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Synthesis of spiroketal fragment of ossamycin via Prins cyclization

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ABSTRACT

An asymmetric synthesis of spiroketal fragment of an antitumour antibiotic, ossamycin is described. Coupling of aldehyde and alkyne fragments followed by spiroketalization has afforded the spiroketal sub unit of ossamycin. Both the sub targets were constructed via Prins cyclization.

The 24-membered macrolide ossamycin is isolated from the culture broth of *Streptomyces* sp.,[1] in 1965. It is a member of such macrolide antibiotics, as cytovaricin,[2] oligomycins,[3] A82548A[4] and rutamycins.[5] Ossamycin has been proved to inhibit oxidative phosphorylation by targeting the mitochondrial FOFl ATP synthase and this is a typical mode of action. It has been considered a promising candidate for an effective antitumour agent from the survey of recent biological screening of the natural products.[6] Nishiyama and co-workers have reported the studies on the synthesis of ossamycin.[7] In view of its biological significance the synthesis of spiroketal moiety via Prins cyclization[8] is investigated. As part of our ongoing successful efforts in exploring Prins cyclization[9] towards the total synthesis of biologically active natural products, herein we report our accomplishment of stereoselective synthesis of the spiroketal moiety via Prins cyclization and reductive ring-opening sequence.

In our retrosynthetic analysis (Fig. 1), we envisaged that the spiroketal moiety **2** could be derived from coupling of aldehyde **3** and alkyne **4** followed by spiroketalization. The fragments **3** and **4** were in turn to be obtained from pyranyl methanol **5** and **7**, respectively. Pyranyl methanol **5** and **7** could be easily constructed via Prins cyclization, in analogy to our previous approaches[9] from known chiral homoallylic alcohols **6** and **8** whereas compounds **6** and **8** could be easily achieved by opening the chiral benzyl ether protected glycidol. Jacobson catalyst could be used for the resolution of protected glycidol. The single stereogenic centre of homoallylic alcohols **6** and **8** could be utilized to create four and three

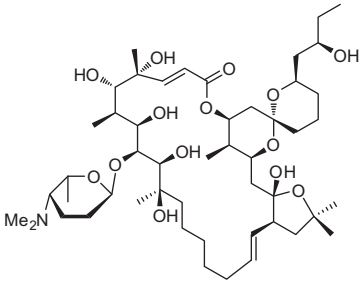

Figure 1. Structure of ossamycin.

stereogenic centres from pyranyl methanol **5** and **7**, respectively in a single operation by using Prins cyclization with high stereoselectivity (Scheme 1).

The first requirement was the preparation of the aldehyde fragment **3**, which was conceived from homo allylic alcohol **6**. Prins cyclization between known homoallylic alcohol **6** and aldehyde **9** in the presence of TFA[8,9] resulted in the trifluoroacetate of **5**, which on treatment with K_2CO_3 in MeOH gave tetrahydropyran diol **5** as the only isolable diastereomer in 65% yield. The stereochemical aspects of such Prins cyclization and structurally similar compounds of **5** were discussed in detail previously.[9] The primary hydroxyl group of the diol **5** was tosylated by using 1.1 equiv of tosyl chloride in the presence of TEA in CH_2Cl_2 produced the corresponding primary tosylated compound **10**, which on exposure to NaI in refluxing acetone gave the corresponding iodide **11**. The reductive elimination of iodide **11** through Boord reaction condition with Zn in refluxing ethanol gave the key intermediate **12** with

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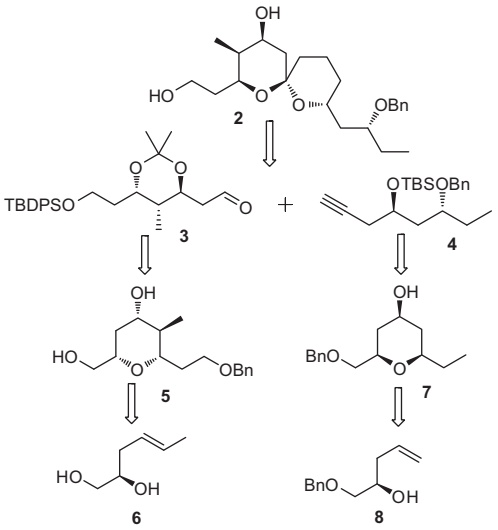
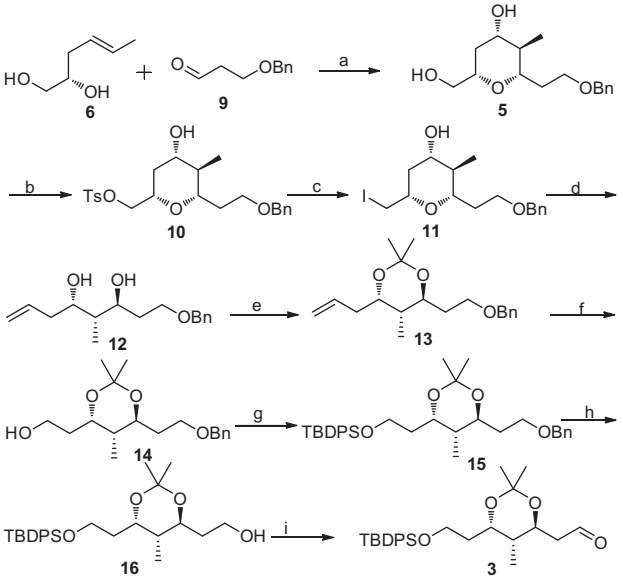


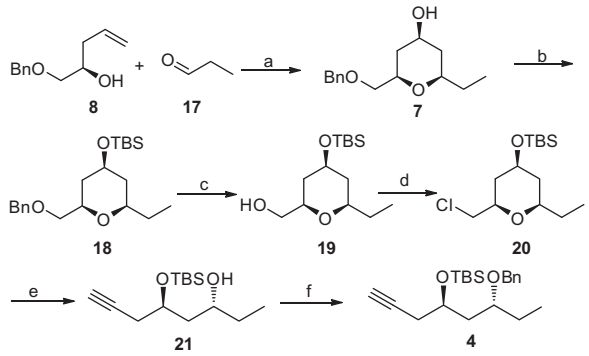
Scheme 1. Retrosynthesis of spiroketal fragment of ossamycin.

required 1,3-anti diol system.[10] Acetonide protection of 1,3-diol using 2,2 DMP in CH_2Cl_2 produced compound **13** which on exposure to ozonolysis followed by reduction with $NaBH_4$ in MeOH afforded primary alcohol **14** in 85% yield. Protection of primary alcohol as its TBDPS ether using TBDPSCl and imidazole in CH_2Cl_2 followed by removal of the benzyl group using Li/naphthalene[11] produced primary alcohol **16**. Compound **16** when subjected to oxidation using Dess–Martin periodinane afforded the aldehyde **3** (Scheme 2).

The synthesis of alkyne moiety **4** is described in Scheme 3. The homoallylic alcohol **8** and propanal **17** to Prins cyclization in the presence of TFA in CH_2Cl_2 followed by hydrolysis of the resulting crude trifluoroacetate with K_2CO_3 in MeOH yielded tetrahydropyran **7** in 65% yield. Protection of secondary hydroxyl functionality of compound **7** as its TBS ether using TBSOTf 2,6 lutidine in CH_2Cl_2



Scheme 2. Reagents and conditions: (a) TFA, CH_2Cl_2 then K_2CO_3, MeOH, rt, 3 h, 65%; (b) TEA, *p*-TsCl, CH_2Cl_2, 0 °C–rt, 3 h, 95%; (c) NaI, acetone, reflux, 24 h, 94%; (d) Zn, EtOH, $NaHCO_3$, reflux, 2 h, 92%; (e) 2,2 DMP, *p*-TSA, CH_2Cl_2, 0 °C–rt, 3 h, 85%; (f) O_3, PPh_3, CH_2Cl_2, then $NaBH_4$, MeOH, 74%; (g) TBDPSCl, imidazole, CH_2Cl_2, 0 °C, 6 h, 86%; (h) Li/naphthalene, THF, −10 °C, 92%; (i) Dess–Martin periodinane (DMP), CH_2Cl_2, 0 °C–rt, 3 h, 95%.

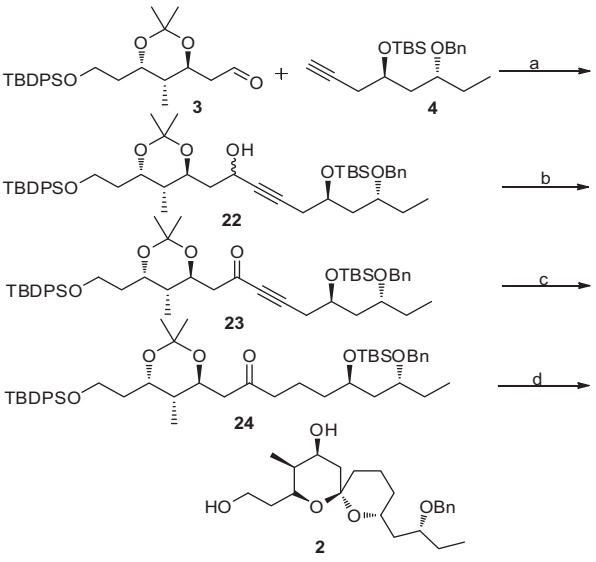


Scheme 3. Reagents and conditions: (a) TFA, CH_2Cl_2 then K_2CO_3, MeOH, r , 3 h, 65%; (b) TBSOTf, 2,6 lutidine, CH_2Cl_2, 0 °C, 3 h, 96%; (c) Li/naphthalene, THF, −10 °C, 1 h, 92%; (d) CCl_4, $NaHCO_3$, reflux, 2 h, 86%; (e) *n*-BuLi, THF, −78 °C, 78%; (f) NaH, BnBr, THF, 0 °C–rt, 88%.

gave compound **18** followed by removal of the benzyl group using Li/naphthalene produced primary alcohol **19**. Primary hydroxyl pyranyl compound **19** was converted to chloro pyranyl compound **20** on treatment with triphenylphosphine (TPP) in CCl_4, $NaHCO_3$ reflux conditions in 86% yield.[12] The corresponding alkyne **21** was obtained by the treatment of **20** with *n*-BuLi at −78 °C in 78% yield. The newly created secondary alcohol of **20** was protected as its benzyl ether in the presence of NaH and BnBr in THF to produce the alkyne fragment **4**.

The union of the two sub targets **3** and **4** was established through the acetylenic anion of **4** and the aldehyde functionality of **3** using *n*-BuLi to generate the targeted carbon framework **22** as a diastereomeric mixture (Scheme 4). The newly created hydroxyl group was oxidized using Dess–Martin periodinane (DMP) in CH_2Cl_2 to the compound **23**. The saturation of the acetylenic functionality of compound **23** was created using hydrogen with $Pd/BaSO_4$ in ethanol to produce saturated keto compound **24** in 96% yield. Compound **24** underwent deprotection of silyl groups followed by spiroketalization using *p*-TSA in methanol to give the corresponding spiroketal fragment **2** of antitumour metabolite, Ossamycin in 72% yield.

In summary, a stereoconvergent approach allowed us to complete the spiroketal portion of the rather complex natural product,



Scheme 4. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 2 h, 86%; (b) DMP, CH_2Cl_2, 3 h, 84%; (c) $Pd/BaSO_4$, H_2, EtOAc, 96%; (d) *p*-TSA, MeOH, rt, 72%.

ossamycin. It has been accomplished in 20 synthetic steps, with 14 steps longest linear sequence, and an overall yield from homoallylic alcohol **6** of 12.6%. Both fragments were successively synthesized from Prins cyclization followed by reductive cleavage sequence. Both fragments were effectively combined to yield the target spiroketal moiety. Progress towards the total synthesis will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.097.

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