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Recent developments in total syntheses of aculeatins

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ABSTRACT

Aculeatins, a growing family of natural products with potent antimalarial and/or anticancer activities, have been the targets for more than 20 total syntheses since the first members (aculeatins A-C) reported in 2000 partially due to their unprecedented and fascinating tricyclic 1,7-dioxadispiro[5.1.5.2]pentadecane (1,7-DODSP) skeleton. This Digest distills the two key strategies (POD/DSK and POD/DOMC) employed in all these syntheses for the construction of the 1,7-DODSP core and summarizes these total syntheses of aculeatins with the focus on different methods for the diastereo- and enantioselective preparation of the essential (5-keto-)1,3-diol substrates.

1. Introduction of aculeatins

Aculeatins A–D (Figure 1) were isolated by Heilmann's group[1-2] from rhizomes of the plant *Amomum aculeatum*, a widely used folk herb medicine against fever and malaria by the indigenous people of Papua New Guinea. In 2007, the structurally related aculeatols A-D ($\Delta^{8,9}$-alkene hydration of the corresponding aculeatins) along with aculeatins A and B were isolated by Kinghorn's group[3] from the hexane and chloroform extracts of the leaves and rachis of *Amomum aculeatum* that collected in Indonesia, which yielded congenerous aculeatins E and F and aculeatol E.[4]

Preliminary biological studies have shown that aculeatins A-D displayed potent *in vitro* antiprotozoal activity (IC_{50} 0.18-0.49 μM) and moderate to high cytotoxicity (IC_{50} 0.38-1.70 μM). Noteworthy is that aculeatin A is three-fold active (antiprotozoal and cytotoxic) than its spiroisomer aculeatin B. Additionally, aculeatin D was found to exhibit moderate to strong antimicrobial activity against *Bacillus cereus*, *Escherichia coli* and *Staphylococcus epidermidis*. However, aculeatin A was deemed to be inactive against P388 lymphocytic leukemia and human A2780S ovarian carcinoma *in vivo* models as reported by Kinghorn's group.[4]

Structurally, aculeatins A-F and aculeatols A-E represent a novel type of natural products with a fascinating and unprecedented 1,7-dioxadispiro[5.1.5.2]pentadecane skeleton (1,7-DODSP, *cf.,* dispiroketal cyclohexadienone). This core structure might hint a common biosynthetic pathway, which could inspire the development of a unified synthetic (biomimetic) strategy amenable to all aculeatins and aculeatols. Within the family, aculeatols were the $\Delta^{8,9}$-double bond hydration products of the aculeatins. Additional structure-differentiating features include the stereochemistry of C8, C6 and C4 and the length of the side chain (except aculeatin C).

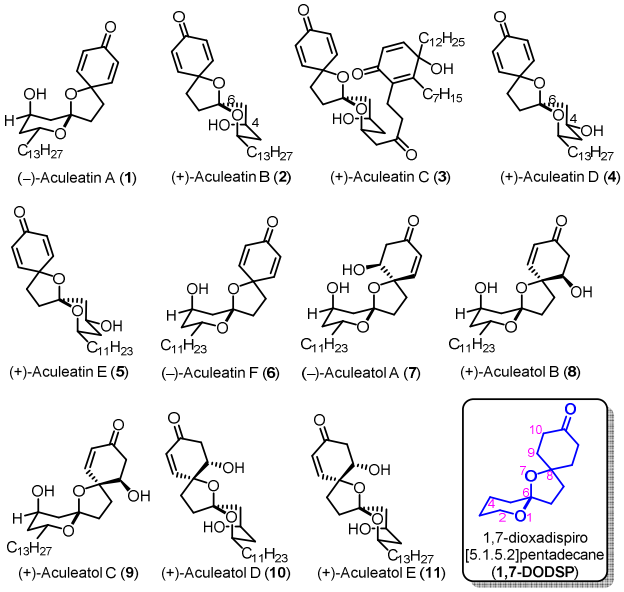

Figure 1. Structures of aculeatins and aculeatols.

Interestingly, the stereochemical differences were found to influence their biological potency: aculeatin A was three times

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