Enantioselective Synthesis of the Sporolide Quinone Acid Fragment

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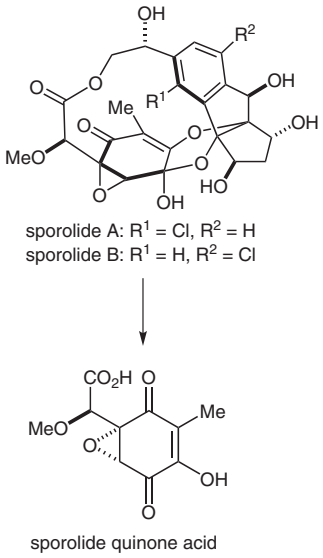
Abstract: The sporolide quinone acid is a key fragment in the biosynthesis of the complex heptacyclic marine metabolite sporolide. We report a concise enantioselective route to this fragment, which is obtained in seven steps with 65% overall yield from trimethoxybenzene. The enantioselective transfer reduction is achieved by Ipc_2BCl, and the absolute configuration of the product secured by X-ray analysis of its cinchonine salt. The target fragment is then obtained by methylation and oxidation to the quinone by AgO.

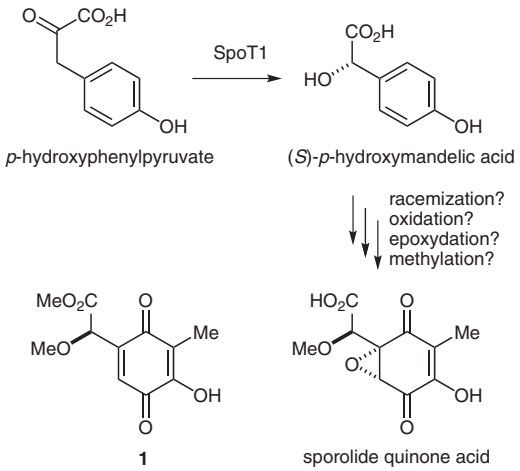
Key words: asymmetric synthesis, natural products, biosynthesis, transfer hydrogenation, quinones

The marine natural products sporolides A and B (Equation 1), isolated in 2005 by Fenical and coworkers,[1] display a complex heptacyclic framework involving a chlorinated cyclopenta[*a*]indene ring and hydrated quinone hydroxy acid fused in a macrocyclic ansa-type structure. This densely functionalized and compact architecture is built from 24 C atoms, out of which 22 are either oxygenated or sp^2 hybridized. Due to its complex structure and unsolved biosynthesis, several research groups embarked on studies on this marine metabolite,[2] and, recently, sporolide had succumbed to total synthesis by Nicolaou and co-workers earlier this year.[3] From a structural point of view, this intramolecularly hydrated macrolide could be degraded by hydrolysis into two key components, the cyclopenta[*a*]indene fragment and a chiral α-methoxy quinone acid. This analysis is also supported by biosynthetic investigations, which demonstrated separate biogenesis of the two fragments.[2b,d]



Equation 1

This hypothesis highlights the importance of the epoxyquinone acid as a key precursor in the biosynthesis of sporolide. The first step in the quinone biosynthesis via (*S*)-*p*-hydroxy mandelic acid [(*S*)-HMA] was recently demonstrated in vitro,[2d] and the putative enzymes (SpoT1-T9) for sporolide quinone acid generation in *Salinospora tropica* have been postulated (Scheme 1). Remaining questions in the biosynthesis of this sporolide acid involve the racemization step of (*S*)-HMA to the final *R*-configured sporolide quinone acid, the sequence of oxidation reactions, and the postulated *S*-adenosyl methionine dependent O- and C-methylations. These open biogenetic questions, as well as its utility in a total synthesis campaign towards the sporolides, renders the sporolide quinone acid fragment **1** a key target. In this letter, we report an efficient stereoselective preparation of this quinone fragment of sporolide.



Scheme 1 Postulated biosynthesis of the sporolide quinone acid according to Moore and co-workers[2d] and target fragment **1**

The synthesis started with commercially available 1,2,4-trimethoxybenzene, which was metalated with *n*-BuLi and quenched with MeI to give **2** in 99% yield (Scheme 2).[4] The pyruvate derivative **3** was directly obtained via Friedel–Crafts acylation[5] in 98% yield and no regioisomer could be detected by NMR analysis. The enantioselective reduction of the keto group was examined next, and catalytic enantioselective reductions such

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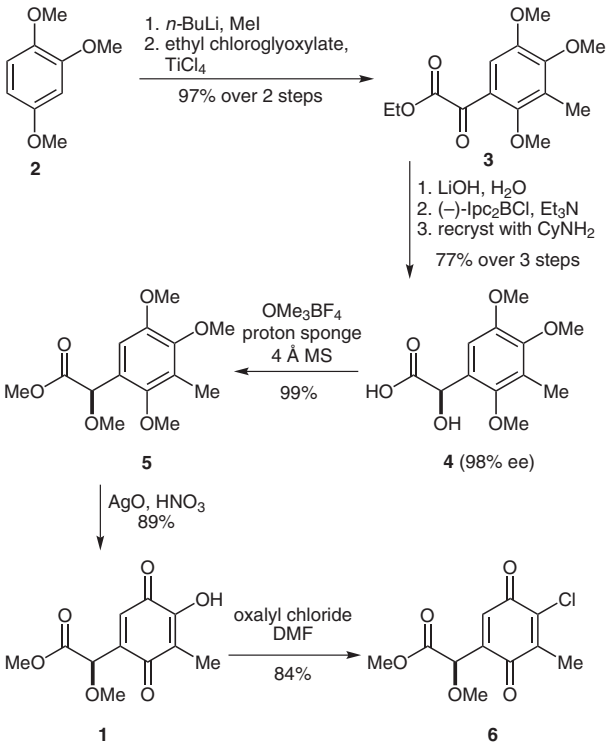
as Corey–Itsuno[6] or the enantioselective Friedel–Crafts hydroxyalkylation developed by Jørgensen[7] have not been successful on this substrate. Gratifyingly, transfer reduction with chlorodiisopinocampheylborane (Ipc_2BCl)[8] was identified as the method of choice.



Scheme 2 Synthesis of the sporolide quinone fragment **1**

After saponification of the ethylester **3** by LiOH and H_2O, the resulting carboxylic acid was deprotonated (Et_3N) and the B reagent was slowly added at low temperature. The α-hydroxy **4**[10] acid was obtained in high enantiomeric purity after a single recrystallization with cyclohexylamine (98% ee and 77% yield over 3 steps), as determined by HPLC on chiral stationary phases. The absolute configuration of the newly formed stereogenic center was unambiguously established by X-ray diffraction of the cinchonine salt (CCDC 742509). Moreover, CH_2Cl_2 was present in the crystal structure, thus providing additional confirmation of the correct configuration.

The *R*-configured hydroxy acid **4** was then reacted with Meerwein's salt to provide the doubly methylated hydroquinone ester **5**. An acidic solution of Ag(II) oxide[9] gave the target sporolide fragment **1**[11] in 89% yield. In addition, this hydroxyquinone can be readily transformed to the chloro-paraquinone **6**.[12] This activated vinylogous acyl chloride can be utilized in further synthetic studies by coupling to the cyclopenta[*a*]indene fragment of sporolide.

In conclusion, we report here a short, enantioselective route to the sporolide quinone acid fragment **1**, which is obtained in seven steps with an overall yield of 65% from commercially available 1,2,4-trimethoxybenzene. Key for the installment of the stereogenic center was a transfer hydrogenation with (–)-Ipc_2BCl, and the absolute configuration was secured by X-ray crystallographic analysis of the cinchonine salt. Further elaboration to the quinone was achieved by deprotection and oxidation with Ag(II) oxide. This fragment and its derivatives can now be utilized in further synthetic studies on the sporolides as well as in biosynthetic investigations.

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(10) **Preparation and Selected Data for Compound 4**
A solution of 2-oxo-2-(2,4,5-trimethoxy-3-methylphenyl)-acetic acid (300 mg, 1.18 mmol, 1.0 equiv) in THF (6 mL) at –40 °C was treated with Et_3N (164 mL, 1.18 mmol, 1.0 equiv) and stirred for 5 min followed by the slow addition of (–)-Ipc_2BCl (417 mg, 1.30 mmol, 1.1 equiv) in THF (2 mL). The reaction mixture was gradually warmed up to r.t. and stirred at r.t. for 3 h. The reaction was quenched with H_2O, treated with NaOH (10%) to pH >12, extracted with Et_2O, and the organic layers were combined and washed with H_2O (25 mL). The aqueous layers were then combined and acidified with 1 N HCl to pH 2 and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Once concentrated, the crude hydroxy acid was purified by recrystallization from hot EtOH as its cyclohexylammonium salt. The title compound was then obtained (233 mg, 0.909 mmol, 77%) as a white crystalline

solid by extraction with Et_2O of the aqueous acid solution of the salt. R_f = 0.21 (CH_2Cl_2–MeOH–AcOH = 9:1:0.05); $[\alpha]_D^{25}$ –81.6 (*c* 0.2325, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 1 H), 5.36 (s, 1 H), 3.84 (s, 6 H), 3.80 (s, 3 H), 2.24 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.66, 174.75, 150.16, 148.35, 125.78, 125.41, 107.98, 68.61, 61.33, 60.33, 55.99, 9.71. ESI-HRMS (TOF): *m/z* calcd for $C_{12}H_{16}O_6$ [M + Na]$^+$: 279.0845; found: 279.0834. IR: ν = 3429 (br m), 2994 (m), 2940 (m), 2858 (w), 1728 (s), 1597 (w), 1489 (s), 1462 (m), 1420 (m), 1335 (m), 1242 (s), 1123 (s), 1084 (s), 1007 (m) cm^{-1}.

(11) **Preparation and Selected Data for Compound 1**
To a stirred solution of (*R*)-methyl 2-methoxy-2-(2,4,5-trimethoxy-3-methylphenyl)acetate (**5**, 250 mg, 0.879 mmol, 1.0 equiv) in dioxane (4 mL) was added AgO (545 mg, 4.397 mmol, 5.0 equiv) followed by 4 N HNO_3 until the silver oxide was completely dissolved. The resulting solution was stirred for 30 min and then diluted with CH_2Cl_2. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to afford the crude product, which was purified by chromatography using hexane–EtOAc (8:2) as eluent. The analytically pure product (188 mg, 0.782 mmol, 89%) was obtained as a red viscous oil. R_f = 0.50 (hexane–EtOAc = 1:1); $[\alpha]_D^{25}$ –33.0 (*c* 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, *J* = 1.3 Hz, 1 H), 4.90 (d, *J* = 1.3 Hz, 1 H), 3.77 (s, 3 H), 3.51 (s, 3 H), 1.96 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.63, 183.06, 169.48, 151.73, 146.22, 128.88, 118.02, 76.81, 59.37, 53.25, 1.45. IR: ν = 3352 (w), 2955 (m), 2920 (s), 2851 (m), 1744 (s), 1659 (s), 1643 (s), 1620 (m), 1458 (w), 1393 (m), 1346 (m), 1269 (m), 1196 (s), 1157 (m), 1107 (m), 1045 (w), 1011 (w) cm^{-1}.

(12) **Preparation and Selected Data for Compound 6**
To a solution of (*R*)-methyl 2-(4-chloro-5-methyl-3,6-dioxocyclohexa-1,4-dienyl)-2-methoxyacetate (**1**, 46 mg, 0.193 mmol, 1.0 equiv) in dry CH_2Cl_2 (1.9 mL) at 0 °C was added oxalyl chloride (33 μL, 0.387 mmol, 2.0 equiv) followed by one drop of DMF. The reaction mixture was stirred for 1 h at 0 °C and 16 h at r.t. The reaction was quenched with H_2O (3 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to afford the crude product, which was purified by chromatography using hexane–EtOAc (9:1) as eluent. The analytically pure product (42 mg, 0.162 mmol, 84%) was obtained as a red viscous oil. R_f = 0.71 (hexane–EtOAc = 1:1); $[\alpha]_D^{25}$ –48.0 (*c* 0.27, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 1.2 Hz, 1 H), 4.88 (d, *J* = 1.2 Hz, 1 H), 3.80 (s, 3 H), 3.54 (s, 3 H), 2.24 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.56, 178.92, 173.23, 168.85, 143.69, 142.41, 132.61, 76.27, 59.05, 52.88, 13.75. ESI-HRMS (TOF): *m/z* calcd for $C_{11}H_{11}ClO_5$ [M + Na]$^+$: 281.0187; found: 281.0189. IR: ν = 2955 (w), 2924 (w), 2847 (w), 2361 (w), 2338 (w), 1748 (s), 1670 (s), 1605 (w), 1439 (w), 1373 (w), 1277 (m), 1246 (m), 1204 (m), 1165 (w), 1111 (m), 1015 (w) cm^{-1}.