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First Total Synthesis of (Z)-11-(2-oxopropylidene)-2,3,11,11a-tetrahydro-1H-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5(10H)-one

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First Total Synthesis of (*Z*)-11-(2-oxopropylidene)-2,3,11,11a-tetrahydro-1*H*-benzo[e]pyrrolo[1,2-*a*][1,4]diazepin-5(10*H*)-one

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Abstract: The first total synthesis of naturally occurring (Z)-11-(2-oxopropylidene)-2,3,11,11*a*-tetrahydro-1*H*-benzo[e]pyrrolo[1,2-*a*][1,4]diazepin-5(10*H*)-one, a unique cycloanthranilylproline derivative, has been achieved from readily available anthranilic acid in five steps.

Keywords: Aza Wittig, benzodiazepines, cyclization, cycloanthranilylproline, α-diazoketone

INTRODUCTION

Benzodiazepine derivatives are privileged scaffolds in medicinal chemistry,[1] prompting the development of combinatorial methods for the synthesis of 1,4-benzodiazepin-2-ones,[2] 1,4-benzodiazepine-2,5-diones,[3] and related heterocycles.[4,5] A number of benzodiazepines are known to be potential biologically active compounds, such as the pyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11(10*H*)-dione moiety, which has been reported to have antitumor,[6] antiphase, analgesic antagonist, anti-inflammatory,[7] psychomotor depressant,[8] and anxiolytic activity.[9] The benzodiazepine is the core structure of various biologically important molecules. The

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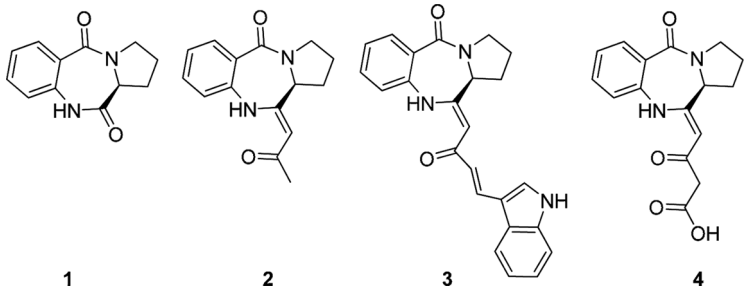


Scheme 1. Cycloanthranilylproline and its derivatives.

biological activities of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11(10*H*)-dione derivatives have attracted considerable interest in their total synthesis and motivated us to explore this work further to synthesize different naturally occurring cycloanthranilylproline derivatives.

Cycloanthranilylproline (**1**) and its derivatives (**2–4**) were isolated from field-collected fruit bodies of a myxomycete *Fuligo candida*, and their chemical structures are depicted in Scheme 1.[10]

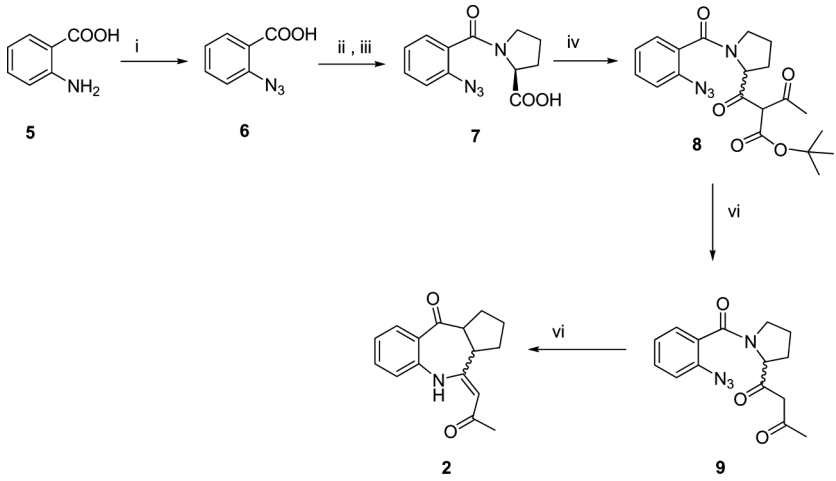
In connection with our ongoing interest in the total synthesis of benzodiazepine natural products, here we report the total synthesis of **2**. To the best of our knowledge, this is the first report of total synthesis of (*Z*)-11-(2-oxopropylidene)-2,3,11,11*a*-tetrahydro-1*H*-benzo[*e*]pyrrolo [1,2-a][1,4]diazepin-5-(10*H*)-one. We report here a potentially significant route to 11-alkenyl substituted cycloanthranilylproline, which is not only concise but also experimentally simple.

RESULTS AND DISCUSSION

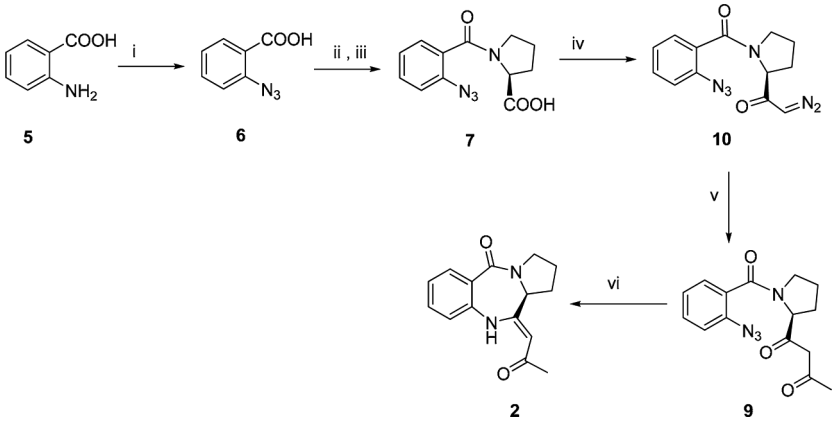
In the first instance, anthranilic acid **5** was converted to 2-azido benzoic acid **6** by diazotization and coupling with sodium azide. 2-Azido benzoic acid **6** was subjected to reflux using thionyl chloride,[11] and the resulting acid chloride was coupled with L-proline to get N-[2-azido benzoyl] L-proline **7** in good yield.[12] This material was converted to acid chloride using thionyl chloride in toluene,[12] and the resulting acid chloride was subjected to condensation with t-butyl acetoacetate in the presence of magnesium chloride in dichloromethane medium to give *tert*-butyl derivative **8**, which on hydrolysis and decorboxylation in toluene at 80°C with para toluene sulfonic acid (*p*-TSA) gave 1-[2-(2-azidobenzoyl)cyclopentyl]-1,3-butanedione **9** in 69% yield. This 1,3-diketo compound **9** was cyclized by aza-Wittig method[13] by treatment with triphenyl phosphine in dichloromethane solvent, and the cyclization occurred selectively to

form the seven-membered rings, leading to the final product benzodiazepine **2**. During the conversion of compound **7** to compound **8**, the acid chloride racemized during coupling with t-butyl acetoacetate, probably because of ketene formation, and the compound **8** was obtained as a racemic mixture. This was confirmed by optical rotation as zero. Because the *tert*-butyl ester derivative **8** was obtained as a racemic compound, the target compound **2** was also obtained as a racemic mixture. The entire strategy is outlined in Scheme 2.

After achieving the total synthesis of **2** in racemic form, we changed our strategy to synthesize compound **2** in optically purity. To get compound **2** in optically pure form, the preparation of optically pure 1,3-diketone **9** intermediate was targeted. The preparation of compound **9** was again started from the same 2-azido benzoic acid **5** by converting it to compound **6** as in Scheme 2. The acid **6** was then converted to the respective α-diazo ketone **10** by treating it with ethyl chloroformate followed by reaction with diazomethane. This diazo ketone **10** was then condensed with acetaldehyde using the known methodology[14] in the presence of anhydrous stannous chloride ($SnCl_2$) to give optically pure 1,3-diketone **9** in 65% yield. The diketone was then cyclized by the aza-Wittig method as per Scheme 2 to give optically pure compound **2**. All the analytical information generated on compound **2** exactly matched



Scheme 2. Reagents and conditions: (i) $NaNO_2$, HCI, −10°C, CH_3COONa; (ii) $SOCl_2$, toluene, reflux; (iii) L-proline, TEA, rt; (iv) $SOCl_2$, toluene, *tert*-butyl acetoacetate, $MgCl_2$, DCM, Hunig's base; (v) toluene, *p*-TSA 80°C; and (vi) PPh_3, DCM, 0°C.



Scheme 3. Reagents and conditions: (i) $NaNO_2$, HCl, NaN_3, $-10°C$, CH_3COONa, $NaNO_2$; (ii) $SOCl_2$, toluene, reflux; (iii) L-proline, TEA, rt; (iv) ethyl chloroformate, TEA, CH_2N_2l; (v) CH_3CHO, $SnCl_2$, DCM: rt; and (vi) PPh_3, DCM, $0°C$.

that previously reported during the isolation of **2** from a natural source.[10] The compounds **7**, **8**, **9**, and **10** were obtained as mixtures of *syn* and *anti* rotamers.[15]

To the best of our knowledge, this cyclization of diketo compound **9** to selective seven-membered ring formation using triphenyl phosphine was a novel methodology resulting in 11-alkenyl substituted benzodiazepines.

The new strategy of total synthesis is outlined in Scheme 3.

CONCLUSION

In summary, we have achieved the total synthesis of pharmaceutically important natural product (*Z*)-11-(2-oxopropylidene)-2,3,11,11a-tetrahydro-1*H*-benzo[e]pyrrolo[1,2-*a*][1,4]diazepin-5(10*H*)-one 2 in racemic as well as in optically pure form. As part of our continuous research in this area, we are on the way to total synthesis of other important cycloanthranilylproline derivatives (**3** and **4**), which will be communicated in due course.

EXPERIMENTAL

General Methods

^1H NMR spectra were determined in $CDCl_3$ and dimethyl sulfoxide (DMSO-d_6) solution on Varian Gemini 200-MHz spectrometers. Proton

chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and are expressed in parts per million (ppm). Spin multiplicities are given as *s* (singlet), *d* (doublet), *t* (triplet), and *m* (multiplet). Coupling constants (*J*) are given in hertz. Melting points were determined using scientific capillary melting-point apparatus and are uncorrected. Mass spectra were obtained on an HP-5989A mass spectrometer. Thin-layer chromatography (TLC) was performed on silica-gel plates (SRL 230–400 mesh). All the solvents used were commercially available and were distilled before use.

2-Azido Benzoic Acid (6)

A solution of anthranilic acid **5** (25.0 g, 0.182 mol) in 6 N aqueous hydrochloric acid (625 ml) was cooled to -5 to -10°C and added dropwise to a solution of sodium nitrite (13.3 g, 0.193 mol) in water (200 ml) white maintaining the temperature at about -10°C. The clear wine-red solution thus obtained was stirred at 0–5°C for 1–2 h and added dropwise to a precooled solution of sodium acetate trihydrate (760 g, 5.58 mol) and sodium azide (12.5 g, 0.193 mol) in water (1100 ml) at 0–5°C. The reaction mixture was stirred for 2–3 h at 0–5°C and left to stir overnight at room temperature. The white precipitate was filtered, washed with water, and dried in vacuo over phosphorous pentoxide, resulting in 27.38 g (92% yield) of 2-azidobenzoic acid, which was identified by spectral means and used without further purification. MS (ES): 344 ($2M + 1$), 181 ($M + NH_4$), IR ν_{max} (KBr) cm^{-1}: 3200–2275, 2105.6, 1693.8, 1268.0; ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.2–7.4 (m, 2H), 7.5–7.7 (t, 1H, $J = 8$ Hz), 8–8.2 (d, 1H), $J = 9$ Hz).

(2*S*)-1-(2-Azido-benzoyl)-pyrrolidine-2-carboxylic Acid (7)

2-Azidobenzoyl chloride was prepared by heating a solution of 2-azidobenzoic acid **6** (15.0 g, 0.0917 mol) in thionyl chloride (75.0 ml, 1.03 mol) for 3 h under a nitrogen atmosphere. The excess thionyl chloride was evaporated under reduced pressure. Dry toluene (2×20 ml) was added to the residue and evaporated. The crude o-azidobenzoyl chloride was then used without further purification in the next condensation stage.

A solution of *o*-azidoaroyl chloride (16.7 g, 0.92 mmol) in dry THF (140 ml) was added dropwise over a period of 30 min to a solution of L-proline (13.8 g, 0.12 mol) and triethyl amine (22.34 g, 0.22 mol) in water (140 ml) cooled to 0°C. The reaction mixture was then stirred at room temperature for 2 h, and then the organic solvent was removed under

vacuum. The resultant aqueous solution was acidified until pH = 1 by the addition of concentrated hydrochloric acid solution, and the solid formed was separated by filtration and crystallized from ethyl acetate to give (2*S*)-1-(2-azido-benzoyl)-pyrrolidine-2-carboxylic acid **7** as an off-white powder in 85% yield (20.3 g), a mixture of *syn* and *anti* rotamers (9:2), with mp 160–163°C.

IR ν_{max} (KBr) cm^{-1}: 3450–2630, 2130, 1744, 1590, 1573, 1494, 1456, 1434, 1283, 1227, 862, 775, 762; MS (ES): 521.2 (2M + 1), 261 (M + 1); ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.8–2.4 (m, 7H), 3.28–3.44 (t, 1.69H, $J = 7$), 3.72–3.86 (t, 0.31H, $J = 7$), 4.17–4.26 (dd, 0.18H, $J = 8.3$, $J = 2.7$ Hz), 4.72–4.82 (dd, 0.82H, $J = 8.2$, $J = 3.9$), 7.1–7.27 (m, 2H), 7.35 (dd, 1H, $J = 7.8$, $J = 2$), 7.45 (dt 1H, $J = 7.6$, $J = 1.6$), SOR [c = 1, methanol] at 24°C: 94.716.

1-[(2*S*)-1-(2-Azido-benzoyl)-pyrrolidine-2-yl]-2-diazo-ethanone (10)

The solution of potassium hydroxide (KOH; 2.32 g, 0.0414 mol) in anhydrous ethanol (50 ml) was added to the round-bottom flask containing the precooled (0–5°C) solution of N-methyl-N-nitroso-4-toluenesulfonamide (12.45 g, 0.0582 mol) in diethyl ether (225 ml) attached to the distillation apparatus. The contents were stirred at 0–5°C for 5–10 min and then placed into a 60°C oil bath. The yellow color distillate containing diazo methane was collected, and the distillation was stopped when the distillate no longer contained the yellow color of diazomethane (approximately 80 ml). In another round-bottom flask under nitrogen atmosphere, ethyl chloroformate (2.29 g, 0.0212 mol) was added to a solution of 1-(2*S*)-1-(2-azido benzoyl)-L-proline (5.0 g, 0.0192 mol) and triethyl amine (2.14 g, 0.0212 mol) in tetrahydrofuran THF, (70 ml) at −20°C. The reaction mixture was stirred at −20°C for 30 min. Then the diazomethane solution (0.0211 mol) was added to the reaction mixture at −20°C. The reaction mixture was stirred for 1 h at −20°C and then stirred for 4–6 h at 0–5°C. The reaction progress was monitored on thin-layer chromatography (TLC). The reaction was degassed for about 1 h with nitrogen. Solvents were evaporated, and the residue was dissolved in dichloromethane. The dichloromethane solution was washed with saturated solution of $NaHCO_3$ and water. The organic phase was dried with anhydrous Na_2SO_4 and evaporated, yielding 5.18 g (95%) of 1-[(2*S*)-1-(2-azido-benzoyl)-pyrrolidine-2-yl]-2-diazo-ethanone **10** as a pale brown oil, a mixture of *syn* and *anti* rotamers (5.2:1).

IR ν_{max} ($CHCl_3$) cm^{-1}: 3670–3200, 3105, 3015, 2883, 2437, 2128, 2110, 1724, 1637, 1630, 1491, 1450, 1419, 1363, 1293, 2126, 1146, 1093, 754, 681, 666, MS (ES): 586.4 ($2M + NH_4$) = 569.2; (2M +1), 285.3

(M + 1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.8–2.3 (m, 4H), 3.2–3.5 (m, 0.1.68H), 3.7–3.9 (t, 0.32H), 4.1–4.2 (bd, 0.16H, $J = 3.4$), 4.6–4.7 (dd, 0.84H, $J = 3.7$, $J = 2.5$), 5.2 (bs, 0.17H), 5.9 (bs, 0.83H), 7.2–7.5 (m, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz): 22.4 & 24.33, 29.15 & 31.23, 46.31 & 48.46, 53.102 & 53.329, 63.08 & 64.79, 118.11 & 118.26, 124.74 & 125.01, 127.78 & 128.16, 128.38 & 128.48, 130.45 & 130.55, 135.87, 161, 193.28 & 193.61. SOR [c = 2.9, in $CHCl_3$] at 22.7°C: 153.43.

4-[(2*S*)-1-(2-Azido-benzoyl)-pyrrolidine-2-yl]-4-hdroxy-but-3-en-2-one (9)

Anhydrous stannous chloride ($SnCl_2$) (1.52 g, 0.0081 mol) was added to a mixture containing the diazo ketone (2.2 g, 0.0073 mol) in methylene chloride (10 ml) with stirring at room temperature. Acetaldehyde (0.4 g, 0.009 mol) in methylene chloride (4 ml) was added to this suspension. After 2–3 h, the reaction progress was monitored with TLC, and anhydrous stannous chloride was added if the reaction was incomplete. After nitrogen evolution had stopped, the reaction was transferred to a separatory funnel, washed with water, and dried over sodium sulfate. Removal of the solvent left a residue, which was column chromatographed on silica gel using ethyl acetate–hexane. The yield was 1.52 g (65%) of **9** as a mixture of *syn* and *anti* rotamers (2:1). The diketone was found to be unstable and was used immediately for the cyclization. However, the reasonably pure compound was isolated by preparative TLC for spectroscopic analysis.

IR ν_{max} ($CHCl_3$) cm^{-1}: 1491, 1450, 1419, 1363, 1293, 2126, 1146, 1093, 754, 681, 666; MS (ES): 601.4 (2M + 1), 301.2 (M + 1); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.8–2.3 (7H), 3.2–3.5 (m, 1.35, H), 3.7–3.9 (m, 0.65), 4.1–4.2 (dd, $J = 8.2$, $J = 2.4$), 4.6–4.7 (m, 0.68H), 5.2 (s, 0.35H), 5.84 (s, 0.65H), 7.0 to 7.6 (m, 4H); ^{13}C NMR ($CDCl_3$, 200 MHz): 24.49 & 24.9, 29.6 & 29.9, 31.6 & 31.8, 48.67 & 48.77, 61.66 & 63.35, 97.18 & 97.47, 118.48, 124.87 & 125.16, 128.1 & 128.28, 130.54 & 130.6, 130.82, 136.19, 167.01, 188.9 & 190.34, 193.5 & 194.7; SOR [c = 3, in $CHCl_3$] at 22.7°C: 123.75.

(*Z*)-11-(2-Oxopropylidene)-2,3,11,11a-tetrahydro-1*H*-benzo[e]pyrrolo-[1,2-*a*][1,4]diazepin-5(10*H*)-one (2)

A solution of the diketone (0.347 g, 0.00116 mol) in drydichloromethane (20 ml) was added to a solution of triphenyl phosphine (0.318, 0.00121 mol) in the same solvent (20 ml) cooled to 0°C. The solution was stirred for 8 h at 0–5°C under nitrogen. The reaction progress was

monitored with TLC. The solvent was removed under reduced pressure, and the residue was purified by column chromatography using ethyl acetate/hexane (1:3) to give 0.238 g (81%) of (*Z*)-11-(2-oxopropylidene)-2,3,11,11a-tetrahydro-1*H*-benzo[e]pyrrolo[1,2-*a*] [1,4]diazepin-5(10*H*)-one as a white solid. The product was further purified by crystallization from toluene/hexane, and analytical results were compared with the literature report of compound **2**.

IR ν_{max} (KBr) cm^{-1}: 3005, 2980, 1635 613, 1592, 1562, 1483, 1454, 1357, 1278, 1261, 1250, 1164, 988, 811, 759, 696, 687; MS (ES): 513.4 (2M + 1), 257.1 (M + 1); HR-MS (M + H): 257.1279 (reported: 257.1289), calculated: 257.1279; HR-MS (M−H): 255.1129, calculated 255.1134; ^{13}C NMR: δ ($CDCl_3$, 200 MHz): 23.36, 26.97, 29.95, 46.79, 55.25, 91.06, 122.05, 124.28, 131.08, 132.36, 137.04, 158.76, 165.64, 198.29; SOR [c = 3, in $CHCl_3$] at 21.7°C: 729.736; mp: 142–144°C; UV: λ_{max} (MEOH): 338 nm.

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