Use of lactamide diastereoisomers to permit resolution of a racemic modulator of cancer drug resistance

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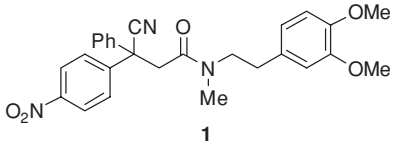
The synthesis of enantiomers of an amidic modulator of cancer multidrug resistance, the chirality of which is not prone to chromatography, has been carried out via formation of the diastereoisomeric esters of the precursor racemic acid with (*S*)-lactamide and separation of the esters on silica gel.

Keywords: diastereoisomeric (*S*)-lactamide esters, diastereoisomer chromatography, enantiomeric synthesis

Multidrug resistance is a cancerous cross-resistance which prevents the effectiveness of a variety of anticancer drugs and presents high incidence. This resistance may be diminished by some chemotherapeutic agents which help to restore the effectiveness of anticancer drugs.[1] Much effort is being devoted to research on chemical modulators of this form of resistance.[2] We found that the racemic amide **1** has high *in vitro* activity



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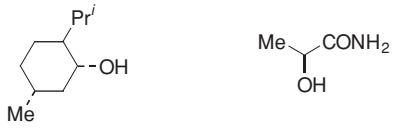
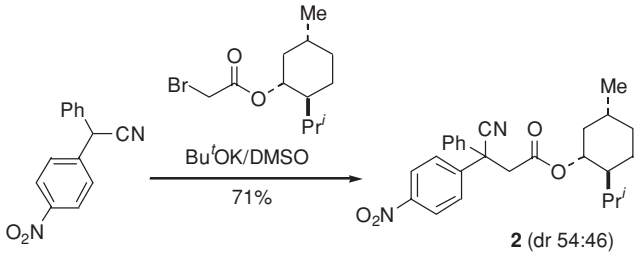
for modulation of the resistance[3,4] and we further desired to know the individual activities of the enantiomers since enantiomers typically have differing biological activities.[5] Hence we planned to carry out the synthesis of enantiomers of the amide (**1**) passing through the resolved enantiomers of the precursor racemic acid, choosing (–)-menthol as a well-known auxiliary for resolution of acids by means of separation



of diastereoisomeric esters using crystallisation or chromatography.[6] However, (–)-menthol turned out to be ineffective and consequently we have considered possible separations based on formation of esters of lactamides (specifically the *S* enantiomer). To achieve the desired resolution, it would be necessary for the lactamides to maintain their stereochemical integrity.

Results and discussion

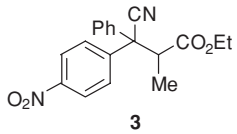
The diastereoisomeric mixture **2** was obtained by alkylation of 4-nitrophenylphenylacetonitrile with the bromoacetic ester of (–)-menthol. The mixture could not be crystallised, preventing the diastereoisomer separation by this means. By TLC on silica gel or aluminium oxide the diastereoisomers could not be separated, and in addition the mixture gave a single peak by reverse-phase HPLC or by GLC. The resistance of these diastereoisomers to separation by adsorption chromatography maybe results, at least in part, from the massiveness of the quaternary chiral moiety which would thwart diastereoisomeric interactions of the molecule with the adsorbent.[4] In addition, this moiety does not have groups with strong affinity to silica.[7] The distance separating the two chiral moieties of the molecule appears to be another factor since the two diastereoisomeric racemates of ester **3**, which has the



2 (dr 54:46)

Scheme 1

chiral centres adjacent and a similar polarity with respect to ester **2**, were separated from each other by column chromatography on silica gel.



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From this information, enantiomeric lactamide was thought of as an alcohol small and bearing a polar aminocarbonyl group with the idea of facilitating in both ways chromatographic distinctness of derived diastereoisomeric esters. The bromoacetic ester of (*S*)-lactamide (**4**) was prepared by *O*-acylation of (*S*)-lactamide in high enantiomeric purity, a preliminary requisite in a resolution auxiliary which was ascertained by chiral-phase GLC with the assistance of the corresponding racemate [**4** (*RS*)] for peak referencing. The higher melting point of this racemate compared with the *S* enantiomer (81 versus 56 °C) indicates that the racemate was rendered in the form of racemic compound and not of racemic conglomerate since the conglomerate (an eutectic) will melt below the enantiomer; the indication is further supported by the unlike IR spectra for the racemate and the enantiomer in the solid state. The relative melting points further indicate that this racemic compound is more stable than the enantiomers, with certainty at the melting point of the conglomerate (somewhere below 56 °C; ref. 8). The required diastereoisomers **5a** and **5b** (obtained by alkylation with the bromo ester and noncrystallisable again) were successfully separated to a high degree by preparative TLC on silica gel. However, the separation was not easy requiring a high proportion of silica gel, recalling the above-mentioned reluctance of ester **2** toward chromatographic diastereoisomeric interactions. A small amount of methanol in the diethyl-ether developing solvent (2.5%) was necessary for a good separation of the diastereoisomers. A trial column chromatography on a larger scale yielded the second eluted diastereoisomer in lower diastereoisomeric purity (85%).

The diastereoisomers **5a** and **5b** were also obtained in a direct way from (*S*)-lactamide by using the chloride of the racemic acid considered, thus serving as a check to the efficiency of

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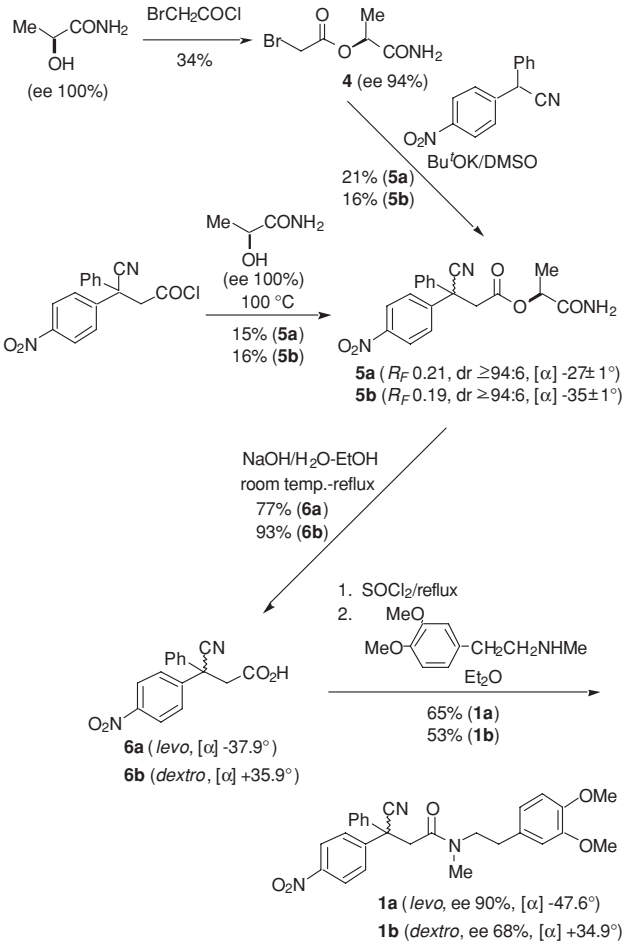

Scheme 2

(*S*)-lactamide as the resolution auxiliary: the optical rotations of diastereoisomeric samples from the two unlike procedures were in agreement (within ±5%) for one and the other diastereoisomer, supporting that the lactamidic configuration was preserved throughout reaction and separation. Hydrolysis of the diastereoisomers gave the resolved antipodal acids **6a** and **6b**, step in which the chirality of the asymmetric carbon cannot be exchanged because is a quaternary carbon.

The final antipodal amides **1a** and **1b** were obtained by way of the acid chlorides. The enantiomeric purity of the amides was checked by chiral-reagent ^{1}H NMR. As obtained actually from a sample of diastereoisomer **5b** with lower diastereoisomeric purity, enantiomer **1b** also had lower enantiomeric purity, but the optical rotation is otherwise in satisfactory agreement with that of antipode **1a**. Using enantiomeric lactamide (either *R* or *S*) along with the procedures herein reported, an enantiomeric purity of *ca* 90% for both **1a** and **1b** may be reached. This level of resolving efficiency is determined mainly by the separation of the lactamide diastereoisomers **5a** and **5b**.

Experimental

General: 4-Nitrophenylphenylacetonitrile,[9] bromoacetic ester of (1*R*,2*S*,5*R*)-menthol,[10] ester **3**[3c] and 3-cyano-3-(4-nitrophenyl)-3-phenylpropionyl chloride[3a] were prepared by literature procedures. (*S*)-Lactamide was prepared by a procedure for (*R*)-lactamide[11a] using instead the antipodal precursor; m.p. 49–52 °C (lit.[11b] m.p. 54 °C), ee(GLC) 100%. Column chromatographies were carried out with MN silica-gel 60. Merck silica-gel 60-F_{254} for TLC; plates of 20 × 20 × 0.2 cm for preparative work. For chiral-phase GLC, it was used a Carlo-Erba HRGC-960 chromatograph equipped with a capillary column of trimethyl β-cyclodextrin in silicone. Melting points were determined with a Reichert-Jung Thermovar hot-stage microscope. Optical rotatory powers were measured with a Perkin-Elmer 241-MC polarimeter, and at least two measurements were carried out for each sample; average [α] values, having <5% standard deviations, are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 681 spectrophotometer. Varian Gemini, Varian XL-300 and Varian Unity-500 spectrometers for ^{1}H and ^{13}C NMR spectrometry; *J* values are given in Hz; (+)-Eu(hfc)$_3$ was used as a chiral reagent. Finnigan TSQ-70 spectrometer for mass spectrometry.

*(3RS)-3-Cyano-3-(4-nitrophenyl)-3-phenylpropionic ester of (1R, 2S,5R)-menthol (**2**):* To a stirred solution of potassium *t*-butoxide (8.5 g, 76 mmol) in DMSO (30 cm^3) under nitrogen, a solution of 4-nitrophenylphenylacetonitrile (17.2 g, 72.2 mmol) in DMSO (20 cm^3) was slowly added, followed by addition of a solution of bromoacetic ester of (1*R*,2*S*,5*R*)-menthol (20.0 g, 72.1 mmol) in DMSO (20 cm^3). Water was added after 70 h and the mixture was extracted using diethyl ether. The ethereal extract was washed with water, dried and evaporated under reduced pressure to an impure residue (30.5 g). A portion (1.0 g) was purified by column chromatography on silica with hexanes/benzene (1:1) as the eluent and gave the mixture of diastereoisomers **2** (0.728 g, 71%) as a glassy solid mass, dr(NMR) 54:46 [Found: C, 71.6; H, 7.25; N, 6.6%; M$^+$, 434. $C_{26}H_{30}N_2O_4$ requires C, 71.85; H, 7.0; N, 6.45%; M, 434]; δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.55 and 0.60 (3 H, 2 d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.77 and 0.78 (3 H, 2 d, *J* 7.0, C*H*$_3$CHCH$_3$), 0.84 and 0.85 (3 H; 2 d; *J* 6.5, 6.4; 5-Me), 0.8–1.0 (3 H, m), 1.2–1.9 (6 H, m), 3.46 and 3.47 (2 H; s, q; J_{AB} 16.2; CH_2CO_2), 4.6–4.7 (1 H, m), 7.38 (s, 5 H, Ph), 7.61 and 7.63 (2 H, 2 d, *J* 9.1), and 8.22 and 8.23 (2 H, 2 d, *J* 9.1).

*Separation of the diastereoisomeric racemates of ester **3**:* A pure sample of ester 3 (40 mg) was caused to undergo column chromatography on silica with hexane/diethyl-ether (4:1) as the eluent and gave the two separated diastereoisomeric racemates as oils. Racemate of R_F 0.10 (14 mg): dr(NMR) 100:0; δ_H (200 MHz; $CDCl_3$; Me_4Si) 1.12 (3 H, t, *J* 7.1), 1.45 (3 H, d, *J* 7.0), 3.70 (1 H, q, *J* 7.0), 4.05 (2 H, q, *J* 7.1), 7.3–7.5 (5 H, m), 7.70 (2 H, d, *J* 9.0) and 8.20 (2 H, d, *J* 9.0). Racemate of R_F 0.082 (13 mg): dr(NMR) 93:7; δ_H(200 MHz; $CDCl_3$; Me_4Si) 1.06 (3 H, t, *J* 7.1), 1.41 (3 H, d, *J* 7.0), 3.66 (1 H, q, *J* 7.0), 4.05 (2 H, q, *J* 7.1), 7.3–7.5 (5 H, m), 7.71 (2 H, d, *J* 9.0) and 8.22 (2 H, d, *J* 9.0).

*Bromoacetic ester of (S)-lactamide (**4**):* A mixture of (*S*)-lactamide (251 mg, 2.82 mmol) and bromoacetyl chloride (550 mg, 3.49 mmol) was stirred in a dry atmosphere for 22 h. The resulting mixture was Kugelrohr distilled under reduced pressure and a collected fraction (oven-temp. 135–140 °C; *p* 0.15 torr) was further purified by crystallisation to obtain enantiomer **4** (201 mg, 34%), m.p. 54–58 °C (from CH_2Cl_2/petroleum-ether), $[\alpha]_D^{22}$ –21.7 (c 2.0 in EtOH), ee(GLC) 94% (Found: C, 28.65; H, 3.7; Br, 37.9; N, 6.5. $C_5H_8BrNO_3$ requires C, 28.6; H, 3.8; Br, 38.0; N, 6.7%); ν_{max} (KBr)/cm^{-1} 3380 (NH_2), 3200 (NH_2), 1738 (carboxylic C=O) and 1650 (amidic C=O); δ_H(200 MHz; $CDCl_3$; Me_4Si) 1.51 (3 H, d, *J* 6.9), 3.89 (2 H, q, J_{AB} 12.2, $BrCH_2$), 5.24 (1 H, q, *J* 6.9), 6.18 (1 H, br s, NH) and 6.26 (1 H, br s, NH); δ_C(50 MHz; $CDCl_3$; Me_4Si) 17.5, 25.4, 71.8, 165.8 and 172.6; *m/z* (EI) 212 [15%, M(^{79}Br) + H], 210 [17, M(^{81}Br) + H], 195 (9), 193 (8), 123 (19), 121 (21) and 44 (100).

*Bromoacetic ester of lactamide [**4** (RS)]:* It was prepared in the same way as enantiomer **4** using instead racemic lactamide (yield 41%); m.p. 79–83 °C (from $CHCl_3$/petroleum-ether) (Found: C, 28.9; H, 3.75; Br, 38.2; N, 6.8. $C_5H_8BrNO_3$ requires C, 28.6; H, 3.8; Br, 38.0; N, 6.7%); ν_{max} (KBr)/cm^{-1} 3380br (NH_2), 1729 (carboxylic C=O) and 1668 (amidic C=O); ^{1}H NMR spectrum identical to that of enantiomer **4**.

*(3Ξ)-3-Cyano-3-(4-nitrophenyl)-3-phenylpropionic esters of (S)-lactamide (**5a** and **5b**)*

Procedure A: 4-Nitrophenylphenylacetonitrile was alkylated with bromoacetic ester of (*S*)-lactamide working similarly to the alkylation of the nitrile to **2** (employed quantities: 108 mg, 0.962 mmol, of *t*BuOK; 250 mg, 1.05 mmol, of the nitrile; 200 mg, 0.952 mmol, of **4**; 3 cm^3 of DMSO; reaction-time 23 h). Using ethyl acetate for extraction, it was obtained a crude product (341 mg). A portion (130 mg) was loaded for preparative TLC on silica (15 plates), using diethyl-ether/methanol (40:1) as the developing solvent (8 developments) and ethyl acetate as the eluent, and yielded the separated diastereoisomers **5a** (R_F 0.21; 28 mg, 21%) and **5b** (R_F 0.19; 21 mg, 16%) in the form of noncrystalline solids. Diastereoisomer **5a**: $[\alpha]_D^{20}$ –28.2 (c 0.95 in EtOH), dr(NMR) 95:5 (Found: C, 62.3; H, 4.5; N, 11.2. $C_{19}H_{17}N_3O_5$ requires C, 26.1; H, 4.7; N, 11.4%); δ_H (500 MHz; $CDCl_3$; Me_4Si)

1.33 (3 H, d, *J* 6.7), 3.57 (2 H, q, J_{AB} 16.5, CH_2CO_2), 5.15 (1 H, q, *J* 6.7), 5.35 (1 H, br s, NH), 6.13 (1 H, br s, NH), 7.4 (5 H, m), 7.62 (2 H, d, *J* 9.2) and 8.26 (2 H, d, *J* 9.2); δ_C (50 MHz; $CDCl_3$; Me_4Si) 17.6, 44.3, 48.3, 71.8, 122.1, 124.4, 126.4, 127.8, 129.3, 129.7, 137.5, 145.5, 146.3, 165.9 and 171.7; *m/z* (EI) 367 (M^+, 8%), 324 (17), 237 (100), 191 (37), 190 (39) and 43 (35). Diastereoisomer **5b**: $[\alpha]_D^{20}$ –35.0 (c 0.87 in EtOH), dr(NMR) 97:3 (Found: C, 62.2; H, 4.7; N, 11.2. $C_{19}H_{17}N_3O_5$ requires C, 62.1; H, 4.7; N, 11.4%); δ_H (500 MHz; $CDCl_3$; Me_4Si) 1.25 (3 H, d, *J* 6.7), 3.56 (2 H, s, CH_2CO_2), 5.16 (1 H, q, *J* 6.7), 5.38 (1 H, br s, NH), 6.33 (1 H, br s, NH), 7.4 (5 H, m), 7.58 (2 H, d, *J* 9.2) and 8.25 (2 H, d, *J* 9.2); δ_H (50 MHz; $CDCl_3$; Me_4Si) 17.4, 44.4, 48.4, 71.9, 122.0, 124.4, 126.5, 127.9, 129.3, 129.7, 136.9, 145.5, 148.3, 165.8 and 171.7; *m/z* (EI) 367 (M^+, 13), 324 (24), 237 (100), 191 (22), 190 (23) and 44 (5).

Procedure B: A stirred mixture of (*S*)-lactamide (944 mg, 10.6 mmol) and 3-cyano-3-(4-nitrophenyl)-3-phenylpropionyl chloride (2.18 g, 6.93 mmol) was heated at 100 °C for 3.5 h. Aqueous sodium carbonate (1 M, 15 cm^3) was added to the cooled mixture, which was then extracted using ethyl acetate. The organic solution was washed with water, dried and evaporated under reduced pressure to a crude product (1.66 g) containing the diastereoisomers **5a** and **5b**, which were separated in the manner described in Procedure A (using a 78-mg portion of the crude product and 8 plates). Diastereoisomer **5a** (18 mg, 15%): $[\alpha]_D^{20}$ –25.8 (c 0.95 in EtOH), dr(NMR) 94:6. Diastereoisomer **5b** (19 mg, 16%): $[\alpha]_D^{20}$ –34.1 (c 0.86 in EtOH), dr(NMR) 94:6. The diastereoisomers were also separated (using a 298-mg portion of the crude product) by column chromatography on silica (column-bore 5 cm; 600 g) with diethyl-ether/methanol (40:1) as the eluent [V_r/dm^3 4.2–4.9 (**5a**) and 5.9–6.7 (**5b**)]. Diastereoisomer **5a** (75 mg, 16%): dr(NMR) 96:4. Diastereoisomer **5b** (61 mg, 13%): dr(NMR) 85:15.

(–)-(3Ξ)-3-Cyano-3-(4-nitrophenyl)-3-phenylpropionic acid **(6a)***:* A mixture of diastereoisomer **5a** (dr 95:5; 16 mg) and a solution of sodium hydroxide in water/ethanol (70:30; 0.6 M, 0.35 cm^3) was stirred in a stoppered flask for 23 h and then heated under reflux for 1 h. Water was added to the cooled mixture, which was then washed with diethyl ether. The clear aqueous solution was acidified with concentrated hydrochloric acid and the suspension formed was extracted with diethyl ether. The ethereal extract was washed with water, dried and evaporated to dryness under vacuum to leave enantiomer **6a** (10 mg, 77%) in the form of a noncrystalline solid, $[\alpha]_D^{20}$ –37.9 (c 0.19 in EtOH) (Found: C, 64.6; H, 3.8; N, 9.7. $C_{16}H_{12}N_2O_4$ requires C, 64.85; H, 4.1; N, 9.45%); ^{1}H NMR spectrum identical to that of the corresponding racemate.[3a]

(+)-(3Ξ)-3-Cyano-3-(4-nitrophenyl)-3-phenylpropionic acid **(6b)***:* Diastereoisomer **5b** (dr 97:3; 12 mg) was treated by the preceding procedure and gave enantiomer **6b** (9 mg, 93%) in the form of a noncrystalline solid, $[\alpha]_D^{20}$+35.9 (c 0.19 in EtOH) (Found: C, 64.7; H, 4.3; N, 9.2. $C_{16}H_{12}N_2O_4$ requires C, 64.85; H, 4.1; N, 9.45%); ^{1}H NMR spectrum identical to that of the corresponding racemate.[3a]

(–)-(3Ξ)-3-Cyano-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-3-(4-nitrophenyl)-3-phenylpropionamide **(1a)**: A mixture of enantiomer **6a** (25 mg, 0.084 mmol; from a sample of **5a** with dr 96:4) and thionyl chloride (0.25 cm^3, 3.5 mmol) was heated under reflux in a dry atmosphere for 1.25 h and then the unreacted thionyl chloride was removed under reduced pressure. The residue was dissolved in dry diethyl ether (1 cm^3), and a solution of 2-(3,4-dimethoxyphenyl)-ethylmethylamine (41 mg, 0.21 mmol) in dry diethyl ether (1 cm^3) was added with stirring in a dry atmosphere. Water was added after 1 h and the mixture was extracted using dichloromethane. The organic solution was dried and evaporated under reduced pressure to a crude product which was purified by TLC on silica with benzene/ethyl-acetate (4:1) as the developing solvent and ethyl acetate as the eluent, giving enantiomer **1a** (26 mg, 65%) in the form of a noncrystalline solid, $[\alpha]_D^{20}$ –47.6 (c 0.53 in CH_2Cl_2), ee(NMR) 90% (Found: C, 68.6; H, 6.0; N, 8.7. $C_{27}H_{27}N_3O_5$ requires C, 68.5; H, 5.75; N, 8.9%); ^{1}H NMR spectrum identical to that of the corresponding racemate.[3a]

(+)-(3Ξ)-3-Cyano-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-3-(4-nitrophenyl)-3-phenylpropionamide **(1b)***:* Optically active **6b** (19 mg, 0.064 mmol; from a sample of **5b** with dr 85:15) was treated by the preceding procedure and gave optically active **1b** (16 mg, 53%) in the form of a noncrystalline solid, $[\alpha]_D^{21}$ +34.9 (c 0.45 in CH_2Cl_2), ee(NMR) 68% (Found: C, 68.6; H, 5.6; N, 8.7. $C_{27}H_{27}N_3O_5$ requires C, 68.5; H, 5.75; N, 8.9%); ^{1}H NMR spectrum identical to that of the corresponding racemate.[3a]

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