A Scalable, Chromatography-free Synthesis of Benzotetramisole

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Abstract: The scalable, chromatography-free synthesis of the chiral isothiourea benzotetramisole (BTM) in two steps from commercially available materials is presented. A detailed procedure for the synthesis of both enantiomers and the racemate on ca. 10 g scale is disclosed.

Key words: Isothiourea, Lewis base catalysis, asymmetric catalysis, kinetic resolution, rearrangement, benzotetramisole

Introduction

The isothiourea benzotetramisole (BTM, 4), the benzannulated derivative of the antihelmintic pharmaceutical tetramisole, was first employed as an organocatalyst in 2006 by Birman and Li in the kinetic resolution of secondary alcohols. Its power as a highly enantioselective acyl transfer catalyst has been further demonstrated by Birman, Shiina, and others. Following the seminal report by Romo and co-workers on the nucleophile-catalysed aldol-lactonisation (NCAL) reaction using ammonium enolates generated from cinchona alkaloids, our group has demonstrated that isothioureas serve as excellent Lewis base organocatalysts for these processes. BTM 4 in particular has enabled the stereoselective synthesis of dihydropyridones and β-lactams, as well as promoting the asymmetric [2,3]-rearrangement of allylic ammonium ylides. Subsequently, Romo has reported the use of BTM 4 in the asymmetric synthesis of bicyclic lactones.

In our hands, Birman’s original procedure (detailed in Scheme 2) was suitable for the synthesis of (R)-BTM on ca. 1 g scale. We found this sequence to be limited by the use of a sealed tube in the first step, chromatographic purifications to obtain both (R)-3 and non-crystalline (R)-BTM 4, and multiple recrystallisations to obtain pure material.

Further syntheses of BTM have been reported, based upon this original procedure. Incremental improvements have been made by Chen and co-workers, finding firstly that intermediate 3 can be purified by recrystallisation from CHCl₃ and secondly that the two reactions could be performed sequentially in ‘one-pot’ without isolation of 3. However, chromatography and recrystallisation was still required to furnish pure BTM and the final yield of crystalline material was not disclosed. Recently, Okamoto and co-workers reported a conceptually different four-step synthesis of BTM starting from o-bromoaniline.

Although (R)- and (S)-BTM 4 are now commercially available (ca. £90 / 1 g), the need for stocks of racemic and enantiopure BTM to support our investigations into its use in catalysis motivated the development of a scalable, operationally simple synthesis. Herein we report the multi-gram synthesis of (R)-, (S)- and (±)-BTM 4 from commercially available 2-chlorobenzothiazole 1 and 2-phenylglycinol 2 without recourse to chromatographic purifications (Scheme 1).

Scheme 1 A practical, multigram synthesis of benzotetramisole 4

Scheme 2 Birman’s original procedure for the synthesis of (R)-BTM 4.

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Results and Discussion

First, the reaction between 2-chlorobenzothiazole 1, phenylglycinol 2 and EtN\textsubscript{2}-Pr\textsubscript{2} to form 3 was optimised. The use of a high-boiling co-solvent (chlorobenzene at reflux) whilst maintaining high concentrations of 1 (ca. 2.0 M) allowed the reaction to be performed in standard glassware under air without the need for sealed tubes or an inert atmosphere. However, extended reaction times (>1.2 h at reflux) were required for high conversions of 1 as measured by GC analysis. Switching to 1,2-dichlorobenzene and increasing the reflux temperature (ca. 195 °C) led consistently and reproducibly to >95% conversion of 1 after 24 h (Scheme 3a).

Reducing the temperature, equivalents of EtN\textsubscript{2}-Pr\textsubscript{2} or diluting the reaction further led to lower conversions and extended reaction times.

Chen\textsuperscript{5a}, \textsuperscript{5c} and Nagano\textsuperscript{5d} observed precipitation of product 3 in the separatory funnel during aqueous work up of the reaction. Seeking to exploit this to improve the work up procedure, the reaction mixture was diluted with water resulting in the formation of a thick paste. Upon addition of an organic solvent (e.g. hexanes or CH\textsubscript{2}Cl\textsubscript{2}), large amounts of a fine solid precipitate of 3 were formed. This could be collected by filtration, followed by washing with further portions of organic solvent to leave crude 3 as a tan solid. In our hands, recrystallisation from hot CHCl\textsubscript{3} as detailed by Chen\textsuperscript{5a} returned the CHCl\textsubscript{3} adduct of 3, from which residual CHCl\textsubscript{3} could not be removed even after extended periods under reduced pressure. Multiple cycles of re-slurring the solid with CH\textsubscript{2}Cl\textsubscript{2} followed by evaporation of the solvent allowed the isolation of solid 3 that was pure by \textsuperscript{1}H and \textsuperscript{13}C\{\textsuperscript{1}H\} NMR analysis (Scheme 3b).

This material contained variable amounts of water as evidenced by droplets present during recrystallisation and slurring. This water was not purged by filtration and had a detrimental effect on the subsequent step. The azeotropic removal of water from 3 was achieved through heating a suspension of 3 at reflux in toluene using a Dean-Stark apparatus. However, 3 was observed to dissolve in toluene at reflux, so direct recrystallisation of crude 3 from toluene in a Dean-Stark apparatus was considered as a possible simplification to access analytically pure, anhydrous 3. Using this process and starting from 10.00 g of (R)-, (S)-, or (±)-2,\textsuperscript{14} this procedure gave analytically pure, fluffy white crystals of 3 consistently in 74-79% yield after one or two recrystallisations from hot toluene in a Dean-Stark apparatus (Scheme 3c).\textsuperscript{15}

With large quantities of 3 easily accessible, the transformation of the alcohol functionality and cyclisation into BTM 4 was examined. Employing Birman’s conditions of MsCl/Et\textsubscript{3}N (Scheme 2) followed by aqueous work up yields a yellow gum which, although relatively pure by \textsuperscript{1}H NMR analysis, proved difficult to transform into high yields of crystalline BTM by trituration or recrystallisation without recourse to chromatography. This tentatively suggested the presence of polymeric impurities that were largely silent by \textsuperscript{1}H NMR. Therefore, alternative activation methods for the alcohol cyclisation were examined.

Both tosyl chloride and thionyl chloride gave unsatisfactory results, with the former giving a complex mixture of products and the latter incomplete conversion of 3 (Scheme 4). Interestingly, the reaction of 3 under Mitsonobu conditions resulted in skeletal rearrangement to give isomeric isothiourea 5 as the major species. The structure was inferred by comparison of the crude \textsuperscript{1}H NMR spectra to that reported by Okamoto and co-workers.\textsuperscript{16} This unexpected reactivity was not pursued further, and the fidelity of stereochemical transfer was not determined.

As alternative activating agents were ultimately unsuccessful, efforts were focused upon understanding and improving the reaction of 3 with MsCl. It was found that >1.25 equivalents of MsCl were required for complete consumption of 3, even with freshly distilled MsCl under strictly anhydrous conditions. TLC and \textsuperscript{1}H NMR analysis of the reaction mixture indicated the formation of two products. Attempted chromatographic isolation of the two species failed to allow isolation of purported O-

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Scheme 3 Optimisation of the first step.

Scheme 4 Alternative activating agents for the cyclisation of 3
mesylate 6 owing to its instability on silica gel. However, a second \( N,O \)-bis-mesylate species 7 was isolated and characterised (Scheme 5). Treating 3 with >2 equivalents of MeSOCl allowed 7 to be produced exclusively without any of the alternative isomeric \( N,O \)-bis-mesylate being observed.\(^{17}\) Interestingly, heating a \( \text{CH}_2\text{Cl}_2 \) solution of 7 at reflux in the presence of \( \text{Et}_3\text{N} \) and MeOH overnight gave BTM 4 as the sole product in excellent yield after chromatography. This observation suggests that under Birman’s original conditions a mixture of mono- and bis-mesylate 6 and 7 forms with complete consumption of MeSOCl. Both components of this mixture cyclise upon heating with base to give 4 exclusively, with the sulfene eliminated from the cyclisation of bis-mesylate 7 quenched by MeOH.\(^{18}\) Indeed, if a nucleophilic co-solvent is absent the reaction turns black and the isolable yield of BTM 4 is significantly reduced.

With this information in hand, optimised conditions for the cyclisation were established (Scheme 6). A suspension of 3 and excess \( \text{Et}_3\text{N} \) (4.0 eq.) in anhydrous \( \text{CH}_2\text{Cl}_2 \) (0.1 m) was cooled in an ice/water bath. A slight excess of MeSOCl (1.3 eq.) was added, sufficient to completely consume 3. The resulting solution was treated with \( i\)-PrOH,\(^{19}\) heated to reflux overnight and checked for completion by \(^1\)H NMR. These conditions consistently led to full conversion of 3 into crude BTM 4. An improved work up procedure was sought to avoid chromatography, with the Brønsted basic nature of BTM 4 considered an exploitable property through acid / base extractions. Hence, the reaction was quenched with \( 1 \) N NaOH to remove acidic impurities (MeOH etc.) and the \( \text{CH}_2\text{Cl}_2 \) layer extracted multiple times with \( 1 \) N HCl to leave an aqueous solution of BTM HCl. Basification (2 N NaOH, pH >14) of the combined aqueous layers, extraction with an organic solvent (EtOAc, \( \text{Et}_2\text{O} \) etc.) and concentration afforded solid BTM 4 that was reasonably pure in ca. 50% yield. This material could be triturated or recrystallised from \( \text{Et}_2\text{O} \) / hexanes to give analytically pure BTM 4, demonstrating that a chromatography-free route was plausible. However, the loss of material was concerning until it was discovered that BTM-HCl is highly soluble in \( \text{CH}_2\text{Cl}_2 \), with multiple extractions with 1 N HCl failing to completely remove it from the organic layer. A solvent switch from \( \text{CH}_2\text{Cl}_2 \) to \( \text{Et}_2\text{O} \) (in which BTM-HCl is only sparingly soluble) was performed after the 1 N NaOH wash and this greatly increased the mass recovery of crude BTM 4 after the acid / base extractions. Final modifications to the work up included a toluene azeotrope during the solvent switch to remove the remaining \( \text{Et}_3\text{N} \), and treatment of the final organic solution of BTM 4 with charcoal to decolourise it. Finally, trituration of the crude with hot \( \text{Et}_2\text{O} \) provided analytically pure BTM 4 in consistently high yield for both enantiomers and the racemate of 73-84% from 3 (Scheme 6).

Reactions were performed in oven-dried glassware, using DrySyn\(^{20}\) blocks for heated reactions. Anhydrous \( \text{CH}_2\text{Cl}_2 \) was obtained from an MBraun SPS-800 system. 2-Chlorobenzothiazole was fractionally distilled under reduced pressure prior to use, \( \text{EtNi-Pr}_2 \) and \( \text{Et}_3\text{N} \) were stored over KOH pellets, and methanesulfonyl chloride was distilled under reduced pressure from \( \text{P}_2\text{O}_5 \) prior to use and stored in a fridge under \( \text{N}_2 \).\(^{20}\) All other solvents and commercial reagents were used as received without further purification. Pet. ether is defined as petroleum ether 40-60 °C. Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica). Plates were visualised under UV light (254 nm) or by staining with KMnO\(_4\) followed by heating. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated. Melting points were recorded on an Electrothermal 9100 melting point apparatus. Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C. HPLC analyses were obtained on a Shimadzu HPLC using a Chiralpak AD-H column. GC analyses were obtained on a Shimadzu GC-2025, with helium (He) used as the carrier gas in split injection mode at constant linear velocity. An
Agilent DB-5 analytical column was used for analyses (30 m, 0.25 mm ID, 0.5 μm film thickness). Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer using a Pike MIRacle ATR accessory. $^1$H and $^{13}$C $^1$H NMR spectra were acquired on Bruker 500 or 400 MHz spectrometers. Chemical shifts, δ, are quoted in parts per million (ppm) and are referenced to the residual solvent peak ($^1$H: CDCl$_3$ 7.26 ppm, MeOH-$d_4$ 3.31 ppm; $^{13}$C: CDCl$_3$ 77.16 ppm, MeOH-$d_4$ 49.00 ppm). Coupling constants, J, are quoted in Hertz (Hz) to the nearest 0.1 Hz. Mass spectrometry (HRMS) data were acquired by electrospray ionisation (ESI) at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Elemental analysis (CHN) was performed by Mr Stephen Boyer at London Metropolitan University.

(R)-(−)-2-(Benzo[d]thiazol-2-ylamino)-2-phenylethanol - (R)-3

A 250 mL round-bottomed flask containing a stirrer bar was charged with (R)-phenylglycinol (R)-2 (10.00 g, 72.80 mmol, 1.05 eq.), o-dichlorobenzene (34.5 mL, 2.0 M), EtNi-P$_2$ (31.0 mL, 173.6 mmol, 2.5 eq.) and 2-chlorobenzothiazole 1 (8.60 mL, 69.43 mmol, 1.0 eq.). The resulting yellow suspension was stirred vigorously and heated to reflux at 195 °C (DrySyn temperature), at which point the suspended solid had dissolved to leave a yellow solution. After 24 h at reflux, the orange reaction mixture was allowed to cool to rt. Once cooled, the reaction mixture was diluted with distilled water (100 mL) and toluene (75 mL) with vigorous stirring. A precipitate formed over the next 15 min and stirring was maintained for a further 1 h. The reaction mixture was filtered through a 1.0 L sintered glass filter funnel (porosity 3) under vacuum to leave the solid precipitate. The solid was washed with toluene (2 × 100 mL) and dried on the sinter under vacuum for 30 min, then transferred to a 1.0 L sintered glass filter funnel and allowed to cool slowly to rt, over which time a precipitate formed. Once cooled, the flask was further cooled to −10 °C in a NaCl/ice/water bath for 30 min. The solid precipitate was recovered by vacuum filtration on a 1.0 L sintered glass filter funnel (porosity 3), and washed with further portions of toluene (2 × 100 mL). The solid was dried on the sinter under vacuum for 30 min, then transferred to a 250 mL round bottomed flask and dried in vacuo to constant weight. This gave title compound (R)-3 (14.81 g, 54.78 mmol, 79%) as fluffy white crystals. A second recrystallisation from toluene at reflux may be required if a powder is obtained from the first attempt. Typical mass loss on second recrystallisation was <500 mg on this scale.

mp 158-159 °C (toluene) [lit.$^5_c$ 159-160 °C (CHCl$_3$)].

$[\alpha]_D^{20}$−102.7 (c 1.04, MeOH) [lit.$^5_c$−103 (c 1.17, MeOH)].

$^1$H NMR (500 MHz, MeOH-$d_4$): δ H 3.80 (1H, dd, J 11.4, 7.4 Hz, C(1)H$^1$); 3.85 (1H, dd, J 11.4, 5.0 Hz, C(1)H$^2$); 5.00 (1H, dd, J 7.4, 5.0 Hz, C(2)H), 7.03 (1H, td, J 7.5, 1.1 Hz, ArH), 7.22 (1H, td, J 7.5, 1.2 Hz, ArH), 7.26 (1H, t, J 7.4 Hz, p-PhH), 7.34 (2H, t, J 7.4 Hz, m-PhH), 7.38 (1H, d, J 8.1 Hz, ArH), 7.44 (2H, d, J 7.4 Hz, o-PhH), 7.55 (1H, d, J 7.8 Hz, ArH).

$^{13}$C $^1$H NMR (126 MHz, MeOH-$d_4$): δ C 30.47, 119.0, 121.7, 122.7, 126.8, 128.1, 128.6, 129.5, 131.3, 141.1, 153.0, 169.0.

Anal. Calcd for C$_{15}$H$_{22}$N$_2$OS: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.57; H, 5.31; N, 10.33.

$^1$H and $^{13}$C NMR data consistent with literature values.$^2$

GC (Agilent DB-5, 40 cm/s (He), inj. temp. 250 °C, FID temp. 325 °C; temp. profile: initial 120 °C (2 min), then ramp to 320 °C (20 °C/min, hold 5 min), total run = 17 min): $r_k$ EtNi-P$_2$ 1.87 min; o-dichlorobenzene 3.20 min; phenylglycinol 2 5.34 min; 2-chlorobenzothiazole 1 5.74 min; 3 12.56 min.

HPLC (Chiralcel AD-H, 10% IPA/Hexane, 1.5 mL/min, 40 °C, 254 nm): $r_k$ 13.75 min (100%), >99% ee.

(S)-(−)-2-(Benzo[d]thiazol-2-ylamino)-2-phenylethanol - (S)-3

An identical procedure to that outlined for (R)-3 using (S)-phenylglycinol (S)-2 (10.00 g) gave the title compound (S)-3 (13.91 g, 51.45 mmol, 74%) as fluffy white crystals after a second recrystallisation.

mp 158-159 °C (toluene).

$[\alpha]_D^{20}$+101.7 (c 1.01, MeOH).

Anal. Calcd for C$_{15}$H$_{22}$N$_2$OS: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.43; H, 5.36; N, 10.33.

All other spectroscopic data identical to (R)-3.

HPLC (Chiralcel AD-H, 10% IPA/Hexane, 1.5 mL/min, 40 °C, 254 nm): $r_k$ 18.06 min (100%), >99% ee.

(±)-2-(Benzo[d]thiazol-2-ylamino)-2-phenylethanol - (±)-3

An identical procedure to that outlined for (R)-3 using a mixture of (R)-phenylglycinol (R)-2 (5.00 g) and (S)-phenylglycinol (S)-2 (5.00 g) gave the title compound (±)-3 (14.52 g, 53.71 mmol, 77%) as fluffy white crystals.

mp 163-164 °C (toluene).
Anal. Calcd for C$_{15}$H$_{14}$N$_{2}$OS: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.49; H, 5.35; N, 10.44.

All other spectroscopic data identical to (R)-3.

HPLC (Chiralcel AD-H, 10% IPA/Hexane, 1.5 mL/min, 40 °C, 254 nm): $t_R$ 13.74 min (50%), 17.33 min (50%).

(R)-(+)2-Phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazole - (R)-(+)BTM 4

A 1.0 L round-bottomed flask containing a stirrer bar was charged with anhydrous CH$_2$Cl$_2$ (460 mL, 0.1 M) followed by (R)-3 (12.42 g, 45.94 mmol, 1.0 eq.) with stirring and fitted with a suba seal and exit needle (19 gauge). Et$_3$N (25.6 mL, 183.8 mmol, 4.0 eq.) was added via syringe and the suspension cooled in an ice/water bath. After 10 min, methanesulfonyl chloride (4.62 mL, 59.72 mmol, 1.3 eq.) was added if (R)-3 remains (stir 15 min, re-check TLC and repeat if necessary). It is crucial that all (R)-3 is consumed. Once complete consumption of (R)-3 was observed, i-PrOH (9.0 mL) was added and the suba seal replaced by a reflux condenser. The reaction was heated to reflux (50 °C DrySyn, sealed) and stirred for 15 min. The reaction was checked by TLC (CH$_2$Cl$_2$ / Et$_2$O 1:1, UV$_{254}$ / KMnO$_4$, R$_f$ (R)-3 ~0.28; 6 0.61; 7 0.81) and a further portion of MsCl (0.1 eq.) added if (R)-3 remains (stir 15 min, re-check TLC and repeat if necessary). The crude residue was azeotroped with toluene (3 × 50 mL) to remove most of the residual Et$_3$N. The residue was triturated with Et$_2$O (200 mL) with sonication and the liquid collected by decantation through a plug of cotton wool. This was repeated with two further portions of Et$_2$O (100 mL), filtering the final portion through the cotton wool. The filter cake was rinsed with a further portion of Et$_2$O (50 mL). The combined ethereal washings were extracted with 1 N NaOH (5 × 50 mL) and the combined aqueous layers basified with 2 N NaOH (pH >14) at which point a cloudy white precipitate formed. The aqueous layer was extracted with Et$_2$O (3 × 100 mL) and the combined organics washed with brine (100 mL). The organic layer was treated with activated charcoal (~5 g) and dried over MgSO$_4$. The suspension was filtered through a pad of Celite®, rinsing with further portions of Et$_2$O. The solvent was removed in vacuo to leave the crude product as a white to pale yellow solid (9.81 g). This solid was suspended in Et$_2$O (50 mL, ~5 mL/g crude), scraping any residues from the side of the flask, and heated to reflux for 30 min (the solid does not completely dissolve). An equal volume of pet. ether (50 mL) was added and the flask allowed to cool to rt with stirring. Once cooled, the solid was collected by vacuum filtration on a 100 mL sintered glass filter funnel (porosity 3), washing with further portions of pet. ether (3 × 50 mL). The solid was dried on the sinter under vacuum for 30 min, then transferred to a 100 mL round bottomed flask and dried in vacuo to constant weight to leave pure (R)-(+)BTM 4 (14.51 g, 35.27 mmol, 77%) as white crystals.

mp 89-90 °C [lit.² 94.5-95 °C (Et$_2$O/hexane)].

[α]$_D^{[20]}$ +255.4 (c 1.05, MeOH) [lit.² +256.7 (c 1.00, MeOH)].

1H NMR (500 MHz, CDCl$_3$): δ 3.72 (1H, dd, J 8.9, 8.1 Hz, C(3)H$^3$H$^5$), 4.28 (1H, dd, J 10.2, 8.9 Hz, C(3)H$^3$H$^5$), 5.67 (1H, dd, J 10.2, 8.1 Hz, C(2)H$^5$), 6.67 (1H, dd, J 8.0, 1.1 Hz, ArH), 6.97 (1H, td, J 7.7, 1.1 Hz, ArH), 7.19 (1H, td, J 7.7, 1.2 Hz, ArH), 7.27-7.32 (1H, m, p-PhH), 7.31 (1H, dd, J 7.7, 1.1 Hz, ArH), 7.35-7.40 (4H, m, o- and m-PhH).

13C [1H] NMR (126 MHz, CDCl$_3$): δc 52.6, 75.5, 108.6, 121.6, 123.3, 126.6, 126.7, 127.5, 127.7, 128.9, 137.2, 143.1, 166.8.

Anal. Calcd C$_{15}$H$_{12}$N$_2$S: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.28; H, 4.67; N, 11.07.

1H and 13C NMR data consistent with literature values.²

HPLC (Chiralcel AD-H, 10% IPA/Hexane, 1.5 mL/min, 40 °C, 254 nm): 10.95 min (100%), >99% ee.

(S)-(−)2-Phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazole - (S)-(−)BTM 4

An identical procedure to that outlined for (R)-(+)BTM 4 using (S)-3 (13.15 g, 48.64 mmol), MsCl (4.89 mL, 63.23 mmol) and Et$_3$N (27.1 mL, 194.6 mmol) in anhydrous CH$_2$Cl$_2$ (490 mL) gave (S)-(−)BTM 4 (8.96 g, 35.51 mmol, 73%) in two crops as white crystals.

mp 89-90 °C.

[α]$_D^{[20]}$ −256.5 (c 0.98, MeOH).

Anal. Calcd for C$_{15}$H$_{12}$N$_2$S: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.25; H, 4.91; N, 10.95.

All other spectroscopic data identical to (R)-(+)BTM 4.

HPLC (Chiralcel AD-H, 10% IPA/Hexane, 1.5 mL/min, 40 °C, 254 nm): $t_R$ 20.98 min (100%), >99% ee.

(±)-2-Phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazole - (±)-BTM 4

An identical procedure to that outlined for (R)-(+)BTM 4 using (±)-3 (14.51 g, 35.67 mmol), MsCl
(5.40 mL, 69.77 mmol) and Et$_3$N (30.0 mL, 214.7 mmol) in anhydrous CH$_2$Cl$_2$ (540 mL) gave (±)-BTM 4 (11.37 g, 45.06 mmol, 84%) in two crops as white crystals.

mp 94-95 °C.

Anal. Calcd for C$_{11}$H$_{12}$N$_2$S: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.28; H, 4.91; N, 10.97.

All other spectroscopic data identical to (R)-(+-)-BTM 4.

HPLC (Chiralcel AD-H, 10% IPA/Hexane, 1.5 mL/min, 40 °C, 254 nm): $t_R$ 13.42 min (50%), 20.95 min (50%).

(R)-2-(N-Benzyl|thiazol-2-yl)methylsulfonamido)-2-phenylethyl methanesulfonate - (R)-7

A 100 mL round bottomed flask containing a stirrer bar was charged with (R)-3 (500 mg, 1.85 mmol, 1.0 eq.) and anhydrous CH$_2$Cl$_2$ (20 mL). Et$_3$N (1.03 mL, 7.40 mmol, 4.0 eq.) was added, the suspension cooled in an ice/water bath and methanesulfonfyl chloride (0.36 mL, 4.63 mmol, 2.5 eq.) added dropwise over 2 min. The reaction was stirred for 10 min, checked by TLC (CH$_2$Cl$_2$ / Et$_2$O 1:1) and quenched with sat. aq. NaHCO$_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH$_2$Cl$_2$ (20 mL). The combined organic phases were washed with 0.1 N HCl (30 mL), dried over MgSO$_4$ and filtered. The solvent was removed in vacuo to leave the crude product that was purified by flash chromatography on silica gel (CH$_2$Cl$_2$) to leave (R)-7 (661 mg, 1.55 mmol, 84%) as a colourless foam.

[a]$_D^{20}$ +31.8 (c 1.0, CHCl$_3$).

IR (film, cm$^{-1}$): 3028, 2936, 1636, 1580, 1454, 1352, 1244, 1173, 1157, 1034, 961.

$^1$H NMR (400 MHz, CDCl$_3$): δ $H$ 2.97 (3H, s, OSO$_2$Me), 3.67 (3H, m, NSO$_2$Me), 4.33-4.52 (2H, m, C(2)H and C(1)H$^2$H$^1$), 4.55 (1H, dd, J 8.4, 7.2, C(1)H$^2$H$^1$), 7.12 (1H, td, J 7.6, 1.1, ArH$^t$), 7.20-7.27 (2H, m, ArH), 7.30-7.40 (3H, m, m- and p-PhH), 7.43-7.46 (2H, m, o-PhH), 7.98 (1H, dd, J 8.5, 0.7, ArH).

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$): δ$_C$ 37.7, 42.7, 68.1, 73.8, 115.8, 122.3, 122.4, 124.6, 126.9, 127.8, 128.6, 129.0, 136.0, 137.2, 154.8.

HRMS (ESI): m/z [M+H$^+$] calc'd for C$_{11}$H$_{12}$N$_2$O$_2$S$_2$: 427.0451, found 427.0441 (−2.5 ppm).

Cyclisation of (R)-7 to form (R)-BTM 4

A 50 mL round bottomed flask containing a stirrer bar and fitted with a reflux condenser was charged with (R)-7 (650 mg, 1.52 mmol, 1.0 eq.), Et$_3$N (0.64 mL, 4.57 mmol, 3.0 eq.), anhydrous CH$_2$Cl$_2$ (15 mL) and MeOH (1.0 mL). The resulting solution was heated to reflux overnight, allowed to cool and quenched with 1 N NaOH (20 mL). The layers were separated and the aqueous layer extracted with CH$_2$Cl$_2$ (20 mL). The combined organic phases were dried over MgSO$_4$, filtered, and the solvent removed in vacuo to leave the crude product that was purified by flash chromatography on silica gel (CH$_2$Cl$_2$→1:4 Et$_2$O/CH$_2$Cl$_2$) to leave pure non-crystalline (R)-BTM 4 (341 mg, 1.35 mmol, 89%) as a white powder. This material was not recrystallised.

$^1$H NMR was identical to that prepared by the optimised route.

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References


(13) From TCI-UK Ltd.: (R)-BTM 4 P/N: B3296, £94.20 / 1 g; (S)-BTM 4 P/N: B3549, £83.45 / 1 g (accessed 22/08/2014).

(14) Racemic phenylglycinol was obtained by mixing equal amounts of the commercially available (R)- and (S)-glycinols.

(15) See experimental for details.


(17) The site of N-mesylation was determined by 1H-15N HMBC spectroscopy, supported by DFT calculations for the 15N chemical shifts. See supporting information for details.

(18) Birman states that the addition of MeOH serves to quench additional MsCl, see ref 2.

(19) MeOH was replaced with i-PrOH as it was considered that the byproduct i-PrOMs from reaction with sulfene would be less reactive as an alkylation agent than MeOMs, thereby reducing polymeric impurities.


(21) GC analysis indicated >95% conversion of 2-chlorobenzothiazole against o-dichlorobenzene as the internal standard. Cu. 200 μL samples of the reaction mixture at t = 0 and 24 h were taken and diluted to ~1.5 mL in CH2Cl2 for analysis.
A Scalable, Chromatography-free Synthesis of Benzotetramisole

![Chemical structure diagram]

(R), (S) and (t) 2 steps  
(R)-, (S)- and (t)-BTM  
ca. 60% yield  
10 g scale  
chromatography free

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