Transformations of isoxazolidine and dihydropyran derivatives to optically active compounds

Angel Díaz-Ortiz,* Enrique Díez-Barra, Antonio de la Hoz, Pilar Prieto and Andrés Moreno

Facultad de Química, Universidad de Castilla-La Mancha, E-13071, Ciudad Real, Spain

Isoxazolidine and dihydropyran spiro derivatives can be easily transformed, by hydrolysis and hydrogenolysis, to give δ-keto esters, δ-keto acids, β-amino esters, β-amino acids and 3-amino alcohols in good yields. Starting from optically active compounds enantiomerically pure products are obtained. In some cases, reactions were induced by microwave irradiation.

The stereoselective synthesis of β-amino acids which are present in many naturally occurring peptides[1] has recently been reviewed.[2] Such optically active compounds have been employed to prepare β-lactam antibiotics.[3] Likewise, δ-keto esters which are precursors in the synthesis of insect pheromones are structurally related to mesembrine alkaloids.[4]

We have recently reported the preparation of optically active spiro compounds, such as **1** and **9**, by cycloaddition induced by microwave irradiation under solvent-free conditions.[5] It is well known that acetals and orthoesters can be easily hydrolysed in acid media to obtain carbonyl compounds and esters, respectively. Here we detail the transformations of the optically active compounds **1** and **9** into enantiomerically pure open-chain molecules useful as chiral intermediates in natural product chemistry upon hydrolysis and reduction. Thus, we obtained 5-isoxazolidinones, β-amino acids, β-amino esters or 3-amino alcohols from **1**, and dihydropyrones, δ-keto acids or δ-keto esters from **9**. Some mechanistic differences in the hydrolysis of the isoxazolidine derivative **1** and the dihydropyran **9** were observed.

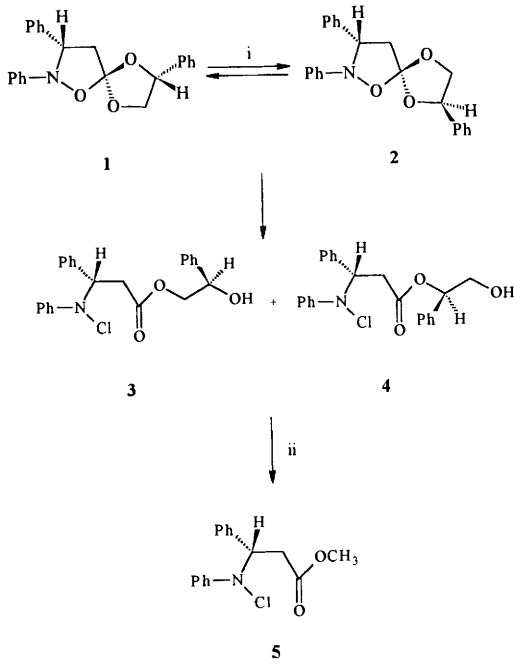
Hydrolyses

We began our studies with the reactions of the spiro compound **1**. This compound when treated with mineral and Lewis acids (0.01 mol dm^{-3} hydrochloric acid, toluene-*p*-sulfonic acid, CF_3CO_2H–MeOH (1:9), $BF_3{\cdot}OEt_2$, $AlCl_3$ or $TiCl_4$) under a variety of reaction conditions only decomposed. Since, however, on treatment with an ion exchange resin, wet Amberlyst 15, compound **1** gave traces of the corresponding 5-isoxazolidone, detected but not isolated, we decided to employ a weaker Lewis acid, tetrachlorosilane. This has been used as a coupling reagent for the preparation of amides[6] and also to prepare β-chloro acetals from α,β-enones;[7] it has also been used as a Lewis acid catalyst for dehydrative cyclization of enamino ketones[8] and, coupled with sodium iodide, for the cleavage of acetals and ketals.[9]

We found that the reaction of **1** with tetrachlorosilane (0.4 equiv.) afforded the open-chain compounds **3** (53%) and **4** (24%) (Scheme 1). The structures of these compounds were established on the basis of their ^1H and ^{13}C NMR spectral results and elemental analyses. The reaction began with a rapid isomerization of **1**, through an oxocarbenium ion, to compound **2** (as shown by ^1H NMR spectroscopy), a favoured process.[5] The mixture **1** + **2** is slowly hydrolysed to the corresponding open-chain esters **3** and **4**, by attack of the Cl^- anion.

Treatment of a mixture of **3** and **4** with methanolic NaOH afforded, by transesterification, the enantiomerically pure (*S*)-β-chloro amine ester **5** (84%). The mass spectrum of **5** supported the structure proposed.

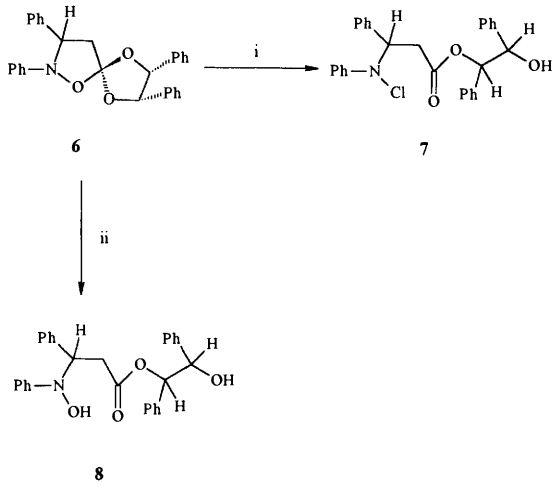
Although not leading to optically active compounds we, nevertheless, analysed the reactions of the spiro compound **6**. Thus, upon hydrolysis with tetrachlorosilane **6** afforded the *N*-chloro amine ester **7**, as the sole compound (77%) (Scheme 2). In contrast to **1**, compound **6** on treatment with wet Amberlyst 15 did not decompose but, instead, gave the *N*-hydroxy amine ester **8** (82%). The structures of **7** and **8** were established on the basis of spectroscopic evidence, elemental analyses and mass spectral results.



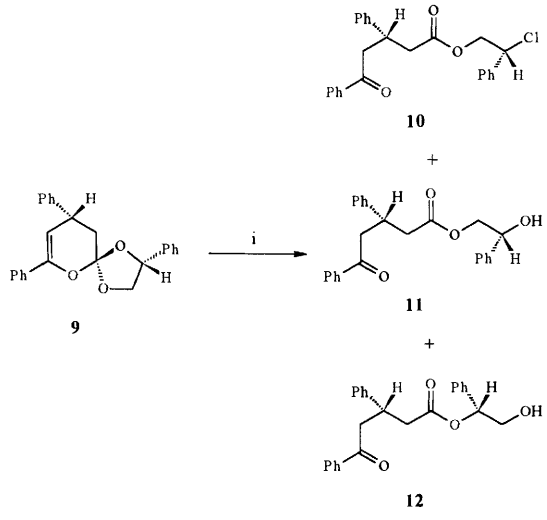
Scheme 1 *Reagents and conditions:* i, $SiCl_4$ (0.4 equiv.), CH_2Cl_2, 2 h, room temp.; ii, NaOH, MeOH, 30 min, room temp.

As we mentioned above, it has been reported recently that iodotrichlorosilane ($SiCl_4$–NaI) regenerates ketones from cyclic ketals.[10] Under the conditions reported by Elmorsy[10] iodotrichlorosilane (2 equiv.) and **1** or **6** (1 equiv.) when allowed to react at room temperature for 1 h, gave not the expected isoxazolidone but, instead, the same products in similar yields as had been obtained with tetrachlorosilane. An ^1H NMR kinetic analysis of these reactions showed that the mechanism is identical with that performed with $SiCl_4$.

We also studied the hydrolysis of dihydropyran spiro derivatives such as **9**. The reaction of **9** with tetrachlorosilane (0.4 equiv.) at room temperature failed to give the corresponding 2-pyrone affording instead a mixture of compounds **10** (63%), **11** (22%) and **12** (8%) (Scheme 3). Compound **10** was the only isolated product bearing a chloro



Scheme 2 *Reagents and conditions:* i, $SiCl_4$, CH_2Cl_2, 2.5 h, room temp.; ii, Amberlyst 15, acetone, 9 h, room temp.



Scheme 3 *Reagents and conditions:* i, $SiCl_4$, CH_2Cl_2, 30 min, room temp.

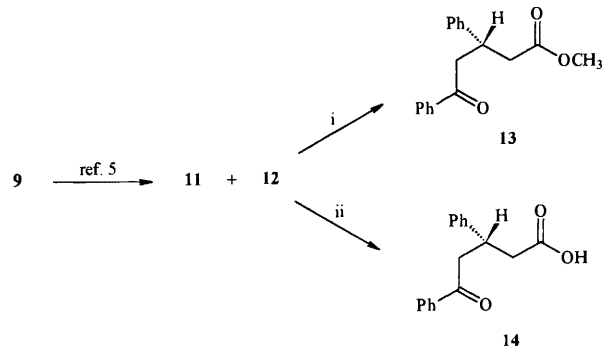
substituent, other expected compounds not being detected. In contrast to the isoxazolidines, a ^1H NMR kinetic analysis of this hydrolysis showed that it takes place without isomerization of **9**, although, as we reported recently,[5] the thermal isomerization of **9** is very easy. A different mechanism may account for the observed reactivity. Spectroscopic results for these compounds established their structural identity.

Treatment of **9** with an acid ion-exchange resin led to opening of its two rings to give the δ-keto esters **11** and **12**, behaviour different from that of **1**.[5] This mixture was easily employed to give simple, optically active compounds. Transesterification of **11** + **12**, performed with NaOH–MeOH, afforded the (*S*)-δ-keto ester **13** quantitatively (Scheme 4).

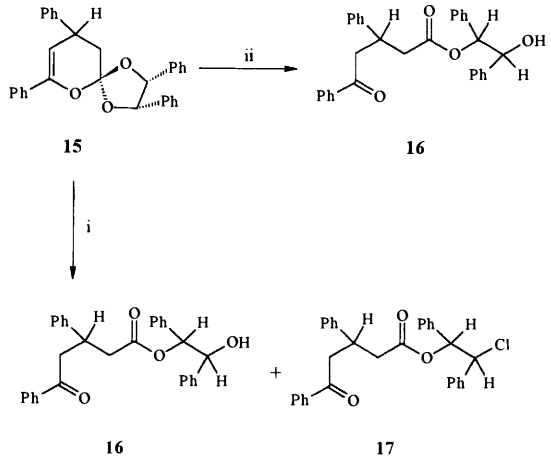
In the same way, a microwave-irradiated solvent-free hydrolysis with KOH–tetrabutylammonium bromide (TBAB) of compounds **11** + **12** gave the (*S*)-δ-keto acid **14** (75%).[11]

Finally, we analysed the hydrolysis of **15**. This with tetrachlorosilane gave an equimolecular mixture of **16** and **17** (90% overall yield) (Scheme 5). However, the treatment of **15** with wet Amberlyst 15 led to the δ-keto ester **16** quantitatively. Compounds **16** and **17** were identified on the basis of ^1H and ^{13}C NMR spectroscopic evidence and from their elemental analyses.

Since the reactions of **9** and **15** with tetrachlorosilane seemed not to occur by the same mechanism as that for compounds **1** and **6**, we studied the reaction of the former with iodotrichlorosilane. We failed both to observe the oxidation–



Scheme 4 *Reagents and conditions:* i, NaOH, MeOH, 2 h, room temp.; ii, KOH, TBAB, MW (450 W), 12 min



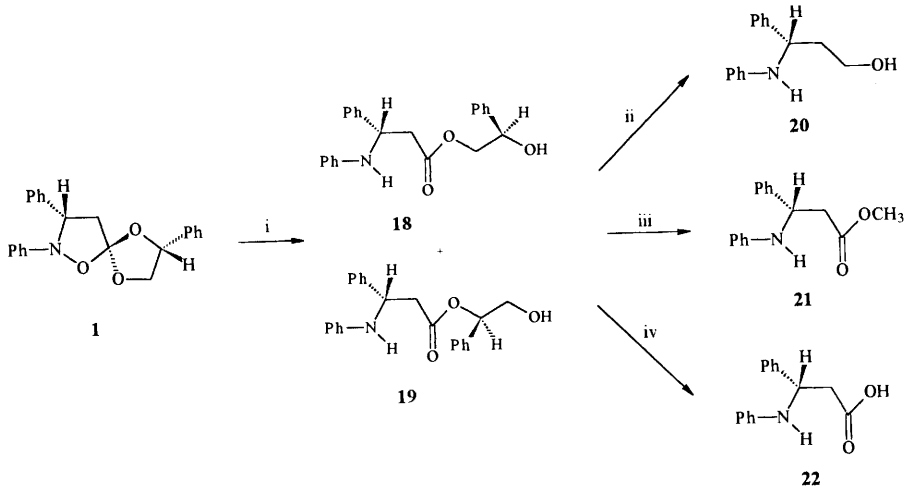
Scheme 5 *Reagents and conditions:* i, $SiCl_4$, CH_2Cl_2, 30 min, room temp.; ii, Amberlyst 15, acetone, 24 h, room temp.

reduction process described by Elmorsy[10] and to obtain the expected 2-pyrone, the hydrolysis products **10**, **11** and **12**, and **16** and **17**, respectively, being obtained instead.

Reductions

Isoxazolidines when hydrogenated, usually undergo N–O bond cleavage to give 3-amino derivatives.[12,13] Our interest in such reactions under non-classical conditions led us to try a microwave-irradiated hydrogenation of isoxazolidine **1** in a domestic oven, a method recently applied to β-lactams.[14] The microwave-irradiated reaction of **1** with ammonium formate as hydrogen source and Pd–C as catalyst in ethylene glycol afforded after 1.5 min the optically active 3-amino esters **18** and **19** (Scheme 6), the structural arrangements of which were supported by their analytical and spectroscopic results. The speed and simplicity of this reaction together with the reasonable overall product yield (65%) suggest that it is a good alternative to the classic hydrogenation procedures. The mixture of compounds **18** and **19** was easily transformed into enantiomerically pure useful compounds. Thus, the reaction of **18** + **19** with $NaBH_4$ in THF–MeOH afforded the (*S*)-3-amino alcohol **20** (96%); the (*S*)-3-amino ester **21** was obtained by transesterification with NaOH–MeOH; and the (*S*)-β-amino acid **22** was obtained after 12 min by a microwave-irradiated solvent-free hydrolysis with KOH–TBAB.

In conclusion, the isoxazolidine and dihydropyran derivatives **1**, **6**, **9** and **15** can be easy hydrolysed to the corresponding open-chain products. Likewise, the isoxazolidine **1** when subjected to microwave-irradiated hydrogenation undergoes N–O bond cleavage. These optically active compounds can be modified to obtain interesting enantiomerically pure products as chiral intermediates.



Scheme 6 *Reagents and conditions:* i, HCO_2NH_4, Pd–C, ethyleneglycol, MW (150 W), 1.5 min; ii, $NaBH_4$, THF–MeOH, 4 h, reflux; iii, NaOH, MeOH, 8 h, room temp.; iv, KOH, TBAB, MW (450 W), 12 min

Experimental

All mps were determined on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and are recorded in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were measured on a Perkin-Elmer 883 Infrared spectrophotometer. ^1H NMR spectra were recorded at 300 MHz on a Varian Unity 300 or at 200 MHz on a Varian Gemini 200 NMR spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on a Varian Unity 300 NMR spectrometer. Chemical shifts were reported in ppm (δ) using Me_4Si as standard, and coupling constants were expressed in Hz. Elemental analysis were determined on a Perkin-Elmer PE2400 CHN apparatus. Mass spectra were obtained on a VG Autospec instrument (70 eV). Column chromatography was carried out with SiO_2 (silica gel, Merck type 60 70–230 mesh). Microwave irradiations were conducted in a Miele Electronic M720 domestic oven. Reagents were purchased from commercial suppliers.

Reaction of compound 1 with tetrachlorosilane

Tetrachlorosilane (0.1 cm^3, 0.85 mmol) was added to a solution of compound **1** (0.76 g, 2.12 mmol) in CH_2Cl_2 (30 cm^3) and the reaction mixture was stirred at room temperature for 2 h. After this the mixture was evaporated under reduced pressure and the products were separated by column chromatography using light petroleum (bp 40–60 °C)–ethyl acetate (3:1) as eluent to give compounds **3** (0.418 g, 53%) and **4** (0.197 g, 24%). Compound **3**: a colourless oil (Found: C, 69.7; H, 5.5; N, 3.4. Calc. for $C_{23}H_{22}ClNO_3$: C, 69.8; H, 5.5; N, 3.5%); $[\alpha]_D$ +28.5 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3405 (OH), 3027 (=CH), 1728 (CO_2) and 1596 (C=C); δ_H(200 MHz, $CDCl_3$) 2.92 (2 H, d, *J* 6.8, CH_2CO_2), 4.12 (1 H, dd, *J* 11.4 and 8.4, CH_2OCO), 4.29 (1 H, dd, *J* 11.4 and 3.2, CH_2OCO), 4.84 [1 H, dd, *J* 8.4 and 3.2, C*H*(Ph)OH], 4.90 [1 H, t, *J* 6.8, C*H*(Ph)N] and 6.45–7.40 (15 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 42.9 (CH_2CO_2), 54.8 (OCH_2), 69.5 and 72.1 [NCHPh and CH(Ph)OH], 112.6, 117.9, 119.5, 126.0, 126.1, 127.6, 127.7, 128.1, 128.5, 128.9, 129.0, 139.4, 141.2, 142.4 (ArC) and 170.7 (CO_2). Compound **4**: mp 94–95 °C (Found: C, 69.75; H, 5.45; N, 3.5. Calc. for $C_{23}H_{22}ClNO_3$: C, 69.8; H, 5.5; N, 3.5%); $[\alpha]_D$ −7.5 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3359 (OH), 1721 (CO_2), 1594 (C=C), 1249 (CO) and 1031 (CO); δ_H(200 MHz, $CDCl_3$) 2.97 (2 H, d, *J* 6.8, CH_2CO_2), 3.73 (1 H, dd, *J* 12.3 and 4.0, CH_2OH), 3.84 (1 H, dd, *J* 12.3 and 7.7, CH_2OH), 4.94 [1 H, t, *J* 6.8, C*H*(Ph)N], 5.86 (1 H, dd, *J* 7.7 and 4.0, C*H*PhOCO) and 6.45–8.0 (15 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 43.1 (CH_2CO_2), 54.7 (CH_2OH), 65.6 (CHN), 77.36 (CHOCO), 112.5, 114.8, 117.8, 119.4, 126.0, 126.4, 127.6, 128.1, 128.3, 128.5, 128.8, 129.0, 136.3, 141.0, 142.2 (ArC) and 170.2 (CO_2).

Methyl (*S*)-3-(*N*-chloroanilino)-3-phenylpropionate 5

Methanolic sodium hydroxide (1 mol dm^{-3}) was added dropwise to a solution of **3** and **4** (0.23 g, 0.6 mmol) in MeOH (15 cm^3) to bring it to pH 9. The reaction mixture was stirred at room temperature for 30 min after which it was evaporated under reduced pressure. The residue was purified by column chromatography using light petroleum–ethyl acetate (5:1) as eluent to give **5** (0.135 g, 84%), mp 74–75 °C (Found: C, 66.3; H, 5.55; N, 4.8. Calc. for $C_{16}H_{16}ClNO_2$: C, 66.35; H, 5.5; N, 4.85%); $[\alpha]_D$ +55.4 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3024 (=CH), 1719 (CO_2), 1592 (C=C) and 1320 (CO); δ_H(300 MHz, $CDCl_3$) 2.86 (2 H, d, *J* 6.8, CH_2), 3.67 (3 H, s, CH_3), 4.87 (1 H, t, *J* 6.8, CH) and 6.43–7.40 (10 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 42.7 (CH_2CO_2), 51.8 (OMe), 54.7 (NCHPh), 112.5, 117.6, 119.3, 125.9, 127.5, 128.7, 128.9, 141.4, 142.5 (ArC) and 171.1 (CO_2); *m/z* (EI-MS) 289 (M^+, 21), 216 (100), 180 (5), 138 (14), 121 (37), 104 (14) and 77 (19).

Reaction of compound 6 with tetrachlorosilane

Tetrachlorosilane (0.05 cm^3, 0.4 mmol) was added to a solution of compound **6** (0.68 g, 1.56 mmol) in CH_2Cl_2 (30 cm^3) and the mixture was stirred at room temperature for 2.5 h. It was then evaporated under reduced pressure and the residue was purified by column chromatography using light petroleum–ethyl acetate (3:1) as eluent to give **7** (0.52 g, 71%) as a colourless oil (Found: C, 73.7; H, 5.5; N, 3.0. Calc. for $C_{29}H_{26}ClNO_3$: C, 73.8; H, 5.5; N, 2.95%); ν_{max}/cm^{-1} 3408 (OH), 3030 (=CH) and 1729 (CO_2); δ_H(300 MHz, [$^2H_6$]-DMSO) 2.74 (1 H, dd, *J* 14.9 and 5.6, CH_2CO_2), 3.01 (1 H, dd, *J* 14.9 and 8.1, CH_2CO_2), 4.79 (1 H, dd, *J* 8.3 and 5.7, C*H*OH), 4.82 (1 H, t, *J* 8.1 and 5.6, NC*H*Ph), 5.71 (1 H, d, *J* 5.7, CO_2C*H*Ph), 5.78 (1 H, d, *J* 8.3, OH) and 6.46–7.29 (20 H, m, ArH); δ_C(75 MHz, [$^2H_6$]-DMSO) 42.3 (CH_2CO_2), 53.4 (NCHPh), 74.8 and 78.8 (OCHPh and HOCHPh), 112.4, 117.0, 126.2, 126.3, 127.0, 127.1, 127.2, 127.3, 127.4, 127.5, 127.6, 128.3, 128.9, 137.5, 141.9, 142.7 (ArC) and 169.0 (CO_2); *m/z* (EI-MS) 471 (M^+, 16), 365 (6), 275 (7), 216 (100), 167 (7), 104 (32) and 77 (14).

Reaction of compound 6 with wet Amberlyst 15

A mixture of compound **6** (0.80 g, 1.83 mmol) and wet Amberlyst 15 (1.2 g) in acetone (30 cm^3) was stirred at room temperature for 9 h. The resin was filtered off and the filtrate was evaporated under reduced pressure to give a pale yellow oil. Flash chromatography of this on silica gel with light petroleum–ethyl acetate (3:1) afforded **8** (0.68 g, 82%) as a white solid; mp 172–173 °C (Found: C, 76.9; H, 6.0; N, 3.2. Calc. for $C_{29}H_{27}NO_4$: C, 76.8; H, 6.0; N, 3.1%); ν_{max}/cm^{-1} 3549, 3403 (OH), 3030 (=CH), 1677 (CO) and 1595 (C=C); δ_H (300 MHz, [$^2H_6$]-DMSO) 2.92 (2 H, d, *J* 7.1, CH_2CO_2), 4.82 (1

H, t, *J* 5.4 and 4.8, HOC*H*Ph), 4.95 (1 H, t, *J* 7.1, NC*H*Ph), 5.67 (1 H, d, *J* 5.4, CO_2CHPh), 5.73 (1 H, d, *J* 4.8, CHO*H*), 6.80–7.27 (20 H, m, ArH) and 8.66 (1 H, s, NOH); δ_C(75 MHz, [$^2H_6$]-DMSO) 36.7 (CH_2CO_2), 64.8 (N*C*HPh), 74.8 and 78.7 (O*C*HPh and HO*C*HPh), 116.1, 120.5, 127.0, 127.1, 127.3, 127.4, 127.5, 128.3, 128.5, 137.5, 138.4, 141.2, 151.7 (ArC) and 169.6 (CO_2); *m/z* (EI-MS) 453 (M^+, 0.1), 239 (10), 182 (38), 131 (41), 107 (92) and 77 (100).

Reaction of compound 9 with tetrachlorosilane

Tetrachlorosilane (0.08 cm^3, 0.75 mmol) was added to a solution of compound **9** (0.7 g, 1.9 mmol) in CH_2Cl_2 (30 cm^3) and the mixture was stirred at room temperature for 30 min. It was then evaporated under reduced pressure and the residue flash chromatographed (silica gel, light petroleum–ethyl acetate 3:1) to yield compound **10** (0.483 g, 63%), compound **11** (0.160 g, 22%) and compound **12** (0.060 g, 8%). Compound **10**: mp 111–112 °C (Found: C, 73.65; H, 5.65. Calc. for $C_{25}H_{23}ClO_3$: C, 73.8; H, 5.65%); ν_{max}/cm^{-1} 3025 (=CH), 1726 (CO_2), 1681 (CO), 1146 (CO) and 699 (CCl); δ_H(300 MHz, $CDCl_3$) 2.69 (1 H, dd, *J* 15.4 and 7.8, PhCOCH_2), 2.84 (1 H, dd, *J* 15.4 and 6.8, PhCOCH_2), 3.22 (2 H, d, *J* 7.1, CH_2CO_2), 3.85 (1 H, q, *J* 7.8 and 7.1, CH_2CHPh), 4.33 (1 H, dd, *J* 11.7 and 6.4, CO_2CH_2), 4.40 (1 H, dd, *J* 11.7 and 7.6, CO_2CH_2), 4.93 (1 H, dd, *J* 7.6 and 6.4, CHCl) and 7.19–7.91 (15 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 37.2 (CH_2CO_2), 40.3 (CH_2COPh), 44.3 ($CH_2CHPhCH_2$), 59.3 (CHCl), 67.6 (OCH_2), 126.7, 127.2, 127.3, 127.9, 128.4, 128.5, 128.8, 133.0, 136.6, 137.3, 137.4, 142.9 (ArC), 171.1 (CO_2) and 197.8 (Ph*C*O). Compound **11**: mp 128 °C (lit.,[5] mp 128–129 °C). Compound **12**: mp 100–102 °C (lit.,[5] mp 101–102 °C).

Methyl (*S*)-3,5-diphenyl-5-oxopentanoate 13

Methanolic sodium hydroxide (1 mol dm^{-3}) was added dropwise to a solution of compounds **11** and **12** (0.20 g, 0.52 mmol) in MeOH (15 cm^3) to bring it to pH 9. The mixture was stirred at room temperature for 2 h after which it was evaporated under reduced pressure and the residue purified by flash chromatography (silica gel, light petroleum–ethyl acetate, 2:1) to give the ester **13** (0.145 g, 100%), mp 102–103 °C (Found: C, 76.5; H, 6.45. Calc. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4%); $[\alpha]_D$ +2.4 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 1728 (CO_2), 1677 (CO), 1594 (C=C) and 1363 (CO); δ_H(300 MHz, $CDCl_3$) 2.70 (1 H, dd, *J* 15.7 and 7.9, PhCOCH_2), 2.83 (1 H, dd, *J* 15.7 and 7.1, PhCOCH_2), 3.34 (1 H, dd, *J* 12.8 and 7.1, CH_2CO_2), 3.40 (1 H, dd, *J* 12.8 and 6.9, CH_2CO_2), 3.59 (3 H, s, OMe), 3.89 (1 H, q, *J* 7.9 and 7.0, C*H*Ph) and 7.20–7.94 (10 H, m, ArH).

(*S*)-3,5-Diphenyl-5-oxopentanoic acid 14

A mixture of compounds **11** and **12** (0.194 g, 0.5 mmol), powdered KOH (0.056 g, 1 mmol) and TBAB (0.004 g) was irradiated in a microwave oven at 450 W for 12 min. The reaction mixture was then diluted with water (5 cm^3) and then extracted with diethyl ether (4 × 10 cm^3). The aqueous layer was acidified with 1 mol dm^{-3} hydrochloric acid to afford a precipitate which was filtered off and identified as **14** (0.096 g, 75%), mp 156–157 °C (Found: C, 75.95; H, 5.95. Calc. for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0%); ν_{max}/cm^{-1} 3028 (=CH), 1704 (CO_2), 1673 (CO) and 1593 (C=C); δ_H(300 MHz, [$^2H_6$]-DMSO) 2.55 (1 H, dd, *J* 15.8 and 8.5, PhCOCH_2), 2.69 (1 H, dd, *J* 15.8 and 6.4, PhCOCH_2), 3.36 (1 H, dd, *J* 17.1 and 6.6, CH_2CO_2H), 3.45 (1 H, dd, *J* 17.1 and 7.8, CH_2CO_2H), 3.65 (1 H, q, *J* 7.8 and 6.5, C*H*Ph), 5.40 (1 H, br s, CO_2H) and 7.11–7.92 (10 H, m, ArH).

Reaction of compound 15 with tetrachlorosilane

Tetrachlorosilane (0.03 cm^3, 0.27 mmol) was added to a solution of compound **15** (0.3 g, 0.67 mmol) in CH_2Cl_2 (15 cm^3) and the mixture was stirred at room temperature for 30 min. It was then evaporated under reduced pressure and the residue purified by flash chromatography (silica gel, light petroleum–ethyl acetate 3:1) to give compounds **16** (0.14 g, 45%) and **17** (0.147 g, 45%). Compound **16**: mp 152–153 °C (Found: C, 80.1; H, 6.05. Calc. for $C_{31}H_{28}O_4$: C, 80.2; H, 6.0%); ν_{max}/cm^{-1} 3415 (OH), 3029 (=CH), 1720 (CO_2), 1681 (CO), 1594 (C=C), 1269 (CO) and 1153 (CO); δ_H(300 MHz, $CDCl_3$) 2.13 (1 H, d, *J* 3.7, OH), 2.75 (2 H, m, CH_2CO_2), 3.23 (2 H, m, PhCOCH_2), 3.82 (1 H, q, *J* 7.3 and 7.0, CH_2CHPh), 4.90 [1 H, dd, *J* 5.9 and 3.7, C*H*(Ph)OH], 5.84 (1 H, d, *J* 5.9, CO_2CHPh) and 7.06–7.87 (20 H, m, ArH); δ_C(75 MHz, [$^2H_6$]-DMSO) 37.0 (CH_2CO_2), 40.4 (PhCOCH_2), 43.7 ($CH_2CHPhCH_2$), 74.6 and 78.4 (CO_2CHPh), 126.1, 126.2, 127.0, 127.1, 127.3, 127.4, 127.5, 127.8, 128.0, 128.6, 133.1, 136.5, 137.8, 141.4, 143.2 (ArC), 170.1 (CO_2) and 198.1 (CO). Compound **17**: colourless oil (Found: C, 76.95; H, 5.6. Calc. for $C_{31}H_{27}ClO_3$: C, 77.1; H, 5.6%); ν_{max}/cm^{-1} 3028 (=CH), 1737 (CO_2), 1681 (CO), 1259 (CO), 1088 (CO) and 800 (CCl); δ_H(300 MHz, $CDCl_3$) 2.81 (1 H, dd, *J* 16.4 and 8.1, CH_2CO_2), 2.93 (1 H, dd, *J* 16.4 and 6.8, CH_2CO_2), 3.36 (2 H, d, *J* 7, PhCOCH_2), 3.92 [1 H, m, $CH_2CH(Ph)CH_2$], 5.02 (1 H, d, *J* 8.5, CHCl), 6.05 (1 H, d, *J* 8.5, CO_2CHPh) and 6.92–7.89 (20 H, m, ArH); δ_C(75 MHz, [$^2H_6$]-DMSO) 37.1 (CH_2CO_2), 40.0 (PhCOCH_2), 43.9 [CH_2-CH(Ph)CH_2], 64.5 (CHCl), 77.9 (O*C*HPh), 126.2, 126.3, 127.4, 127.7, 127.9, 128.0, 128.1, 128.3, 128.5, 133.0, 136.4, 136.6, 137.4, 143.1 (ArC), 170.1 (CO_2) and 198.1 (CO).

Reaction of compound 15 with wet Amberlyst 15

A mixture of compound **15** (0.3 g, 0.67 mmol) and wet Amberlyst 15 (0.82 g) in acetone (30 cm^3) was stirred at room temperature for 24 h. The resin was filtered off and the filtrate evaporated under reduced pressure to give a pale yellow solid. Flash chromatography of this on silica gel with light petroleum–ethyl acetate (3:1) as eluent afforded compound **16** (0.31 g, 100%) as a white solid, mp 152–153 °C.

Hydrogenolysis of the isoxazolidine derivative 1

A Teflon vessel was charged with Pd–C (0.042 g), ethyleneglycol (1.4 cm^3), compound **1** (0.200 g, 0.56 mmol) and ammonium formate (0.176 g, 2.8 mmol) and then closed and the reaction mixture irradiated in a microwave oven at 150 W for 1.5 min (final temp. 110 °C). The catalyst was filtered off and washed with CH_2Cl_2 (2 × 5 cm^3) and the combined filtrate and washings were dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil. Flash chromatography of this on silica gel with light petroleum–ethyl acetate (2:1) afforded compounds **18** (0.093 g, 46%) and **19** (0.039, 19%). Compound **18**: mp 94–95 °C (Found: C, 76.3; H, 6.35; N, 3.9. Calc. for $C_{23}H_{23}NO_3$: C, 76.45, H, 6.4; N, 3.9%); $[\alpha]_D$ −19.3 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3395 (NH), 3026 (=CH), 1728 (CO_2), 1595 (C=C), 1160 (CO) and 1026 (CO); δ_H(300 MHz, $CDCl_3$) 2.89 (2 H, d, *J* 6.3, CH_2CO_2), 4.12 (1 H, dd, *J* 11.4 and 8.3, CO_2CH_2), 4.28 (1 H, dd, *J* 11.4 and 3.1, CO_2CH_2), 4.83 [1 H, dd, *J* 8.3 and 3.1, C*H*(Ph)OH], 4.87 (1 H, t, *J* 6.3, NC*H*Ph) and 6.57–7.37 (15 H, m, ArH); δ_C(75 MHz, [$^2H_6$]-DMSO) 42.6 (CH_2CO_2), 53.5 (CO_2CH_2), 68.9 and 70.1 [N*C*HPh and *C*H(Ph)OH], 113.0, 116.1, 126.2, 126.5, 126.9, 127.3, 128.1, 128.2, 128.3, 128.7, 128.8, 141.8, 143.1, 147.5 (ArC) and 170.3 (CO_2). Compound **19**: mp 81–82 °C (Found: C, 76.4; H, 6.45; N, 3.95. Calc. for $C_{23}H_{23}NO_3$: C, 76.45; H, 6.4; N, 3.9%); ν_{max}/cm^{-1} 3386 (NH), 3023 (=CH), 1726 (CO_2), 1565 (C=C), 1158 (CO) and 1025 (CO); δ_H(300 MHz, $CDCl_3$) 2.94 (2 H, d, *J* 6.9, CH_2CO_2), 3.72 (1 H, dd, *J* 12.2 and 4.1, CH_2OH), 3.80 (1 H, dd, *J* 12.2 and 7.6, CH_2OH), 4.89 (1 H, t, *J* 6.9, NC*H*Ph), 5.82 (1 H, dd, *J* 7.6 and 4.1, CO_2CHPh), 6.54–7.39 (15 H, m, ArH).

(*S*)-3-Anilino-3-phenylpropanol 20

Methanol (0.7 cm^3) was added dropwise to a solution of compounds **18** and **19** (0.3 g, 0.86 mmol) and $NaBH_4$ (0.031 g, 0.83 mmol) in THF (3.5 cm^3) and the reaction mixture was heated under reflux for 4 h. After this it was poured into water

(4 cm^3) and evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (5 × 6 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography of the residue on silica gel with light petroleum–ethyl acetate (2:1) afforded compound **20** (0.181 g, 96%), mp 94–95 °C (Found: C, 79.2; H, 7.45; N, 6.3. Calc. for $C_{15}H_{17}NO$: C, 79.3; H, 7.5; N, 6.2%); $[\alpha]_D$ −221.4 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3278 (OH), 3020 (=CH), 1602 (C=C) and 1026 (CO); δ_H(300 MHz, $CDCl_3$) 2.04 (2 H, q, *J* 6.6, $PhCHC\mathit{H}_2$), 2.95 (1 H, br s, NH), 3.77 (2 H, ddd, *J* 6.6, $C\mathit{H}_2OH$), 4.57 (1 H, t, *J* 6.6, $NC\mathit{H}Ph$) and 6.53–7.36 (10 H, m, ArH).

Methyl (*S*)-3-anilino-3-phenylpropionate 21

Methanolic NaOH (1 mol dm^{-3}) was added dropwise to a solution of compounds **18** and **19** (0.2 g, 0.55 mmol) in methanol (15 cm^3) to bring it to pH 10 after which the mixture was stirred at room temperature for 8 h. It was then evaporated under reduced pressure and the residue purified by flash chromatography (silica gel, light petroleum–ethyl acetate, 2:1) to give the ester **21** (0.118 g, 84%), mp 113–114 °C (Found: C, 75.35; H, 6.65; N, 5.45. Calc. for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7; N, 5.5%); $[\alpha]_D$ +5.1 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3382 (NH), 3019 (=CH), 1717 (CO_2), 1600 (C=C) and 1292 (CO); δ_H(300 MHz, $CDCl_3$) 2.81 (2 H, d, *J* 6.7, CH_2), 3.64 (3 H, s, OCH_3), 4.58 (1 H, br s, NH), 4.83 (1 H, t, *J* 6.7, $C\mathit{H}Ph$) and 6.54–7.39 (10 H, m, ArH).

(*S*)-3-Anilino-3-phenylpropionic acid 22

A mixture of compounds **18** and **19** (0.23 g, 0.64 mmol), powdered KOH (0.071 g, 1.28 mmol) and tetrabutylammonium bromide (TBAB) (0.004 g) was irradiated in a domestic oven at 450 W for 12 min. It was then diluted with water (10 cm^3) and extracted with cold diethyl ether (3 × 10 cm^3). The aqueous layer was acidified with 1 mol dm^{-3} hydrochloric acid until a precipitate was formed. This was filtered off and identified as compound **22** (0.104 g, 64%), mp 125–126 °C (lit.,[13] mp 118–120 °C); $[\alpha]_D$ −32.2 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 3211 (OH, NH), 1705 (CO_2) and 1599 (C=C); δ_H(300 MHz, $CDCl_3$) 3.62 (1 H, dd, *J* 11.4 and 8.0, $C\mathit{H}_2CO_2H$), 3.72 (1 H, dd, *J* 11.4 and 3.6, $C\mathit{H}_2CO_2H$), 4.20 (1 H, br s, NH), 4.79 (1 H, dd, *J* 8.0 and 3.6, $C\mathit{H}Ph$), 6.56–7.38 (10 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 42.9 (CH_2), 53.6 ($NCHPh$), 112.9, 115.8, 126.2, 126.5, 126.6, 128.2, 128.6, 143.3, 147.6 (ArC) and 172.0 (CO_2H).

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