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The preparation of enantiomerically enriched γ-amino acids (GABAs) using palladium catalysed allylic substitution

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Abstract

Enantioselective palladium catalysed allylic substitution reactions have been employed as the asymmetry-producing step in the synthesis of enantiomerically enriched γ-amino acids.

1. Introduction

Highly enantioselective palladium catalysed allylic substitution reactions have been achieved by many research groups.[1] The ligand **1** has been used by ourselves[2] and others[3] to effect an efficient enantioselective reaction, such as the conversion of the standard allyl acetate **2** into the substitution product **3**. It therefore comes as no surprise that we have been able to apply the reaction to related nucleophiles, and thereby generate the substitution products **4**–**7** with high enantioselectivity (for products **4**–**6**, two diastereomers were formed with little control of selectivity, 8–27% *de*, probably representing a thermodynamic ratio).

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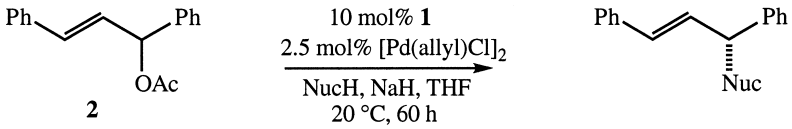
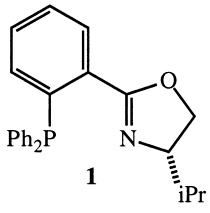
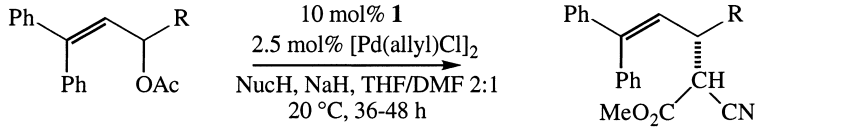




Product	*Nuc*	*ee*	*yield*
3	-$CH(CO_2Me)_2$	>96% ee	>95%
4	-$CH(COMe)CO_2Et$	>96% ee	>95%
5	-$CH(COMe)SO_2Ph$	96% ee	76%
6	-$CH(CN)CO_2Me$	92% ee	73%
7	-$CH(CN)_2$	86% ee	93%

This research group has previously demonstrated that substrates of the type exemplified by allylic acetates **8**–**11** are synthetically useful, since they are easy to prepare from commercially available β-phenylcinnamaldehyde, and are therefore more accessible for a wider range of substrates than for those compounds (such as substrate **2**) which proceed via symmetrical allylpalladium complexes.[4] We were pleased to find that using methyl cyanoacetate as the incoming nucleophile, we were able to record high yields and enantioselectivities in the allylic substitution reaction to generate the substitution products **12**–**15** (again with little control of diastereoselectivity). The enantioselectivities were determined by chiral HPLC (Chiralcel OD, hexane:isopropanol, 99:1).

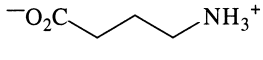


R =	Me	**8**	R =	Me	**12** 78% y, 64% ee
	Et	**9**		Et	**13** 90% y, 90% ee
	Ph	**10**		Ph	**14** 74% y, 96% ee
	ClC_6H_4	**11**		ClC_6H_4	**15** 81% y, 93% ee

Previous results from these laboratories have demonstrated how α- and β-amino acids can be prepared using enantioselective palladium catalysed allylic substitution reactions as the key step.[5] Herein, we demonstrate how the cyano ester products **12** and **14** can be converted into γ-amino acids.

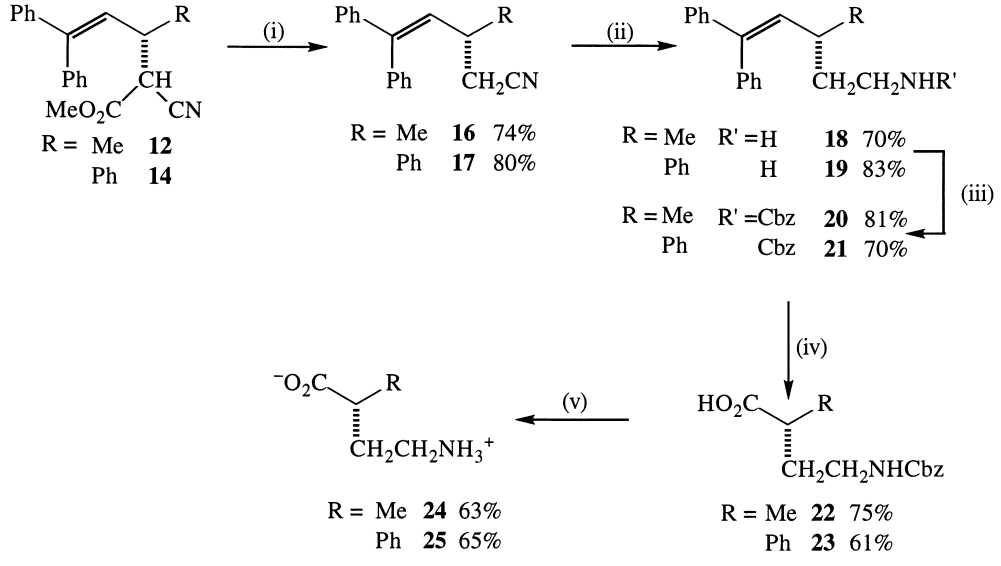
2. Results and discussion

The parent compound, GABA, is an important inhibitor neurotransmitter with several roles in the mammalian central nervous system, and virtually all central neurones appear to be under the inhibitory control of GABA.[6] The importance of chirality in GABA analogues has been described with respect to interaction with GABA receptors.[7]



γ-Aminobutyric acid (GABA)

The following simple sequence was employed to convert the substitution products into the corresponding γ-amino acids. The cyanoesters **12** and **14** underwent a Krapcho decarboxylation reaction to afford the corresponding nitriles **16** and **17**. Reduction of the nitrile afforded the amines **18** and **19** which were protected to give the carbamates **20** and **21**. Oxidative cleavage of the alkene affords the carboxylic acids **20** and **21**, which were deprotected to afford the γ-amino acids **22** and **23**.



Conditions: (i) NaCl, wet DMSO, reflux (ii) $LiAlH_4$, Et_2O
(iii) Cbz-Cl, DMAP, Et_3N, CH_2Cl_2 (iv) CrO_3, CH_3CO_2H
(v) H_2, Pd on C, MeOH

3. Experimental

General experimental details, including the purification of solvents and the spectrometers employed have been detailed elsewhere.[2b] The preparation of ligand **1** and acetates **8**–**11** has also been previously reported.[2b,4]

*3.1. General procedure for the palladium catalysed allylic alkylation of acetate **2** with various nucleophiles*

The preparation of compounds **4**–**7** is typified by the formation of compound **6**.

A solution of sodiomethyl cyanoacetate (0.21 ml, 1.2 mmol) in dry THF (2 ml) was added slowly to a solution of *rac*-(*E*)-1,3-diphenyl-3-acetoxy-1-propene **2** (200 mg, 0.8 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (7.3 mg, 20 μmol) and (4*S*)-4,5-dihydro-4-isopropyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole **1** (30 mg, 80 μmol) in dry THF (3 ml) under an inert atmosphere and stirred for 16 h at ambient temperature. The reaction was diluted with dichloromethane (50 ml) and washed with a saturated aqueous ammonium chloride solution (50 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate:light petroleum, 1:20) to yield compound **6** as a pale yellow oil (168 mg, 73%). (Found: M^+, 291.1260. $C_{19}H_{17}NO_2$ requires M^+, 291.1259.) $[\alpha]_D^{20}$ 18.57 (*c* 16.8; $CHCl_3$). ν_{max} (neat) cm^{-1} 2250 (CN), 1747 (C=O), 1599 (C=C) and

1262 (C–O). δ_H (250 MHz; $CDCl_3$) for both diastereomers 7.41–7.24 (10H, m, Ar–*H*), 6.61–6.44 (2H, m, Ph(*H*)C=C*H*), 4.22 (1H, m, Ph–C*H*), 3.94 and 3.89 (1H, 2×d, *J*=7.5, C*H*CO_2Me), 3.70 and 3.68 (3H, 2×s, OCH_3). δ_C (63 MHz; $CDCl_3$) 165.6 and 165.3 (*C*=O), 139.1, 134.3, 129.2, 129.05, 129.0, 128.8, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 127.6, 126.7, 126.5 and 126.4 (arom. *C* and *C*=C), 115.2 (*C*N), 53.2 (O*C*H_3), 49.8 and 49.5 (*C*HPh), 45.3 and 44.9 (*C*HCN).

Compound **4** as a colourless oil (90%). (Found: M^+, 322.1574. $C_{21}H_{22}O_3$ requires M^+, 322.1569.) $[\alpha]_D^{20}$ −17.2 (*c* 0.23; $CHCl_3$). ν_{max} (neat) cm^{-1} 1743 (CO_2Et), 1717 (C=O), 1649 (C=C) and 1153 (C–O). δ_H (250 MHz; $CDCl_3$) 7.31–7.18 (10H, m, Ar–*H*), 6.47 (1H, d, *J*=9.2, Ph(*H*)C=CH), minor diastereomer), 6.41 (1H, d, *J*=9.2, Ph(*H*)C=CH, major diastereomer), 6.29 (1H, dd, *J*=12.6 and 8, Ph(H)C=C*H*, major diastereomer), 6.24 (1H, dd, *J*=12.6, 8, Ph(H)C=C*H*, minor diastereomer), 4.30 (1H, d, *J*=8, CH_3COC*H*, minor diastereomer), 4.26 (1H, d, *J*=8, CH_3COC*H*, major diastereomer), 4.22–4.05 (3H, m, PhC*H* and OCH_2, both diastereomers), 2.29 (3H, s, CH_3CO) and 1.28–1.18 (3H, m, OCH_2CH_3, both diastereomers). δ_C (100.6 MHz; $CDCl_3$) 201.7 and 201.4 (*C*=O), 167.9 and 167.6 (*C*O_2Et), 140.2, 136.8, 131.8, 131.5, 129.5, 129.3, 128.9, 128.8, 128.5, 128.0, 127.9, 127.6, 127.5, 127.2, 126.4 and 126.3 (arom. *C* and *C*=C), 65.6 and 65.2 (*C*HCO_2Et), 61.6 and 61.4 (OCH_2), 48.9 and 48.7 (Ph-*C*H), 30.1 and 30.0 (*C*H_3O), 14.3 and 14.2 (CH_2CH_3).

Compound **5** as a white solid (76%). Mp 134–135°C. (Found: M^+, 390.1297. $C_{24}H_{22}O_3S$ requires M^+, 390.1290.) $[\alpha]_D^{20}$ −58.9 (*c* 0.48; $CHCl_3$). ν_{max} (Nujol) cm^{-1} 1722 (C=O), 1598 (C=C), 1307 and 1144 (SO_2). δ_H (250 MHz; $CDCl_3$) 7.49–7.06 (15H, m, Ar–*H*), 6.41 (1H, d, *J*=15.7, Ph(*H*)C=CH), 6.09 (1H, dd, *J*=15.2 and 4.0, Ph(H)C=C*H*), 4.72 (1H, d, *J*=10.4, CH_3COC*H*, minor diastereomer), 4.67 (1H, d, *J*=10.4, CH_3COC*H*, major diastereomer), 4.33 (1H, t, *J*=9.5, PhC*H*) and 2.41 (3H, s, CH_3CO). δ_C (63 MHz; $CDCl_3$) 199.9 and 199.8 (*C*=O), 139.3, 136.5, 134.4, 134.0, 133.3, 132.9, 132.6, 129.7, 129.2, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 126.4 and 126.3 (arom. *C* and *C*=C), 79.7 and 79.3 (*C*HCO), 48.8 and 48.7 ((Ph–*C*H), 32.4 and 31.5 (*C*H_3O).

Compound **7** as a colourless oil (93%). (Found: M^+, 276.1501. $C_{18}H_{18}N_3$ requires M^+, 276.1501.) $[\alpha]_D^{20}$ 20.0 (*c* 2.76; $CHCl_3$). ν_{max} (neat) cm^{-1} 2360 (CN) and 1648 (C=C). δ_H (250 MHz; $CDCl_3$) 7.45–7.22 (10H, m, Ar–*H*), 6.68 (1H, d, *J*=15.7, PhC*H*=CH), 6.45 (1H, dd, *J*=15.6 and 7.4, PhCH=C*H*) and 4.12–4.03 (2H, m, NCC*H*CN and PhC*H*). δ_C (63 MHz; $CDCl_3$) 136.5, 135.8, 134.6, 129.4, 129.1, 128.9, 128.7, 128.6, 128.4, 127.9, 126.8 and 123.9 (arom. *C* and *C*=C), 111.7 (*C*N), 49.7 (Ph*C*H) and 30.2 (NC*C*HCN).

*3.2. General procedure for the palladium catalysed allylic alkylation of acetates **8–11***

The preparation of compounds **12**–**15** is typified by the preparation of compound **13**.

Methyl cyanoacetate (0.19 ml, 2.1 mmol) was added slowly to a slurry of sodium hydride (51 mg, 2.1 mmol) in dry THF (2 ml) and DMF (1 ml) at 0°C whilst under a nitrogen atmosphere. The resultant anion was added to a solution of 1,1-diphenylpent-1-enyl-3-acetate **9** (200 mg, 0.7 mmol), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (7 mg, 19 μmol) and (4*S*)-4,5-dihydro-4-isopropyl-2-[2-(diphenylphosphino)phenyl]-1,3-oxazole **1** (28 mg, 75 μmol) in dry THF (1 ml) and DMF (0.5 ml) which had been stirred under an inert atmosphere for 15 min at ambient temperature. The reaction was monitored by TLC for the disappearance of acetate. Once all the acetate had been converted to product (36–48 h) the reaction was quenched with ammonium chloride solution. The aqueous phase was extracted with dichloromethane (3×30 ml), the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the crude product which was purified by flash chromatography (ethyl acetate:light petroleum, 1:10) to yield the desired product **13**, as a yellow solid. Mp 97–98°C. (Found: M^+, 319.1572. $C_{21}H_{21}NO_2$ requires M^+, 319.1572.) $[\alpha]_D^{20}$ −10.3 (*c* 0.348; $CHCl_3$). ν_{max} (Nujol) cm^{-1} 2252 (CN) and 1748 (C=O). δ_H (250 MHz; $CDCl_3$) 7.43–7.12

(10H, m, Ar–*H*), 5.97 and 5.90 (1H, d, *J*=10.7, $Ph_2C{=}CH$), 3.72 and 3.67 (3H, s, OCH_3), 3.56 and 3.50 (1H, d, *J*=4.6, $CHCO_2Me$), 2.98–2.86 (1H, m, $CHCH_2$), 1.72–1.59 (2H, m, CH_2CH_3) and 0.98–0.90 (3H, m, CH_2CH_3). δ_C (100.6 MHz; $CDCl_3$) 166.0 and 165.9 (*C*=O), 146.1, 146.07, 139.2, 129.5, 129.4, 128.5, 128.3, 128.3, 128.3, 127.8, 127.8, 127.6, 127.5, 127.5, 127.3, 126.8 and 126.1 (arom. *C* and *C*=C), 115.5 and 115.2 (*C*N), 60.3 (OCH_3), 43.2, 42.8, 41.4 and 41.2 ($CHCO_2Me$ and $CHCH_2$), 27.0 and 25.6 (CH_2CH_3) and 11.7 and 11.5 (CH_2CH_3).

Compound **12** as a viscous pale yellow solid (78%). Mp 69–70°C. (Found: M^+, 305.1416. $C_{20}H_{19}NO_2$ requires M^+, 305.1416.) $[\alpha]_D^{20}$ −67.4 (*c* 0.392; $CHCl_3$). ν_{max} (Nujol) cm^{-1} 2252 (CN) and 1748 (C=O). δ_H (250 MHz; $CDCl_3$) 7.43–7.12 (10H, m, Ar–*H*), 6.02 and 5.96 (1H, d, *J*=10.5, $Ph_2C{=}CH$), 3.80 and 3.79 (3H, s, OCH_3), 3.45 (1H, d, *J*=6.0, $CHCO_2Me$), 3.17–3.06 (1H, m, $CHCH_3$) and 1.26 (3H, t, *J*=7.0, $CHCH_3$). δ_C (100.6 MHz; $CDCl_3$) 171.1 (*C*=O), 146.7, 141.3, 138.7, 138.3, 129.4, 129.3, 129.27, 129.2, 129.0, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.5, 124.6 and 123.4 (arom. *C* and *C*=C), 115.1 and 115.0 (*C*N), 60.4 (OCH_3), 45.3 ($CHCO_2Me$), 45.1 ($CHCH_3$) and 44.8 and 44.7 ($CHCH_3$).

Compound **14** as a yellow solid (74%). Mp 115–116°C. (Found: M^+, 367.1572. $C_{25}H_{21}NO_2$ requires M^+, 367.1572.) $[\alpha]_D^{20}$ −121.9 (*c* 0.476; $CHCl_3$). ν_{max} (Nujol) cm^{-1} 2252 (CN) and 1748 (C=O). δ_H (250 MHz; $CDCl_3$) 7.39–7.05 (15H, m, Ar–*H*), 6.50 and 6.43 (1H, d, *J*=10.6, $Ph_2C{=}CH$), 4.24–4.10 (1H, m, PhC*H*), 3.80 (1H, m, $CHCO_2Me$) and 3.63 (3H, s, OCH_3). δ_C (63 MHz; $CDCl_3$) 165.2 and 165.0 (*C*=O), 146.2, 145.2, 141.1, 141.3, 129.4, 129.4, 129.1, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8, 127.7, 127.7, 127.7, 127.5, 127.47, 125.2 and 123.9 (arom. *C* and *C*=C), 115.3 and 115.2 (CN), 53.3 and 53.2 (OCH_3), 45.7, 45.4, 45.3 and 44.9 ($CHCO_2Me$ and *C*HPh).

Compound **15** as a pale yellow oil (81%). (Found: M^+, 401.1183. $C_{25}H_{20}ClNO_2$ requires M^+, 401.1182.) $[\alpha]_D^{20}$ −139.33 (*c* 3.0; $CHCl_3$). ν_{max} (neat) cm^{-1} 2252 (CN) and 1748 (C=O). δ_H (250 MHz; $CDCl_3$) 7.39–6.99 (14H, m, Ar–*H*), 6.45 and 6.38 (1H, d, *J*=10.5, $Ph_2C{=}CH$), 4.22–4.07 (1H, m, CHC_6H_4Cl), 3.81–3.75 (1H, m, $CHCO_2Me$) and 3.66 and 3.64 (3H, s, OCH_3). δ_C (100.6 MHz; $CDCl_3$) 165.7 (*C*=O), 144.8, 141.5, 139.2, 139.0, 129.4, 129.2, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.8, 127.7, 127.6, 127.4, 127.36 and 127.0 (arom. *C* and *C*=C), 115.4 and 115.2 (*C*N), 53.4 and 53.2 (OCH_3), 44.4 and 44.0 ($CHCO_2Me$) and 35.1 and 35.0 (CHC_6H_4Cl).

3.3. *Procedure for the Krapcho decarboxylation of **12** and **14***[8]

A solution of compound **14** (90 mg, 0.24 mmol), sodium chloride (50 mg, 0.8 mmol) and water (20 mg, 1 mmol) in DMSO (5 ml) was heated under reflux for 4 h. The reaction was cooled to ambient temperature before being diluted with ethyl acetate (50 ml). The organic phase was washed with water (3×20 ml) and brine (3×20 ml) before being dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate:light petroleum, 1:6) to yield the desired product **17** as a pale yellow solid (80%). Mp 81–82°C. (Found: M^+, 309.1517. $C_{23}H_{19}N$ requires M^+, 309.1517.) $[\alpha]_D^{20}$ −91.3 (*c* 0.46; $CHCl_3$). ν_{max} (Nujol) cm^{-1} 2252 (CN) and 1599 (C=C). δ_H (250 MHz; $CDCl_3$) 7.42–7.15 (15H, m, Ar–*H*), 6.29 (1H, d, *J*=10.4, $Ph_2C{=}CH$), 3.81 (1H, m, PhC*H*) and 2.71 (2H, d, *J*=6.9). δ_C (100.6 MHz; $CDCl_3$) 144.3, 141.5, 141.4, 129.6, 129.1, 128.5, 128.2, 127.7, 127.6, 127.4 and 127.0 (arom. *C* and *C*=C), 118.1 (*C*N), 41.5 (Ph*C*H) and 25.3 (CH_2CN).

Compound **16** as a pale yellow oil (74%). (Found: M^+, 247.1361. $C_{18}H_{17}N$ requires M^+, 247.1361.) $[\alpha]_D^{20}$ −18.0 (*c* 0.60; $CHCl_3$). ν_{max} (neat) cm^{-1} 2252 (CN) and 1599 (C=C). δ_H (250 MHz; $CDCl_3$) 7.43–7.16 (10H, m, Ar–*H*), 5.91 (1H, d, *J*=10.1, $Ph_2C{=}CH$), 2.78–2.67 (1H, m, $CHCH_3$), 2.32 (2H, d, *J*=6.3, CH_2CN) and 1.18 (3H, d, *J*=6.7, $CHCH_3$). δ_C (100.6 MHz; $CDCl_3$) 143.4, 141.5, 139.5, 130.5, 129.7, 129.4, 129.2, 128.9, 128.8, 128.7, 128.5, 128.2, 128.0, 127.9, 127.7, 127.5, 127.4 and 127.2 (arom. *C* and *C*=C), 118.3 (*C*N), 34.1 ($CHCH_3$), 25.0 (CH_2CN) and 21.0 ($CHCH_3$).

3.4. Procedure for the reduction with lithium aluminium hydride of **16** and **17**

A solution of compound **17** (550 mg, 1.77 mmol) in dry diethyl ether (3 ml) was added slowly to a stirring slurry of lithium aluminium hydride (202 mg, 0.64 mmol) in diethyl ether (5 ml) at 0°C whilst under a nitrogen atmosphere. The resultant solution was heated under reflux for 2 h before being cooled to 0°C. The reaction was quenched by the careful addition of 'wet' diethyl ether (20 ml). A 10% solution of sulfuric acid (10 ml) was added slowly to the white slurry and the mixture was stirred until all the precipitate had dissolved (15 min). The aqueous phase was extracted with ethyl acetate (3×50 ml) and the combined organics were dried over $MgSO_4$ before being reduced in vacuo. The crude product was purified by flash chromatography to yield the desired amine **19** as a white solid. Mp 75–76°C. (Found: M^+, 313.1830. $C_{23}H_{23}N$ requires M^+, 313.1830.) $[\alpha]_D^{20}$ −89.7 (*c* 0.584; $CHCl_3$). ν_{max} (Nujol) cm^{-1} 3405 (NH_2) and 1599 (C=C). δ_H (250 MHz; $CDCl_3$) 8.19 (2H, br. s, NH_2), 7.39–7.05 (15H, Ar–*H*), 6.17 (1H, d, *J*=10.4, Ph_2C=C*H*), 3.38 (1H, m, PhC*H*), 2.93–2.84 (1H, m, C*H*H′NH_2), 2.72–2.61 (CH*H*′NH_2) and 2.19–2.09 (2H, m, CHCH_2). δ_C (100.6 MHz; $CDCl_3$) 142.9, 142.8, 141.6, 139.4, 130.2, 129.6, 128.9, 128.5, 128.2, 127.4, 127.2, 127.1 and 126.8 (arom. *C* and *C*=C), 43.2 (Ph*C*H), 38.5 (*C*H_2NH_2) and 34.5 (CH*C*H_2).

Compound **18** as a colourless oil (70%). (Found: M^+, 251.1674. $C_{18}H_{21}N$ requires M^+, 251.1674.) $[\alpha]_D^{20}$ −86.0 (*c* 1.60; $CHCl_3$). ν_{max} (neat) cm^{-1} 3405 (NH_2) and 1599 (C=C). δ_H (250 MHz; $CDCl_3$) 7.38–7.12 (10H, m, Ar–*H*), 5.82 (1H, d, *J*=10.3, Ph_2C=C*H*), 5.29 (2H, br. s, NH_2), 2.81–2.62 (2H, m, CH_2NH_2), 2.37–2.30 (1H, m, C*H*CH_3), 1.61 (2H, q, *J*=7.6, CHCH_2) and 1.02 (3H, d, *J*=6.6, CHCH_3). δ_C (100.6 MHz; $CDCl_3$) 142.0, 141.5, 140.1, 124.1, 129.8, 129.8, 129.6, 129.3, 129.2, 128.7, 128.6, 128.4, 128.1, 127.9, 127.3, 127.1 and 126.7 (arom. *C* and *C*=C), 39.4 (*C*H_2NH_2), 38.3 (CH*C*H_2), 30.8 (*C*HCH_3) and 21.4 (CH*C*H_3).

3.5. Procedure for N-protection with benzyl chloroformate of compounds **18** and **19**

Triethylamine (0.25 ml, 1.74 mmol) was added to a stirring solution of amine **19** (500 mg, 1.59 mmol) and DMAP (10 mg, 82 μmol) in dichloromethane (10 ml). The resultant solution was stirred for 10 min at ambient temperature before the dropwise addition of benzyl chloroformate (0.25 ml, 1.74 mmol). The reaction was then heated under reflux for 2 h, cooled to ambient temperature and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate:light petroleum, 1:6) to yield the desired product **21** as a pale yellow oil (70%). (Found: $(M+NH_4)^+$, 465.2542. $C_{31}H_{33}N_2O_2$ requires M^+, 465.2542.) $[\alpha]_D^{20}$ −82.6 (*c* 0.344; $CHCl_3$). ν_{max} (neat) cm^{-1} 3424 and 3340 (NH), 1713 (C=O) and 1028 (C–O). δ_H (250 MHz; $CDCl_3$) 7.41–7.09 (20H, m, Ar–*H*), 6.21 (1H, d, *J*=10.5, Ph_2C=C*H*), 5.04 (2H, s, CH_2Ph), 4.51 (1H, br. s, N*H*), 3.50–3.40 (1H, m, C*H*Ph), 3.25–3.01 (2H, m, CH_2NHCbz) and 1.93 (2H, q, *J*=7.2, CHCH_2). δ_C (100.6 MHz; $CDCl_3$) 156.2 (C=O), 144.3, 142.0, 142.0, 139.8, 136.6, 131.7, 131.0, 129.7, 128.7, 128.5, 128.4, 128.1, 128.04, 128.0, 127.3, 127.2 and 126.4 (arom. *C* and *C*=C), 66.5 (*C*H_2Ph), 43.0 (*C*HPh), 39.4 (*C*H_2NHCbz) and 37.1 (CH*C*H_2).

Compound **20** as a colourless oil (81%). (Found: MH^+, 386.2120. $C_{26}H_{27}NO_2$ requires MH^+, 386.2137.) $[\alpha]_D^{20}$ −41.0 (*c* 0.80; $CHCl_3$). ν_{max} (neat) cm^{-1} 3424 and 3340 (NH), 1713 (C=O) and 1028 (C–O). δ_H (250 MHz; $CDCl_3$) 7.39–7.14 (15H, m, Ar–*H*), 5.84 (1H, d, *J*=10.3, Ph_2C=C*H*), 5.09 (2H, s, CH_2Ph), 4.48 (1H, br. s, N*H*Cbz), 3.25–3.15 (1H, m, C*H*H′NHCbz), 3.07–2.99 (1H, m, CH*H*′NHCbz), 2.42–2.30 (1H, m, C*H*CH_3), 1.59–1.46 (2H, m, CHCH_2) and 1.05 (3H, d, *J*=6.6, CHCH_3). δ_C (100.6 MHz; $CDCl_3$) 156.2 (*C*=O), 142.2, 141.3, 140.2, 136.8, 134.6, 129.6, 128.7, 128.5, 128.4, 128.2, 128.0, 128.0, 127.1 and 127.1 (arom. *C* and *C*=C), 66.5 (*C*H_2Ph), 39.4 (*C*H_2NHCbz), 37.5 (CH*C*H_2), 31.6 (*C*HCH_3) and 21.4 (CH*C*H_3).

3.6. Procedure for the oxidative cleavage with chromium trioxide of compounds **20** and **21**

A solution of chromium trioxide (1.27 g, 12.7 mmol) in glacial acetic acid (7 ml) was added slowly to a stirring solution of compound **21** (570 mg, 1.27 mmol) in glacial acetic acid (3 ml). The resultant solution was stirred for 16 h at ambient temperature before being poured onto water (50 ml). The aqueous phase was extracted with dichloromethane (6×20 ml) and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (dichloromethane:light petroleum, 3:1, then dichloromethane:methanol, 9:1) to yield the desired acid **23** as a colourless oil. (Found: M^+, 313.1314. $C_{18}H_{19}NO_4$ requires M^+, 313.1314.) $[\alpha]_D^{20}$ −15.84 (*c* 0.404; $CHCl_3$). ν_{max} (neat) cm^{-1} 3354 (CO_2H and NH), 1785 (CO_2H), 1717 (C=O). δ_H (250 MHz; $CDCl_3$) 7.60–7.20 (10H, m, Ar–*H*), 5.34–5.20 (3H, m, C*H*Ph and CH_2Ph), 3.96–3.87 (1H, m, CHC*H*H′), 3.62–3.51 (1H, m, CHCH*H*′) and 2.42 (2H, t, *J*=6.7, CH_2NHCbz). δ_C (100.6 MHz; $CDCl_3$) 197.5 (*C*O_2H), 153.8 (*C*=O), 133.4, 130.2, 129.3, 128.9, 128.7, 128.6, 128.6, 128.5, 128.4, 128.2 and 127.8 (arom. *C*), 67.9 (*C*H_2Ph), 52.7 (*C*HPh), 36.9 (CH*C*H_2) and 35.2 (*C*H_2NHCbz).

Compound **22** as a colourless oil (75%). (Found: M^+, 251.1157. $C_{13}H_{17}NO_4$ requires M^+, 251.1157.) $[\alpha]_D^{20}$ −16.55 (*c* 0.29; $CHCl_3$). ν_{max} (neat) cm^{-1} 3369 (CO_2H and NH), 1754 (CO_2H), 1722 (C=O). δ_H (400 MHz; $CDCl_3$) 7.57–7.16 (5H, m, Ar–*H*), 5.31 (2H, s, CH_2Ph), 3.85–3.79 (1H, m, C*H*H′NHCbz), 3.66–3.59 (1H, m, CH*H*′NHCbz), 2.56 (1H, m, C*H*CH_3), 2.23–2.15 (1H, m, CHC*H*H′), 1.66–1.61 (1H, m, CHCH*H*′) and 1.22 (3H, d, *J*=7.0, CHCH_3). δ_C (100.6 MHz; $CDCl_3$) 176.4 (*C*O_2H), 151.7 (*C*=O), 128.9, 128.8, 128.5, 128.3, 128.2 and 128.0 (arom. *C*), 68.0 (*C*H_2Ph), 44.3 (*C*H_2NHCbz), 38.5 (*C*HCH_3), 26.5 (CH*C*H_2) and 15.3 (CH*C*H_3).

3.7. Procedure for N-deprotection of compounds **22** and **23**

A solution of compound **23** (200 mg, 0.64 mmol) and 10% palladium on carbon powder (20 mg) in anhydrous methanol (5 ml) was stirred for 24 h under an atmosphere of hydrogen. The reaction mixture was filtered through Celite®, the Celite® pad was washed with methanol (5×10 ml) and the filtrate was concentratred in vacuo. The resultant oil was dissolved in dichloromethane (20 ml) and the organic phase was extracted with water. The aqeuous phase was then reduced in vacuo to yield the product **25** as a white solid (65%). Mp 152–153°C. (Found: $M-H^+$, 178.0868. $C_{10}H_{13}NO_2$ requires $M-H^+$, 178.0868.) $[\alpha]_D^{20}$ 9.7 (*c* 0.62; H_2O). ν_{max} (KBr) cm^{-1} 3288 (CO_2H and NH_2) and 1692 (CO_2H). δ_H (250 MHz; D_2O) 7.91–7.34 (5H, m, Ar–*H*), 4.80 (D_2O peak obscuring C*H*Ph), 3.61–3.37 (2H, m, CH_2NH_2) and 2.69–2.44 (2H, m, CHCH_2). δ_C (100.6 MHz; D_2O) 179.7 (*C*O_2H), 141.4, 131.8, 129.3, 128.8, 125.6 and 125.2 (arom. *C*), 79.1 (*C*HPh), 39.1 (*C*H_2NH_2) and 38.2 (CH*C*H_2).

Compound **24** as a white solid (63%). Mp 192–193°C. (Found: M^+, 117.0790. $C_5H_{11}NO_2$ requires M^+, 117.0790.) $[\alpha]_D^{20}$ 3.5 (*c* 0.4; H_2O). Lit. $[\alpha]_D^{24}$ −6.7 (*c* 2.8; H_2O).[9] ν_{max} (KBr) cm^{-1} 3290 (CO_2H and NH_2) and 1698 (CO_2H). δ_H (400 MHz; D_2O) 3.42–3.36 (2H, m, CH_2NH_2), 2.63–2.57 (1H, m, C*H*CH_3), 2.40 (1H, m, CHC*H*H′), 1.87–1.78 (1H, m, CHCH*H*′) and 1.20 (3H, d, *J*=6.9, CHCH_3). δ_C (100.6 MHz; D_2O) 184.9 (*C*O_2H), 40.3 (*C*H_2NH_2), 36.6 (*C*HCH_3), 29.3 (CH*C*H_2) and 15.6 (CH*C*H_3).

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