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Stereoselective synthesis of spicigerolide

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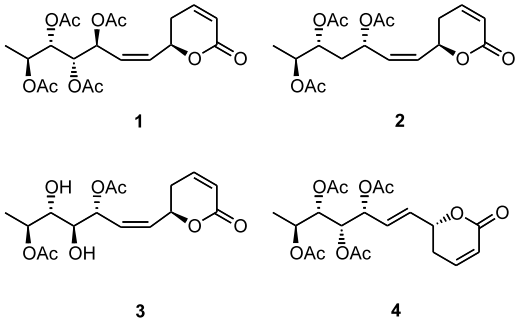
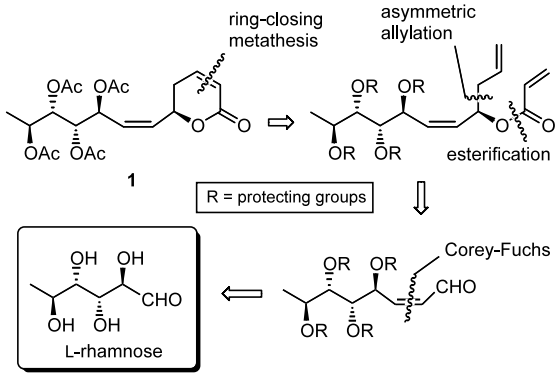
Abstract—The first total synthesis of the naturally occurring, cytotoxic lactone spicigerolide is described. The commercially available sugar L-rhamnose was the chiral starting materal. Key steps in the synthesis were an aldehyde two-carbon homologation via the Corey–Fuchs protocol, an asymmetric Brown-type aldehyde allylation and a ring-closing metathesis.

Lactone rings constitute a structural feature of many natural products.[1,2] A good deal of naturally occurring lactones, most particularly those being α,β-unsaturated,[3] display pharmacologically relevant properties (e.g. antitumoral or else tumor-promoting activity). Among the latter, the α,β-unsaturated δ-lactones spicigerolide (−)-**1**,[4] hyptolide (+)-**2**,[5] synrotolide (−)-**3**[6] and anamarine (+)-**4**[7] have been isolated from several *Hyptis* species and other botanically related genera (Scheme 1). These compounds contain a polyoxygenated chain connected with an α,β-unsaturated six-membered lactone and have been found to show a range of pharmacological properties, such as cytotoxicity against human tumor cells, antimicrobial or antifungal activity, etc. Spicigerolide (−)-**1**, for instance, has been found to exhibit cytotoxicity ($ED_{50} = 1.5$ μg/mL) in the human nasopharyngeal carcinoma (KB) assay system.[4,8] Other structurally similar lactones from *Hyptis* and taxonomically related species have been found to be antimicrobial.[9] Pharmacological properties of these types make these compounds interesting synthetic goals. However, only for anamarine (both enantiomers) have total syntheses been published so far.[10–12]

Within our recently initiated program on synthesis of natural lactones using ring-closing metathesis (RCM) reactions as one of the key steps,[13] we have devised a stereoselective synthesis for **1**. The nature of the polyoxygenated chain of compounds **1**–**4** suggests a sugar as the starting material but only in lactone **1** does this chain exhibit a configuration coincident with that of a commercially available and low-priced monosaccharide, here L-rhamnose. This sugar was thus selected as the starting material. The retrosynthetic concept is depicted in Scheme 2.



Scheme 1.



Scheme 2.

Keywords: spicigerolide; ring-closing metathesis; asymmetric allylboration; chiral pool.

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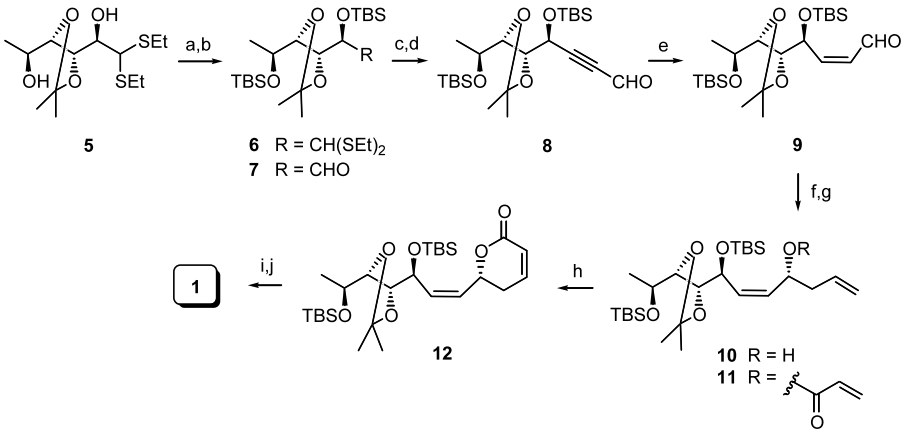

Scheme 3. *Reagents and conditions*: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, Δ (84%); (b) $HgCl_2$, $CaCO_3$, aq. MeCN, rt (89%); (c) CBr_4, PPh_3, Zn, CH_2Cl_2, 0°C; (d) *n*BuLi, −78°C, then DMF (75% overall for both steps); (e) H_2, Lindlar catalyst (95%); (f) AllylBIpc$_2$ (prepared from (+)-DIP-chloride as described in Ref. 17b), Et_2O, −78°C (85%, 88:12 diastereoisomeric mixture); (g) acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, rt (80%); (h) 10% PhCH=RuCl$_2$(PCy$_3$)$_2$, CH_2Cl_2, Δ (86%); (i) PPTS, MeOH, 70°C; (j) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (61% overall yield from **12**). Abbreviations: TBS, *t*-butyldimethylsilyl; Ipc, *iso*pinocamfeyl; DMAP, 4-dimethylaminopyridine; PPTS, pyridinium *p*-toluenesulphonate.

Suitable protecting groups for the rhamnose moiety were first to be found. An early introduction of the acetate groups present in **1** was discarded because of their anticipated instability to the planned reaction conditions. The starting compound was thus the known thioacetal **5**[14] (Scheme 3), readily prepared in two steps and 83% overall yield from L-rhamnose. Silylation of **5** under standard conditions (TBS chloride, DMF, imidazole, 80°C) caused selective silylation of the hydroxyl group at C-5, leaving the hindered 2-OH untouched. The more reactive TBS triflate was required to perform silylation of both hydroxyl functions in an one-pot procedure, which furnished the required disilylated derivative **6**. Mercury-promoted hydrolysis of the thioacetal group in the latter unveiled the latent aldehyde function to yield **7**, which was then subjected to Corey–Fuchs homologation.[15] Treatment of the resulting dibromomethylene derivative with *n*-BuLi generated an alkynyl lithium derivative, which was formylated in situ with DMF. This gave the acetylenic aldehyde **8**, which was then semihydrogenated to the (*Z*)-α,β-unsaturated aldehyde **9**. Asymmetric allylation of the latter was unsuccessful with Keck's methodology[16] but Brown's protocol[17] afforded in good yield the *cis*-allylic alcohol **10**, accompanied by its epimer at the newly formed stereogenic carbon (an 88:12 diastereomeric mixture).[17b] Acylation of **10** with acryloyl chloride yielded ester **11**, which could then be easily separated from its diastereoisomer by standard chromatography on silica gel. RCM of acrylate **11** to lactone **12** took place with good yield under the catalysis of Grubbs' ruthenium complex PhCH=RuCl$_2$(PCy$_3$)$_2$[18,19] and did not require the addition of Ti(O*i*Pr)$_4$ as in other instances.[13b,c,20] Finally, hydrolytic cleavage of all three protecting groups in **12**, followed by acetylation of the four liberated hydroxyl functions (seven steps altogether) was performed in an excellent 61% overall yield to provide **1**, identical in all its spectral properties with natural spicigerolide.[4,21,22]

In summary, the structure of the cytotoxic lactone **1** has been confirmed by means of total synthesis from the commercially available sugar L-rhamnose (twelve operative steps with an overall 15% yield). Sizeable amounts of **1** are thus made available for further pharmacological studies. Small modifications in the synthetic route described above (*trans* reduction of the triple bond, use of the enantiomeric Ipc$_2$Ballyl reagent) will lead to nonnatural diastereoisomers of the naturally occurring lactone, to be used for studies on structure–biological activity relationships. Such synthetic and biological studies are underway and will be disclosed in full in the near future.

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21. Colorless oil; $[\alpha]_D$ −15.0 (*c* 1.3, $CHCl_3$) (value not indicated in the original literature paper); HR EIMS *m*/*z* (rel. int.) 427.1591 [M+H$^+$] (3), 367 (16), 231 (38), 204 (40), 178 (79), 136 (100). Calcd for $C_{20}H_{27}O_{10}$: 427.1604. CD, ^{1}H and ^{13}C NMR spectra identical to those of the original sample.
22. An alternative synthetic route was also investigated. Aldehyde **8** was subjected to Brown's allylation conditions to yield an 88:12 mixture of diastereoisomers in 88% yield. However, we experienced difficulties in the selective semihydrogenation of the triple bond of the obtained propargyl alcohol (competitive reduction of the C=C bond). We thus treated it with acryloyl chloride and subjected the acrylate to ring-closing metathesis to yield an alkynyl lactone. Here again, the selective semihydrogenation of the triple bond to yield **12** proved troublesome. In view of this, we discarded this route.