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A STEREOSELECTIVE SYNTHESIS OF THE (9Z,11Z) TETRAPONERINES T4 and T8

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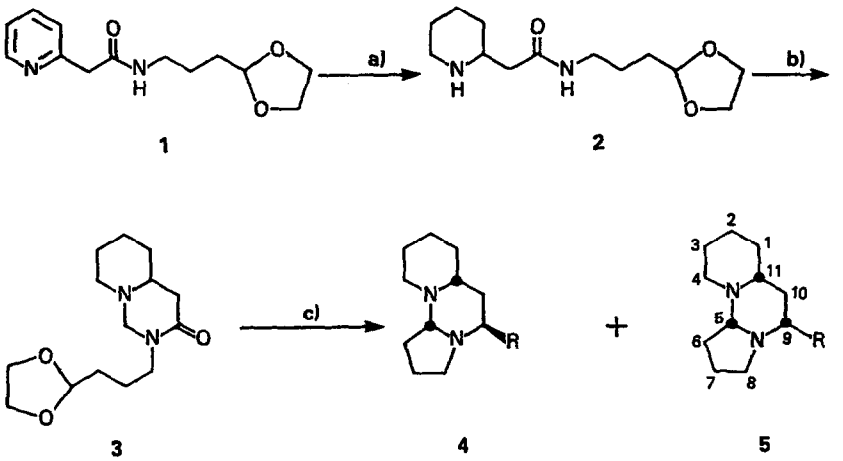
Summary: A highly stereoselective synthesis of (±) tetraponerine T4 **5** ($R=C_3H_7$) and (±) tetraponerine T8 **5** ($R=C_5H_{11}$) from the bicyclic lactam **3**, is described.

The tetraponerines, a group of unique tricyclic alkaloids containing an aminal function are the toxic components of the venom of ants in the genus *Tetraponera*.[1] Two major components of the natural mixture of tetraponerines are T4 and T8, (**5**, $R=C_3H_7$ and C_5H_{11} respectively) which have the (9Z,11Z) configuration in which the three methine hydrogens are *cis*. Three syntheses of these compounds, including Husson's elegant enantioselective synthesis of T8 have been reported.[2] We sought a shorter, stereoselective route to these compounds to provide material for our ongoing investigation of the repellencies and toxicities of the ant venom alkaloids.[3]

The pyridyl amide **1** was prepared in 80% yield by coupling [DCC, DMAP, Et_3N(1 equiv.), CH_2Cl_2] 2-pyridylacetic acid hydrochloride and 2-(3-aminopropyl)-1,3-dioxolane[4], and could be hydrogenated to **2** nearly quantitatively. Treatment of **2** with aqueous formaldehyde in the presence of a catalytic amount of KOH provided the bicyclic aminolactam **3** in 89% yield.[5] It seemed that the stereochemistry at C-9 could be controlled by the appropriate choice of reducing agent after the addition of an organometallic reagent to the amide carbonyl[6], and this proved to be the case. Two equivalents of C_3H_7MgCl were added to **3** in ether and the mixture was subsequently treated with $LiAlH_4$. After acidification with 10% HCl, treatment with 5N KOH produced 30% of a 1:3 mixture of the unnatural (9E,11Z) isomer **4** and **5** = tetraponerine-4 ($R=C_3H_7$). Unfortunately, the major product (> 65%) of this reaction sequence was the noralkyl aminal (**4** or **5**, R=H). However, when the reduction step was carried out using lithium tri-*tert*-butoxyaluminohydride, a similar yield of **5** was obtained containing less than 5% of **4**. The addition of one equivilant of TMEDA[6], increased the overall yield of **5** to 70% with less than 1% of **4** detectable. Tetraponerine-8 (**5**, $R=C_5H_{11}$) was obtained in the same manner using pentylmagnesium bromide. Synthetic T4 and T8 had ^1H and ^{13}C NMR and MS identical to those previously reported.[1,2]

While not enantioselective, this synthesis is much more efficient than those previously published, providing stereoselectively the all-*cis* tetraponerines in four operations from commercially available starting materials.



Reagents: a) 5% Rh/Al_2O_3, H_2 3 atm., MeOH; b) CH_2O, KOH(cat.), THF, 12hr; c) RMgCl (2 equiv.) and TMEDA, 0 -r.t. 12hr, excess reducing agent (3 hr), 15%HCl, then 20% KOH.

References and Notes

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2. P. Merlin, J. C. Braekman, and D. Daloze, *Tetrahedron Lett.*, **1988**, *29*, 1691; C.Yue, J Royer, and H.-P. Husson, *J. Org. Chem.*, **1990**, *55*, 1140; T. H. Jones, *Tetrahedron Lett.*, **1990**, *31*, 1535.
3. T. H. Jones, M. S. Blum, and H. G. Robertson, *J. Nat. Prod.*, **1990**, *53*, 429.
4. M. Shimizu, M. Ishikawa, Y. Komoda, and T. Nakajima, *Chem. Pharm. Bull. (Tokyo)*, **1982**, *30*, 909. 4-Aminobutyraldehyde diethyl acetal is commercially available.
5. All reactions were followed by gas chromatography; 1, 2, and 3 were purified by kugelrohr distillation, and satisfactory spectral data were obtained in accord with their structures. The most definitive, ^{13}C nmr and MS, are as follows: 1: ^{13}C nmr δ=169.1(C), 156.0(C), 149.1(CH), 137.1(CH), 124.0(CH), 122.0(CH), 104.1(CH), 64.9($2CH_2$), 45.5(CH_2), 39.3(CH_2), 31.1(CH_2), 23.9(CH_2); MS m/z(rel intensity) 250(0.5, M+), 178(20), 140(17), 120(22),93(100), 92(36), 73(30), 65(15), 45(20). 2: ^{13}C nmr δ=171.7(C), 104.1(CH), 64.8($2CH_2$), 53.9(CH), 46.6(CH_2), 43.3(CH_2), 38.8(CH_2), 32.7(CH_2), 31.2(CH_2), 26.4(CH_2), 24.6(CH_2), 23.9(CH_2); MS m/z(rel intensity) 256(0.5,M+), 213(1), 211(1), 184(4), 156(4), 124(10), 98(12), 97(27), 84(100), 73(30), 70(25), 56(28). 3: ^{13}C nmr δ=167.4(C), 104.1(CH), 70.6(CH_2), 64.9($2CH_2$), 57.0(CH), 50.9(CH_2), 44.7(CH_2), 37.8(CH_2), 32.0(CH_2), 31.1(CH_2), 25.1(CH_2), 22.5(CH_2), 21.8(CH_2); MS m/z(rel intensity) 268(15,M+), 267(50), 223(11), 196(20), 195(50), 153(50), 125(18), 124(20), 96(38) 95(36), 84(100), 83(21), 82(34), 73(84), 55(57), 45(50), 42(61), 41(55).
6. Y. C. Hwang, M. Chu, and F.W. Fowler, *J. Org. Chem.*, **1985**, *50*, 3885.

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