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Enantioselective synthesis and absolute configurations of aculeatins A and B

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Abstract—The two naturally occuring, bioactive spiroacetals aculeatins A and B have been synthesized for the first time in enantiopure form using an asymmetric allylation as the only chirality source. A further key step was a stereoselective aldol reaction with remote induction. The absolute configurations of the natural products have been established and the previously assigned relative configurations have been corrected.

The aculeatins A and B are two epimeric spiroacetals isolated five years ago from the terrestrial plant species *Amomum aculeatum* Roxb. (fam. Zingiberaceae). They were assigned structures (*relative* configurations) **1** and **2**, respectively. A more complex variant, aculeatin C **3**, was also isolated from the same plant (Fig. 1). Later, the same authors reported the isolation of a fourth member of this compound family, named aculeatin D and assigned structure and relative configuration **4**.[1,2] These compounds were found to display antiprotozoal activity against some *Plasmodium* and *Trypanosoma* species. In addition, they showed antibacterial activity and were cytotoxic against the KB cell line.

The aculeatins A–D represent a novel type of natural compounds displaying the unusual, previously unreported 1,7-dioxadispiro[5.1.5.2]pentadecane system. The observed biological activity of the aculeatins may be related to the presence of a Michael acceptor moiety.[3] The spiroacetals themselves are also interesting molecular fragments, which are present in many pharmacologically relevant substances such as macrolide or polyether antibiotics.[4] In view of this and of the aforementioned biological activities, it is not surprising that the aculeatins have already aroused interest in the synthetic community. As a matter of fact, two papers have very recently appeared, which deal with the synthesis of aculeatins A, B, and D, in all cases in racemic form.[5] Both syntheses relied upon the same type of phenolic oxidation to form the 1,7-dioxadispiro[5.1.5.2]pentadecane system (see below). In this communication, we present the first synthesis of **1** and **2** in enantiopure form.

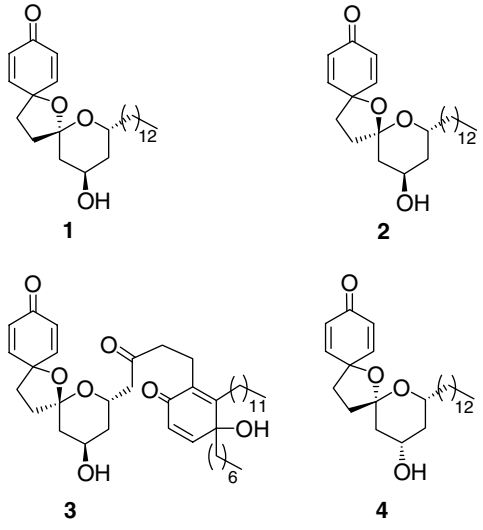

Figure 1. Published structures and relative configurations of aculeatins A–D.

The retrosynthetic concept is depicted in Scheme 1. Thus, the dispirocyclic system is to be created via pheno-

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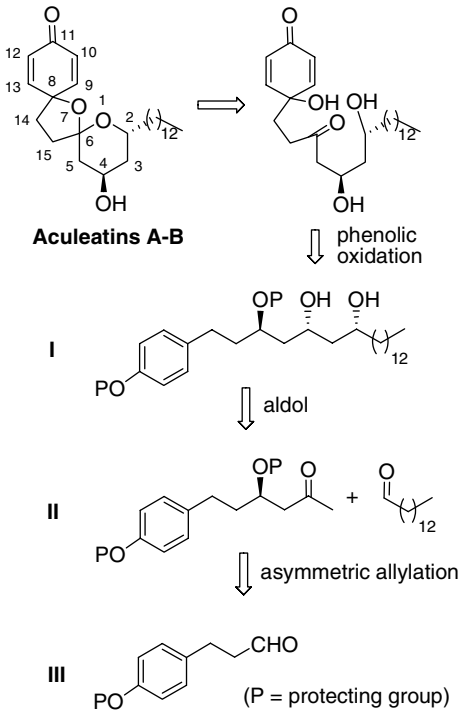
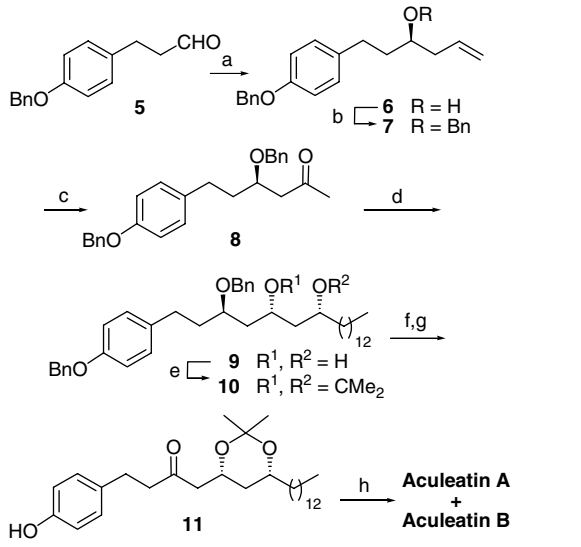


Scheme 1.

lic oxidation of an appropriately substituted intermediate ketone, related in turn to the protected triol **I**. The latter is derived from the aldol reaction of ketone **II** with *n*-tetradecanal. Intermediate **II** should be obtained from a suitably protected dihydro-*p*-coumaraldehyde **III** by means of asymmetric allylation and functional manipulation.

Scheme 2 shows the details of the synthesis. Thus, the known 3-(*p*-benzyloxyphenyl)propanal **5**[6] was subjected to asymmetric allylation using the chiral allylborane prepared as reported from allylmagnesium bromide and (−)-DIP-Cl [(−)-diisopinocampheylchloroborane].[7] Homoallyl alcohol **6** was obtained in over 96% ee as judged by NMR examination of the Mosher ester.[8] Benzylation of the hydroxyl group followed by Wacker oxidation[9] provided methyl ketone **8**. Boron aldol reaction[10] of this ketone with *n*-tetradecanal followed by in situ reduction with $LiBH_4$ afforded the monobenzylated *anti*,*syn*-1,3,5-triol **9** as a single diastereomer.[11] Protection of the two free hydroxyl groups as an acetonide followed by debenzylation and Swern oxidation afforded **11**. Hydrolytic cleavage of the acetonide moiety furnished the expected β,δ-dihydroxy ketone albeit in low yield (<35%). Fortunately, treatment of acetonide **11** with phenyliodonium bis(trifluoroacetate) not only caused the desired phenolic oxidation[5,12] but also acetonide hydrolysis and subsequent spiroacetalization. This yielded a 5.5:1 mixture of two optically active products with spectral properties identical to those reported for aculeatin A and aculeatin B.[1]

A more close examination of the respective NMR spectral properties revealed, however, an important issue. The major product exhibited in fact the optical rotation



Scheme 2. Reagents and conditions: (a) allylBIpc$_2$ from (−)-DIP-Cl and allylmagnesium bromide, Et_2O, 3 h, −90 °C; (b) NaH; THF, then BnBr, rt, overnight, 85% overall from **5**; (c) $PdCl_2$, $CuCl_2$, aq DMF, O_2, 2 d, 75%; (d) Bu_2BOTf, $EtNiPr_2$, CH_2Cl_2, −78 °C, 1 h, then addition of *n*-tetradecanal, 3 h, −78 °C, then $LiBH_4$, 2 h, −78 °C, 65% overall; (e) 2,2-dimethoxypropane, camphorsulfonic acid (cat.), Me_2CO, rt, 1 d, 72%; (f) H_2 (1 atm), 10% Pd/C, EtOAc, rt, 6 h, 70%; (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 → 0 °C, 87%; (h) $PhI(OOCCF_3)_2$, Me_2CO/H_2O (9:1), rt, 24 h, 65% overall, 5.5:1 mixture of aculeatins A and B.

and spectral properties associated with aculeatin A.[1] It was stable and showed no noticeable tendency to isomerize to the minor stereoisomer. NOE measurements evidenced the absence of dipolar correlations between the methine proton H-2 and one methylene proton at C-15 (for numbering, see Scheme 1). This strongly suggests that its configuration has to be represented as **2** (see Fig. 2), not **1** as proposed.[1] In addition, structure **2** ben-

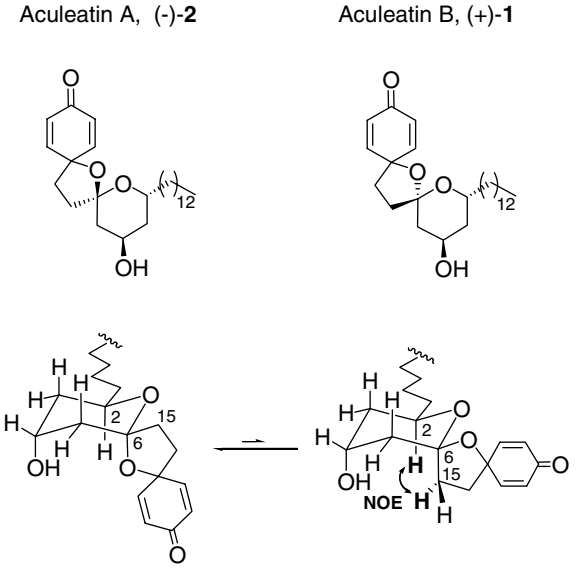


Figure 2. Corrected structures and absolute configurations of aculeatins A and B.

efits from a favorable anomeric effect,[13] in agreement with the higher stability of aculeatin A. In support of this reasoning, the minor isomer, which was unstable and isomerized slowly to the major one, showed a marked NOE between the methine proton H-2 and one methylene proton at C-15. These properties, which are associated to aculeatin B, are only compatible with stereostructure **1** (Fig. 2), which does not exhibit a favorable anomeric effect. A further support is given by the markedly higher δ value of H-2 in aculeatin A (δ 4.10 vs δ 3.86 ppm in aculeatin B), which points to its 1,3-diaxial relation with the anomeric oxygen atom. In summary, the Swiss workers[1] erroneously interchanged the relative stereostructures of the aculeatins A and B, *which are in consequence* **2** *and* **1**, *respectively*.[14]

The optical rotation values of the synthetic compounds were very similar to those of the natural compounds and the signs are the same. Our synthesis therefore has led to the natural enantiomers of both aculeatins and permitted the establishment of their *absolute* configurations (Fig. 2).[15]

Acknowledgments

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15. Physical and spectral data of the synthetic aculeatins. *Aculeatin A:* oil; $[\alpha]_D$ −5.2 (*c* 0.9; $CHCl_3$), lit.[1] $[\alpha]_D$ −5.3 (*c* 0.2; $CHCl_3$); IR ν_{max} 3550 (br, OH), 1673 (ketone C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (1H, dd, $J = 10.0$, 3.0 Hz), 6.76 (1H, dd, $J = 10.0$, 3.0 Hz), 6.14 (1H, dd, $J = 10.0$, 1.7 Hz), 6.10 (1H, dd, $J = 10.0$, 1.7 Hz), 4.15–4.10 (2H, m), 3.35 (1H, br d, $J = 10.0$ Hz, OH), 2.38 (1H, m), 2.24 (1H, m), 2.05–2.00 (3H, m), 1.93 (1H, br d, $J = 14.0$ Hz), 1.79 (1H, br dd, $J = 13.7$, 2.0 Hz), 1.60–1.40 (5H, br m), 1.40–1.20 (20H, br m), 0.88 (3H, t, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 109.2, 79.8 (C), 150.9, 148.7, 127.4, 127.2, 65.4, 64.9 (CH), 39.2, 38.0, 36.0, 34.2, 32.0, 29.7 (several overlapped signals), 29.4, 25.7, 22.7 (CH_2), 14.1 (CH_3); HR EIMS *m/z* (rel int.) 418.3117 (M^+, 2), 400 (M^+-H_2O, 6), 310 (6), 236 (25), 165 (100), 107 (73). Calcd for $C_{26}H_{42}O_4$, $M = 418.3083$. *Aculeatin B:* oil; $[\alpha]_D$ +53.2 (*c* 0.4; $CHCl_3$), lit.[1] $[\alpha]_D$ +50 (*c* 0.8; $CHCl_3$); IR ν_{max} 3460 (br, OH), 1670 (ketone C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, dd, $J = 10.0$, 2.9 Hz), 6.77 (1H, dd, $J = 10.0$, 2.9 Hz), 6.13 (1H, dd, $J = 10.0$, 1.8 Hz), 6.10 (1H, dd, $J = 10.0$, 1.8 Hz), 4.36 (1H, apparent quintuplet, $J = 3.2$ Hz), 3.86 (1H, m), 2.68 (1H, br dd, $J = 12.8$, 7.2 Hz), 2.30 (1H, td, $J = 12.3$, 7.2), 2.10–2.00 (2H, m), 1.95–1.85 (2H, m), 1.60–1.40 (8H, br m), 1.40–1.20 (19H, br m), 0.88 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 108.6,

77.6 (C), 152.2, 149.2, 127.2, 127.1, 69.5, 65.2 (CH), 40.7, 38.0, 35.8, 35.4, 35.3, 31.9, 29.7 (several overlapped signals), 29.4, 29.3, 25.9, 22.7 (CH_2), 14.1 (CH_3); HR EIMS m/z (rel int.) 418.3108 (M^+, 9), 400 (M^+-H_2O, 24), 310 (16), 235 (85), 165 (100), 107 (23). Calcd for $C_{26}H_{42}O_4$, $M = 418.3083$.