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Stereochemical assignment of the fungal metabolite xestodecalactone A by total synthesis ☆

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Abstract—The first synthesis of the macrocyclic natural product xestodecalactone A, a metabolite of a sponge-derived fungus, is described. By the use of methyl 5-hydroxyhexanoate in its *R*- or *S*-configured form, or as its racemate as the precursors, both enantiomers of xestodecalactone A as well as the racemic compound were obtained. Comparison of these synthetic products with the natural product by circular dichroism (CD) spectroscopy and by HPLC on a chiral phase revealed the natural product to have the (*R*)-configuration.

The xestodecalactones A (**1**), B (**2a**) and C (**2b**) are secondary metabolites of an isolate of the fungus *Penicillium cf. montanense* obtained from the marine sponge *Xestospongia exigua*.[1] Structurally, they constitute 10-membered macrolides with a fused 1,3-dihydroxybenzene ring. Xestodecalactone B (**2a**) has been shown to exhibit antifungal activity against *Candida albicans*.[2] The constitutions and, in the case of **2a** and **2b**, relative configurations of these compounds, initially assigned to a far degree by using hyphenated HPLC techniques like LC–MS/MS and LC–NMR, were subsequently confirmed off line, after isolation of the compounds. The stereostructures of the xestodecalactones were investigated by HPLC coupled to circular dichroism (CD) spectroscopy in combination with quantum chemical CD calculations. The absolute configurations, however, could not be unambiguously attributed, due to the conformational flexibility of the lactone ring and the occurrence of pseudoenantiomeric conformations with near-identical energetic contents but opposite CD contributions, in combination with the unprecedented structural type, thus not permitting a simple empirical comparison with related compounds of known absolute configuration.[1–3]

Previously described fungal metabolites structurally related to the xestodecalactones are curvularin (**3**),[4] which is the 12-ring homologue of **1**, and sporostatin (**4**),[5] which differs from **1** only by having an additional double bond in the lactone ring. While the former is known to have the (*S*)-configuration,[6] the configuration of **4** has not yet been determined (Fig. 1).

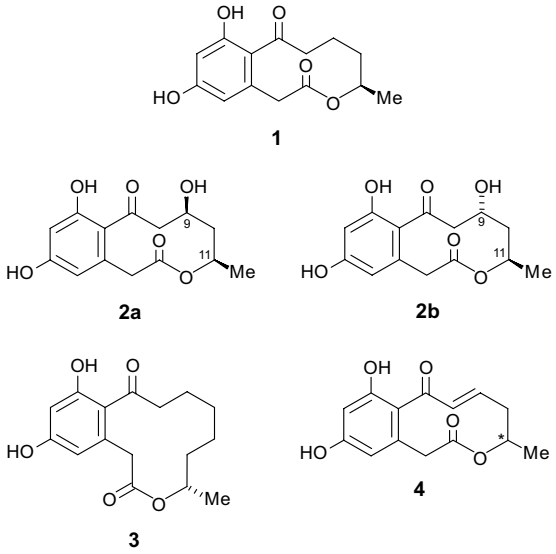

Figure 1. Macrocyclic benzo-annellated lactones from fungi: xestodecalactone A (**1**), B (**2a**) and C (**2b**), curvularine (**3**) and sporostatin (**4**).

Keywords: Xestodecalactones; Total synthesis; Absolute configuration; Natural products; Chiral phase; Circular dichroism spectroscopy.

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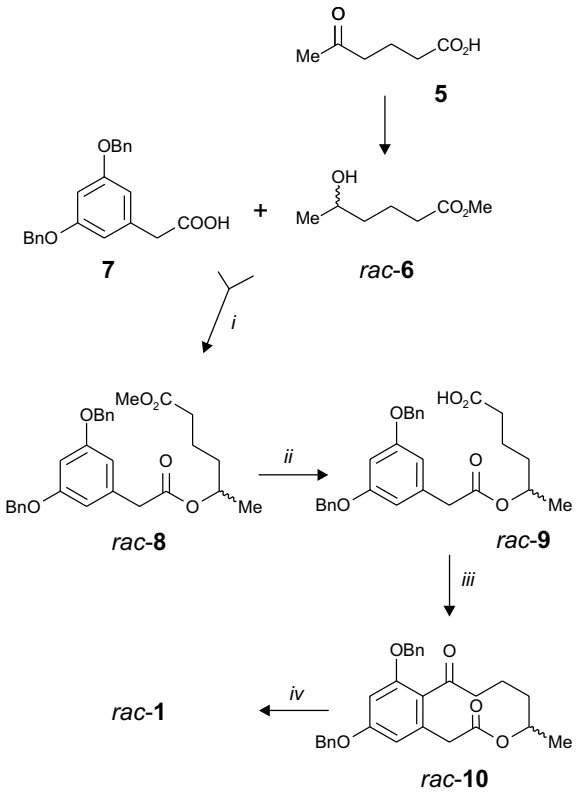
In this paper, we report on the assignment of the absolute configuration of xestodecalactone A (**1**), by its stereochemically unequivocal total synthesis, both as its *S*- and its *R*-enantiomer, and as the respective racemate, and comparison of these three synthetic products with natural xestodecalactone A by CD spectroscopy and by chromatography on a chiral phase.

In analogy to a synthetic strategy developed for the synthesis of the related, but larger ring system of curvularin (**3**) by Bracher et al.[7] compound **1** was built up from (3,5-dibenzyloxyphenyl)acetic acid (**7**) and methyl 5-hydroxyhexanoate (**6**). For a first, exploratory synthesis of racemic xestodecalactone A (*rac*-**1**), *rac*-**6** was easily obtained from 5-oxohexanoic acid (**5**) by reduction with sodium borohydride and treatment of the product with a cation exchanger (Bayer, Lewatit SC108, H^+ form) in methanol (see Scheme 1).[8]

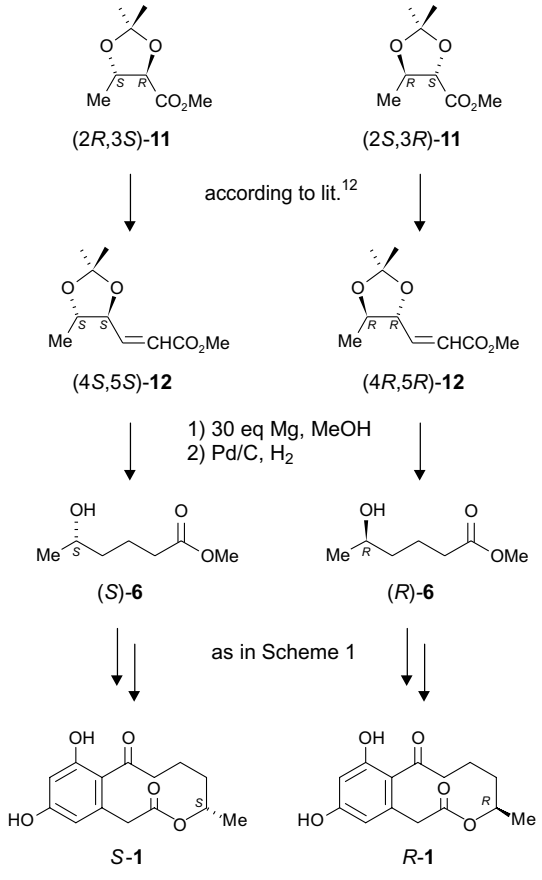
Esterification of the aromatic acid building block **7** with *rac*-**6** gave the diester *rac*-**8** in 79% yield.[9] Since the ring closure required the presence of a free terminal acid function, the methyl ester group of **8** was selectively cleaved by reaction with NaCN in HMPA,[7,10,11] delivering the carboxylic acid *rac*-**9** in 80% yield. Ring closure by intramolecular acylation was achieved in TFA/TFAA resulting in the dibenzylether *rac*-**10** of xestodecalactone A. The yield of this reaction was 42%, which was thus markedly higher than the 15% yield reported for the corresponding cyclization reaction in the synthesis of curvularin (**3**).[7] Subsequent hydrogenolytic O-debenzylation using Pd/C (10%) as the catalyst eventually completed the first synthesis of racemic xestodecalactone A (*rac*-**1**).

For the analogous synthesis of *R*- and *S*-xestodecalactone A, (*R*)-**1** and (*S*)-**1**, enantiopure methyl 5-hydroxyhexanoate (**6**) was required in both enantiomeric forms. Compounds (*S*)-**6** and (*R*)-**6** were synthesized from the acetonides of methyl (2*R*,3*S*)-dihydroxybutyrate, (2*R*,3*S*)-**11**, and of its enantiomer, (2*S*,3*R*)-**11**, respectively (see Scheme 2), following a known procedure.[12] Reduction of the respective enantiomer of **11**, Swern oxidation, and Wittig reaction gave the acetonides of the respective methyl 4,5-dihydroxy-2-hexenoate, (4*S*,5*S*)- and (4*R*,5*R*)-**12**. In contrast to the literature, these compounds could, even with an excess of magnesium, not be completely reduced to *S*- and *R*-**6**, but only to a mixture of regioisomeric methyl 5-hydroxy-2- and -3-hexenoates. Conversion of this mixture to the respective enantiomer of **6** was achieved by hydrogenation with Pd/C as the catalyst under atmospheric pressure. As before for *rac*-**6**, *S*- and *R*-**6** were smoothly transformed to *S*- and *R*-**1**, respectively.

With (*R*)-, (*S*)- and *rac*-**1** available, these synthetic products could now be stereochemically compared with natural xestodecalactone A, by HPLC analysis on a chiral phase (Chiralcel OD-RH 4.6×150 mm; eluents: water + 0.05% TFA (A) and MeCN (B); linear gradient:



Scheme 1. Reagents and conditions: (i) DCC, DMAP, CH_2Cl_2, 79%; (ii) NaCN, HMPA, 80%; (iii) TFA, TFAA, 42%; (iv) Pd/C, H_2, 36%.



Scheme 2.

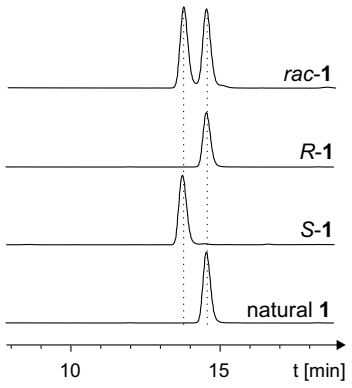


Figure 2. HPLC of *rac*-**1**, (*R*)-**1**, and (*S*)-**1**, as well as natural xestodecalactone A on a chiral phase.

0 min—20% B, 30 min—35% B; flow rate: 0.5 mL/min). The racemic material, *rac*-**1**, gave two well separated peaks for the two enantiomers (*R*)-**1** and (*S*)-**1** (see Fig. 2), eluting after 14.5 and 13.9 min, respectively, as clarified by chromatographic comparison with the pure synthetic enantiomers. By its retention time and with the help of co-elution experiments, natural xestodecalactone A was shown to possess the (*R*)-configuration. This result was confirmed by the identical CD spectra of (*R*)-**1** and natural xestodecalactone A.[13] The xestodecalactones B and C (**2a** and **2b**) both have similar CD spectra as **1**,[1] so that an (11*R*)-configuration of these compounds—and thus 9*S*,11*R* for **2a** and 9*R*,11*R* for **2b**—can be tentatively assumed.

Interestingly, natural xestodecalactone A (**1**) thus possesses the opposite configuration at C-11 as compared to its configurationally assigned[6] 12-ring homologue, (*S*)-curvularin (**3**).

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