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Synthesis of *R*- and *S*-MDMA via nucleophilic ring-opening of homochiral *N*-tosylaziridines

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ABSTRACT

Homochiral (*R*)- and (*S*)-3,4-methylenedioxymethamphetamine (MDMA) were prepared in six steps (each) from the chiral pool precursors D- and L-alanine, respectively. The key step, copper-catalysed regioselective ring-opening of an *N*-tosylaziridine with an aryl Grignard reagent, proceeded in high yield with complete regioselectivity. Elaboration was achieved with preservation of configurational integrity, affording *R*- and *S*-MDMA hydrochlorides with enantiopurities of >99.5%, as determined by enantioselective HPLC with fluorescence detection. Attempts to apply the synthetic methodology to the synthesis of the homochiral enantiomers of the α-phenyl analogue of MDMA (UWA-001) were thwarted by a switch in regioselectivity in the key step.

Keywords: aziridine, chiral pool, enantiopurity determination, HPLC with fluorescence detection, nucleophilic ring-opening, organic chemical synthesis, (*R*)- and (*S*)-3,4-methylenedioxymethamphetamine, *R*- and *S*-MDMA, X-ray crystal structure.

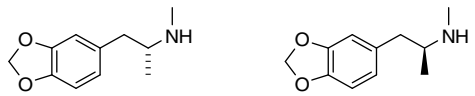
Introduction

3,4-Methylenedioxymethamphetamine (MDMA), better known by its street name 'ecstasy', is a popular recreational drug with a long and interesting history[1–5] (see also the primer in this special issue).[6] The best-known member of a sub-class of psychedelic drugs known as the entactogens, MDMA has prosocial, mood-elevating, anxiolytic and fear-extinguishing behavioural effects that make it an attractive adjunct to psychotherapy.[7–9] Indeed, MAPS, the Multidisciplinary Association for Psychedelic Studies, have completed two successful Phase III clinical trials of MDMA-assisted psychotherapy for post-traumatic stress disorder (PTSD) in which MDMA was found to be highly efficacious.[10,11] On the back of these trials, and in a world first, MDMA was rescheduled from S9 (drugs and poisons that may only be used for research) to S8 (medicines with strict legislative controls) by the Therapeutic Goods Administration of Australia specifically for use in PTSD.[12] MDMA also has potential application in the treatment of eating disorders,[13,14] alcohol[15–20] and other substance abuse,[21,22] anxiety,[23–27] chronic pain,[28] depression and other mood disorders,[23–27] and clinical trials for some of these indications are being planned.[11]

Like all amphetamines, MDMA is chiral (Fig. 1), and recreational 'ecstasy' is probably exclusively racemic. The enantiomers contribute synergistically to the subjective effects of racemic MDMA.[29,30] The *S*-(+)-enantiomer is the more potent psychoactive agent and psychostimulant, and is a more effective releaser of the monoamine neurotransmitters serotonin,[31,32] dopamine[7,32] and noradrenaline.[32] In non-human primates, *R*-MDMA was shown to release serotonin but not dopamine.[33] *R*-MDMA is also a low-efficacy partial agonist of 5-HT_{2A}[1] receptors,[34–37] canonically associated with psychedelia. In addition, the *R*-enantiomer causes release of prolactin,[33,38] and may have enhanced prosocial activity, and fewer adverse side effects compared with *S*-MDMA or

[1]5-HT, the neurotransmitter 5-hydroxtrypamine or serotonin.

the racemate.[39] Thus, it has been suggested that *R*-MDMA may be preferred over the racemate for psychotherapy.[22,39] Indeed, a small clinical trial ($n = 24$) in healthy volunteers is currently under way, examining the acute autonomic, biochemical and behavioural effects of racemic, *R*- and *S*-MDMA.[40] The chemistry and pharmacology of MDMA enantiomers are covered in more detail in recent excellent reviews.[5,22]

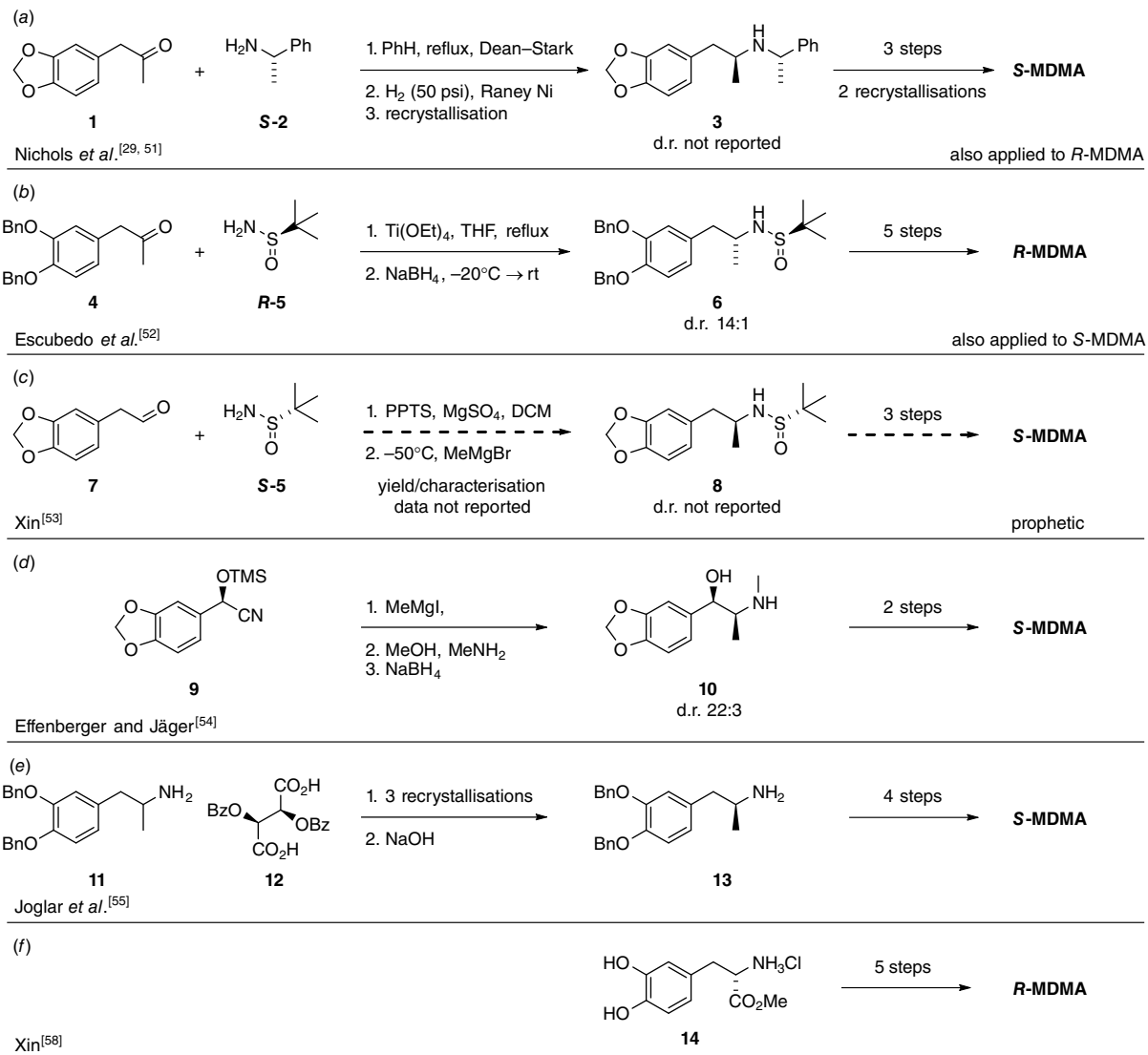


***R*-MDMA** ***S*-MDMA**

Fig. 1. Structures of the enantiomers of 3,4-methylenedioxymethamphetamine.

Racemic MDMA has been shown to alleviate the motor side-effects of long-term dopaminergic therapy for Parkinson's disease (PD), both anecdotally in a single human with disabling levodopa-induced dyskinesia[41] and in related animal models.[42–47] There are also suggestions that MDMA could positively address cognitive impulsive/compulsive behaviours and visual hallucinations associated with extended use of dopaminergic agents in PD.[42,43] In addition, MDMA was reported to be selectively toxic to a Burkitt's lymphoma cell line, perhaps via a serotonergic mechanism.[48–50] We required homochiral *R*- and *S*-MDMA for evaluation in both PD and Burkitt's lymphoma models.

Syntheses of enantiopure or enriched MDMA have been reviewed;[5] the chiral pool precursor or key stereoselective/resolution steps are outlined in Scheme 1. Nichols, Shulgin and co-workers described the first synthesis



Scheme 1. Syntheses of enantioenriched MDMA. rt, room temperature; d.r., diastereomeric ratio.

of homochiral *R*- and *S*-MDMA using a diastereoselective reductive amination of piperonyl methyl ketone (**1**) with the chiral derivatisation agents *R*- or *S*-α-methylbenzylamine (**2**), respectively.[29,51] Escubedo and colleagues developed syntheses of both enantiomers of MDMA involving a similar diastereoselective reductive sulfonamidation of ketone **4** with the two enantiomers of Ellman's sulfinamide, as exemplified by the conversion of ***R*-5** to **6** with good diastereoselectivity.[52] A shorter route using the same methodology, but beginning with piperonal, was recently patented by Xin, although this claim was not supported by any experimental data.[53] The patent also proposed a prophetic diastereoselective methylation of the *N*-sulfinylimine derived from homopiperonal (**7**) and the same chiral auxiliary to give **8**. Diastereoselective addition of methylmagnesium iodide to the chemoenzymatically derived *O*-silyl cyanohydrin **9**, followed by *in situ* transimination with methylamine and borohydride reduction, afforded the amino alcohol **10**, which was proto-dehydroxylated in two steps, providing *S*-MDMA.[54]

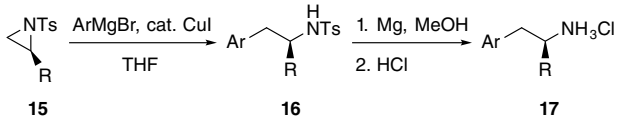
Surprisingly, a resolution of racemic MDMA via diastereomeric salts or amides has never been reported; however, Joglar and co-workers resolved racemic 3,4-di(benzyloxy) amphetamine (**11**) as the dibenzoyl-D-(+)-tartaric acid (**12**) salt, and advanced the *S*-enantiomer of amine **13** to *S*-MDMA.[55] Semi-preparative enantioselective chromatography has also been used to resolve racemic MDMA,[56,57] including a tritiated isotopologue.[57] Finally, Xin patented (and exemplified) a chiral pool synthesis of *R*-MDMA, beginning with levodopa methyl ester hydrochloride (**14**).[58]

Herein, we report our contribution to the synthesis of homochiral MDMA using amino acid-derived chirons.

Results and discussion

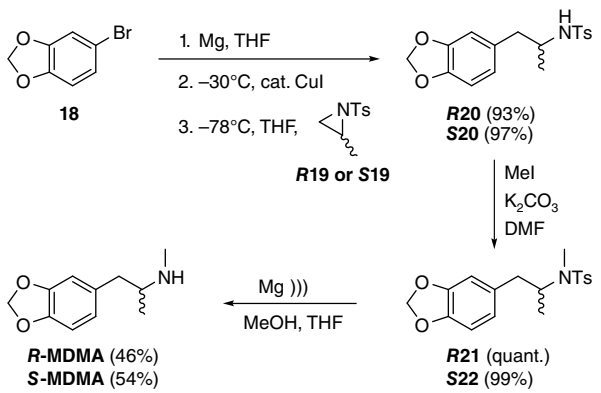
Nenajdenko and co-workers reported the copper-catalysed regioselective ring-opening of L-amino acid-derived *N*-tosylaziridines **15** by (hetero)aryl Grignard reagents to give sulfonamides **16**, which were deprotected without racemisation to afford the corresponding primary amines, isolated as the hydrochlorides **17** (Scheme 2).[59]

This methodology was adapted to the synthesis of the (homochiral) enantiomers of MDMA, as depicted in Scheme 3. The required *N*-tosylaziridines ***R*19** and ***S*19** were synthesised in three steps from D- and L-alanine, respectively.[60,61] Copper-catalysed ring-opening of the aziridines by the Grignard reagent derived from 5-bromobenzodioxole (**18**)[62] gave the secondary sulfonamides ***R*20** and ***S*20** in excellent yield. The complete regioselectivity of the ring-opening step is attributed to steric hindrance at C2 of the aziridine,[63] the strongly electron-withdrawing tosyl group, which favours an S_N2 mechanism,[64] and the soft nucleophilic character of the intermediate organocuprate. The reaction of activated aziridines with harder nucleophiles such as Grignard reagents (in the absence of a copper catalyst) has been shown to give a mixture of regioisomers[64,65] and lower yields.[66] Quantitative *N*-methylation affording ***R*21** and ***S*21** was followed by reductive deprotection. Unsurprisingly, given the stability of sulfonamides,[67] deprotection proved troublesome. Conditions used are summarised in Table 1.



Scheme 2. Precedent adapted to the current work.[59]

Sonication with magnesium in methanol was reported to be sufficiently gentle to avoid racemisation or ring-opening during deprotection of chiral *N*-tosylaziridines,[68] and this methodology was later adapted to deprotection of secondary sulfonamides related to the current work (Scheme 2).[59] When these conditions were applied to the tertiary sulfonamides ***S*21** and ***R*21** (Scheme 3), deprotection was clean, but stalled for no obvious reason, and neither addition of fresh magnesium nor extended sonication helped the reactions progress. As a result, yields of the free base MDMA enantiomers were moderate. However, in each instance, >40% of starting sulfonamide was recovered after chromatography.



Scheme 3. Synthesis of *R*- and *S*-MDMA.))), sonication. The wavy bonds indicate a single configuration, defined by the compound labels for each enantiomeric series.

Table 1. Reductive deprotection of tertiary sulfonamides to give enantiopure MDMA.

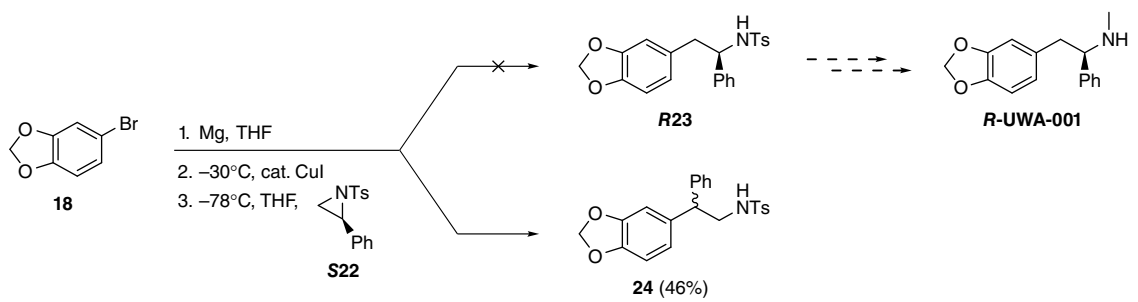
Substrate	Conditions[A]	% yield	Refs
***R*21**	Mg, MeOH,)))	56	[59,68]
***R*21**	Mg, MeOH, THF,)))	46	
***S*21**		54	
***S*21**	Na, naphthalene, DME	50	[69]
***S*21**	1,4-dimethoxybenzene, $NaBH_4$, MeCN, EtOH, *hv* 254 nm	33	[70,71]

[A])))), sonication; DME, 1,2-dimethoxyethane.

Table 2. Specific rotation data for *R*- and *S*-MDMA prepared by various methods.

Approach[A]	Free base $[a]_D$		Hydrochloride $[a]_D$		Ref.
	***R*-MDMA**	***S*-MDMA**	***R*-MDMA**	***S*-MDMA**	
(*a*)	ND	ND	$[a]_D$ −18.2°	$[a]_D$ +17.2°	Shulgin[29,51]
(*a*)	ND	ND	$[a]_D$ −17.5° (*c* 1, H_2O)	$[a]_D$ +17.4° (*c* 1, H_2O)	Nichols[29,51]
(*b*)	ND	ND	$[a]_D$ −12.4° (*c* 0.6, H_2O)	$[a]_D$ +14.2° (*c* 0.6, H_2O)	Escubedo[52]
(*c*)	ND	ND	ND	ND	Xin[53]
(*d*)	ND	ND	ND	$[\alpha]_D^{20}$ +17.9° (*c* 1.00, H_2O)	Effenberger[54]
(e)	ND	ND	ND	$[\alpha]_D^{20}$ +15.2° (*c* 0.79, H_2O)	Joglar[55]
Enantioselective HPLC	ND	ND	ND	ND	Moreau[56]
Enantioselective HPLC	$[\alpha]_D^{28}$ −6.7° (*c* 0.1, EtOH)[B]	$[\alpha]_D^{28}$ +9.4° (*c* 0.1, EtOH)[B]	ND	ND	Hashimoto[57]
(e)	ND	ND	ND	ND	Xin[58]
Present work	$[\alpha]_D^{23}$ −34.5° (*c* 1.1, $CHCl_3$)[C]	$[\alpha]_D^{23}$ +32.7° (*c* 1.2, $CHCl_3$)[C]	$[\alpha]_D^{23}$ −19.3° (*c* 1.1, H_2O)	$[\alpha]_D^{23}$ +18.3° (*c* 1.0, H_2O)	Present work
	$[\alpha]_D^{23}$ −33.7° (*c* 1.0, $CHCl_3$)[D]	$[\alpha]_D^{23}$ +33.1° (*c* 1.0, $CHCl_3$)[E]			
		$[\alpha]_D^{23}$ +33.0° (*c* 1.0, $CHCl_3$)[F]			

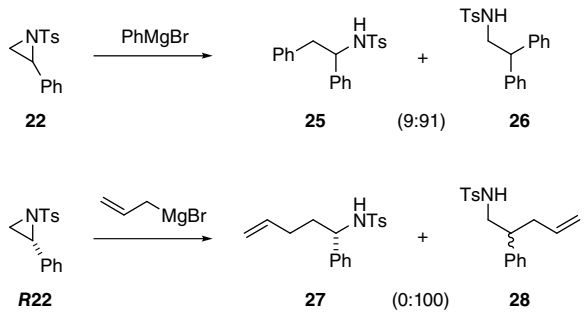
ND, no specific rotation data reported.
[A]Refer to Scheme 1.
[B]Not specified whether the specific rotations reported were obtained for MDMA free base, MDMA hydrochloride, or MDMA trifluoroacetate (the latter is included as the eluent utilised by Hashimoto *et al.* contained trifluoracetic acid), or indeed some other salt of MDMA.[57]
[C]*R*- and *S*-MDMA prepared from sulfonamides **21** using Mg in THF/MeOH with sonication.
[D]*R*-MDMA prepared from ***R*21** using 1,4-dimethoxybenzene and $NaBH_4$ in MeCN/EtOH under UV irradiation (λ 254 nm).
[E]*S*-MDMA prepared from ***S*21** using Mg in MeOH with sonication.
[F]*S*-MDMA prepared from ***S*21** using sodium naphthalenide in DME.



Scheme 4. Attempted synthesis of ***R*-UWA-001**. The wavy bond represents a single but undefined configuration.

Deprotection of ***S*21** with sodium naphthalenide radical anion[69] was also inefficient, and photolytic reductive cleavage of ***R*21**[70,71] gave an even lower yield of *R*-MDMA, which was surprising given that quantitative yields have been reported with similar substrates.[72] On a positive note, all of these methods retained the configurational integrity of the stereocentre (Table 2). It is likely that the efficiency of the synthesis presented here could be improved by judicious choice of a more easily removed aziridine-activating group, such as nosyl,[73] or phosphoryl.[74]

We previously investigated analogues of MDMA with selective toxicity toward Burkitt's lymphoma cell lines.[48,49] These studies revealed an order of magnitude increase in the cytotoxic potency of the α-phenyl analogue of MDMA (UWA-001;



Scheme 5. Regioselectivity in nucleophilic ring-opening of *N*-tosylaziridine **22**.[78] The wavy bond represents a single but undefined configuration.

the *R*-enantiomer is shown in Scheme 4) relative to MDMA. Hence, we were interested in the homochiral enantiomers of UWA-001, and the ring-opening methodology was applied to the *N*-tosylaziridines (***R*22** and ***S*22**) derived in two steps from phenylglycine.[75–77] However, surprisingly, the copper-catalysed reaction of the Grignard reagent derived from **18** with ***S*22** did not give the expected α-phenylsulfonamide ***R*23**; instead, the regioisomer **24**, arising from nucleophilic attack at the more sterically hindered tertiary carbon of the aziridine ***S*22**, was the only isolated product that could be identified.

The absolute configuration of **24** was not determined, but it was optically active and no indication of diastereomeric signals was detected in a ^{1}H NMR spectrum in the presence of the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)]-(+)-camphorate. Thus, to the limit of ^{1}H NMR sensitivity, **24** appears to be a single enantiomer. Toshimitsu and co-workers previously observed that ring-opening of racemic **22** with four equivalents of phenylmagnesium bromide, and no copper catalyst, favoured nucleophilic attack on the benzylic carbon, giving **26** in preference to **25** (Scheme 5).[78] When enantioenriched ***R*22** was treated with allylmagnesium bromide, the regioselectivity was complete and the enantiopurity of the aziridine (94% e.e.) was preserved in the product **28**. However, the configuration of **28** was not determined, so there is still more to learn about the stereochemistry and mechanism of the ring-opening of 2-arylaziridines by Grignard reagents.

Structural characterisation of MDMA hydrochloride and evidence for enantiopurity

Table 2 summarises specific rotation data for (*R*)- and (*S*)-MDMA prepared by various methods. Reductive aminations, such as used in Nichols and co-workers' first synthesis of enantioenriched MDMA,[29,51] (Scheme 1*a*) are unlikely to be 100% diastereoselective, but they did not report diastereomeric ratios. They recrystallised the hydrochlorides of **3** (Scheme 1) and its enantiomer to enrich the major diastereomer in each case. Following cleavage of the chiral auxiliaries, the enantiomeric hydrochlorides were also recrystallised twice, which presumably further enriched the enantiopurity.

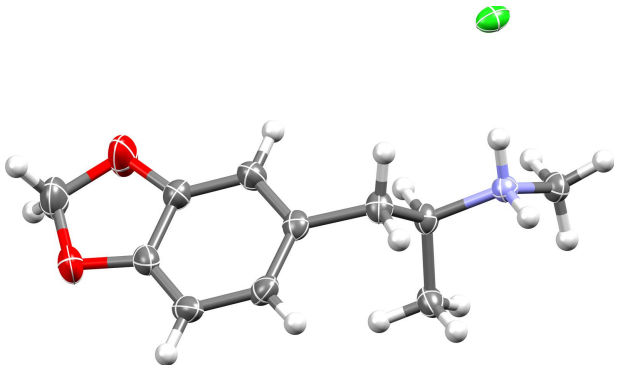


Fig. 2. Representation of the X-ray crystal structure of *S*-MDMA hydrochloride. Displacement ellipsoids for non-H atoms are drawn at 50% probability. Grey = C, white = H, blue = N, red = O. The crystal structure of the *R*-enantiomer (Supplementary Fig. S1) is identical except for absolute configuration. Crystallographic data have been deposited in the Cambridge Structural Database: CCDC 1825534 (*S*) and 1825511 (*R*). The X-ray crystal structure of racemic MDMA.HCl has been reported previously.[80]

The specific rotations they obtained are close to those acquired in the current work (Table 2). At the time, there were no authentic specific rotations for Nichols *et al.* to compare with, and thus the configurations of the isolated MDMA hydrochlorides were uncertain. Interestingly, they stated that 'it was anticipated that these enantiomers had the *R*-(−) and *S*-(+) absolute configurations, by analogy to earlier studies.[79] Recently, single-crystal X-ray crystallographic studies have confirmed this (manuscript in preparation).'[51] Subsequent work has shown the prediction to be correct; however, it seems that the promised X-ray crystallography manuscript never manifested. The X-ray crystal structure of *S*-MDMA.HCl obtained in the current work is depicted in Fig. 2. As expected, aside from the configuration, the crystal structure of the enantiomer is identical (see Supplementary Fig. S1).

The purity of both homochiral MDMA.HCl samples was first assessed by quantitative ^{1}H NMR spectroscopy (Table 3) according to methodology outlined by the European Network of Forensic Science Institutes.[81] Subsequent assessment of the enantiopurity was attempted by enantioselective HPLC–UV at several wavelengths. However, for fairly concentrated (400–1000 µg/mL) samples of both *R*- and *S*-MDMA.HCl, traces of the opposite enantiomer (*S* and *R*, respectively) could not be reliably detected at all concentrations at any of the wavelengths assessed (Supplementary Fig. S2).

Sensitivity was enhanced by using fluorometric detection (excitation 285 nm, emission 320 nm)[82] (Supplementary Fig. S3). Quantification of the trace enantiomeric impurity by HPLC is best achieved when the minor enantiomer elutes before the major,[83] and this order was achieved for the *S*-MDMA sample (Supplementary Fig. S3*b*). Fortunately, a recent study suggests that the disadvantages of a non-ideal

Table 3. Enantiopurities of *R*- and *S*-MDMA and related parameters and quantities.

	Q ^{1}H NMR purity[B] (%)	LOD (μg/mL)	LOQ (μg/mL)	MDMA conc. (μg/mL)[C]	Enantiomeric impurity (μg/mL)	Enantiopurity (%)
R-MDMA[A]	97.7	0.035	0.12	391	0.62	99.8
S-MDMA[A]	99.4	0.039	0.13	398	1.4	99.6

Q, quantitative; LOD, limit of detection; LOQ, limit of quantification.
[A]Sample concentration 400 μg/mL.
[B]1,3,5-Trimethoxybenzene was used as the internal standard.
[C]Concentration of both enantiomers in the sample; calculated by factoring in wt-% purity (determined by Q ^{1}H NMR) of each sample.

elution order, as for the *R*-MDMA sample (Supplementary Fig. S3*a*), do not prevent our objective of assessing enantiopurity to 0.1% accuracy.[84]

To quantify the enantiomeric impurity in each sample, measurements were carried out for (±)-MDMA hydrochloride over the concentration range 0.1–20 μg/mL ($n = 5$) using fluorescence detection. Calibration curves using peak areas as a function of concentration were obtained for each enantiomer from unweighted least-squares linear regression analysis of the data (Supplementary Fig. S4). Coefficients of determination (R^2) were greater than 0.997 for both calibration curves. Limits of detection (LOD) and quantification (LOQ) were estimated from signal-to-noise ratios.[85] Enantiopurities of both *R*- and *S*-MDMA were thus, unequivocally, shown to be >99.5% (Table 3).

Conclusion

A novel synthesis of *R* and *S*-MDMA, taking advantage of *N*-tosylaziridine chirons readily available from the chiral pool, was developed. The efficiency in terms of number of steps, overall yield and enantiopurity of the target amphetamines compare favourably with previously reported methods, with further gains possible through use of more easily removed aziridine-activating groups. Indeed, during our revisions of this manuscript, Sherwood and colleagues reported similar syntheses of the homochiral enantiomers of MDMA and the corresponding primary amine MDA (3,4-methylenedioxyamphetamine) from *N*-Boc aziridines (Boc, *tert*-butoxycarbonyl).[86] The methodology reported herein should be adaptable to the synthesis of other *N*-alkylamphetamines and related α-alkyl-substituted phenethylamines.

The homochiral MDMA synthesised as described in this paper was investigated in non-human primate models of levodopa-induced dyskinesia in PD.[37] This study shed some light on the mechanism by which racemic MDMA alleviates major side effects of levodopa therapy. Specifically, the enantiomers work synergistically, with *R*-MDMA reducing severity of dyskinesia, while *S*-MDMA extends the therapeutic duration of levodopa. These insights have informed ongoing research into non-psychoactive MDMA analogues that improve the quality of levodopa therapy in PD animal models.[87–89]

Experimental

General

All solvents were distilled prior to use and, where appropriate, dried according to standard methods. K_2CO_3 was dried overnight in an oven at 140°C. Anhydrous reactions were performed using glassware that was dried in an oven at 140°C, then cooled under argon. Sonication was achieved with a Soniclean 120T (50/60 Hz, 60 W).

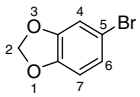
Flash chromatography and rapid silica filtration (RSF) were conducted using Merck silica gel 60 (63 200 μm). Thin-layer chromatography was conducted on Merck aluminium-supported silica sheets (silica gel 60 F254). Plates were visualised using UV light (254 nm) and amines were stained with ninhydrin.

Melting points were determined using a Reichert hot-stage melting point apparatus. Specific rotations were measured with a PerkinElmer 141 polarimeter (1 mL, 10 cm pathlength). Infrared spectra were recorded on a PerkinElmer SpectrumOne FTIR spectrometer (4000–400 cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker ARX500 (500.1 MHz for ^{1}H and 125.8 MHz for ^{13}C), AV600 (600.1 MHz for ^{1}H and 150.9 MHz for ^{13}C) or AM300 (300 MHz for ^{1}H) spectrometers. Chemical shifts are expressed in parts per million (ppm) relative to residual $CHCl_3$ (^{1}H, δ 7.26) or $CDCl_3$ (^{13}C, δ 77.16). Routine assignments of ^{13}C spectra were made with the assistance of DEPT 135 and DEPT 90 experiments (DEPT, distortionless enhancement by polarisation transfer). High-resolution mass spectra (HRMS) were recorded with a VG-Autospec spectrometer using electron impact (EI) or fast-atom bombardment (FAB) ionisation, as indicated.

Enantioselective analytical HPLC was carried out on an Agilent 1200 Series HPLC instrument equipped with G1311A quaternary pump, G1315B diode-array detector (DAD) and G1321B fluorescence detector (FLD). Separation of enantiomers was performed on a Regis® amylose tris(3,5-dimethylphenylcarbamate) column (Reflect I-Amylose A, 5 μM, 250 × 4.6 mm, Regis Technologies, Inc., IL, USA) with a flow rate of 1.0 mL/min and 20 μL injection volume. All samples were subjected to isocratic elution with a 95:4.95:0.05 (v/v/v) *n*-hexane/EtOH/diethylamine mobile phase. UV detection was performed at 236, 254 and 280 nm;

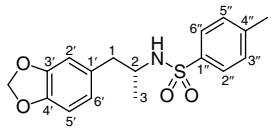
fluorescence detection was performed at an excitation wavelength of 285 nm and an emission wavelength of 320 nm.[82]

Synthesis



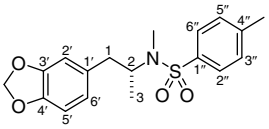
5-Bromo-1,3-benzodioxole (18)[62]

A solution of Br_2 (5.1 mL, 0.10 mol) in DCM (100 mL) was added dropwise over 6 h to a stirred solution of 1,3-benzodioxole (11 mL, 0.10 mol) in DCM (150 mL) at 0°C. The mixture was allowed to warm to room temperature and stirring was continued overnight, after which time GC-MS analysis showed the starting material to have been consumed. The reaction mixture was diluted with sat. aq. $Na_2S_2O_7$ (100 mL) and stirred for 10 min, the phases were separated and the aqueous phase was extracted with DCM (3 × 100 mL). The extract was washed with water (100 mL) and brine (100 mL), dried and concentrated under vacuum. The residue was distilled under reduced pressure to afford the bromide **18** as a pale yellow oil (18 g, 89%); bp 98–100°C at 3 mm Hg (lit.[90] 85°C at 1 mm Hg). ^{1}H NMR (600 MHz) δ 6.96–6.93 (m, 2H, H4/H7), 6.69 (m, 1H, H6), 5.97 (s, 2H, H2) ppm. The ^{1}H NMR spectrum matched the reported data.[91]



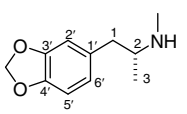
(*R*)-*N*-Tosyl-3,4-methylenedioxymethamphetamine (*R*20)

Mg flakes (2.44 g, 100 mmol) were stirred under argon overnight. THF (40 mL) was added to the blackened Mg, followed by dropwise addition of a solution of bromide **18** (4.02 g, 20.0 mmol) in anhydrous THF (20 mL). Initiation of Grignard reagent formation was indicated by warming of the reaction vessel and darkening of the solution. The reaction mixture was stirred for 4 h at rt, then 1 h at 45°C. The suspension was allowed to settle; the supernatant was cannulated from the remaining Mg, and was then cooled to −30°C. CuI (0.58 g, 3.0 mmol) was added and the pale yellow mixture was stirred for 45 min, then cooled to −78°C, and treated dropwise with a solution of aziridine ***R*19**[60,61] (2.113, 10.00 mmol) in THF (40 mL). The reaction mixture was allowed to warm gradually to rt and stirring was continued overnight. The reaction mixture was diluted with sat. aq. NH_4Cl (120 mL) and concentrated under reduced pressure. The aqueous residue was extracted with Et_2O (3 × 40 mL) and the extract was washed with brine (40 mL), dried and evaporated. The residue was subjected to flash chromatography. Elution with 1:7 EtOAc/petrol afforded the sulfonamide ***R*20** as a colourless gum (3.10 g, 93%), which solidified to give an amorphous, colourless solid over a period of months; mp 59–63°C. $[\alpha]_D^{20}$ +6.1° (*c* 1.2, $CHCl_3$). IR ν_{max} (film, DCM) 3286 (N–H), 1490, 1248, 1159, 1039 cm^{-1}. ^{1}H NMR (600 MHz) δ 7.62–7.59 (m (pseudo d), 2H, H2′/6′), 7.25–7.22 (m (pseudo d), 2H, H3′/5′), 6.65 (d, J = 7.8 Hz, 1H, H5′), 6.46 (dd, J = 7.9, 1.7 Hz, 1H, H6′), 6.42 (d, J = 1.7 Hz, 1H, H2′), 5.92 (d, J = 1.4 Hz, 1H, O_2CH_2a), 5.91 (d, J = 1.4 Hz, 1H, O_2CH_2b), 4.24 (br d, J = 7.1 Hz, 1H, NH), 3.47–3.40 (m, 1H, H2), 2.59 (dd, J = 13.8, 6.3 Hz, 1H, H1a), 2.55 (dd, J = 13.8, 6.9 Hz, 1H, H1b), 2.42 (s, 3H, 4″–CH_3), 1.11 (d, J = 6.5 Hz, 3H, H3). ^{13}C NMR (150.9 MHz) δ 147.8 (ArO), 146.5 (ArO), 143.3 (Ar), 137.6 (Ar), 130.9 (C1′), 129.7 (2 × ArH), 127.1 (2 × ArH), 122.5 (ArH), 109.6 (ArH), 108.4 (ArH), 101.1 (CH_2O_2), 51.1 (C2), 43.2 (C1), 21.64 (CH_3), 21.63 (CH_3). HRMS (EI): *m/z* calcd for $C_{17}H_{19}O_4S^{+}$ $[M]^{\cdot+}$ 333.1029; observed 333.1028.



(*R*)-*N*-Methyl-*N*-tosyl-3,4-methylenedioxymethamphetamine (*R*21)

K_2CO_3 (3.32 g, 24.0 mmol) and MeI (1.0 mL, 16 mmol) were added to a solution of sulfonamide ***R*20** (2.66 g, 8.00 mmol) in anhydrous DMF (25 mL) under argon. The mixture was stirred for 20 h, after which time TLC indicated the reaction was complete. The reaction mixture was diluted with water (250 mL) and extracted with Et_2O (3 × 80 mL). The extract was washed with water (2 × 80 mL) and brine (80 mL), dried and evaporated, and the residue was subjected to flash chromatography. Elution with DCM gave ***R*21** as a colourless gum (2.77 g, quant.). $[\alpha]_D^{20}$ −36.8° (*c* 1.5, $CHCl_3$). IR ν_{max} (film, DCM) 3422, 1490, 1335, cm^{-1}. ^{1}H NMR (600 MHz) δ 7.60–7.56 (m, 2H, H2″/6″), 7.25–7.21 (m, 2H, H3″/5″), 6.68 (d, J = 7.9 Hz, H5′), 6.58 (d, J = 1.7 Hz, 1H, 2′), 6.55 (dd, J = 7.9, 1.7 Hz, 1H, H6′), 5.93 (AB, (pseudo d 'J' = 1.5 Hz), 1H, CH_2O_2a), 5.92 (AB, (pseudo d 'J' = 1.5 Hz), 1H, CH_2O_2b), 4.24–4.17 (m, 1H, H2), 2.74 (s, 3H, NCH_3), 2.61 (dd, J = 13.6, 6.5 Hz, 1H, H1′a), 2.49 (dd, J = 13.6, 8.3 Hz, 1H, H1′b), 2.40 (s, 3H, 4″-CH_3), 0.95 (d, J = 6.7 Hz, 3H, H3). ^{13}C NMR (150.9 MHz) δ 147.7 (ArO), 146.3 (ArO), 143.0 (Ar), 137.2 (Ar), 132.1 (C1′), 129.6 (2 × ArH), 127.2 (2 × ArH), 122.2 (ArH), 109.5 (ArH), 108.3 (ArH), 101.0 (CH_2O_2), 54.6 (C2), 40.8 (C1), 28.0 (NCH_3), 21.6 (CH_3), 17.0 (CH_3). HRMS (EI): *m/z* calcd for $C_{18}H_{21}O_4S^{+}$ $[M]^{\cdot+}$ 347.1186; observed 347.1186.

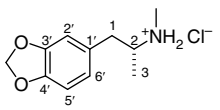


(*R*)-3,4-Methylenedioxymethamphetamine (*R*-MDMA)

Method A. A solution of sulfonamide ***R*21** (2.72 g, 7.80 mmol) in anhydrous THF (50 mL) was added to a

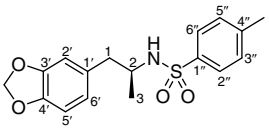
suspension of Mg powder (1.90 g, 78.0 mmol) in dry MeOH (100 mL) under argon. The suspension was sonicated for 1 h, during which time a colourless precipitate formed and the Mg was consumed. Additional Mg powder (0.95 g, 39 mmol) was added, and sonication was continued for 1 h. Most of the solvent was evaporated, and the residue was diluted with saturated $NaHCO_3$ (100 mL) and extracted with Et_2O (3 × 30 mL). The extract was washed with brine, dried and evaporated, and the reside subjected to RSF. Elution with 48:1:1 Et_2O/MeOH/NEt_3 gave unreacted ***R*21** as a colourless oil (1.42 g, 52%). Further elution afforded ***R*-MDMA** as a colourless oil (690 mg, 46%), $[\alpha]_D^{23}$ −34.5° (*c* 1.1, $CHCl_3$). ^{1}H NMR (600 MHz) δ 6.74 (d, J = 7.9 Hz, 1H, H5′), 6.67 (d, J = 1.7 Hz, 1H, H2′), 6.63 (dd, J = 7.9, 1.7 Hz, 1H, H6′), 5.93 (s, 2H, CH_2O_2), 2.75–2.69 (m, 1H, H2), 2.61 (dd, J = 13.5, 7.2 Hz, 1H, H1a), 2.54 (dd, J = 13.5, 6.2 Hz, 1H, H1b), 2.39 (s, 3H, NCH_3), 1.58 (br s, 1H, NH + H_2O), 1.05 (d, J = 6.2 Hz, 3H, H3). ^{13}C NMR (125.8 MHz) δ 147.8 (ArO), 146.1 (ArO), 133.3 (C1′), 122.3 (ArH), 109.6 (ArH), 108.3 (ArH), 101.0 (CH_2O_2), 56.6 (C2), 43.3 (C1), 34.1 (NCH_3), 19.8 (C3). HRMS (EI): *m/z* calcd for $C_{18}H_{21}O_4S^{\cdot+}$ $[M]^{\cdot+}$ 193.1097; observed 193.1102. The ^{1}H spectrum matched the data previously reported for the racemate.[49]

Method B. A solution of the sulfonamide ***R*21** (0.17 g, 0.50 mmol), $NaBH_4$ (0.19 g, 5.0 mmol) and 1,4-dimethoxybenzene (0.28 g, 2.0 mmol) in 1:2 MeCN/EtOH (15 mL) in a quartz tube was irradiated at 254 nm in a Rayonet reactor for 5 h, after which time the reaction had stalled based on TLC analysis. The volatiles were evaporated and the residue was subjected to RSF. Elution with 25:73:2 EtOAc/petrol/NEt_3 yielded ***R*-MDMA** as a colourless oil (32 mg, 33%), $[\alpha]_D^{23}$ −33.7° (*c* 1.0, $CHCl_3$), identical in all other respects with the material described above.



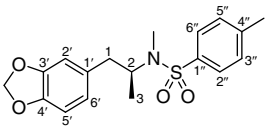
(*R*)-3,4-Methylenedioxymethamphetamine hydrochloride (*R*-MDMA.HCl)

***R*-MDMA** was dissolved in excess methanolic HCl. The solution was evaporated under a stream of N_2, and the solid residue was crystallised from ^{i}PrOH to afford ***R*-MDMA.HCl** as colourless shards, mp 185–186°C (lit.[51] 192–193°C (EtOH/Et_2O)). $[\alpha]_D^{23}$ −19.3° (*c* 1.1, H_2O) (lit.[51] −17.5° (*c* 1, H_2O)). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.64 (v br s, 2H, NH_2), 6.75 (d, J = 7.9 Hz, 1H, H5′), 6.70 (d, J = 1.6 Hz, 1H, H2′), 6.68 (dd, J = 7.9, 1.7 Hz, 1H, H6′), 5.94 (AB (pseudo d 'J' = 1.5 Hz), 1H, CH_2O_2a), 5.94 (AB (pseudo d 'J' = 1.5 Hz), 1H, CH_2O_2b), 3.37 (dd, J = 13.2, 4.2 Hz, 1H, H1a), 3.30–3.22 (m, 1H, H2), 2.77 (dd, J = 13.2, 10.4 Hz, 1H, H1b), 2.69 (s, 3H, NCH_3), 1.34 (d, J = 6.5 Hz, 3H, H3). The ^{1}H NMR spectrum matched the previously reported data.[51]



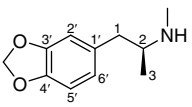
(*S*)-*N*-Tosyl-3,4-methylenedioxymethamphetamine (S20)

Ring-opening as described for ***R*20** from aziridine ***S*19**[60,61] (1.06 g, 5.02 mmol) afforded sulfonamide ***S*20** as a colourless gum (1.62 g, 97%), $[\alpha]_D^{20}$ −6.3° (*c* 1.3, $CHCl_3$). HRMS (EI): *m/z* calcd for $C_{17}H_{19}O_4S^{\cdot+}$ $[M]^{\cdot+}$ 333.1029; observed 333.1036. The IR, ^{1}H and ^{13}C NMR spectra were identical to those for the enantiomer ***R*20**.



(*S*)-*N*-Methyl-*N*-tosyl-3,4-methylenedioxymethamphetamine (S21)

Methylation of sulfonamide ***S*20** (1.50 g, 4.50 mmol) as described above for ***R*21** afforded ***S*21** as a colourless gum (1.54 g, 99%). $[\alpha]_D^{20}$ +38.4° (*c* 1.2, $CHCl_3$). HRMS (EI): *m/z* calcd for $C_{18}H_{21}O_4S^{\cdot+}$ $[M]^{\cdot+}$ 347.1186; observed 347.1189. The IR, ^{1}H and ^{13}C NMR spectra were identical to those for the enantiomer ***R*21**.



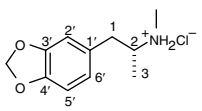
(*S*)-3,4-Methylenedioxymethamphetamine (S-MDMA)

Method A. Mg powder (485 mg, 20.0 mmol) was added to a solution of ***S*21** (695 mg, 2.00 mmol) in dry MeOH (20 mL) under argon, and the suspension was sonicated for 1 h, during which time a colourless precipitate formed, and the Mg was consumed. Additional Mg powder (485 mg, 20.0 mmol) was added and sonication was continued for 1 h. The reaction mixture was diluted with sat. aq. NaHCO3 (200 mL) and extracted with Et_2O (3 × 60 mL). The extract was washed with brine, dried and evaporated, and the residue was subjected to RSF. Elution with 25:73:2 EtOAc/petrol/NEt_3 afforded unreacted ***S*21** as a colourless oil (217 mg, 56%). Further elution gave ***S*-MDMA** as a colourless oil (169 mg, 44%), $[\alpha]_D^{23}$ +33.1° (*c* 1.2, $CHCl_3$). HRMS (EI): *m/z* calcd for $C_{18}H_{21}O_4S^{\cdot+}$ $[M]^{\cdot+}$ 193.1097; observed 193.1096. The ^{1}H and ^{13}C NMR spectra were identical to those for ***R*-MDMA**.

Method B. A solution of ***S*21** (0.87 g, 2.5 mmol) in THF (10 mL) was added to a suspension of Mg powder (0.61 g,

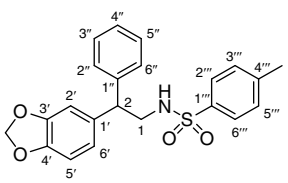
25 mmol) in dry MeOH (15 mL) under argon, and the suspension was sonicated for 1 h. Additional Mg powder (0.61 g, 25 mmol, 2 h) was added and sonication was continued for 2 h. Workup as described for Method A was followed by flash chromatography. Elution with Et_2O then 98:2 Et_2O/NEt_3 afforded unreacted ***S*21** as a colourless oil (0.27 g, 31%). Further elution gave ***S*-MDMA** as a colourless oil (0.26 g, 54%), $[\alpha]_D^{23}$ +32.7° (*c* 1.0, $CHCl_3$), identical in all other respects to its enantiomer (***R*)-MDMA**.

Method C. DME (50 mL) was added to a mixture of naphthalene (1.28 g, 10.0 mmol) and Na pieces (230 mg, 10.0 mmol) under argon. The surface of the Na immediately turned dark green. The reaction mixture was stirred for 2 h during which time the green colour darkened and persisted. The sodium naphthalide solution so formed was added dropwise to a solution of ***S*21** (1.40 g, 4.03 mmol) in DME (30 mL) at −78°C. A persistent green endpoint was not discernible. The reaction mixture was stirred at −78°C for 1 h and at rt for 2 h, before being quenched with EtOH (10 mL) and evaporated. The solid residue was dissolved in Et_2O, and the solution was washed with brine, dried and evaporated. The residue was subjected to RSF. Elution with petrol afforded naphthalene. Further elution with 1:3 EtOAc/petrol gave unreacted ***S*21** as a colourless oil. Further elution with 25:73:2 EtOAc/petrol/NEt_3 afforded ***S*-MDMA** as a colourless oil (392 mg, 50%), $[\alpha]_D^{23}$ +33.0° (*c* 1.0, $CHCl_3$) identical in all other respects to its enantiomer ***R*-MDMA**.



(*S*)-3,4-Methylenedioxymethamphetamine hydrochloride (*S*-MDMA.HCl)

The hydrochloride was prepared as described above for *R*-MDMA, affording ***S*-MDMA.HCl** as colourless crystals; mp 184–186.0°C (MeOH/Et_2O) (lit.[51] 192–193°C (EtOH/Et_2O)). $[\alpha]_D^{23}$ +18.3° (*c* 1.0, H_2O) (lit.[51] +17.43° (*c* 1, H_2O)), identical in all respects with its enantiomer ***R*-MDMA.HCl**.



N-Tosyl-2-phenyl-2-(3,4-methylenedioxyphenyl) ethylamine (24)

CuI (57 mg, 0.30 mmol) was added to a stirred solution of Grignard reagent (prepared as described above for ***R*20** from 5-bromobenzodioxole **18** (402 mg, 2.00 mmol)) in anhydrous THF (3 mL) at −78°C under argon. After 2 h, a solution of aziridine ***S*22** (287 mg, 1.05 mmol) in anhydrous THF (5 mL) was added dropwise to the reaction mixture and stirring was continued for 2 h, whereupon a brown solution formed. The reaction mixture was gradually warmed to −10°C over a period of 4 h, held at this temperature for 30 min, then quenched with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 × 30 mL). The extract was washed with water (30 mL) and brine (30 mL), dried and evaporated. The brown residue was subjected to flash chromatography. Elution with 1:9 EtOAc/petrol afforded slightly impure **24** as a colourless gum that crystallised from MeOH/H_2O to give **24** as fine colourless flakes (189 mg, 46%); mp 115–116°C. R_f (1:9 EtOAc/petrol) 0.15. IR (KBr) ν_{max} cm^{-1}: 3202, 1248, 1159, 1038. $[\alpha]_D$ 4.3° (*c* 1.50, $CHCl_3$). ^1H NMR (500 MHz) δ 7.70–7.66 (m, 2H, H2‴/H6‴), 7.33–7.29 (m, 2H, H3‴/H5‴), 7.29–7.24 (m, 2H, H3″/H5″ + $CHCl_3$), 7.23–7.19 (m, 1H, H4″), 7.09–7.06 (m, 2H, H2″/H6″), 6.71 (d, J = 8.0 Hz, 1H, H5′), 6.57 (ddd, J = 8.0, 1.8, 0.4 Hz, 1H, H6′), 6.53 (d, J = 1.8 Hz, 1H, H2′), 5.91 (q [AB], J = 1.4 Hz, 2H, CH_2O_2), 4.29 (dd (app. t), J = 6.2 Hz, 1H, NH), 3.97 (dd (app. t), J = 7.9 Hz, 1H, H2), 3.54–3.43 (m, 2H, H1), 2.45 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz) δ 148.2 (ArO), 146.8 (ArO), 143.7 (Ar), 140.9 (Ar), 136.9 (Ar), 134.7 (Ar), 129.9 (2 × ArH), 129.0 (2 × ArH), 127.9 (2 × ArH), 127.31 (2 × ArH), 127.30, 121.2 (ArH), 108.6 (ArH), 108.4 (ArH), 101.2 (CH_2O_2), 50.4 (C1 or C2), 47.4 (C1 or C2), 21.7 (CH_3). HRMS (FAB): *m/z* calcd for $C_{22}H_{21}NO_4S^{\cdot+}$ $[M]^{\cdot+}$ 395.1186; observed 395.1173. ^1H NMR spectroscopic assignments were made with the assistance of D_2O exchange and COSY (correlation spectroscopy) experiments.

Supplementary material

Supplementary material is available online.

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