Asymmetric Synthesis of 4,1-Benzoxazepine-2,5-Diones — Effect of the Halogen of (2S)-α-Haloacids

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Abstract: Novel chiral 4,1-benzoxazepine-2,5-diones have been unusually synthesized in a single step by exploiting the chiral pool methodology. Substituted anthranilic acids afford N-acylanthranilic acids and (3R)-3-alkyl-4,1-benzoxazepines-2,5-dione upon coupling with α-chloroacids or α-bromoacids, respectively.

Keywords: (3R)-3-alkyl-4,1-benzoxazepine-2,5-diones; asymmetric synthesis; α-chloroacids; α-bromoacids; anthranilic acid; chiral pool methodology

1. Introduction

The benzoxazepines belongs to the heterocycles class of compounds, which are obligatory components of biologically important molecules such as nucleic acids, hormones and therapeutic drugs. The benzoxazepine scaffolds are very versatile and of therapeutic use in many important fields. They have acquired tremendous importance in recent years owing to their wide applications in the
medicinal and pharmaceutical industry. For example, benzoxazepines have shown anti-tumor [1,2], anti-HIV [3], and tranquilizing activities [4], among a long list of other effects. Most of the conventional synthesis methods reported in literature produce racemic/achiral syntheses of 4,1-benzoxazepine. Leptit et al. reported the synthesis of 4,1-benzoxazepine by N-alkylation of 2-amino benzhydrol, followed by cyclization in the presence of ethanolic Na solution to yield 5-phenyl-1,3,5-trihydro-4,1-benzoxazepine-2-ones [5]. Bergman et al., reported N-alkylation of N-methylanthranilic acid with an α-chloroacid followed by intramolecular cyclization to afford 4,1-benzoxazepine-3,5-dione [6]. Yar et al., reported a single step synthesis of 4,1-benzoxazepine in which N-tosyl-1,3-aminoalcohols were treated with bromoethylsulfonium salts, via vinyl sulfonium salt formation, which upon intramolecular cyclization afforded 4,1-benzoxazepines [7]. Because of the variety of their biological activities, these are heterocycles of intense chemical and biological significance.

Asymmetric synthesis is acquiring greater significance in pharmaceutical industry because of the wider application of enantiopure drugs. Mostly medicines used are racemic modifications of two enantiomers and side-effect of these medicines is being found due to presence of the vestigial enantiomers [8,9]. Asymmetric synthesis of thus heterocycles attracting greater attention in synthetic chemistry. The accessibility of drug for a community depends on the cost as well. A more efficient drug with high purchase value may not be accessible for all economical levels. This can be avoided by using inexpensive starting materials, especially, those from natural sources. Our methodology employs the chiral pool strategy that involves the use of absolutely enantiopure starting materials, which can be obtained easily from natural resources and tailors a/several chiral centre(s) in a target molecule with up to 100% stereoselectivity. The natural amino acids are inexpensive and readily available chiral starting materials. Many strategies reported in the literature are inspired by chiral pool methodology which makes use of naturally occurring chiral amino acids [10,11]. Our previous work also involved chiral pool strategy which employs inexpensive (S)-amino acids as starting materials to afford (3R)-4,1-benzoxazepines in high ee (up to 81%) [12].

2. Results and Discussion

This strategy involved chiral pool methodology in which chiral substrates are coupled with achiral anthranilic acids to afford chiral 4,1-benzoxazepine-2,5-diones. We planned to synthesize 4,1-benzoxazepines in two steps, which involve the coupling of α-haloacids with various anthranilic acids followed by intramolecular cyclization to afford the corresponding 4,1-benzoxazepine-2,5-diones. For this purpose (−)-(S)-2-chloroacids or (−)-(S)-2-bromoacids 3a–c were prepared in high ee (95%–98%) via diazotization of naturally occurring (+)-(S)-amino acids [13]. The coupling of α-chloroacids 3a–b with 1a–e afforded N-acylanthranilic acid as expected, but the use of α-bromoacid 3c resulted in the formation of seven member ring compounds 4a–c in most cases (Scheme 1 and Table 1).

The reaction of anthranilic acid 1a–e with α-chloroacids 3a–b and 3d affords (3S)-N-acylanthranilic acids 6b–g. When the reaction mixture was poured into ice chilled H2O the compounds 6a–c precipitated out as white solids that were purified by crystallization from EtOAc, whilst 6d–g were purified by column chromatography. However, under such conditions the coupling of 1a and 1e–e with (S)-2-bromopropanoic acid 3c affords either (3R)-4,1-benzoxazepines 4a–c as a major product in most cases or (3S)-N-acylanthranilic acid 6a after transhalogenation. The Br atom is a good leaving group
and it is replaced by a Cl ion (transhalogenation), because chlorine ion is present in the reaction mixture resulting in the formation of (R)-2-chloropropanoic acid which upon coupling with anthranilic acids gave a mixture of both Cl- and Br-substituted products.

Scheme 1. Synthesis of N-acylanthranilic acids 6a–g and benzoazepines 4a–d.

Reagents and Conditions: (a) SOCl₂ (1.5 eq), DMF (1 drop); (b) dropwise addition of 3 to 1, DMF, 0 °C; (c) K₂CO₃, DMF, 80 °C (3 h).

Table 1. The %yield and specific rotations of 4a–d, 5 and 6a–g.

|     | 4a | 4b | 4c | 4d | 5 | 6a | 6b | 6c | 6d | 6e | 6f | 6g |
|-----|----|----|----|----|---|----|----|----|----|----|----|----|
| % Yield | 50 | 78 | 66 | 57 | 32 | 67 | 86 | 70 | 71 | 68 | 67 | 46 |
| c | 0.5 | 0.2 | 0.2 | 0.2 | 0.3 | 0.5 | 0.6 | 1.0 | 1.0 | 1.0 | 0.2 |
| [α]D | +12.0 | +80.0 | +67.9 | +54.0 | -19.0 | +80.0 | +16.9 | +17.0 | +32.0 | +16.2 | +35.2 | +23.3 |
| (°C) | (30) | (30) | (30) | (30) | (23) | (30) | (30) | (30) | (30) | (25) | (25) | (26) |

* MeOH, taken in g/100 mL unit and measured in a cell of 1 dm length; § mixture of both 5a and 5b (82:18).

The coupling of 1c–e with 3c affords the unusual (3R)-4,1-benzoxazepines 4a–c in the majority of the cases. The Br is replaced by either the O of the COOH group in N-acylanthranilic acid or with the Cl ion to afford 4,1-benzoxazepine directly or the Cl-substituted N-acylanthranilic acid, respectively. The coupling of 1a with 3c afforded the Cl-substituted N-acylanthranilic acid 6a exclusively. In this case, the Br is replaced by the Cl ion during the acid halide formation of (S)-2-bromopropanoic acid 3c with SOCl₂.

The formation of Cl-substituted N-acylanthranilic acid in 6a was confirmed by the appearance of the molecular ion observed in LR EIMS; the [M]⁺ appeared at 261, 263 and 265 amu in a 9:6:1 ratio that proves the transhalogenation (presence of two Cl) has occurred. It is observed that a slight excess of SOCl₂ (2 eq) in the acid halide formation step affords benzoazinones 5a/5b as a side-product along with 4,1-benzoxazepine 4c as major product. It is proposed that N-acylanthranilic acid reacts with SOCl₂ to form the acid halide which undergoes cyclization to the six member benzoazinones 5a/5b (Scheme 2).

The benzoazinone is also a mixture of two products 5a/5b (both Cl- and Br-substituted) in which mainly the Cl-substituted benzoazinone 5a dominates. Transhalogenation was confirmed by the presence of both Cl- and Br-substituted molecular ion signals in 9:6:1 and 6:9:2 respectively, observed in LR EIMS (Figure 1a).
Scheme 2. Mechanism showing the formation of 6-chloro-2-(1′-haloethyl-8-methyl-3,1-benzoxazine-4-one 5a–b.

\[
\begin{align*}
\text{Cl} & \quad \text{N} \\
\text{O} & \quad \text{Cl} \\
\text{X} & \quad \text{Cl} \quad \text{H}^+ \\
\text{O} & \quad \text{H}^{-} \\
\text{X} & \quad \text{Cl} \\
\text{O} & \quad \text{Cl} \\
\text{N} & \quad \text{Cl} \\
\end{align*}
\]

\(X = (S)\text{-Br/ } (R)\text{-Cl}\)

Figure 1. A part of (a) LR EIMS showing the predominance of 5a molecular ions; (b) the \(^1\)H-NMR elaborating the level of predominance of Cl-substituted benzoxazinone 5a over Br-substituted benzoxazinone 5b.

The LR EIMS revealed molecular ion signals at 301, 303, 305 and 257, 259, 261 amu which confirm the presence of both Br and Cl atoms at C\(^2\) respectively. It shows that the Cl-substituted product 5a dominates over the Br-substituted product 5b since the signals of the former radical cation show more abundance in the LR EIMS. Each aromatic proton shows a pair of signals of unequal size in \(^1\)H NMR (Figure 1b); the integration of each signal pair revealed the level of predominancy of the Cl-substituted compound 5a (82%) over Br substituted benzoxazinone 5b (18%).

In the case of 6a–g no cyclized product was formed; probably the ease of C-Br bond dissociation is the reason for such behavior (direct cyclization). The Br is a better leaving group than Cl and for cyclization of the Cl substituted N-acylanthranilic acids 6a–g, base (K\(_2\)CO\(_3\)) catalysis is required to get the cyclized 4,1-benzoxazepines [12]. The formation of 4,1-benzoxazepine in a single step was confirmed by single crystal XRD (Figure 2), which indicates the disappearance of C-Br and the formation of a new C-O bond (1.455 and 1.448 Å in 4c and 4a respectively) [14].
The base mediated the intramolecular cyclization of the N-acylated anthranilic acid 6a, obtained by the coupling of anthranilic acid 1a with acid chlorides 3c, to afford the 4,1-benzoxazepine-2,5-dione 4d that was purified by column chromatography. The $^{1}$H-NMR spectra of the 4,1-benzoxazepine 4d showed no prominent changes as compared to the N-acylated anthranilic acid precursor 6a. A small shift is observed for the proton present at the chiral centre, which appeared slightly downfield ($\delta = 4.79$ ppm) as compared to corresponding precursor acid 6a ($\delta = 4.45$ ppm) due to the electron withdrawing inductive effect of O.

3. Experimental

General Information

The pre-coated silica gel (0.25 mm thick layer over Al sheet, Merck, Darmstadt, Germany) TLC plates were used to monitor the reactions. Glass column packed silica gel (0.6–0.2 mm, 60 Å mesh size, Merck) were used for purification. The $^{1}$H-NMR and $^{13}$C-NMR were recorded in the designated solvents on a Bruker AVANCE DPX (300, 400, 500 or 600 MHz) spectrometer (Bruker, Billarica, MA, USA) using TMS as internal standard. The optical rotation was measured on an Atago (AP-300) polarimeter (Atago, Tokyo, Japan). The HR ESI was recorded on a Q-TOF Ultima API instrument (Micromass, Waters, Milford, MA, USA) at the Biomedical Mass Spectrometry Facility (BMSF), UNSW, Sydney (Australia). The single crystal X-Ray data were recorded on a Bruker Kappa APEX 11 CCD diffractometer. The IR and UV/Vis spectra were recorded on a Prestige 21 FTIR spectrometer (Shimadzu, Tokyo, Japan) and a Thermo Spectronic UV-1700 spectrophotometer (Thermo, Waltham, MA, USA), respectively.

Representative procedure for the synthesis of 4a–c, 5a–b and 6a–g: A mixture of (S)-2-bromopropanoic acid (5 mmol, 2 eq), SOCl₂ (7.5 mmol, 2.5 eq) and catalytic amount of DMF (1 drop) was heated at 60 °C for 30 min. The resulting 2-haloacid chlorides 3a–d, without further purification, was slowly added dropwise to a stirred chilled solution of 5-cholo-3-methylanthranilic acid (1e) (2.5 mmol, 1 eq) and Et₃N (2.5 mmol, 1 eq) in DMF (2 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature. An excess of H₂O was added and extracted with EtOAc (3 × 15 mL). The combined
organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure till a brownish liquid was obtained. This crude product was subjected to column chromatography on silica gel that afforded 5 (200 mg, 32%) and/or 4 (390 mg, 66%), both as white solids, by elution with 2% and 5% EtOAc in n-hexane.

(3R)-7,9-Dibromo-3-methyl-4,1-benzoxazepine-2,5-dione (4a): Rf: 0.75 (EtOAc/n-hexane 3:7); [α]ᵣ⁰ = +12.0 (c 0.5, MeOH); MP: 165 °C; ¹H-NMR (300 MHz, CD₂OD): δ (ppm) 2.60 (3H, d, J = 6.9 Hz, CH₃), 4.35 (1H, q, J = 6.9 Hz, H⁵), 7.70 (1H, d, J = 1.5 Hz, H⁶), 7.94 (1H, d, J = 1.8 Hz, H⁶); IR (KBr): νmax (cm⁻¹) 1697 (a broad signal of OC=O and NC=O); UV-Vis (MeOH): λₘₚₓ 304 nm (log ε = 3.21670 L cm⁻¹ M⁻¹); LR EIMS: m/z in amu (% abundance) 351, 349, 347 (6, 12, 6 in 1:2:1 ratio) [M]⁺, 279, 277 and 275 (39, 77 and 40 in 1:2:1 ratio) [M-C₆H₄O₂, A]⁺, 251, 249 and 247 (8, 17 and 9 in 1:2:1 ratio) [A-CO]⁺, ESI MS (m/z) for C₁₀H₇Br₂NO₃: 373.8649, 371.8669 and 369.8690 found for 373.8645 [M+4+Na], 371.8665 [M+2+Na] and 369.8686 [M+Na] in 1:2:1.

(3R)-3,9-Dimethyl-4,1-benzoxazepine-2,5-dione (4b): Rf: 0.65 (EtOAc/n-hexane 3:7); [α]ᵣ⁰ = +80.0 (c 0.2, MeOH); MP: 190 °C; ¹H-NMR (300 MHz, CDCl₃): δ (ppm) 1.83 (3H, d, J = 6.9 Hz, CH₃), 2.27 (3H, s, Ar-CH₃), 4.55 (1H, q, J = 6.9 Hz, H⁵), 7.24 (1H, t, J = 7.5 Hz, H⁶), 7.49 (1H, d, J = 7.5 Hz, H⁶), 7.90 (1H, d, J = 7.8 Hz, H⁸), 9.56 (1H, s, NH); ¹³C-NMR (75 MHz, CDCl₃): δ (ppm) 18.8 (Ar-CH₃), 22.8 (C⁵), 55.9 (C³), 126.2 (C⁶), 126.3 (C⁷), 129.3 (C⁸), 129.4 (C⁵a), 136.5 (C⁶), 136.6 (C⁷a), 168.0, 170.6 (C² and C⁵); IR (KBr): νmax (cm⁻¹) 1697 (a broad signal of OC=O and NC=O); UV-Vis (MeOH): λₘₚₓ 294 nm (log ε = 3.32135 L cm⁻¹ M⁻¹); LR EIMS: m/z in amu (% abundance) 205 (72) [M]⁺, 133 (100) [M-C₆H₄O₂, A]⁺, 105 (100) [A-CO]⁺, ESI MS (m/z) for C₁₁H₁₁NO₃: 228.0636 found for 228.0631 [M+Na].

(3R)-7-Chloro-3,9-dimethyl-4,1-benzoxazepine-2,5-dione (4c): Rf: 0.61 (EtOAc/n-hexane 3:7); [α]ᵣ⁰ = +67.9 (c 0.2, EtOAc); MP: 187 °C; ¹H-NMR (300 MHz, CD₂OD): δ (ppm) 1.73 (3H, d, J = 6.9 Hz, H³), 2.26 (3H, s, Ar-CH₃), 4.67 (1H, q, J = 6.9 Hz, H⁵), 7.50 (1H, broad s, H⁶), 7.76 (1H, d, J = 2.4 Hz, H⁶); ¹³C-NMR (75 MHz, CD₂OD): δ (ppm) 18.2 (Ar-CH₃), 22.1 (C⁵), 55.7 (C³), 129.4 (C⁸), 129.8 (C⁵a), 135.0 (C⁶), 135.6 (C⁷), 168.0, 170.6 (C² and C⁵); IR (KBr): νmax (cm⁻¹) 3362 (N-H), 1693 (a broad signal of OC=O and NC=O); UV-Vis (MeOH): λₘₚₓ 306 nm (log ε = 3.25701 L cm⁻¹ M⁻¹); LR EIMS: m/z in amu (% abundance) 241, 239 (13, 37 in 1:3 ratio) [M]⁺, 169, 167 (29, 100 in 1:3 ratio) [M-(3-methylxirane-2-one), A]⁺, 141, 139 (31, 90 in 1:3 ratio) [A-CO]⁺; ESI MS (m/z) for C₁₁H₁₁NO₃: 261.0246 found for 261.0247 [M+Na] in 1:3 ratio.

(1'R)-6-Chloro-2-(1'-chloroethyl)-8-methyl-3,1-benzoxazine-4-one (5a): Rf: 0.87 (EtOAc/n-hexane 3:7); [α]ᵣ⁰ = -19.0 (c 0.3, EtOAc); MP: 129 °C; ¹H-NMR (300 MHz, CDCl₃): δ (ppm) 2.04 (3H, d, J = 6.9 Hz, H³), 2.53 (3H, s, Ar-CH₃), 4.82 (1H, q, J = 6.9 Hz, H⁵), 7.61 (1H, broad s, H²), 8.00 (1H, broad s, H⁸), IR (KBr): νmax (cm⁻¹) 1764 (lactonic OC=O), 1528 (C=N); UV-Vis (MeOH): λₘₚₓ 326 nm (log ε = 3.96534 L cm⁻¹ M⁻¹); LR EIMS: m/z in amu (% abundance) 261, 259 and 257 (2.5, 16 and 24 in 1:6:9 ratio) [M with 2 Cl]⁺, 224, 222 (22, 63 in 1:3 ratio) [M-Cl]⁺, 196, 194 (31, 100 in 1:3 ratio) [M-CHCl(C=O-Cl)]⁺, ESI MS (m/z) for C₁₃H₁₂Cl₂NO₂: 283.9846, 281.9878 and 279.9908 found for 283.9846 [M+4+Na], 281.9875 [M+2+Na] and 279.9905 [M+Na] in 1:6:9 ratio.
(1'S)-2-(1'-Bromoethyl)-6-chloro-8-methyl-3,1-benzoxazine-4-one (5b): Rf: 0.87 (EtOAc/n-hexane 3:7); [α]23° = −19.0 (c 0.3, EtOAc); MP: 129 °C; 1H-NMR (300 MHz, CDCl3): δ (ppm) 1.95 (3H, d, J = 6.6 Hz, H2'), 2.24 (3H, s, Ar-CH3), 4.51 (1H, q, J = 6.9 Hz, H1'), 7.45 (1H, broad s, H 7), 7.86 (1H, broad s, H5), IR (KBr): vmax (cm−1) 1761 (lactonic OC=O), 1528 (C=N); UV-Vis (MeOH): λmax 326 nm (log ε = 3.96534 L cm−1 M−1); LR EIMS: m/z in amu (% abundance) 305, 303 and 301 (2:9:6 ratio) [M with Br and Cl]+, 224, 222 (63, 1:3) [M-•Br]+, 196, 194 (100, 1:3 ratio) [M-H3CC•(H)Br]+; ESI MS (m/z) for C11H9BrClNO2: 327.9352, 325.9373 and 323.9402 found for 327.9350 [M+4+Na], 325.9370 [M+2+Na] and 323.9400 [M+Na] in 2:9:6 ratio.

(2'R)-4-Chloro-2-(2'-chloropropanamido)benzoic acid (6a): The product (0.39 g, 67%) was precipitated out when reaction mixture was poured into ice chilled H2O. Rf: 0.56 (EtOAc/n-hexane 3:7); [α]30°D = +80.0 (c 0.5, EtOAc); MP: 187 °C; 1H-NMR (400 MHz, CDCl3): δ (ppm) 1.82 (3H, d, J = 7.2 Hz, H 3'), 4.54 (1H, q, J = 7.2 Hz, H 2'), 7.15 (1H, dd, J = 8.4, 1.6 Hz, H 5), 8.07 (1H, d, J = 8.8 Hz, H 6), 8.82 (1H, d, J = 1.5 Hz, H3'), 11.7 (1H, s, NH); IR (KBr): vmax (cm−1) 1678 (OC=O), 1583 (NC=O); UV-Vis (MeOH): λmax 306 nm (log ε = 3.950121 L cm−1 M−1); LR EIMS: m/z in amu ( % abundance) 265, 263 and 261 (2, 11 and 21 in 1:6:9 ratio) [M] +•, 200, 198 (15, 45 in 1:3 ratio) [M-H3CC•(H)Cl, A]+, 182, 180 (45, 100) [A-H2O]+.

(2'S)-4-Chloro-2-(2'-chloro-3'-methylbutanamido)benzoic acid (6b): Rf: 0.45 (EtOAc/n-hexane 3:7), [α]30°D = +16.9 (c 0.6, MeOH); MP: 178 °C; 1H-NMR (300 MHz, CDCl3): 1.00 (3H, d, J = 6.3 Hz, CH3), 1.09 (3H, d, J = 6.6 Hz, H4'), 2.55 (1H, m, H3'), 4.35 (1H, d, J = 4.5 Hz, H2'), 7.13 (1H, dd, J = 8.7, 1.5 Hz, H5), 8.06 (1H, d, J = 8.6 Hz, H 3), 8.83 (1H, d, J = 1.5 Hz, H6), 11.78 (1H, s, NH); IR (KBr): vmax (cm−1) 3500 (O-H), 3383 (N-H), 1666 (OC=O) , 1595 (NC=O); UV-Vis (MeOH): λmax 336 nm (log ε = 3.01872 L cm−1 M−1). ESI MS (m/z) for C12H13Cl2NO3: 316.0111, 314.0140 and 312.0170 found for 316.0108 [M+4+Na], 314.0136 [M+2+Na] and 312.0167 [M+Na] in 1:6:9 ratio.

(2'S)-5-Bromo-2-(2'-chloro-3'-phenylpropanamido)benzoic acid (6c): Rf: 0.14 (EtOAc/n-hexane 3:7), [α]30°D = +17.0 (c 1.0, MeOH); MP: 110 °C; 1H-NMR (500 MHz, CD3OD): 3.21 (1H, dd, J = −14.0, 8.0 Hz, Hα 3'), 3.43 (1H, dd, J = −14.0, 8.0 Hz, Hβ 3'), 4.69 (1H, dd, J = 8.0, 6.0 Hz, H 2'), 7.17-7.24 (5H, m, Ph), 7.63 (1H, dd, J = 9.0, 2.5 Hz, H 4), 8.11 (1H, d, J = 2.5 Hz, H 6), 8.48 (1H, d, J = 9.0, H 3); 13C-NMR (125 MHz, CD3OD) δ (ppm): 42.46 (C 3'), 62.29 (C 2'), 116.76 (C 1''), 119.97 (C 1), 123.08 (C4''), 128.18 (C3'), 129.45, 130.54 (C3'' and C 2''), 134.92 (C 4), 137.47 (C 5), 137.71 (C 6), 140.58 (C 2), 169.23 (NC=O), 169.57 (OC=O); IR (KBr): vmax (cm−1) 3028 (O-H), 2916 (N-H), 1709 (OC=O), 1531 (NC=O); UV-Vis (MeOH): λmax 317 nm (log ε = 3.56741 L cm−1 M−1); LR EIMS: m/z in amu (% abundance) 385, 383, 381 (1, 5, 3 in 2:9:6 ratio) [M]+, 226, 224 (16, 15 in 1:1 ratio) [M-CH2(Cl)Bn and H2O, A]+, 217, 215 (53, 52 in 1:1) [M-CH2(Cl)Bn and CO]+, 198, 196 (56, 56) [A-CO]+.

(2'S)-5-Bromo-2-(2'-chloro-3'-methylbutanamido)benzoic acid (6d): Rf: 0.45 (EtOAc/n-hexane 3:7), [α]30°D = +32.0 (c 1.0, MeOH); MP: 178 °C; 1H-NMR (300 MHz, CDCl3): 1.00 (3H, d, J = 6.3 Hz, CH3), 1.09 (3H, d, J = 6.6 Hz, H4'), 2.55 (1H, m, H3'), 4.35 (1H, d, J = 4.5 Hz, H2'), 7.13 (1H, dd, J = 8.7, 1.5 Hz, H 5), 8.06 (1H, d, J = 8.6 Hz, H 3), 8.83 (1H, d, J = 1.5 Hz, H6), 11.78 (1H, s, NH); IR (KBr): vmax (cm−1) 3500 (O-H), 3383 (N-H), 1666 (OC=O), 1595 (NC=O); UV-Vis (MeOH): λmax 336 nm (log ε = 3.950121 L cm−1 M−1).
(2'S)-4-Chloro-2-(2'-chloro-3'-methylenexanamido)benzoic acid (6e): Rf: 0.15 (EtOAc/n-hexane 3:7); [α]25D = +16.2 (c 1.0, MeOH); MP: 126 °C; 1H-NMR (600 MHz, CD3OD): 0.96 (3H, d, J = 6.6 Hz, CH3), 0.98 (3H, d, J = 6.6 Hz, H3'), 1.85–1.98 (3H, m, H3 and H4'), 4.51 (1H, dd, J = 9.6, 4.8 Hz, H2'), 7.18 (1H, dd, J = 8.4, 1.8 Hz, H5'), 8.06 (1H, d, J = 8.4 Hz, H6'), 8.69 (1H, d, J = 1.8, H3'); 13C-NMR (125 MHz, CD3OD) δ (ppm): 21.56 (Me), 23.06 (C5'), 26.52 (C4'), 45.44 (C3'), 60.48 (C2'), 116.42 (C1), 120.97 (C5), 124.53 (C3), 133.99 (C6), 141.13 and 142.81 (C2 and C4), 170.39 (OC=O), 170.44 (NC=O); IR (KBr): ʋmax (cm⁻¹) 3221 (O-H), 3120 (N-H), 1640 (OC=O), 1550 (NC=O); UV-Vis (EtOAc): λmax 307 nm (log ε = 3.44321 L cm⁻¹ M⁻¹); LR EIMS: m/z in amu (% abundance) 307, 305 and 303 (0.1, 1.2 and 2.1 in 1:6:9 ratio) [M] +•, 251, 249 and 247 (6, 45 and 77 in 1:6:9 ratio) [M-C4H8, A] +•, 200, 198 (3, 7 in 1:3) [A-CH2Cl, B] +, 182, 180 (37, 80) [B-H2O, C] +, 173, 171 (29, 100) [B-CO]+, 155, 153 (17, 52) [C-CO]+.

(2'S)-5-Bromo-2-(2'-chloro-3'-methylpentanamido)benzoic acid (6g): Rf: 0.12 (EtOAc/n-hexane 3:7); [α]25D = +23.3 (c 0.2, MeOH); MP: 118 °C; 1H-NMR (500 MHz, CD3OD): 0.96 (3H, d, J = 6.5 Hz, CH3), 0.98 (3H, d, J = 6.0 Hz, H3'), 1.84–1.97 (3H, m, H3 and H4'), 4.51 (1H, dd, J = 9.0, 5.0 Hz, H2'), 7.69 (1H, dd, J = 9.0, 2.5 Hz, H4'), 8.17 (1H, d, J = 2.5 Hz, H3'), 8.53 (1H, d, J = 9.0, H6'); 13C-NMR (125 MHz, CD3OD) δ (ppm): 21.59, 23.06 (CH3 and C5'), 25.53 (C4'), 45.49 (C3'), 60.53 (C2'), 116.75 (C1), 119.97 (C5), 123.20 (C6), 135.02 (C7), 137.87 (C6'), 140.89 (C2), 169.76 (NC=O), 170.26 (OC=O); IR (KBr): ʋmax (cm⁻¹) 3259 (O-H), 3044 (N-H), 1685 (OC=O), 1531 (NC=O); UV-Vis (MeOH): λmax 310 nm (log ε = 3.09876 L cm⁻¹ M⁻¹); LR EIMS: m/z in amu (% abundance) 304, 302 (9, 31 in 1:3 ratio) [M-Cl]+, 182, 180 (25, 8) [M-CH2(Cl)Bn and H2O, A]+.

(3R)-8-Chloro-3-methyl-4,1-benzoxazepine-2,5-dione (4d): A mixture of 6a (1 mmol, 1 eq) and anhydrous K2CO3 (1.5 mmol, 1.5 eq) in DMF (1 mL) was heated at 80 °C for 3 h. Excess of chilled H2O was added, the mixture was neutralized with dilute HCl (5 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layer was dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to afford the crude product. It was purified by column chromatography using 5% EtOAc in n-hexane as mobile phase to afford pure 4d. Rf: 0.57 (EtOAc/n-hexane 3:7); [α]20D = +54.0 (c 0.2, MeOH); MP: 134 °C; 1H-NMR (400 MHz, CDCl3): δ (ppm) 1.61 (3H, d,
$J = 6.8\text{ Hz, } H^1$, 4.79 (1H, $q, J = 4.8\text{ Hz, } H^2$), 7.00 (1H, $d, J = 1.6\text{ Hz, } H^3$), 7.26 (1H, dd, $J = 8.4$, 1.6 Hz, $H^7$), 7.92 (1H, $d, J = 8.4\text{ Hz, } H^6$), 7.94 (1H, s NH); IR (KBr): $\nu_{\text{max}} (\text{cm}^{-1})$ 3262 (N-H), 1707 (a broad signal of OC=O and NC=O); UV-Vis (MeOH): $\lambda_{\text{max}} 302\text{ nm}$ ($\log\epsilon = 3.98631\text{ L cm}^{-1}\text{ M}^{-1}$); LR EIMS: $m/z$ in amu (% abundance) 227 and 225 (10 and 30 in 1:3) $[M]^+$, 155 and 153 (30 and 100 in 1:3 ratio) $[M-(3\text{-methyl} \text{oxirane-2-one})]^+$, 183 and 181 (3 and 10 in 1:3 ratio) $[M-\text{CO}]^+$.  

4. Conclusions

This strategy leads towards the one-pot synthesis of novel (3R)-4,1-benzoxazepines-2,5-diones exploiting the chiral pool methodology. The use of (S)-2-bromopropanoic acid results in the formation of (3R)-4,1-benzoxazepines-2,5-diones with chances of racemization due to transhalogenation; on the other hand the use of (S)-2-chloroacids affords (S)-N-acylanthranilic acids exclusively although another base mediated step is mandatory to achieve the same product but with high ee [12]. Thus, the use of (S)-2-chloroacids for such coupling reactions is recommended to achieve high ee for the synthesis of (3R)-4,1-benzoxazepines-2,5-diones. In future, these (3R)-4,1-benzoxazepines-2,5-diones shall be available for various biological applications, a few of which are currently under examination.

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Conflicts of Interest

The authors declare no conflict of interest.

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14. Crystallographic data in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. 946961 and 946962 for 4a and 4c respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk). The X-ray structure was obtained by Prof. Dr. Muhammad Nawaz Tahir, Department of Physics, University of Sargodha, Sargodha, Pakistan.

Sample Availability: Samples of the compounds 4a–d, 5 and 6a–g are available from the authors.

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