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The First Total Synthesis of the Novel β-Carboline Alkaloid Oxopropaline G

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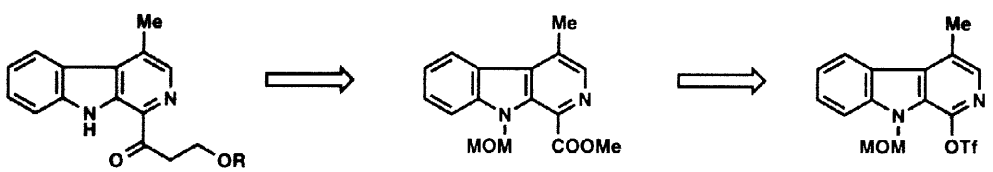
Abstract: The first total synthesis of the new type of cytocydal β-carboline alkaloid oxopropaline G was achieved in 12 steps.

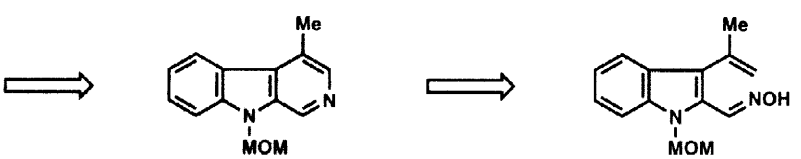
Oxopropalines (**1**) isolated from *Streptomyces* sp. G324[1,2] producing lavendamycin,[3] are novel β-carboline alkaloids. These compounds are structurally composed of five constituent compounds, A, B, D (**1b**), E and G (**1a**), were elucidated by physico-chemical studies by Abe and co-workers.[2] This new type of β-carboline alkaloids, possessing an acyl group and a methyl group at the 1- and 4-positions, respectively, exhibit the cytocydal activity.[1]



1a: oxopropaline G (R=H)
1b: oxopropaline D (R=rhamnose)

2

3



4

5

Scheme 1

We are currently developing the synthesis of biologically active condensed-heteroaromatic compounds, including natural products by the thermal electrocyclic reaction of either hexatriene[4] or

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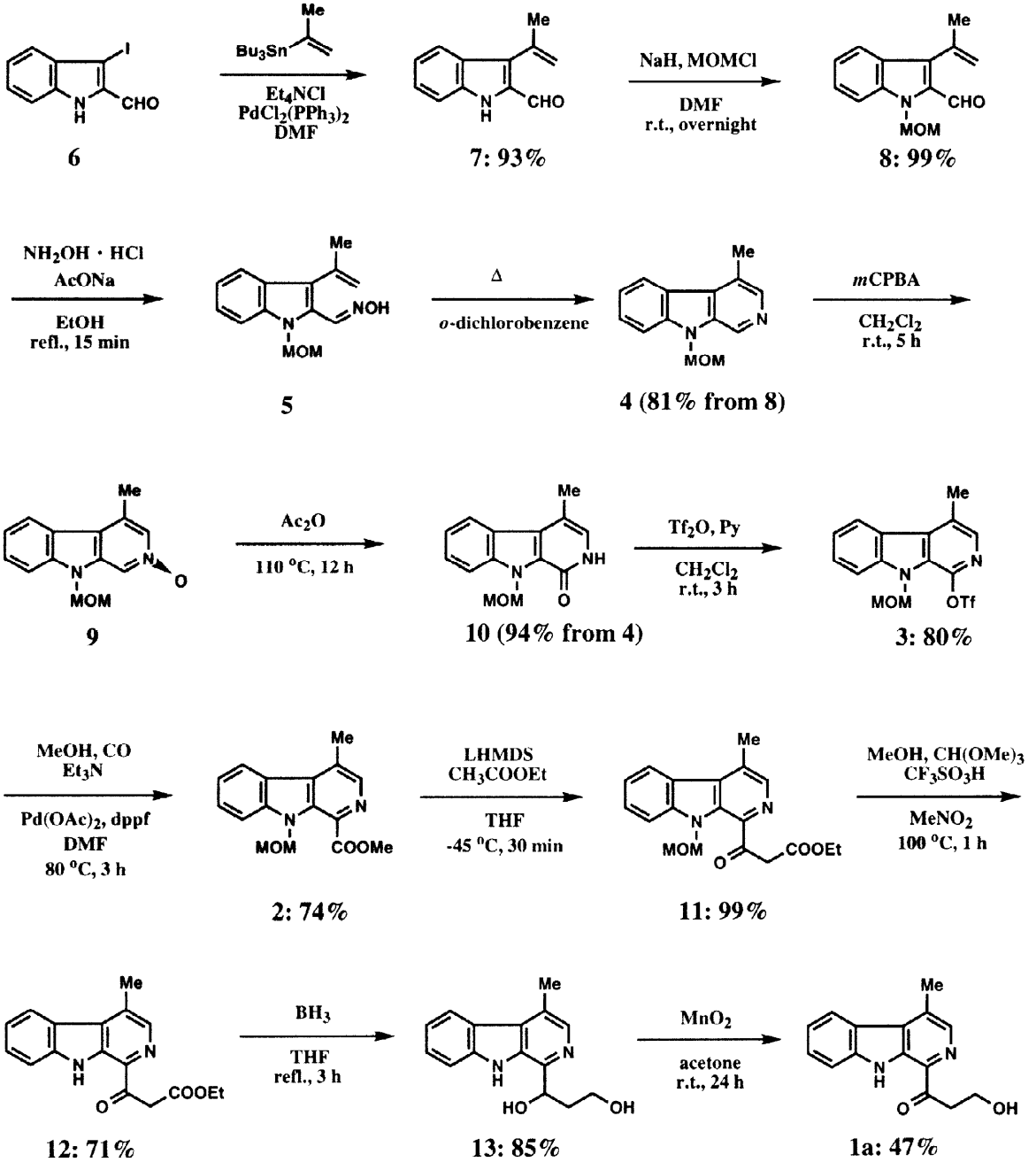
monoazahexatriene systems[5] incorporating one double bond of aromatic or heteroaromatic portion. We here describe the first total synthesis of oxopropaline G (**1a**) by application of this pyrido-annelation. The present methodology is based on the thermal electrocyclic reaction of 1-azahexatriene system (**5**) involving the indole 2,3-bond to prepare a new 4-methyl-β-carboline ring (**4**). 1-Methoxycarbonyl-4-methyl-β-carboline (**2**) derived from **4** was envisaged as a key compound for the total synthesis of oxopropaline G (**1a**) and D (**1b**) (Scheme 1).



Scheme 2

The required β-carboline (**4**) was prepared in four steps starting from 2-formyl-3-iodoindole (**6**)[5c] (Scheme 2). The cross-coupling reaction between **6** and isopropenyl tributyltin[6b] in the presence of $PdCl_2(PPh_3)_2$ in DMF gave the isopropenylindole (**7**) (93%),[7] which on *N*-protection with chloromethyl methyl ether (MOMCl) provided *N*-MOM-indole (**8**) (99%). Subsequent treatment of **8** with hydroxylamine produced the oxime (**5**) as the 1-azahexatriene system, which was subjected to the thermal electrocyclic reaction in *o*-dichlorobenzene (190 °C, 1 hr) to yield the 4-methyl-β-carboline (**4**) (81% from **8**).

The key compound (**2**) was synthesized from β-carboline (**4**) in four steps. Treatment of **4** with *m*-chloroperbenzoic acid (*m*CPBA) followed by heating in acetic anhydride (Ac_2O) yielded the 1-hydroxy-β-carboline (**10**) (94% from **5**), which was treated with trifluoromethnesulfonic anhydride (Tf_2O) to obtain the triflate (**3**) (80%). The triflate (**3**) was converted to the desired 1-methoxycarbonyl-4-methyl-β-carboline (**2**) with the three component cross-coupling reaction[6a,8] [triflate (**3**), carbon monooxide (1 atm), methanol, triethylamine, $Pd(OAc)_2$, and 1,1'-bis(diphenylphosphino)-ferrocene (dppf) in DMF] in 74% yield.

At the final stage, oxopropaline G (**1a**) was synthesized from the key compound (**2**) in four steps. Nucleophilic addition reaction to **2** with the acetate carbanion[9] [prepared from ethyl acetate with lithium hexamethyldisilazide (LHMDS)] produced the β-keto ester (*N*-MOM, **11**) (99%), which was deprotected with trifluoromethanesulfonic acid in the presence of methanol and trimetyl orthoformate in nitromethane[10] to give the keto ester (**12**) (71%). Reduction of **12** with diborane in THF followed by selective oxidation of the 1,3-diol (**13**) with activated manganase dioxide provided oxopropaline G (**1a**) (40% from **12**). All spectral data of synthetic oxopropaline G (**1a**)[11] was in good agreement with that reported for the natural product.[2]

In conclusion, the first total synthesis of a new type of cytocydal β-carboline alkaloid oxopropaline G (**1a**) was completed in a twelve-step sequence (11.7% overall yield from **6**) by thermal electrocyclic reaction of a 1-azahexatriene system involving the indole 2,3-bond for the construction of the β-carboline framework (**4**) followed by formation of the acyl group at the 1-position *via* the key compound, 1-methoxycarbonyl-4-methyl-β-carboline (**2**).

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References and Notes

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10. This reaction conditions reported by the following literature was utilized for the ketalization of ketone group of **11**. However, the deprotection of *N*-MOM group of **11** occurred instead of the ketalization: Thurkauf, A.; Jacobson, A.E.; Rice, K.C. *Synthesis* **1988**, 233.
11. Oxopropaline G: mp 155-157 °C ($CHCl_3$); Ir (KBr) 3518, 3320, 1663 cm^{-1}; ^{1}H-nmr (500 MHz, MeOH-d_4) 2.90 (3H, s), 3.54 (2H, t, *J*=6.4 Hz), 4.07 (2H, t, *J*=6.4 Hz), 7.33 (1H, dd, *J*=7.9, 7.1 Hz), 7.58 (1H, dd, *J*=8.2, 7.1 Hz), 7.71 (1H, d, *J*=8.2 Hz), 8.23 (1H, d, *J*=7.9 Hz), 8.24 (1H, s); ^{13}C-nmr (125 MHz, MeOH-d_4) 17.9, 41.8, 58.8, 113.3, 121.7, 122.1, 124.5, 129.6, 131.1, 134.0, 135.2, 135.9, 139.7, 143.2, 203.1. Ms (CI) *m/z* 255 (M^++1).