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Asymmetric Synthesis of *N*-(Ethoxycarbonyl)-β-methylphenylalanine Esters

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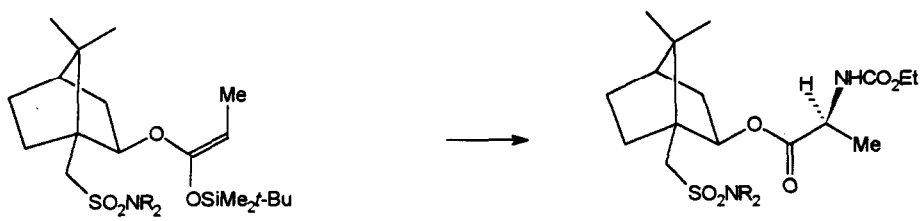
Abstract: Amination of the silyl ketene acetal of methyl (*R*)-3-phenylbutanoate (**3**) by photolysis with ethyl azidoformate gave the derivative of (2*R*,3*S*)-β-methylphenylalanine (**4**) with a low diastereomeric excess in spite of the resident chirality. Using the silyl ketene acetal **6**, also bearing an Oppolzer's chiral auxiliary, the (2*R*,3*S*)-β-methylphenylalanine derivative (**7**) was obtained with a higher diastereomeric excess indicating a matching effect. It was possible to obtain the (2*S*,3*S*)-β-methylphenylalanine derivative (**10**) as the major product, starting from **9** bearing the enantiomeric chiral auxiliary.

The development of efficient approaches to the asymmetric synthesis of nonproteinogenic amino acids remains a topic of considerable interest.[1] In this field some methods to effect the direct electrophilic amination of silyl ketene acetals were introduced by us and other authors.[2] We have reported the amination of silyl ketene acetals by (ethoxycarbonyl)nitrene (NCO_2Et) to produce *N*-substituted α-amino esters.[3] We also reported good diastereoselectivity in the photolysis reaction of ethyl azidoformate (N_3CO_2Et) with the silyl ketene acetal **1**, coming from propanoyl chloride and (1*S*,2*R*)-*N*,*N*-dicyclohexyl-10-sulphamidoisoborneol, one of the Oppolzer's chiral alcohols.[4] We obtained compound **2**,[5] a derivative of (*S*)-alanine in 70% diastereomeric excess.[6]



1 **2**

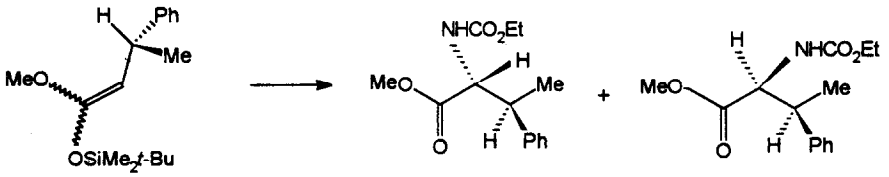
R = Cyclohexyl

Scheme 1

We describe here the amination reaction of silyl ketene acetal derivatives of the (*R*)-3-phenylbutanoic acid by the photolysis with N_3CO_2Et to obtain derivatives of α-amino acids with two stereogenic centres.

At first, we studied the asymmetric induction controlled only by the resident chirality of the silyl ketene acetal **3** prepared from the methyl ester of the (*R*)-3-phenylbutanoic acid, then, starting from the same acid, we prepared the silyl ketene acetal **6** bearing Oppolzer's (1*R*,2*S*) auxiliary and the silyl ketene acetal **9** bearing the enantiomeric (1*S*,2*R*) auxiliary to study the relative influence of these chiral auxiliaries with respect to the resident chirality.

The photolysis reaction of N_3CO_2Et in the presence of **3**, gave two diastereomeric products **4** and **4a** with a diastereomeric ratio (HPLC) of 70:30 (61% yield), easily separated by flash chromatography. The major isomer is the methyl (2*R*,3*S*)-*N*-(ethoxycarbonyl)-β-methylphenylalaninate (**4**), as we expected considering that in the preferred conformation, according to the Houk rule,[7] the phenyl group partially hinders the *Si* face of the starting silyl ketene acetal.[8]

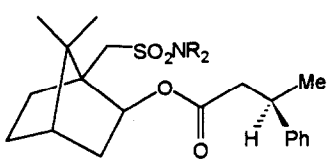


3 **4** **4a**

Scheme 2

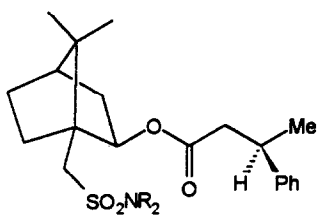
The configuration of the two diastereomers was confirmed by comparison of the ^1H NMR spectrum of (2*S*,3*S*)-*N*-acetyl-β-methylphenylalanine, obtained from **4a** by hydrolysis and acetylation, with that reported.[9]

In the presence of an appropriate chiral auxiliary we obtained a higher diastereoselectivity. The photolysis reaction of N_3CO_2Et was carried out in the presence of the silyl ketene acetal **6** (*E* configuration)[10] prepared from the (*R*)-3-phenylbutanoate of the (1*R*,2*S*) Oppolzer's alcohol (**5**) and the products **7** and **7a** were obtained with a diastereomeric ratio of 88:12 (84% yield). Starting from **9** (*E* configuration)[10] prepared from the ester **8** bearing the (1*S*,2*R*) enantiomeric Oppolzer's auxiliary, the diastereomeric ratio for the products **10** and **10a** was 77:23 (89% yield). In all cases the major diastereomer was easily separated by flash chromatography.



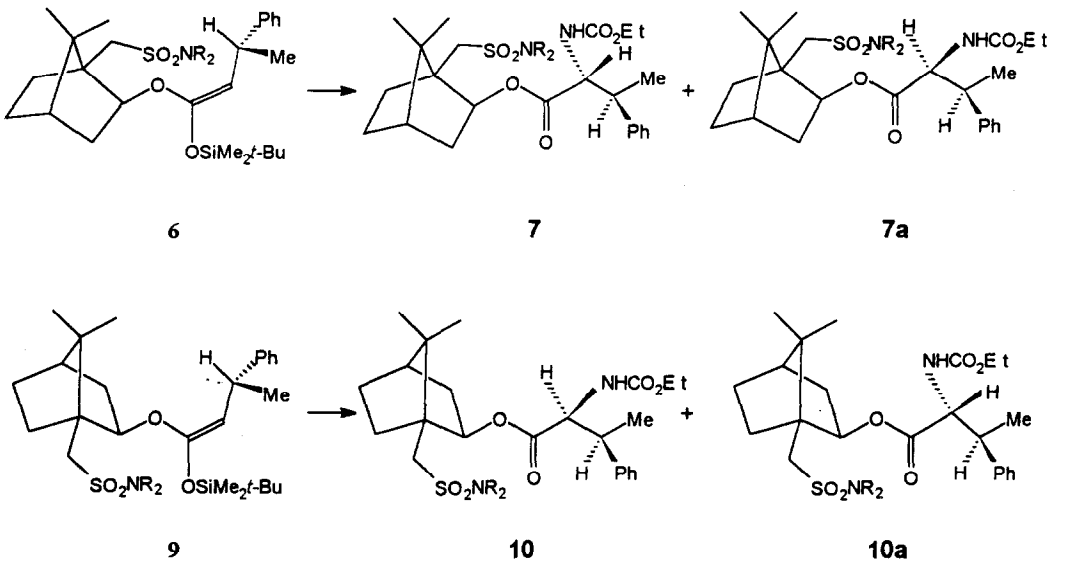
5

R = Cyclohexyl



8

The enantiomeric auxiliaries confer high π-face differentiation on the double bond in the silyl ketene acetals and we assume that, as reported by Oppolzer for the reaction of this kind of acetals with several electrophiles,[11] the attack occurs on **6** preferentially from the less hindered *Cα-Re*-face because one cyclohexane ring blocks the olefinic *Cα-Si*-face,[12] the same face that is partially hindered by the phenyl group. We observed the same stereochemistry (2*R*,3*S*) that we obtained in **4**, with increased diastereoselectivity because of a matching effect. Accordingly, the reagent attacks **9** from the *Cα-Si*-face and we had the opportunity to obtain as the major isomer the derivative of (2*S*,3*S*)-β-methylphenylalanine even if in a lower (53%) diastereomeric excess as expected by a mismatching effect.



Scheme 3

Flash chromatography furnished **10** in virtually 100% diastereomeric excess. This product could be of interest as (2*S*,3*S*)-β-methylphenylalanine[13] is a component of the bottromicin,[14] an antibiotic isolated from *Streptomices Bottropensis* and of other biologically important molecules.[15]

In conclusion, in the synthesis of *N*-substituted α-amino esters by the photolysis of N_3CO_2Et on silyl ketene acetals the diastereoselectivity seems to be affected more by the chirality present in the ester mojety [5] than by the resident chirality at the β-carbon.

EXPERIMENTAL

GC analyses were performed on a Carlo Erba 4100 gas chromatograph with a 2 m x 2 mm column of 3% SP 2250 on 100/120 Supelcoport support. ^1H NMR and ^{13}C NMR spectra ($CDCl_3$ unless otherwise specified) were obtained on a Varian Gemini 200 and on a Varian XL-300 with $CHCl_3$ as an internal standard.

IR spectra (CCl_4) were obtained on a Perkin-Elmer 298 instrument. MS and HRMS were obtained with a Finnigan Mat 90 spectrometer. Optical rotations were obtained at the sodium *D* line with a Perkin-Elmer 241 polarimeter (1-cm cell). HPLC analyses were performed on a Violet Clar 002 instrument equipped with a IOTA Jobin-Yvon differential refractometer. All solvents were purified and dried according to conventional methods. Ethyl azidoformate (*CAUTION! it is toxic and can decompose explosively at 160 °C*) was prepared from ethyl chloroformate and sodium azide.[16] (*R*)-3-Phenylbutanoic acid and methyl (*R*)-3-phenylbutanoate (**3**) were commercial products (Fluka). (*R*)-3-Phenylbutanoyl chloride was obtained from the acid by the action of oxalyl chloride.

(1*R*,2*S*,4*S*)-10-(*N*,*N*-Dicyclohexylaminosulphonyl)born-2-yl (*R*)-3-Phenylbutanoate (5). The title compound was prepared from (*R*)-3-phenylbutanoyl chloride and (1*R*,2*S*)-*N*,*N*-dicyclohexyl-10-sulphamidoisoborneol (Aldrich) in the presence of AgCN:[12] mp 131-133 °C (hexane); IR 1730 cm^{-1}; ^1H NMR (300 MHz) δ 0.76 (s, 3 H), 0.81 (s, 3 H), 1.02-1.42 (m, 7 H), 1.30 (d, 3 H), 1.50-1.95 (m, 20 H), 2.52 (d, 2 H), 2.61 (d, 1 H),3.15-3.32 (m, 4 H), 4.86 (dd, 1 H), 7.12-7.29 (m, 5 H); ^{13}C NMR δ 19.82 (CH_3), 20.41 (CH_3), 21.97 (CH_3), 25.18 (CH_2), 26.50 (CH_2), 26.96 (CH_2), 30.09 (CH_2), 32.69 (CH_2), 32.84 (CH_2), 36.60 (CH), 39.38 (CH_2), 43.27 (CH_2), 44.40 (CH), 49.02 (C), 49.21 (C), 53.71 (CH_2), 57.48 (CH), 78.44 (CH), 126.38 (CH), 126.37 (CH), 128.44 (CH), 145.64 (C), 170.82 (CO); $[\alpha]_D$ = +22.5 (c 1.5, EtOH); MS (150 °C) *m/z* (relative intensity) 543 (M^+, 9), 382 (8), 381 (25), 380 (100), 299 (9), 298 (44), 246 (10), 245 (9), 244 (46), 228 (17), 182 (12), 181 (33), 180 (30), 179 (17), 147 (35), 138 (27), 136 (14), 135 (38), 121 (11), 107 (14), 106 (11), 105 (98), 98 (13), 93 (18), 91 (17), 83 (20), 81 (10), 79 (13), 77 (8), 67 (9), 56 (7), 55 (20); HRMS, 543.3328 (M^+), calcd for $C_{32}H_{49}NO_4S$, 543.3382.

(*S*,2*R*,4*R*)-10-(*N*,*N*-Dicyclohexylaminosulphonyl)born-2-yl (*R*)-3-Phenylbutanoate (8). The title compound was prepared from (*R*)-3-phenylbutanoyl chloride and (1*S*,2*R*)-*N*,*N*-dicyclohexyl-10-sulphamidoisoborneol (Aldrich) in the presence of AgCN:[12] mp 138-140 °C (hexane); IR 1730 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (s, 3 H), 0.95 (s, 3 H), 1.01-1.35 (m, 7 H), 1.33 (d, 3 H), 1.48-1.88 (m, 18 H), 1.98 (m, 2 H), 2.54 (m, 1 H), 2.64-2.76 (m, 2 H), 3.12-3.40 (m, 4 H), 4.95 (dd, 1 H), 7.15-7.34 (m, 5 H); ^{13}C NMR δ 19.96 (CH_3), 20.36 (CH_3), 21.89 (CH_3), 25.07 (CH_2), 26.36 (CH_2), 26.94 (CH_2), 30.10 (CH_2), 32.67 (CH_2), 32.72 (CH_2), 36.04 (CH), 39.50 (CH_2), 42.75 (CH_2), 44.41 (CH), 49.01 (C), 49.28 (C), 53.78 (CH_2), 57.40 (CH), 78.57 (CH), 126.24 (CH), 126.48 (CH), 128.39 (CH), 145.70 (C), 170.75 (CO); $[\alpha]_D$ = -25.3 (c 2.2, EtOH). MS (140 °C) *m/z* (relative intensity) 543 (M^+, 5), 382 (5), 381 (17), 380 (69), 298 (28), 246 (7), 244 (30), 228 (13), 182 (11), 181 (26), 180 (22), 179 (10), 147 (31), 138 (24), 136 (12), 135 (86), 121 (11) 107 (14), 106 (11), 105 (100), 98 (12), 93 (18), 91 (20), 83 (20), 81 (10), 79 (16), 77 (10), 67 (9), 56 (7), 55 (21); HRMS, 543.3319 (M^+), calcd for $C_{32}H_{49}NO_4S$, 543.3382.

Photolysis of Ethyl Azidoformate with Silyl Ketene Acetals. General Procedure. A solution of ethyl azidoformate (0.8 ml) and silyl ketene acetal, synthesised from the corresponding ester (3.5 mmol) according to the reported procedure,[12] directly used in pentane after concentration to 8 ml, in an atmosphere of argon, was photolysed at 0 °C in a quartz vessel, using a medium pressure Hanovia PCR lamp (100 W) for 8 h. After pentane evaporation the mixture was analysed by HPLC and then cromatographed on silica gel (flash chromatography; hexane/ethyl acetate 9 : 1) giving the amino esters **4** (40%), **4a** (10%), **7** (67%) and **10** (60%) with a 99% purity, **7a** and **10a** were always contaminated by the corresponding major diastereomers.

Methyl (2*R*,3*S*)-*N*-(Ethoxycarbonyl)-β-methylphenylalaninate (4): IR 3450, 1730 cm^{-1}; ^1H NMR (200 MHz) δ 1.14 (t, 3 H), 1.27 (d, 3 H), 3.15 (m, 1 H), 3.50 (s, 3 H), 4.16 (q, 2 H), 4.50 (m, 1 H), 5.22 (d, 1

H), 7.07-7.35 (m, 5 H); ^{13}C NMR δ 14.26 (CH_3), 16.38 (CH_3), 42.65 (CH_3), 51.85 (CH), 59.35 (CH), 61.11 (CH_2), 127.22 (CH), 127.73 (CH), 128.52 (CH), 141.44 (C), 156.24 (CO), 172.32 (CO); $[\alpha]_D$ = +11 (c 1.0, EtOH); MS (20 °C) *m/z* (relative intensity) 265 (M^+, <1), 220 (2), 206 (8), 176 (26), 161 (12), 160 (9), 106 (10), 105 (100), 103 (8), 91 (9), 88 (13), 79 (9), 77 (11); HRMS, 220.0975 (M^+- 45), calcd for $C_{12}H_{14}NO_3$, 220.0973.

Methyl (2*S*,3*S*)-*N*-(Ethoxycarbonyl)-β-methylphenylalaninate (4a): IR 3450, 1730 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.14 (t, 3 H), 1.30 (d, 3 H), 3.3 (m, 1 H), 3.62 (s, 3 H), 4.01 (q, 2 H), 4.50 (dd, 1 H), 4.87 (d, 1 H), 7.08 (d, 2 H), 7.15-7.27 (m, 3 H); ^{13}C NMR δ 14.43 (CH_3), 17.55 (CH_3), 41.88 (CH_3), 52.06 (CH), 59.01 (CH), 61.18 (CH_2), 127.26 (CH), 127.52 (CH), 128.58 (CH), 140.56 (C), 156.39 (CO), 172.06 (CO); MS (20 °C) *m/z* (relative intensity) 265 (M^+, <1), 220 (1), 206 (6), 176 (24), 161 (11), 160 (8), 106 (10), 105 (100), 103 (7), 91 (9), 88 (19), 79 (10), 77 (12), 56 (10); HRMS, 220.0974 (M^+- 45), calcd for $C_{12}H_{14}NO_3$, 220.0973.

(1*R*,2*S*,4*S*)-10-(*N*,*N*-Dicyclohexylaminosulphonyl)born-2-yl (2*R*,3*S*)-*N*-(Ethoxycarbonyl)-β-methyl phenylalaninate (7): IR 3440, 1725 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.72 (s, 3H), 0.77 (s, 3 H), 1.14 (t, 3 H), 1.00-1.35 (m, 7 H), 1.24 (d, 3 H),1.40-1.95 (m, 20 H), 2.56 (d, 1 H), 3.08-3.24 (m, 4 H), 3.97 (q, 2 H), 4.45 (dd, 1 H), 4.89 (dd, 1 H), 5.23 (d, 1 H), 7.23 (m, 5 H); ^{13}C NMR δ 14.55 (CH_3), 16.33 (CH_3), 19.92 (CH_3), 20.40 (CH_3), 25.19 (CH_2), 26.35 (CH_2), 26.45 (CH_2), 26.94 (CH_2), 30.59 (CH_2), 32.65 (CH_2), 33.00 (CH_2), 38.99 (CH_2), 42.88 (CH), 44.39 (CH), 49.03 (C), 49.45 (C), 53.94 (CH_2), 57.58 (CH), 59.08 (CH), 60.87 (CH_2), 79.38 (CH), 126.95 (CH), 127.77 (CH), 128.40 (CH), 142.01 (C), 155.92 (CO), 170.49 (CO); $[\alpha]_D$ = +23.6 (c 4.4, EtOH); MS (175 °C) *m/z* (relative intensity) 630 (M^+, <1), 541 (4), 526 (9), 525 (27), 382 (8), 381 (24), 380 (100), 298 (8), 246 (10), 228 (15), 206 (27), 181 (14), 180 (30), 162 (10), 138 (13), 136 (10), 135 (31), 134 (9) 107 (9), 105 (44), 93 (12), 83 (11), 79 (9), 55 (11); HRMS, 525.2988 (M^+ - 105), calcd for $C_{27}H_{45}N_2O_6S$, 525.2998.

(1*R*,2*S*,4*S*)-10-(*N*,*N*-Dicyclohexylaminosulphonyl)born-2-yl (2*S*,3*S*)-*N*-(Ethoxycarbonyl)-β-methylphenylalaninate (7a): IR 3440, 1725 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.81 (s, 3 H), 0.90 (s, 3 H), 1.12 (t, 3 H), 0.90-1.42 (m, 10 H), 1.54-1.92 (m, 20 H), 2.60 (d, 1 H), 3.08-3.29 (m, 4 H), 3.98 (q, 2 H), 4.39 (dd, 1 H), 4.71 (d, 1 H), 4.83 (dd, 1 H), 7.19 (m, 5 H).

(1*S*,2*R*,4*R*)-10-(*N*,*N*-Dicyclohexylaminosulphonyl)born-2-yl (2*S*,3*S*)-*N*-(Ethoxycarbonyl)-β-methylphenylalaninate (10): IR 3450, 1730 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.76 (s, 3 H), 0.82 (s, 3 H), 1.18 (t, 3 H), 0.87-1.34 (m, 7 H), 1.36 (d, 3 H), 1.52-1.94 (m, 20 H), 2.57 (d, 1 H), 3.07 (d, 1 H), 3.10-3.39 (m, 3 H), 4.04 (q, 2 H), 4.49 (dd, 1 H), 4.97 (m, 1 H), 5.16 (d, 1 H), 7.23 (m, 5 H); ^{13}C NMR δ 14.56 (CH_3), 17.17 (CH_3), 19.93 (CH_3), 20.43 (CH_3), 23.21 (CH_2), 26.39 (CH_2), 26.50 (CH_2), 27.01 (CH_2), 30.59 (CH_2), 32.70 (CH_2), 33.00 (CH_2), 39.12 (CH_2), 41.84 (CH), 44.53 (CH), 48.10 (C), 49.55 (C), 53.78 (CH_2), 57.60 (CH), 59.19 (CH), 60.94 (CH_2), 79.52 (CH), 127.01 (CH), 127.76 (CH), 128.46 (CH), 140.50 (C), 169.82 (CO), 188.90 (CO); $[\alpha]_D$ = -31.1 (c 4.5, EtOH); MS (180 °C) *m/z* (relative intensity) 630 (M^+, <1), 541 (4), 526 (8), 525 (22), 382 (8), 381 (25), 380 (100), 298 (12), 246 (10), 228 (17), 206 (22), 181 (15), 180 (31), 162 (8), 138 (15), 136 (12), 135 (34), 134 (9) 107 (9), 105 (36), 93 (12), 91 (9), 83 (12), 79 (9), 55 (11); HRMS, 525.2989 (M^+ - 105), calcd for $C_{27}H_{45}N_2O_6S$, 525.2998.

(1*S*,2*R*,4*R*)-10-(*N*,*N*-Dicyclohexylaminosulphonyl)born-2-yl (2*R*,3*S*)-*N*-(Ethoxycarbonyl)-β-methylphenylalaninate (10a): IR 3450,1735 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.85 (s, 3 H), 0.92 (s, 3 H), 1.15

(t, 3 H), 0.89-1.33 (m, 7 H), 1.33 (d, 3 H), 1.50-1.98 (m, 20 H), 2.65 (d, 1 H), 3.11-3.82 (m, 4 H), 3.98 (q, 2 H), 4.55 (dd, 1 H), 4.87 (m, 1 H), 5.27 (d, 1 H), 7.24 (m, 5 H).

Hydrolysis and *N*-Acetylation of 4a: **4a** (0.6 mmol) was hydrolysed by refluxing with a 2 M sodium hydroxide solution (4 ml) for 2 h. Then to the mixture, cooled at 0 °C, 1 M sodium hydroxide solution (2 ml) and acetic anhydride (0.22 ml) were simultaneously added, the mixture was stirred under ice cooling and after 1 h, 1 M sodium hydroxide solution (4 ml) and acetic anhydride (0.22 ml) were added. After 30 min the mixture was acidified with concentrated hydrochloric acid, extracted with ethyl acetate and dried to obtain (2*S*,3*S*)-*N*-acetyl-β-methylphenylalanine.[9]

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