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MOSTUEINE: SYNTHESIS AND STRUCTURE REVISION[1]

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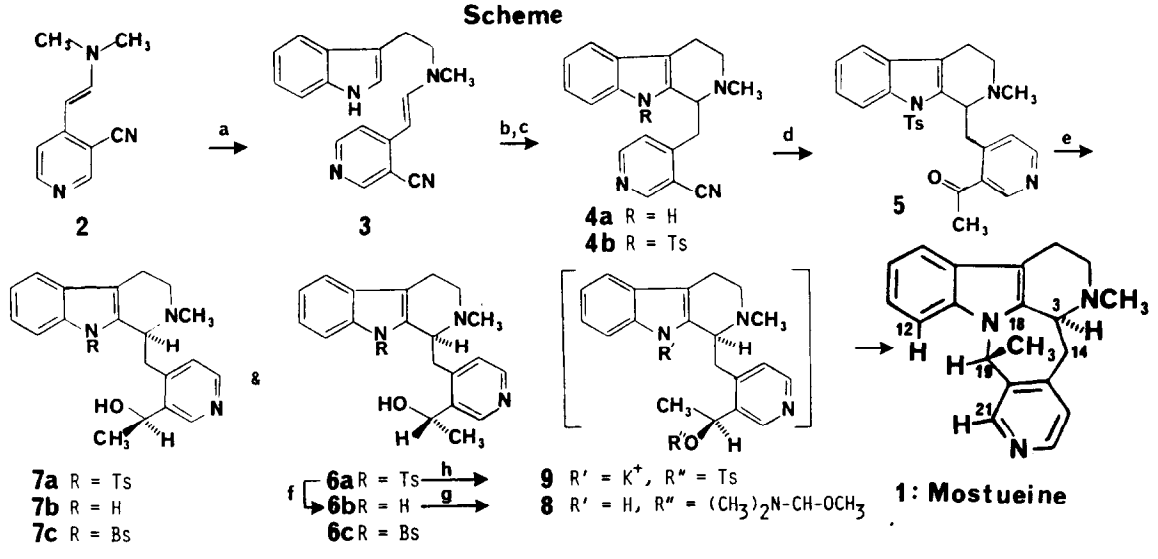
ABSTRACT: A total synthesis of mostueine (1) based upon the intramolecular alkylation of the indole nitrogen is described. A revision of the reported sterochemistry of mostueine to **3SR, 19RS** as elucidated by synthesis and NOE data is disclosed.

Mostueine (1) is a pentacyclic indole alkaloid isolated from the leaves of Mostuea brunonis (loganiacies).[2,3] Recently the relative configuration of Mostueine was assigned as **3SR,19SR** on the basis of its total synthesis.[4] We have also completed the synthesis of mostueine but our results lead to the opposite stereochemical assignment. We discuss here these findings along with NOE experiments on the natural product which require the reassignment of the relative configuration of mostueine as **3SR,19RS** as illustrated.

Scheme



a) n-methyl-tryptamine[6], toluene, 1 mole% toluenesulphonic acid, reflux, 72 hr., 87%; **b**) sat. HCl in CH_3OH, 0°C → r.t., 30 min.; NH_4OH, 91%: **c**) KOH, glyme, TsCl, 88%; **d**) 7 eq. CH_3Li-LiBr, THF, -78°C, 2 hr.; HOAc, THF, -78°C → r.t.; 2N H_2SO_4; NH_4OH, 81%; **e**) $LiAlH_4$, THF, -98°C, 2hr., 92% **6a**; 6% **7a**; **f**) 10% KOH/CH_3OH, reflux, 15 hr., 79%; **g**) DMF-DMA, toluene, reflux, 6%; **h**) KOtBu, THF, 0°C → r.t., 20 HR., 17%

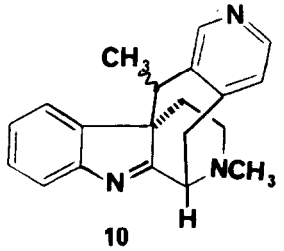
Our synthetic scheme is similar to that of the published synthesis for the production of diastereomeric alcohols **6a** and **7a**. The dimethyl enamine **2**[5] provides a useful functional equivalent to the corresponding pyridylacetaldehyde for the formation of enamine **3**. Ring closure[7] to the tetrahydrocarboline **4a** must be carefully monitored to avoid decomposition. We

utilized p-toluenesulfonyl (Ts) in contrast to benzenesulfonyl (Bs) as the indole protecting group[8] required in the conversion to methyl ketone 5. Reduction of 5 with $LiAlH_4$ in THF gave a 2:1 mixture of the alcohol isomers **6a** and **7a** which were easily separated by medium-pressure liquid chromatography (MPLC).[9,10] Reduction at lower temperatures increased the proportion of **6a** at the expense of longer reaction times. Thus, reduction at -98°C for 2 hours afforded a 93:7 ratio. We removed the sulfonyl-protecting group[11] independently from alcohols **6a** and **7a** to afford respectively the diastereomeric alcohols **6b** and **7b** distinguishable by ^1H NMR each uncontaminated by the other.[12,13]

Initially, mostueine was obtained in low yield by cyclodehydration of diastereomeric alcohol **6b** with dimethylformamide - dimethylacetal in refluxing toluene.[14,15] The presumed intermediate **8** releases dimethylformamide and methoxide under Sn2 attack by the indole ring. The same conditions with alcohol **7b** returned starting material. Attempts to force the reaction with **7b** or to increase the conversion from **6b** led to destruction of the starting material and products.

We were pleased to find that our material was indeed identical by 360 MHz ^1H NMR and 100 MHz ^{13}C NMR to a sample of the natural diastereomer kindly provided by Prof. F. Khuong-Huu. We were concerned that their synthesis proceeded from the opposite diastereomer successful in our procedure. Their structural assignment rests on the x-ray structure determination of their major alcohol diastereomer, **7c**. The NMR spectral data reported for **6c** and **7c** closely matched our own data for **6a** and **7a**. Repetition of the $NaBH_4$ reduction conditions on ketone 5 afforded **6a** and **7a** in a 1:2 ratio confirming that the toluenesulfonyl group did not alter the reaction course reported with the benzenesulfonyl group.

The possibility that configuration inversion had occurred during our indole deprotection step was considered. Intramolecular transfer of the tosyl group to the hydroxyl function to form tosylate **9** followed by hydroxide displacement with inversion seemed possible.[16] An attempt to form mostueine by tosylation of the free alcohols **6b** and **7b** in the presence of base, however, regenerated the original tosylamides **6a** and **7a** respectively, each contaminated by a slight amount of its diastereomer indicating that some epimerization occured during the re-tosylation. The tosylamide **6a** was treated with potassium t-butoxide in THF under anhydrous conditions in an attempt to force the intramolecular tranfer. Indeed, mostueine was isolated by MPLC in 17% yield, again identical with the natural diastereomer. Analysis of the crude reaction mixture by 360 MHz ^1H NMR revealed the major product to be the C-alkylated product **10**[17] along with a trace amount of the free indole **7b**. These results are consistent with intramolecular transfer to form the tosylate **9** which is then captured by intramolecular C- or N- alkylation as well as by trace hydroxide contamination. Since alcohol **6b** was obtained cleanly under the usual deprotection conditions, we conclude that deprotection occurred with retention of configuration.



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With synthetic and natural mostueine in hand we turned to physical measurements to confirm the structure. Dreiding molecular models of the two possible diastereomers reveal a very limited number of conformations available to the central azepine ring. The CH_3-18 group

must lie above the planes of the aromatic rings because of otherwise significant van-der-Walls overlap with H-12 and H-21. From the ^{1}H NMR spectrum it is apparent that H-3 and H-14a are anti-periplanar to each other with a coupling of 13Hz.[18] Each diastereomer possesses only a single conformation which satisfies both of these conditions. In the **3SR,19RS** diastereomer illustrated in the figure, the CH_3-18 group is quite close to H-14a while in the other diastereomer H-3 is in proximity to the methyl group. NOE difference measurements[19] (see Table) upon pre-saturation at the methyl signal reveal a significant enhancement at the signal for H-14a. The substantial enhancements observed at the signals for H-12 and H-21 upon pre-saturation at H-19 confirm the configurational placement of CH_3-18 out of the planes of the aromatic rings. These results require the reassignment of the relative configuration of Mostueine as **3SR,19RS** and confirm our synthetic results.

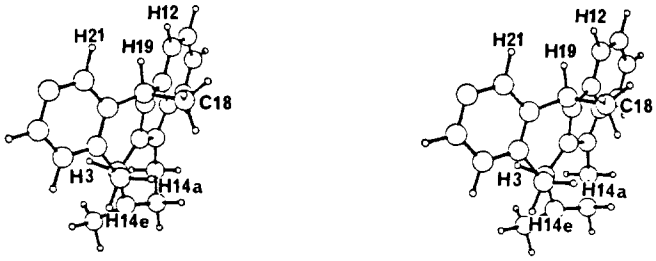

Figure: Stereoview of **3SR, 19RS** Mostueine

Table: Difference NOE Measurements in %

pre-saturated signal	observed signals CH3-18	H-3	H-14a	H-14e	H-19	H-12	H-21	H-11
CH_3-18	SAT.	1.0	6.7	-1.3	7.6	3.0	0.3	0.8
H-3	---	SAT.	-3.3	2.8	---	---	---	---
H-14a	2.0	-10.5	SAT	18.0	---	---	---	---
H-19	3.1	---	---	---	SAT	16.4	22.3	-2.0

It is apparent, therefore, that synthetic efforts alone, even with an x-ray structure of a precursor, are not sufficient to establish stereochemistry when the stereocenter itself is involved in the chemistry. The reported synthesis must have proceeded with net retention of configuration. This is not surprising since the first portion of the ring-closure procedure (CH_3SO_2Cl, Et_3N, THF, -20°C)[4] is very similar to the method prescribed for the formation of 3-(1-chloroethyl)pyridine from the corresponding alcohol.[20] The resulting chloride could then serve as the alkylating agent. This double inversion reaction may be the basis of the structural misassignment.

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9. ^{1}H NMR for **6a** ($CDCl_3$,360MHz): 1.601, 3H, d, J=6.6Hz, $CHC\underline{H}_3$; 2.351, 3H, s, NCH_3; 3.340 and 3.519, 2H, ABX, J_{AB}=-14.1Hz, J_{AX}=7.6Hz, J_{BX}=3.5Hz, CH_2-14; 4.459, 1H, dd J=7.3, 3.2Hz, H-3; 5.15, 1H, q, J=6.6Hz, H-19.
10. ^{1}H NMR for **7a** ($CDCl_3$, 360 MHz): 1.683, 3H, d, J=6.5, $CHC\underline{H}_3$; 2.252, 3H, s, NCH_3; 3.158 and 3.363, 2H, ABX, J_{AB}=-14Hz, J_{AX}=10.2Hz, J_{BX}= 0Hz, CH_2-14; 4.231, 1H, d, J=10Hz, H-3; 5.022, 1H, q, J=6.5Hz, H-19.
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13. ^{1}H NMR for **7b** ($CDCl_3$, 360 MHz): 1.668, 3H, s, J=6.5Hz, $CHC\underline{H}_3$; 2.329, 3H, s, NCH_3; 3.030 and 3.306, 2H, ABX, J_{AB}=-13.8Hz, J_{AX}=9.2Hz, J_{BX}=2.6Hz, CH_2-14; 3.722, 1H, br d, J=8Hz, H-3; 5.07, 1H, q, J=6.5Hz, H-19.
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17. ^{1}H NMR for **10** (the isomer derived from **6b**) ($CDCl_3$, 360 MHz): 1.72, 3H, d, J=7.2Hz, $CHC\underline{H}_3$; 2.383, 3H, s, NCH_3; 2.78, 1H, q, J=7.2Hz, $CHCH_3$; 4.12, 1H, dd, J=6.4Hz, 2.0Hz, H-3; 3.11 and 3.47, 2H, ABX, J_{AB}=-14.9Hz, J_{AX}=6.3Hz, J_{BX}=1.9Hz, CH_2-14.
18. ^{1}H NMR for mostueine NOE experiments. (360MHz,$CDCl_3$): 1.666, 3H, d, J=7Hz, CH_3-18; 2.545, 3H, s, NCH_3; 3.163, 1H, dd, J=13Hz, 1.8Hz, H-14e; 3.517, 1H, t, J=13Hz, H-14a; 3.850, 1H, dd, J=13Hz, 1.5Hz, H-3; 5.788, 1H, q, J=7Hz, H-19; 7.282, 1H, t, J=7.3Hz, H-11; 7.462, 1H, d, J=8.2Hz, H-12; 8.610, 1H, s, H-21.
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