HETEROCYCLES, Vol. 98, No. 6, 2019, pp. 798 - 803. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 26th March, 2019, Accepted, 7th May, 2019, Published online, 28th May, 2019
DOI: 10.3987/COM-19-14077

TOTAL SYNTHESIS OF PROPOSED STRUCTURE OF AZEPINOBISINDOLE ALKALOID RHODOZEPINONE

Tomoki Itoh and Takumi Abe*

Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan. *E-mail; abe-t@hoku-iryo-u.ac.jp

Abstract – Total synthesis of the proposed structure of azepinobisindole alkaloid rhodozepinone has been accomplished from simple starting materials in 4 steps for the first time.

INTRODUCTION

Rhodozepinone (**1**) was isolated by Refaat and co-workers from the marine actinomycete *Rhodococcus* sp. UA13, a bacterium previously recovered from the Red Sea sponge *Callyspongia* aff. *implexa* in Sanai, Egypt (Figure 1).[1] Rhodozepinone (**1**) exhibits some interesting biological activities, such as both antitrypanosomal and antibacterial activities.

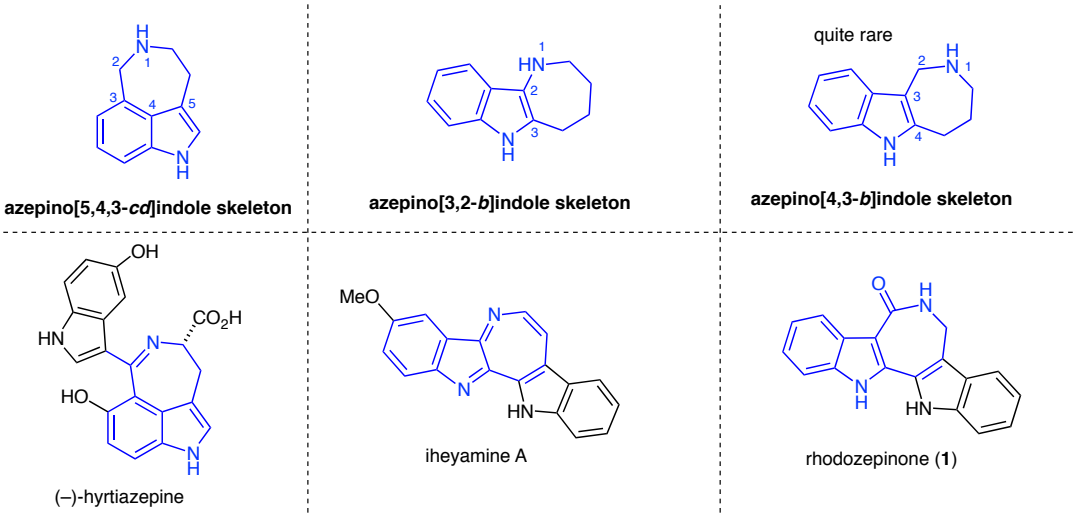


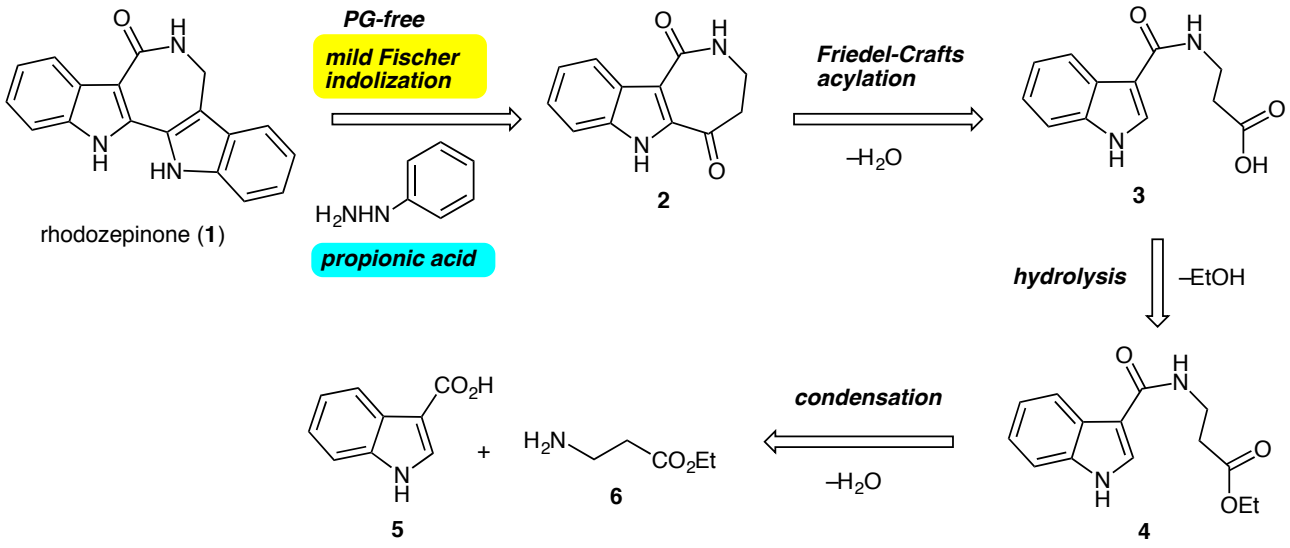
Figure 1. Rhodozepinone and related azepinobisindole alkaloids

Its azepino[4,3-*b*:5,6-*b*']diindole ring system, which is a indole-fused azepino[4,3-*b*]indole, is unprecedented among reported azepinoindole alkaloids, such as hyrtiazepine[2] and iheyamine A.[3] In addition to the interesting biological activities, azepinobisindole alkaloids possess rare structures that

would render **1** attractive target for total synthesis.[4] However, there is no report of either a total synthesis or a synthetic study. In 2017, Sperry and co-workers reported that related azepino[2,3-*b*]indole systems could not be tolerated under acidic conditions, resulting the isolation of a undesired compound.[3c] This pioneer work revealed that acid[3c] or oxidants[3e] mediated conditions prevent the construction of azepinobisindole skeleton due to their instability toward acid, which would prefer a formation of spirocyclic compound. Thus, the development of concise method for the construction of these azepinobisindoles still remains unexplored. Based on our ongoing research on the synthesis of azepinoindoles[5] and the above reactivity of azepinoindole,[2-4] we herein describe the first total synthesis of the proposed structure of rhodozepinone (**1**).

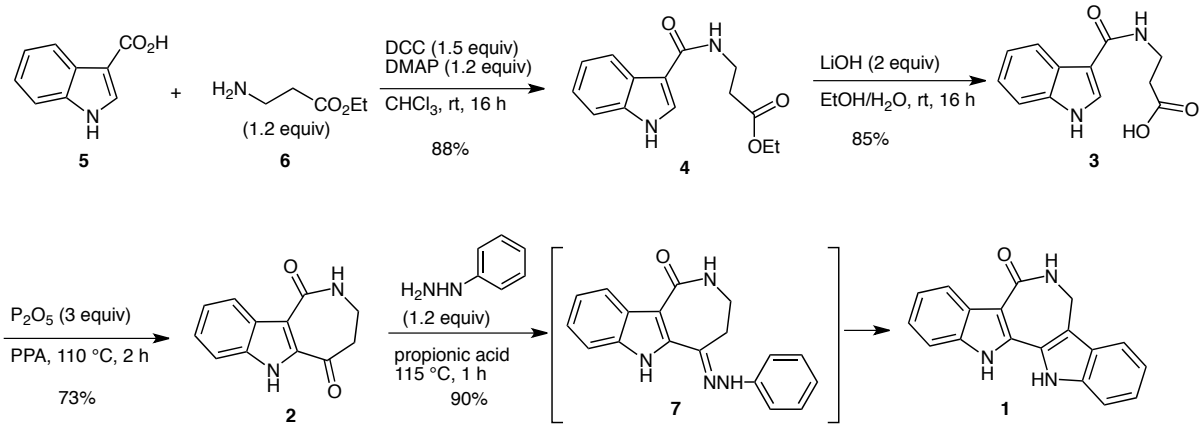
RESULTS AND DISCUSSION

Retrosynthesis of **1** was depicted in Scheme 1. We envisioned known ketone **2**[6] to be a precursor to access rhodozepinone (**1**). Ketone **2** can be obtained from carboxylic acid **3** through Friedel–Crafts acylation. Carboxylic acid **3** can be obtained from indole-3-carboxylic acid (**5**) and β-alanine ethyl ester (**6**), via condensation, and hydrolysis of ester **4**.



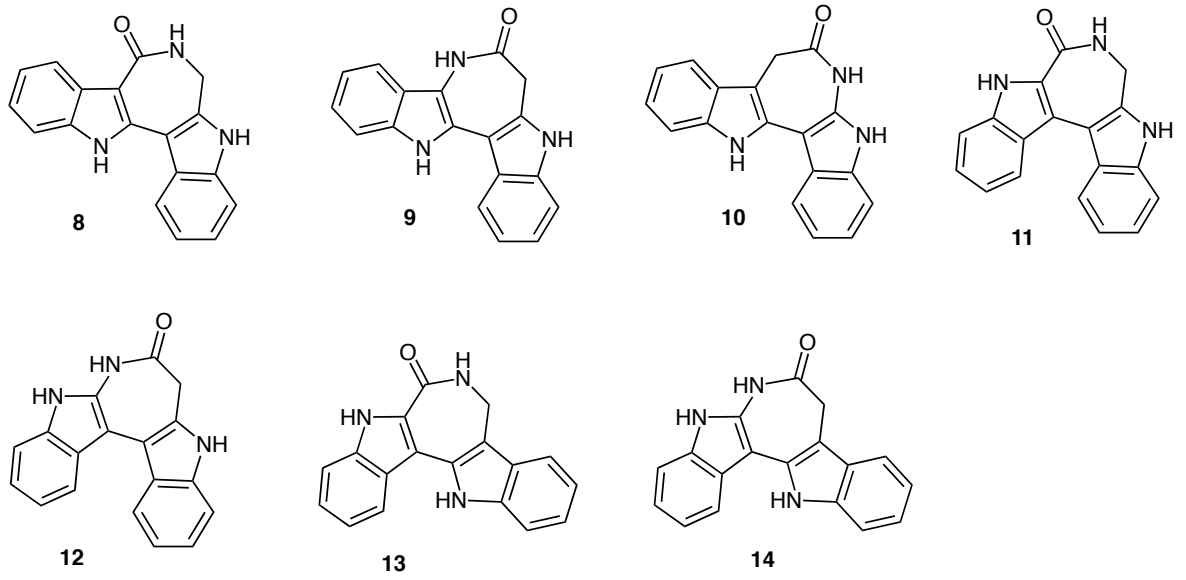
Scheme 1. Retrosynthesis of rhodozepinone (**1**)

Ester **4** was prepared from indole-3-carboxylic acid (**5**) and β-alanine ethyl ester (**6**) in 88% yield using modified Tepe's method.[6] The ester **4** was then transformed into carboxylic acid **3** by hydrolysis using LiOH. The carboxylic acid **3** was treated with P_2O_5 in PPA at 110 °C,[7] and the Friedel–Crafts acylation proceeded smoothly to afford desired ketone **2** in 73% yield.



Scheme 2. Synthesis of proposed structure of rhodozepinone (**1**)

With compound **2** in hand, we next set out to investigate the Fischer indolization of **2** and phenylhydrazine. Initially, **2** and phenylhydrazine were subjected to PPA cyclization.[7] Unfortunately, polymerized product was mainly produced under acidic conditions while neither the desired **1** nor hydrazone **7** could be obtained. The reason for the failure of the Fischer indolization is probably because of the strong acidity of the reaction media. We investigated an alternative procedure of Fischer indolization to produce **1**. When the reaction was performed with propionic acid instead of strong acids, the reaction was completed in 1 h and gave **1** in 90% yield. However, we found that the ^{1}H- and ^{13}C-NMR spectra for synthetic **1** were not identical to those reported for natural rhodozepinone.



Scheme 3. Possible isomers of rhodozepinone (**1**)

In conclusion, the first total synthesis of the proposed structure of rhodozepinone (**1**) has been accomplished from indole-3-carboxylic acid (**5**) and β-alanine ethyl ester (**6**) in 4 steps. Further investigations to synthesize possible real structures of rhodozepinone isomers (**8**-**14**) are currently underway (Scheme 3).[8]

EXPERIMETAL

Melting points were recorded with a Yamato MP21 and are uncorrected. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer and absorbance bands are reported in wavenumbers (cm^{-1}). The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer. Chemical shifts in ^{1}H- and ^{13}C-NMR are expressed in ppm (δ). All ^{13}C-NMR spectra were determined with complete proton decoupling. Column chromatography and Flash column chromatography were performed on silica gel (Silica Gel 60N, Kanto Chemical Co., Ltd.). High-resolution MS spectra were recorded with Micromass AutoSpec 3100 and JEOL JMS-T100LP mass spectrometers. All reagents were obtained from commercial suppliers and used without further purification.

Ethyl 3-(1*H*-indole-3-carboxamido)propanoate (4)[6]

To a solution of **5** (8.0 g, 50 mmol) in $CHCl_3$ (300 mL) was subsequently added **6**·HCl salt (9.2 g, 60 mmol), DMAP (7.3 g, 60 mmol), and DCC (15.5 g, 75 mmol) at 0 °C. After stirring at rt for 16 h, the colorless precipitate was filtered off and the solvent was evaporated in vaccuo. The residue was dissolved in AcOEt (300 mL) and washed with 10% HCl (3 x 150 mL), and brine (2 x 100 mL), and dried over $MgSO_4$. The solvent was removed, and the residue was purified by silica gel column chromatography with AcOEt/hexane (1/4) to give **4** (11.5 g, 88% yield) as a colorless solid. The spectra data matched with those previously reported.[6]

Yield: 11.5 g (88%); colorless solid; mp 123–125 °C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.23 (br s, 1H), 7.92–7.94 (m, 1H), 7.80 (d, J = 2.9 Hz, 1H), 7.41–7.44 (m, 1H), 7.22–7.27 (m, 2H), 6.89 (br s, 1H), 4.18 (q, J = 6.9 Hz, 2H), 3.78 (t, J = 5.7 Hz, 2H), 2.68 (t, J = 5.8 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 173.2, 165.7, 136.5, 129.2, 129.0, 124.5, 123.1, 121.9, 119.7, 112.3, 61.0, 35.1, 34.3, 14.3.

HRMS (ESI): m/z [MNa^+] calcd for $C_{14}H_{16}N_2NaO_3$: 283.1059; found: 283.1059.

3-(1*H*-Indole-3-carboxamido)propanoic acid (3)[6]

To a solution of **4** (10.4 g, 40 mmol) in EtOH/water (v/v = 4/1, 150 mL) was added $LiOH·H_2O$ (3.4 g, 80 mmol) at rt. After 16 h, the mixture was cooled to 0 °C and concentrated HCl (50 mL) was added. A

colorless precipitate was collected by filtration and washed with water (100 mL) and dried affording **3** (7.9 g, 85% yield) as a colorless solid. The spectra data matched with those previously reported.[6]

Yield: 7.9 g (85%); colorless solid; mp 157–159 °C.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.18 (br s, 1H), 11.49 (br s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 2.9 Hz, 1H), 7.91 (t, J = 5.2 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 3.41 (dd, J = 6.9, 13.2 Hz, 2H), 2.48 (t, J = 6.9 Hz, 2H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ 173.7, 165.2, 136.6, 128.3, 126.6, 122.3, 121.5, 120.8, 112.3, 111.1, 35.4, 34.9.

HRMS (ESI): m/z [MNa$^+$]: calcd for $C_{12}H_{12}N_2NaO_3$: 255.0746; found 255.0748.

3,4-Dihydroazepino[4,3-*b*]indole-1,5(2*H*,6*H*)-dione (2)[6]

To a solution of polyphosphoric acid (90 g) and P_2O_5 (8.5 g, 60 mmol) was added **3** (4.6 g, 20 mmol) at 85 °C. After stirring at 110 °C for 2 h, the mixture was cooled to rt and the mixture was added to ice/water (600 mL) and stirred for 2 h. A purple precipitate was collected by filtration and washed with water (200 mL) and dried affording **2** (3.1 g, 73% yield) as a purple solid. The spectra data matched with those previously reported.[6]

Yield: 3.1 g (73%); purple solid; mp 280–282 °C (decomposed).

^{1}H-NMR (500 MHz, DMSO-d_6): δ 12.20 (br s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.14 (t, J = 5.2 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 3.40 (dd, J = 5.2, 10.4 Hz, 2H), 2.86–2.88 (m, 2H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ 193.2, 166.6, 137.1, 133.6, 127.8, 126.6, 124.3, 122.2, 113.5, 113.3, 43.9, 36.7.

HRMS (ESI): m/z [MNa$^+$] calcd for $C_{12}H_{10}N_2NaO_2$: 237.0640; found: 237.0641.

6,7,12,13-Tetrahydro-5*H*-azepino[4,3-*b*:5,6-*b*']diindol-5-one (proposed rhodozepinone, 1)[1]

A solution of **2** (214 mg, 1 mmol) in propionic acid (10 mL) was heated at 115 °C for 1 h, then cooled to rt, and poured into 10% NaOH. The residue was extracted with AcOEt (2 x 50 mL) and washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography (hexane/AcOEt = 3/1) to give **1** (260 mg, 90%). The spectra data do not match with the previously reported one.[1]

Yield: 260 mg (90%); colorless solid; mp over 342 °C.

^{1}H-NMR (500 MHz, DMSO-d_6): δ 11.70 (br s, 1H), 11.40 (br s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.58 (t, J = 5.2 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 6.9 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 4.26 (d, J = 5.2 Hz, 2H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ 168.0, 137.4, 136.7, 132.5, 129.1, 129.0, 125.8, 123.4, 123.2, 122.4, 121.3, 120.4, 119.1, 115.5, 112.6, 112.0, 109.4, 36.5.

HRMS (ESI): *m/z* [MNa^+] calcd for $C_{18}H_{13}N_3NaO$: 310.0956; found: 310.0954.

ACKNOWLEDGEMENTS

This work was financially supported by JSPS (KAKENHI Grant Number 16K18849 for T.A.) as a Grant-in-Aid for Young Scientists (B).

REFERENCES AND NOTE

1. Y. Elsayed, J. Refaat, U. R. Abdelmohsen, S. Ahmed, and M. A. Fouad, *Med. Chem. Res.*, 2017, **26**, 2751.
2. (a) P. Sauleau, M.-T. Martin, M.-E. Dau, D. T. A. Youssef, and M.-L. Bourguet-Kondracki, *J. Nat. Prod.*, 2006, **69**, 1676; (b) F. Ito, K. Shudo, and K. Yamaguchi, *Tetrahedron*, 2011, **67**, 1805; (c) T. Abe, T. Haruyama, and K. Yamada, *Synthesis*, 2017, **49**, 4141.
3. (a) T. Sasaki, I. I. Ohtani, J. Tanaka, and T. Higa, *Tetrahedron Lett.*, 1999, **40**, 303; (b) A. C. Lindsay, I. K. H. Leung, and J. Sperry, *Org. Lett.*, 2016, **18**, 5404; (c) A. C. Lindsay and J. Sperry, *Tetrahedron*, 2017, **73**, 4355; (d) T. Abe and K. Yamada, *Org. Lett.*, 2018, **20**, 1469; (e) T. Abe, S. Satake, and K. Yamada, *Heterocycles*, 2019, **99**, 379.
4. For a nice review, see: A. C. Lindsay, S. H. Kim, and J. Sperry, *Nat. Prod. Rep.*, 2018, **35**, 1347.
5. (a) K. Yamada, Y. Namerikawa, T. Abe, and M. Ishikura, *Heterocycles*, 2009, **77**, 825; (b) K. Yamada, Y. Namerikawa, T. Haruyama, Y. Miwa, R. Yanada, and M. Ishikura, *Eur. J. Org. Chem.*, 2009, **2009**, 5752; (c) K. Yamada, S. Yamaguchi, N. Hatae, T. Abe, T. Iwamura, and M. Ishikura, *Heterocycles*, 2011, **83**, 815; (d) T. Abe and K. Yamada, *J. Nat. Prod.*, 2017, **80**, 241.
6. T. N. T. Nguyen, R. S. Z. Saleenm, M. J. Luderer, S. Hovde, R. W. Henry, and J. J. Tepe, *ACS Chem. Biol.*, 2012, **7**, 172.
7. G. Papeo, H. Posteri, D. Borghi, and M. Varasi, *Org. Lett.*, 2005, **7**, 5641.
8. During the preparation of this manuscript, the original isolation paper was retracted because of inconsistence between structure and spectra data of rhodozepinone.