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CONVERSION OF DIBENZOXEPINONES TO ARISTOCULARINE ALKALOIDS

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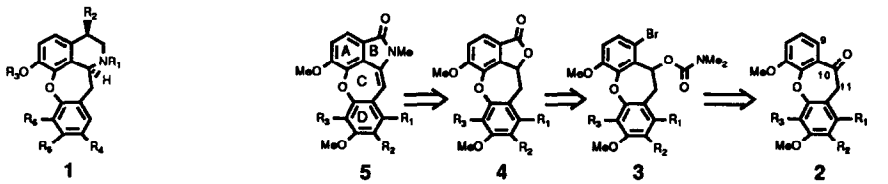
Abstract: A new synthesis of the aristocularine alkaloids, from the corresponding dibenzoxepinones, is described.

The cularines (**1**) are a large group of isoquinoline alkaloids with a dihydrodibenzoxepine system in their skeletons.[1] Among them, aristoyagonine (**5b**) is unique having a five-membered lactam as ring B. To date, **5b** has only been synthesized by multistep contraction of ring B of 4-hydroxysarcocapnine (**1**, R_1=R_3= Me, R_2= OH, R_4= H, R_5=R_6= OMe).[2]

We have now developed a general approach to the synthesis of aristocularines **5** which is based on an efficient annulation procedure starting from 10,11-dihydrodibenz(b,f)oxepin-10-ones **2**, which can be readily obtained.[3]



a, R_1=R_3= H, R_2= OMe; **b**, R_1=R_2= H, R_3= OMe; **c**, R_1=R_2= Br, R_3= OMe

For the construction of the lactam ring we initially thought of converting the keto function of **2** in an *ortho* directing group[4] in order to metalate at C-9; the resulting organometallic intermediate was then to be trapped by an appropriate electrophile. However, the tertiary amino function we select as directing group[5] proved impossible to metalate because β-elimination occurred.

We next decided to generate the organometallic unit at C-9 by halogen-metal exchange in a 9-bromoderivative **3**, in which the urethane group would act as an internal electrophile. To establish the validity of this strategy we first prepared the non-natural aristocularine **5a**. The monobromo compound **3a**[6] was treated with *t*-BuLi (1.1 equivalents) in THF at -90° C and the mixture was slowly heated for 1 hour at -40° C to afford, after addition of a few drops of MeOH and work-up, the desired **4a** (92% yield). This lactone was then transformed into **5a** (mp. 187-189° C)[7,8] by opening the ring with 40% aqueous $MeNH_2$ followed, after work-up, by Jones oxidation and final treatment with HCl(10%)/THF (1:5), RT, 4 h. (52% unoptimized overall yield).

Having proved the validity of our approach, we then addressed the synthesis of the natural cularine aristoyagonine (**5b**). In this case, attempted bromination at C-9 failed, a mixture of compounds with different degrees of bromination being obtained. In order to work with a uniformly brominated compound, we therefore used excess bromine to get the tribrominated compound **3c**

(69% overall yield from **2b**).[7,9] We now expected that *t*-BuLi treatment as above would bring about both the metalation of the ring A and the exchange of one of the bromine atoms on the lower ring; and to avoid the undesired possibility of benzyne formation in this latter position, we decided to carry out the reaction at very low temperature and at high dilution to favour intramolecular trapping rather than intermolecular condensation via the aryllithium on ring D. To this end, a 0.015 M THF solution of **3c** at -90° C was treated with 4 equivalents of *t*-BuLi and after 10 minutes, with the bath temperature at -70° C, the reaction was quenched with a few drops of MeOH. The solvent was evaporated to dryness and the residue was dissolved in CH_2Cl_2, washed with H_2O and purified by silicagel chromatography. Surprisingly we ended up with a 77% yield of the fully debrominated derivative **4b**.[7] This unexpected result can be explained as a consequence of the avidity of *t*-BuLi for bromine, even in the presence of a proton donor.[10]

Finally, using the same protocol as before, we obtained aristoyagonine (**5b**) from **4b** in 45% overall yield. We are currently investigating the synthetic potential of dibenzoxepinones **2** as precursors of other types of cularine alkaloid.

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6.- The dibenzoxepinone **2a** was reduced with $NaBH_4$ in MeOH (93%), followed by reaction with NaH in DMF and trapping of the alkoxide with *N-N*-dimethylcarbamoyl chloride (89%). The resulting urethane was brominated with Br_2 (1.5 equivalents) in AcOH in the presence of anhydrous NaOAc to give **3a** (88%).

7.- All new compounds were fully characterized spectroscopically and had satisfactory elemental analyses and/or high resolution MS.

8.- **5a**: ^{1}H-NMR (250 MHz, $CDCl_3$), δ: 7.19 (d, 1H, J= 8.2, Ar-H), 6.82 (d, 1H, J= 8.2, Ar-H), 6.48 (s, 1H, Ar-H), 6.31 (s, 1H, Ar-H), 5.51 (s, 1H, -CH=C-), 3.85 (s, 3H, Ar-OMe), 3.82 (s, 3H, Ar-OMe), 3.77 (s, 3H, Ar-OMe), 3.12 (s, 3H, *-NMe*). ^{13}C-NMR (62.83 MHz, $CDCl_3$), δ: 165.85 (CO), 151.42 (C), 149.54 (C), 147.20 (C), 145.57 (C), 141.67 (C), 136.17 (C), 127.11 (C), 121.87 (C), 118.82 (C), 118.17 (CH), 114.58 (CH), 113.74 (CH), 107.55 (CH), 106.47 (CH), 56.35 (CH_3), 56.08 (CH_3), 55.98 (CH_3), 25.30 (N-CH_3). IR (KBr), $\nu_{max.}$: 1100, 1220, 1240, 1450, 1510, 1530, 1620, 1670 and 1700 (C=O), 2840, 2940. MS m/z (%): 339 (M^+, 100), 324 (32), 311 (8), 296 (31), 281 (12), 266 (8), 252 (5), 238 (8), 210 (6), 171 (11), 154 (3), 139 (3), 127 (3).

9.- Compound **3c** was prepared from **2b** in a similar way as used for **3a**.

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