TOTAL SYNTHESIS OF THE HOMOERYTHRINAN ALKALOIDS, SCHELHAMMERICINE AND 3-EPISCHELHAMMERICINE

Yoshisuke Tsuda,*,a Shinzo Hosoi,a Takeshi Ohshima,a Satomi Kaneuchi,a Masami Murata,a Fumiuki Kiuchi,a Jun Toda,b and Takehiro Sanob
Faculty of Pharmaceutical Sciences, Kanazawa University,a 13-1 Takara-machi, Kanazawa 920, Japan and Showa College of Pharmaceutical Sciences,b 5-1-8 Tsurumaki, Setagaya-ku, Tokyo 154, Japan

This stereo-controlled total synthesis of the title alkaloids, both in racemic form, is the first synthesis of the naturally occurring homoerythrinan alkaloids.

KEYWORDS——homoerythrinan alkaloid; schelhammericine; 3-epischelhammericine; total synthesis; stereo-controlled synthesis

The alkaloids corresponding to the C-homo analog of the erythrinan group are found in the plant genera Schelhammera (Liliaceae), Phelline (Aquifoliaceae), Cephalotaxus (Cephalotaxaceae), and recently in Anthrotaxis (Taxodiaceae) and Dysoxylum (Meliaceae). The total synthesis of these homoerythrinan alkaloids has failed in spite of many attempts. This communication describes the first total syntheses of two of the alkaloids of this group, schelhammericine 1 and 3-epischelhammericine 2.[5]

![Chart 1]

1: $R^1=\text{OMe}, R^2=\text{H}$ schelhammericine
2: $R^1=\text{H}, R^2=\text{OMe}$ 3-epischelhammericine

The key step in our synthesis of the homoerythrinan ring system lies in the [2+2] photocycloaddition of a benzazepino-pyrollinedione to an activated butadiene followed by the anionic 1,3-rearrangement of the resulting vinyl-oxy-cyclobutane.[6]

$\gamma-(3,4$-Methylenedioxyphenyl)butyric acid[7] 3 was converted to isocyanate 4 by a conventional method (i.e. CICOEt/ Et$_3$N, ii. NaN$_3$/Me$_2$CO, iii. Δ/toluene) and then cyclized to benzazepine 5, mp 137-138°C, by PDCl$_3$-SnCl$_4$ in 63% yield from 3.$^9$ Treatment of 5 with P$_2$S$_5$ (benzene, reflux, 96%) followed by Eschenmoser's alkenylation$^{10}$ (i.e. BrCH$_2$COOEt, ii. KHCO$_3$, iii. Ph$_3$P/t-BuOK/DMF, reflux, 7 h) to the resulting thio-lactam$^{11}$ 6, mp 188-190°C, gave (96%) the ethyl-ester 7b, mp 118-119°C, which was smoothly converted (80%) to benzazepino-pyrollinedione 8b, mp 248-250°C, by action of oxalyl chloride in ether (74% from 5).

Irradiation of a mixture of 8b and 1-methoxy-3-trimethylsilyloxybutadiene (1.4 eq) in CH$_3$CN with >300 nm light gave a single [2+2] adduct 9b, mp 168-170°C, in a site-, regio-, and stereo-specific manner (81%).$^{12}$ Borohydride reduction of 9b (MeOH, 0°C, 100%) followed by treatment of the resulting alcohol 10b, mp 171-173°C, with tetra-n-butylammonium fluoride (1.4 eq in
a: R=Me   b: R=Et

a. Et₃N/ClC00Et, b. NaN₃, c. Δ/toluene, d. POCl₃/SnCl₄, e. P₂S₅/benzene
f. BrCH₂COOR, g. KHCO₃, h. Ph₃P/t-BuOK/DMF, i. (COD)₂/ether, j. MeOCH=CHC(OTMS)=CH₂/hυ/CH₃CN
k. NaBH₄,  l. n-Bu₄NF/THF, m. Pd-C/H₂, n. CH₃SO₂C/Pyridine, o. DBU/toluene/Δ
p. 2% NaOMe-MeOH, q. PhSeCl-BF₃·Et₂O/THF, r. MPC/MeOH, s. NaH/CS₂/CH₃I, t. n-Bu₃SnH/Δ
u. 2% HCl/aceton, v. CaCl₂/DMSO-Et₃CSH/Δ, w. n-Bu₄NBH₄/MeOH, x. NaBH₄-CeCl₃/MeOH
y. NaH/CH₃I/n-Bu₄NHSO₄, z. LiAlH₄-AlCl₃/THF

Chart 2
tetrahydrofuran (THF), -30°C→r.t., 2 h) gave (91%) the homoerythrin derivative 11b, mp >300°C, which was hydrogenated (5% Pd-C/H₂, THF-acetone, 4 Kg/cm², 2.5 h) quantitatively to 12b, mp 283-286°C. Methanesulfonylation (CH₃SO₂Cl, 4 eq in pyridine, r.t., 15 h) of 12b followed by mesylation with 1,5-diazabicyclo[5.4.0]undecene-5 (8% in toluene, reflux, 4 h) of the resulting mesylate gave the cyclom homoerythrin 13b, mp 178-180°C, in 81% yield.⑩③

Since the methyl-ester is required at a later step of the synthesis, ester exchange of 13b to 13a, mp 243-245°C, was performed at this stage (2% NaOH-MeOH, r.t., 1.5 h) in 90% yield; the other esters such as 12b resisted the base catalysed transesterification. The overall yield of 13a from benzazepine 5 was 37%. The same methyl-ester 13a was also synthesized from 5 by utilizing the corresponding methyl-ester through a similar sequence of reactions, but in lower yield (15% from 5).⑥⑧

Heating of 13a with PhSeCl (1.5 eq) and a catalytic amount of BF₃·Et₂O in THF (reflux, 8 h) followed by treatment with mercury(II) perchlorate (4 eq) in methanol⑭ gave, in 76% yield, the α,α-dimethoxyketone 14, mp 228-229°C, which was reduced (NaBH₄ in MeOH, r.t., 1 h) to an α-alcohol 15, mp 285-287°C. This was converted to the dithiocarbonate 16 (i. NaH/imidazole, ii. C₅₂H, iii. CH₃I in THF), which, on reduction with tributyltin hydride (excess in toluene, reflux, 1 h) followed by acid hydrolysis (2% HCl-acetone, 50°C, 2 h), afforded the enone 17, mp 220-222°C, in 47% yield from 14. Heating this with calcium chloride⑮ (8 eq, 160°C, 1 h) in dimethylsulfoxide in the presence of t-heptylmercaptan⑯ resulted in demethoxycarbonylation to yield (83%) the enone 18, mp 192-194°C. This is the product in which the intermediate dienolate has been kinetically trapped by a proton.

When the enone 18 was reduced with tetra-n-butylammonium borohydride (MeOH, 0°C, 1 h), the 8-alcohol 19, mp 111-114°C, was produced stereoselectively (80%) (19:20=6:1). Reduction of 18 with NaBH₄-CeCl₃ (MeOH, 0°C, 1 h) gave the α-alcohol 20, gum, as a major product (81%) (19:20=1:5).⑭⑭⑭ Methylation of 19 (i. NaH/imidazole in THF, reflux, 1 h. ii. CH₃I/tetra-n-butylammonium hydrogen sulfate) afforded the 0-methyl ether 21, mp 162-165°C, in 44% yield. The isomerolic alcohol 20 similarly gave the isomeric 0-methyl ether 22, mp 182-183°C, in 73% yield. Reduction of 21 with LiAlH₄-AlCl₃ (1:1) in THF (r.t., 1 h) gave (98%) the amine 1, gum, whose 1H-NMR spectrum proved to be identical with that of schelhammerine (dihydrorschelhammeridine) as reported by Johns et al.⑮⑮ Similar reduction of the isomeric 0-methyl ether 22 afforded (94%) a crystalline base 2, mp 91-93°C, which was identical with 3-epischelhammerine as proved by 1H-NMR, IR, and TLC comparisons.⑮⑮ Thus was accomplished the total synthesis of these alkaloids, both in racemic form.

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REFERENCES AND NOTES

7) The acid 3 was prepared from safrrole in 43% yield in three steps (i. O₃/Me₂S, 
   ii. CH₂(COOH)₂/piperidine-AcOH, iii. Pd-C/H₂), or more conveniently (65%) by carboxylation 
   through the titanium chloride catalyzed Grignard exchange reaction [cf. H.L. Finkbeiner and 
9) The same cyclization in 53% yield by use of PPA was recently reported [I.H. Sanchez, M.I. 
   Larraza, H.J. Flores, E.A. Martell, I. Linzaga, and A.A. Carter, Heterocycles, 23, 251 
   (1985)].
11) All new compounds in this communication gave satisfactory NMR, IR, and MS spectral data 
    and/or elementary analyses.
12) Details of the stereochemical assignment of all compounds will be given in a full 
    publication.
13) A similar cyclization from the both α- and β-alcohol to the same 1,7-cyclo derivative was 
    shown in the erythrian series [Y. Tsuda, Y. Sakai, M. Kaneko, K. Akiyama, and K. Isobe, 
    Heterocycles, 16, 921 (1981)].
16) To prevent coloration of the reaction mixture, the addition of bulky thiols instead of 
    ethanethiol (ref. 15) was found to be particularly useful since they are poor Michael addends 
    to the enone.
17) A similar stereoselective reduction depending on the reducing agents was reported in an 
19) The sample and spectra of 3-epischelhammericine were provided by Profs. Ito and Furukawa.

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