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Expeditious synthesis of saponin P57, an appetite suppressant from *Hoodia* plants†

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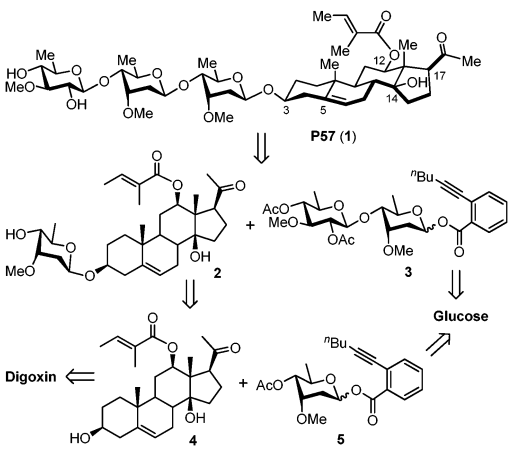
Pregnane glycoside P57, the appetite suppressant component from *Hoodia*, was synthesized expeditiously, featuring preparation of the aglycone Hoodigogenin A from digoxin and assembly of the deoxytrisaccharide with glycosyl *o*-alkynylbenzoates as donors.

Overweight and obesity, which are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer, have become a major health concern nowadays.[1] Thus, the discovery of the appetite suppressant property of *Hoodia* plants growing in the desert of South Africa attracts great attention and has led to many commercial preparations.[2,3] A series of pregnane glycosides have been isolated from *Hoodia* species,[4] among them only P57 (or P57AS3, **1**) is reported to have the activity.[2,3a,4a] Animal studies show that P57 increases the content of ATP in hypothalamic neurons and this might be relevant to the appetitive responses.[5] However, the detailed structure-activity relationship and mechanism of action of P57 is yet to be determined. Synthesis of P57 has only been mentioned in a patent,[3a] in that the aglycone was synthesized from progesterone employing a micro-organism transformation to introduce the 12,15-OH for further elaboration and the trisaccharide was assembled onto the aglycone *via* sequential glycosylation with fluoride donors in low yields (<15% for each of the steps). Recently, Miesch *et al*. reported a synthesis of the aglycone employing a Norrish type I–Prins reaction as the key step for introduction of the 14β-OH, albeit in low yield.[6] Herein, we describe an expeditious synthesis of P57.

Considering the difficulty in constructing the glycosidic linkage to the aglycone, we planned to adopt the tactic of glycosylation of the aglycone (**4**) at monosaccharide level followed by assembly of the whole glycan (Scheme 1).[7] Thus, glycosyl *o*-alkynylbenzoates **5** and **3** were designed as donors, which could undergo glycosylation in the presence of a gold(I) catalyst under mild conditions without affecting the acid-labile 2-deoxy-β-glycosidic linkages.[8] The aglycone, Hoodigogenin A (**4**) would be prepared from the commercially available digoxin, in which the 12β,14β-OH is already installed.[9]

Attempts at direct cleavage of the sugar moiety in digoxin under acidic conditions led to digoxigenin in low yields.[10] Nevertheless, acetylation[11] followed by acid hydrolysis provided the 12-*O*-acetyl digoxigenin **6** in good yield (Scheme 2). Protection of the 3-OH with a *tert*-butyldiphenylsilyl group afforded **7**. Ozonolysis followed by reduction with zinc-acetic acid led to the desired methyl ketone **8** (71%).[12] The resulting ketone was protected with ethylene glycol under mild conditions to provide **9**,[13] which was subjected to removal of the 3-*O*-silyl group (with TBAF)[14] and subsequent Dess–Martin oxidation[15] to afford the C3 ketone **10** in excellent yield. Subsequent introduction of the C4,5 double bond turned out to be a difficult task. Treatment of **10** with IBX/$(PhSe)_2$ gave mainly the diene derivative.[16] Further screening conditions revealed that subjection of **10** to LiHMDS and TMSCl in the presence of Et_3N afforded the C3,4 enolate, which could be oxidized by $Pd(OAc)_2$ into the $\Delta^{4,5}$ derivative **12** in high yield and selectivity.[17] In view of the acid lability of the 14-OH, we opted to use basic conditions followed by kinetic protonation to realize the alkene-walking (**12** → **13**).[18] However, many tries with *t*BuOK/*t*BuOH, *t*BuOK/DMSO and sodium acetylide/DMSO led to complex mixtures, showing that the resulting enolate from **12** was very sensitive to oxygen.[19] Finally, we found that freeze-pump-thaw and using a solid addition adapter for adding *t*BuOK to exclude oxygen worked best for this transformation; subsequent reduction of the C3 ketone



Scheme 1 Retrosynthetic plan for P57 (**1**).

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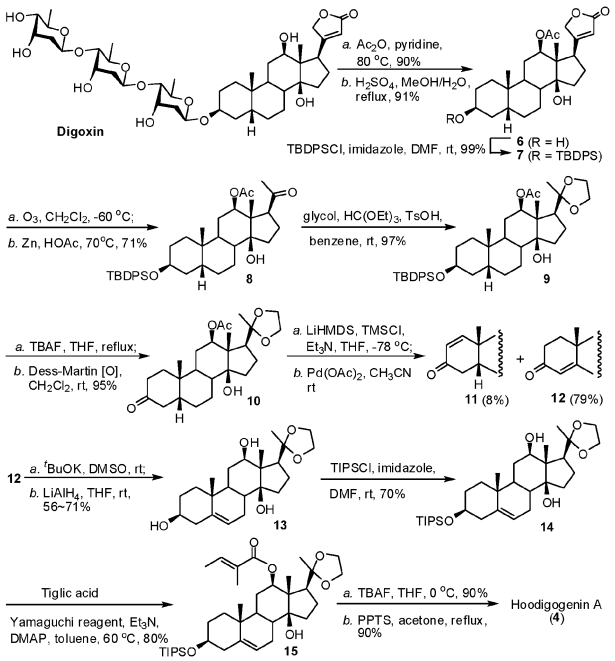
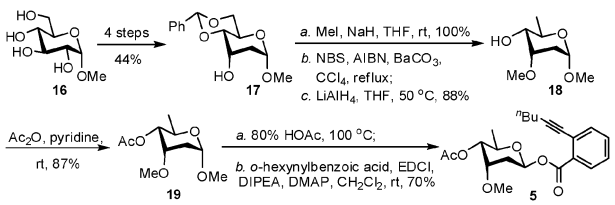


Scheme 2 Synthesis of Hoodigogenin A (**4**).

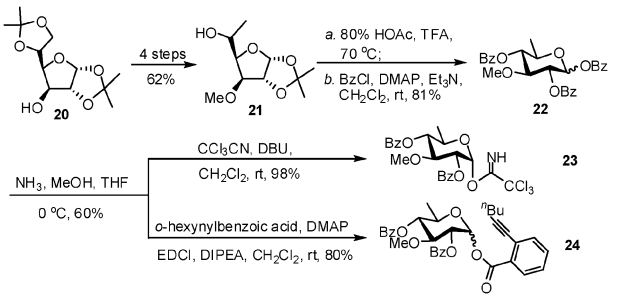
gave the desired $\Delta^{4,5}$-3β-ol **13** in a reproducible manner in satisfactory yields. The triisopropylsilyl group was selected to protect the 3-OH in triol **13** to provide **14** in good yield (70%). Although the selective protection with the *tert*-butyldiphenylsilyl group gave a better yield, the deprotection afterwards was found to be difficult; while protection with a *tert*-butyldimethylsilyl group led to poor regioselectivity. Treatment of diol **14** with tiglic acid under the Yamaguchi conditions[20] afforded **15**. Finally, removal of the 3-*O*-TIPS and C20-ethylene glycol ketal furnished Hoodigogenin A (**4**).[3a,4a,c]

The preparation of the desired sugar donors **3** and **5** are depicted in Schemes 3–5. Starting from methyl α-D-glucopyranoside **16**, methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside **17** was readily prepared in four steps according to literature procedures (Scheme 3).[21] Methylation of the 3-OH in **17** followed by the Hanessian–Hullar ring opening[22]-reduction process[21] led to methyl α-D-cymaropyranoside **18** in high yield. After acetylation of the 4-OH of **18**, the resulting methyl cymaropyranoside **19** was subjected to hydrolysis with 80% acetic acid to give the corresponding cymaropyranose, which was condensed with *o*-hexynylbenzoic acid to afford the desired cymarosyl *o*-hexynylbenzoate **5** in good yield in predominantly the β-configuration.[8]

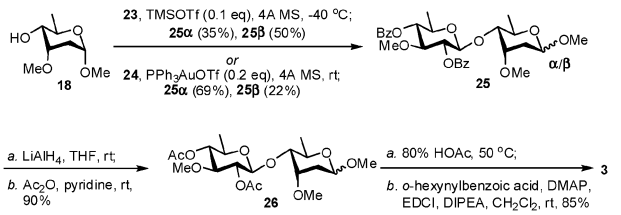
Preparation of the thevetosyl donors **23** and **24** commenced from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranoside **20**, which was converted into 6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranoside **21** in an easily scalable and highly efficient approach (62% in 4 steps)



Scheme 3 Preparation of the cymarosyl *o*-hexynylbenzoate **5**.



Scheme 4 Preparation of thevetosyl donors **23** and **24**.

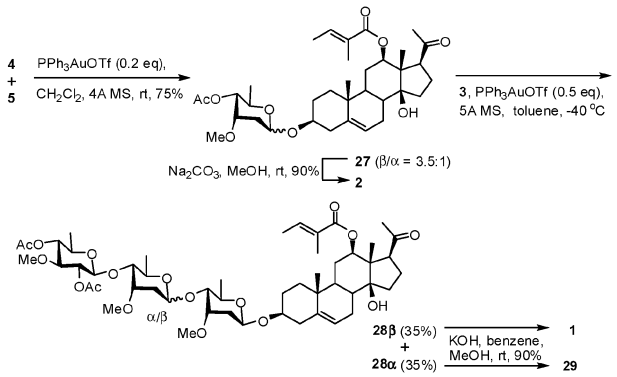


Scheme 5 Preparation of the disaccharide *o*-hexynylbenzoate **3**.

adopting modification of the literature methods (Scheme 4).[23] Treatment of **21** with 80% acetic acid containing 0.6% CF_3COOH followed by benzoylation provided pyranose tribenzoate **22** (α/β = 1/1) in 81% yield. Selective deprotection of the anomeric benzoate was achieved with NH_3 in MeOH/THF, affording 2,4-di-*O*-benzoyl-thevetose in 60% yield, which was condensed with trichloroacetonitrile or *o*-hexynylbenzoic acid to afford the desired thevetosyl donors **23** and **24**, respectively.

The glycosidic coupling of methyl α-D-cymaropyranoside **18** with thevetosyl trichloroacetimidate **23** was conducted in the presence of TMSOTf (0.1 equiv.) in CH_2Cl_2 at −40 °C, the typical glycosylation conditions for Schmidt donors, leading to disaccharide **25** in a high 85% yield (Scheme 5). However, during this reaction the anomerization at the cymarose unit took place readily. Coupling of **18** with *o*-hexynylbenzoate **24** with $Ph_3PAuOTf$ as the catalyst led to **25** in a higher 91% yield and with less anomerization. Hydrolysis of the benzoates in **25** was unexpectedly sluggish, therefore reductive deprotection was adopted; subsequent acetylation led to **26**. The replacement of the benzoates with acetates at this stage ensured the final deprotection in the presence of the tiglic ester. Selective cleavage of the anomeric methyl group in **26** was easily effected with 80% acetic acid at 50 °C, condensation of the resulting lactol with *o*-hexynylbenzoic acid afforded the desired disaccharide donor **3** in 85% yield.

With building blocks **3**, **4** and **5** at hand, the final stage was set for elaboration of the pregnane trisaccharide P57 (Scheme 6). The coupling conditions of Hoodigogenin A (**4**) with cymarosyl *o*-hexynylbenzoate **5** was carefully screened, including the gold(I) catalyst (PPh_3AuOTf, PPh_3AuNTf_2 or PPh_3AuSbF_6), solvent and temperature. The best results were attained with $Ph_3PAuOTf$ (0.2 equiv.) as the catalyst in CH_2Cl_2 at rt, leading to glycoside **27** in 75% yield with a β/α ratio of 3.5 : 1; the anomers could be separated by silica gel column chromatography. Selective removal of the 4-*O*-acetyl group on **27**β was achieved with Na_2CO_3 in MeOH, providing cymaroside **2** cleanly. The coupling of **2** with disaccharide *o*-hexynylbenzoate **3** was more problematic. The reaction in the presence of $Ph_3PAuOTf$ (0.5 equiv.) and 5 Å



Scheme 6 Elaboration of P57 (**1**).

molecular sieves in toluene at −40 °C led to trisaccharide **28**α and **28**β in nearly equal amounts. Trisaccharide **28**β was subjected to the final deprotection of the acetyl groups in the presence of the 12-*O*-tiglic ester, thus exposure of **28** to KOH in a mixed solvent of MeOH and benzene at rt furnished saponin P57 (**1**) smoothly (90%).[24] All the spectral data of the synthetic material were identical to those reported for the natural product.[3a,4c] Similar treatment of **28**α afforded **29**, a stereoisomer of the natural P57.

In summary, we have accomplished the synthesis of P57 in a linear 20 steps and 2.4% yield from digoxin. The present synthesis provides a consulting strategy to other Hoodia saponins and analogues; the availability of these pregnane glycosides (including stereoisomers such as compound **29**) shall facilitate the studies on the structure–activity relationship (SAR) and mechanisms of the appetite suppressant activity of P57. For a practical synthesis of P57, however, the stereoselectivity of glycosylation in the present synthesis remains as a challenge to address.

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