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Formal stereoselective synthesis of (±)-akagerine

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A stereoselective synthesis of pentacyclic dilactam 1, a known precursor of the indole alkaloid akagerine, involving addition of the enolate of 1-acetylindole 2 to 3-acetyl-2-fluoropyridinium salt 3, cyclization of the resultant 1,4-dihydropyridine, elaboration of the (*E*)-ethylidene substituent and closure of the C ring by Pummerer reaction, is reported.

Akagerine is a tetracyclic indole alkaloid isolated in 1975 from *Strychnos usambarensis*[1] and later from several *Strychnos* species.[2] This Corynanthean[3] alkaloid has a peculiar skeleton lacking the characteristic piperidine (D) ring and containing an additional link between N-1 and C-17 (biogenetic numbering);[4] consequently, it incorporates a perhydroazepine ring fused to a tetrahydro-β-carboline unit. Akagerine has received little attention from the synthetic standpoint: only one total synthesis in the racemic series *via* dilactam **1**[5] (Scheme 1) and one enantioselective synthesis of (−)-akagerine[6] through a completely different route have been reported to date.

We present here a short, stereoselective route to pentacyclic dilactam **1**. Our approach takes advantage of our previously developed methodology for the synthesis of bridged indole alkaloids, based on the addition of indole-containing enolates to *N*-alkyl-3-acylpyridinium salts, with subsequent acid-promoted cyclization of the resultant 1,4-dihydropyridine.[7] Taking into account the easy hydrolysis of the C–F bond in 2-fluoropyridines,[8] we thought that the use of a pyridinium salt bearing a fluorine atom at the 2-position in the above two-step sequence would lead to a bridged tetracyclic intermediate embodying the required 2-piperidone moiety present in **1**. On the other hand, the closure of the C ring would be effected by electrophilic cyclization of a thionium ion generated by Pummerer rearrangement,[9] taking advantage of the functionalized two-carbon substituent present at the piperidone nitrogen.

The synthetic sequence is outlined in Scheme 2. Thus, reaction of the enolate derived from 1-acetylindole **2** with 3-acetyl-2-fluoropyridinium salt **3** gave (25%) 1,4-dihydropyridine **4**,[10] which underwent cyclization (58% yield) upon the indole 2-position with concomitant cleavage of the C–F bond by treatment with TsOH in the presence of LiI.[11] The spectroscopic data of the resulting tetracyclic lactam **5**[12] clearly showed that the acetyl carbonyl group was in an enolized form, presumably with a *Z* double bond configuration.

The elaboration of the C-20 (*E*)-ethylidene double bond was effected in a stereoselective fashion by conversion of the 1-hydroxyethylidene group of **5** into the corresponding triflate, followed by Pd^0 catalyzed reduction with Bu_3SnH.[13] Following this protocol **6** was obtained in 45% overall yield from **5**.

MCPBA oxidation of tetracyclic sulfide **6** gave the corresponding sulfoxide (mixture of stereoisomers), which smoothly underwent Pummerer rearrangement with TFAA in CH_2Cl_2 in the presence of 2,6-di(*tert*-butyl)pyridine at room temperature.[14] When the presumed acyloxy sulfide intermediate was refluxed in CH_2Cl_2 the desired pentacyclic sulfide **7** (a single diastereomer, undetermined configuration at C-6) was obtained in 71% overall yield from **6**.

Finally, desulfurization of **7** with Bu_3SnH–AIBN gave the desired pentacyclic dilactam **1** in 72% yield. The ^1H NMR data of **1** are in agreement with those previously reported.[5,15] Taking into account the previous work by Winterfeldt,[5] the synthesis of **1** represents a formal total synthesis of (±)-akagerine.

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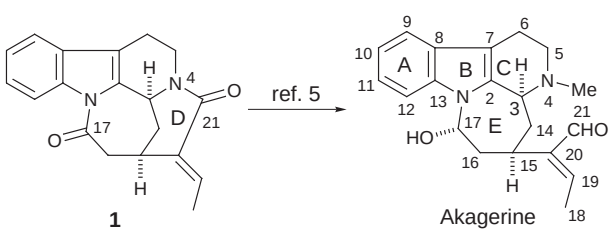
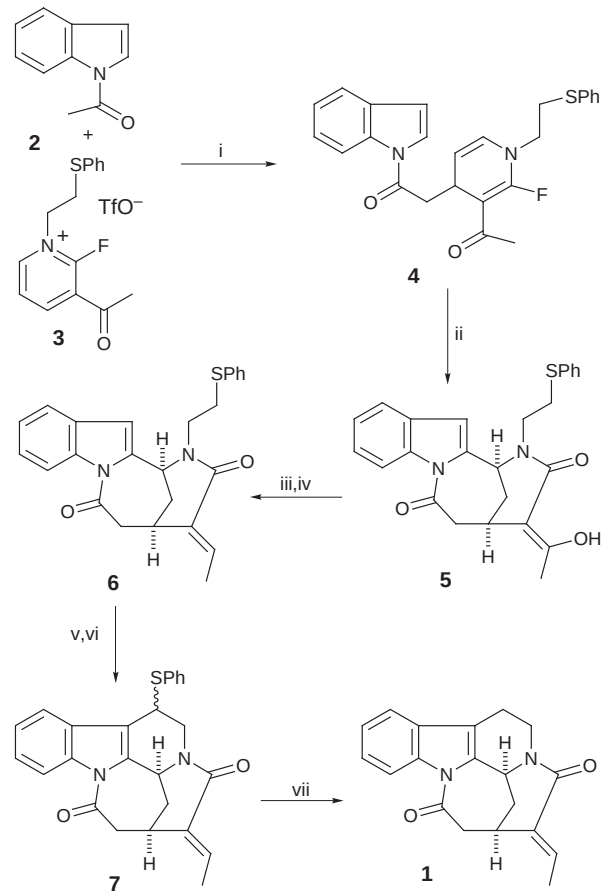


Scheme 1



Scheme 2 *Reagents and conditions*: i, LDA, THF, −30 °C, 1.5 h; ii, C_6H_6, TsOH, MeOH, LiI, room temp., 2 h; iii, Tf_2O, 1,8-bis(dimethylamino)naphthalene, −30 to −10 °C, 1 h; iv, Bu_3SnH, $Pd(Ph_3P)_4$, LiCl, THF, reflux, 1 h; v, MCPBA, CH_2Cl_2, −70 °C, 30 min; vi, TFAA, 2,6-di(*tert*-butyl)pyridine, CH_2Cl_2, room temp., 30 min, then reflux, 1.5 h; vii, Bu_3SnH, AIBN, benzene, reflux, 1 h.

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Notes and references

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12 *Selected data* for **5**: δ_H(300 MHz, $CDCl_3$) 2.09 (s, 3H, 18-H), 2.32 (dm, *J* 14, 1H, 14-H), 2.44 (m, 1H, 14-H), 2.81 (m, 1H, 5-H), 2.96 (br d, *J* 12.8, 1H, 16-H), 3.15 (m, 4H, 6-H, 15-H, 16-H), 3.60 (m, 1H, 5-H), 4.80 (d, *J* 5.1, 1H, 3-H), 6.16 (s, 1H, 7-H), 7.26–7.33 (m, 7H, Ar), 7.42 (d, *J* 7.6, 1H, 9-H), 8.13 (d, *J* 8.2, 1H, 12-H); δ_C(75 MHz, $CDCl_3$) 18.4 (C-18), 29.3 (C-15), 30.7 (C-6), 32.3 (C-14), 44.4 (C-5), 47.7 (C-16), 56.9 (C-3), 96.7 (C-20), 112.5 (C-7), 115.5 (C-12), 120.6 (C-9), 123.7 (C-10), 125.8 (C-11), 126.3 (Ph), 129.2 (Ph), 129.5 (C-8), 135.0 (Ph), 135.2 (C-2), 138.4 (C-13), 168.9 (C-19), 171.7, 172.7 (C-17, C-21).
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15 *Selected data* for **1**: δ_C(75 MHz, $CDCl_3$) 14.3 (C-18), 20.0 (C-6), 27.6 (C-15), 27.3 (C-14), 42.4 (C-5), 47.0 (C-16), 51.9 (C-3), 115.2 (C-12), 117.8 (C-9), 120.1 (C-7), 123.9 (C-10), 125.2 (C-11), 132.6 (C-20), 135.8 (C-2), 136.8 (C-13), 138.1 (C-19), 166.1 (C-21), 172.1 (C-17).

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