Communications to the Editor

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TOTAL SYNTHESIS OF THE HOMOERYTHRINAN ALKALOIDS, SCHELHAMMERICINE AND 3-EPISCHELHAMMERICINE[1)]

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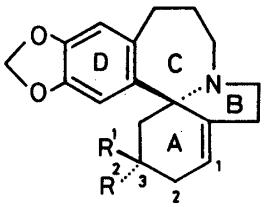
This stereo-controlled total synthesis of the title alkaloids, both in racemic form, is the first synthesis of the naturally occurring homoerythrinan alkaloids.

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),[2)] and recently in Anthrotaxis (Taxodiaceae)[3)] and Dysoxylum (Meliaceae).[4)] 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)]



1: R^1=OMe, R^2=H schelhammericine

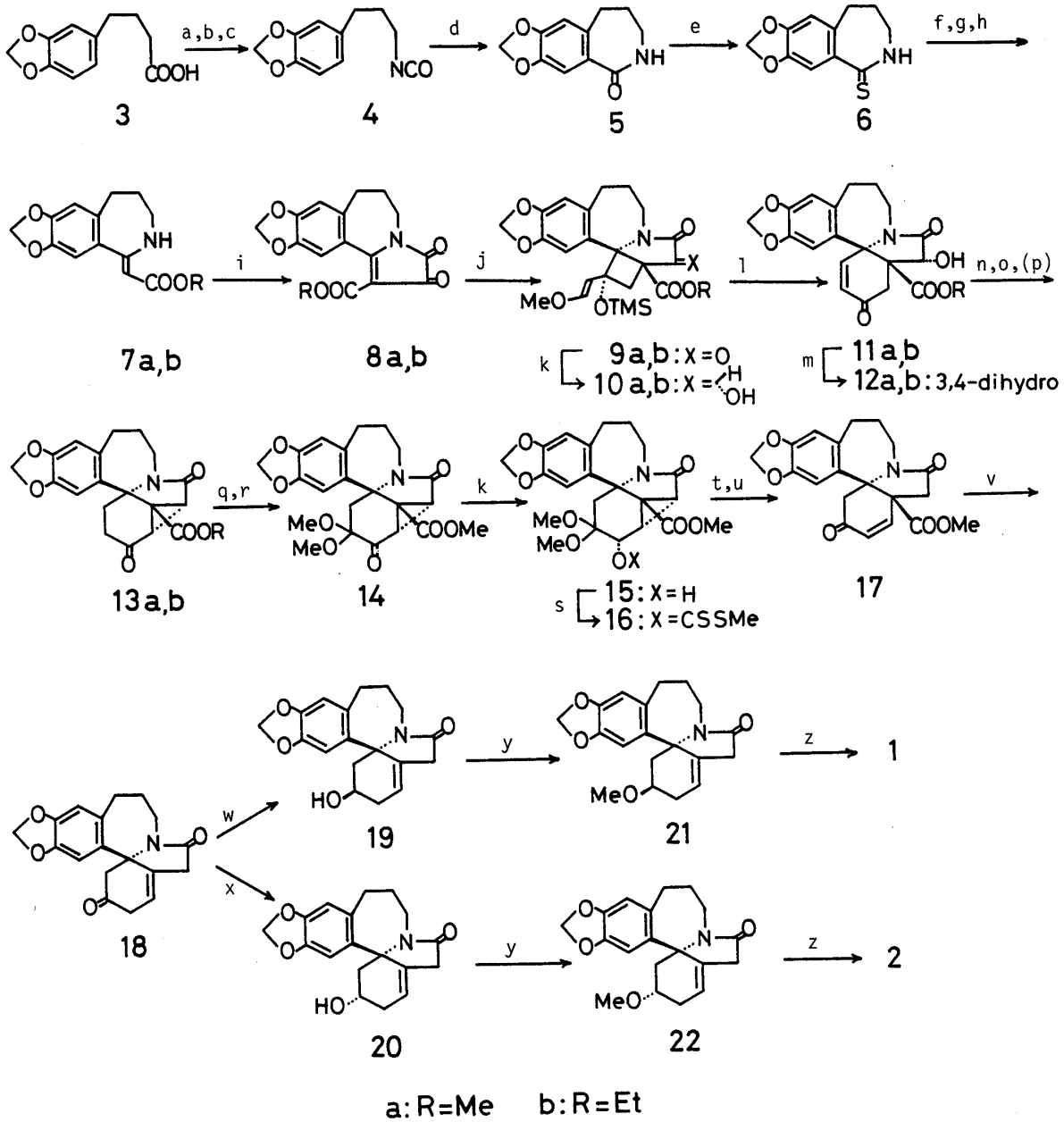
2: R^1=H, R^2=OMe 3-epischelhammericine

Chart 1

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

γ-(3,4-Methylenedioxyphenyl)butyric acid[7)] **3** was converted to isocyanate **4** by a conventional method (i. ClCOOEt/Et_3N, ii. NaN_3/Me_2CO, iii. Δ/tolwene) and then cyclized to benzazepinone **5**, mp 137-138°C, by $POCl_3$-$SnCl_4$[8)] in 63% yield from **3**.[9)] Treatment of **5** with P_2S_5 (benzene, reflux, 96%) followed by Eschenmoser's alkenylation[10)] (i. $BrCH_2COOEt$, ii. $KHCO_3$, iii. Ph_3P/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-pyrrolinedione **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_3CN with >300 nm light gave a single [2+2] adduct **9b**, mp 168-170°C, in a site-, regio-, and stereospecific 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. $Et_3N/ClCOOEt$, b. NaN_3, c. Δ/toluene, d. $POCl_3/SnCl_4$, e. P_2S_5/benzene

f. $BrCH_2COOR$, g. $KHCO_3$, h. Ph_3P/t-BuOK/DMF, i. $(COCl)_2$/ether, j. $MeOCH{=}CHC(OTMS){=}CH_2/h\nu/CH_3CN$

k. $NaBH_4$, l. n-Bu_4NF/THF, m. Pd-C/H_2, n. CH_3SO_2Cl/pyridine, o. DBU/toluene/Δ

p. 2% NaOMe-MeOH, q. PhSeCl-$BF_3{\cdot}Et_2O$/THF, r. MPC/MeOH, s. $NaH/CS_2/CH_3I$, t. n-Bu_3SnH/Δ

u. 2% HCl/acetone, v. $CaCl_2$/DMSO-Et_3CSH/Δ, w. n-Bu_4NBH_4/MeOH, x. $NaBH_4$-$CeCl_3$/MeOH

y. NaH/CH_3I/n-Bu_4NHSO_4, z. $LiAlH_4$-$AlCl_3$/THF

Chart 2

tetrahydrofuran (THF), -30°C→r.t., 2 h) gave (91%) the homoerythrinan derivative **11b**, mp >300°C, which was hydrogenated (5% Pd-C/H_2, THF-acetone, 4 Kg/cm^2, 2.5 h) quantitatively to **12b**, mp 283-286°C. Methanesulfonylation (CH_3SO_2Cl, 4eq in pyridine, r.t., 15 h) of **12b** followed by demesylation with 1,5-diazabicyclo[5.4.0]undecene-5 (8% in toluene, reflux, 4 h) of the resulting mesylate gave the cyclohomoerythrinan **13b**, mp 178-180°C, in 81% yield.[13]

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% NaOMe-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 benzazepinone **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**).[6]

Heating of **13a** with PhSeCl (1.5 eq) and a catalytic amount of $BF_3.Et_2O$ in THF (reflux, 8 h) followed by treatment with mercury(II) perchlorate (4 eq) in methanol[14] gave, in 76% yield, the α,α-dimethoxyketone **14**, mp 228-229°C, which was reduced ($NaBH_4$ 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. CS_2, iii. CH_3I 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 chloride[15] (8 eq, 160°C, 1 h) in dimethylsulfoxide in the presence of t-heptylmercaptan[16] 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 β-alcohol **19**, mp 111-114°C, was produced stereoselectively (80%) (**19**:**20**=6:1). Reduction of **18** with $NaBH_4$-$CeCl_3$ (MeOH, 0°C, 1 h) gave the α-alcohol **20**, gum, as a major product (81%) (**19**:**20**=1:5).[17] Methylation of **19** (i. NaH/imidazole in THF, reflux, 1 h. ii. CH_3I/tetra-n-butylammonium hydrogen sulfate) afforded the O-methyl ether **21**, mp 162-165°C, in 44% yield. The isomeric alcohol **20** similarly gave the isomeric O-methyl ether **22**, mp 182-183°C, in 73% yield. Reduction of **21** with $LiAlH_4$-$AlCl_3$ (1:1) in THF (r.t., 1 h) gave (98%) the amine **1**, gum, whose ^{1}H-NMR spectrum proved to be identical with that of schelhammericine (dihydroschelhammeridine) as reported by Johns et al.[18] Similar reduction of the isomeric O-methyl ether **22** afforded (94%) a crystalline base **2**, mp 91-93°C, which was identical with 3-epischelhammericine as proved by ^{1}H-NMR, IR, and TLC comparisons.[19] Thus was accomplished the total synthesis of these alkaloids, both in racemic form.

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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 erythrinan series [Y. Tsuda, Y. Sakai, M. Kaneko, K. Akiyama, and K. Isobe, Heterocycles, 16, 921 (1981)].
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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 erythrinan-dienone derivative [T. Sano, J. Toda, and Y. Tsuda, Heterocycles, 18, 229 (1982)].
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19) The sample and spectra of 3-epischelhammericine were provided by Profs. Ito and Furukawa.

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