A Novel Chiral Base Mediated Glutarimide Desymmetrisation: Application to the Asymmetric Synthesis of (–)-Paroxetine

Daniel A. Greenhalgh, Nigel S. Simpkins*

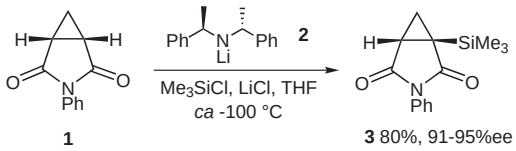
School of Chemistry, The University of Nottingham, University Park, Nottingham NG7 2RD, UK
Fax +44(115)9513564; E-mail: nigel.simpkins@nottingham.ac.uk

Received 3 October 2002

Abstract: The asymmetric desymmetrisation of certain 4-aryl substituted glutarimides has been accomplished with high levels of selectivity (up to 97% ee) by enolisation with a chiral *bis*-lithium amide base. The selectivity of the reaction is shown to be the result of asymmetric enolisation, followed by a kinetic resolution. One of the chiral imides synthesised was converted into the selective seratonin reuptake inhibitor (–)-paroxetine.

Key words: chiral lithium amide, kinetic resolution, asymmetric synthesis, glutarimide, paroxetine

Previously, we have achieved high levels of enantioselectivity in the chiral lithium amide base mediated substitution reactions of certain types of imide, e.g. the conversion of imide **1** into silylated derivative **3**, by base **2** (Scheme 1).[1]

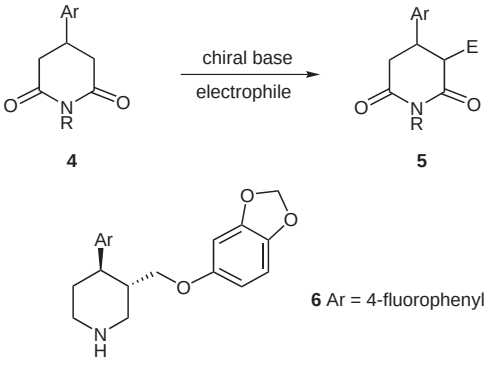


1 **3** 80%, 91-95%ee

Scheme 1

In all such reactions a ring-fused imide was chosen so as to avoid issues of diastereoselectivity in either the deprotonation or electrophilic quenching steps. However, this places limitations on the use of this desymmetrisation approach, and we considered the more challenging chiral base metallations of other types of imide an attractive goal. Foremost amongst these was the transformation of *meso*-glutarimides, such as **4** into chiral products **5**, (Scheme 2).

The success of this process would depend upon the selectivity in both the metallation and quenching steps, and neither aspect appeared straightforward (see later). However, this chemistry appeared enticing, given that an asymmetric route to the drug substance (–)-paroxetine **6** could be anticipated should access to appropriately substituted imides **5** be possible.[2]



Scheme 2

Here we describe the successful realisation of the asymmetric process outlined in Scheme 2, and its use in a new asymmetric synthesis of **6**.

The literature concerning the reactions of metal enolates derived from glutarimides is sparse.[3] In our hands enolate alkylation reactions of glutarimides **4** were low yielding when using LDA as the base, and some doubly substituted products **7** were also obtained. Chiral base **2** also gave rather disappointing yields, and we were prompted to use the *bis*-lithium amide **8**,[4] which gave the results shown in the Table 1.

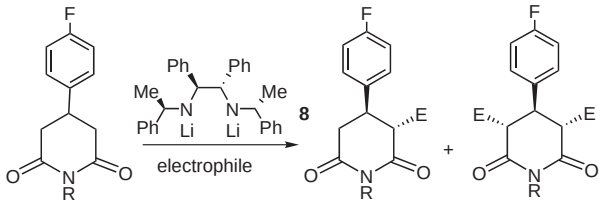
The use of **8** in its *bis*-lithiated form enabled the formation of the desired products **5** in good yields, with good to excellent levels of ee, and as single diastereoisomers.[5] The *trans* arrangement of the newly installed substituent, relative to the fluorophenyl group was evident from the *J* values of associated ring protons (J_{H3}–J_{H4} typically 11–13 Hz). The absolute configurations shown follow from the conversion of one adduct **5i** into paroxetine, as shown below.

The somewhat variable nature of the levels of ee attracted our attention. Overall the NBn series of compounds appeared to give better levels of induction than the NMe series, but in both cases the results were found to be variable. We noticed a broad correlation between reactions that gave significant amounts of *bis*-substituted by-product **7** and those that gave the highest levels of asymmetric induction. For example, in the reaction leading to **5i**, high levels of ee were found if the desired product was accompanied by 10–20% of **7**, whereas in reactions that produced very little of **7** the ee could drop as low as 80%.[6]

Synlett 2002, No. 12, Print: 02 12 2002.
Art Id.1437-2096,E;2002,0,12,2074,2076,ftx,en;D20802ST.pdf.

ISSN 0936-5214

Table 1 Enantioselective Substitution of Glutarimides **4**

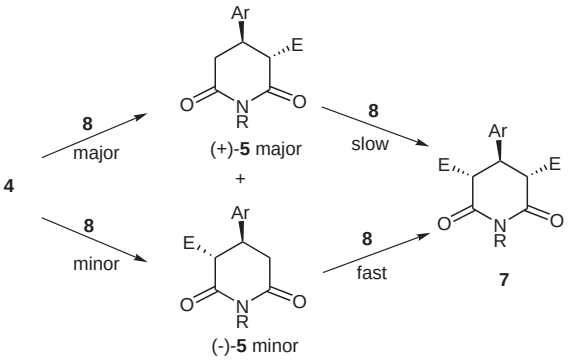


4 R = Me, Bn **5** **7**

R	Electrophile	Product **5** (%yield)	ee of **5**	**5**:**7**[a]
Me	MeI	**5a** (73)	86	2:1
Me	BnBr	**5b** (58)	74	2.5:1
Me	$ArCH_2Br$[b]	**5c** (63)	77	3:1
Me	MeO_2CCN	**5d** (87)	75	20:1
Bn	MeI	**5e** (64)	97	3:1 (14)
Bn	allylBr	**5f** (52)	90	nd (7)
Bn	BnBr	**5g** (61)	97	2:1 (22)
Bn	PhCHO[c]	**5h** (40)	97	nd
Bn	MeO_2CCN	**5i** (71)	97	6.5:1

[a] Ratio estimated from ^{1}H NMR of crude reaction mixture. Figures in brackets are isolated yields of **7**.
[b] Ar = 4-bromophenyl.
[c] Isolated as a single diastereomer.

These findings suggested that the observed ee for the products **5** was the result of an initial asymmetric enolisation of the starting imide **4**, followed by an ee enhancing kinetic resolution of **5**, Scheme 3.



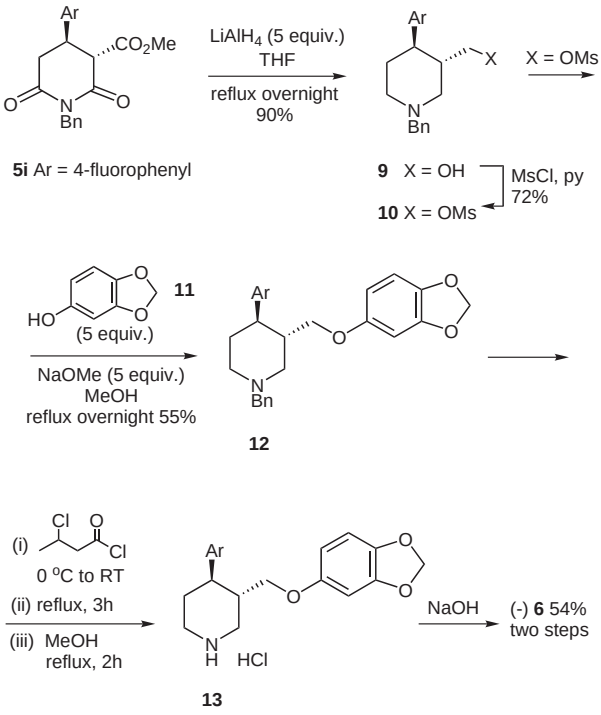
Scheme 3

Precisely this type of effect has been reported previously, for example in catalytic asymmetric desymmetrisation processes involving coupling of prochiral *bis*-triflates or dihalides.[7,8]

In order to test this idea we exposed racemic **5a** to an excess of *bis*-lithiated base **8** and then alkylated with MeI to generate **7a**. When a 46% conversion into **7a** was achieved the remaining (–)-**5a** showed an ee of 13%. Although this level of enrichment is rather low, representing a selectivity factor *S* below 2, our findings broadly parallel the observations of Gotov and Schmalz.[8] We also found that carboxymethyl derivative **5i** could be enriched from ca. 44% ee to 81% ee by further metallation with base **8** and reaction with MeO_2CCN.

These results support the picture of 'constructive kinetic resolution' superimposed upon the initial asymmetric enolisation, illustrated in Scheme 3. We assume that this type of process may be operative in all of the asymmetric substitutions described here, although the extent of kinetic resolution may be dependent upon the nature of the substituent introduced as well as the extent to which 'overalkylation' is allowed to proceed.

The availability of highly enantioenriched imides in synthetically useful quantities via this method should be useful for the preparation of a range of targets, including biologically potent piperidines. To illustrate this point, and to establish the sense of asymmetric induction in the chiral base reactions, we carried out the conversion of imide **5i** into the aforementioned drug substance (–)-paroxetine, Scheme 4.



Scheme 4

Global reduction of imide **5i** (97% ee) gave piperidine alcohol **9**, to which the appropriate sesamol side-chain **11** was introduced by conventional means.[9] Deprotection of the piperidine nitrogen then gave the desired drug substance as the free amine after base treatment.

The synthetic paroxetine prepared this way had $[\alpha]^{20}_D$ –84 (c = 0.77, MeOH), which is comparable with reported values,[10] allowing us to assign the absolute stereochemistry of intermediates as shown in Scheme 4.

The results described above further extend the utility of the chiral base method in the area of imide desymmetrisation. Further applications of this chemistry to the synthesis of naturally occurring alkaloids are underway and will be reported shortly.

Acknowledgement

We thank The University of Nottingham for support of D.A.G.

References

(1) (a) Adams, D. J.; Simpkins, N. S.; Smith, T. J. N. *Chem. Commun.* **1998**, 1605. (b) For our full report of this work, see: Adams, D. J.; Blake, A. J.; Cooke, P. A.; Gill, C. D.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4603; this issue of the journal is dedicated entirely to chiral base chemistry and is an excellent source of leading references in the area.

(2) For recent asymmetric syntheses of paroxetine, see: (a) de Gonzalo, G.; Brieva, R.; Sanchez, V. M.; Bayod, M.; Gotor, V. *J. Org. Chem.* **2001**, *66*, 8947. (b) Cossy, J.; Mirguet, O.; Gomez Pardo, D.; Desmurs, J.-R. *Tetrahedron Lett.* **2001**, *42*, 7805. (c) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004. (d) Liu, L. T.; Hong, P.-C.; Huang, H.-L.; Chen, S.-F.; Wang, C.-L. W.; Wen, Y.-S. *Tetrahedron: Asymmetry* **2001**, *12*, 419. (e) Amat, M.; Bosch, J.; Hidalgo, J.; Canto, M.; Perez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074.

(3) (a) Rama Rao, R.; Singh, A. K.; Varaprasad, C. V. N. S. *Tetrahedron Lett.* **1991**, *32*, 4393. (b) Goehring, R. R.; Greenwood, T. D.; Nwokogu, G. C.; Pisipati, J. S.; Rogers, T. G.; Wolfe, J. F. *J. Med. Chem.* **1990**, *33*, 926.

(4) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.

(5) *1-Benzyl-4-(4-fluorophenyl)-3-methyl -piperidine-2,6-dione* **5e**: A solution of the chiral *bis*-lithium amide base **8** was prepared by dropwise addition of a solution of *n*-BuLi (1.0 mL, of a 1.6 M in hexanes, 1.60 mmol) to the chiral diamine (342 mg, 0.81 mmol) in THF (4 mL) at –78 °C. The resulting red coloured solution was warmed to room temperature for 20 min before cooling to –78 °C and addition via cannula, to a stirred solution of the starting imide **4** (200 mg, 0.67 mmol) in THF (10 mL) at ca. –78 °C (internal temperature). The mixture was stirred for 45 min at this temperature before being diluted with THF (14 mL). Excess methyl iodide (3 mL) was then added, the mixture warmed to –40 °C (internal temperature) and then stirred at this temperature for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted into Et_2O (3 × 20 mL). The extracts were washed sequentially with 2 M HCl (3 × 60 mL), saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL). The combined extracts were then dried ($MgSO_4$) and concentrated under reduced pressure to yield a crude product which was purified by flash column chromatography on silica gel (40% Et_2O in petroleum ether) to give the product as an off white solid (128 mg, 64%), mp 115–118 °C; $[\alpha]_D^{22}$ –21 (*c* = 1.02 in $CHCl_3$); IR ($CHCl_3$)/cm^{-1}: 1726 (C=O), 1681 (C=O), 1606 (Ar), 1512 (Ar); δ_H (400 MHz, $CDCl_3$): 1.11 (3 H, d, *J* = 7 Hz, CH_3), 2.72 (1 H, dq, *J* = 11 Hz, 7 Hz, C*H*CH_3), 2.78 [1 H, dd, *J* = 18 Hz, 13 Hz, C(O)CH_{2ax}], 2.94 (1 H, m, CHAr), 2.94 [1 H, dd, *J* = 18 Hz, 4 Hz, C(O)CH_{2eq}], 4.97 (1 H, d, *J* = 14 Hz, NC*H*HPh), 5.02 (1 H, d, *J* = 14 Hz, NCH*H*Ph), 7.02 (2 H, m), 7.11 (2 H, m), 7.29 (3 H, m) and 7.38 (2 H, m); δ_C (125 MHz, $CDCl_3$): 14.4 (CH_3), 40.8 [C(O)*C*H_2], 41.9 (CHAr), 43.4 (NCH_2Ph), 43.5 (*C*HCH_3), 116.1 ($J_{C\text{-}F}$ = 21.5 Hz, CH), 127.6 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 136.3 (C), 137.3 (C), 162.1 (d, $J_{C\text{-}F}$ = 246 Hz, C), 171.0 (C=O) and 174.5 (C=O); HRMS(EI) Found: $[M]^+$ 311.1334, $C_{19}H_{18}NO_2F$ requires 311.1322.
The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column with 5% *i*-PrOH in hexane as eluant, at a flow rate of 0.8 mL/min, using UV detection at 215 nm. Retention times were 49.8 min(minor) and 59.5 min(major).
1-Benzyl-4-(4-fluorophenyl)-2,6-dioxo-piperidine-3-carboxylic acid methyl ester **5i**:
The reaction was carried out as described above, starting with imide **4** (200 mg, 0.67 mmol) and quenching of the intermediate enolate with excess methyl cyanoformate (0.11 mL). After 30 min at –78 °C the mixture was worked up as described above to give a crude product which was purified by flash column chromatography on silica gel (30% EtOAc in petroleum ether followed by DCM) to give the product **5i** as a white solid (168 mg, 71%), mp 137–139 °C; $[\alpha]_D^{28}$ –31 (*c* = 0.74 in $CHCl_3$); IR ($CHCl_3$)/cm^{-1}: 1749 (C=O), 1729 (C=O), 1680 (C=O), 1608 (Ar), 1512 (Ar); δ_H (400 MHz, $CDCl_3$): 2.82 [1 H, dd, *J* = 17.5 Hz, 11, C(O)CH_{2ax}], 3.02 [1 H, dd, *J* = 17.5 Hz, 4.5 Hz, C(O)CH_{2eq}], 3.65 (3 H, s, OCH_3), 3.68 (1 H, ddd, *J* = 11 Hz, 11 Hz, 4.5 Hz, CHAr), 3.81 (1 H, d, *J* = 11 Hz, $CHCO_2Me$), 4.96 (1 H, d, *J* = 14 Hz, NC*H*HPh), 5.03 (1 H, d, *J* = 14, NCH*H*Ph), 7.00 (2 H, m), 7.13 (3 H, m), 7.29 (2 H, m), 7.37 (2 H, m); δ_C (125 MHz, $CDCl_3$): 37.5 (CHAr), 38.8 [C(O)*C*H_2], 43.5 (NCH_2Ph), 52.9 (OCH_3), 56.4 (*C*HCO_2Me), 116.2 (d, $J_{C\text{-}F}$ = 21.5 Hz, CH), 127.8 (CH), 128.4 (CH), 128.6 (CH), 129.1 (CH), 134.4 (C), 136.5 (C), 163.5 (d, $J_{C\text{-}F}$ = 247 Hz, C), 168.1 (C=O), 168.3 (C=O), 170.1 (C=); HRMS(EI): Found: $[M]^+$ 355.1220, $C_{20}H_{18}NO_4F$ requires 355.1220.
The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column with 3% EtOH in hexane as eluant, at a flow rate of 0.8 mL/min, using UV detection at 215 nm. Retention times were 75.8 min(minor) and 88.5 min(major).

(6) The use of *bis*-lithiated base **8** may seem to invite the formation of unwanted products **7** but we achieved much poorer yields of desired compounds **5** by using the base in mono-lithiated form.

(7) Kamikawa, T.; Hayashi, T. *Tetrahedron* **1999**, *55*, 3455.

(8) Gotov, B.; Schmalz, H.-G. *Org. Lett.* **2001**, *3*, 1753.

(9) Many syntheses of paroxetine use this approach, see for example: Yu, M. S.; Lantos, I.; Peng, Z.-Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647; see also ref.[2] and references therein.

(10) The reported values for paroxetine include $[\alpha]_D^{20}$ –75.5 (*c* = 1.2, MeOH) for >97:3 er,[2c] and $[\alpha]_D^{22}$ –80.8 (*c* = 1.25, MeOH) via enantiopure intermediates.[2e]