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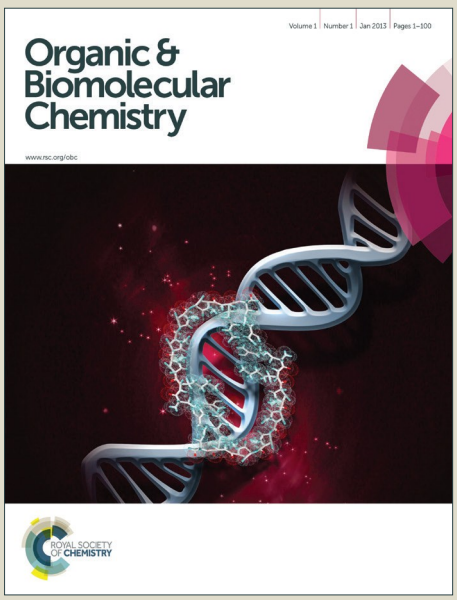

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Isolation and structural determination of non-racemic tertiary cathinone derivatives

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The racemic tertiary cathinones *N*,*N*-dimethylcathinone (**1**), *N*,*N*-diethylcathinone (**2**) and 2-(1-pyrrolidinyl)-propiophenone (**3**) have been prepared in reasonable yield and characterized using NMR and mass spectroscopy. HPLC indicates that these compounds are isolated as the anticipated racemic mixture. These can then be co-crystallized with (+)-*O*,*O*′-di-*p*-toluoyl-*D*-tartaric, (+)-*O*,*O*′-dibenzoyl-*D*-tartaric and (−)-*O*,*O*′-dibenzoyl-*L*-tartaric acids giving the single enantiomers *S* and *R* respectively of **1**, **2** and **3**, in the presence of sodium hydroxide through a dynamic kinetic resolution. X-ray structural determination confirmed the enantioselectivity. The free amines could be obtained following basification and extraction. In methanol these are reasonably stable for the period of several hours, and their identity was confirmed by HPLC and CD spectroscopy.

Introduction

Because of both market trends and legislative controls, there has been an increasing number of recreational 'designer' entactogenic drugs available on the market, often miss sold as "legal highs".[1,2] In particular, *β*-ketone derivatives of amphetamine, commonly known as "cathinones", have been found in many samples analysed forensically (Figure 1).[3,4] Cathinone itself is a stimulative alkaloid found in *Catha edulis*, or *Khat*, widely cultivated in Eastern Africa and the Arabian Peninsula,[5] but the synthetic *N*-methylated derivatives methcathinone and 4-methylmethcathinone or "mephedrone" have been shown to be considerably more potent.[6,7] The latter has become a major international concern,[8] being the first of many derivatized cathinones to be identified in drug seizures and commercially available products sold under a variety of guises such as "plant food" or "bath salts".[9-11] Yet an understanding of both the long, and short-term pharmacological effects of many of these recently identified materials is limited which is, in part, due to the difficulty in obtaining pure characterized materials from reliable sources.

The forensic identification of the ever-expanding range of cathinone derivatives has relied upon GC / MS detection against known standards, however the rapid proliferation of these new materials means that routine identification is now a considerable challenge.[12-15] Several new techniques are now being applied to both rapidly screen seized samples,[16-19] and to identify metabolized products.[20-23] These include electrochemistry[24] and the use of SERS Raman spectroscopy studied by both Mabbott *et al.*[25,26] and ourselves,[27] in addition to the traditional chromatographic mass spectrometric techniques. The availability of legitimate synthetic procedures has, until relatively recently, also lagged behind the presence of these new substances in the market place.[6,7] Studies have now shown that a wide range of cathinone derivatives can be reliably obtained using a synthetic pathway initially reported in 1950[28] *via* the acid-catalyzed bromination of the appropriate aryl ketone, followed by amination to give the target as a racemic product.[29-37]

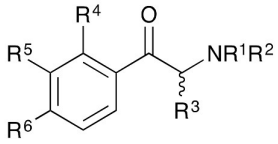

Fig. 1 The structure of *β*-ketone derivatives of amphetamine; cathinones.

The majority of the seized derivatized cathinone materials are assumed to be racemic, although there has not been a systematic study to demonstrate this. They are normally obtained in a stable protonated solid form, generally assumed to be the chloride salt. As the free amine, cathinone derivatives are unstable to decomposition, and undergo racemization due to keto-enol tautomerism.[3] Calculations have predicted the pK_a to be in the range of 8.4 to 9.5, suggesting that these compounds remain protonated at physiological pH, and unlike the analogous amphetamine derivatives, it is

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† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra, additional CD Spectra for compounds 1-3 and HPLC traces for the separated enantiopure species 1-3. And the cif file for CCDC 1407691. See DOI: 10.1039/x0xx00000x

predicted that the ketone group increases both the planarity of the compound, and the hydrophilicity so lowering their activity with respect to the parent amphetamine, being less likely to cross cell membranes.[38] Despite these limitations, studies have shown that as with amphetamine, *S*-(-)-cathinone and *S*-(-)-methcathinone have a greater pharmacological effect in rats over the *R*-forms,[6,39] although the pharmacological effects appear to be species dependent.[40]

To gain a good understanding of the pharmacological effects of these cathinone derivatives, and to possibly gain a forensic advantage on seized materials, a range of chromatographic techniques have been considered for their enantiomeric separation. These include using HPLC with either a chiral stationary phase[41-44] or a chiral additive to the eluent,[45] GC following chiral derivatization of the analyte,[30,42,46-48] capillary electrophoresis,[49-52] and NMR spectroscopy using appropriate chiral auxiliaries.[30,53] However, many cathinone derivatives, particularly those with larger groups appended to the nitrogen do not readily provide clear baseline chromatographic separation, and can decompose / racemize in the process. Consequently these techniques are unsuitable to provide enantiopure materials in reasonable quantity. *S*-(-)-*N*,*N*-dimethylcathinone,[37,42,54] *S*-(-)-*N*-methylcathinone[6,29,30,42] and *S*-(-)-cathinone[55] have however been isolated from the natural products *R/S*-*N*-methylephedrine, *R/S*-ephedrine and *R/S*-norephedrine respectively by either permanganate or chromate oxidation. This route does limit the isolation of enantiopure materials to the availability of naturally occurring precursors, and potentially results in products contaminated with carcinogenic metal ions. Osorio-Olivares *et al.* also demonstrated that non-racemic cathinone derivatives can be isolated with high enantiopurity *via* a Friedel-Crafts acylation of substituted aromatic systems with *S*- or *R*-*N*-trifluoro-acetylalanyl chloride.[56] Whilst the chloride salt of these non-racemic materials appear to be stable over several months, it is reported that racemization is possible during basification in the final isolation of a free amine.[52]

To investigate the possibilities to obtain non-racemic cathinone derivatives preparatively, we report here a method to separate three cathinone derivatives with tertiary amines

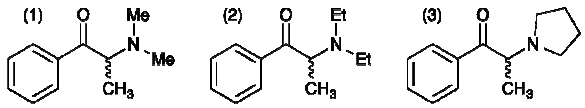
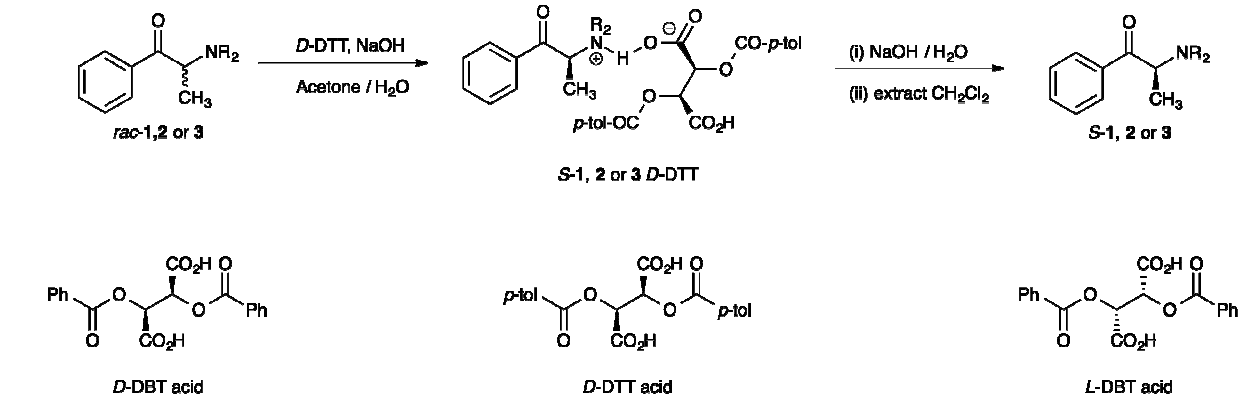


Fig. 2 Identity of compounds *rac*-**1**, **2** and **3**.

groups by co-crystallization of the protonated forms from aqueous solution. The tertiary amines, unlike the amphetamine analogues appear to have a significant pharmacological effect,[37,54] pressumably because of the greater lipophilicity. In particular, the pyrrolidine function has been identified in a number of materials being regularly found in forensic analysis such as 4-methylpyrrolidinopropiophenone (MPPP), pyrovalerone and 3,4-methylenedioxypyrovalerone (MDPV).[9-11] Importantly to this study, they appear to be more stable to decomposition in comparison to the primary and secondary amines permitting determination of their enantiopurity with relative ease.

Results and discussion

The targeted tertiary amines *N*,*N*-dimethylcathinone (**1**), *N*,*N*-diethylcathinone (**2**) and 2-(1-pyrrolidinyl)-propiophenone (**3**) were prepared *via* 2-bromopropiophenone using an adapted procedure previously reported for the preparation of (±)-4'-methyl-2-bromopropiophenone,[31] giving characterization data consistent with that recently reported by Smith *et al*.[24] This compound is a severe lachrymator and should be handled with extreme care. This was then readily converted to compounds **1**, **2** and **3** by the addition of just under a stoichiometric amount of either dimethylamine hydrochloride or diethylamine hydrochloride in an excess of triethlyamine, or pyrrolidine respectively in reasonable yields (60 to 85%).[37,54] The identity of compounds **1**, **2** and **3** were confirmed by both ^{1}H NMR and ^{13}C NMR spectroscopy (Figure S1-3), as well has high resolution TOF EI mass spectrometry. In comparison to *N*-methylcathinone and mephedrone previously prepared by ourselves,[27] the free amines of **1**, **2** and **3** were observed to be



Scheme 1: The route to enantio-separation of cathinones **1**, **2** and **3**.

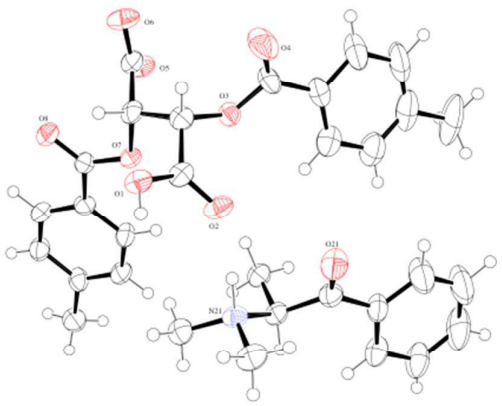


Fig. 3 ORTEP plot of **1**-*D*-DTT with ellipsoids at 50% probability.

considerably more stable to decomposition, however they were stored under nitrogen and at -30 °C prior to use.

The addition of a non-racemic chiral acid should permit the selective co-crystallization, with the preferential formation of a single diastereoisomer. Enantiopure (+)-*O,O'*-di-*p*-toluoyl-*D*-tartaric acid (*D*-DTT) was initially investigated, in a range of stoichiometries, with the best results found using one equivalent of the di-acid relative to the cathinones derivative, alongside one equivalent of sodium hydroxide on the rationale that the orientation of the two aromatic functions could enhance the diastereomeric differences through π-stacking interactions from the aqueous solution, consistent with the ideas previously reported by Berrang *et al.* with (±)-norephedrine.[55] This proved to be correct, with good quality crystals forming over the period of several days. Attempts were made to optimize the conditions using a small amount of sodium hydroxide solution to encourage solubility of the selected chiral anions (Scheme 1). No success was observed however with organic acids such as *L*-tartaric acid, or (1*S*)-(+)-10-camphorsulfonic acid in keeping with earlier studies observed with cathinone itself.[55]

With *D*-DTT in the presence of sodium hydroxide and compound **1**, needle like crystals (**1**-*D*-DTT) readily formed following the evaporation of the acetone in a yield of up to 68%. The yield itself was initially surprising assuming that the observed process is a diastereoselective crystallization process. However given the possibility of a degree of racemization occurring in the basic solution presumably by keto-enol tautomerism,[3] the selective removal of one enantiomer allows re-equilibration providing opportunities for a dynamic resolution, and a yield of up to 78% was recorded in the case of **2**-*D*-DTT. However, lower yields, typically 22% (**3**-*D*-DTT) were obtained in many cases, especially with compound **3**, as the product was isolated before complete precipitation had occurred. It was observed that if a longer period of time was required for the crystallization procedure, the product darkened in colour, resulting in poorer quality crystals / precipitates, presumably caused by partial decomposition of the parent cathinone. The ^{1}H NMR solution spectra of the co-crystallized products indicated that in each case a one to one stoichiometry of one cathinone is associated with one *D*-DTT (DMSO-D_6; Figures S4-S12). Similarly, the electrospray mass spectrometry confirmed the association through the detection of the ion pairs at 564.2187 and 590.1918 for **1**-*D*-DTT and **3**-*D*-DTT respectively, although the dominant species in each case was unsurprisingly the protonated cathinone itself.

Following the initial success with *D*-DTT, both (+)-*O,O'*-dibenzoyl-*D*-tartaric and (−)-*O,O'*-dibenzoyl-*L*-tartaric acids (*D*- and *L*-DBT) were also considered under the same conditions resulting in colourless crystals with compound **1** giving **1**-*D*-DBT and **1**-*L*-DBT respectively. Compounds **2** and **3** again took longer to crystallize typically giving coloured precipitates rather than distinct crystals suggesting that a larger functionality on the nitrogen atom frustrates the crystallization process. Similarly, the quality of the material obtained using *L*-DBT was significantly lower than those obtained using either the *D* form or with *D*-DTT, which was assumed to arise from the marginally lower enantiopurity (97%) of the starting material used. For each of the salts obtained, a one to one

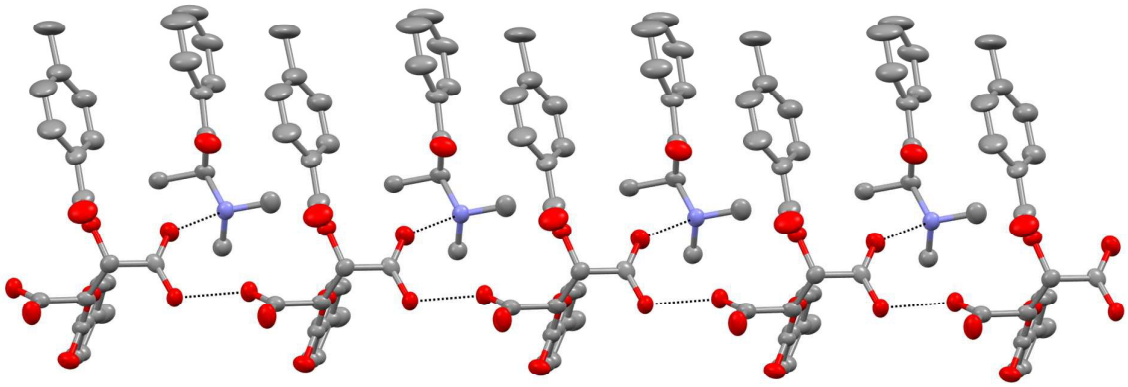


Fig. 4 Illustration of the linear hydrogen bond chain along the b-crystallographic axis in the X-ray structure of **1**-D-DTT.

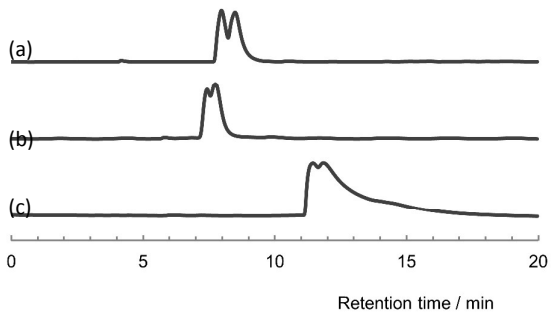


Fig. 5 HPLC traces of (a) *rac*-**1**, (b) *rac*-**2** and (c) *rac*-**3** (CHIRACEL® OJ-H HPLC column, 2% 2-propanol in n-hexane, 298K)

Table 1 HPLC Enantioseparation on compounds **1**, **2** and **3**.

Compound	t_1 (min)	t_2 (min)
1	7.47	7.88
2	7.43	7.74
3	11.45	11.89

Conditions: CHIRACEL® OJ-H HPLC column (250 x 10 mm, 5 µm), 2% 2-propanol in *n*-hexane, 298K, flow: 1 ml min^{-1}, UV: 215 nm, injection: 1 µL

stoichiometry was again confirmed by both ^{1}H NMR spectroscopy and the electrospray mass spectrometry.

The X-ray structural determination of **1**-*D*-DTT similarly confirmed the solution based stoichiometry and proved that the crystallisation process resulted in a diastereoselectivity in the product, with di-*p*-toluoyl-*D*-tartaric acid crystallizing solely as the *S*-isomer (Figure 3). The stereochemistry was assigned relative to the starting tartaric acid and whilst only one crystal was evaluated, the morphology was consistent with the bulk sample. The close contact between the cathinone amine and one of the two tartaric carboxylic acid groups is 2.708 Å, suggesting a hydrogen bond, and possible displacement of the acid proton to the nitrogen in the solid-state. Interestingly for the cathinone itself the aromatic ring, and the ketone are close to being planar, with a torsion angle of 19.38°, bringing the ketone and amine in close contact (2.521 Å). These findings are in keeping with the calculations reported by Gibbons *et al.*[38] and the previously reported hydrogen chloride salt of both mephedrone and pentedrone.[57] The tartaric acid itself has a *trans* configuration enabling a chain like hydrogen bonded conformation with itself (2.469 Å) along the b crystallographic axis and a secondary N-H-O hydrogen bond with the ketone (Figure 4).

Converting the crystalline salts back to the free amines allowed analysis of the enantioselectivity of the co-precipitation with the aromatic tartaric acids. This was achieved by dissolving a small quantity of the crystals up in dilute aqueous sodium hydroxide solution and extraction into dichloromethane followed by evaporation. Given that the

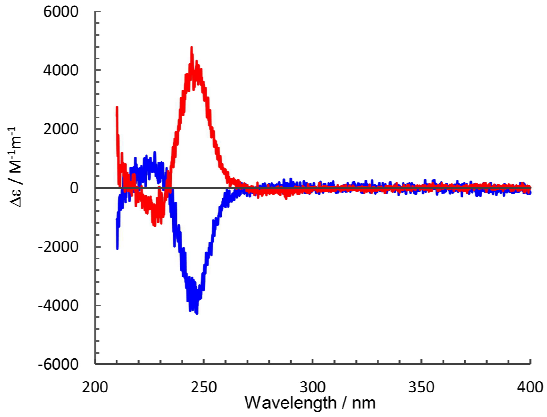


Fig. 6 Circular Dichroism spectra of (a) *S*-**1** (blue) and (b) **R**-**1** (red) obtained following extraction from the salts of **1**-*D*-DTT and **1**-*L*-DBT respectively ($8x10^{-2}$ mol dm^{-3} in methanol 293 K).

compounds were observed to racemize in basic solution, this procedure was completed as quickly as possible, and samples were only prepared directly before subsequent use. In each case, an oil of similar appearance to the racemate was obtained, each giving identical ^{1}H NMR and ES mass spectra to the starting compounds **1**, **2** and **3** respectively (Figures S13-16), and given the necessity to work quickly, the extraction process was not optimized. If the procedure was completed using either aqueous sodium bicarbonate, or triethylamine as the base, lower yields were typically obtained.

The chiral stationary phase HPLC studies on both the racemic cathinones **1**, **2** and **3** along side the materials retrieved following co-crystallization with the aromatic tartrate salts were attempted with the best separation observed with *n*-hexane and 2-propanol (98:2) on an OJ-H column. For compound **1**, while two peaks are observed, clear baseline separation could not be obtained (Figure 5a). For the resolved enantiomers of **1**, formed from the extraction of the *D*-DTT, *D*-DBT and *L*-DBT salts, only a single peak is observed under similar conditions by HPLC, albeit being relatively broad (Figure S17). Given that the absolute stereochemistry determined by crystallography within **1**-*D*-DTT, is the *S*-form (*S*-1), it appears that this elutes before *R*-**1**. A very similar result obtained from **1**-*D*-DBT suggests that the use of *D*-DTT and *D*-DBT result in the same selectivity and is assumed to be *S*-**1** although due to the experimental constraints to determine the samples directly after preparation to avoid racemization and decomposition, and the fact that samples could not be run sequentially, there is unfortunately a degree of variation in the data obtained.

For racemic compound **2**, two well-resolved peaks were again not observed, although a variety of different temperatures and eluent ratios (2-propanol in *n*-hexane) were explored. However, the principle peak had a notable shoulder consistent with the presence of the two enantiomers (Figure 5b). The traces for the products obtained from the crystalline tartrate salts gave narrower peaks with the two potentially separated enantiomers having marginally different retention

times (Figure S18). Possible variation in the data given the experimental requirements is acknowledged however. Similarly for compound **3**, the result was not ideal (Figure 5c) possessing a long tail assigned as compound decomposition on the column. Again with no clear baseline separation, but the compounds isolate from **3**-*D*-DBT ad **3**-*L*-DBT eluted with different retention times as single broad peaks indicating success in the chiral separation (Figure S19).

Analysis of the optical rotation of each of the samples obtained from extraction from the co-crystallized products proved problematic, which is unsurprising given the limitations in the quantity of available material, and possible tartrate contamination in the materials obtained; the rotations were unsurprisingly inconsistent in their magnitude. Significantly, all the materials obtained following extraction for *D*-DTT and *D*-DBT salts were observed to give positive rotations, whilst the sample isolated following co-precipitation with *L*-DBT resulted in samples with a negative rotation. CD spectroscopy proved to be more reliable however; for the samples isolated from either *D*-DTT or *D*-DBT, a positive Cotton effect was observed at approximately 240 nm, and an equal and opposite effect for the samples realised by co-crystallisation with *L*-DBT (Figure 6 and S16).

The relative stability of the isolated materials were investigated, with a sample of *R*-**2** being left overnight in the spectrometer to racemize, (20 hours at 20 °C) resulting in a half life of approximately 13.6 hours assuming first order racemization kinetics (k = 1.4 x 10^{-5} s^{-1}), whilst repeating the experiment at 40 °C resulted in the half life decreasing to just 4.6 hrs, with the other compounds showing similar half lives determined at 40 °C (3.5 and 6.4 hrs for R-***1*** and *R*-**3**). There was however no observed degradation of the crystalline tartaric salt co-crystals over the period of 6 months.

Conclusions

The tertiary cathinones **1**, **2** and **3** have been prepared in reasonable yield and characterized using NMR and mass spectroscopy. Chiral stationary phase HPLC indicates that the two enantiomers can be observed, but despite our best efforts, clear baseline separation could not be achieved. The co-crystallized aromatic tartaric acid salts appear to result in single enantiomeric form, with basic sodium hydroxide solutions encouraging a dynamic resolution probably *via* a keto-enol tautomerism, with the identity of the enantiopure cathinone confirmed by X-ray crystallography. Significantly, the free non-racemic amines could be obtained following basification and extraction and in methanol these appear to be reasonably stable at room temperature permitting their identity to be determined by HPLC and CD spectroscopy.

Given the increasing interest in these materials due to both their legal status, and their biological activity, these results are of interest in a number of important areas of current research. For example, these materials are being used as "recreational" drugs, yet the potency of the two enantiomeric forms remains unknown. This study demonstrates that these two forms can now be readily isolated by a dynamic resolution, and in the crystalline form they are sufficiently stable to be stored for long periods of time. The free amines themselves, whilst subject to slow racemization in methanol, are reasonably persistent, and potentially show similar behavior at physiological pH. This is within a timescale that would permit their differential effects to be evaluated in biological media.

Experimental

All reagents were obtained from Sigma-Aldrich and used as obtained unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker AVX (300MHz) or Bruker AVX (400MHz). Chemical shifts (δ ppm) are reported relative to $CDCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). HPLC spectra were recorded on Agilent 1100 Series. CHIRALCEL® OJ-H chiral column from Daicel Chemical Industries was used and the eluent employed was 1 to 3% 2-propanol (HPLC grade) in *n*-hexane (HPLC grade). CD spectra were recorded on J-815 spectrometer under N_2 at 20 C and all the samples for CD test were dissolved in methanol. Optical rotation was recorded on Perkin Elmer 341 polarimeter.

The compounds (±)-*N,N*-dimethylcathinone (**1**) (±)-*N,N*-dimethylcathinone (**2**) and (±)-2-(1-pyrrolidinyl)-propiophenone (**3**) are subject to legislation under the UK Misuse of Drugs Act 1971. The materials reported here were prepared and used under a Schedule 1: Licence to produce, possess and supply (Ref DH001/11) issued by the Department of Health, Social Services and Public Safety (Northern Ireland) to SJEB and NCF.

Synthetic procedures

(±)-2-Bromopropiophenone[24,31] Propiophenone (3.0 mL, 22.4 mmol) was dissolved in glacial acetic acid (63 mL). Bromine (1.15 mL, 22.4 mmol) was added dropwise into the flask and the reaction was stirred at room temperature for 22 hrs. Aqueous Na_2SO_3 (0.1M, 50 mL) was added and the mixture extracted with dichloromethane (3 x 35 mL). The organic layer was washed with a saturated aqueous Na_2CO_3 solution (100 mL) and dried with $MgSO_4$ and concentrated under vacuum giving the product as a yellow oil, which was used without further purification. Yield = 90%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 8.02 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.58 (1H, t, Ar**H**), 7.47 (2H, t, *J* = 7.4 Hz, Ar**H**), 5.30 (1H, q, *J* = 7.0 Hz, $CHBrCH_3$), 1.90 (3H, d, *J* = 7.0 Hz, $CH\mathbf{CH_3}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 193.4, 134.0, 133.7, 128.9, 41.4, 20.1; *m/z* TOF MS EI$^+$: 211.9861 ($[M^{79}Br]^+$, theoretical = 211.9837), 132.0760 ($[C_9H_8O]^+$), 118.0514 ($[C_8H_6O]^+$), 77.0400, ($[C_9H_8O]^+$).

(±)-*N*,*N*-dimethylcathinone (1)[37,54] Dimethylamine hydrochloride (297 mg, 3.65 mmol) and triethylamine (0.98 mL, 7.00 mmol) dissolved in dichloromethane (38 mL) were added to 2-bromopropiophenone (773 mg, 3.63 mmol) in dichloromethane (23.5 mL) and stirred at room temperature for 21 hrs. The aqueous layer was acidified with aqueous HCl solution (0.1 M, 100 mL) and washed with dichloromethane (100 mL). The pH was then adjusted to 10 using an aqueous

NaOH solution (0.5 M, 20 mL) and extracted into dichloromethane (2 × 100 mL), dried with $MgSO_4$ and concentrated under vacuum giving the product as a yellow oil. Yield = 511 mg, 80% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 8.07 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.56 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.46 (2H, t, *J* = 7.5 Hz, Ar**H**), 4.07 (1H, q, J = 6.8 Hz, **CH**CH_3), 2.32 (6H, s, N**(CH$_3$)$_2$**), 1.27 (3H, d, *J* = 6.8 Hz, CH**CH$_3$**); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 199.8, 135.2, 131.6, 127.6, 63.3, 40.3, 9.8; *m/z* TOF MS EI$^+$: 177.1222 ([M]$^+$, theoretical = 177.1154), 133.0605 ([C_9H_9O]$^+$), 105.0304 ([C_7H_5O]$^+$), 77.0343 ([C_6H_5]$^+$); HPLC retention time: 7.47 min and 7.88 min (OJ-H chiral column, 3% 2-propanol in *n*-hexane, 298 K).

(±)-*N*,*N*-diethylcathinone (2) was prepared according to the same procedure to 2-(*N*,*N*-dimethylamino)-propiophenone using diethylamine hydrochloride (372 mg, 3.10 mmol), triethylamine (0.95 mL, 6.86 mmol) and 2-bromopropiophenone (811 mg, 2.99 mmol) as a yellow oil. Yield = 395 mg, 62%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 8.10 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.53 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.43 (2H, t, *J* = 7.5 Hz, Ar**H**), 4.37 (1H, q, *J* = 6.7 Hz, **CH**CH_3), 2.59-2.47 (4H, m, N(**CH$_2$**CH_3)$_2$), 1.23 (3H, d, *J* = 6.7 Hz, CH**CH$_3$**), 1.01 (6H, t, J = 7.1 Hz, N(CH_2**CH$_3$**)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 202.20, 136.83, 132.52, 129.00, 60.44, 44.14, 13.61, 10.10; *m/z* TOF MS EI$^+$: 205.1454 ([M]$^+$, theoretical = 205.1467), 133.0589 ([C_9H_9O]$^+$), 100.1049 ([$C_6H_{14}N$]$^+$), 77.0332 ([C_6H_5]$^+$); HPLC retention time: 7.43 min, 7.74 min (OJ-H chiral column, 3% 2-propanol in *n*-hexane, 298 K).

(±)-2-(1-pyrrolidinyl)-propiophenone (3) was prepared according to the same procedure to 2-(*N*,*N*-dimethylamino)-propiophenone using pyrrolidine (0.30 mL, 3.65 mmol) and 2-bromopropiophenone (942 mg, 4.44 mmol) as a brown oil. Yield = 481 mg, 65%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ_H = 8.11 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.56 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.46 (2H, t, *J* = 7.5 Hz, Ar**H**), 3.98 (1H, q, *J* = 6.9 Hz, **CH**CH_3), 2.66-2.59 (4H, m, N**CH$_2$CH$_2$**), 1.83-1.77 (4H, m, **CH$_2$CH$_2$**-), 1.39 (3H, d, *J* = 6.9 Hz, CH**CH$_3$**); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 202.20, 136.83, 132.52, 129.00, 60.44, 44.14, 13.61, 10.10; *m/z* TOF MS EI$^+$: 203.1328 ([M]$^+$, theoretical 203.1310), 98.0943 ([$C_6H_{12}N$]$^+$) 77.0354 ([C_6H_5]$^+$), 68.0471, ([C_4H_8N]$^+$); HPLC retention time: 11.45 min, 11.89 min (OJ-H chiral column, 3% 2-propanol in *n*-hexane, 298 K).

(+)-*O*,*O*'-di-*p*-toluoyl-*D*-tartaric, (+)-*O*,*O*'-dibenzoyl-*D*-tartaric (*D*-DTT), (+)-*O*,*O*'-dibenzoyl-*L*-tartaric (*L*-DBT) and (-)-*O*,*O*'-dibenzoyl-*L*-tartaric (*L*-DBT) acid salts of *N*,*N*-dimethylcathinone (1), *N*,*N*-dimethylcathinone (2) and 2-(1-pyrrolidinyl)-propiophenone (3) In a typical procedure, compound **1**, **2** or **3** (in the range of 0.5 mmol to 4.0 mmol depending on availability) was dissolved in acetone (approx. 0.1M), the appropriate tartaric acid (one equivalent relative to the cathinone) in water (approx. 0.1 M) and aqueous NaOH solution (0.1 M, one equivalent relative to the cathinone) were left to crystallize at room temperature in a loosely covered beaker over the period of several days. The resulting crystals / precipitates were collected by filtration, washed with a little distilled water and dried at room temperature.

***S*-*N*,*N*-Dimethylcathinone *D*-DTT salt (1-*D*-DT)** large white crystals, yield = 68%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.02 (2H, d, *J* = 8.0 Hz, ArH), 7.85 (4H, d, *J* = 8.1 Hz, Tol), 7.68 (1H, t, *J* = 7.3 Hz, ArH), 7.56 (2H, dd, *J* = 7.3, 8.0 Hz, ArH), 7.35 (4H, d, *J* = 8.1 Hz, Tol), 4.69 (1H, q, *J* = 6.7 Hz, $CHCH_3$), 2.45 (6H, s, TolCH_3), 2.38 (6H, s, N$(CH_3)_2$), 1.25 (3H, d, *J* = 6.7 Hz, $CHCH_3$); *m/z* TOF MS EI$^+$: 741.3358 ([MH+**1**]$^+$, theoretical = 741.3387), 564.2187 ([MH]$^+$, theoretical = 564.2234), 178.1153 ([MH-DTT]$^+$, theoretical = 178.1232).

***S*-*N*,*N*-Dimethylcathinone *D*-DBT salt (1-*D*-DBT)** white crystals, yield = 60%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.02 (2H, d, *J* = 7.5 Hz, ArH), 7.98 (4H, d, *J* = 7.5 Hz, Benz), 7.71-7.66 (3H, m, ArH), 7.58-7.52 (6H, m, Benz), 4.71 (1H, br, $CHCH_3$), 2.47 (6H, s, N$(CH_3)_2$), 1.26 (3H, m, $CHCH_3$);); *m/z* TOF MS EI$^+$: 536.2458 ([MH]$^+$, theoretical 536.1921), 178.1098 ([MH-DBT]$^+$, theoretical = 178.1232).

***R*-*N*,*N*-Dimethylcathinone *L*-DBT salt (1-*L*-DBT)** white crystals, Yield = 54%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.02 (2H, d, *J* = 7.5 Hz, ArH), 7.98 (4H, d, *J* = 7.5 Hz, Benz), 7.71-7.66 (3H, m, ArH), 7.58-7.52 (6H, m, Benz), 4.70 (1H, br, $CHCH_3$), 2.45 (6H, s, N$(CH_3)_2$), 1.26 (3H, t, *J* = 6.7 Hz, $CHCH_3$); *m/z* TOF MS EI$^+$: 536.3618 ([MH]$^+$, theoretical = 536.1921), 178.1176 ([MH-DBT]$^+$, theoretical = 178.1232).

***S*-*N*,*N*-Diethylcathinone *D*-DTT salt (2-*D*-DTT)** yellow precipitate, yield = 78%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.05 (2H, d, *J* = 7.8 Hz, ArH), 7.85 (4H, d, J = 8.1 Hz, Tol), 7.66 (1H, t, *J* = 7.5 Hz, ArH), 7.54 (2H, dd, *J* = 7.8, 7.5 Hz, ArH), 7.35 (4H, d, *J* = 8.1 Hz, ArH), 4.75 (1H, q, *J* = 6.9 Hz, $CHCH_3$), 2.88-2.68 (4H, m, N$(CH_2CH_3)_2$), 2.37 (6H, s, TolCH_3), 1.24 (3H, d, *J* = 6.9 Hz, $CHCH_3$), 1.06 (6H, t, *J* = 6.9 Hz, N$(CH_2CH_3)_2$); *m/z* TOF MS EI$^+$: 796.2039 ([MH+**2**]$^+$, theoretical = 796.3935), 206.1425 ([MH-DTT]$^+$, theoretical = 206.1545).

***S*-*N*,*N*-Diethylcathinone *D*-DBT salt (2-*D*-DBT),** yellow precipitate, yield = 85%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.05 (2H, d, *J* = 7.6 Hz, ArH), 7.98 (4H, d, *J* = 7.7 Hz, Benz), 7.72-7.64 (3H, m, ArH), 7.58-7.52 (6H, m, Benz), 4.85 (1H, br, $CHCH_3$), 2.83-2.72 (4H, br, N$(CH_2CH_3)_2$), 1.24 (3H, d, *J* = 6.4 Hz, $CHCH_3$), 1.05 (6H, t, *J* = 6.9 Hz, N$(CH_2CH_3)_2$); *m/z* TOF MS EI$^+$: 769.4525 ([MH+**2**]$^+$, theoretical = 769.3700), 564.2867 ([M]$^+$, theoretical 564.2233), 206.1601 206.1425 ([MH-DBT]$^+$, theoretical = 206.1545).

***R*-*N*,*N*-Diethylcathinone *L*-DBT salt (2-*L*-DBT)** off white precipitate, yield = 24%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.06 (2H, d, *J* = 7.5 Hz, ArH), 7.98 (4H, d, *J* = 7.6 Hz, Benz), 7.72-7.64 (3H, m, ArH), 7.58-7.52 (6H, m, Benz), 4.83(1H, br, $CHCH_3$), 2.83-2.72 (4H, br, N$(CH_2CH_3)_2$), 1.25 (3H, d, *J* = 6.3 Hz, $CHCH_3$), 1.06 (6H, d, *J* = 6.8 Hz, N$(CH_2CH_3)_2$); *m/z* TOF MS EI$^+$: 769.3741 ([MH+**2**]$^+$, theoretical = 769.3700), 564.2441 ([M]$^+$,

theoretical 564.2233), 206.1317 206.1425 ([MH-DBT]$^+$, theoretical = 206.1545).

***S*-2-(1-Pyrrolidinyl)-propiophenone *D*-DTT salt (3-*D*-DTT),** white precipitate, yield = 22%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.03 (2H, d, *J* = 7.9 Hz, ArH), 7.84 (4H, d, *J* = 8.1 Hz, Tol), 7.72 (1H, t, *J* = 7.5 Hz, ArH), 7.59 (2H, dd, *J* = 7.5, 7.9 Hz, ArH), 7.32 (4H, t, *J* = 8.1 Hz, Tol), 4.98 (1H, q, *J* = 6.3 Hz, $CHCH_3$), 3.11-3.02 (4H, m, NCH_2CH_2), 2.37 (6H, s, TolMe), 1.89-1.80 (4H, m, CH_2CH_2), 1.39 (3H, d, J = 6.3Hz, $CHCH_3$); *m/z* TOF MS EI$^+$: 793.3068 ([MH+**3**]$^+$, theoretical = 793.3700), 590.1918 ([M]$^+$, theoretical = 590.2390), 204.1028 ([MH-DTT]$^+$, theoretical = 204.1388).

***S*-2-(1-Pyrrolidinyl)-propiophenone *D*-DBT salt (3-*D*-DBT),** pale orange precipitate, yield = 53%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.02 (2H, d, *J* = 7.5 Hz, ArH), 7.96 (4H, d, *J* = 7.8 Hz, Benz), 7.72 (1H, t, *J* = 7.5 Hz, ArH), 7.66 (2H, t, J = 7.5 Hz, ArH), 7.59 (2H, t, *J* = 7.8 Hz, Benz), 7.52 (4H, t, *J* = 7.8 Hz, Benz), 5.00 (1H, br, $CHCH_3$), 3.12-3.03 (4H, br, NCH_2CH_2), 1.85-1.77 (4H, m, CH_2CH_2), 1.37 (3H, d, *J* = 6.7 Hz, $CHCH_3$); *m/z* TOF MS EI$^+$: 765.3441 ([MH+**3**]$^+$, theoretical = 765.3387), 562.2391 ([M]$^+$, theoretical 562.2077), 204.1170 ([MH-DBT]$^+$, theoretical = 204.1388).

***R*-2-(1-Pyrrolidinyl)-propiophenone *L*-DBT salt (3-L-DBT)** orange precipitate, yield = 61%. ^{1}H NMR (DMSO-D_6, 400 MHz): δ_H = 8.04 (2H, d, *J* = 7.5 Hz, ArH), 7.95 (4H, d, *J* = 7.8 Hz, Benz), 7.73 (1H, t, *J* = 7.5 Hz, ArH), 7.65 (2H, t, *J* = 7.5 Hz, ArH), 7.59 (2H, t, *J* = 7.8 Hz, Benz), 7.52 (4H, t, *J* = 7.8 Hz, Benz), 5.00 (1H, br, $CHCH_3$), 3.12-3.03 (4H, br, NCH_2CH_2), 1.85-1.77 (4H, m, CH_2CH_2), 1.37 (3H, d, *J* = 6.7 Hz, $CHCH_3$); *m/z* TOF MS EI$^+$: 765.3456 ([MH+**3**]$^+$, theoretical = 765.3387), 562.2148 ([M]$^+$, theoretical = 562.2077), 204.1349 ([MH-DBT]$^+$, theoretical = 204.1388).

Conversion of the tartaric acid salts to the non-racemic-free amines. In a typical procedure, the tartrate salts (20 mg, approx. 0.10 mmol) were dissolved in aqueous sodium hydroxide solution (0.1M, 15mL). The mixture was extracted by dichloromethane (20 mL) and the organic layer dried with $MgSO_4$ and concentrated under vacuum to give a yellow oil in was obtained in a range of 56 to 83% yield (0.005g). ^{1}H, ^{13}C NMR and OF MS EI$^+$ characterization of samples was in accordance with that of the racemic mixtures of **1**, **2** and **3**.

***S*-2-(Dimethylamino)-propiophenone (*S*-1)** CD λ_{max} ([$\Delta\varepsilon$]) (methanol, 293K): 235 nm (+ 3.43 x 10^3 $M^{-1}cm^{-1}$); $[\alpha]_{589nm}^{25°C}$ = +10.8 ° (c= 1.01 mg mL^{-1}, methanol).

***R*-2-(Dimethylamino)-propiophenone (*R*-1)** CD λ_{max} ([$\Delta\varepsilon$]) (methanol, 293K): 235 nm (- 3.16 x 10^3 $M^{-1}cm^{-1}$); $[\alpha]_{589nm}^{25°C}$ = -8.7 ° (c= 2.31 mg mL^{-1}, methanol).

***S*-2-(Diethylamino)-propiophenone (*S*-2)** CD λ_{max} ([$\Delta\varepsilon$]) (methanol, 293K): 240nm (+ 1.80 x 10^3 $M^{-1}cm^{-1}$); $[\alpha]_{589nm}^{25°C}$ = +9.854° (c= 1.76 mg mL^{-1}, methanol)

***R*-2-(Diethylamino)-propiophenone (*R*-2)** CD λ_{max} ([$\Delta\varepsilon$]) (methanol, 293K): 240 nm (- 1.83 x 10^3 $M^{-1}cm^{-1}$); $[\alpha]_{589nm}^{25°C}$ = -15.444° (c= 2.59 mg mL^{-1}, methanol)

***S*-2-(1-Pyrrolidinyl)-propiophenone (*S*-3)** CD λ_{max} ([$\Delta\varepsilon$]) (methanol, 293K): 240 nm (+ 0.61 x 10^3 $M^{-1}cm^{-1}$); $[\alpha]_{589nm}^{25°C}$ = +8.139° (c= 2.33 g mL^{-1}, methanol)

***R*-2-(1-Pyrrolidinyl)-propiophenone (*R*-3)**; CD λ_{max} ($\Delta\varepsilon$) (methanol, 293K): 240 nm (- 0.61 x 10^3 $M^{-1}cm^{-1}$); $[\alpha]_{589nm}^{25°C}$ = -6.301° (c= 1.75 g mL^{-1}, methanol).

Crystallography

***S*-2-(Dimethylamino)-propiophenone *D*-DTT salt (1-*D*-DTT)** Data were collected on a *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with VHF *Varimax* optics (70µm focus). Cell determination, data collection, data reduction, cell refinement and absorption correction were completed using *CrystalClear-SM Expert 3.1 b27*.[58] Structure solution was performed using *SUPERFLIP*[59] and the Structure refinement using *SHELXL-2015*.[60] Graphics were prepared using *ORTEP3 for Windows*[61] and Mercury 3.5.1.[62] Additional material available from the Cambridge Crystallographic Data Centre comprises relevant tables of atomic coordinates, bond lengths and angles, and thermal parameters (CCDC Number 1407691). It was not possible to accurately determine the absolute configuration; the enantiomer has been assigned by reference to the absolute configuration of (+)-*O*,*O*′-di-*p*-toluoyl-*D*-tartaric acid. $C_{31}H_{33}F_{12}NO_9$:- M = 563.58, Monoclinic, space group $P2_1$, *a* = 8.2681(5) Å, *b* = 7.5543(5) Å, *c* = 23.4201(17) Å, *β* = 96.148(3)°, Vol. = 1454.40(17) Å^3, *Z* = 2, Absorb. coef. = 0.095 mm^{-1}, a total of 13021 reflections were measured for the angle range 2.478 – 27.514°, 6380 [R_{int} = 0.0994] independent reflections were used in the refinement. The final *R* indices [$F^2 > 2\sigma(F^2)$]] were *R1* = 0.0865, *wR2* = 0.1920, and a GOF on F^2 at 1.037.

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