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Studies directed towards the total synthesis of lycoperdinosides: stereoselective construction of the C1–C9 and C10–C21 segments of the molecules☆

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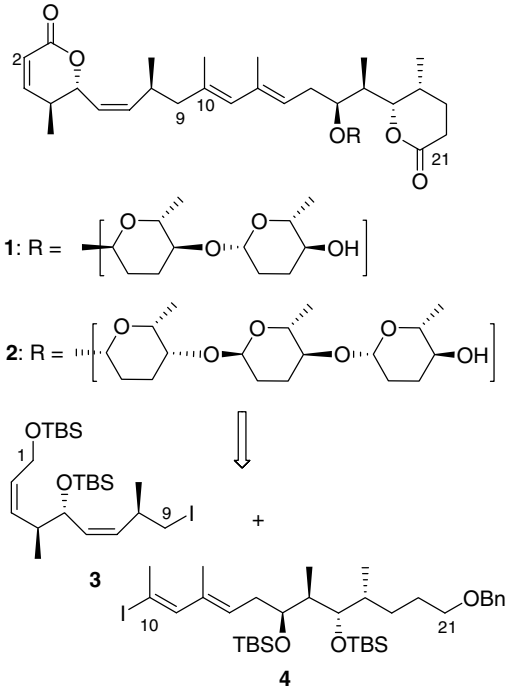
Abstract—The three chiral centres of the C1–C9 moiety of the six-membered lactone glycosides, lycoperdinosides A and B, have been derived from a common starting material containing a single chiral centre. In contrast, the C10–C21 segment of these molecules has been synthesized using, as key steps, a highly stereoselective aldol reaction, a Ti(III)-mediated opening of a trisubstituted epoxy alcohol and an efficient directed hydrostannylation of a suitably substituted internal alkyne.

Lycoperdinosides A (**1**) and B (**2**) were isolated from the slime mold *Enteridium lycoperdon*.[1] Their structures, including the absolute configurations of the hydroxyl and methyl groups, were determined by means of extensive spectroscopic data such as MS, IR, UV, 1D and 2D NMR spectra along with chemical degradation. The intricate structures of these molecules make them attractive targets to synthetic organic chemists. The total synthesis of these molecules would not only provide access to larger quantities necessary for further biological studies, but also help to prepare useful analogues. We envisaged that the two-halves of the molecules, the C1–C9 unit **3** and the C10–C21 unit **4**, could be combined by a Suzuki coupling reaction[2,3] to give the lycoperdinoside backbone. As part of our studies directed towards the synthesis of lycoperdinosides, we describe herein the syntheses of the highly functionalized C1–C9 (**3**) and C10–C21 (**4**) moieties of these molecules in suitably protected forms.



Scheme 1 outlines the details of the synthesis of iodide **3**. Commercially available (*S*)-3-hydroxy-2-methylpropionic acid methyl ester (**5**) was transformed into two differently protected alcohols **7** and **9**, which were then linked together through an acetylene. Oxidation of **9** was followed by the conversion of the aldehyde into an acetylenic group. The anion generated from this acetylenic intermediate was next added to the aldehyde derived from alcohol **7** to give the desired *anti* isomer

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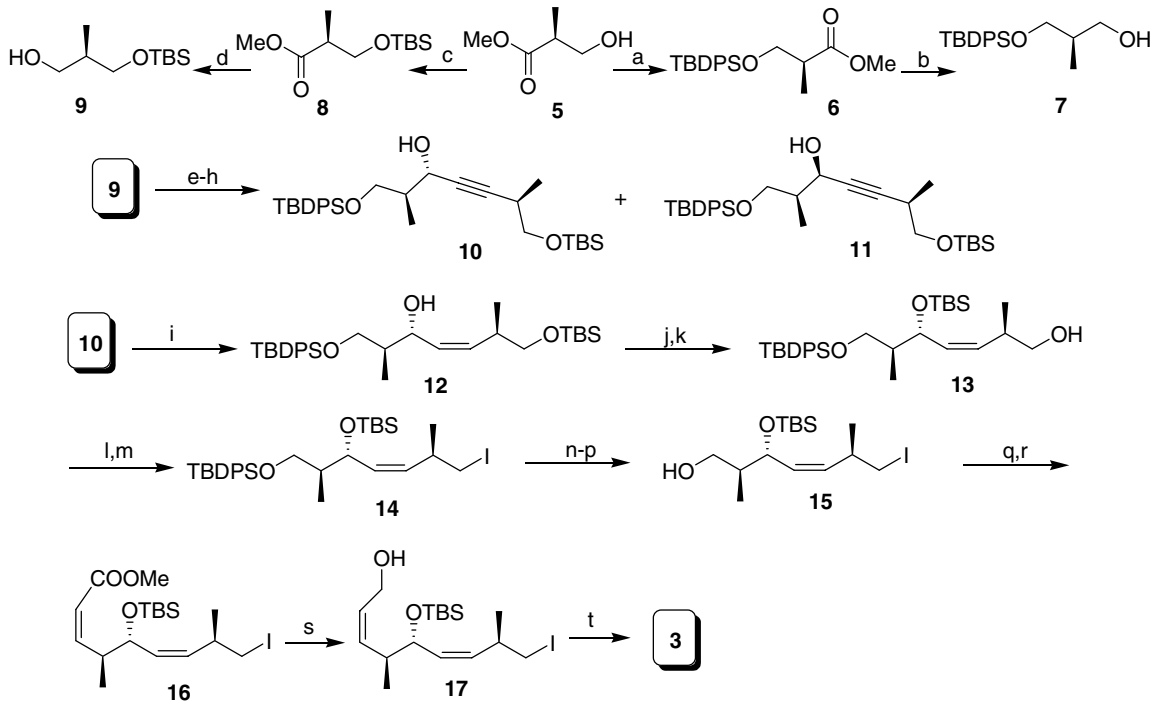

Scheme 1. Synthesis of **3**. Reagents and conditions: (a) TBDPSCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C to rt, 2 h, 88%; (b) $LiBH_4$, THF, 0 °C to rt, 24 h, 95%; (c) TBSCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C to rt, 2 h, 80%; (d) same as in step b, 36 h, 81%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C, 2 h; (f) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to rt, 45 min; (g) same as in step e from compound **7**; (h) dibromo product of **9** from step f, ^{n}BuLi, THF, −78 °C to rt, 1 h, cooled to −78 °C, aldehyde from step g, THF, 30 min, 89% from compound **7**; (i) $Ni(OAc)_2{\cdot}H_2O$, $NaBH_4$, ethylenediamine, EtOH, overnight, 88%; (j) TBSOTf, 2,6-lutidine, 0 °C, 10 min, 93%; (k) HF–Py, THF, 0 °C to rt, 6 h, 85%; (l) TsCl, Et_3N, DMAP (cat), CH_2Cl_2, 0 °C to rt, overnight, 91%; (m) NaI, DMF, 80 °C, 3 h, 74%; (n) same as in step k, overnight, 87%; (o) same as in step j, 0 °C, 10 min, 97%; (p) same as in step k, 64%; (q) same as in step e; (r) $CH_3O_2CCH_2P(O)(OCH_2CF_3)_2$, NaH, THF, 0 °C, 40 min, then aldehyde from step q, −78 °C to rt, 1.5 h, 98% after two steps; (s) DIBAL–H, CH_2Cl_2, −78 °C, 10 min, 80%; (t) same as in step j, 5 min, 95%.

10 and *syn* isomer **11** in almost equal amounts.[4] The two diastereomers were separated easily by standard silica gel column chromatography and *syn* isomer **11** could be recycled to the required diastereomer **10** in two steps—oxidation with SO_3–py and stereoselective hydride reduction with DIBAL–H to give **10** as the major isomer in ca. 2:1 ratio.[5]

Controlled hydrogenation of the acetylenic moiety of **10** was achieved using P2-Ni[6] to give *Z*-allylic alcohol **12**. Silylation of **12** was followed by the selective deprotection of the primary-OTBS to give **13**. Tosylation of **13** gave the primary tosylate, which was transformed into iodide **14**. Our failure to selectively desilylate the primary *O*-silyl group in **14** required us to deprotect both the silyl groups, reprotect them as TBS–ethers and then carry out the desired selective desilylation to give **15**.

Oxidation of **15** was followed by selective *Z*-olefination using the ketophosphonate, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$,[7] to give **16** as the major product in ca. 10:1 ratio. The minor isomer could be removed chromatographically after the reduction step. Reduction of **16** with DIBAL–H was followed by silylation to furnish the target intermediate **3**.[8]

Synthesis of the C10–C21 segment **4** is described in Schemes 2 and 3. The starting material **18** was prepared following the method reported earlier by us[5] for the synthesis of its enantiomer using, in the key steps, a chiral *N*-propanoyl oxazolidinethione auxiliary to prepare a 'non-Evans' *syn* aldol adduct[9] and a Ti(III)-mediated opening of a trisubstituted '2,3-epoxy alcohol' to prepare the '2-methyl-1,3-diol' moiety present in **4**.[10]

Acetonide protection of **18** gave **19**, which was then subjected to debenzylation using Li/liq. NH_3 to furnish **20**. Tritylation of **20** gave **21**, which was desilylated and the resulting primary alcohol was oxidized to an aldehyde and reacted with a stabilized ylide to yield α,β-unsaturated ester **22**. Reduction of **22** gave **23**, which was protected as the corresponding Bn–ether **24**. Acid treatment of **24** removed the trityl as well as the acetonide protection. The resulting triol **25** was persilylated and then subjected to selective deprotection of the primary silyl ether to give **26**. Oxidation of **26** was followed by reaction with the stabilized ylide (carbethoxyethylidene)triphenylphosphorane to furnish α,β-unsaturated ester **27**. Reduction of the ester group of **27** gave alcohol **28**, which was converted to acetylene **29**.

Methylation of the terminal acetylenic moiety of **29** and conversion of the resulting internal alkyne to target **4** using a hydrozirconation–iodination sequence[11] failed to provide the desired product. Even Pd(0)-catalyzed hydrostannylation[12] did not yield the expected result. Finally, we adopted the protocol developed by Marshall and Bourbeau to synthesize the polypropionate subunit