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Bromine Addition to α-(1-Hydroxyalkyl)- and α-(1-Alkoxyalkyl)-α,β-unsaturated Esters: an Approach to Hydroxyfimbrolide and Bromobeckerelide

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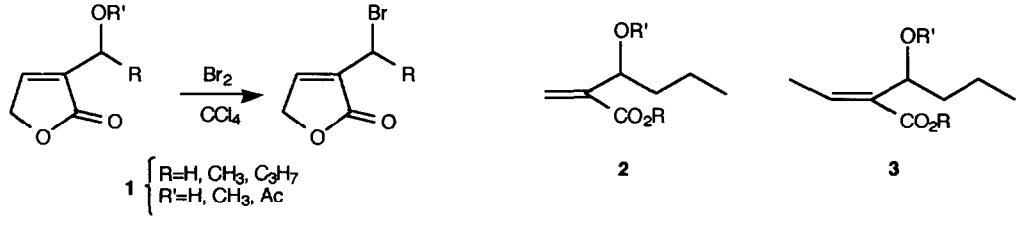
Abstract: Conventional ionic bromination of electron-poor olefins, 2-(1-hydroxyalkyl)- and 2-(1-alkoxyalkyl)propenoates, **2b-d**, and methyl (*E*)-2-(1-hydroxyethyl)-2-butenoate, **3a**, proceeds with yields higher than 80%. Treatment of (*E*)-3-bromo-2-[1-[(2-methoxyethoxy)methoxy]butyl]propenoic acid, **16**, with two equivalents of strong bases, reaction related with a possible hydroxyfimbrolide and bromobeckerelide synthesis, resulted in the halogen-metal exchange reaction affording the acrylic acid **18**, presumably through the generation of dianion **19**.

INTRODUCTION

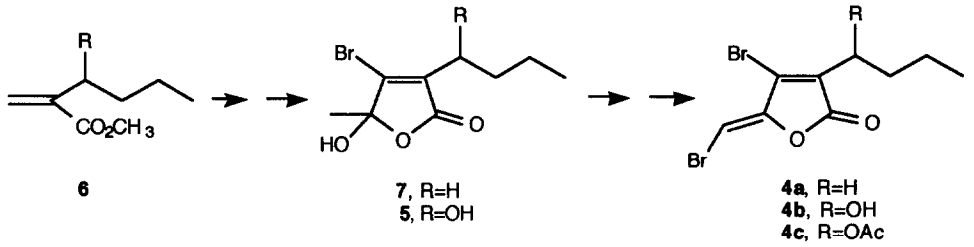
In a previous paper we described unexpected substitution reactions when 3-(1-hydroxyalkyl)-2(5*H*)-furanones, **1**, were treated with bromine[1] (Scheme 1) and very recently other authors have described that several α-methylene-γ-butyrolactones did not add bromine efficiently.[2] In order to study the possible effect of the heterocyclic system in the bromination reaction we decided to synthesize some acyclic di- and trisubstituted olefins with the general structure **2** and **3** having similar functionalization like lactones **1**. In addition to this



Scheme 1

study some of these compounds could be useful intermediates in the synthesis of hydroxyfimbrolide (**4b**), acetoxyfimbrolide (**4c**), and bromobeckerelide, **5**, highly functionalized secondary metabolites of marine origen (Scheme 2).[3,4] All these metabolites present the structure of 4-bromo-3-butyl-2(5*H*)-furanone. No synthesis of hydroxy- nor acetoxyfimbrolide has been yet reported and only two syntheses of fimbrolides, **4a**,[5] and one of bromobeckerelide[6] have been described. One of these methods[5b] uses methyl 2-butylpropenoate, **6** (R=H), as starting material to synthesize **4a** through the intermediate **7** (R=H). The incorporation of a hydroxyl

group -free or protected- to the starting material of the previously described sequence, would allow us to prepare hydroxy- and acetoxyfimbrolides, **4b** and **4c**, and bromobeckerelide, **5**, using a common intermediate (**6**, R=OR' or **2**).



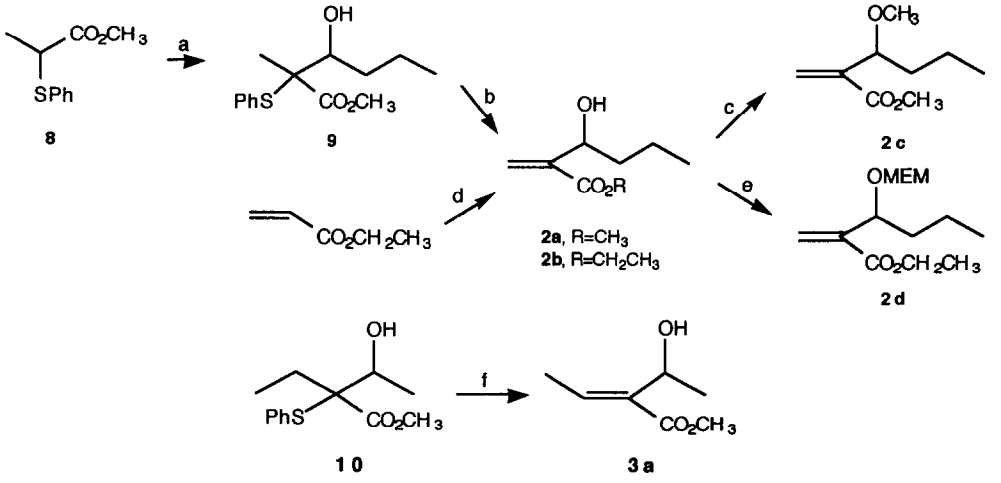
Scheme 2

Therefore, in this paper the synthesis of several new α-(1-hydroxyalkyl)- and α-(1-alkoxyalkyl)-α,β-unsaturated esters is described; their bromination reactions studied and the subsequent dehydrobrominated derivatives being used as intermediates in an approach to the synthesis of hydroxyfimbrolide and bromobeckerelide.

RESULTS AND DISCUSSION

Synthesis of terminal olefins 2a-d and trisubstituted olefin 3a

For the study indicated above we have synthesized the terminal olefins **2a-d** and the trisubstituted olefin **3a** (Scheme 3). Unsaturated esters **2a** and **2b** had been synthesized before by the reaction of acrylic esters with butanal using a trialkylphosphine[7] or 1,4-diazabicyclo[2.2.2]octane as catalyst, Baylis-Hillman reaction.[8] Nevertheless, we wanted to apply our methodology for the synthesis of lactones **1**[1] to open chain products; therefore, we treated the anion of **8**[9] with butyraldehyde at -50°C in the absence of Lewis catalysts isolating the



a) LDA, THF, butanal; b) $NaIO_4$, MeOH, H_2O; $CHCl_3$, reflux; c) MeI, KOH, DMSO; d) DABCO, butanal; e) MEMchloride, $(iPr)_2NEt$, CH_2Cl_2; f) $NaIO_4$, MeOH, H_2O; pyrolysis at 140°C

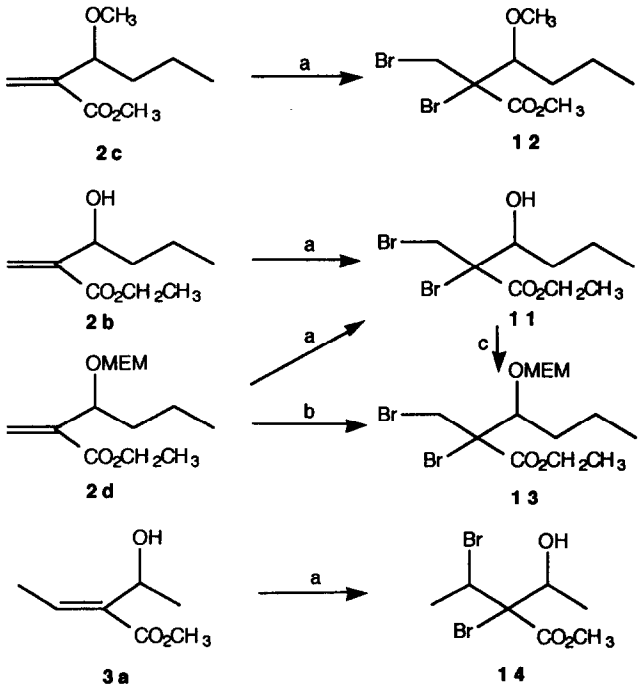
Scheme 3

ester **9** in 84% yield. This represents a new example where the condensation between an α-phenylthioester and an aldehyde is satisfactory without the addition of catalysts,[1] although this is not always the case[10] (*vide infra*). Oxidation of **9** with sodium periodate in methanol/water at room temperature followed by pyrolysis of the corresponding sulphoxides afforded **2a** in 86% yield. The free hydroxyl group could be converted to the methyl ether **2c** by treatment with methyl iodide in dimethylsulphoxide. Also olefin **2d** was synthesized in quantitative yield by treatment of **2b**, prepared now by the Baylis-Hillman reaction,[8] with MEMchloride in the presence of *N,N*-diisopropylethyl amine.[11] The incorporation of the acetal group was demonstrated by the singlet at δ 4.66 in its pmr spectrum and the absorption at δ 93.7 in the cmr spectrum.

Although Hill and Isaacs[12] recently described the synthesis of **3a** in 50% yield by a Baylis-Hillman reaction at high pressure, we have synthesized this ester by oxidation and subsequent pyrolysis of methyl 2-ethyl-3-hydroxy-2-(phenylthio)butanoate, **10** (Scheme 3), prepared by condensation of methyl 2-(phenylthio)butanoate[13] with acetaldehyde in the presence of a Lewis acid catalyst (*vide supra*). The pyrolysis of the sulphoxides of **10** led to a crude containing a 5:1 mixture of (*E*)-**3a** and (*Z*)-**3a**, and methyl 2-ethyl-3-oxobutanoate (minor product), as shown by the presence of two quartets at δ 6.82 and 6.20 and a singlet at δ 2.14 respectively. Formation of the acetoacetate ester can be explained by elimination of phenylsulphenic acid through the proton attached at C-3. Column chromatography of this crude allowed only the isolation of pure (*E*)-**3a** (62% yield) and ethyl acetoacetate (10% yield).

Bromination reaction of olefins 2b-d and 3a

At this point, to compare the behaviour of these α,β-unsaturated esters with the one observed on lactones **1**, we submitted **2b-d** and **3a** to conventional ionic bromination conditions. Reaction of these olefins with



a) Br_2,CCl_4; b) Br_2, CCl_4, $NaHCO_3$; c) MEMchloride, $AgNO_3$, DMF

Scheme 4

molecular bromine proceeded smoothly, allowing the isolation of the dibromo derivatives **11**, **12**, and **13**, and **14** in 93%, 80%, 83%, and 85% yield respectively (Scheme 4). The only required precaution was the addition of sodium bicarbonate to the reaction mixture of **2d**, since its absence resulted in the hydrolysis of the acetal group, being **11** the only isolated product in good yield. The pmr spectrum of the diastereoisomers of **12** presented three singlets at δ 3.53, 3.83, and 3.93 assignables to the methyl ether, methyl ester, and the bromomethyl group respectively. Its chemical ionization mass spectrum (NH_3) had signals at *m/e* 352-350-348 corresponding to the ion $(C_9H_{16}Br_2O_3+18)^+$. The crude of the bromination reaction of **2b** yielded after column chromatography pure analytical samples of the diastereoisomers **11a** and **11b** in a ratio 1:1.5. The less polar isomer **11a** presents an intramolecular hydrogen bond as indicated by an absorption at δ 3.33 (doublet) in its pmr spectrum, while the corresponding signal of **11b** appears at δ 2.00. Based on this observation and molecular model analysis we assigned the relative stereochemistry (2*RS*,3*SR*) to **11a** (Figure 1, conformation **A**); the formation of a hydrogen bond in **11b** would imply a gauche position for the bulkiest groups (conformation **B**), being **C** the most stable conformer. In compound **11a** the diastereotopic protons of

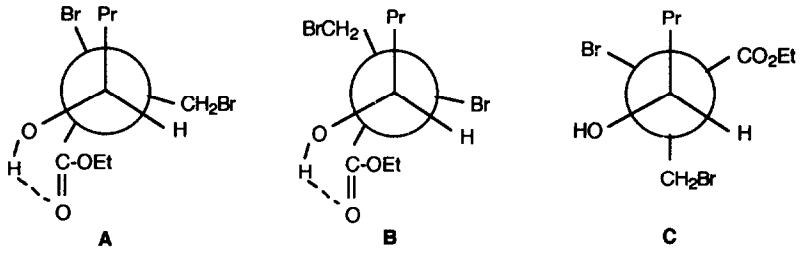


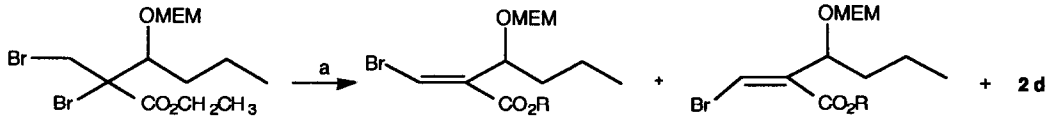
Figure 1

the bromomethyl group absorb as a well resolved AB system at δ 3.82 and 4.13 (J=10.9 Hz) as a consequence of steric hindrance to rotation due to the propyl group. This assignment is confirmed by the cmr spectra: C-4 and C-1' are upfield shifted (δ 32.9/33.7) in isomer **11a** compared to **11b** (δ 35.4/37.1) due to a γ gauche effect. The bromination reaction of **2d** yielded two isomers, **13a** and **13b** by elution order, in a ratio 1:4, being the chemical shift differences too small for a stereochemical assignment. Nevertheless, the acetalization reaction of **11a** allowed the isolation of pure **13b**, therefore establishing the relative stereochemistry (2*RS*,3*SR*) for the more polar isomer. This acetalization reaction presented some problems, since treatment of alcohol **11** with MEMchloride under the previously utilized reaction conditions[11] or with triethylmethoxyethoxymethyl ammonium chloride in dry acetonitrile solution at reflux[11a] yielded only unreacted starting material. We next tried MEMchloride in the presence of silver nitrate and *N,N*-dimethylformamide (DMF), reaction conditions already described for the preparation of methoxymethyl ethers.[14] After several attempts by changing temperature, reaction time, and the number of equivalents of added silver salt, only 39% yield of acetal **13** could be isolated in the best case and the yield was not always reproducible. Therefore, for our synthetic purposes we prepared **13** by bromination of olefin **2d.**

The rate of electrophilic attack of bromine to a double bond decreases with the presence of an electron-withdrawing substitutent at the allylic position.[15] The main difference between the acyclic olefins submitted to bromination in this work and the lactones **1** of our previous work is the presence of a third electron-withdrawing substituent in the heterocyclic compounds (allylic oxygen atom of the lactone ring) that should be crucial for the progress of the reaction. The present work shows that a di- or trisubstituted open chain olefin with only two electron-withdrawing substituents (an ester group and an allylic alcohol) is still nucleophilic enough to attack bromine and it can be assumed that is the presence of the γ-lactone ring which introduces additional stereoelectronic effects to the normal bromine addition to those electron-poor olefins.

Approach to the synthesis of hydroxyfimbrolide and bromobeckerelide

Having in our hands the highly functionalized ester **13** we turned our attention to the synthetic approach to hydroxyfimbrolide and bromobeckerelide. The next required step was the dehydrobromination of **13** (Scheme 5), a reaction described as difficult and with moderate yields using sodium *iso*-propoxide as base with 2-bromo-2-bromomethylhexanoate as substrate.[5b] This reaction conditions applied to **13** yielded a crude containing at least seven compounds (gc). The use of triethyl amine in ether left the dibromo derivative unaltered and treatment with lithium bromide in hot DMF[16] gave a complex mixture. We turned our attention to 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[17] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[17] frequently used in dehydrohalogenation reactions. Reaction of **13b** with DBN unexpectedly yielded **2d** almost quantitatively. After an exhaustive study of the reaction conditions the best results were obtained when using DBU in tetrahydrofuran at 4°C after one week of reaction time. These conditons applied to **13b** allowed us the isolation of the dehalogenated compound **2d** (21%) and propenoates (*E*)-**15** (21%) and (*Z*)-**15** (28%). Isomer **13a** yielded mainly the undesired derivative **2d**. The assignment of the double bond configuration of **15** was based on the chemical shifts of the olefinic protons: the isomer with a low field absorption (δ 7.54) due to the anisotropic effect of the ester group[18] was identified as (*E*)-**15**, while the (*Z*)-isomer presented this absorption at δ 6.65. Cmr data support this assignment, since the β-olefinic carbon atoms absorb at δ 122.8 and 110.9 respectively.[19]

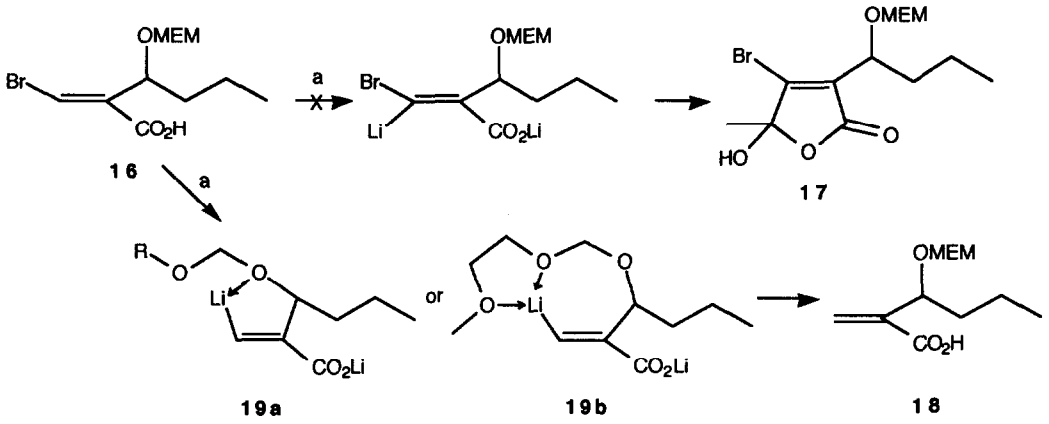


13 **15**, R=CH_2CH_3; **16**, R=H

a) DBU, THF, 4°C, 7 d; KOH, EtOH, H_2O

Scheme 5

Both esters **15** were independently submitted to hydrolysis using potassium hydroxide in aqueous ethanol affording acids (*E*)- and (*Z*)-**16** in *ca.* 70% yield. The olefin configuration was again deduced from the chemical shifts of the olefinic protons: δ 7.69 for isomer (*E*) and δ 6.78 for the (*Z*) configuration. Condensation of (*E*)-**16** with acetic anhydride in the presence of two equivalents of *n*-BuLi[5b] did not allow the isolation of the desired lactone **17** (Scheme 6). The only identified compounds were starting material (41%) and the debrominated acid **18** (18%, two singlets at δ 5.90 and 6.42 corresponding to the terminal methylene group). The recovery of significant quantities of starting material can be explained by competitive deprotonation of the acylating agent.[20] Compound **18** results from the halogen-metal exchange reaction, process also known for the preparation of β-lithio-α,β-unsaturated acid salts.[21] A possible interpretation for the undesired evolution of this reaction is that the presence of the three oxygen atoms from the ether chain would favour the halogen-metal exchange reaction over the desired acid-base one due to the formation of dipole stabilized[22] cyclic chelated lithium compounds like **19a** or **19b**. The directing effect of the analogous methoxymethoxy group by formation of chelates is already well documented.[23] We also performed the reaction using *sec*-BuLi, but results were similar. Therefore, this route to hydroxyfimbrolide and bromobeckerelide seems to be unvalidated.



a) 2 eq. *n*-BuLi or *sec*-BuLi, THF, -78°C, Ac_2O

Scheme 6

EXPERIMENTAL SECTION

The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The 80 MHz pmr and 20 MHz cmr spectra were recorded on a Bruker WP80SY spectrometer from deuterated chloroform solutions; chemical shifts are given in ppm relative to TMS (δ values). Distillation of small amounts were effected on a Büchi KRV 65/30 rotational distillator (only oven temperature given). Mass spectra and gc-ms analyses (70 eV for electron impact and ammonia as reagent gas for chemical ionization) were recorded on a Hewlett-Packard 5985B gc-ms system; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments. In all column chromatographies was used silica gel 230-400 mesh. Methyl 2-(phenylthio)propanoate, **8**, and methyl 2-(phenylthio)butanoate were prepared following the methods of Leyendecker *et al.*[9] and Pandit *et al.*[13] respectively.

Methyl 3-hydroxy-2-methyl-2-(phenylthio)hexanoate, **9**

To a stirred solution of 9.0 mmol of lithium diisopropylamide (LDA) in 9 mL of THF at -70°C a solution of ester **8** (1.5 g, 7.6 mmol) in THF (15 mL) was slowly added over a period of 30 minutes. The solution was kept at the same temperature for 2 h. Then, a solution of butyraldehyde (1.0 g, 15 mmol) in THF (5 mL) was added. The crude mixture was left at -50°C during other 2 h and it was poored over 45 mL of cold saturated ammonium chloride solution. The ether extracts (3x30 mL) were dried over anhydrous sodium sulphate and the solvent was eliminated under reduced pressure to yield 2.1 g of a yellow oil, which was chromatographed through a silica gel column affording the following fractions: i) with hexane-ethyl acetate (9:1) as eluent 157 mg (10% yield) of starting material **8**, followed by 615 mg (30% yield) of one diastereoisomer of methyl 3-hydroxy-2-methyl-2-(phenylthio)hexanoate, **9a**; ii) with hexane-ethyl acetate (8:2) as eluent 1.08 g (54% yield) of the other isomer **9b**. Both diastereoisomers were separately distilled (bp 110-120°C/0.1 torr) affording colorless oils. **9a**: ir (neat) 3600-3300, 3060, 2970, 2880, 1720, 1440, 1260, 1110, 1070 cm-1; pmr 0.95 (t, J=6.2 Hz, 3H), 1.15-1.66 (m, 7H; 1.35, s), 2.73 (br. s, 1H), 3.60 (s, 3H), 3.80-3.97 (m, 1H), 7.28-7.50 (m, 5H); cmr 13.7, 16.4, 19.8, 34.2, 51.7, 61.1, 72.1, 128.6, 129.4, 129.9, 136.8, 172.4. **9b**: ir (neat) 3600-3300, 3060, 2970, 2880, 1720, 1440, 1250, 1130, 1090 cm-1; pmr 0.98 (t, J=6.2 Hz, 3H), 1.29-1.87 (m, 7H; 1.38, s), 2.48 (br. s, 1H), 3.64 (s, 3H), 3.77-4.00 (m, 1H), 7.29-7.43 (m, 5H); cmr 13.8, 17.1, 19.7, 32.7, 51.8, 59.3, 73.7, 128.5, 129.3, 130.2, 136.7, 173.4; ms m/e 268 (M+, 2), 196 (100), 164 (89),

137 (62), 135 (30), 109 (26), 105 (81), 71 (26), 59 (36), 55 (27), 43 (47). Anal. Calcd. for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51; S, 11.95. Found: C, 62.78; H, 7.53; S, 11.95.

Methyl 2-(1-hydroxybutyl)propenoate, **2a**

To a magnetically stirred solution of ester **9** (300 mg, 1.1 mmol) in methanol (4 mL) at 0°C, a water solution (4 mL) of sodium periodate (287 mg, 1.3 mmol) was slowly added during 20 minutes. The solution was kept at room temperature for 20 h. Then chloroform (20 mL) was added and the resulting organic phase was washed successively with $NaHCO_3$ solution and water, dried over anhydrous sodium sulphate and the solvent was eliminated under reduced pressure. The crude was dissolved in chloroform (6 mL) and was heated at reflux during 6 h. Elimination of the solvent by vacuum distillation afforded a yellow oil, which was chromatographed through a silica gel column. With methylene chloride-ether (9:1) as eluent 149 mg (86% yield) of a colorless oil identified as **2a** were obtained: bp 100-105°C/13 torr; lit.[7a] 77-78°C/5 torr; ir ($CHCl_3$) 3600-3300, 3020, 2960, 2880, 1710, 1630 cm^{-1}; pmr 0.95 (t, J=6.2 Hz, 3H), 1.28-1.70 (m, 4H), 2.20 (br. s, 1H), 3.80 (s, 3H), 4.43 (t, J=6.1 Hz, 1H), 5.80 (m, 1H), 6.23 (m, 1H); cmr 13.6, 18.7, 38.3, 51.5, 70.9, 124.4, 142.8, 166.9; ms *m/e* 143 (M^+-15, 3), 115 (95), 98 (20), 89 (25), 83 (100), 71 (44), 57 (20), 56 (31), 55 (43), 43 (29), 41 (33).

Ethyl 2-(1-hydoxybutyl)propenoate, **2b**

This product was prepared in 85% yield by the Baylis-Hillman reaction[8a,e] of butanal with ethyl acrylate in the presence of DABCO: bp 123-125°C/11 torr; lit.[7b] bp 70-71°C/0.3 torr.

Methyl 2-(1-methoxybutyl)propenoate, **2c**

A suspension of potassium hydroxide (224 mg, 4 mmol) in dimethyl sulphoxide (DMSO, 15 mL) was prepared in a flask. Hydroxyester **2a** (158 mg, 1 mmol) in DMSO (0.5 mL) and then methyl iodide (456 mg, 3.2 mmol) were added at room temperature. After 3 h water (20 mL) was added and the mixture was extracted with methylene chloride (3x20 mL). The organic layer was washed with water (5x20 mL), dried over anhydrous sodium sulphate and the solvent was eliminated under reduced pressure yielding a yellow oil (140 mg). This crude was purified by column chromatography through silica gel using methylene chloride as eluent. This process allowed the isolation of 70 mg (41% yield) of ester **2c**: pmr 0.77-1.00 (m, 3H), 1.27-1.63 (m, 4H), 3.23 (s, 3H), 3.73 (s, 3H), 4.05 (m, 1H), 5.73 (s, 1H), 6.23 (s, 1H).

Ethyl 2-[1-[(2-methoxyethoxy)methoxy]butyl]propenoate, **2d**

Hydroxyester **2b** (3.0 g, 17 mmol) was dissolved in anhydrous methylene chloride (20 mL) in a flask with argon atmosphere at 0°C. *N,N*-Diisopropylethylamine (5.05 g, 29 mmol) was added to the stirred solution, which was kept 10 min at the same temperature. MEMchloride (3.4 mL, 29 mmol) dissolved in CH_2Cl_2 (10 mL) was slowly added during 30 min. The mixture was left 40 h at room temperature and other 24 h at 30°C. Methylene chloride was added and the organic phase was successively washed with HCl 5% (2x10 mL) and saturated NaCl solution (30 mL). It was dried over anhydrous sodium sulphate and the solvent was eliminated by vacuum distillation to afford an orange oil (7.1 g), that was purified by column chromatography using chloroform-ether (9:1) as eluent. This process allowed the isolation of 4.48 g (98% yield) of pure **2d** as a colorless liquid: bp 98-100°C/0.2 torr; ir (neat) 2960, 2940, 2880, 1720, 1630 cm^{-1}; pmr 0.92 (t, J=6.2 Hz, 3H), 1.16-1.70 (m, 7H; 1.30, t, J=7.5 Hz), 3.36 (s, 3H), 3.45-3.76 (m, 4H), 4.20 (q, J=7.5 Hz, 2H), 4.53 (m, 1H), 4.66 (s, 2H), 5.76 (m, 1H), 6.26 (m, 1H); cmr 13.6, 14.0, 18.6, 37.8, 58.7, 60.4, 67.1, 71.6, 74.4, 93.7, 124.5, 141.7, 165.9; ms *m/e* 217 (M^+-43, 2.3), 155 (26), 109 (25), 89 (100), 81 (26), 59 (100),

45 (53), 43 (23). Anal. Calcd. for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 60.23; H, 9.63.

Methyl (2RS,3RS)- and *(2RS,3SR)-2-ethyl-3-hydroxy-2-(phenylthio)butanoate,* **10**

A solution of methyl 2-(phenylthio)butanoate[13] (5.0 g, 23.8 mmol) in anhydrous THF (50 mL) was slowly added (90 min) at -70°C to a stirred solution of LDA (28.5 mmol) in THF (30 mL) . This solution was added to a flask that contained $ZnCl_2$ (6.48 g, 47.6 mmol) at 0°C under inert atmosphere. The mixture was stirred until dissolution of the salt and acetaldehyde (2.09 g, 47.6 mmol) in THF (15 mL) was added. The mixture was left at 0°C during 90 min and it was poored over 100 mL of cold saturated ammonium chloride solution. The corresponding ether extracts (3x50 mL) were dried over anhydrous sodium sulphate and the solvent was eliminated under reduced pressure to yield a crude (6.58 g), that was purified by column chromatography affording the following fractions: i) with hexane-ethyl acetate (9:1) as eluent 510 mg (10%) of starting material; ii) with hexane-ethyl acetate (3:1) 4.5 g (75% yield) of diastereoisomers **10** as colorless oil with bp 100-105°C/0.7 torr: ir ($CHCl_3$) 3600-3400, 2980, 2950, 1720, 1700, 1430, 1240 cm^{-1}; pmr 0.92 (t, J=7.4 Hz) + 1.06 (t, J=7.4 Hz) (3H), 1.34 (d, J=6.2 Hz) + 1.36 (d, J=6.2 Hz) (3H), 1.58-2.00 (m, 2H), 3.09 (br. s, 1H), 3.65 (s) + 3.70 (s) (3H), 4.00 (q, J=6.2 Hz) + 4.20 (q, J=6.2 Hz) (1H), 7.25-7.60 (m, 5H); cmr 9.4, 17.2, 25.0, 26.4, 51.7, 64.6, 64.8, 68.8, 69.5, 128.3, 128.5, 129.1, 129.2, 130.2, 136.7, 137.3, 172.6, 173.5; ms *m/e* 254 (M^+, 5), 237 (2), 210 (82), 178 (81), 151 (39), 149 (37), 121 (36), 109 (66), 105 (100), 73 (50), 65 (35), 45 (52). Anal. Calcd. for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13; S, 12.60. Found: C, 61.30; H, 6.95; S, 12.50.

Methyl (E)-2-(1-hydroxyethyl)-2-butenoate, **3a**

The procedure described for the synthesis of **2a** was applied to the esters **10** (1.43 g, 5.6 mmol) with the only difference that the crude sulphoxides were pyrolysed directly. The pyrolysis was performed at 140°C/190 torr during 3 h and afforded 1.37 g of crude **3a** as an (*E*)- and (*Z*)- mixture (*ca.* 5:1). Column chromatography of this material using methylene chloride as eluent (caution: the solvent of the fractions was eliminated under reduced pressure at <15°C) gave methyl 2-ethyl-3-oxobutanoate (82 mg, 10% yield) and pure (*E*)-**3a**[12] (490 mg, 62% yield): bp 90-95°C/100 torr; ir ($CHCl_3$) 3600-3400, 3000, 2980, 2950, 1680, 1640, 1430, 1280, 1080, 1050, 1010, 870 cm^{-1}; pmr 1.40 (d, J=6.8 Hz, 3H), 1.84 (d, J=7.5 Hz, 3H), 2.90 (m, 1H), 3.78 (s, 3H), 4.75 (q, J=6.8 Hz, 1H), 6.82 (q, J=7.5 Hz, 1H); cmr 13.5, 23.0, 51.4, 64.6, 135.2, 137.6, 167.6; ms *m/e* 129 (M^+-15, 94), 101 (13), 97 (100), 69 (20). Isomer (*Z*)-**3a** presented in its pmr spectrum a quartet at δ 6.20 (J=7.5 Hz).

Ethyl (2RS,3RS)- and *(2RS,3SR)-2-bromo-2-bromomethyl-3-hydroxyhexanoate,* **11**

To a light protected and stirred solution of ester **2b** (4.0 g, 23 mmol) in CCl_4 (40 mL) at 0°C a solution of bromine (3.72 g, 23 mmol) in the same solvent (20 mL) was slowly added over a period of 90 min. The mixture was kept at 0°C for three additional hours (colorless solution) and it was successively washed with saturated sodium bisulphite solution (40 mL) and water. The organic layer was dried over anhydrous sodium sulphate and the solvent was eliminated under reduced pressure to yield 7.8 g of a yellow oil. Column chromatography using chloroform-ether (95:5) as eluent allowed the isolation of both diastereoisomers **11a** and **11b** pure, allong with several fractions containing mixtures (7.12 g, 93% yield). **11a**: ir (neat) 3600-3300, 2980, 2880, 1720, 1290, 1190 cm^{-1}; pmr 0.84-1.07 (t, 3H), 1.24-1.73 (m, 7H; 1.35, t, J=7.2 Hz), 3.33 (br. d, J=4.8 Hz, 1H), 3.82 (d, J=10.9 Hz, 1H), 3.97-4.51 (m, 4H; 4.13, d, J=10.9 Hz; 4.34, q, J=7.2 Hz); cmr 13.7, 18.7, 32.9, 33.7, 62.9, 67.6, 71.9, 169.1; ms *m/e* 335-333-331 (M^++1, 1.4, 2.7, 1.6), 317-315-313 (1.8, 3.5, 1.8), 181 (93), 179 (100), 153 (56), 151 (58), 83 (22), 55 (40), 43 (25); ms *m/e* (CI/NH_3) 352-

350-348 (M^++18). Anal. Calcd. for $C_9H_{16}Br_2O_3$: C, 32.55; H, 4.86; Br, 48.13. Found: C, 32.55; H, 4.83; Br, 48.23. **11b**: ir (neat) 3600-3300, 2980, 2880, 1740, 1290, 1190 cm^{-1}; pmr 0.86-1.05 (t, 3H), 1.21-180 (m, 7H; 1.33, t, J=7.2 Hz), 2.00 (d, J=7.9 Hz, 1H), 3.97-4.42 (m, 5H; 4.04, d, J=9.7 Hz; 4.12, d, J=9.7 Hz; 4.25, q, J=7.2 Hz); cmr 13.70, 13.75, 19.3, 35.4, 37.1, 62.6, 69.7, 72.9, 167.4; ms *m/e* 335-333-331 (M^++1, 0.8, 1.6, 0.8), 317-315-313 (1.1, 2.4, 1.2), 181 (44), 179 (44), 153 (25), 151 (28), 83 (36), 55 (95), 43 (100), 41 (89). Anal. Calcd. for $C_9H_{16}Br_2O_3$: C, 32.55; H, 4.86; Br, 48.13. Found: C, 32.58; H, 5.04; Br, 47.98.

Methyl 2-bromo-2-bromomethyl-3-methoxyhexanoate, **12**

To a light protected and stirred solution of ester **2c** (63 mg, 0.4 mmol) in carbon tetrachloride (1 mL) a solution of 58 mg (0.4 mmol) of bromine in CCl_4 was slowly (25 min) added at 0°C. The mixture was stirred at 20°C for 17 h, it was successively washed with saturated sodium bisulphite and water, the organic phase was dried over anhydrous sodium sulphate, and the solvent was eliminated under reduced pressure to afford a yellow oil (97 mg, 80% yield) identified as **12**: pmr 0.86-1.10 (m, 3H), 1.46-1.63 (m, 4H), 3.30-3.70 (m, 4H; 3.53, s), 3.83 (s, 3H), 3.93 (s, 2H); ms *m/e* (CI/NH_3) 352-350-348 (M^++18).

Ethyl (2RS,3RS)- and *(2RS,3SR)-2-bromo-2-bromomethyl-3-[(2-methoxyethoxy)methoxy]hexanoate*, **13**

A) A suspension of isomers **11a** and **11b** (98 mg, 0.3 mmol) and silver nitrate (300 mg, 1.8 mmol) in DMF (1 mL) was placed in a septum stopped flask with magnetical stirring and argon atmosphere. After 10 min 0.34 mL (3.0 mmol) of MEMchloride were added. The mixture was diluted with ether (20 mL) after 7 h and the precipitate was filtered off. The organic layer was washed with water (5x10 mL), dried over anhydrous sodium sulphate, the solvent was eliminated, and the crude was chromatographed through a silica gel column using chloroform-ether (99:1) as eluent allowing the recovery of 29% of starting material and 39% of a mixture of diastereoisomers **13a** and **13b**.

B) To a light protected and magnetically stirred suspension of acrylate **2d** (1.0 g, 3.8 mmol) and sodium bicarbonate (5.0 g) in CCl_4 (10 mL) at 0°C a solution of bromine (614 mg, 3.8 mmol) in the same solvent (5 mL) was slowly (40 min) added. The mixture was left overnight at room temperature. Non reacted halogen was eliminated by washing with a 0.5 M solution of $NaHSO_3$. The resulting mixture was extracted with ether, the organic phase was dried over anhydrous sodium sulphate, and the solvent was eliminated under reduced pressure. Column chromatography of the residue using chloroform-ether (99:1) as eluent yielded **13a** (250 mg) and **13b** (1.09 g; total yield 83%). **13a**: ir (neat) 2970, 2940, 2880, 1740, 1270, 1040 cm^{-1}; pmr 0.80-1.09 (t, 3H), 1.33 (t, J=7.5 Hz, 3H), 1.53-1.76 (m, 4H), 3.40 (s, 3H), 3.46-3.80 (m, 4H), 3.85-4.21 (m, 3H), 4.30 (q, J=7.5 Hz, 2H), 4.90 (s, 2H); cmr 13.8, 14.0, 19.9, 36.1, 37.6, 58.9, 62.6, 68.0, 69.0, 71.6, 80.2, 97.0, 167.4; ms *m/e* 347-345-343 (M^+-75, 0.4, 0.7, 0.5), 125 (30), 89 (80), 59 (100), 45 (31). **13b**: ir (neat) 2970, 2940, 2880, 1740, 1270, 1030 cm^{-1}; pmr 0.80-1.09 (t, 3H), 1.33 (t, J=7.5 Hz, 3H), 1.50-1.83 (m, 4H), 3.40 (s, 3H), 3.46-3.80 (m, 4H), 3.93-4.10 (m, 3H), 4.30 (q, J=7.5 Hz, 2H), 4.90 (s, 2H); cmr 13.8, 13.9, 19.9, 35.38, 35.47, 58.9, 62.7, 68.0, 69.2, 71.6, 82.4, 97.6, 167.3; ms *m/e* 347-345-343 (M^+-75, 0.2, 0.3, 0.2), 89 (100), 59 (95), 45 (26); ms *m/e* (CI/NH_3) 440-438-436 (M^++18). Anal. Calcd. for $C_{13}H_{24}Br_2O_5$: C, 37.16; H, 5.76; Br, 38.04. Found: C, 37.24; H, 6.13; Br, 38.00.

Methyl 2-bromo-2-(1'-bromoethyl)-3-hydroxybutanoate, **14**

To a light protected and stirred solution of 100 mg (0.7 mmol) of ester (*E*)-**3a** in CCl_4 (2 mL) a solution of bromine (110 mg, 0.7 mmol) in the same solvent (1 mL) was slowly added at 0°C. The mixture was stirred overnight at room temperature and the solvent was eliminated under reduced pressure to afford 195 mg of a yellow oil, that was column chromatographed using methylene chloride as eluent. This purification process

afforded 177 mg (85% yield) of **14** as a diatereoisomeric mixture: ir (neat) 3600-3200, 2980, 2940, 1740, 1420, 1250 cm^{-1}; pmr 1.37 (d, J=6.2 Hz) + 1.40 (d, J=6.2 Hz) (3H), 1.75 (d, J=7.0 Hz) + 1.84 (d, J=7.0 Hz) (3H), 2.24-2.52 (br. s, 1H), 3.84 (s) + 3.87 (s) (3H), 4.29 (m, 1H), 4.59 (q, J=7.0 Hz), + 4.83 (q, J=7.0 Hz) (1H). Repeated column chromatography of this fraction using methylene chloride-ethyl acetate (19:1) as eluent allowed the isolation of the more polar isomer of **14** pure: bp 90-94°C/0.6 torr; pmr 1.37 (d, J=6.2 Hz, 3H), 1.84 (d, J=7.0 Hz, 3H), 2.30-2.50 (br. s, 1H), 3.84 (s, 3H), 4.29 (m, 1H), 4.59 (q, J=7.0 Hz, 1H); cmr 19.0, 23.7, 52.5, 53.6, 73.8, 81.8, 167.0; ms *m/e* 291-289-287 (M^+-15, 0.2, 0.4, 0.3), 259-257-255 (0.3, 0.5, 0.2), 181 (100), 179 (95), 149 (32), 147 (30), 83 (26); ms *m/e*(CI/NH_3) 324-322-320 (M^++18). Anal. Calcd. for $C_7H_{12}Br_2O_3$: C, 27.66; H, 3.98. Found: C, 27.82; H, 3.94.

Ethyl (E)- and *(Z)-3-bromo-2-[1-[(2-methoxyethoxy)methoxy]butyl]propenoate,* **15**

To a magnetically stirred solution of **13b** (498 mg, 1.2mmol) in anhydrous THF (10 mL) kept at -30°C under argon atmosphere, a solution of diazabicycloundecene (DBU, 0.2 mL, 1.4 mmol) in the same solvent (2 mL) was slowly added (30 min). The mixture was left at 4°C during 5 d and DBU (0.1 mL) was again added and the crude was maintained at 4°C for other 2 d. The mixture was diluted with water (10 mL), slightly acidified with HCl 5%, and extracted with ether (3x20 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent was eliminated at reduced pressure yielding a yellow oil (324 mg), that was purified by column chromatography using methylene chloride-ethyl acetate (19:1) as eluent. This operation allowed the isolation of 45 mg (9%) of starting ester **13b**, 112 mg (28%) of (*Z*)-**15** as a colorless oil (bp 100-105°C/0.3 torr), 84 mg (21%) of colorless (*E*)-**15** (bp 95-98°C/0.5 torr), and 65 mg (21%) of debrominated compound **2d**. (*Z*)-**15**: ir ($CHCl_3$) 2960, 2940, 2880, 1725, 1620, 1040 cm^{-1}; pmr 0.84-1.08 (t, 3H), 1.26-1.71 (m, 7H; 1.32, t, J=7.5 Hz), 3.40 (s, 3H), 3.48-3.68 (m, 4H), 4.29 (q, J=7.5 Hz, 2H), 4.39 (br. t, 1H), 4.68 (d, J=9.7 Hz, 1H), 4.93 (d, J=9.7 Hz, 1H), 6.65 (s, 1H); cmr 13.6, 14.0, 18.5, 37.0, 58.8, 61.0, 67.3, 71.6, 77.0, 93.5, 110.9, 140.1, 165.3; ms *m/e* 265-263 (M^+-75, 0.8, 0.8), 89 (100), 59 (82). Anal. Calcd. for $C_{13}H_{23}BrO_5$: C, 46.03; H, 6.83; Br, 23.56. Found: C, 46.55; H, 6.53; Br, 23.25. (*E*)-**15**: ir ($CHCl_3$) 2970, 2940, 2880, 1720, 1600, 1040 cm^{-1}; pmr 0.84-1.03 (t, 3H), 1.22-2.10 (m, 7H; 1.32, t, J=7.5 Hz), 3.40 (s, 3H), 3.48-3.77 (m, 4H), 4.26 (q, J=7.5 Hz, 2H), 4.70 (s, 2H), 4.87 (dd, J=7.7 Hz, J'=6.2 Hz, 1H), 7.54 (s, 1H); cmr 13.7, 14.0, 18.9, 35.5, 58.8, 60.9, 67.1, 71.6, 75.0, 94.2, 122.8, 138.0, 163.6; ms *m/e* (CI/NH_3) 358-356 (M^++18). Anal. Calcd. for $C_{13}H_{23}BrO_5$: C, 46.03; H, 6.83. Found: C, 46.18; H, 7.16.

(Z)-3-bromo-2-[1-[(2-methoxyethoxy)methoxy]butyl]propenoic acid, (*Z*)-**16**

A sample of ester (*Z*)-**15** (119 mg, 0.35 mmol) was dissolved in 2.4 mL of a 0.2 M solution of KOH in ethanol-water (3:1) at room temperature. The ethanol was eliminated at reduced pressure after 24 h and ether and 1 M NaOH solution were added. The water phase was acidified with HCl 1M to pH 4 and it was extracted with ether. The organic layer was dried over anhydrous sodium sulphate and the solvent was eliminated affording pure (*Z*)-**16** (77 mg, 71% yield) as a colorless oil: ir ($CHCl_3$) 3500-2400, 2970, 2940, 1690, 1600, 1040 cm^{-1}; pmr 0.95 (t, 3H), 1.20-1.84 (m, 4H), 3.40 (s, 3H), 3.50-3.66 (m, 4H), 4.34 (t, J=6.8 Hz, 1H), 4.65 (d, J=7.5 Hz, 1H), 4.94 (d, J=7.5 Hz, 1H), 6.78 (s, 1H), 7.44 (br. s, 1H); cmr 13.7, 18.8, 37.2, 59.0, 67.4, 71.7, 78.2, 94.3, 113.5, 139.3, 168.1; ms *m/e* (CI/NH_3) 330-328 (M^++18).

(E)-3-bromo-2-[1-[(2-methoxyethoxy)methoxy]butyl]propenoic acid, (*E*)-**16**

The same hydrolysis procedure described for (*Z*)-**15** was applied to the (*E*) isomer (140 mg, 0.4 mmol) allowing the isolation of pure (*E*)-**16** as a colorless oil in 73% yield: ir ($CHCl_3$) 3500-2400, 2970, 2940, 1690, 1600, 1040 cm^{-1}; pmr 0.96 (t, 3H), 1.25-2.00 (m, 4H), 3.37 (s, 3H), 3.46-3.78 (m, 4H), 4.72, (s,

2H), 4.91 (dd, J=8.5 Hz, J'=6.2 Hz, 1H), 7.69 (s, 1H), 8.31 (br. s, 1H); cmr 13.8, 16.8, 35.4, 58.9, 67.5, 71.6, 75.0, 94.5, 125.9, 136.7, 167.0; ms *m/e* (CI/NH_3) 330-328 (M^++18).

Reation of (E)-16 with acetic anhydride in the presence of base

To a stirred solution of acid (*E*)-**16** (46 mg, 0.15 mmol) in THF (3 mL) at -78°C and under argon atmosphere, 0.18 mL (0.3 mmol) of 1.6 M solution of *n*-BuLi in hexane were slowly added (40 min), and the mixture was left at this temperature during 2 h. This solution was slowly added (20 min) to acetic anhydride (28 μL, 0.3 mmol) in THF (1 mL) at -78°C. The resulting mixture was left at this temperature during 3 h, it was warmed up to room temperature, diluted with water, acidified with HCl 5% to pH 4, and extracted with ether (2x5 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent was eliminated affording a crude (45 mg) that was column chromatographed yielding two fractions: i) 6 mg (18%) of 2-[1-[(2-methoxyethoxy)methoxy]butyl]propenoic acid, **18**, using hexane-ethyl acetate (1:1) as eluent; and ii) 19 mg (41%) of starting material using ethyl acetate-ethanol (1:1) as mobile phase. **18**: pmr 0.93 (t, 3H), 1.16-1.77 (m, 4H), 3.38 (s, 3H), 3.48-3.67 (m, 4H), 4.52 (t, J=5.7 Hz, 1H), 4.70 (s, 2H), 5.90 (s, 1H), 6.42 (s, 1H); ms *m/e* (CI/NH_3) 250 (M^++18).

A 22% yield of **18** and 37% of recovered acid (*E*)-**16** were obtained when the reaction was repeated using *sec*-BuLi as base.

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REFERENCES

1. Calderón, A.; Font, J.; de March, P. *J. Org. Chem.* **1987**, *52*, 4631-4633.
2. a) Collado, I.G.; Madero, J.G.; Massanet, G.M.; Luis, F.R. *Tetrahedron Lett.* **1990**, *31*, 563-566; b) Collado, I.G.; Massanet, G.M.; Alonso, M.S. *Tetrahedron Lett.* **1991**, *32*, 3217-3220.
3. a) Kazlauskas, R.; Murphy, P.T.; Quinn, R.J.; Wells, R.J. *Tetrahedron Lett.* **1977**, 37-40; b) Pettus, J.A., Jr.; Wing, R.M.; Sims, J.J. *Tetrahedron Lett.* **1977**, 41-44.
4. Ohta, K. *Agric. Biol. Chem.* **1977**, *41*, 2105-2106.
5. a) Beechan, C.M.; Sims, J.J. *Tetrahedron Lett.* **1979**, 1649-1652; b) Caine, D.; Ukachukwu, V.C. *J. Org. Chem.* **1985**, *50*, 2195-2198.
6. Jefford, C.W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1989**, *30*, 1237-1240.
7. a) Morita, K. *Chem. Abstr.* **1968**, *69*, 58828s; b) Morita, K. *Chem. Abstr.* **1969**, *70*, 19613u.
8. a) Baylis, A.B.; Hillman, M.E.D. *Chem. Abstr.* **1972**, *77*, 34174q; b) Ameer, F.; Drewes, S.E.; Emslie, N.D.; Kaye, P.T.; Mann, L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2293-2295; c) Rabe, J.; Hoffmann, H.M.R. *Angew. Chem., Int. Ed. Engl.* **1983**, 22, 796-797; d) Hoffmann, H.M.R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849-3859; e) Drewes, S.E.; Roos, G.H.P. *Tetrahedron* **1988**, *44*, 4653-4670.
9. Leyendecker, F.; Comte, M.T. *Tetrahedron* **1986**, *42*, 1413-1421.
10. a) Trost, B.M.; Mao, M.K.T. *Tetrahedron Lett.* **1980**, *21*, 3523-3526; b) Hoye, T.R.; Kurth, M.J. *J. Org. Chem.* **1980**, *45*, 3549-3554.
11. a) Corey, E.J.; Gras, J.L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809-812; b) Canonica, S.; Ferrari, M.; Jommi, G.; Sisti, M. *Synthesis* **1988**, 697-699.
12. Hill, J.S.; Isaacs, N.S. J. *Chem. Res. (S)* **1988**, 330-331.
13. Stoit, A.R.; Pandit, U.K. *Tetrahedron* **1985**, *41*, 3345-3354.

14. Hardinger, S.A.; Fuchs, P.L. *J. Org. Chem.* **1987**, *52*, 2738-2749.
15. Dubois, J.E.; Goetz, E. *Tetrahedron Lett.* **1965**, 303-308.
16. Gharbi-Benarous, J.; Essayegh, M.M.; Dana, G. *Can. J. Chem.* **1987**, *65*, 2031-2038; b) Font. J.; Gracia, A.; de March, P. *Tetrahedron Lett.* **1990**, *31*, 5517-5520.
17. a) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591-598; b) Aberhart, D.J.; Tann, C.H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 939-942; c) Wolkoff, P. *J. Org. Chem.* **1982**, *47*, 1944-1948.
18. Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden*; Springer-Verlag: Berlin 1976.
19. Rappe, C.; Lippmaa, E.; Pehk, T.; Andersson, K. *Acta Chem. Scand.* **1969**, *23*, 1447-1450; b) Font, J.; Gracia, A.; de March, P. *Tetrahedron* **1990**, *46*, 4407-4416.
20. Caine, D.; Ukachukwu, V.C. *Tetrahedron Lett.* **1983**, *24*, 3959-3960.
21. Caine, D.; Frobese, A.S. *Tetrahedron Lett.* **1978**, 5167-5170.
22. Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; van Hülsen, E. *Chem. Ber.* **1985**, *118*, 2822-2851 and references cited therein.
23. Winkle, M.R.; Ronald, R.C. *J. Org. Chem.* **1982**, *47*, 2101-2108 and references cited therein.