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SYNTHESIS OF OPTICALLY ACTIVE TETRAHYDRO-3-BENZAZEPINE-2-CARBOXYLIC ACID DERIVATIVES *VIA* THE RING EXPANSION REACTION OF ISOQUINOLINES AND ENZYMATIC RESOLUTION

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Abstract – The facial approach to 3-benzazepine-2-carboxylic acid derivatives (**1**) *via* the ring expansion reactions of 10b-hydroxymethyloxazoloisoquinolines (**3**) to 3-benzazepines (**2**) is described. Utilizing enzymatic resolution, the synthesis of (-)-(*S*)-*N*-Cbz-3-benzazepine-2-carboxylic acid (**1b**) was achieved.

2,3,4,5-Tetrahydro-1*H*-3-benzazepine derivatives have been of interest in synthesis[1] due to their pharmacological activities,[2] such as dopaminometric or antidopaminergic agents[3] and the inhibitory effect[4] of reverse transcriptase. In our laboratory, the synthesis of isoindolobenzazepine alkaloids, such as lennoxamine and chilenine, utilizing the ring expansion reaction of isoindoloisoquinoline to isoindolobenzazepine has been reported.[5] We attempted to apply this strategy to the synthesis of 2,3,4,5-tetrahydro-1*H*-3-benzazepine derivatives. In this paper, the facial synthesis of benzazepine derivatives, especially 2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carboxylic acid (**1**)(R^1, R^2, R^3 = H),[6,7] which is the used as a replacement for phenylalanine in the peptide,[8] *via* the ring-expansion reaction of 10b-hydroxymethyloxazoloisoquinolines (**3**) is described (Figure 1).

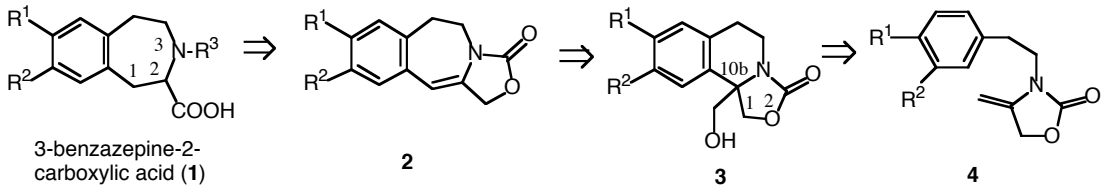
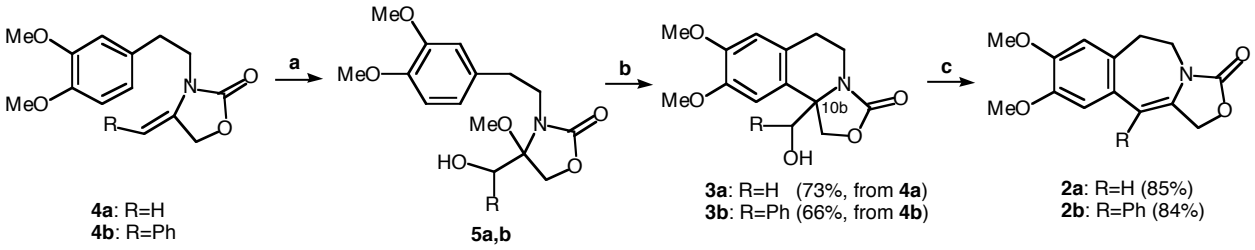


Figure 1

There are many reports involving the ring expansions of isoquinoline-rings to 3-benzazepine rings *via* azirizines.[9] In a similar method, the ring expansion of spirocyclic ammonium ylides for the synthesis of 3-benzazepines has been reported by Padwa *et al.*[10] In addition, ring expansions through the 1,2-aryl migrated reaction without the formation of azirizine have been reported.[9] However, only one such example of a ring expansion to form an acyliminium ion intermediate has been reported by ourselves.[5] At first, the synthesis of isoquinoline derivatives (**3**) as key compounds from alkylidenelactams (**4**)[11] *via* the acyliminium ion equivalents (**5**) was conducted according to our previous report.[12] The results are shown in Scheme 1.



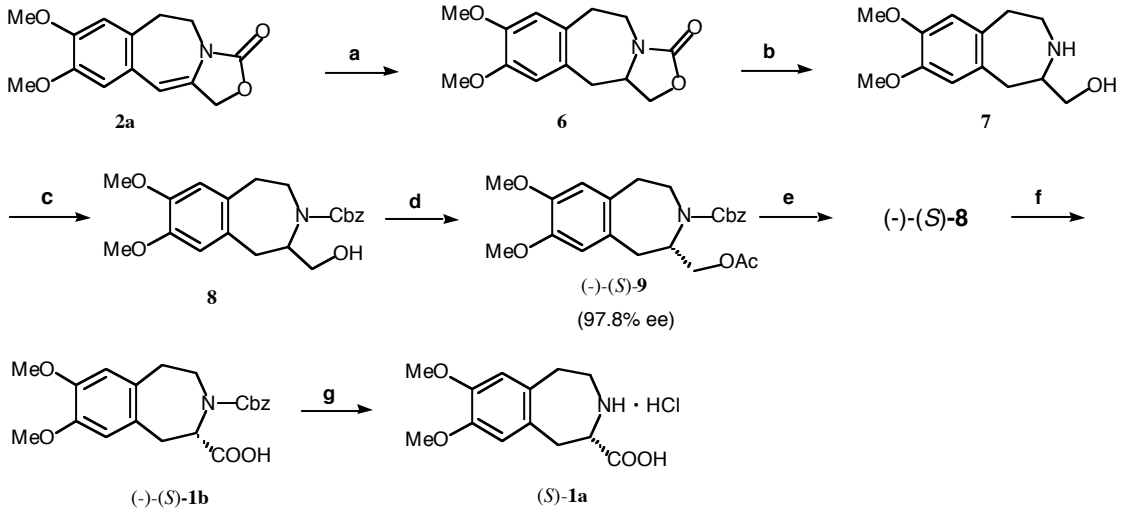
Scheme 1 *Reagents and conditions:* (a) MCPBA (1.2 equiv.), MeOH, -50 °C to rt; (b) $BF_3{\cdot}OEt_2$ (2.1 equiv.), CH_2Cl_2, -40 to 0 °C; (c) SO_2Cl_2 (3 equiv.), Et_3N (5 equiv.), $CHCl_3$/Py (4:1), -78 °C to rt.

The conversion of **4** into the acyliminium ion equivalent (**5**) through the oxidation[13] of the exocyclic enamide moiety with MCPBA was performed in quantitative yields, followed by cyclization[14] *via* an acyliminium ion in the presence of $BF_3{\cdot}OEt_2$ to afford **3**[15] in a satisfactory isolated yield. The obtained isoquinoline derivatives (**3**) in hand were then applied to the ring expansion[5] with SO_2Cl_2 in the presence of Et_3N and pyridine in order to construct the 3-benzazepine ring system. When the ring expansion of **3a** was conducted with 3 equiv. of SO_2Cl_2, the reaction proceeded smoothly to give the corresponding seven-membered ring compound (**2a**) in a good yield (85%).[16] Furthermore, the ring expansion of **3b** (R = Ph) possessing the secondary hydroxy group at the 10b-position of the oxazoloisoquinoline ring progressed to 1-phenyl-3-benzazepine (**2b**) in 84% yield. After this efficient synthesis of 3-benzazepines (**2**), compound (**2a**) was used for the synthesis of tetrahydrobenzazepine-2-carboxylic acid (Scheme 2).

We initially attempted to convert **2a** into **6** or **7**, however, neither the catalytic reduction of enamide (**2a**) to **6** nor the hydrolysis of the carbamate moiety of **2a** occurred. Then, the reduction of **2a** utilizing $BF_3{\cdot}2AcOH$–Et_3SiH system *via* an acyliminium ion intermediate was conducted to afford **6** in 94% yield. Saponification (10% KOH–MeOH) of **6** followed by protection of the amino moiety of **7** afforded **8** in 92% yield. Next, the asymmetric synthesis of **1** was attempted by enzyme-mediated chiral resolution utilizing lipase. To the best of our knowledge, there is no report for asymmetric synthesis of **1**. The lipase (Novozym 435®)-catalyzed acylation of alcohol (**8**) was performed with vinyl acetate as the acylating agent in THF at 20 °C. The *ca.* 50%-conversion was achieved within 30 min, and then the acylated

alcohol and the unreacted alcohol were separated by silica gel column to give (*S*)-(-)-**9** (97% ee) in 49% isolated yields.[17] However, in the gram-scales, their enantiomeric excess yields decreased to 92—94% ee. The low-temperature method[18] (at 0 °C for 45 min) in the gram-scale resolution of **8** succeeded in overcoming this disadvantage and the reproducible ee yields (96–97.8%) of (*S*)-**9** were obtained.

The removal of the acetyl group on (*S*)-**9** using 0.05N NaOH[19] gave (*S*)-**8** in a good isolated yield.[17] On the other hand, the conversion of **7** to **1a** by Jones oxidation was carried out, but the isolation of amino acid (**1a**) was unsuccessful. Then, the oxidation of (*S*)-**8** was carried out according to Zao's method[20] to afford (*S*)-**1b**[21] in 92% yield. The subsequent hydrogenolysis of the Cbz-group of (*S*)-**1b** proceeded smoothly to afford (*S*)-**1a** as a rigid analogue of L-(*S*)-phenylalanine.[22]



Scheme 2 *Reagents and conditions:* (a) Et_3SiH (5 equiv.), BF_3·2AcOH (1.2 equiv.), CH_2Cl_2, rt, 94%; (b) KOH (10 equiv.), MeOH, reflux; (c) CbzCl (1.3 equiv.), $NaHCO_3$ (1.3 equiv.), THF–H_2O (1:1), rt, 92% (from **6**); (d) Novozym 435®, CH_2=CHOAc, THF, 0 °C, 46 %; (e) 0.05N NaOH, MeOH, 0 °C, 94%; (f) $NaClO_2$ (2 equiv.), 5% NaClO (cat.), TEMPO (cat.), MeCN, pH 6.86 buffer, 35 °C, 92%; (g) 5% Pd–C (cat.), H_2 (1 atm), MeOH, rt, then, 4N HCl, AcOEt, 88%.

The absolute configuration of (*S*)-**9** was determined by single-crystal X-Ray diffraction analysis. Figure 2 shows the crystal structure of the salt (**10**) consisting of (*R*)-mandelic acid and amino alcohol ((*S*)-**7**) obtained by saponification of (-)-**9** (Figure 2).[23]

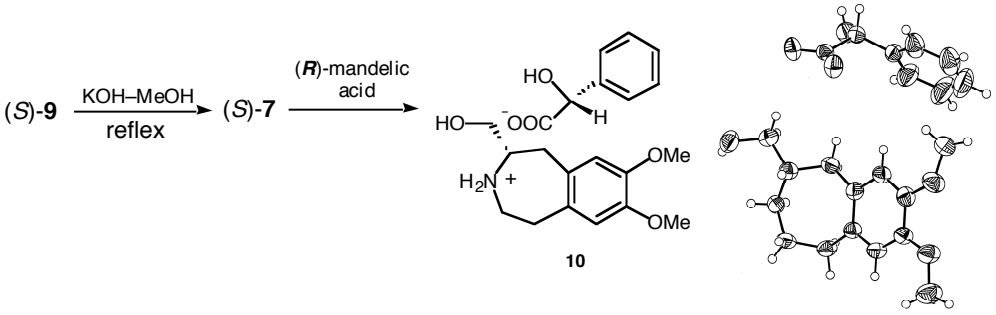


Figure 2 ORTEP drawing of salt (**10**)

In conclusion, the authors have established a new method for the synthesis of 3-benzazepine-2-carboxylic acid derivatives utilizing the ring-expansion of isoquinolines. Furthermore, the synthesis of (*S*)-**1b** was achieved. The investigations into their biological activities are now in progress.

ACKNOWLEDGEMENTS

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16. The general procedure for the ring expansion reaction of isoquinolines (**3**) (preparation of **2a**): To the solution of **3a** (12.5 g, 44.8 mmol) in a mixed solvent (dist. $CHCl_3$/pyridine = 120 mL/30 mL) was added Et_3N (31 mL, 224 mmol) and then, added dropwise SO_2Cl_2 (10.8 mL, 134 mmol) at –78 °C under Ar. The solution was allowed to warm to rt over 0.5 h followed by stirring overnight. The reaction mixture was quenched with sat. aq $NaHCO_3$, and the mixture was extracted with $CHCl_3$ followed by a conventional work-up. The residue was chromatographed (silica gel, hexane–AcOEt = 10:1) to give **2a** (9.9 g) in 85% yield.
17. The ee values of (*S*)-**9** and (*S*)-**8** were determined by HPLC on a CHIRALCEL OJ–H, (0.46 cm×25 cm, DAICEL CHEMICAL IND. LTD.), with hexane/EtOH (100:1 to 50:1 over 40 min) as eluent, respectively. **Compound (-)-(*S*)-9**: colorless oil; $[\alpha]_D^{24}$ -52.2° (c 1.01, $CHCl_3$) (97% ee); HRMS (EI) *m*/*z* calcd for $C_{23}H_{27}NO_6$ (M^+) 413.1838, found: 413.1820. **Compound (-)-(*S*)-8**: colorless crystals; mp 97-99 °C (from *t*-BuOMe); $[\alpha]_D^{22}$ -53.8° (c 1.01, $CHCl_3$) (98.5% ee); Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N; 3.77. Found: C, 67.79; H, 6.78; N, 3.70.
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21. **Compound (-)-(*S*)-1b**: White paste, $[\alpha]_D^{22}$ –29.5° (c 1.32, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80-3.40 (m, 5H) , 3.82-3.84 (each s, 3H×2, two rotamers), 4.25, 4.37 (each br d, *J* = 1.5 Hz, 1H, two rotamers), 5.05-5.30 (m, 2H+1H, two rotamers), 6.56, 6.61, 6.64, 6.68 (each s, 1H×2, two rotamers), 7.10-7.20 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ: 34.7, 35.2, 36.1, 41.9, 42.4, 55.7, 55.9, 57.1, 57.5, 67.5, 67.7, 112.8, 112.9, 114.1, 114.4, 127.2, 127.5, 127.7, 127.9, 128.0, 128.3, 128.4, 131.7, 136.2, 136.3, 146.8, 146.9, 147.5, 147.7, 155.8, 156.6, 175.6, 175.9; MS(ES) *m/z* 408 (MNa^+), 386 (MH^+); HRMS (ES) *m/z* calcd for $C_{21}H_{24}NO_6$ (MH^+) 386.1604, found 386.1601.
22. The analytical and spectral data of pure (*S*)-**1a** were not obtained because its insolubility in organic and aqueous solvents (e.g., $CHCl_3$, THF, MeOH, toluene, H_2O). To a suspension of the crude paste (**(*S*)-1a**) in AcOEt was added 4N HCl, and the solution was concentrated to give (*S*)-**1a**·HCl as a white solid. The spectral data for (*S*)-**1a**·HCl are as follows. ^{1}H NMR (400 MHz, D_2O) δ: 2.99 (m, 2H), 3.12 (m, 1H), 3.26 (m, 2H), 3.54 (m, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 4.06 (d, *J* = 8.2 Hz, 1H), 6.80 (s, 1H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 31.38, 34.69, 45.49, 56.52, 56.58, 58.52, 113.9, 114.8, 129.4, 132.6, 147.4, 147.8, 171.5.
23. Crystal data of **10**: $C_{24}H_{22}N_2O_7$, MW 389.448, T 297 K, monoclinic, space group $P2_1$: *a* = 6.678 (10) Å, *b* = 8.814 (5) Å, β = 93.217 (6)°, *c* = 17.248 (2) Å, *V* 1013.6 (2) Å^3, *Z* 2, D_{calc} 1.276 mg m^{-3}, θ range 2.60 to 27.18°, prism 0.09 x 0.22 x 0.2 mm, Mo Kα (Kα = 0.71073 Å), μ = 0.093 mm^{-1}, absorption correction: none, 2243 measured reflections, 2242 independent reflections (R_{int} = 0.024), 1896 observed reflections [$I>2\sigma(I)$], R(all) 0.0483, R(gt) 0.0384, wR(ref) 0.1012, wR(gt) 0.0953, S(ref) 1.044, refinement on F^2 (fullmatrix least squares refinement), 2242 reflections, 258 parameters, $\Delta\rho_{max}$ = 0.137eÅ^3, $\Delta\rho_{min}$ = -0.163eÅ^3, all diagrams and calculations were performed using maXus crystallographic software package,[24] the refinement was performed using SHELX-97.[25]
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