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Structure revision of the rare sponge metabolite echinosulfone A, and biosynthetically related echinosulfonic acids A–D

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ABSTRACT

A short Friedel-Crafts mediated total synthesis has informed structure revision of the rare marine sponge natural product echinosulfone A (**1a**) and the biosynthetically related echinosulfonic acids A–D (**2a**–**5a**).
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Introduction

The bis-indole natural products echinosulfone A (**1**) and echinosulfonic acids A–C (**2**–**4**) were first reported by Capon et al. in 1999 from a southern Australian marine sponge, *Echinodictyum* sp., with structures assigned by detailed spectroscopic analysis (Fig. 1) [1]. In addition to being unprecedented examples of bis-indole sulfonic acids, the echinosulfonic acids displayed intriguing chemical properties, undergoing rapid (equilibrium) solvolysis during handling. This latter property proved particularly challenging during isolation and handling, which relied on the use of hydroxylic solvents (*viz.*, MeOH, EtOH and H_2O). A subsequent 2006 report by Sévenet et al. described a related bis-indole, echinosulfonic acid D (**5**) as a co-metabolite with echinosulfonic acid B (**3**), from a new Caledonian sponge *Psammoclemma* sp. (Fig. 1) [2]. Lacking the C-1″ tertiary OH moiety pivotal to the solvolytic instability of **2**–**4**, echinosulfonic acid D (**5**) was stable to solvolysis during handling.

Despite the discovery of a vast array of structurally diverse natural products from marine sources, especially sponges, published examples of the echinosulfone/echinosulfonic acid structure class are limited to **1**–**5**, making them both very rare and unique to marine sponges. Re-examining authentic samples and spectroscopic data for **1**–**4** we speculated that the published structures were incorrect. To test this hypothesis, we undertook a total synthesis of **1a**, leading to a structure revision for both echinosulfone A, and echinosulflonic acids A–D (Fig. 1).

Results and discussion

In a model synthesis, Friedel-Crafts acylation of indole [3] as outlined in Scheme 1 (R = H) yielded a bis-indole ketone (60%),

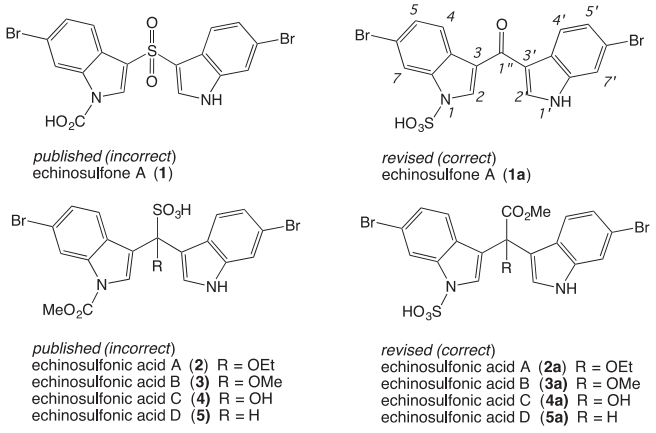

Fig. 1. Echinosulfone A and echinosulfonic acids A–D.

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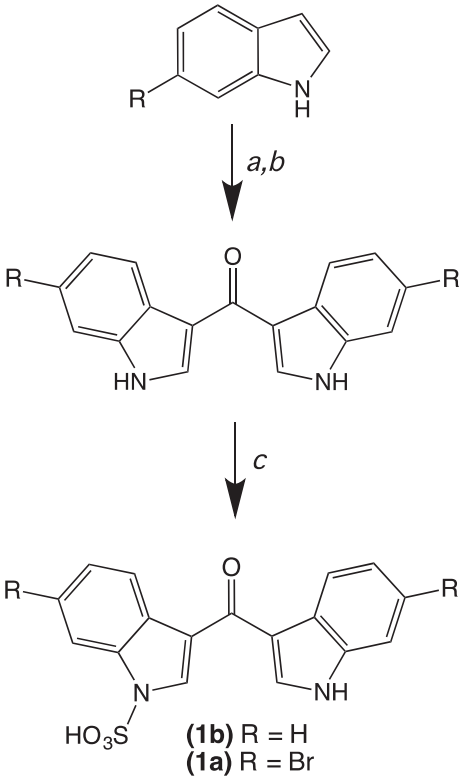

Scheme 1. (a) DCM, SO_2Cl_2, cat. DMF, 25 °C 12 h, N_2 gas; (b) DCE, indole, $ZrCl_4$, 0 °C, 30 min, 30 °C, 5 h, N_2 gas, (c) Py.SO_3, pyridine, 120 °C 12 h.

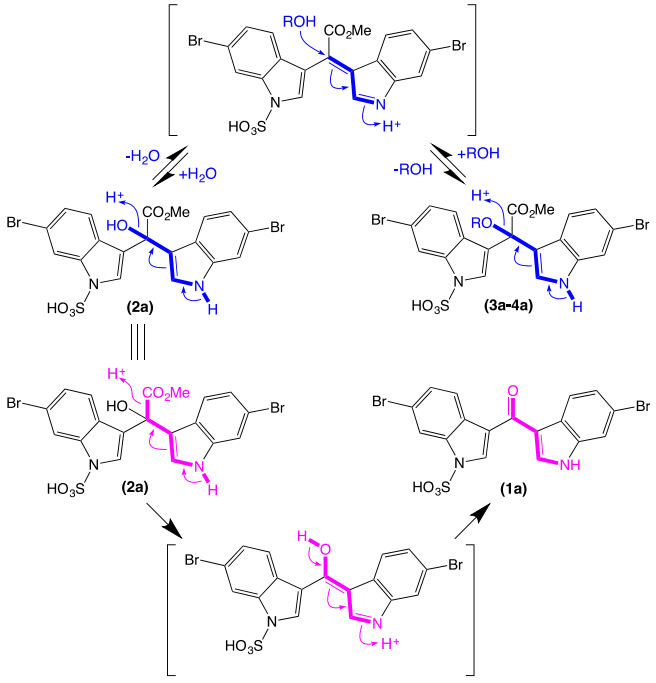

Fig. 2. Plausible biosynthetic relationship.

which following sulfonation with pyridinium-sulfonate returned didebromoechinosulfone A (**1b**) (38%). The structure for **1b** was confirmed by spectroscopic analysis (Table S1 and Figs. S1, S2). With a successful synthetic methodology in hand, Friedel-Crafts acylation of commercially available 6-bromoindole as outlined in Scheme 1 (R = Br) yielded the corresponding brominated bis-indole ketone (60%), which following sulfonation returned a product **1a** (20%), identical in all respects with an authentic sample of echinosulfone A (Tables 1, S2 and Figs. S3, S4). Given these observations we propose the revised structure for echinosulfone A as shown (Fig. 1).

Table 1
Comparison of 1D NMR (600 MHz, DMSO d_6) data for synthetic and natural echinosulfone (**1a**).

Pos.	*Synthetic* ***1a***		*Natural* ***1a***	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
2	132.8	8.07, br s	132.7	8.08, s
3	115.5		115.4	
3a	126.3		126.2	
4	123.1	8.13, d (*8.1*)	122.9	8.13, d (*8.6*)
5	124.6	7.37, d (*8.5*)	124.4	7.37, dd (*8.6, 1.9*)
6	115.8		115.6	
7	116.4	8.02, br s	116.4	8.02, (d, *1.9*)
7a	135.7		135.6	
1′-NH		11.94, br s		12.00, br s
2′	133.1	8.16, d (*2.7*)	132.9	8.15, br s
3′	116.4		114.2	
3a′	125.4		125.3	
4′	123.1	8.14, d (*8.1*)	122.9	8.14, (d, *8.5*)
5′	124.1	7.32, d (*8.5*)	123.9	7.32, dd (*8.5, 1.7*)
6′	115.3		115.1	
7′	114.8	7.70, br s	114.7	7.70, (d, *1.7*)
7a′	137.5		137.5	
1″	183.8		183.7	

A plausible biosynthetic relationship (Fig. 2) linking **1a** with the co-metabolite echinosulfonic acids A–C, supports the proposition that their structures should be revised, from **2**–**5** to **2a**–**5a**. This relationship draws on the likely solvolysis mechanism, in which an acid-mediated enamine-imine rearrangement centred on 1′-NH catalyses the loss of H_2O to yield a highly coloured intermediate. This transient species spontaneously reacts with available nucleophiles (*i.e.,* hydroxylic solvents), facilitating the equilibrium observed between echinosulfonic acids A–C (**2a–4a**) (Fig. 2 blue pathway).

In a parallel manner (Fig. 2 pink pathway), during the biosynthetic process an enamine-imine rearrangement could initiate the loss of HCO_2Me, generating a highly reactive enol intermediate. The latter could collapse via synchronised enol-keto and imine-enamine rearrangements, linking echinosulfonic acids to echinosulfone A (**1a**). Given this relationship, it seems plausible that the structures for echinosulfonic acids A–C should be revised, to bring them in line with that for echinosulfone A (Fig. 1).

Similarly, as echinosulfonic acid D was reported as a co-metabolite with echinosulfonic acid B, its structure should also be revised. All the revised structures for echinosulfonic acids A-D are in full accord with the reported 1D and 2D NMR data.

Conclusion

Total synthesis of echinosulfone A has prompted the assignment of revised structures for echinosulfone A (**1a**) and echinosulfonic acids A–D (**2a–5a**).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151651.

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