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Synthesis, resolution, and absolute configuration of novel tricyclic benzodiazepines

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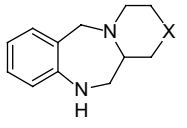
Abstract—The synthesis, resolution, and stereochemical characterization of novel piperazino-, thiazino-, and oxazinobenzodiazepines are described. The absolute stereochemistry of the heterotricycles was determined by using X-ray crystallography and the enantiomeric purity was determined by using Pirkle-solvent NMR techniques and chiral HPLC.

1. Introduction

The benzodiazepine chemotype has been found in numerous biologically active compounds, such as opiate antagonists, anti-inflammatory agents, psychomotor depressants, vasopressin receptor antagonists, and antibiotics.[1–3] This quality of the benzodiazepine ring system has engendered its classification as a 'privileged structure' for drug discovery.[4] Although the synthesis of various heterocyclo[1,4]benzodiazepines has been reported,[5] there are no publications on the synthesis of piperazino-, thiazino-, or oxazinobenzodiazepines, such as **1a**–**c**. Recently, we discovered compounds based on a racemic benzodiazepine backbone with exciting biological activity.[6] Our biological evaluation and structure–activity relationship (SAR) development was expedited by the synthesis of racemic products; however, we ultimately needed to assess the biological properties of the individual enantiomers to define the potency, pharmacology, and toxicology. While an enantioselective synthesis of each enantiomer would be extremely helpful to this end, the most feasible route appeared to be a classical resolution of each benzodiazepine. Herein, we describe the synthesis, resolution, and stereochemical characterization of benzodiazepine tricycles **1a**–**c**. The enantiomeric purity of each resolved tricycle was determined by ^{1}H NMR with Pirkle's solvent[7] and by chiral HPLC. The absolute configurations of the piperazino- and thiazinobenzodiazepines were determined by X-ray crystallography, while the absolute configuration of the oxazinobenzodiazepine was determined by vibrational circular dichroism (VCD), as reported earlier.[8]



a: X = NMe
b: X = S
c: X = O

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2. Results and discussion

The syntheses of the respective benzodiazepines are outlined in Schemes 1 and 2. Methyl 4-methylpiperazine-2-carboxylate dihydrochloride **5a** was prepared as shown in Scheme 1. Bis-protected piperazine **2** was prepared from piperazine-2-carboxylic acid according to literature precedent.[9] Deprotection of **2** provided piperazine intermediate **3**, which was reductively aminated with aqueous formaldehyde to provide *N*-methyl intermediate **4**, in 96% overall yield for the two steps. Catalytic hydrogenolysis of **4** provided racemic methyl piperazate **5a** in high yield.

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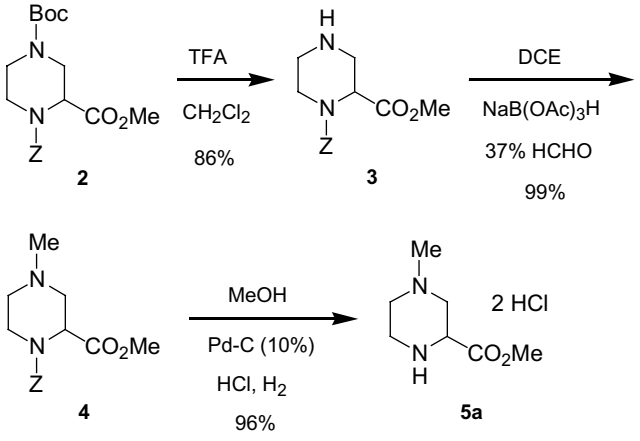
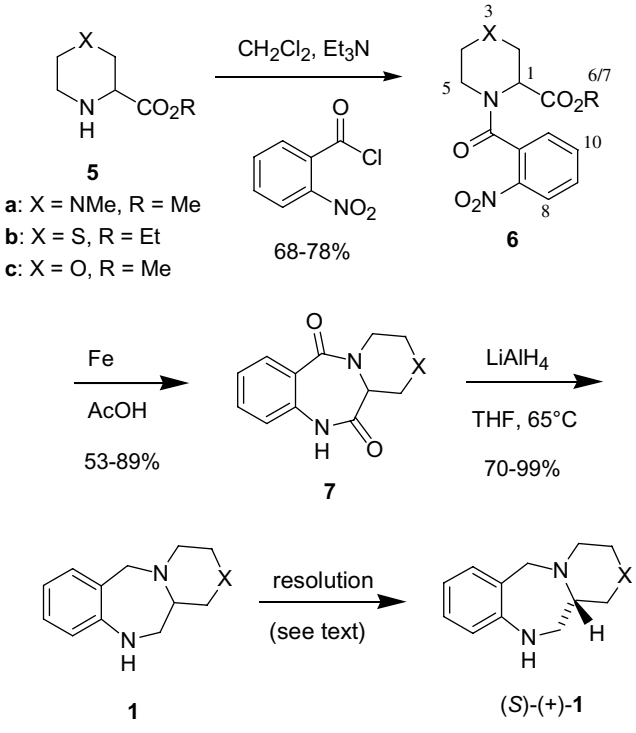


Scheme 1. Synthesis of methyl piperazate **5a**.



Scheme 2. Synthesis and resolution of **1a**–**c**.

Methyl thiomorpholine carboxylate **5b**[10] and morpholino amino ester **5c**[11] (both racemic) were prepared according to literature procedures. As shown in Scheme 2, acylation of amino esters **5a**–**c** with 2-nitrobenzoyl chloride provided amides **6a**–**c**, which were subsequently cyclized to lactams **7a**–**c** using iron-mediated conditions.[12] Hydride reduction of lactams afforded racemic benzodiazepines **1a**–**c**. To identify a suitable resolving agent/solvent for providing single enantiomers of racemates **1a**–**c**, we initially tested several enantiomerically pure acids and solvent conditions as part of a 5×10 screening matrix (Table 1) with each heterocycle, **1a**–**c**. Individual reactions that resulted in crystals were filtered and cracked with aqueous base to separate the enantiomerically enriched free base from the resolving agent. After finding an effective acid for the resolution (see below), each opposite enantiomer was obtained by crystallization with the opposite, applicable chiral acid.

Our initial approach for measuring the ees of tricycles **1a**–**c**, and their corresponding enantiomers, was based on ^{1}H NMR with chiral solvating agents.[7] In the NMR studies we employed Pirkle's solvent, 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE). Figure 1 (panel A) depicts the spectra of racemate **1a** in the absence of TFAE. The aromatic triplet between δ 6.81–6.86 (identified through COSY and NOESY experiments) is the signal that we focused on to determine the initial enantiomeric purity. Figure 1 (panel B) shows racemate **1a** in the presence of 0.45% TFAE in $CDCl_3$. As shown in Figure 1 (panel B), an approximate enantiomeric shift of 0.2 ppm and a pair of multiplets was created on addition of 0.45% TFAE

Table 1. Resolution of racemates **1a**–**c**

Substrate	Salt[a]	Solvent[b]	Recovery[c] (%)	Ee[d] (%)	Configuration
1a	Dibenzoyl-D-tartaric acid	Ethanol	96	⩾98[e]	(*S*)-(+)-**1a**[f]
1a	Dibenzoyl-L-tartaric acid	Ethanol	78	⩾98[e]	(*R*)-(−)-**1a**[g]
1b	(*R*)-BNPH	Methanol	70	⩾98[e]	(*S*)-(+)-**1b**[f]
1b	(*S*)-BNPH	Methanol	72	94.8	(*R*)-(−)-**1b**[g]
1c	Di-*p*-toluoyl-D-tartaric acid	Methanol–ether	52	98.3	(*S*)-(+)-**1c**[h]
1c	Di-*p*-toluoyl-L-tartaric acid	Methanol–ether	64	95.4	(*R*)-(−)-**1c**[g]

[a] The acid–substrate ratio was 1:1, except for **1a**, where a 1:2 ratio was utilized. BNHP=binaphthyl-2,2′-diyl hydrogen phosphate. Chiral acids employed in the screening 5×10 crystallization array were (*R*)-2-hydroxy-5,5-dimethyl-4-phenyl-1,2,3-dioxaphosphorane-2-oxide, (*R*)-(−)-4-chloromandelic acid, di-*p*-tolyl-D-tartaric acid, (*R*)-(−)-mandelic acid, (1*S*)-(+)-10-camphorsulfonic acid, D-tartaric acid, dibenzoyl-D-tartaric acid, (*S*)-(+)-2-phenylbutyric acid, (*R*)-BNHP, and (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid.

[b] Solvents employed in the screening 5×10 crystallization array were MeOH, EtOH, *i*-PrOH, EtOAc, and THF (or a combination).

[c] The recovery is based on a possible 50% of the desired enantiomer after one recrystallization. Evaporation of the mother liquor followed by multiple recrystallizations provided higher yields.

[d] The enantiomeric excess (ee) after one crystallization was determined by chiral HPLC and ^{1}H NMR by utilizing 0.45% (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's solvent) as an additive in $CDCl_3$. The enantiomeric purities were determined by using a Hewlett Packard 1100 system (Chiralcel AS column, 0.46 cm × 25 cm; mobile phase 85:15 hexanes:*i*-PrOH containing 0.1% diethylamine; detection at 254 nM).

[e] The opposite enantiomer was not detected using chiral HPLC or ^{1}H NMR by utilizing 0.45% (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle's solvent) as an additive in $CDCl_3$.

[f] The absolute configuration was determined by X-ray crystallography.

[g] The absolute configuration was assigned by comparison of the sign of its specific rotation to that of the opposite enantiomer.

[h] The absolute configuration was assigned based on VCD analysis.[8]

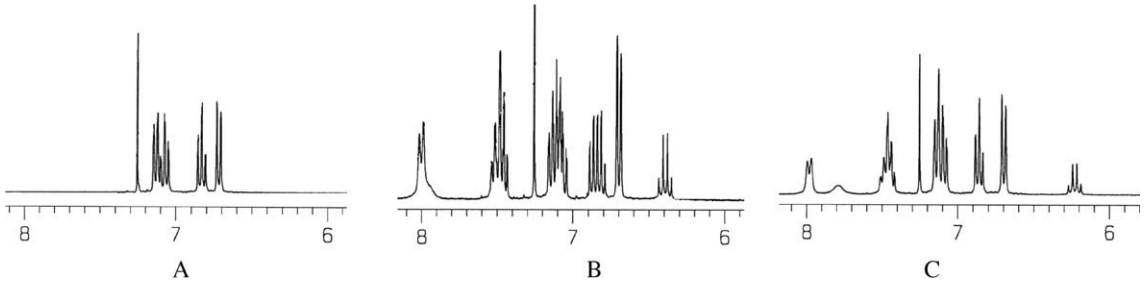


Figure 1. Downfield regions of three ^{1}H NMR spectra. Panel A: Racemate **1a** with no TFAE. Panel B: Racemate **1a** with 0.45% TFAE. Panel C: (*S*)-(+)-**1a** with 0.45% TFAE.

to racemate **1a**. This separation was deemed to have enough analytical utility for an adequate ee measurement (±3%). Crystallization of **1a** with dibenzoyl-D-tartaric acid and basification provided (*S*)-(+)-**1a**, the ^{1}H NMR of which with 0.45% TFAE is shown in Figure 1 (panel C). This material is highly enriched with an ee of greater than 97% (±3%), according to the criterion mentioned above.

Chiral HPLC confirmed this ^{1}H NMR result in that compound (*S*)-(+)-**1a** was determined to have ⩾98% ee (Table 1). The same type of ^{1}H NMR and chiral HPLC measurements were performed on racemates **1b** and **1c**, as well, and high enantiomeric excesses were obtained for (*S*)-(+)-**1b** and (*S*)-(+)-**1c**, respectively (Table 1).

As indicated in Table 1, the resolution of racemate **1a** was accomplished efficiently by using dibenzoyl-D-tartaric acid in ethanol to provide compound (*S*)-(+)-**1a** in 48% yield with ⩾98% ee. Racemate **1b** was resolved to afford (*S*)-(+)-**1b** through crystallization with (*R*)-(−)-binaphthyl-2,2′-diyl hydrogen phosphate (BNHP) from methanol in 35% yield and an ee of ⩾98%. Compound (*S*)-(+)-**1c** was obtained in 35% yield and 98.3% ee by crystallization of the di-*p*-toluoyl-D-tartrate salt of **1c** from methanol-ether. It should be noted that high enantiopurities were obtained after just a single crystallization, and the enantiomeric excess could be improved by further crystallization. The opposite enantiomers, (*R*)-(−)-**1a**, (*R*)-(−)-**1b**, and (*R*)-(−)-**1c**, were obtained in a similar way by crystallization of salts from the opposite acid, with ee's of ⩾98%, 94.8%, and 95.4%, respectively (Table 1).

To establish the absolute configuration unambiguously, crystals of (*S*)-(+)-**1a** and (*S*)-(+)-**1b** were grown for an X-ray crystallographic structure determination. The molecular structure of (*S*)-(+)-**1a** along with one molecule of dibenzoyl-D-tartaric acid is shown in Figure 2 (panel A). By reference to the acid subunit, the absolute configuration of the tricycle is determined to be *S*. Figure 2 (panel B) shows the molecular structure of (*S*)-(+)-**1b** paired with (*R*)-BNHP. Interestingly, two equivalents of the chiral acid are coordinated with each basic nitrogen, which apparently causes (*S*)-(+)-**1b** to adopt a more puckered conformation than that present in (*S*)-(+)-**1a**. By reference to the acid subunit, the absolute configuration of (*S*)-(+)-**1b** is determined to be *S*. Although **1c** formed a nice crystalline salt with di-*p*-toluoyl-D-tartaric acid for resolution, resulting in (*S*)-(+)-**1c** with high ee (98.3%), the crystals were initially not of sufficient quality for an X-ray diffraction study. Thus, the absolute configuration of (*S*)-(+)-**1c** was first assigned by comparing the sign of its specific rotation to

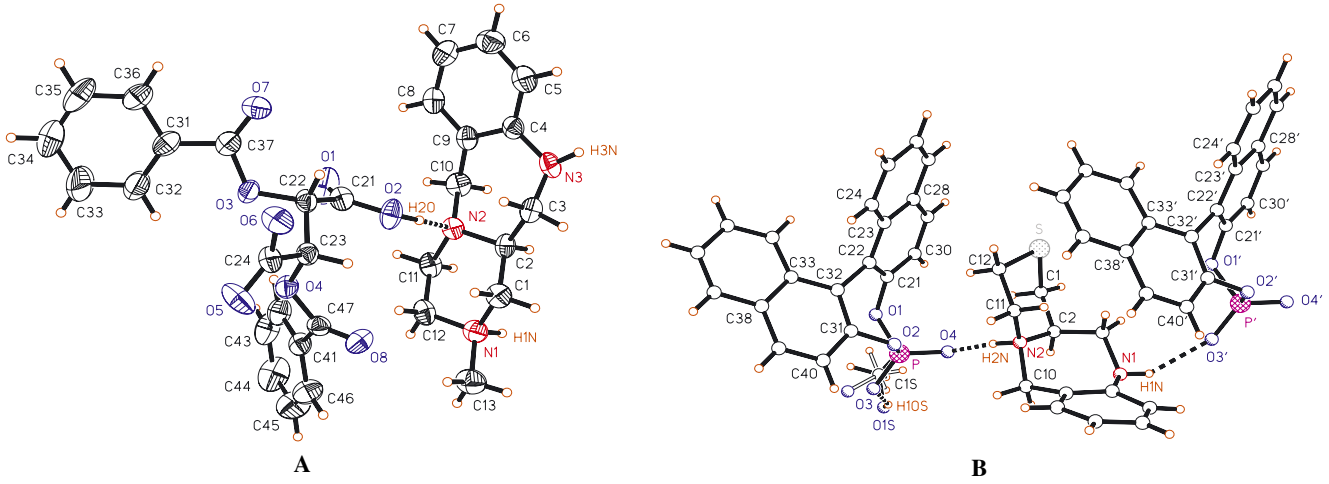


Figure 2. Panel A: ORTEP plot of the molecular structure of (*S*)-(+)-**1a** with dibenzoyl-D-tartaric acid (with the atom-numbering scheme). Panel B: Ball-and-stick model of the molecular structure of (*S*)-(+)-**1b** with (*R*)-binaphthyl-2,2′-diyl hydrogen phosphate (with the atom-numbering scheme). A single molecule of CH_3OH of crystallization is shown (C15, O15).

that for (*S*)-(+)-**1a** and (*S*)-(+)-**1b**. Also, we employed vibrational circular dichroism (VCD), which has become a powerful technique for determining the absolute configuration for structurally rigid compounds in solution phase, to corroborate the assignment for (*S*)-(+)-**1c**, as discussed elsewhere.[8] Eventually, we were able to obtain X-ray diffractable crystals of **1c**·di-*p*-toluoyl-D-tartaric acid and perform the crystallography, the results of which agreed with the prior stereochemical assignment. Figure 3 shows the molecular structure of (*S*)-(+)-**1c**.

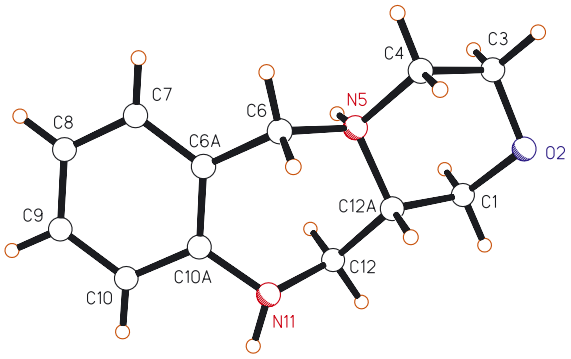


Figure 3. Ball-and-stick model of the molecular structure of (*S*)-(+)-**1c** as a salt with di-*p*-toluoyl-D-tartaric acid, showing only the ammonium cation (with its atom-numbering scheme).

In the three X-ray structures, the conformations adopted by ammonium cations **1a** and **1c** are similar, but that adopted by cation **1b** differs (Figs. 1–3). In cations **1a** and **1c**, the saturated six-membered ring is fused to the tetrahydrobenzazepine ring in a *trans* configuration with the proton on the bridgehead nitrogen in an axial orientation. However, in cation **1b**, the saturated six-membered ring is fused to the tetrahydrobenzazepine ring in a *cis* configuration with the proton on the bridgehead nitrogen axial. In all three compounds, the six-membered ring consistently has a chair conformation, as expected, and the tetrahydrobenzazepine ring has a chair-like conformation, with the unprotonated aniline nitrogen somewhat pyramidalized. The *N*-methyl group in doubly protonated **1a** is in an equatorial orientation. The aniline nitrogen in **1b** is involved in a hydrogen-bond donor interaction with a carboxylate oxygen of the anion. The differences observed between **1a**/**1c** and **1b** (phosphate-type derivatives are probably related to the counteranion in the salt form (diaroyltartrate vs binaphthylphosphate) and the attendant effects on crystal-packing forces.

3. Conclusions

The syntheses of novel heterocyclic benzodiazepines have been executed. After exploring a panel of crystallization conditions (5×10 array), the classical resolution of benzodiazepines **1a**–**c** was accomplished in high yield and high enantiomeric excess, as demonstrated by Pirkle-solvent ^{1}H NMR and chiral HPLC. X-ray diffraction of acid-addition salts of (*S*)-(+)-**1a** and (*S*)-(+)-**1b** established the absolute configurational assignments.

4. Experimental

4.1. General methods

All commercially available chemicals were used as purchased. Melting points were obtained with using a Mel-Temp capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-400 spectrometer (unless otherwise noted) with TMS as an internal standard. Electrospray ionization mass spectra (ESI) were obtained using a Fisons spectrometer (Hewlett–Packard HPLC driven electrospray MS instrument). The purities of each compound were determined using a Hewlett–Packard LC 1100 system (YMC J'Sphere H80 S4 column, 4.0×50 mm, 4 mm C_{18}; mobile phase of 90% H_2O (0.1% TFA) to 10% H_2O (0.1% TFA) with a flow rate of 1 mL/min; detection at 220 and 254 nM). The enantiopurities were determined using a Hewlett–Packard LC 1100 system (Chiralcel AS column, 0.46×25 cm; mobile phase of 85/15 hexanes/*i*-PrOH containing 0.1% diethylamine, flow rate of 1 mL/min; detection at 254 nM). Optical rotations were obtained using a Perkin–Elmer 241 polarimeter. Elemental analyses were conducted by Robertson Microlit Laboratories. X-ray data were obtained by Crystalytics Company. For (*S*)-(+)-**1a** and (*S*)-(+)-**1b**, X-ray data were collected on a computer-controlled Bruker P4 Single Crystal Diffractometer by using 1.0°-wide ω-scans and graphite-monochromated MoK_α radiation. For (*S*)-(+)-**1c**, X-ray data were collected on a Bruker SMART CCD Single Crystal Diffraction System by using 0.30°-wide ω-scans and graphite-monochromated MoK_α radiation. All of the structures were solved and refined with the Bruker SHELXTL-PC (version 5.0) software package.

4.2. Synthesis of 4-methylpiperazine-2-carboxylic acid methyl ester 5a

4.2.1. Synthesis of piperazine-1,2,4-tricarboxylic acid 1-benzyl ester 4-*tert*-butyl ester 2-methyl ester 3. To **2**[9] (21.8 g, 57.6 mmol), dissolved in dichloromethane (150 mL) was added triflouroacetic acid (150 mL) and the reaction was stirred at ambient temperature for 3 h (monitored by HPLC). The solvent was evaporated in vacuo and the residual oil was partitioned between ethyl acetate and 10% $NaHCO_3$. The aqueous phase was extracted with ethyl acetate (3×) and the organic extracts were combined and washed with 1 N aqueous HCl (2×). The combined HCl extracts were washed with ethyl acetate (1×), carefully neutralized to pH 8 with 1 N aqueous NaOH, and extracted with dichloromethane (3×). The organic extracts were combined, washed with H_2O and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo afforded **3** (13.8 g, 86%), as a viscous oil. ^{1}H NMR ($CDCl_3$) δ 2.70–2.89 (m, 1H), 2.91–3.27 (m, 3H), 3.48–3.56 (t, 1H), 3.71–3.77 (d, 3H),

3.87–3.97 (t, 1H), 4.64–4.76 (m, 1H), 5.09–5.29 (m, 2H), 7.32–7.36 (m, 3H); MS, *m/z*: 279.0 (M+1).

4.2.2. Synthesis of 4-methylpiperazine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester 4. To a solution of **3** (15.5 g, 55.6 mmol), dissolved in 1,2-dichloroethane (200 mL) was added 37% aqueous formaldehyde (5 mL, 178 mmol) followed by sodium triacetoxyborohydride (16.5 g, 77.8 mmol), in one portion, and the reaction mixture was stirred at room temperature until total consumption of **3** (24–72 h, monitored by HPLC). The reaction was quenched with 1 N aqueous NaOH and diluted with dichloromethane. The organic layer was washed with H_2O and dried over Na_2SO_4. The solvent was filtered and evaporated in vacuo to afford **4** (16.1 g, 99%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.63–2.01 (m, 1H), 2.16–2.21 (m, 1H), 2.26 (s, 3H), 2.68–2.78 (m, 1H), 3.20–3.38 m, 2H), 3.70–3.76 (d, 3H), 3.88–3.99 (m, 1H), 4.68–4.80 (d, 2H), 5.09–5.20 (m, 2H), 7.27–7.36 (m, 5H); HRMS, *m/z*: 293.1 (M+1); acc. mass: ($C_{15}H_{20}N_2O_4$) calcd 293.1501, found 293.1502.

4.2.3. Synthesis of 4-methylpiperazine-2-carboxylic acid methyl ester 5a. Compound **4** (11.4 g, 38.9 mmol) was suspended in ethanol (70 mL) and conc. HCl (4.2 mL, 136 mmol) was added followed by 10% Pd–C (1.4 g). The suspension was reacted under a hydrogen atmosphere for 24 h, filtered through a pad of Celite, and washed several times with ethanol. The combined organic washes were evaporated in vacuo to afford **5a** (8.5 g, 96%) as a viscous oil. ^{1}H NMR (CD_3OD) δ 3.07 (s, 3H), 3.43–3.52 (m, 1H), 3.56–3.70 (m, 2H), 3.78–3.88 (m, 2H), 3.95 (s, 3H), 4.10–4.20 (m, 1H), 4.80–4.85 (m, 1H); MS, *m/z*: 159.2 (M+1).

4.3. Synthesis of acylated derivatives 6a–c. General procedure

To a cyclic amino ester **5a**, **5b**,[10] or **5c**,[11] suspended in anhydrous dichloromethane (4 mL/mmol), was added diisopropylethylamine (3.3 equiv) and the reaction mixture was cooled to 0 °C. A solution of 2-nitrobenzoyl chloride (1.2 equiv) in dichloromethane (0.66 mL/mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction was diluted with dichloromethane, washed with H_2O, and dried over Na_2SO_4. The reaction was filtered and the solvent was concentrated in vacuo to afford a crude product, which was purified by flash chromatography (hexane/EtOAc as eluent) to afford pure **6a**, **6b**, or **6c**.

4.3.1. 4-Methyl-1-(2-nitrobenzoyl)piperazine-2-carboxylic acid methyl ester 6a. According to the general procedure, reaction between **5a** (11.8 g, 51 mmol) and 2-nitrobenzoyl chloride (8.0 mL; 60 mmol) afforded **6a** as a viscous oil (11.9 g, 76%). ^{1}H NMR (500 MHz, DMSO-d_6, 2 amide rotamers, $T = 75$ °C) δ 1.90–1.95 (m, 0.7H, H4), 1.96–2.02 (m, 0.3H, H4), 2.16 (m, 0.3H, H2), 2.20 (s, 3H, H3), 2.23–2.28 (dd, $J = 7.5$, 11.5 Hz, 0.7H, H2), 2.60–2.63 (d, $J = 11.0$ Hz, 0.7H, H4′), 2.80–2.83 (d, $J = 11.0$ Hz, 0.3H, H4′), 3.09–3.12 (m, 0.3H, H5), 3.17–3.20 (m, 0.7H, H5), 3.29–3.31 (d, $J = 11.5$ Hz, 0.7H, H2′), 3.34–3.40 (m, 0.7H, H5′), 3.69 (s, 0.3H, H6), 3.78 (s, 0.7H, H6), 4.19 (s, 0.3H, H1), 4.40–4.42 (d, $J = 13.0$ Hz, 0.3H, H5′), 5.20 (s, 0.7H, H1), 7.34–7.35 (d, $J = 6.5$ Hz, 0.3H, H11), 7.47–7.49 (d, $J = 7.5$ Hz, 0.7H, H11), 7.69–7.74 (m, 1H, H9), 7.79–7.80 (t, $J = 7.0$ Hz, 0.3H, H10), 7.86–7.89 (t, $J = 7.5$ Hz, 0.7H, H10), 8.17–8.19 (m, 1H, H8); HRMS, *m/z*: 308.1 (M+1); acc. mass: ($C_{14}H_{17}N_3O_5$) calcd 308.1233, found 308.1238.

4.3.2. 4-(2-Nitrobenzoyl)thiomorpholine-3-carboxylic acid methyl ester 6b. According to the general procedure, reaction of **5b** (4.2 g, 20 mmol) and 2-nitrobenzoyl chloride (3.2 mL; 25.2 mmol) afforded **6b** as a viscous oil (4.4 g, 68%), ^{1}H NMR (500 MHz, DMSO-d_6, 2 amide rotamers, $T = 75$ °C) δ 1.22–1.25 (m, 0.9H, H7), 1.29–1.33 (t, $J = 7.0$ Hz, 2.1H, H7), 2.43–2.46 (d, $J = 13.0$ Hz, 0.7H, H4), 2.62–2.71 (m, 0.7H, H6′), 2.74–2.79 (m, 0.3H, H6), 2.89–2.96 (m, 0.7H, H2), 3.03–3.07 (m, 0.7H, H2), 3.33–3.14 (m, 0.7H, H2), 3.17–3.22 (m, 0.3H, H5), 3.46–3.51 (t, $J = 12.5$ Hz, 0.7H, H5′), 3.58–3.61 (m, 0.7H, H5), 4.19–4.29 (m, 2H, H6), 4.57 (s, 0.3H, H1), 4.80–4.83 (d, $J = 13.5$ Hz, 0.3H, H5′), 5.61 (s, 0.7H, H1), 7.40 (m, 0.3H, H11), 7.50–7.52 (d, $J = 6.5$ Hz, 0.7H, H11), 7.71–7.74 (m, 1H, H9), 7.81–7.83 (m, 0.3H, H10), 7.86–7.89 (t, $J = 7.5$ Hz, 0.7H, H10), 8.19-8.20 (d, $J = 8.5$ Hz, 1H, H8); HRMS, *m/z*: 326.2 (M+1); acc. mass: $C_{13}H_{14}N_2O_5S$ calcd 325.0858, found 325.0856.

4.3.3. 4-(2-Nitrobenzoyl)morpholine-3-carboxylic acid methyl ester 6c. According to the general procedure, reaction of **5c** (5.5 g, 38 mmol) and 2-nitrobenzoyl chloride (5.5 mL; 42 mmol) afforded **6c** as a viscous oil (8.7 g, 78%); ^{1}H NMR (500 MHz, DMSO-d_6, 2 amide rotamers, $T = 75$ °C) δ 3.15–3.19 (m, 1H, H5), 3.38–3.45 (m, 1.4H, H5′/H4), 3.48–3.50 (m, 0.3H, H4), 3.60–3.62 (d, $J = 11.0$ Hz, 0.3H, H2), 3.72–3.73 (m, 2H, H2/H6/H4), 3.80 (s, 1.7H, H6), 3.92–3.95 (d, $J = 10.5$ Hz, 0.3H, H4′), 4.12–4.14 (d, $J = 11.5$ Hz, 0.3H, H2′), 4.20 (s, 0.3H, H1), 4.32–4.34 (m, 1H, H5′/H2′), 7.38–7.39 (m, 0.3H, H11), 7.50–7.52 (d, $J = 7.5$ Hz, 0.7H, H11), 7.72–7.75 (m, 1H, H9), 7.82 (m, 0.3H, H10), 7.87–7.90 (t, $J = 7.5$ Hz, 0.7H, H10), 8.19–8.20 (d, $J = 8.5$ Hz, 1H, H8); HRMS, *m/z*: 295.1 (M+1); acc. mass: ($C_{13}H_{14}N_2O_6$) calcd 295.0930, found 295.0931.

4.4. Synthesis of benzodiazepinones 7a–c. General procedure

To acylated amino esters **6a**, **6b**, or **6c**, dissolved in glacial acetic acid (4.5 mL/mmol), was added iron filings (10 mol equiv) and the reaction mixture was heated at 110 °C until total consumption of starting material (4–6 h, monitored by TLC). For **7b** or **7c**, the reaction was cooled and poured into water. The precipitate was filtered, washed with water, and dried in vacuo. For **7a**,

the reaction was carefully neutralized with 10% aqueous $NaHCO_3$ and the aqueous phase was saturated with NaCl and extracted several times with ethyl acetate. The extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide crude **7a**–**c**. The solids were triturated with ether, filtered, and dried in vacuo to afford pure **7a**–**c**.

4.4.1. 2-Methyl-1,3,4,11a-tetrahydro-2H,10*H*-2,4a,10-triazabenzo[*a*,*d*]cycloheptene-5,11-dione 7a. According to the general procedure, reaction of **6a** (4.7 g, 15 mmol) with iron filings (8.6 g; 153 mmol) afforded **7a** as a white solid (2.61 g, 69%), mp >230 °C; ^{1}H NMR (DMSO-d_6) δ 1.92–1.97 (m, 1H), 2.03–2.07 (m, 1H), 2.22 (s, 3H), 2.78–2.80 (m, 1H), 2.88–2.93 (m, 1H), 3.09–3.11 (d, $J = 12$ Hz, 1H), 4.12–4.13 (d, $J = 4.9$ Hz, 1H), 4.26–4.29 (d, $J = 13.2$ Hz, 1H), 7.06–7.08 (d, $J = 8.1$ Hz, 1H), 7.18–7.21 (t, $J = 7.6$ Hz, 1H), 7.46–7.49 (t, $J = 7.3$ Hz, 1H), 7.68–7.70 (d, $J = 7.7$ Hz, 1H), 10.34 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 45.84, 50.37, 51.58, 52.73, 120.42, 123.83, 126.58, 130.31, 131.89, 137.04, 167.56, 170.54. MS, m/z: 246.3 (M+1). Anal. Calcd for $C_{13}H_{15}N_3O_2$ (245.28): C, 63.66; H, 6.16; N, 17.13. Found: C, 63.19; H, 6.20; N, 17.01.

4.4.2. 1,3,4,11a-Tetrahydro-10*H*,2-thia-4a,10-diaza-dibenzo[*a*,*d*]cycloheptene-5,11-dione 7b. According to the general procedure, reaction of **6b** (4.4 g, 13 mmol) with iron filings (7 g; 125 mmol) afforded **7b** as a white solid (3.0 g, 89%), mp >230 °C; ^{1}H NMR ($CDCl_3$) δ 2.50–2.2.68 (m, 1H), 2.77–2.82 (m, 1H), 2.87–2.90 (m, 1H), 3.13–3.19 (m, 1H), 3.32–3.39 (m, 1H), 4.17–4.21 (m, 1H), 4.55–4.59 (m, 1H), 7.11–7.13 (d, $J = 8.1$ Hz, 1H), 7.23–7.26 (t, $J = 7.1$ Hz, 1H), 7.51–7.55 (t, $J = 7.1$ Hz, 1H), 7.79–7.81 (d, $J = 7.8$ Hz, 1H), 10.56 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.17, 24.40, 35.95, 54.67, 120.86, 124.02, 125.77, 130.96, 132.30, 136.55, 166.60, 169.74. MS, m/z: 249.9 (M+1). Anal. Calcd for $C_{12}H_{12}N_2O_2S$ (248.30): C, 58.05; H, 4.87; N, 11.28. Found: C, 57.70; H, 4.95; N, 11.15.

4.4.3. 1,3,4,11a-Tetrahydro-10*H*,2-oxa-4a,10-diaza-dibenzo[*a*,*d*]cycloheptene-5,11-dione 7c. According to the general procedure, reaction of **6c** (8.67 g, 29.4 mmol) with iron filings (16.5 g; 294 mmol) afforded **7c** as a white solid (3.67 g, 53%), mp >230 °C; ^{1}H NMR (DMSO-d_6) δ 2.95–3.00 (m, 1H), 3.44–3.49 (m, 1H), 3.53–3.56 (m, 1H), 3.92–3.95 (m, 1H), 4.05–4.06 (d, $J = 3.8$ Hz, 1H), 4.14–4.21 (m, 2H), 7.08–7.09 (d, $J = 7.3$ Hz, 1H), 7.20–7.24 (t, $J = 6.7$ Hz, 1H), 7.48–7.51 (t, $J = 6.5$ Hz, 1H), 7.70–7.71 (m, $J = 6.3$ Hz, 1H), 10.42 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 50.14, 62.57, 64.71, 120.62, 124.04, 126.39, 130.43, 132.03, 136.89, 167.84, 170.16. MS, m/z: 233.3 (M+1). Anal. Calcd for $C_{12}H_{12}N_2O_3$ (232.24): C, 62.06; H, 5.21; N, 12.06. Found: C, 61.92; H, 5.24; N, 12.01.

4.5. Synthesis of benzodiazepines 1a–c. General procedure

To benzodiazepinone **7a**, **7b**, or **7c** in dry tetrahydrofuran (7.5 mL/mmol), cooled at −10 °C, was added a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran (3 equiv), dropwise. On completion of the addition, the reactions were allowed to warm to ambient temperature and refluxed until total consumption of starting material (4–9 h, monitored by TLC). The reactions were cooled to 0 °C, quenched carefully with H_2O, and extracted with ethyl acetate (3×). The organic extracts were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford pure **1a**–**c**.

4.5.1. 2-Methyl-1,2,3,4,5,10,11,11a-octahydro-2,4a,10-triazadibenzo[*a*,*d*]cycloheptene 1a. According to the general procedure, reaction of **7a** (5.5 g, 23 mmol) and lithium aluminum hydride–tetrahydrofuran (69 mL; 69 mmol) afforded **1a** as a yellow solid (4.8 g, 98%), mp 106–107 °C; ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 1H), 2.27–2.30 (m, 4H), 2.52–2.64 (m, 3H), 2.72–2.80 (m, 2H), 2.91–2.96 (m, 1H), 3.11–3.16 (dd, $J = 1.95$, 13.1 Hz, 1H), 3.58–3.66 (m, 2H), 3.80–3.81 (s, 1H), 6.71–6.73 (m, 1H), 6.82–6.85 (m, 1H), 7.06–7.09 (m, 1H), 7.12–7.14 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 46.01, 52.07, 55.17, 58.93, 62.57, 64.33, 118.15, 120.96, 127.89, 129.32, 130.89, 150.21. MS, m/z: 218.2 (M+1). Anal. Calcd for $C_{13}H_{19}N_3$ (217.31): C, 71.85; H, 8.81; N, 19.34. Found: C, 71.43; H, 8.74; N, 19.16.

4.5.2. 3,4,5,10,11,11a-Hexahydro-1*H*,2-thia-4a,10-diaza-dibenzo[*a*,*d*]cycloheptene 1b. According to the general procedure, reaction of **7b** (3.0 g, 12 mmol) and 1.0 M $LiAlH_4$–THF (36 mL; 36 mmol) afforded **1b** as a yellow solid (1.86 g, 70%), mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 2.60–2.75 (m, 5H), 2.96–3.00 (m, 1H), 3.00–3.07 (m, 1H), 3.12–3.15 (m, 1H), 3.33–3.37 (m, 1H), 3.70–3.73 (d, $J = 14.3$ Hz, 1H), 3.73 (s, 1H), 3.93–3.96 (d, $J = 14.3$ Hz, 1H), 6.71–6.73 (d, $J = 7.7$ Hz, 1H), 6.83–6.84 (t, $J = 6.4$ Hz, 1H), 7.06–7.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.06, 31.75, 49.92, 52.52, 62.15, 63.08, 118.06, 120.65, 127.94, 128.28, 130.57, 149.52. MS, m/z: 221.9 (M+1). Anal. Calcd for $C_{12}H_{16}N_2S$ (220.33): C, 65.41; H, 7.32; N, 12.71. Found: C, 65.16; H, 7.30; N, 12.77.

4.5.3. 3,4,5,10,11,11a-Hexahydro-1*H*-2-oxa-4a,10-diaza-dibenzo[*a*,*d*]cycloheptene 1c. According to the general procedure, reaction of **7c** (12.6 g, 54 mmol) and 1.0 M $LiAlH_4$–THF (165 mL; 165 mmol) afforded **1c** as a yellow solid (11.0 g, 99%), mp 111–113 °C; ^{1}H NMR ($CDCl_3$): δ 2.50–2.55 (m, 2H), 2.74–2.85 (m, 2H), 3.04–3.07 (d, $J = 12.8$ Hz, 1H), 3.27–3.31 (t, $J = 1.9$ Hz, 1H), 3.55–3.67 (m, 1H), 3.69–3.81 (m, 4H), 3.82–3.85 (m, 1H), 6.74–6.77 (d, $J = 7.7$ Hz, 1H), 6.84–6.87 (t, $J = 7.3$ Hz, 1H), 7.07–7.09 (m, 1H), 7.10–7.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 49.52, 53.73, 62.90, 64.28, 67.09, 69.48, 118.36, 121.11, 128.02, 129.17, 130.85, 150.01. MS, m/z: 205.2 (M+1). Anal. Calcd for $C_{12}H_{16}N_2O$ (204.27): C, 70.56; H, 7.90; N, 13.71. Found: C, 70.26; H, 7.83; N, 13.68.

4.6. Resolution of benzodiazepines 1a–c. General procedures

4.6.1. 2-Methyl-1,2,3,4,5,10,11,11a-octahydro-2,4a,10-triazadibenzo[*a*,*d*]cycloheptene, (*S*)-(+)- and (*R*)-(−)-1a. To benzodiazepine **1a** (3.88 g; 17.8 mmol) in ethanol (100 mL) was added dibenzoyl-D-tartaric acid (3.2 g; 8.9 mmol) and the suspension was heated until dissolution. The mixture was cooled and the solvent was evaporated in vacuo. The residue was redissolved in a minimum amount of ethanol and heated to initiate crystallization. Once a solid crystallized, the heat was removed and the reaction mixture was cooled to ambient temperature and allowed to sit for 24 h. The resultant crystals were filtered, washed with ethanol, ether, and dried under vacuo to provide a white solid (2.69 g, 33%). The solid was partitioned between 3 N NaOH and ethyl acetate. The organic phase was separated, washed with H_2O and brine, and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo afforded (*S*)-(+)-**1a** (0.93 g, 48%) as a white solid, $[\alpha]_D^{20} = +132.7$ (*c* 0.808, $CHCl_3$). The opposite enantiomer is isolated by combining **1a** (6.2 g) and dibenzoyl-L-tartaric acid (0.51 g), with the experimental shown above, to afford (*R*)-(−)-**1a** (1.22 g, 39%) as a white solid, $[\alpha]_D^{20} = -139.8$ (*c* 0.766, $CHCl_3$).

4.6.2. 3,4,5,10,11,11a-Hexahydro-1*H*,2-thia-4a,10-diazadibenzo[*a*,*d*]cycloheptene, (*S*)-(+)- and (*R*)-(−)-1b. To benzodiazepine **1b** (10.3 g; 46.8 mmol) in methanol (100 mL) was added (*R*)-binaphthyl-2,2′-diyl hydrogen phosphate (16.3 g; 46.8 mmol) and the suspension was heated until dissolution. The reaction mixture was cooled and the solvent was evaporated in vacuo. The residue was redissolved in a minimum amount of methanol and the reaction mixture was allowed to sit for 24 h at ambient temperature. The resultant crystals were filtered, washed with methanol, ether, and dried in vacuo to afford a white solid (9.3 g, 35%). The solid was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The organic phase was separated, washed with H_2O, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo afforded (*S*)-(+)-**1b** (3.6 g, 35%) as a white solid. $[\alpha]_D^{20} = +260.8$ (*c* 0.125, $CHCl_3$). The opposite enantiomer is isolated using **1b** (0.9 g) and (*S*)-binaphthyl-2-2′-diyl hydrogen phosphate (0.56 g), with the experimental described above, to afford (*R*)-(−)-**1b** (0.32 g, 35%) as a white solid, $[\alpha]_D^{20} = -280.6$ (*c* 0.124, $CHCl_3$).

4.6.3. 3,4,5,10,11,11a-Hexahydro-1*H*-2-oxa-4a,10-diazadibenzo[*a*,*d*]cycloheptene, (*S*)-(+)- and (*R*)-(−)-1c. To benzodiazepine **1c** (6.16 g; 30 mmol) in methanol (35 mL) was added di-*p*-toluoyl-D-tartaric acid (5.82 g; 30 mmol) and the suspension was heated until dissolution. The reaction mixture was cooled and the solvent was evaporated in vacuo. The resultant residue was redissolved in a minimum amount of methanol (35 mL) and ether (80 mL) was added to give a cloudy solution. Methanol was added dropwise until clarity was restored. The solution was allowed to sit at ambient temperature for 72 h. The resultant crystals were filtered, washed with cold ether, and dried under vacuo to afford a white solid (3.4 g, 58%). The solid was partitioned between 1 N NaOH and ethyl acetate and the layers were partitioned. The organic phase was washed with water, brine and dried over Na_2SO_4. Filtration and evaporation of the solvent in vacuo afforded (*S*)-(+)-**1c** (1.58 g; 26%) as a white solid, $[\alpha]_D^{20} = +163.6$ (*c* 0.264, MeOH). The opposite enantiomer was isolated using **1c** (0.94 g) and di-*p*-toluoyl-L-tartaric acid (0.88 g), with the experimental shown above, to afford (*R*)-(−)-**1c** (0.32 g; 32%) as a white solid, $[\alpha]_D^{20} = -147.6$ (*c* 0.88, MeOH).

4.7. X-ray crystallography for (*S*)-(+)-1a, (*S*)-(+)-1b, and (*S*)-(+)-1c

4.7.1. X-ray crystallography for (*S*)-(+)-1a-dibenzoyl-D-tartrate. Single crystals of $[C_{13}H_{20}N_3][(-)\text{-}(S,S)\text{-}C_{18}H_{13}O_8]$ from ethanol are (at -50 ± 2 °C) trigonal, space group $P3_2\text{-}C_3^3$ (No. 145) with $a = 10.231(2)$ Å, $c = 24.166(7)$ Å, $V = 2190.4(8)$ Å^3 and $Z = 3$ cation/anion formula units [$d_{calcd} = 1.309\ g\,cm^{-3}$; $\mu_a(MoK_\alpha) < 50.7°$]. A total of 3654 reflections having $2\theta(MoK_\alpha) < 50.7°$ (the equivalent of 0.8 limiting CuK_α sphere) were collected; 2865 of these reflections were unique and gave $R_{int} = 0.029$. Lattice constants were determined with the Bruker XSCANS software package using 32 centered reflections. Direct methods techniques were used to solve the structure and the resulting structural parameters were refined with F^2 data to convergence by using counter-weighted full-matrix least-squares techniques and a structural model that incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The final agreement factors are: R_1 (unweighted, based on F)=0.045 for 1938 independent reflections having $2\theta(MoK_\alpha) < 50.7°$ and $I > 2\sigma(I)$; R_1 (unweighted, based on F)=0.086 and wR_2 (weighted, based on F^2)=0.089 for all 2865 independent reflections having $2\theta(MoK_\alpha) < 50.7°$. The absolute configuration assigned to the chiral cation is based on the known configuration of the anion; it could not be confirmed crystallographically since the 'Flack' absolute structure parameter refined to a value of 0(2). Amine hydrogen atoms H_{1N} and H_{3N} and carboxyl hydrogen atom H_{2O} were located from a difference Fourier map and refined as independent isotropic atoms. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms (assuming sp^2- or sp^3-respective carbon atoms and C–H bond lengths of 0.94–0.99 Å) 'riding' on their respective carbon atoms. The methyl group (C_{13} and its hydrogens) was refined as a rigid rotor (using idealized sp^3-hybridized geometry and a C–H bond length of 0.96 Å) with three rotational parameters in least-squares cycles. The refined values of these rotational parameters resulted in N–C–H angles ranging from 107–111°. The isotropic thermal parameters for H_{1N}, H_{3N}, and H_{2O} refined to final U_{iso} values of 0.08(2), 0.03(1), and 0.17(4) Å^2, respectively; those for the remaining hydrogens were fixed at values of 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameters of the carbon atoms to which they are bonded. CCDC 233778.[13]

4.7.2. X-ray crystallography for (*S*)-(+)-1b-(*R*)-binaphthyl-2,2′-diyl hydrogen phosphate. Single crystals of [(*R*,*R*)-$C_{12}H_{17}N_2S$][(*S*)-(+)-($C_{20}H_{12}O_4P$)] from MeOH are (at 20±2 °C) monoclinic, space group $P3_1$-C_2^2 (No. 4) with $a = 10.3195(8)$ Å, $b = 12.1227(9)$ Å, $c = 12.3904(10)$ Å, $\beta = 108.591(6)°$, $V = 1469.2(2)$ Å^3 and $Z = 2$ [$d_{calcd} = 1.358$ g cm^{-3}; $\mu_a(MoK_\alpha) = 0.210$ mm^{-1}]. A total of 4483 independent reflections having $2\theta(MoK_\alpha) < 55.0°$ (equivalent of 1.0 limiting CuK_α sphere) were collected. Lattice constants were determined with the Bruker XSCANS software package using 51 centered reflections. Direct methods techniques were used to solve the structure and the resulting structural parameters were refined with F^2 data to convergence using counter-weighted full-matrix least-squares techniques and a structural model with incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. Final agreement factors are: R_1 (unweighted, based on F)=0.033 for 3455 independent absorption-corrected reflections have $2\theta(MoK_\alpha) < 55.0°$ and $I > 2\sigma(I)$; and wR_2 (weighted, based on F^2)=0.086 for all 3860 independent absorption-corrected reflections having $2\theta(MoK_\alpha) < 55.0°$. The methanol solvent molecule is disordered with two preferred orientations in the lattice. The major (67.6%) orientation is specified by H_{1OS}, O_{1S}, C_{1S}, H_{1Sa}, H_{1Sb} and H_{1Sc}; the minor (32.4%) orientation is specified by $O_{1S'}$, C_{1S}, H_{1Sd}, H_{1Se} and H_{1Sf}. Since the hydroxyl hydrogen for the minor orientation could not be located from difference Fourier syntheses, it was not included in the structural model. Hydrogen atoms H_{1N} and H_{2N}, H_2, and H_{1OS} were located from a difference Fourier map and refined as independent isotropic atoms. The remaining hydrogen atoms of the cation and anion were included in the structure factor calculations as idealized atoms (assuming sp^2- or sp^3-hybridization of the carbon atoms and C–H bond lengths of 0.93–0.97 Å) 'riding' on their respective carbon atoms. Each alternate orientation for the methyl group of the disordered methanol solvent molecule (C1S and its hydrogens) was refined as a rigid rotor (using idealized sp^3-hybridized geometry and a C–H bond length of 0.96 Å), which was free to rotate about the O–C bond. The isotropic thermal parameters for H_{1N}, H_{2N}, H_2, and H_{1OS} refined to final U_{iso} values of 0.06(1), 0.06(1), 0.05(1) and 0.12(3) Å^2, respectively. The isotropic thermal parameters of the remaining hydrogen atoms were fixed at values 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameters of the carbon atoms to which they are covalently bonded. CCDC 233779.[13]

4.7.3. X-ray crystallography for (*S*)-(+)-1c as a salt with di-*p*-toluoyl-D-tartaric acid. Single crystals of [(*S*,*S*)-$C_{12}H_{17}N_2O]_2$ [(*S*,*S*)-($C_{20}H_{16}O_8$)]·H_2O are (at −80±2 °C) orthorhombic, space group $P2_12_12_1$-*D* (No. 19) with $a = 11.057(2)$ Å, $b = 13.208(3)$ Å, $c = 27.336(6)$ Å, $V = 3992(1)$ Å^3 and $Z = 4$ formula units [$d_{calcd} = 1.352$ g cm^3; $\mu_a(MoK) < 0.098$ mm^{-1}]. A total of 18067 integrated reflection intensities having $2\theta(MoK) < 46.55°$ were produced using the Bruker program SAINT software package; 5734 of these were independent and gave $R_{int} = 0.113$. Lattice constants were determined with Bruker SAINT using peak centers for 765 reflections. Direct methods techniques were used to solve the structure and the resulting structural parameters were refined with F^2 data to convergence using counter-weighted full-matrix least-squares techniques and a structural model that incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. Final agreement factors at convergence are: R_1 (unweighted, based on F)=0.047 for 3108 independent reflections have $2\theta(MoK) < 46.55°$ and $I > 2\sigma(I)$; R_1 (unweighted, based on F)=0.125 and wR_2 (weighted, based on F^2)=0.081 for all 5734 independent reflections having $2\theta(MoK) < 46.55°$. The structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All amine hydrogen atoms (H_{5N}, H_{11N}, H_{25N}, and H_{31N}) were located from a difference Fourier synthesis and refined as independent isotropic atoms. The two methyl groups (C_{52}, C_{60}, and their hydrogens) were refined as rigid rotors (using idealized sp^3-hybridized geometry and a C–H bond length of 0.98 Å), which were allowed to rotate about their C–C bonds in least-squares cycles. The two hydrogens for the water molecule of crystallization were located from a difference Fourier synthesis and included in the structural model as isotropic atoms fixed at these difference Fourier positions. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms (assuming sp^2- or sp^3-hybridization of the carbon atoms and C–H bond lengths of 0.95–1.00 Å) 'riding' on their respective carbon atoms. The isotropic thermal parameters for H_{5N}, H_{11N}, H_{25N}, and H_{31N} refined to final U_{iso} values of 0.07(2), 0.04(2), 0.13(2), and 0.02(1) Å^2, respectively. The isotropic thermal parameters of the remaining hydrogen atoms were fixed at values 1.2 (nonmethyl and water) or 1.5 (methyl) times the equivalent isotropic thermal parameters of the carbon or oxygen atom to which they are covalently bonded. CCDC 233780.[13]

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13. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 11EZ UK [fax: +44 (0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].