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A CONVENIENT SYNTHESIS OF EUPOLAURAMINE

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Summary: A highly practical new route for the 10-steps total synthesis of eupolauramine in which synthesis of azaphenanthrene skeleton by regiospecific cyclization of **4** and acid catalyzed regiospecific direct methoxylation of **5** to give **6** are key steps is disclosed.

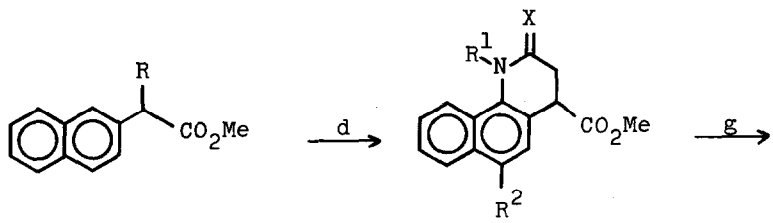
6-Methoxy-5-methylbenzo[h]pyrrolo[4,3,2-de]quinolin-4(5H)-one (eupolauramine) (**11**) is a structually unusual azaphenanthrene alkaloid isolated from Eupomatia laurina.[1] Low concentration of **11** in natural sources has stimulated interest in new convenient synthesis of **11** and its related compounds and two groups have already published the total synthesis of **11**.[2,3]

We report here a convenient 10-steps total synthesis of **11** that relied heavily on new methods developed in our laboratory including (1) the first example of new application of an intramolecular aromatic substitution with a N-methoxy-N-acylnitrenium ion to the synthesis of a natural product containing nitrogen atom (**4**→**5**)[4], (2) the direct introduction of a methoxy group into the para-position of N-methoxyamide function (**5**→**6**)[5], and (3) the aromatization of dihydrocarbostyril moiety in the presence of other functional groups to quinoline moiety via thiolactam formation by the desulfurization and simultaneously occurring dehydrogenation with Raney Ni (**7**→**8**).

The reaction sequence employed is outlined in Scheme 1. The starting material for the synthesis was the commercial available methyl 2-naphthylacetate **1** which was converted to **4**, mp 103-104°C, in 3 steps. **4** was easily cyclized to **5**, mp 128-130°C, by our previously reported method.[4] Acid catalyzed reaction of **5** resulted in the direct introduction of a methoxy group to give **6**, mp 263-265°C.[5] In order to convert **6** to **8**, both the dehydration with Pd-C and the chlorination of **6** with $POCl_3$ failed. Thionation of **6** gave **7**, mp 170-171°C, and desulfurization and simultaneous dehydrogenation using Raney Ni[6] produced **8**, mp 138-139°C, directly from **7**. Although several attempts to nitrate **8** were reported to be unsuccessful,[3] the nitration of **8** with $Cu(NO_3)_2/Ac_2O$ afforded the desired nitro compound **9**, mp 181-183°C (58%), and the quinone **12**, mp 187-188°C (22%). The yield of **9** was increased to 68% by the addition of ascorbic acid to the reaction mixture. Catalytic hydrogenation of **9** gave directly the cyclized product **10**, mp 295-297°C, which

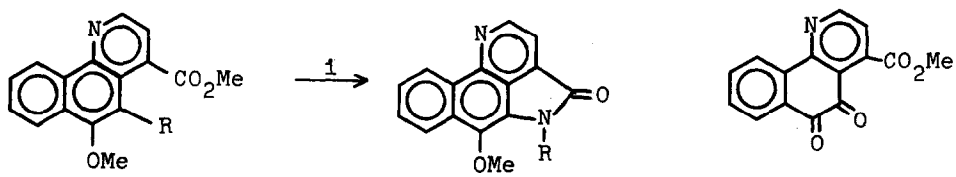
was readily methylated to afford eupolauramine **11**, mp 189-190°C, identical with eupolauramine[1,7] in mp, IR, MS, and ^{1}H NMR. The overall yield in the 10 steps from **1** was 27%.

Scheme 1[a]



a **1**: R=H
b **2**: R=CH_2CO_2Bn
c **3**: R=CH_2CO_2H
4: R=$CH_2CONHOMe$

e **5**: R^1=OMe, R^2=H, X=O
f **6**: R^1=H, R^2=OMe, X=O
7: R^1=H, R^2=OMe, X=S



h **8**: R=H
9: R=NO_2

j **10**: R=H
11: R=Me

12

[a]Reagents and Conditions: (a) $BrCH_2CO_2Bn$/LDA/THF (95%); (b) H_2/10% Pd-C/AcOEt (96%); (c) $MeONH_2$·HCl/1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl/1-hydroxybenzotriazole/Et_3N/$ClCH_2CH_2Cl$ (95%); (d) (1) tert-BuOCl/CH_2Cl_2, (2) $Zn(OAc)_2$/$MeNO_2$ (88%); (e) c.H_2SO_4/MeOH (75%); (f) P_2S_5/pyridine (96%); (g) Raney Ni/xylene (79%); (h) $Cu(NO_3)_2$/ascorbic acid/Ac_2O (68%); (i) H_2/10% Pd-C/DMF-MeOH (94%); (j) MeI/NaH/DMF (96%).

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