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Synthesis of the Aglycone of the Shark Repellent Pavoninin-4 Using Remote Functionalization

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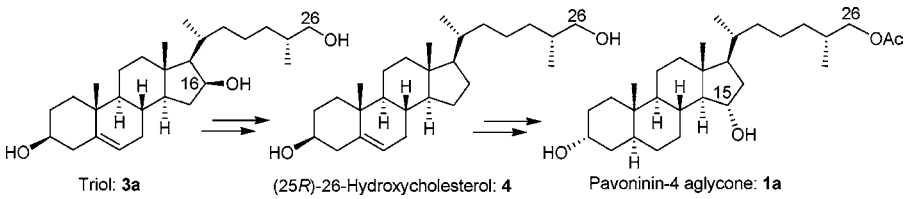
ABSTRACT



The aglycone of shark repellent pavoninin-4, (25*R*)-5α-cholestan-3α,15α,26-triol 26-acetate 1a, was synthesized from (25*R*)-cholest-5-en-3*β*,-26-diol 4 (26-hydroxycholesterol) in eight steps in 18% overall yield. Breslow's remote functionalization strategy was used as a key step to introduce the C-15α alcohol on a steroid D ring. An efficient synthesis of the 26-hydroxycholesterol from the 16*β* hydroxyl steroid, (25*R*)-cholest-5-ene-3*β*,16*β*,26-triol (3a), is also reported.

During the latter half of the 20th century, chemists have sought to discover nonmicrobial methods for the functionalization of unactivated carbon atoms of various molecules.[1] Breslow and co-workers were pioneers in this area, whose works involved the generation of a tertiary carbon radical on the α-face of the steroid nucleus by an attached template through a radical relay reaction (Breslow reaction) and benzophenone irradiation.[1] In 1973, Breslow et al. reported that the reaction of a series of esters derived from 3α-hydroxy-5α-cholestane and *p*-benzoylphenylalkanoic acids, on irradiation in benzene, underwent intramolecular attack by the attached benzophenone on the steroid hydrogens and gave alkenes in moderate yield.[2] The remote functionalization of the C-14 of steroids by photolysis of benzophenone esters α-linked to the steroid backbone at C-3 can be also used to introduce the C-15 keto[2] and C-15α hydroxy[3] groups in steroids. Recently, the remote functionalization technique has been found to be useful in the synthesis of natural steroids.[4]

In our approaches to the synthesis of the shark repellents, pavoninin-4, **1b**, and -5, **2b**[5,6] (Figure 1), diosgenin was

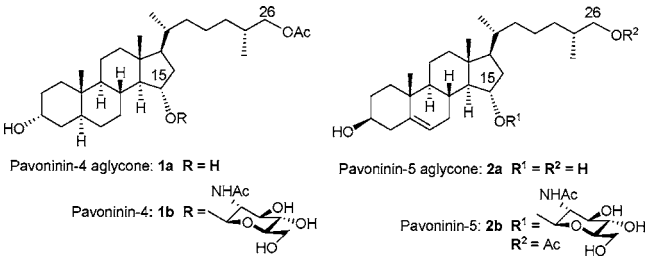


Figure 1. Shark repellents pavoninin-4, **1b**, and pavoninin-5, **2b**.

chosen as the starting material because it has an appropriately placed oxygen functionality. Reduction of diosgenin resulted in the preparation of the (25*R*)-cholest-5-en-3*β*,16*β*,26-triol (**3a**). Transposition of the C-16*β* hydroxyl of the triol **3a** to

(1) For reviews on remote functionalization reactions in steroids, see: (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170. (b) Reese, P. B. *Steroids* **2001**, *66*, 481.

(2) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251.

(3) For a recent reference, see: Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057.

(4) For example, the first total synthesis of xestobergsterol A: (a) Jung, M. E.; John, T. W. *Org. Lett.* **1999**, *1*, 1671. (b) Jung, M. E.; John, T. W. *J. Am. Chem. Soc.* **1997**, *119*, 12412.

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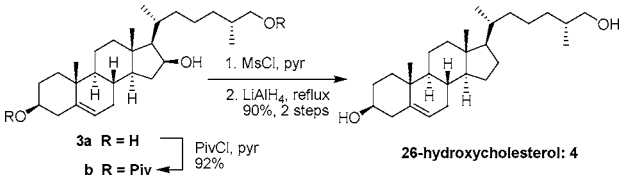
the 15α position afforded a method for the synthesis of the aglycone of 26-*O*-deacetyl pavoninin-5, **2a**.[7] Recently, we reported a more efficient method for transposition of a C-16β hydroxyl to the 15α position, via the unexpected β-reduction of a C-15 ketone.[8] On the basis of this 1,2-transposition methodology, the first synthesis of pavoninin-4, **1b**, from diosgenin has been achieved.[9] In this paper, we report an alternative synthesis of the aglycone of pavoninin-4 (**1a**) from (25*R*)-26-hydroxycholesterol **4**, an intermediate in the metabolic pathway of cholesterol, using Breslow's remote functionalization strategy to biomimetically introduce a C-15α hydroxyl on a steroid D ring. A very efficient synthesis of the starting (25*R*)-26-hydroxycholesterol **4**, from diosgenin, is also reported.

The synthesis of the aglycone of pavoninin-4, **1a**, started from (25*R*)-26-hydroxycholesterol **4** because it is suitably substituted with alcohols at C-3 and C-26. The syntheses of (25*R*)-26-hydroxycholesterol **4** have been reported mainly from two readily available natural products, kryptogenin and diosgenin, and by addition of a side-chain building block to the steroid backbone.[10] The best yield achieved so far was 58% in four steps from diosgenin, via a modified Clemmensen reduction followed by a Barton deoxygenation reaction.[10] To remove the C-16β hydroxy of the (25*R*)-cholest-5-en-3β,16β,26-triol (**3a**), selective protection of the C-3β and C-26 hydroxyl groups is needed. This can be achieved by chemoselective reaction of the cholest-5-en-3β,-16β,26-triol (**3a**) with *tert*-butyldimethylsilyl chloride[10] or benzoyl chloride[11] under basic conditions into the corresponding 3,26-disilyl ethers or 3,26-dibenzoyl esters, respectively. However, normally flash column chromatography is required to separate the desired disubstituted alcohol from other di- and trisubstituted byproducts. Actually, the benzoyl group is not bulky enough for this chemoselective protection because the expected selective product (25*R*)-cholest-5-en-3β,26-dibenzoyloxy-16-ol was formed in only 36% yield.[11] We found that trimethylacetyl chloride was a very good alternative to benzoyl chloride for the chemoselective conversion of the C-3 and C-26 alcohols of the triol **3a** to the corresponding C-3 and C-26 esters (Scheme 1).

Trimethylacetyl chloride has been used as an excellent reagent for selective acylation of a primary alcohol over a secondary one.[12] The selectively diprotected 3β,26-dipivaloate **3b** was formed almost quantitatively so that the product could be easily purified by a simple recrystallization from ethyl acetate to yield pure 3β,26-dipivaloate **3b**. Mesylation of the free C-16 alcohol of **3b** and subsequent $LiAlH_4$ reduction of the C-3 and C-26 diprotected 16β-mesylate under reflux conditions proceeded smoothly to reduce off both dipivaloates and at the same time displace the C-16 mesylate. Recrystallization afforded (25*R*)-26-hydroxycholesterol **4** in 90% yield and 97% purity based on a GC-MS analysis.[13] Therefore, this method provides an efficient method for the synthesis of (25*R*)-26-hydroxycholesterol (**4**) from the triol **3** in 83% yield over three steps. This represents a considerable improvement over the Barton deoxygenation described in our previous paper.[10] More importantly, this synthesis can be easily scaled up, because all purifications were achieved by recrystallization, without requiring column chromatography.

Scheme 1. Synthesis of (25*R*)-26-Hydroxycholesterol, **4**



Starting from (25*R*)-26-hydroxycholesterol **4**, the aglycone of pavoninin-4 (**1a**) was synthesized using Breslow's remote functionalization strategy, as shown in Scheme 2.

Catalytic reduction of (25*R*)-26-hydroxycholesterol **4** afforded the saturated diol **5a**, which was chemoselectively protected[14] at the primary C-26 hydroxyl by 3-pivaloyl-1,3-thiazolidine and sodium hydride as the 3β,26-diol 26-pivaloate **5b** in 80% yield. Treatment of the 3β alcohol **5b** under Mitsunobu conditions with the known acid[15] **7** yielded the inverted ester **8** in 87% yield, with the required 3α stereochemistry for pavoninin-4, **1b**. Photolysis of **8** using a 450-W medium-pressure Hanovia lamp with a Pyrex filter and subsequent hydrolysis of the C-3 and C-26 esters with potassium hydroxide in reflux conditions, followed by conversion of the resulting 3α,26-diol into a diacetate, provided a mixture of the desired (25*R*)-5α-cholestan-14-en-3α,26-diol 3α,26-diacetate **9a** and the unreacted saturated (25*R*)-5α-cholestan-3α,26-diol 3α,26-diacetate **9b** in a 3:2 ratio in 65% combined yield. Subsequent hydroboration and oxidation[16] of the unsaturated and saturated mixture **9a**,**b**, accompanied by a simultaneous hydrolysis of bisprotected acetyl groups at C-3 and C-26 hydroxyls, afforded an easy separation of the more polar (25*R*)-5α-cholestan-3α,15α,-26-triol, **10**. The chemical shift for the C-15β hydrogen in **10** is a doublet of triplets (J = 9.1, 3.0 Hz) at 3.80 ppm. These values are consistent with (25*R*)-5α-cholestan-3β,-15α,26-triol, the 15α configuration of which was confirmed by an X-ray structure.[8]

(5) (a) Tachibana, K.; Sakaitani, M.; Nakanishi, K. *Science* **1984**, *226*, 703. (b) Tachibana, K.; Sakaitani, M.; Nakanishi, K. *Tetrahedron* **1985**, *41*, 1027.

(6) For a recent review, see: Williams, J. R.; Gong, H. *Lipids* **2004**, *39*, 795.

(7) Williams, J. R.; Chai, D.; Bloxton , J. D., II; Gong, H.; Solvibile, W. R. *Tetrahedron* **2003**, *59*, 3183.

(8) Williams, J. R.; Gong, H.; Hoff, N.; Olubodun, O. I.; Carroll, P. J. *Org. Lett*. **2004**, *6*, 269.

(9) Williams, J. R.; Gong, H.; Hoff, N.; Olubodun, O. I. *J. Org. Chem*. **2005**, *70*, 10732.

(10) Williams, J. R.; Chai, D.; Wright, D. *Steroids* **2002**, *67*, 1041 and references therein.

(11) Noam, M.; Tamir, I.; Breuer, E.; Mechoulam, R. *Tetrahedron* **1981**, *37*, 597.

(12) (a) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453. (b) Boschelli, D.; Takemasa, Y.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, *26*, 5239. (c) Nagaoka, H.; Rutsch, W.; Schmid, G.; Ilio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc*. **1989**, *102*, 7962.

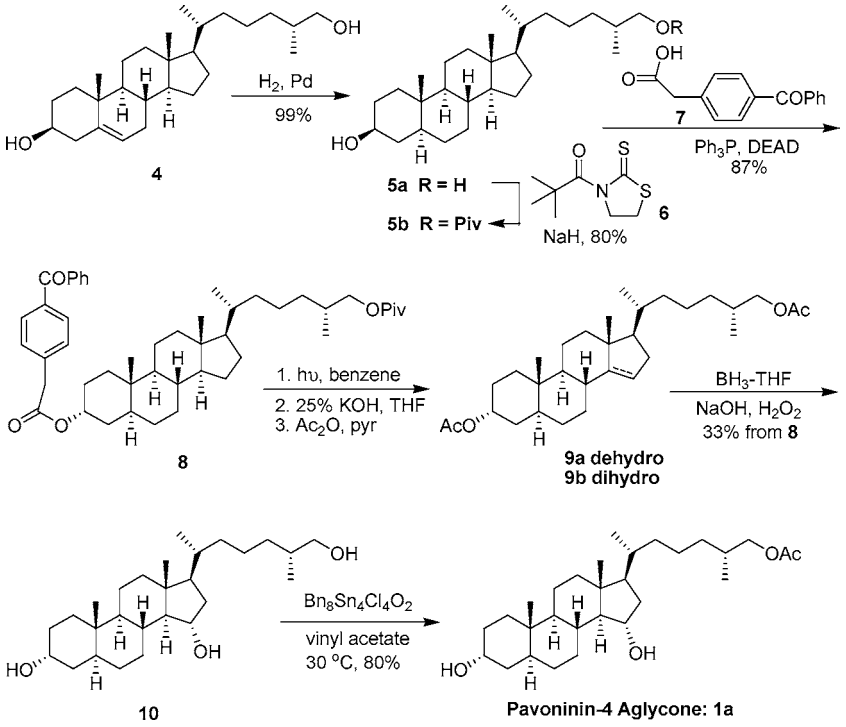
(13) GC-MS analysis was provided by Dr. J. Goodman at the University of Kentucky.

(14) Yamada, S. *J. Org. Chem*. **1992**, *57*, 1591.

(15) Zderic, J. A.; Kubitschek, M. J.; Bonner, W. A. *J. Org. Chem*. **1961**, *26*, 1635.

(16) Taylor, E. J.; Djerassi, C. *J. Org. Chem*. **1977**, *42*, 3571.

Scheme 2. Synthesis of the Aglycone of the Shark Repellent Pavoninin-4, **1a**



Finally, selective acetylation of the primary C-26 hydroxyl by Otera's transesterification strategy,[17] using vinyl acetate with distannoxane as a catalyst, afforded the aglycone of pavoninin-4 (**1a**) in 80% yield. This represents a new formal synthesis of the shark repellent pavoninin-4.[9]

In conclusion, we report a highly efficient method for the synthesis of the (25*R*)-26-hydroxycholesterol **4** in 83% yield over three steps, from the (25*R*)-cholest-5-en-3β,16β,26-triol **3a**. From this useful intermediate **4**, the synthesis of the aglycone of pavoninin-4, **1a**, was achieved in 18% overall yield over eight steps, using Breslow's remote functionalization strategy as a key step.

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Supporting Information Available: General experimental procedures and ^{1}H and ^{13}C NMR spectra for all synthesized compounds **3b**, **4**, **5a**,**b**, **6**−**8**, **10**, and pavoninin-4 aglycone **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Orita, A.; Mistutome, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 2420. (b) Orita, A.; Sakamoto, K.; Hamada, K.; Mistutome, A.; Otera, J. *Tetrahedron* **1999**, *55*, 2899.