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Total Syntheses of Makaluvamines A, B, C and D, Metabolites of The Fijian Sponge *Zyzza* cf. *marsailis* Exhibiting Inhibitory Activities against Topoisomerase II

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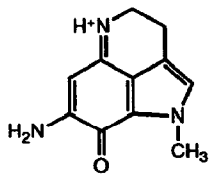
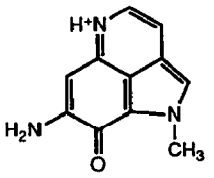
Abstract: Total syntheses of the tetrahydropyrroloquinoline-alkaloids, makaluvamines A, B, C and D (**1**, **2**, **3** and **4**) have successfully been carried out starting from the appropriate derivatives (**5**, **8** and **10**).

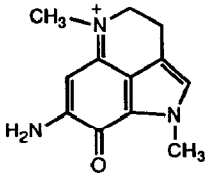
The tetrahydropyrroloquinoline-alkaloid families [prianosins[1a] (discorhabdins),[1b] batzellines,[1c] isobatzellines,[1c] wakayin[1d] and damirones[1e]] have been regarded as challenging targets by organic chemists for their rigidly fused ring structures and concomitant biological activities. Actually, many synthetic investigations of these natural products[2] including recent publication on synthesis of damirones by Cava,[2i] have been accumulated, since synthesis of dehydrobufotenine, the toad poison isolated from *Bufo marinus*.[2a]



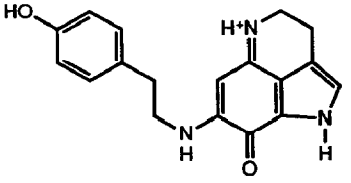
Makaluvamine A (1)



Makaluvamine B (2)

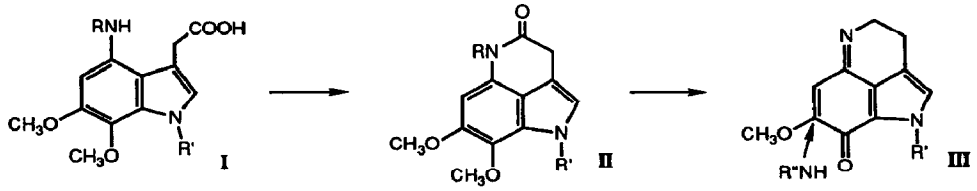


Makaluvamine C (3)

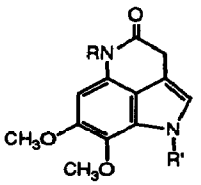


Makaluvamine D (4)

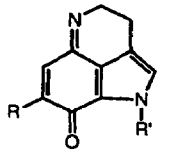
Very recently, these alkaloid families included as new members makaluvamines, isolated from the Fijian sponge *Zyzza* cf. *marsailis*, which possess potent inhibitory activities against the function of topoisomerase II as well as the growth of human ovarian tumor.[3] In this context, we had achieved the first total syntheses of discorhabdin C,[4a] batzelline C and isobatzelline C,[4b] and availability of the intermediates in hand would promise facile access to makaluvamines. These situations prompted us to initiate syntheses of makaluvamines A, B, C and D (**1**, **2**, **3** and **4**), as a part of our extensive investigations of biologically active marine natural products. Our synthetic methodology consists of i) lactamization of indole **I** to **II**, ii) reduction and oxidation to iminoquinone **III**, and iii) final introduction of appropriate amino functions. We describe herein our synthetic process.



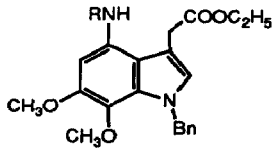
The known lactam (**5**)[4b] was submitted to reduction, followed by CAN oxidation to provide iminoquinone **6** [i. BH_3·SMe_2 / THF; ii. CAN / 60% aq.CH_3CN (48% in two steps)]. Exposure of **6** to NH_4Cl effected substitution substitution of the methoxy group to produce **7**, which on addition of TFA gave makaluvamine A



5: R = H, R' = CH_3
9: R = CH_3, R' = H



6: R = OCH_3, R' = CH_3
7: R = NH_2, R' = CH_3
10: R = OCH_3, R' = H



8: R = $COOCH_2CH_2Si(CH_3)_3$

(**1**)[5] as TFA salt [i. NH_4Cl / MeOH; ii. TFA / MeOH (98% in two steps)]. On the other hand, upon heating in the presence of palladium catalysts, **7** underwent oxidation, leading to makaluvamine B salt (**2**)[5] [i. 10% Pd-C / refluxing benzene; ii. TFA / MeOH (41% in two steps)]. After methylation, the indole (**8**)[4a] was successively deprotected to give a free amino acid, which was submitted to intramolecular cyclization to give lactam **9** [i. MeI, NaH / DMF (77%); ii. H_2, Pd-black / AcOH - 60% $HClO_4$ (10:1); iii. 10M KOH / MeOH; iv. DCC / THF (41% in three steps)]. According to essentially the same procedure as in the case of **5**, **9** was converted into makaluvamine C (**3**)[5] [i. BH_3•SMe_2 / THF; ii. CAN / 60% aq.CH_3CN; iii. NH_4OH / MeOH - $CHCl_3$; iv. TFA / MeOH (26% in four steps). Additionally, makaluvamine D (**4**)[5] was synthesized by coupling of iminoquinone **10**[4a] with tyramine hydrochloride [i. tyramine hydrochloride, $NaHCO_3$ / MeOH; ii. TFA / MeOH (92% in two steps)].

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5. 1: IR (KBr) 1670, 1605, and 1325 cm^{-1}; δ_H (DMSO-d_6) 2.84 (2H, t, J= 7.6 Hz), 3.76 (2H, t, J= 7.6 Hz), 3.89 (3H, s), 5.62 (1H, s), 7.31 (1H, s), 8.38 (1H, broad s), 9.15 (1H, broad s), and 10.60 (1H, broad s); δ_C (DMSO-d_6) 18.0, 35.8, 42.0, 86.5, 117.8, 122.3, 123.0, 131.0, 155.9, 156.7, and 168.2. 2: IR (KBr) 1680, 1600, 1495, and 1330 cm^{-1}; δ_H (DMSO-d_6) 3.42 (2H, broad s), 4.28 (3H, s), 6.34 (1H, s), 7.61 (1H, d, J= 6.8 Hz), 7.95 (1H, d, J= 6.8 Hz), 8.17 (1H, broad s), and 8.35 (1H, s); δ_C (DMSO-d_6) 38.0, 88.4, 111.3, 118.8, 120.6, 122.5, 129.9, 133.4, 144.0, 155.7, and 166.3. 3: IR (KBr) 1670 and 1615 cm^{-1}; δ_H (DMSO-d_6) 2.92 (2H, t, J= 7.6 Hz), 3.32 (3H, s), 3.90 (2H, t, J= 7.6 Hz), 5.69 (1H, s), 7.30 (1H, s), 8.68 (1H, broad s), and 9.40 (1H, broad s); δ_C (DMSO-d_6) 18.9, 39.1, 52.6, 85.4, 118.0, 123.2, 123.4, 126.6, 155.7, 156.5, and 167.4. 4: IR (KBr) 1680, 1635, and 1555 cm^{-1}; δ_H (DMSO-d_6) 2.79 (2H, t, J= 7.0 Hz), 2.88 (2H, t, J= 7.6 Hz), 3.47 (2H, complex), 3.81 (2H, t, J= 7.6 Hz), 5.55 (1H, s), 6.71 (2H, t, J= 8.4 Hz), 7.06 (2H, d, J= 8.4 Hz), 7.33 (1H, broad s), 8.99 (1H, broad signal), 9.35 (1H, broad s), 10.78 (1H, broad s), and 13.13 (1H, broad s); δ_C (DMSO-d_6) 18.0, 32.3, 42.3, 45.0, 84.1, 115.2, 118.6, 122.5, 123.7, 126.8, 128.1, 129.5, 152.9, 155.9, 157.0, and 167.4. The structures of other new compounds cited herein were supported by their spectral data.

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