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# Nucleophilic substitution on α-mesyloxy-O-alkyloximes — I. Enantiospecific synthesis of 2-(imidazol-1-yl)-1,3-diphenylpropan-1-one O-alkyloximes

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***Abstract:*** An enantiospecific synthesis of (S)- and (R)-(E)-5-[1,3-diphenyl-2-(imidazol-1-yl)propylidene] aminooxypentanoic acids **1** using homochiral phenylalanines as starting material is described. Chiral α-hydroxyketones **9** were obtained from α-hydroxyacids **7** by Weinreb's ketone synthesis. Imidazole introduction by nucleophilic substitution on mesylate **10** led to 2-(imidazol-1-yl)propan-1-one derivative **3**, key intermediate in the synthesis of **1**. However, the low configurational stability displayed by compound **3** compromised its use in an enantiospecific synthesis. Homochiral compounds **1** were then obtained by a nucleophilic substitution on α-mesyloxy-O-alkyloximes **14** which were in turn obtained from **9**. This nucleophilic substitution on α-mesyloxy-O-alkyloximes was not previously reported either on homochiral compounds or on racemic derivatives.


In the search for agents endowed with both thromboxane A2 (TxA2) synthase inhibition and TxA2 receptor antagonism, we identified (±)-(E)-5-[1,3-diphenyl-2-(imidazol-1-yl)propylidene]aminooxypentanoic acid **1** (Scheme 1) as a lead showing both properties satisfactorily. The presence in **1** of a stereogenic centre raised the question of a possible enantioselectivity towards both biological mechanisms of action.

The synthesis of racemic **1** (Scheme 1) was carried out through the benzylation of imidazolylacetophenone **2** and subsequent reaction of ketone **3** with 5-aminooxypentanoic acid to provide E/Z mixture of O-alkyloximes **4**, whose chromatographic separation led to desired E isomer **1**. Since any attempt of resolution either of racemic **1** or intermediate **3** by classical fractional crystallization of diastereoisomeric salts seemed impracticable, we considered the possibility of an enantiospecific synthesis[2] of **1**. We discarded the possibility of an enantioselective benzylation leading to enantiomers of ketone **3**, following Ender's approach used in the case of SAMP/RAMP hydrazones[3] **5** (Scheme 2), for two reasons: the relatively low enantiospecificity experienced in the case of SAMP hydrazones when an aromatic ring was adjacent to the alkylation centre[3], and the possible configurational instability of hydrazones **5** during the deblocking step.

A retrosynthetic analysis for compound **1** showed a phenylalanine framework embedded in the synthon **3** (Scheme 3), thus suggesting a possible enantiospecific synthesis using an aminoacid as homochiral starting material[4].

Although Reetz's chiral α-aminoketone synthesis[5] allows the direct preparation of the intermediate enantiomers **6** from phenylalanine, the synthesis of the imidazole ring[6] affording compound **3** appeared

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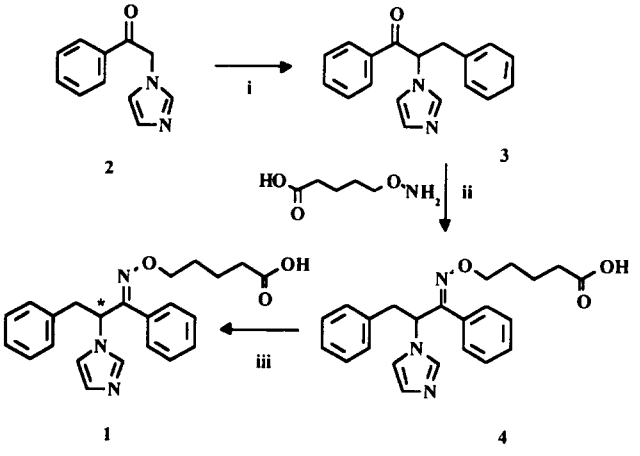
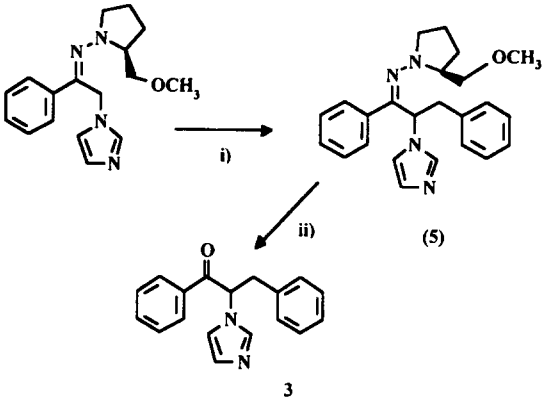
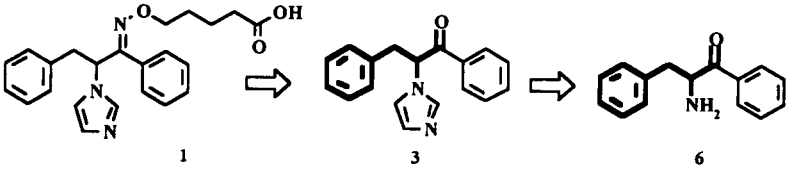


**Scheme 1.** (i) NaH, benzyl bromide, THF; (ii) pyridine; (iii) chromatographic separation.



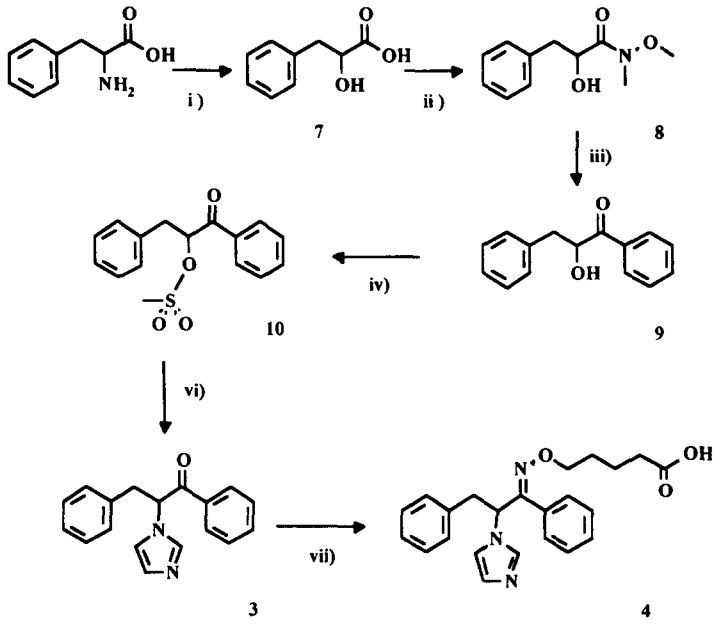
**Scheme 2.** (i) LDA, THF then $PhCH_2Br$; (ii) $O_3$, MeOH.



**Scheme 3.**

slow and with risk of racemization. On the other hand, the introduction of heterocycles bearing basic nitrogen by nucleophilic substitution on $\alpha$-mesyloxy or $\alpha$-haloketones has been reported[7], though this did not concern chiral compounds.

We applied this approach to the synthesis of non-racemic chiral intermediates **3**, starting from the corresponding $\alpha$-hydroxyketones **9** (**9a**=S; **9b**=R), that may be easily prepared from homochiral phenylalanine derivatives by Weinreb's ketone synthesis[8] (Scheme 4). Thus homochiral $\alpha$-hydroxy acids **7**

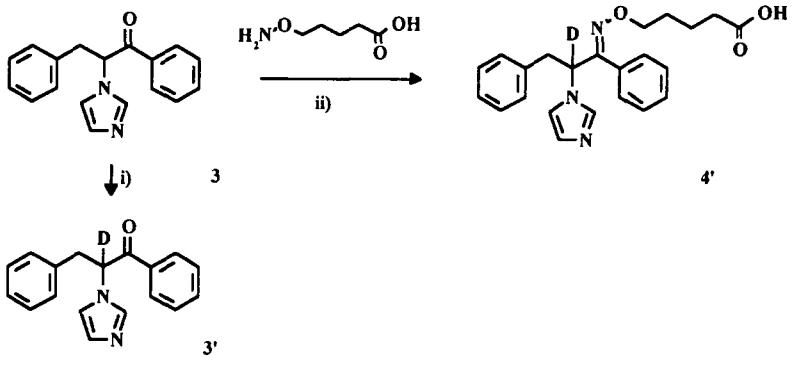



**Scheme 4.** (i) Acetic acid, $HNO_2$, 0°C→r.t.; (ii) $NH(CH_3)(OCH_3)\cdot HCl$, N-methylmorpholine, DCC, DMAP, $CH_2Cl_2$, 0°C→r.t.; (iii) PhMgBr, $Et_2O$, reflux; (iv) MsCl, $Et_3N$, $CH_2Cl_2$, 0°C; (vi) imidazole, DMF, r.t.; (vii) 5-aminooxypentanoic acid, pyridine, 0°C.

(**7a**=S; **7b**=R), available on the large scale by diazotisation of (R)- or (S)-phenylalanine with retention of configuration[9], were condensed without hydroxyl protection, with N,O-dimethylhydroxylamine using N,N′-dicyclohexylcarbodiimide (DCC), to provide the corresponding N-methyl-N-methoxy-amides **8** in 70% yield. These were in turn reacted with phenylmagnesium bromide in refluxing diethyl ether to yield the α-hydroxyketones **9** of good enantiomeric excess and with yields (68–75%) better than those previously reported[10] for an analogous reaction involving 3-phenyllactic amide. Nucleophilic displacement of the mesylate **10** with imidazole led to the ketone **3** in 88% yield.

However, a preliminary reaction of the racemic **3**, prepared from racemic **9**, with 5-amino-oxypentanoic acid, carried out in the presence of $D_2O$ in order to detect a possible enolization during the oxime formation, revealed a 40% to 60% deuterium uptake at the α-position of oxime **4** when the reaction was carried out in pyridine or in ethanol, respectively[11] (Scheme 5). This unexpected extensive deuterium uptake, probably due to the presence of the electron-withdrawing 1-imidazolyl group in the α-position, prompted us to verify the configurational stability of compound **3** itself. Thus a solution of the ketone **3** and imidazole in DMF containing 10% of $D_2O$, was stirred at room temperature for 24 hours in conditions similar to those of imidazole nucleophilic substitution on mesylate **10**. The assessment of deuterium uptake[11], indicated approximately 50% deuteration at position 2. Configurational instability of the ketone **3** may occur either during its synthesis or during the reaction leading to **4**.

On the contrary, deuterium uptake was not detected[11] on oximation of the racemic α-hydroxyketone **9** either using the aminooxyacid or its ethyl ester. This evidence suggested intermediate **9** as a configurationally more stable precursor for enantiospecific synthesis of **1**. Though nucleophilic substitution on α-halo-oximes are known to proceed *via* an elimination/addition double step process[12], that does not allow their involvement in enantiospecific synthesis, this mechanism is not possible for α-halo or α-mesyloxy-O-alkyloximes. Homochiral α-hydroxy-O-alkyloximes **11a** or **b** and **12a** or **b** (Scheme 6), were prepared as a E/Z diastereoisomeric mixture, by reaction of the α-hydroxyketones

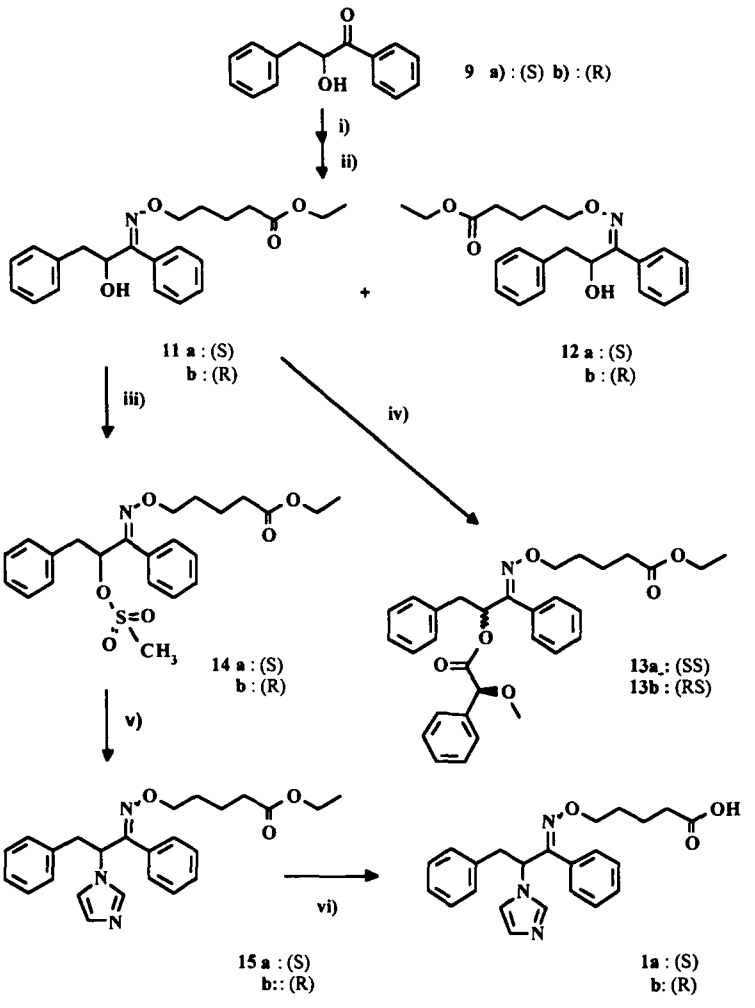



**Scheme 5.** (i) Imidazole, $D_2O$, DMF, r.t.; (ii) $D_2O$, pyridine, r.t.; or EtOH/NaOAc, r.t.; or EtOH reflux.

(S)-**9a** or (R)-**9b** with ethyl 5-aminooxypentanoate in pyridine. Column chromatography allowed the separation of the oximes **11a** and **b** from the corresponding Z-diastereoisomers **12a** and **b**. The E or Z configurations for oximes **11** and **12**, were assessed by $^1$H NMR spectroscopy, as previously described[1], on the basis of chemical shift differences observed for the protons on carbon adjacent to the oxime moiety, according to the assignments reported in the literature[14].

The enantiomeric purity of the E-oximes **11a** and **11b** was evaluated by esterification with (S)-$\alpha$-methoxy-phenylacetic acid[13]. The diastereoisomeric couple of esters (SS)-**13a** and (RS)-**13b** (Scheme 6) were analyzed by $^1$H NMR spectroscopy[15]. The spectrum corresponding to the diastereoisomeric mixture of mandelate esters **13** showed significant differences in the resonances of the methoxy (3.22 $\delta$ (SS), 3.25 $\delta$ (RS)) and the methine $\alpha$- to the oxime moiety (5.92 $\delta$ (SS), 5.82 $\delta$ (RS)). Evaluation of **13a** and **13b** indicated a diastereoisomeric excess higher than 98%, the signals corresponding to the other diastereoisomer being absent in each spectrum. The $\alpha$-hydroxyoximes **11a** and **11b**, by reaction with mesyl chloride provided the mesylates **14a** or **b** (Scheme 6) which were in turn converted to the corresponding esters **15** in 72–79% yield by reaction with imidazole in DMF. Mesylates **14** were found to be not stable enough for further purification, but were usually obtained adequately pure to be used in the next step. However, in order to exclude the formation of the corresponding chloride under the reaction conditions, a small amount of the racemic mesylate **14** was purified by column chromatography and analyzed by $^1$H NMR spectroscopy. The presence of the methanesulfonic ester signal at 2.50 ppm, confirmed the structure assigned for compound **14**, and at the same time excluded a double inversion of configuration, during the conversion of the $\alpha$-hydroxyoxime **11** into the imidazolyl-derivative **15**. Final hydrolysis of the esters **15** (LiOH, THF/water) provided the enantiomers of compounds **1**. The enantiomeric excess of compounds **1a** and **1b** was evaluated by HPLC on a chiral stationary phase. Separation of racemic compound **1** into its enantiomers was achieved using an Ultron ES-OVM column[16], the retention time for the enantiomers (S)-**1a** and (R)-**1b** being 15.1 min and 11.7 min, respectively. Compounds **1a** and **1b**, displayed an enantiomeric excess of 85% and 92% respectively, corresponding to a racemization of 7.8% and 4.1%. Whether this small amount of racemization was mainly due to an $SN_1$ component accompanying the prevalent $SN_2$ nucleophilc substitution of imidazole on mesylate **14**, or to racemization occuring during the hydrolysis of the ester **17** was not established[17].

In conclusion, in this paper we report an enantiospecific route to the O-alkyloxime **1** starting from enantiomerically pure $\alpha$-amino acids, based on an hitherto undescribed enantiospecific nucleophilic substitution on an $\alpha$-mesyloxy-O-alkyloxime.




**Scheme 6.** (i) Ethyl-5-aminooxypentanoate hydrochloride, pyridine; (ii) column chromatography; (iii) $CH_3SO_2Cl$, $Et_3N$, $CH_2Cl_2$; (iv) (S)-2-methoxyphenylacetyl chloride, $CH_2Cl_2$, $K_2CO_3$; (v) imidazole, DMF; (vi) LiOH, THF/$H_2O$.

## Experimental

Melting points were determined in open glass capillaries, with a Buchi 535 melting point apparatus and are uncorrected. $^1H$ NMR spectra were recorded on a Varian VXR-200, a Varian VXR-400 or a Bruker WP-80 SY spectrometer, using the solvent as internal standard, chemical shifts are expressed in $\delta$ (ppm), coupling constants (J), are expressed in Hertz. Field desorption (FD), or electron impact (EI) mass spectra (MS) were obtained on Varian MAT 311A and Varian MAT CH7 instruments. Specific rotations were taken with a Jasco DIP 140 polarimeter operating at 25°C ($\lambda$=589 nm), using a 10 cm cuvette. Products, where applicable, were dried over anhydrous $Na_2SO_4$ and evaporated using an Heidolph VV 2000 rotary evaporator at 15 mmHg. Flash column chromatographic separations were carried out according to the method of Still[18], on 40/60 $\mu$m silica gel (Carlo Erba). Thin-layer chromatography was performed on Whatman silica gel 60 plates coated with 250 $\mu$m layer, with fluorescent indicator. Components were visualized by UV light ($\lambda$:254 nm), or by spraying with suitable reagents: 2,4-dinitrophenylhydrazine was used to detect ketones, Druggendorff's reagent was used to detect imidazole containing compounds. Dichloromethane ($CH_2Cl_2$) and benzene were distilled

from $P_2O_5$ and stored over 4Å molsieves. Diethyl ether ($Et_2O$) and tetrahydrofuran (THF) were dried over sodium benzophenone, distilled and stored over 4Å molsieves. All reactions dealing with air or moisture-sensitive materials were performed in flame dried glassware under dry nitrogen atmosphere. Air and moisture-sensitve solutions were transferred with hypodermic syringes or doubled-ended needles. Starting materials, unless otherwise specified, were commercially available (Aldrich, Fluka), of the best grade and were used without further purification. (L)- and (D)-3-phenyllactic acids were obtained from (L)-or (D)-phenylalanine by diazotization in aqueous acetic acid according to known procedure[15], mp 125–126°C, $[\alpha]_D$=+21.3 (water, c=0.3), Lit.+21.2 (water, c=0.8)[9].

*(R,S)-N-Methyl-N-methoxy-2-hydroxy-3-phenylpropionamide* ***8***

N-Methyl-morpholine (15.8 mL, 0.144 mol) dissolved in $CH_2Cl_2$, was added dropwise to an ice-cooled suspension of N,O-dimethylhydroxylamine hydrochloride (14 g, 0.144 mol) in $CH_2Cl_2$ (150 mL), over 20 min; then (R,S)-3-phenyllactic acid (18.2 g, 0.11 mol) was added portionwise at 0°C. To the resulting stirred suspension, dimethylaminopyridine (DMAP) (0.366 g, 3 mmol) was added in one portion, then a solution of DCC (33.4 g, 0.162 mol) in $CH_2Cl_2$ (150 mL) was slowly added, maintaining the temperature below 5°C. The reaction mixture was stirred at 0°C for 2 h, and at r.t. overnight (TLC: Hexane/EtOAc 70:30). The precipitated dicyclohexylurea (DCU) was filtered and the filtrate concentrated to a pale yellow oil, which was taken up with EtOAc. A further amount of DCU was precipitated on standing and separated by filtration, the filtrate was washed with saturated $NaHCO_3$ aqueous solution, water 2N HCl, and finally brine. Drying and evaporation yielded a colorless oil which after chromatograpy (Hexane/EtOAc, 80:20) afforded pure **8** (13 g, 70%), colorless prisms, mp. 52–53°C ($Et_2O$/hexane). $^1$H NMR (80 MHz; $CDCl_3$) $\delta$: 2.70–3.20 (2H, m, $CH_2$CH, ABX system, AB part); 3.23 (s, 3H, $NCH_3$); 3.72 (s, 3H, $OCH_3$); 4.60 (1H, m, $CH_2CH$, ABX system, X part);7.28 (s, 5H, Phenyl). IR (KBr) cm$^{-1}$: 3600–3200; 2840; 1660; 1450; 1370; 1170; 980.

*(S)-N-Methyl-N-methoxy-2-hydroxy-3-phenylpropionamide* ***8a***

The title compound was prepared in 75% yield starting from (S)-3-phenyllactic acid as described above; mp. 54–55°C (diisopropyl ether/hexane). $[\alpha]_D$=−53.76 (Acetone, c=0.88).

*(R)-N-Methyl-N-methoxy-2-hydroxy-3-phenylpropionamide* ***8b***

The title compound was prepared in 68% yield starting from (R)-3-phenyllactic acid as described above; mp. 54–55°C (diisopropyl ether/hexane). $[\alpha]_D$=+51.6 (Acetone, c=1.14).

*(R,S)-1,3-Diphenyl-2-hydroxy-propanone* ***9***

A solution of phenylmagnesium bromide (from bromobenzene, 7.4 mL, 70 mmol, and magnesium turnings 1.9 g, 78 mmol) in dry $Et_2O$ (85 mL), was added by a double-ended needle to a stirred solution of compound **8** (6.7 g, 27.8 mmol) in dry THF (150 mL) cooled at 0°C, under $N_2$ atmosphere, over 10 min, applying a positive nitrogen pressure to the Grignard reaction vessel. The resulting reaction mixture was stirred at 0°C for 30 min, then allowed to warm to r.t. and refluxed for 3 h (TLC, Hexane/EtOAc 70:30). The reaction mixture was quenched by adding saturated $NH_4Cl$ on cooling at 0°C, $Et_2O$ was added and the organic layer separated, washed twice with saturated $NH_4Cl$, then with brine, and then dried. Evaporation of the solvents and column chromatography (Hexane/$Et_2O$ 30%) provided the pure compound **9** (4.5 g, 72%), colorless needles, mp. 51–53°C ($Et_2O$/hexane). $^1$H NMR (400 MHz; $CDCl_3$) $\delta$: 2.90 (dd, $J_{AB}$=14.3, $J_{AX}$=7.0, 1H, *A*BX system, $CH_2$CH); 3.20 (dd, $J_{AB}$=14.3, $J_{AX}$=4.1, 1H, A*B*X system, $CH_2$CH); 3.70 (d, J=6.7, 1H, O*H*); 5.38 (m, 1H, AB*X* system, $CH_2CH$); 7.12 (m, 2H, $H_2$+$H_6$ unconjugated phenyl); 7.23 (m, 3H, unconjugated phenyl's H); 7.54 (m, 2H, $H_3$+$H_5$, conjugated phenyl); 7.64 (m, 1H, $H_4$ , conjugated phenyl); 7.94 (m, 2H, $H_2$+$H_6$ conjugated phenyl). 11229MS (EI) m/z: 208 $(M\text{-}H_2O)^{+\cdot}$; 121 $(M\text{-}C_7H_5O)^+$; 105 $(C_7H_5O)^+$; 91 $(C_7H_7)^+$. IR (KBr) cm$^{-1}$: 3580–3260; 2910; 1680; 1580; 1450; 1260.

*(S)-1,3-Diphenyl-2-hydroxy-propanone* ***9a***[10]

The title compound was prepared in 60% yield as reported above starting from compound **8a**. Colorless needles, mp. 52–53°C, $[\alpha]_D$=−15.5 (Acetone, c=0.8); Lit: −13 (c=0.14; acetone)[10].

*(R)-1,3-Diphenyl-2-hydroxy-propanone* ***9b***

The title compound was prepared in 70% yield as reported above starting from compound **8b**. Colorless needles, mp. 52–53°C, $[\alpha]_D$=+16.8 (Acetone, c=1.2).

*(R,S)-1,3-Diphenyl-2-(1H-imidazol-1yl)-propanone* ***3***

Mesylchloride (0.28 mL, 3.6 mmol) was added to a stirred, ice-cooled solution of compound **9** (280 mg, 1.23 mmol) in dry $CH_2Cl_2$ (20 mL), followed by addition of triethylamine (0.51 mL, 3.6 mmol). The reaction was completed by stirring at 0°C for 30 min (TLC:hexane/EtOAc 80:20). The pale yellow reaction mixture was poured into 0.5N HCl/ice, the organic layer was separated and the aqueous layer extracted with $CH_2Cl_2$, the combined organic extracts were washed with water, dried and evaporated (30°C), to afford the crude mesylate (365 mg). This material was dissolved in DMF (15 mL), and while stirring at r.t., imidazole (856 mg, 12.3 mmol) was added. The resulting solution was stirred at r.t. for 24 h, then poured into water and extracted with EtOAc. The combined organic extracts were then washed with water, dried and evaporated. Column chromatography ($CH_2Cl_2$/methanol, 95:5) provided the pure compound **3**, as a colorless viscous oil (265 mg, 88%). Spectroscopic characteristics were identical to those previously reported[1].

*Reaction of (RS)-1,3-diphenyl-2-(1H-imidazol-1yl)-propan-2-one* ***3*** *with 5-aminooxypentanoic acid in pyridine, in the presence of* $D_2O$

5-Aminooxypentanoic acid hydrochloride[1] (180 mg, 1.1 mmol) was added to an ice-cooled solution of **3** (250 mg, 1 mmol) in pyridine (5 mL) containing $D_2O$ (0.5 mL), while stirring, and the resulting solution was stirred at r.t. overnight. Solvents were evaporated and the residue taken up with water, the pH of the resulting suspension was adjusted to 5 by adding AcOH. $CHCl_3$ was added and the organic layer separated, the aqueous layer was extracted with chloroform and the combined organic extracts were dried and concentrated to an oil (346 mg, 87%), E/Z mixture of the oximes. This crude material was found (TLC, $CH_2Cl_2$/MeOH, 94.5:5) pure enough to be analyzed by $^1$H NMR spectroscopy without further purification. $^1$H NMR (400 MHz; $CDCl_3$) $\delta$: 1.7 (4H, m, $OCH_2CH_2CH_2CH_2$); 2.35 (2H, m, $CH_2COO$); 3.29 (0.75H, dd, J=14.1, J=9.4; $PhCH_ACH_B$, E oxime); 3.35 (0.25H, dd, J=16.8, J=3.2, $PhCH_ACH_B$, Z oxime); 3.49 (1H, m, $PhCH_ACH_B$); 4.15 (2H, m, $OCH_2$); 5.09 (0.49H, dd, J=9.4, J=2.1 C*H*=NO, E oxime); 6.00 (0.16H, dd, J=3.2, J=2.6; C*H*=NO, Z oxime); 6.8–7.7 (13H, Phenyl+imidazole).

As previously described[1] also in this case the reaction afforded a 75:25 mixture of E/Z diastereoisomeric oximes, as assessed comparing the integrals of the corresponding α-methine signals at 5.09 and 6.00 ppm. However, in this experiment the whole amount of the integrals corresponding to the methine in α-position to the E and Z oximes is only 0.65 and not one proton as usually occurred in the same reaction carried out without using $D_2O$.

*Reaction of (RS)-1,3-diphenyl-2-(1H-imidazol-1yl)-propane* ***3*** *with 5-aminooxypentanoic acid in ethanol, in the presence of* $D_2O$

Anhydrous AcONa (246 mg, 3 mmol) was added to a solution of 5-aminooxypentanoic acid hydrochloride (340 mg, 3 mmol) in 95% ethanol (25 mL) containing $D_2O$ (2.5 mL), at 0°C, the resulting solution was stirred 5 min, then compound **3** (740 mg, 3 mmol) was added in one portion at 0°C. The resulting mixture was allowed to warm to r.t., then stirred for 24 h. Heating at reflux for 8 h completed the reaction. Ethanol was evaporated and the residue diluted with water, the pH was adjusted to 5 by adding AcOH, and the resulting suspension extracted with EtOAc. The combined organic extracts were washed with water, dried and concentrated to provide the crude E/Z regioisomeric mixture of the oximes (560 mg). Column chromatography ($CH_2Cl_2$/MeOH 90:10) was necessary to

yield a E/Z mixture of oximes (350 mg, 59%) pure enough for $^1$H NMR analysis (400 MHz; $CDCl_3$). Though the ratio of E/Z regioisomers found in this reaction closely resembled that previously obtained (65:35), evaluation of the methine integrals as reported above, indicated a 60% deuterium uptake in this case, the total amount of integrals at 5.09 and 6.00 ppm being 40% of the integral for a proton.

*Deuterium–hydrogen exchange for 1,3-diphenyl-2-(1H-imidazol-1-yl)-propanone, in DMF in the presence of imidazole*

$D_2O$ (0.6 mL) was added, to a solution of compound **3** (120 mg, 0.5 mmol) in DMF (6 mL), followed by imidazole (340 mg, 5 mmol). The resulting solution was stirred at r.t. for 24 h, then poured into water and extracted with EtOAc. The combined organic extracts were washed with water, dried and concentrated to afford compound **3** (78 mg). $^1$H NMR analysis (400 MHz; $CDCl_3$) of this product, revealed 50% of deuterium uptake.

*Ethyl 5-aminooxy pentanoate hydrochloride*

5-Aminooxypentanoic acid hydrochloride[1] (16.8 g, 0.1 mol) was dissolved in absolute ethanol (250 mL), the resulting solution was cooled to −10°C and HCl was slowly bubbled through the solution for 30 min, the resulting mixture was allowed to warm to r.t., and stirred overnight. The solvent was evaporated, and the resulting colorless solid dissolved in hot EtOAc, then filtered and the filtrate concentrated and poured into hexane, the ethyl ester hydrochloride (17.4 g, 88%), precipitated on standing, mp. 92–94°C. $^1$H NMR (80 MHz, $d_6$-DMSO) $\delta$: 1.1 (t, 3H, $COOCH_2CH_3$); 1.4–1.6 (m, 4H, O-$CH_2CH_2CH_2$); 2.1–2.35 (m, 2H, $CH_2COO$); 3.8–4.2 (m,4H,NO-$CH_2$+$COOCH_2CH_3$).

*Reaction of (RS)-1,3-diphenyl-2-hydroxy-propan-2-one* **9** *with ethyl-5-aminooxypentanoate in pyridine, in the presence of $D_2O$*

Ethyl 5-aminooxypentanoate hydrochloride (198 mg, 1 mmol) was added to an ice-cooled solution of compound **9** (113 mg, 0.5 mmol) in pyridine (5 mL), containing $D_2O$ (0.5 mL), while stirring. The reaction was completed on stirring at 0°C 1 h and then at r.t. overnight. Solvents were evaporated and the residue partitioned between EtOAc and 1N HCl, the organic layer was washed with 1N HCl, water; dried and concentrated to provide a colorless oil, pure enough for $^1$H NMR evaluation. No deuterium uptake was observed comparing the total integral at the $\alpha$-methine protons (4.84 and 5.18 ppm) of the E and Z oximes, with the other signals present in the spectrum.

*(E)-(RS)-Ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden]pentanoate* **11** *and (Z)-(RS)-ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden] pentanoate* **12**

Ethyl 5-aminoxypentanoate (1.74 g, 8.8 mmol) was added portionwise to a stirred, ice-cooled solution of **9** (1 g, 4.4 mmol) in pyridine (50 mL), over 30 min. The resulting solution was stirred at 0°C an additional hour. The reaction was then completed on stirring at r.t. overnight. Evaporation of the solvent afforded an oil, which was partitioned between EtOAc and 1N HCl, the organic layer was washed with 1N HCl and water, then dried and concentrated to a colorless oil (1.52 g), mixture of E/Z oximes in a ratio of about 70:30. Column chromatography ($SiO_2$, 8×16 cm) eluting with Hexane/EtOAc 10% afforded the Z diastereoisomer **12** (460 mg, 28.7%), colorless oil: IR (neat)$cm^{-1}$: 3600–3200; 1720; 1600; 1440; 1370; 1060; 700. $^1$H NMR (400 MHz; $CDCl_3$) $\delta$: 1.25 (t, J=7.0, 3H, $COOCH_2CH_3$); 1.80 (m, 4H $CH_2CH_2CH_2COO$); 2.40 (m, 2H, $CH_2COO$); 3.15 (m, 2H, $CH_2CH$); 3.40 (broad s, 1H, O*H*); 4.14 (q, J=7.0, 2H, $COOCH_2CH_3$); 4.22 (m, 2H, $NOCH_2$); 5.15 (broad s, 1H, $CH_2CH$); 7.20–7.48 (m, 10 H, phenyls). MS (EI) m/z: 278 $(M^{-\cdot}C_7H_7)^+$; 224 $(M^{-\cdot}OC_4H_6COOC_2H_5)^+$; 129 $(C_9H_7N)^+$; 104 $(C_8H_8)^{+\cdot}$;91 $(C_7H_7)^{+\cdot}$. Further elution of the column using Hexane/EtOAc (80:20) as eluant provided the E diastereoisomer **11** (1.06 g, 64%), colorless oil: IR (neat)$cm^{-1}$: 3600–3200; 1720; 1600; 1440; 1370; 1060; 700. $^1$H NMR (400 MHz; $CDCl_3$) $\delta$: 1.25 (t, J=7.0, 3H, $COOCH_2CH_3$); 1.60 (m, 4H $CH_2CH_2CH_2COO$); 2.27 (m, 2H, $CH_2COO$); 2.68 (dd, J=14.1, J=6, 1H, ABX system A part, $CH_2CH$); 2.94 (dd, J=14.1, J=4.1, 1H, ABX system B part, $CH_2CH$);, 3.22 (d,J=5.6, 1H, O*H*); 4.03 (m, 2H, $NOCH_2$); 4.12 (q, J=7.0, 2H, $COOCH_2CH_3$); 4.88

(m, 1H, ABX system, X part $CH_2CH$); 7.10–7.30 (m, 5 H, phenyl); 7.40 (m, 5H, phenyl). MS (EI) m/z: 278 $(M^{-\cdot}\ C_7H_7)^+$; 224 $(M^{-\cdot}OC_4H_6COOC_2H_5)^+$; 129 $(C_4H_7N)^+$; 104 $(C_8H_8)^{+\cdot}$ 91$(C_7H_7)^{+\cdot}$.

*(E)-(S)-Ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden]pentanoate* ***11a***

The title compound was obtained along with **12a**, as described above starting from **9a** in 61% yield. Colorless oil, $[\alpha]_D$=+0.688 (c=0.87; acetone).

*(Z)-(S)-Ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden]pentanoate* ***12a***

The title compound was obtained along with **11a**, as described above starting from **9a** in 21% yield. Colorless oil, $[\alpha]_D$=−20.9 (c=0.62; acetone).

*(E)-(R)-Ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden]pentanoate* ***11b***

The title compound was obtained along with **12b**, as described above starting from **9b** in 53% yield. Colorless oil, $[\alpha]_D$=−0.647 (c=1.52; acetone).

*(Z)-(R)-Ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden]pentanoate* ***12b***

The title compound was obtained along with **11b**, as described above starting from **9b** in 22% yield. Colorless oil, $[\alpha]_D$=+19.08 (c=1.74; acetone).

*Reaction of (E)-(RS)-ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden]pentanoate* ***11*** *with (S)-2-methoxyphenylacethyl chloride*

Anhydrous $K_2CO_3$ (500 mg) and DMAP (10 mg) were added to a stirred solution of **11** (100 mg, 0.27 mmol) in dry $CH_2Cl_2$ (5 mL). (S)-2-Methoxyphenylacetyl chloride (70 mg, 0.37 mmol) dissolved in $CH_2Cl_2$ (200 μL) was added dropwise to the resulting suspension, under $N_2$ atmosphere, at r.t. The resulting suspension was stirred at r.t. over 3 h. The reaction mixture was poured into an ice-cooled, $NaHCO_3$ saturated solution, stirred a few minutes, then extracted with $Et_2O$. The combined organic extracts were washed with $NaHCO_3$, water and 1N HCl, dried and concentrated to a chromatographically pure, colorless oil (126 mg). $^1$H NMR analysis indicated separation of most of the proton resonances of the two diastereoisomers. No evidence for a kinetic resolution during the reaction was displayed, the integrals of the corresponding protons of the diastereoisomers being exactly 50:50.

*Reaction of (E)-(S)-ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden]pentanoate* ***11a*** *with (S)-2-methoxyphenylacethyl chloride*

The reaction was carried out as described above starting from **11a**, analogous work-up provided **13a**, colorless oil, 86% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 1.20 (t, J=7.0, 3H, $COOCH_2CH_3$); 1.53 (m, 4H, $CH_2CH_2CH_2COO$); 2.30 (m, 2H, $CH_2COO$); 3.01 (dd, $J_{AB}$=14.1, $J_{AX}$=8.8, 1H, ABX system, A part $CH_2CHC{=}N$); 3.10 (dd, $J_{AB}$=14.1, $J_{BX}$=5.3,1H, ABX system, B part $CH_2CHC{=}N$); 3.22 (s, 3 H, $OCH_3$ ); 3.93 (m, 2H, N-O-$CH_2$); 4.12 (q, J=7.0, 2H, $COOCH_2CH_3$); 4.61 (s,1H, $CH$-$OCH_3$); 5.92 (dd, $J_{AX}$=8.8, $J_{BX}$=5.3, 1H, ABX system, X part, $CH_2CHC{=}N$); 7.10–7.50 (m, 15 H, phenyls).

The presence of the other diastereoisomer signals was not detectable in this spectrum.

*Reaction of (E)-(R)-Ethyl 5-aminooxy-[2-hydroxy-1,3-diphenyl-propylyliden]pentanoate* ***11b*** *with (S)-2-methoxyphenylacethyl chloride*

The reaction was carried out as described above, analogous work-up provided **13b**, colorless oil, 93% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 1.24 (t, J=7.0, 3H, $COOCH_2CH_3$); 1.60 (m, 4H, $CH_2CH_2CH_2COO$); 2.26 (m, 2H, $CH_2COO$); 2.94 (dd, $J_{AB}$=14.3, $J_{AX}$=8.8, 1H, ABX system, A part $CH_2CHC{=}N$); 3.05 (dd, $J_{AB}$=14.3, $J_{BX}$=5.3, 1H, ABX system, B part $CH_2CHC{=}N$); 3.25 (s, 3 H, $OCH_3$ ); 4.02 (m, 2H, N-O-$CH_2$); 4.12 (q, J=7.0, 2H, $COOCH_2CH_3$); 4.66 (s,1H, $CH$-$OCH_3$); 5.82 (dd, $J_{AX}$=8.8, $J_{BX}$=5.3, 1H, ABX system, X part, $CH_2CHC{=}N$); 6.98–7.40 (m, 15 H, phenyls).

The presence of the other diastereoisomer signals was not detectable in this spectrum.

*(E)-(RS)-Ethyl-5-aminooxy-[(2-imidazol-1-yl)-1,3-diphenyl-propylyliden]pentanoate* ***15***

Mesyl chloride (0.34 mL, 4.39 mmol) was added dropwise to a solution of **12** (530 mg, 1.44 mmol) in dry $CH_2Cl_2$ (20 mL), cooled at 0°C, under $N_2$ atmosphere, followed by addition of triethylamine (0.62 mL, 4.4 mmol). The resulting mixture was stirred at r.t. for 30 min (TLC, Hexane/EtOAc, 70:30). The reaction mixture was then poured into 0.5N HCl; $CH_2Cl_2$ was added and the organic layer separated, washed with water and dried. Removal of the solvent led to a chromatographically homogeneous, light yellow oil (643 mg). A sample (65 mg) of this crude product was purified by chromatography (Hexane/EtOAc, 80:20) to provide the pure mesylate **14** (28 mg) as a colorless oil. $^1H$ NMR (80 MHz, $CDCl_3$) $\delta$: 1.20 (t, J=7.0, 3H, $COOCH_2CH_3$); 1.50–1.80 (m, 4H, $CH_2CH_2CH_2COO$); 2.28 (m, 2H, $CH_2COO$); 2.50 (s, 3H, $SO_2$-$CH_3$); 3.5 (d, J=8,1H, $CH_2CHC{=}N$); 3.95 (m, 2H, N-O-$CH_2$); 4.10 (q, J=7.0, 2H, $COOCH_2CH_3$); 5.92 (dd, J=8, J=8, 1H, $CH_2CHC{=}N$); 7.10–7.50 (m, 10 H, phenyls). Imidazole (820 mg, 12 mmol) was added at r.t. to a stirred solution of the above mesylate **14** (560 mg, 1.2 mmol) in DMF (20 mL). The resulting solution was heated to 40°C for 8 h, under $N_2$ atmosphere. The reaction mixture was poured into ice/water and extracted with EtOAc, the combined organic extracts were washed with water, dried and concentrated to provide an oily product. Column chromatography ($CH_2Cl_2$/MeOH, 95:5), provided the pure **15** (362 mg, 73%). $^1H$ NMR (80 MHz, $CDCl_3$) $\delta$: 1.22 (t, J=7.0, 3H, $COOCH_2CH_3$); 1.5–1.75 (m, 4H, $CH_2CH_2CH_2COO$); 2.30 (m, 2H, $CH_2COO$); 3.1–3.7 (m, 2H, ABX system, AB part $CH_2CHC{=}N$); 4.0–4.30 (m, 4H, N-O-$CH_2$+$COOCH_2CH_3$); 5.15 (dd, J=6, J=10, 1H, ABX system, X part, $CH_2CHC{=}N$); 6.9–7.5 (m, 12 H, phenyls+$H_4$ and $H_5$ imidazol); 8.1 (s, 1H, $H_2$ imidazole).

*(E)-(S)-Ethyl-5-aminooxy-[(2-imidazol-1-yl)-1,3-diphenyl-propylyliden]pentanoate* ***15a***

The title compound was prepared as described above starting from **11b** in 72% yield. Colorless oil, $[\alpha]_D$=−18.79 (c=0.98, acetone).

*(E)-(R)-Ethyl-5-aminooxy-[(2-imidazol-1-yl)-1,3-diphenyl-propylyliden]pentanoate* ***15b***

The title compound was prepared as described above starting from **11a** in 79% yield. Colorless oil, $[\alpha]_D$=+18.95 (c=1.3, acetone).

*(E)-(S)-5-Aminooxy-[(2-imidazol-1-yl)-1,3-diphenyl-propylyliden]pentanoic acid* ***1a***

1N LiOH (3 mL, 3 mmol) was added to a solution of **15a** (0.897 mg, 2.16 mmol) in THF (12 mL) and water (4 mL), while stirring at 0°C. The resulting solution was stirred at 0°C over 2 h, then allowed to warm to r.t. and stirred a further 30 min; after this time the reaction was complete (TLC: $CH_2Cl_2$/MeOH, 95:5). Water was added and the pH adjusted to 5 by adding glacial acetic acid. The resulting mixture was extracted with EtOAc and the combined organic extracts were dried and concentrated under reduced pressure to an oil. Column chromatography over $SiO_2$ ($CH_2Cl_2$/MeOH, 95:5) afforded the pure **1a** (684 mg, 82%) as a viscous oil which crystallized on treatment with $Et_2O$/hexane. Colorless oil $[\alpha]_D$=−64.5 (c=0.57, acetone). $^1H$ NMR (400 MHz; $CDCl_3$) $\delta$: 1.60–1.80 (m, 4H $CH_2CH_2CH_2COO$); 2.38 (t, 2H, $CH_2COO$); 3.29 (dd, $J_{AB}$=14.1, $J_{AX}$=9.4,1H, ABX system, A part $CH_2CHC{=}N$); 3.55 (dd, $J_{AB}$=14.1, $J_{BX}$=5.9, 1H, ABX system, B part $CH_2CHC{=}N$); 4.15 (m, 2H, N-O-$CH_2$); 5.12 (dd, $J_{AX}$=9.4, $J_{BX}$=5.9, 1H, ABX system, X part, $CH_2CHC{=}N$); 6.90 (s,1H, $H_4$, imidazole); 6.95–7.08 (m, 5H, phenyl); 7.20–7.32 (m, 6 H, phenyl+$H_5$ imidazole); 7.53 (s, 1H, $H_2$, imidazole).

*(E)-(R)-5-Aminooxy-[(2-imidazol-1-yl)-1,3-diphenyl-propylyliden]pentanoic acid* ***1b***

The title compound was prepared as described above starting from **15b** in 58% yield. Colorless oil, $[\alpha]_D$=+67.18 (c=1.67, acetone).

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## References


1. Cozzi P.; Giordani A.; Menichincheri M.; Pillan A.; Pinciroli V.; Rossi A.; Tonani R.; Volpi D.; Tamburin M.; Ferrario R.; Fusar D.; Salvati P. *J. Med. Chem.* **1994**, *37*, 3588–3604.
2. (a) Kagan K. B.; Fiaud J. C. *Topics in Stereochem.* **1978**, *10*, 175; (b) Meyers A. I. *Acc.Chem. Res.* **1978**, *11*, 375.
3. Enders D. *Asymmetric Synthesis* **1984**, 3, 275–339.
4. Hanessian S. *Total Synthesis of Natural Products: The 'Chiron' Approach*, Pergamon Press (1983).
5. Reetz M. T.; Drewes M. W.; Lennik K.; Schmitz A.; Holdgrun X. *Tetrahedron Asymmetry*, **1990**, *1*, 375–378.
6. (a) Kruse L. T.; Caiser C.; De Wolf W. E.; Frazee J. S.; Garvey E.; Hilbert E. L.; Faulkner W. A.; Flaim K. E.; Sawyer J. L.; Berkowitz B. A. *J. Med. Chem.*, **1986**, *28*, 2465–2472; (b) Cannon W. N.; Powell C. E.; Jones R. G. *J. Org. Chem.* **1957**, *22*, 1323–1328.
7. Hoffman R. V.; Jankowsky B. C.; Corr S.; *J. Org. Chem.*, **1986**, *51*, 130–135; (b) Cristalli G.; Eleutori A.; Volpini R; Vittori S.; Lupidi E. *J. Med. Chem.* **1994**, *37*, 201–205.
8. Nahm S.; Weinreb S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
9. Wintz M.; .loch-Frankenthal L.; Izumiya N.; Birnbaum S. M.; Baker C. G.; Greenstein J. P. *J. Am. Chem. Soc.* **1956**, *30*, 2423–30.
10. Marsman B.; Wynberg H. *J. Org. Chem.* **1979**, *44*, 2312–2314.
11. Deuterium uptake was assessed by $^1$H NMR spectroscopy at 400 MHz.
12. Corey E. J.; Dittami J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256–257.
13. Dale J. A.; Mosher H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
14. The oxime configuration was assessed on the basis of the down-field deshielding effect (due to the N–O group), or up-field shielding effect (due to the N lone pair), exerted differently by the oxime moiety on the adjacent protons. (a) Karabatsos G. J.; Taller R. A. *Tetrahedron* **1968**, *24*, 3347–3360. (b) Karabatsos G.; Hsi N. *Tetrahedron* **1968**, *24*, 3347–3360. (c) Karabatsos G. J.; Taller R. A.; Floie G.; Vane A. *J. Am. Chem. Soc.* **1963**, *85*, 2327–2328. (d) Mixich V. G.; Thiele K. E. *Arzneim-Forsch.* **1979**, *29*, 1510–1513.
15. All $^1$H NMR determination for diastereoisomeric mandelate esters refers to 400 MHz spectra.
16. 16) Ultron ES-OVM column (15 cm×4.6 mm), phosphate buffer (pH 7)/acetonitrile (92/8) was used as eluant, at a flow of 0.8 ml/min.
17. This issue will be addressed in the following paper.
18. Still, W. C.; Kahn, M.; Mitra A. *J. Org. Chem.* **1978**, *43*, 2923–2925.


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