxyacrylic acids derived from allylic alcohols suffer Claisen rearrangement-decarboxylation to yield γ,δ-unsaturated aldehydes[8].

The title compounds can be prepared by addition of the corresponding nucleophile to propiolic acid derivatives[9] or by conjugate addition-elimination to acrylic derivatives substituted at the β-position by the group trimethylamino[8] or by a halogen atom[9a, 10] (also prepared in general from propiolic acid derivatives) and by base-promoted elimination in ketals derived from β-ketoesters[6]. *(E)*-β-Arylsulfonyl-α,β-unsaturated carbonyl and carboxylic compounds **2** (easily accessible from the corresponding α,β-unsaturated compounds by a sequential iodosulfonylation-dehydroiodination procedure[11]) are very stable crystalline compounds and can be stored for years at room temperature. These type of vinyl sulfones are versatile reagents[12] and have been used: (a) as β-acylvinyl anions[13] **3** and **4** by lithiation of the corresponding ketal and amide, respectively, in the synthesis of butenolides, furans, 1,4-enedicarbonyl compounds and cyclopentenones; (b) as α-acylvinyl cation equivalents

5[14] by reaction of *(E)-N*-isopropyl-β-tosylacrylamide with Grignard reagents in the synthesis of α-substituted acrylic amides; (c) as β-acylvinyl cation equivalents **6**[15] in nucleophilic vinylic substitution also with Grignard reagents (for R= OR and piperidino) in the synthesis of β-alkyl substituted acrylic esters and amides[15a] and (for R=Me) with ketone enolates in the preparation of hyndranol related to vitamin D[15b,c]; and (d) as dienophiles[16] or dipolarophiles[17] in cycloaddition reactions. We report here a new application of *(E)*-β-tosylacrylic derivatives as synthons of the type **6** in the stereoselective synthesis of β-alkoxy- and β-alkylthio-acrylic derivatives.



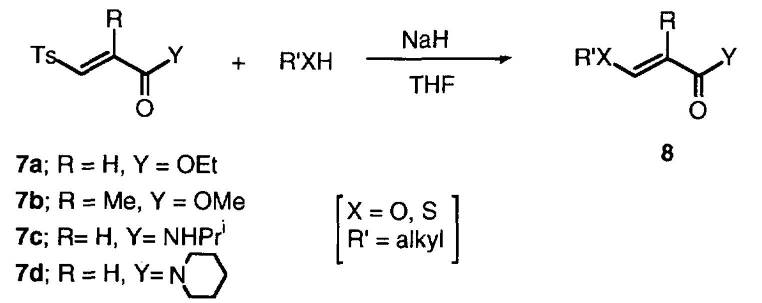
1 **2**



3 **4** **5** **6**

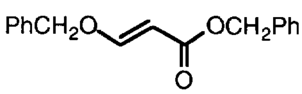
RESULTS AND DISCUSSION

When *(E)*-β-tosylacrylic derivatives **7**[11] were allowed to react with alcohols and thiols in the presence of sodium hydride in THF *(E)*-β-alkoxy- and β-thioalkoxy-acrylic derivatives **8** were stereoselectively obtained in high yields (Scheme 1 and Table 1). The reaction was carried out at room temperature for 3 h and with methacrylic esters at 0°C. An excess of 1 equiv. of NaH was necessary for esters **7a,b** and amide **7d** and 2 equiv. for amide **7c**, because the deprotonation of the amidic hydrogen takes also place. The required stoichiometry to carried out the nucleophilic vinylic substitution seems to be in agreement with an elimination-addition mechanism. However, with methacrylic derivatives the same stoichiometry was also necessary and therefore an addition-elimination[18] mechanism is more probable.

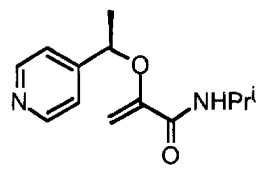


Scheme 1

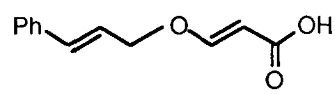
Racemic and scalemic, primary and secondary, alcohols and thiols[20] have been used as nucleophiles (Table 1), whereas tertiary alcohols such as tert-butanol or hindered secondary alcohols such as (-)-menthol failed. With ester derivatives competitive transesterification reaction was observed when primary alcohols were used as nucleophiles, e.g. in the case of ethyl *(E)*-β-tosylacrylate (**7a**) and benzyl alcohol (Table 1, entry 1) benzyl *(E)*-benzyloxyacrylate (**9aa**) was also obtained. In the case of the reaction of *(E)*-*N*-isopropyl-β-tosylacrylamide (**7c**) with secondary alcohols such as *(R)*-2-(4-pyridyl)ethanol (Table 1, entry 11) compound **10cd** was also obtained due to the competitive Michael addition over the vinyl sulfone (α-attack)[14]. This secondary reaction in the case of amides can be avoided using *N,N*-disubstituted amides such as compound **7d** (Table 1, entries 14 and 15).



9aa



10cd



11ab

With thiols the substitution reaction took place in all cases regio- and stereoselectively at the β-position of compounds **7** to afford *(E)*-β-alkylthioacrylic derivatives **8ae,be,bf,ce,cf** with retention of the configuration according to an addition-elimination mechanism[18]. With alcohols the reaction occured also with retention of the configuration, except in the case of methacrylates (Table 1, entries 6 and 7) which gave mainly *E*-diastereomers. The configuration of methacrylates **8bd,be,bf** was confirmed by NOE experiments.

This methodology has been applied to the synthesis of *(E)*-3-[*(E)*-3-phenyl-2-propenoxy]acrylic acid (**11ab**), which has been previously prepared starting from *(E)*-(carboxyvinyl)trimetylammonium betaine[8b] followed by further substitution with cinnamyl alcoholate in 52% overall yield. This acid suffered an easy Claisen rearrangement-decarboxylation to give 3-phenyl-4-pentenal[8]. The reaction of ethyl *(E)*-β-tosylacrylate (**7a**) with the mentioned alcoholate provided compound **8ab** (Table 1, entry 2), which after hydrolysis with 1 N NaOH in dioxane afforded the acid **11ab** in 70% yield (based on the starting sulfone **7a**).

Finally, we have synthetized sinharine (**8eh**) an antifungal metabolite recently isolated from the Malaysian Rutaceae *Glycosmis cyanocarpa*[21a]. The starting sulfone **7e** [prepared by iodosulfonylation-dehydroiodination of *N*-phenethylacrylamide (**12**) in 78% yield] reacted with lithium methylthiolate (prepared by reaction of dimethyl disulfide with n-butyllithium) at room temperature to provide stereoselectively sinharine (**8eh**) in 77% yield (Scheme 2 and Table 1, entry 16). This synthesis is a more simple and stereoselective way to prepare this natural product than the previously described one, which starts from propiolic acid and methylthiol to give *Z/E* mixtures of 3-(methylthio)propenoic acid[21b].

We conclude that the above two step procedure is an adequate and useful methodology for the general regio- and stereo-selective synthesis of β-alkoxy- and β-alkylthio-acrylic derivatives using very stable β-tosylacrylic

Table 1. Synthesis of β-Alkoxy- and β-Alkylthio-Acrylic Esters and Amides **8**

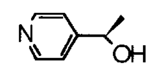
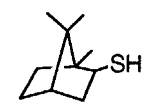
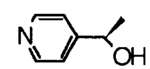
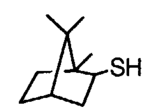
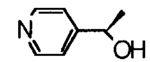
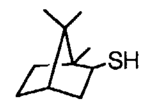
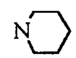
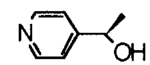
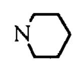
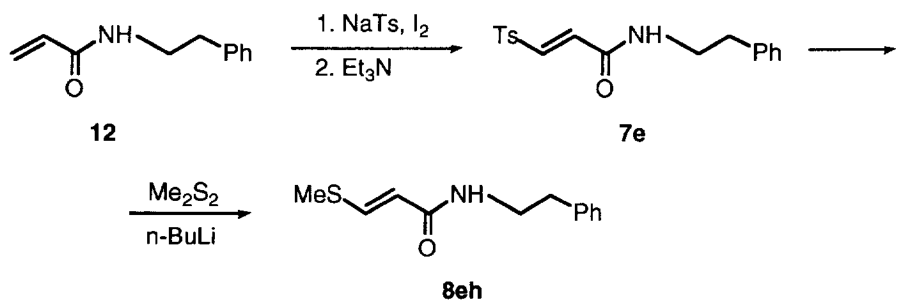
	Starting Sulfone			Reaction Conditions			Product		
Entry	No.	R	X	R'XH	NaH (equiv)	T(°C)	No.	Yield (%)[a]	Mp (°C)[b] or R_f[c]
1	**7a**	H	OEt	$PhCH_2OH$	2	rt	**8aa**	70[d]	0.48[e]
2	**7a**	H	OEt	(*E*)-$PhCH=CHCH_2OH$	2	rt	**8ab**	87	0.52
3	**7a**	H	OEt	(±)-PhCH(Me)OH	2	rt	**8ac**	90	0.57[f]
4	**7a**	H	OEt		2	rt	**8ad**[g]	92	0.48[h]
5	**7a**	H	OEt		2	rt	**8ae**[i]	83	0.78
6	**7b**	Me	OMe	$PhCH_2OH$	2	0	**8ba**[j]	76	0.55
7	**7b**	Me	OMe		2	0	**8bd**[k,l]	83	0.48[h]
8	**7b**	Me	OMe		2	0	**8be**[m]	93	0.69
9	**7b**	Me	OMe	$PhCH_2SH$	2	0	**8bf**	96	0.51

Table 1. cont.

10	**7c**	H	NHPr^i	$PhCH_2OH$	3	rt	**8ca**	85	100-101
11	**7c**	H	NHPr^i		3	rt	**8cd**[n]	80	0.41[o,p]
12	**7c**	H	NHPr^i		3	rt	**8ce**[q]	86	157-158
13	**7c**	H	NHPr^i	$PhCH_2SH$	3	rt	**8cf**	91	92-93
14	**7d**	H			2	rt	**8dd**[r]	84	0.49[p]
15	**7d**	H		Me_2CHOH	2	rt	**8dg**	86	0.74[h]
16	**7e**	H	$NHCH_2CH_2Ph$	-[s]	-[t]	rt	**8eh**	77	91-92[u]

[a] Isolated yield after column chromatography (silica gel), based on starting sulfone **7**. [b] Hexane/ethyl acetate. [c] Hexane/ethyl acetate: 4/1. [d] A 14% of benzyl β-benzyloxyacrylate (**9aa**) was also obtained. [e] Lit.[19]. [f] Lit.[5]. [g] $[\alpha]_D^{28}$ = +92.5 (c 1.0, $CHCl_3$). [h] Hexane/ethyl acetate: 1/1. [i] $[\alpha]_D^{28}$ = +88.8 (c 1.4, $CHCl_3$). [j] Mixture of *ca.* 1/2: *Z/E* diastereomers (^1H NMR). [k] Mixture of *ca.* 1/20: *Z/E* diastereomers (^1H NMR). [l] $[\alpha]_D^{28}$ = +16.7 (c 1.0, $CHCl_3$). [m] $[\alpha]_D^{28}$ = +89.1 (c 1.7, $CHCl_3$). [n] A mixture 3/1 of compounds **8cd**/**10cd** was obtained. [o] Of the mixture. [p] Dichloromethane/ethanol: 97/3. [q] $[\alpha]_D^{28}$ = +82.9 (c 1.2, $CHCl_3$). [r] $[\alpha]_D^{28}$ = +40.0 (c 1.2, $CHCl_3$). [s] Lithium methylthiolate was prepared from dimethyl disulfide and n-butyllithium. [t] 1.2 equiv of lithium methylthiolate was used. [u] Lit.[21a] mp 74-75°C.

compounds as β-acylvinyl cation equivalents which are accessible from simple and cheap acrylic compounds.



Scheme 2

EXPERIMENTAL PART

General. Melting points were obtained with a Reichert Thermovar apparatus and are uncorrected. Optical rotations were measured in a Optical Activity AA-100 polarimeter. IR spectra were obtained as films in a Pye Unicam SP3-200 spectrophotometer. ^1H and ^{13}C spectra were recorded on a Bruker AC-300 spectrometer with $SiMe_4$ as internal standard using $CDCl_3$ as solvent and the coupling constants (*J*) are measured in Hz. ^{13}C-NMR assignements were made on the basis of DEPT experiments. MS spectra were measured in a Hewlett-Packard 5988A (EI, 70eV). High resolution MS spectra were measured in the corresponding Service at the University of Zaragoza. Elemental analyses were performed by the Microanalyses Service at the University of Alicante. Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1500/LS 254 plates coated with a 0.2 mm layer of silica gel and UV visualization. Flash chromatography was performed using silica gel 60 of 230-400 mesh (hexane/EtOAc). All starting materials were commercially available (Aldrich, Fluka) of the best grade and were used without further purification. THF was dried over benzophenone ketyl under argon atmosphere and distilled before use.

Preparation of β-Alkoxy- and β-Alkylthio-Acrylic Esters and Amides* (8). *General Procedure. To a suspension of sodium hydride as a 60% dispersion in mineral oil (1 or 1.5 mmol, see Table 1) and the corresponding alcohol or thiol (0.5 mmol) in THF (3 mL) was added dropwise a solution of the corresponding acrylic sulfone **7**[11] (0.5 mmol) in THF (1 mL) at 0°C or at room temperature (see Table 1). The resulting mixture was strirred for 3h and then water (5 mL) was added. The resulting solution was extracted with ether (3x5 mL), the organic layer was washed with brine (3 mL), dried (Na_2SO_4) and evaporated to give crude products **8**, which were purified by column chromatography on silica gel and by recrystallization. Physical data are included in Table 1, spectral and analytical data follow. The preparation of compound **8eh** is described below.

Ethyl (E)-*3-(Benzyloxy)propenoate* (**8aa**)[19]: ν 3040, 1630, 970 (CH=CH), and 1710 cm^{-1} (C=O); δ_H 1.27 (t, *J*=7, 3H, CH_3), 4.16 (q, *j*=7, 2H, CH_2CH_3), 4.09 (s, 2H, $PhCH_2O$), 5.31 (d, *J*=12.5, 1H, CCHCO), 7.36 (m, 5H, ArH) and 7.68 (d, *J*=12.5, 1H, $C{=}CHOCH_2$); δ_C 14.33 (CH_3), 59.83 (CH_2CH_3), 72.85 ($PhCH_2O$), 97.45 (C=*C*HCO), 127.66, 128.53, 128.71, 135.23 (ArC), 161.93 (OCH=C) and 167.66 (C=O); *m/z* 206 (M^+, 0.2%), 91 (100) and 65 (20) (Found: M^+ 206.0938. Calcd. for $C_{12}H_{14}O_3$ 206.0943).

Ethyl (E)-*3-[*(E)-*3-Phenyl-2-propenoxy]propenoate* (**8ab**): ν 3020, 1650, 970 (CH=CH) and 1720 cm^{-1} (C=O); δ_H 1.25 (t, *J*=7.3, 3H, CH_3), 4.16 (q, *J*=7.3, 2H, CH_2CH_3), 4.48 (d, *J*= 6.1, 2H, $C{=}CHCH_2O$), 5.28 (d, *J*=12.5, 1H, C=CHCO), 6.25 (dt, *J*=15.9, 6.1, 1H, $C{=}CHCH_2O$), 6.63 (d, *J*= 15.9, 1H, C=CHPh), 7.30 (m, 5H, ArH) and 7.63 (d, *J*= 12.5, 1H, $C{=}CHOCH_2$); δ_C 14.17 (CH_3), 59.59 (OCH_2CH_3), 71.31 ($C{=}CHCH_2O$), 97.11 (C=*C*HCO), 122.43, 126.48, 128.08, 128.47, 134.12, 135.73 (ArC, Ph*C*H=*C*H), 161.69 (OCH=C) and 167.47 (C=O).

Ethyl (±)-(E)-*3-(1-Phenylethoxy)propenoate* (**8ac**)[5]: ν 3020, 1640, 970 (CH=CH) and 1710 cm^{-1} (C=O); δ_H 1.23 (t, *J*=7.3, 3H, CH_2CH_3), 1.58 (d, *J*=6.7, 3H, $PhCHCH_3$), 4.09 (q, *J*=7.3, 1H, $CHHCH_3$), 4.10 (q, *J*=7.3, 1H, $CHHCH_3$), 5.03 (q, *J*=6.7, 1H, $PhCHCH_3$), 5.23 (d, *J*=12.5, 1H, C=CHCO), 7.30 (m, 5H, ArH) and 7.52 (d, *J*=12.5, 1H, C=CHOCH); δ_C 14.25 (CH_2CH_3), 23.31 ($CHCH_3$), 59.63 (CH_2CH_3), 80.34 (ArCHO), 98.31 (C=CHCO), 125.65, 128.10, 128.69, 141.21 (ArC), 161.23 (OCH=C) and 167.78 (C=O); *m/z* 202 (M^+-18, 1%), 105 (100), 103 (10), 79 (13) and 77 (17).

Ethyl (R)-(E)-*3-[1-(4-Pyridyl)ethoxy]propenoate* (**8ad**): ν 3020, 1640 (CH=CH) and 1710 cm^{-1} (C=O); δ_H 1.24 (t, *J*=7, 3H, CH_2CH_3), 1.58 (d, *J*=6.4, 3H, $ArCHCH_3$), 4.12 (q, *J*=7, 1H, $CHHCH_3$), 4.13 (q, *J*=7, 1H, $CHHCH_3$), 5.03 (q, *J*=6.4, 1H, ArCH), 5.22 (d, *J*=12.5, 1H, C=CHCO), 7.22 (m, 2H, ArH), 7.50 (d, *J*=12.5, 1H, C=CHOCH) and 8.64 (m, 2H, ArH); δ_C 14.24 (CH_2CH_3), 22.93 ($ArCHCH_3$), 59.86 (CH_2CH_3), 78.46 (ArCHO), 99.06 (C=CHCO), 120.44, 149.98, 150.22 (ArC), 160.48 (OCH=C) and 167.38 (C=O); *m/z* 203 (M^+-18, 2%), 106 (100), 104 (11), 76 (32), 77 (31), 69 (15), 51 (24) and 43 (13).

Ethyl (E)-*3-{*[(1S)-exo]-*Bornylthio}propenoate* (**8ae**): ν 1680 (C=O), 1560 and 930 cm^{-1} (CH=CH); δ_H 0.85 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.24 (m, 2H, CHHCHH), 1.28 (t, *J*=7.1, 3H, OCH_2CH_3), 1.70-2.01 (m, 5H, CHHCHH, CH, CH_2CHS), 3.13 (dd, *J*=9.1, 5.8, 1H, CHS), 4.17 (q, *J*=7.1, 2H, OCH_2), 5.76 (d, *J*=15.2, 1H, C=CHCO) and 7.68 (d, *J*=15.2, 1H, C=CHS); δ_C 13.54 (CH_2CH_3), 14.29 (CCH_3), 20.03, 20.16 [$C(CH_3)_2$], 27.19, 38.16, 39.55 (3xCH_2), 45.62 (CH_2CHCH_2), 47.50 (CHS) , 49.55 [$C(CH_3)_2$], 54.36 (CCH_3), 59.98 (CH_2CH_3), 112.84 (C=CHCO), 148.66 (SCH=C) and 165.55 (C=O); *m/z* 268 (M^+, 6%), 137 (61), 95 (32), 93 (10), 81 (100), 77 (10), 69 (18), 67 (27), 55 (15), 43 (14) and 41 (37) (Found: M^+ 268.1486. Calcd. for $C_{15}H_{24}O_2S$: 268.1497).

Methyl 3-Benzyloxy-2-methylpropenoate (**8ba**). (*Z*)-Isomer: δ_H 1.81 (d, *J*=1.2, 3H, $C=CCH_3$), 3.79 (s, 3H, OCH_3), 5.15 (s, 2H, $PhCH_2O$), 7.34 (m, 5H, ArH) and 7.48 (q, *J*=1.2, 1H, C=CH); δ_C 9.31 (CCH_3), 61.12 (OCH_3), 65.61 ($PhCH_2$), 106.70 ($C=CCH_3$), 127.88, 127.94, 128.35, 136.63 (ArC), 157.22 (OCH=C) and 168.55 (C=O); (*E*)-Isomer: δ_H 1.79 (d, *J*=1.2, 3H, $C=CCH_3$), 3.68 (s, 3H, OCH_3), 5.00 (s, 2H, $PhCH_2O$), 7.30 (m, 5H, ArH) and 7.42 (q, *J*=1.2, 1H, C=CH); δ_C 9.27 (CCH_3), 51.16 (OCH_3), 75.37 ($PhCH_2$), 106.73 ($C=CCH_3$), 127.35, 128.42, 128.65, 136.31 (ArC), 158.73 (OCH=C) and 169.14 (C=O); *m/z* 206 (M^+, 4%), 99 (12), 91 (100) and 65 (31).

Methyl (R)-(E)-*2-Methyl-3-[1-(4-pyridyl)ethoxy]propenoate* (**8bd**): ν 3020, 1640 (CH=CH) and 1710 cm^{-1} (C=O); δ_H 1.59 (d, *J*=6.4, 3H, $ArCHCH_3$), 1.84 (d, *J*=1.2, 3H, $C=CCH_3$), 3.68 (s, 3H, OCH_3), 4.99 (q, *J*=6.4, 1H, ArCH), 7.22 (m, 2H, ArH), 7.30 (q, *J*=1.2, 1H, C=CH) and 8.60 (m, 2H, ArH); δ_C 9.35 (CCH_3), 23.11 ($CHCH_3$), 51.23 (OCH_3), 80.04 (ArCH), 107.50 ($C=CCH_3$), 120.41, 150.15, 150.68, 155.24 (ArC, OCH=C) and 168.91 (C=O); *m/z* 221 (M^+, 3%), 106 (100), 79 (10), 78 (19), 77 (23), 56 (12), 55 (19) and 51 (15) (Found: M^+ 221.1052. Calcd. for $C_{12}H_{15}NO_3$: 221.1052).

Methyl (E)-*3-{*[(1S)-exo]-*Bornylthio}-2-methylpropenoate* (**8be**): ν 1710 (C=O) and 1590 cm^{-1} (CH=CH); δ_H 0.85 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.20 (m, 2H, CHHCHH), 1.72 (m, 3H, CHHCHH and CH), 1.84 (d, *J*=1.2, 3H, $C=CCH_3$), 1.91 (m, 1H, CHHCHS), 2.00 (dd, *J*=13.1, 9.2, 1H, CHHCHS), 3.08 (dd, *J*=9.2, 5.8, 1H, CHS), 3.72 (s, 3H, OCH_3) and 7.49 (q, *J*=1.2, 1H, C=CH); δ_C 13.87, 13.93 ($C=CCH_3$, CCH_3), 20.13, 20.19 (2xCCH_3), 27.20, 38.18, 39.80, 45.68, 47.40, 49.53 [CH_2CH_2, $CHCH_2$, $C(CH_3)_2$, CHS], 51.60 (OCH_3), 57.56 (CCH_3), 120.80 ($C=CCH_3$), 145.11 (SCH=C) and 165.56 (C=O); *m/z* 268 (M^+, 6%), 137 (59), 95 (22), 81 (100), 71 (18), 69 (16), 67 (23), 59 (15), 55 (13) and 41 (24) (Found: M^+ 268.1499. Calcd. for $C_{15}H_{24}O_2S$: 268.1497).

Methyl (E)-*3-Benzylthio-2-methylpropenoate* (**8bf**): ν 3020, 1580 (CH=CH) and 1710 cm^{-1} (C=O); δ_H 1.84 (d, *J*=0.9, 3H, $C=CCH_3$), 3.68 (s, 3H, OCH_3), 4.00 (s, 2H, $PhCH_2$), 7.30 (m, 5H, ArH) and 7.49 (q, *J*=0.9, 1H, C=CH); δ_C 13.87 ($C=CCH_3$), 38.16 ($PhCH_2$), 51.57 (OCH_3), 122.91 ($C=CCH_3$), 127.48, 128.62, 128.70, 137.03, 141.28 (ArC, SCH=C) and 166.08 (C=O); *m/z* 222 (M^+, 6%), 189 (11), 131 (13), 91 (100), 71 (16), 65 (24) and 44 (11) (Found: M^+ 222.0712. Calcd. for $C_{12}H_{14}O_2S$: 222.0715).

(E)-*3-Benzyloxy*-N-*isopropylpropenamide* (**8ca**): ν 3300 (NH), 3090, 1610, 970 and 1680 cm^{-1} (C=O); δ_H 1.15 (d, *J*=6.5, 6H, 2xCH_3), 4.14 [sept, *J*=6.5, 1H, $CH(CH_3)_2$], 4.86 (s, 2H, $PhCH_2O$), 5.23 (br s, 1H, NH), 5.25 (d, *J*=12.1, 1H, C=CHCO), 7.34 (m, 5H, ArH) and 7.60 (d, *J*=12.1, 1H, $C=CHOCH_2$); δ_C 22.87 (2xCH_3), 41.01 (NCH), 73.02 ($PhCH_2$), 99.92 (C=CHCO), 127.59, 128.39, 128.65, 135.65 (ArC), 159.25

(OCH=C) and 165.70 (C=O); *m/z* 219 (M^+, 1.2%), 91 (100), 71 (10), 65 (22) and 42 (10) (Found: M^+ 219.1252. Calcd. for $C_{13}H_{17}NO_2$: 219.1259).

(R)-(E)-N-*Isopropyl-3-[1-(4-pyridyl)ethoxy]propenamide* (**8cd**): δ_H 1.13 [d, *J*=6.6, 6H, CH(C*H*$_3$)$_2$], 1.56 (d, *J*=6.6, 3H, ArCHC*H*$_3$), 4.09 [sept, *J*=6.6, 1H, C*H*(CH$_3$)$_2$], 4.96 (q, J=6.6, 1H, ArC*H*CH$_3$), 5.20 (d, *J*=12, 1H, C=CHCO), 5.43 (br s, 1H, NH), 7.20 (m, 2H, ArH), 7.42 (d, *J*=12, 1H, C=C*H*OCH) and 8.57 (m, 2H, ArH); δ_C 22.74, 22.94 [CH*C*H$_3$, CH(*C*H$_3$)$_2$], 41.05 (NCH), 78.51 (ArCH), 101.50 (C=*C*HCO), 120.41, 150.05, 150.14 (ArC), 157.79 (O*C*H=C), and 165.43 (C=O); *m/z* 131 (M^+-103, 4%), 106 (100), 78 (20), 77 (25), 71 (22), 69 (19), 51 (19), 44 (52), 43 (29), 42 (39) and 41 (18).

(E)-*3-{*[(1S)-exo]-*Bornylthio}*-N-*isopropylpropenamide* (**8ce**): ν 3240 (NH), 3040, 1580, 950 (CH=CH) and 1630 cm^{-1} (C=O); δ_H 0.84 (s, 3H, CH$_3$), 0.94 (s, 3H, CH$_3$), 0.96 (s, 3H, CH$_3$), 1.17 [d, *J*=6.4, 6H, CH(C*H*$_3$)$_2$], 1.23 (m, 2H, C*H*HC*H*H), 1.74 (m, 3H, CH*H*CH*H* and CH), 1.85 (m, 1H, C*H*HCHS), 1.98 (dd, *J*=13.1, 9.2, 1H, CH*H*CHS), 3.08 (dd, *J*=9.2, 5.8, 1H, CHS), 4.13 [sept, *J*=6.4, 1H, C*H*(CH$_3$)$_2$], 5.27 (br s, 1H, NH), 5.70 (d, *J*=14.7, 1H, C=CHCO) and 7.54 (d, *J*=14.7, 1H, C=CHS); δ_C 13.72 (C*C*H$_3$), 20.09, 20.19 [C(*C*H$_3$)$_2$], 22.86 [CH(*C*H$_3$)$_2$], 27.25, 38.20, 39.77 (3xCH$_2$), 41.29 (NCH), 45.66, 47.46 (CH$_2$*C*HCH$_2$, CHS), 49.55 [*C*(CH$_3$)$_2$], 55.23 (*C*CH$_3$), 115.89 (C=*C*HCO), 144.60 (S*C*H=C) and 163.97 (C=O); *m/z* 281 (M^+, 16%), 145 (13), 137 (32), 113 (20), 112 (21), 95 (61), 91 (26), 86 (28), 81 (100), 79 (28), 69 (30), 67 (42), 58 (40), 55 (30), 44 (41), 43 (57) and 41 (74) (Found: M^+ 281.1813. Calcd. for $C_{16}H_{27}NOS$: 281.1813).

(E)-*3-Benzylthio*-N-*isopropylpropenamide* (**8cf**): ν 3290 (NH), 3080, 1590, 950 (CH=CH) and 1640 cm^{-1} (C=O); δ_H 1.14 (d, *J*=6.6, 6H, 2xCH$_3$), 4.00 (s, 2H, PhCH$_2$S), 4.12 [sept, *J*=6.6, 1H, C*H*(CH$_3$)$_2$], 5.45 (br s, 1H, NH), 5.76 (d, *J*=14.8, 1H, C=CHCO), 7.30 (m, 5H, ArH) and 7.56 (d, *J*=14.8, 1H, C=C*H*SCH$_2$); δ_C 22.75 (2xCH$_3$), 36.88 (PhCH$_2$), 41.32 (NCH), 117.61 (C=*C*HCO), 127.55, 128.69, 128.74, 136.05 (ArC), 141.30 (S*C*H=C) and 163.54 (C=O); *m/z* 235 (M^+, 2%), 144 (27), 91 (100), 86 (14), 65 (31), 58 (24), 44 (13), 42 (14) and 41 (17) (Found: M^+ 235.1031. Calcd. for $C_{13}H_{17}NOS$: 235.1031).

N-*{*(R)-(E)-*3-[1-(4-Pyridyl)ethoxy]acryloyl}piperidine* (**8dd**): ν 3040, 1580 (CH=CH) and 1640^{-1} (C=O); δ_H 1.40-1.70 [m, 6H, -(CH$_2$)$_3$-], 1.57 (d, *J*=6.7, 3H, CH$_3$), 1.62 (br s, 4H, CH$_2$NCH$_2$), 4.99 (q, *J*=6.7, 1H, ArCH), 5.77 (d, *J*=11.6, 1H, C=CHCO), 7.23 (m, 2H, ArH), 7.45 (d, *J*=11.6, 1H, C=C*H*OCH) and 8.60 (m, 2H, ArH); δ_C 22.86 (CH*C*H$_3$), 24.52 (CH$_2$*C*H$_2$CH$_2$), 26.25 (br, 2xNCH$_2$*C*H$_2$), 42.80 (br, NCH$_2$), 46.74 (br, NCH$_2$), 78.86 (ArCH), 98.38 (C=*C*HCO), 120.46, 150.08, 150.41 (ArC), 159.50 (O*C*H=C) and 165.26 (C=O); *m/z* 154 (M^+- 105, 4%), 138 (13), 106 (100), 84 (44), 78 (36), 77 (41), 71 (10), 69 (15), 56 (20), 51 (24) and 42 (34).

N-*[*(E)-*3-(1-Methylethoxy)acryloyl]piperidine* (**8dg**): ν 1660 (C=O) and 1600 cm^{-1} (CH=CH); δ_H 1.29 (d, *J*=6.4, 6H, 2xCH$_3$), 1.45-1.70 [m, 6H, -(CH$_2$)$_3$-], 3.50 (br s, 4H, CH$_2$NCH$_2$), 4.19 [sept, *J*=6.4, 1H, C*H*(CH$_3$)$_2$], 5.73 (d, *J*=11.6, 1H, C=CHCO) and 7.51 (d, *J*=11.6, 1H, C=C*H*OCH); δ_C 22.06 (2xCH$_3$), 24.53 (CH$_2$*C*H$_2$CH$_2$), 25.91 (br, NCH$_2$*C*H$_2$), 42.81 (br, NCH$_2$), 46.35 (br, NCH$_2$), 75.67 (OCH), 96.48 (C=*C*HCO), 160.33 (O*C*H=C) and 165.87 (C=O); *m/z* 197 (M^+, 5%), 139 (20), 138 (49), 84 (80), 71 (100), 69 (10), 56 (16), 55 (13), 43 (46), 42 (23) and 41 (43) (Found: M^+ 197.1427. Calcd. for $C_{11}H_{19}NO_2$: 197.1416).

(R)-N-*Isopropyl-2-[1-(4-pyridyl)ethoxy]propenamide* (**10cd**): δ_H 1.24 (d, *J*=6.6, 3H, *H*$_3$CCHCH$_3$), 1.26 (d, *J*=6.6, 3H, H$_3$CHC*H*$_3$), 1.61 (d, *J*=6.5, 3H, ArCHC*H*$_3$), 4.16 [sept, *J*=6.6, 1H, C*H*(CH$_3$)$_2$], 4.19 (d, *J*=2.6, 1H, *H*HC=C), 5.06 (q, *J*=6.5, 1H, ArC*H*CH$_3$), 5.39 (d, *J*=2.6, 1H, H*H*C=C), 6.55 (br s, 1H, NH), 7.20 (m, 2H, ArH) and 8.57 (m, 2H, ArH); δ_C 22.58, 22.61, 23.30 (3xCH$_3$), 41.33 (NCH), 75.37 (ArCH), 93.11 (CH$_2$=C), 120.10, 150.45, 150.55 (ArC), 161.11 (CH$_2$=*C*) and 165.40 (C=O); *m/z* 121 (M^+-113, 11%), 106 (100), 79 (13), 78 (27), 77 (25), 57 (15), 51 (21), 43 (42), 42 (88) and 41 (36).

***Hydrolysis of* 8ab. *Preparation of* (E)-*3-[*(E)-*3-Phenyl-2-propenoxy]propenoic acid* (11ab)**[8b]. To a solution of ester **8ab** (116 mg, 0.5 mmol) in dioxane (1 mL) was added aqueous 1N NaOH (1 mL) and the resulting mixture was stirred overnight at room temperature. Water (3 mL) was then added and the solution was extracted with ether (2x5 mL). The aqueous layer was neutralized with concd. HCl and the suspension was extracted with ether (3x5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo* (15 Torr) afforded the title acid which was purified by recrystallization (83 mg, 81%): mp 139-140°C (hexane); ν 3200-2500 (OH), 1690 (C=O), 1620, 970 and 920 cm^{-1} (CH=CH); δ_H 4.57 (d, *J*=6.1, 2H, C=CHC*H*$_2$O), 5.28 (d, *J*=12.5, 1H, C=CHCO), 6.28 (dt, *J*=15.9, 6.1, 1H, C=C*H*CH$_2$O), 6.68 (d, *J*=15.9, 1H, C=CHPh), 7.34 (m, 5H, ArH), 7.72 (d, *J*=12.5, 1H, C=C*H*OCH$_2$) and 9.50 (br s, 1H, CO$_2$H); δ_C 71.94 (CH$_2$O), 96.56 (C=*C*HCO), 122.21, 126.69, 128.35, 128.66, 134.74, 135.78 (ArC, CH=CH), 163.97 (O*C*H=C) and 173.44 (C=O).

***Synthesis of* N*-Phenethylpropenamide* (2e).** A solution of acryloyl chloride (1.2 mL, 15 mmol) in ethyl ether (3 mL) was added dropwise to a solution of phenethylamine (3.8 mL, 30 mmol) in ethyl ether (150 mL) at 0°C. The mixture was stirred at room temperature for 3 h and then washed with 1N HCl (2x50 mL), saturated aqueous NaHCO$_3$ (50 mL) and brine (25 mL). The organic layer was dried (Na$_2$SO$_4$) and evaporated (15 Torr) yielding 2.2 g of amide **2e** (85%): *R*$_f$ 0.37 (Hexane/EtOAc: 1/1); ν 3260 (NH), 3040, 1650 (C=O), 1610, 970 and 950 cm^{-1} (C=CH$_2$); δ_H 2.85 (t, *J*=7.1, 2H, CH$_2$Ph), 3.58 (q, J=7.1, 2H, CH$_2$N), 5.60 (d, *J*=10.4, 1H, C=C*H*H), 6.00 (br s, 1H, NH), 6.06 (dd, *J*=17.1, 10.4, 1H, C=CHCO), 6.24 (d, *J*=17.1, 1H, C=CH*H*), and 7.25 (5H, m, PhH); δ_C 35.49 (PhCH$_2$), 40.65 (NCH$_2$), 126.25, 126.46, 128.57, 128.69, 130.79, 138.74 (ArC, CH$_2$=CH) and 165.61 (C=O); *m/z* 175 (*M*$^+$, 24%), 104 (100), 91 (25), 84 (36), 65 (12) and 54 (80).

***Iodosulphonylation-dehydroiodination of 2e*[11]*. Preparation of* (E)-N*-Phenethyl-3-tosyl-propenamide* (7e).** Iodine (2.69 g, 10.6 mmol) was added to a suspension of the amide **11** (1.86 g, 10.6 mmol) and sodium *p*-toluenesulphinate monohydrate (2.9 g, 14.8 mmol) in CH$_2$Cl$_2$ (150 mL). The mixture was stirred at room temperature for 2 days and then a solution of triethylamine (3.4 mL, 21.2 mmol) in CH$_2$Cl$_2$ (10 mL) was slowly added at 0°C. The resulting solution was stirred at room temperature for 3 h and then successively washed with water (2x50 mL), 1N HCl (2x50 mL), saturated aqueous NaHCO$_3$ (50 mL) and 0.1M aqueous Na$_2$S$_2$O$_3$ (50 mL). The organic layer was dried (Na$_2$SO$_4$) and evaporated (15 Torr) to afford the crude title compound which was purified by elution through a plug of silica gel (hexane/ethyl acetate: 1/1) (2.73 g, 78%): *R*$_f$ 0.55 (Hexane/EtOAc: 1/1); mp 192°C (MeOH); ν 3300 (NH), 3040, 960 (CH=CH), 1640 (C=O), 1300 and 1140 cm^{-1} (SO$_2$); δ_H 2.45 (s, 3H, ArC*H*$_3$), 2.83 (t, *J*=7, 2H, C*H*$_2$Ph), 3.59 (q, *J*=7, 2H, CH$_2$N), 6.15 (br s, 1H, NH), 6.85 (d, *J*=14.7, 1H, C*H*=CH), 7.18-7.37 (m, 8H, PhH, CH=C*H*, 2H of *p*-TolH) and 7.76 (d, *J*=8.6, 2H, *p*-TolH); δ_C 21.68 (ArCH$_3$), 35.18 (PhCH$_2$), 41.12 (NCH$_2$), 126.75, 128.14, 128.65, 128.77, 130.18, 133.09, 135.75, 138.15, 140.32, 145.42 (ArC, CH=CH) and 166.55 (C=O); *m/z* 329 (*M*$^+$, 4%), 139 (52), 104 (100), 91 (38) and 65 (14) (Found: C, 62.70; H, 5.85; N, 4.16; S, 8.77. Calcd. for $C_{18}H_{19}NO_3S \cdot H_2O$: C, 62.23; H, 6.09; N, 4.03; S, 9.23%).

***Synthesis of* (E)*-3-Methylthio-*N*-phenethylpropenamide (Sinharine)* (8eh)**[21]. To a solution of dimethyl disulfide (43 μL, 0.48 mmol) in THF (3 mL) was added n-butyllithium (1.6 M in hexanes, 0.3 mL, 0.48 mmol) at room temperature and under argon. This cloudy suspension was added dropwise to a stirred solution of the tosylamide **7e** (132 mg, 0.4 mmol) in THF (4 mL) at room temperature during *ca.* 30 min. After 15 min of additional stirring, water (15 mL) was added and the mixture was extracted with ether (2x10 mL). Evaporation of the dried (Na$_2$SO$_4$) solvent and elution of the resulting residue from silica gel (hexane/ethyl acetate: 4/1) afforded sinharine (**8eh**; 68 mg, 77%): *R*$_f$ 0.42 (Hexane/EtOAc: 1/1); δ_H 2.27 (s, 3H, SCH$_3$), 2.83 (t, *J*=7, 2H, CH$_2$Ph), 3.56 (q, *J*=7, 2H, CH$_2$N), 5.61 (d, *J*=14.6, 1H, C=CHCO), 5.90 (br s, 1H, NH), 7.24 (m, 5H, PhH) and 7.58 (d, *J*=14.6, 1H, C=CHS); δ_C 14.46 (SCH$_3$), 35.62 (PhCH$_2$), 40.61 (NCH$_2$), 115.80 (C=*C*HCO), 126.34, 128.49, 128.63 and 138.84 (ArC), 142.46 (S*C*H=C) and 164.52 (C=O); *m/z* 221 (*M*$^+$, 5%), 174 (15), 101 (100), 91 (15) and 73 (10).

ACKNOWLEDGMENTS

We thank DGICYT (Project PB91-0751) from the Spanish Ministerio de Educación y Ciencia (MEC) for financial support. R. C. thanks MEC for a postdoctoral fellowship.

REFERENCES AND NOTES

1. Larock, R. C. In *Comprehensive Organic Transformations;* VCH Publishers: New York, 1989; pp. 187-188.

2. (a) Schmidt, R. R. In *Organic Synthesis: An Interdisciplinary Challenge;* Streith, J.; Prinzbach, H.; Schill, G., Eds.; Blackwell Scientific Publications: Oxford, 1985; p. 281. (b) Barua, N. C.; Schmidt, R. R. *Tetrahedron* **1986**, *42*, 4471-4474. (c) Barua, N. C.; Schmidt, R. R. *Chem. Ber.* **1986**, *119*, 2066-2068. (d) Barua, N. C.; Schmidt, R. R. *Synthesis* **1986**, 891-893. (e) Barua, N. C.; Schmidt, R. R. *Synthesis* **1986**, 1067-1070. (f) Plewe, M.; Schmidt, R. R. *Synthesis* **1989**, 534-536. (g) Hirsenkorn, R.; Schmidt, R. R. *Liebigs Ann. Chem.* **1990**, 883-889. (h) Jatzke, H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1991**, 753-757.
3. (a) Jatzke, H.; Evertz, U.; Schmidt, R. R. *Synlettt* **1990**, 191-193. (b) Datta, A.; Datta, D.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 8035-8038.
4. Datta, A.; Schmidt, R. R. *Synlett* **1992**, 429-430.
5. Datta, A.; Schmidt, R. R. *Tetrahedron Lett.* **1993**, *34*, 4161-4164.
6. Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1994**, *35*, 3103-3104.
7. (a) Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831-4834. (b) Lee, E.; Tae, J. S.; Chong, Y. H.; Park, C. M. *Tetrahedron Lett.* **1994**, *35*, 129-132. (c) Lee, E.; Park, C. M. *J. Chem. Soc., Chem. Commun.* **1994**, 293-294.
8. (a) Büchi, G. H.; Vogel, D. E. *J. Org. Chem.* **1983**, *48*, 5406-5408. (b) Vogel, D. E.; Büchi, G. H. *Org. Synth. Coll. Vol. VIII*, pp. 536-539.
9. (a) Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450-458. (b) Perlmutter, P. in *Conjugate Addition Reactions in Organic Synthesis*, Baldwin, J. E.; Magnus, P. D. Eds., Pergamon Press: Oxford, 1992.
10. Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73-80.
11. Nájera, C.; Baldó, B.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1029-1032.
12. (a) Schank, K. In *Methoden der Organischen Chemie (Houben-Weyl)*; Georg Thieme Verlag: Stuttgart, 1985; vol. E/11. (b) *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C. Eds.; J. Wiley & Sons: Chichester, 1988. (c) Simpkins, N. S. In *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993.
13. (a) Nájera, C.; Yus, M. *Tetrahedron Lett.* **1987**, *28*, 6709-6712. (b) Nájera, C.; Yus, M. *J. Org. Chem.* **1988**, *53*, 4708-4715. (c) Nájera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1387-1391.
14. Nájera, C.; Mancheño, B.; Yus, M. *Tetrahedron Lett.* **1989**, *30*, 6085-6088.
15. (a) Nájera, C.; Yus, M. *Tetrahedron Lett.* **1989**, *30*, 173-176. (b) Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1987**, 92-94. (c) Haynes, R. K.; Vonwiller, S. C.; Hambley, T. W. *J. Org. Chem.* **1989**, *54*, 5162-5170.
16. (a) Buss, A. D.; Hirst, G.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1836-1837. (b) Jung, M E.; Truc, V. C. *Tetrahedron Lett.* **1988**, *29*, 6059-6062. (c) León, F. M.; Carretero, J. C. *Tetrahedron Lett.* **1991**, *32*, 5405-5408.
17. (a) Chiericato, M.; Dalla Croce, P.; Carganico, G.; Maiorana, S. *J. Heterocyclic Chem.* **1979**, *16*, 383-384. (b) Jungheim, L. N.; Barnett, C. J.; Gray, J. E.; Horcher, L. H.; Shepherd, T. A.; Sigmund, S. K. *Tetrahedron* **1989**, *44*, 3119-3126.
18. (a) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7-15. (b) Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474-479.
19. Croxall, W. J.; Van Hook, J. O. U.S. Patent 2 535 009, 1950; *Chem. Abstr.* **1951**, *45*, 3869e.
20. (1*S*-*exo*)-2-Bornanethiol has been prepared according to: Blanco, J. M.; Caamaño, O.; Eirín, A.; Fernández, F.; Medina, L. *Synthesis* **1990**, 584-586.
21. (a) Greger, H.; Hofer, O.; Kählig, H.; Wurz, G. *Tetrahedron* **1992**, *48*, 1209-1218. (b) Hinterberger, S.; Hofer, O.; Greger, H. *Tetrahedron* **1994**, *50*, 6279-6286.

(*Received in UK* 22 *November* 1994; *revised* 24 *January* 1995; *accepted* 27 *January* 1995)