Stereospecific construction of substituted piperidines. Synthesis of (−)-paroxetine and (+)-laccarin†

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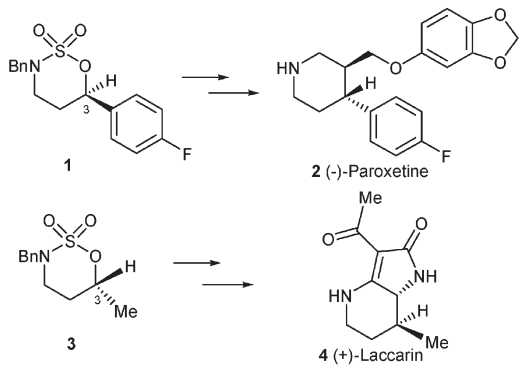
Short and efficient enantioselective syntheses of (−)-paroxetine and (+)-laccarin are described based on the highly stereospecific cleavage of C(3)-substituted 1,3-cyclic sulfamidates.

Piperidines represent a class of heterocycles frequently associated with biologically active natural products and often embedded within scaffolds recognised as privileged by medicinal chemists.[1] Accordingly, new entries to substituted piperidines are of widespread interest and we have recently outlined methodologies based on the reactivity of 1,2- and 1,3-cyclic sulfamidates towards nucleophiles that provide a versatile approach to a range of enantiomerically pure N-heterocycles, including piperidines and piperidinones.[2] A key feature of this is the high reactivity exhibited by the C(3)–O bond towards nucleophiles, and in this sense 1,2- and 1,3-cyclic sulfamidates offer highly activated synthetic equivalents of aziridines and azetidines respectively.[3]

Stereocontrol during nucleophilic displacement is an important proviso in this regard, and the focus of this paper is the stereospecific (*i.e.* clean S_N2) cleavage of C(3)-substituted 1,3-cyclic sulfamidates with synthetically useful C-nucleophiles.[4] Here we report on the reactivity of C(3)-aryl and C(3)-alkyl cyclic sulfamidates **1** and **3** respectively towards enolate nucleophiles, and the resulting reactivity profiles (efficient inversion at C(3)) provide concise, asymmetric entries to two biologically and structurally interesting 3,4-disubstituted piperidines, (−)-paroxetine **2** and (+)-laccarin **4** (Scheme 1).

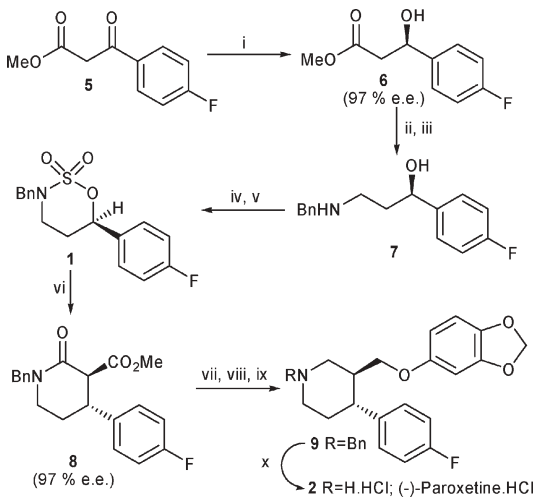
The therapeutically important antidepressant (−)-paroxetine **2**[5] is representative of an emerging group of pharmacologically active 4-aryl piperidines and this target has received extensive attention and a number of synthetic approaches to both racemic and enantiomerically pure **2** have been described.[6]

Our approach to (−)-paroxetine is shown in Scheme 2, with the key feature being the intermediacy of the C(3)-aryl substituted 1,3-cyclic sulfamidate **1** and the high degree of stereochemical control exercised during the reaction of **1** with the enolate of dimethyl malonate. Commercially available keto ester **5** was reduced using a [Ru][Cl-MeO-BIPHEP] catalyst system[7] to give alcohol **6** in 95% yield and 97% ee (as assessed by chiral GC).‡ Aluminium-mediated amidation, followed by amide reduction gave amino



Scheme 1 Structural relationships between 1,3-cyclic sulfamidates and 3,4-disubstituted piperidine scaffolds.

alcohol **7**, and two-step cyclic sulfamidate formation proceeded smoothly to give the key intermediate **1** in excellent (81%) overall yield from **6**. The key step in this sequence involved the reaction of **1** with the sodium enolate of dimethyl malonate. Following nucleophilic displacement, the crude product was immediately subjected to mild acid hydrolysis (to cleave the intermediate *N*-sulfate) and then thermolysis (to achieve ring closure) which



Scheme 2 *Reagents and conditions*: i, [((*S*)-Cl-MeO-BIPHEP)Ru-(cymene)Cl]Cl·CH_2Cl_2 (0.5 mol%), H_2 (8 bar), MeOH, 60 °C (95%); ii, $AlMe_3$, $BnNH_2$, PhMe, 0 °C to rt (100%); iii, $LiAlH_4$, THF, reflux (98%); iv, $SOCl_2$, Et_3N, imidazole, CH_2Cl_2, −20 °C to 0 °C (95%); v, $RuCl_3$ (0.25 mol%), $NaIO_4$, MeCN–H_2O, 0 °C (87%); vi, dimethyl malonate, NaH, DMF, 60 °C; then 5 M HCl; then PhMe, reflux (70%); vii, $LiAlH_4$, THF, reflux; viii, MsCl, Et_3N, CH_2Cl_2; ix, sesamol, NaH, DMF, 90 °C (52% from **8**); x, 10% Pd/C (35%), H_2 (6 bar), *i*-PrOH, AcOH, 50 °C, then aq. HCl, *i*-PrOH (82%).

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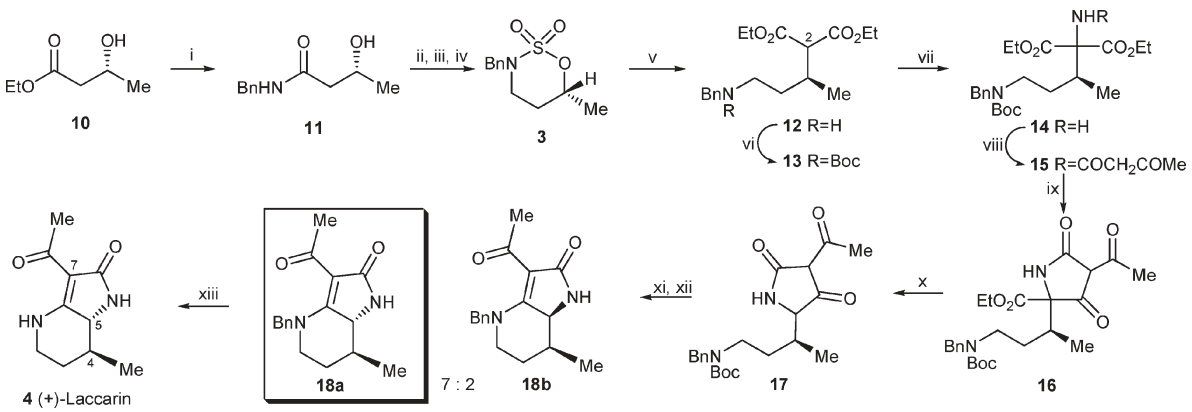
gave lactam **8** as essentially a single diastereomer (>95 : 5 dr as determined from the ^{1}H NMR spectrum of the crude reaction product) in 70% overall yield. Analysis of **8** by chiral HPLC (using the corresponding racemate as a standard) showed that no detectable erosion of enantiomeric purity had occurred during nucleophilic ring cleavage.† This demonstrates that the aryl-substituted C(3) stereocentre of **1** undergoes highly efficient inversion with malonate, which was confirmed by subsequent conversion of **8** to (−)-paroxetine **1**. The latter involved global reduction followed by transformation to **9** in 52% yield over 3 steps. *N*-Debenzylation of **9** then gave (−)-paroxetine **1** which was isolated and characterised as the HCl salt. This material was correlated with the data reported for (−)-paroxetine, ($[\alpha]_D^{20}$ −78.1 (*c* 1.0, MeOH); lit.[6c] $[\alpha]_D^{20}$ −80.8 (*c* 1.3, MeOH), lit.[6l] $[\alpha]_D^{20}$ −86.5 (*c* 1.0, MeOH)). The overall sequence from **5** to (−)-**2** (97% ee) proceeds in 24.1% overall yield over ten synthetic operations.

(+)-Laccarin **4** was the second target chosen for exploring this critical stereochemical aspect of cyclic sulfamidate-based methodology. Laccarin is a fungal metabolite which was first isolated and characterised from *Laccaria vinaceoavellanea* in 1996 by Ohta, Nozoe *et al.*[8a] and is reported to have phosphodiesterase inhibitory activity. Recently Yue and co-workers[8b] also isolated laccarin, together with an unstable *N*-acylated variant laccarin A, from *Lactarius subplinthogalus*. Laccarin is a densely functionalised alkaloid based on a piperidine core, but the synthesis of laccarin has yet to be reported. Here we report the first total (and asymmetric) synthesis of laccarin, based on a stereochemically efficient nucleophilic cleavage step involving a C(3)-alkyl substituted cyclic sulfamidate **3**. This serves to confirm the assignment of the relative stereochemistry between C(4) and C(5) of **4** and we are also able to assign for the first time the absolute configuration of (+)-laccarin.

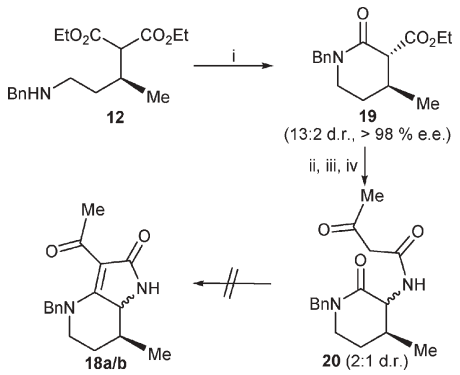
Commercially available ethyl (3*R*)-hydroxybutyrate **10** (99% ee) was converted to *N*-benzyl amide **11**, followed by reduction and conversion of the resulting amino alcohol to the target cyclic sulfamidate **3** in 62% overall yield. The sodium enolate of diethyl malonate reacted efficiently with cyclic sulfamidate **3** and, following ring cleavage (and *N*-sulfate cleavage), the resulting adduct **12** was protected as its *N*-Boc derivative **13**. The reason for this protection step is discussed below, but this was done to inhibit premature lactam formation.

The functional array associated with laccarin demanded amination at C(2) of **13**, which was achieved using monochloramine[9]§ under basic conditions to give **14** in 75% isolated yield (and 98% yield based on recovered **13**). *N*-Acylation of **14** using diketene gave **15**, which was not isolated but cyclised under Claisen conditions (to give **16**) followed by ester hydrolysis and decarboxylation using aqueous acid. *N*-Boc cleavage from **17** (using TFA) then neutralisation and thermolysis gave *N*-benzyl laccarin **18a** and the *cis* diastereomer **18b** as a 7 : 2 mixture¶ in 68% overall yield from **14**; intermediates **15–17** were not isolated during this sequence.‖ The structure of **18a** was based on detailed spectroscopic analysis and X-ray crystallography.** Hydrogenation of *N*-benzyl laccarin **18a** in acetic acid was very slow, but in the presence of TFA, debenzylation was rapid, efficient and chemoselective leading to (+)-laccarin **4** [mp > 250 °C; $[\alpha]_D^{20}$ +176.9 (*c* 0.5, $CHCl_3$); lit.[8a] $[\alpha]_D^{31}$ +188.0 (*c* 0.5, $CHCl_3$)] in 93% yield.†† Correlation of the identity of synthetic laccarin with the natural product itself was achieved by direct comparison (HPLC, ^{1}H and ^{13}C NMR, CD and optical rotation; for full details see ESI†) using an authentic sample of the natural product. Based on this, we assign the absolute configuration of natural laccarin as shown in **4**. This represents the first synthesis of this natural product and the route outlined in Scheme 3 proceeds in 18.4% overall yield. This route is efficient and is convergent in terms of the functionality that can be incorporated within the bicyclic framework, which opens the way to explore more fully the biological profile of this interesting natural product.

One other aspect of our strategy to laccarin merits comment. The initial malonate adduct **12** underwent facile base-mediated lactamisation to give **19** (13 : 2 dr, major diastereomer shown) in 52% yield from **3**.‡‡ The enantiomeric purity of **19** was assessed by chiral HPLC as >98% ee† and this determination provided the basis for our conclusions concerning the enantiomeric purity of **13** and ultimately (+)-laccarin **4**. Amination (using monochloramine) of **19**, followed by decarboxylation and acylation (with diketene) produced **20** (2 : 1 dr), but despite extensive efforts we were unable to convert **20** to *N*-benzyl laccarin **18a** (or **18b**) (Scheme 4).



Scheme 3 *Reagents and conditions*: i, $AlMe_3$, $BnNH_2$, PhMe, 0 °C to rt (88%); ii, $LiAlH_4$, THF, reflux (98%); iii, $SOCl_2$, Et_3N, imidazole, CH_2Cl_2, −20 °C to 0 °C (84%); iv, $RuCl_3$ (0.25 mol%), $NaIO_4$, MeCN–H_2O, 0 °C (85%); v, diethyl malonate, NaH, DMF, 110 °C; then 5 M HCl; vi, Boc_2O, $NaHCO_3$, MeCN (81% from **3**); vii, NH_2Cl (*ca.* 0.15 M in Et_2O), *t*-BuOK, THF, 0 °C to rt (75% + 23% recovered **13**); viii, diketene, cat. DMAP, THF, 60 °C; ix, NaOEt, EtOH, 60 °C; x, H_2O, then 5 M HCl; xi, TFA, CH_2Cl_2 then Et_3N; xii, PhMe, 80 °C (68% of **18a** and **18b** from **14**); xiii, 10% Pd/C (65 wt%), H_2 (5.5 bar), TFA (93%).



Scheme 4 *Reagents and conditions*: i, NaOEt, EtOH, reflux (52% from **3**); ii, NH_2Cl (*ca.* 0.15 M in Et_2O), NaH, THF, 0 °C to rt (63% ± 30% recovered **19**); iii, KOH, dioxane, H_2O, reflux, then 5 M HCl (92%); iv, diketene, Et_3N, THF (86%).

In summary, we have demonstrated that C(3)-aryl and -alkyl substituted 1,3-cyclic sulfamidates undergo stereochemically and chemically efficient nucleophilic ring cleavage with stabilised enolates to provide the basis of an effective and stereocontrolled entry to substituted piperidines. This represents an important advance that significantly enhances the utility of cyclic sulfamidates as effective, synthetically useful electrophiles. The scope of this methodology has been demonstrated using two biologically active heterocyclic targets. In the laccarin case, this serves an additional purpose of establishing, for the first time, the absolute stereochemistry of this natural product, based on the use of (3*R*)-**10** as the starting point for the synthetic scheme.

We acknowledge the EPSRC and GSK for financial support, and thank Professor J.-M. Yue for a sample of natural laccarin.

Notes and references

‡ Chiral GC and HPLC were used extensively and in all cases analyses were performed using the corresponding racemate as a standard (see ESI†).
§ The use of a glycine enolate (rather than malonate) as the nucleophilic component would provide a direct entry to amino esters such as **14**, obviating the need to carry out a separate amination step. An extensive range of glycine enolates (or equivalents) were examined and, while we have achieved the synthesis of α-amino lactams using the Stork glycine-derived imine,[10] these transformations were neither efficient nor tolerant of sterically demanding cyclic sulfamidates such as **3**.
¶ We have compared our spectroscopic data for laccarin **4** to that reported earlier by both Ohta, Nozoe *et al.*[8a] and Yue *et al.*[8b] Using the numbering system shown on **4** in Scheme 3, the coupling constants observed for the *N*-benzyl diastereomers **18a** and **18b** are diagnostic: **18a** $^3J_{H(5)–H(4)}$ = 10.5 Hz; **18b** $^3J_{H(5)–H(4)}$ = 7 Hz. Laccarin shows $^3J_{H(5)–H(4)}$ = 10.5 Hz.
‖ The intermediacy of **16** and **17** is assumed. These intermediates could be isolated but were difficult to analyse because of the presence of diastereomers/enol tautomers/rotamers. Accordingly, we are unable to determine the isomer ratio associated with **17**.
** Full details of the crystal data for **18a** are available in the ESI.† CCDC 621099. For crystallographic data in CIF format see DOI: 10.1039/b617260a
†† Debenzylation of **18a** using acetic acid as solvent gave **4** in 27% yield after 3 days. Using 20% $Pd(OH)_2$ on carbon as catalyst in acetic acid (H_2, 5.5 bar, 12 h) gave **4** in 52% yield. Attempted debenzylation of **18a** using dissolving metal conditions (Na–liquid ammonia) was unsuccessful and resulted in reduction of the enamine (C(6)/C(7)) double bond. An approach based on benzylic bromination[11] resulted in decomposition. Interestingly, to date, we have been unable to deprotect *N*-benzyl 5-*epi*-laccarin **18b** under acidic hydrogenation conditions. Isomerisation of **18a** (Et_3N, PhMe, 85 °C, 36 h) gave a 14 : 1 mixture of **18a** and **18b**.
‡‡ Lactamisation of **12** to generate **19** occurs relatively readily and it was to block this cyclisation that we carried out immediate Boc protection of **12** to give **13** (see Scheme 3).

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