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Inversion of the Sterically Constrained C_{13}-Hydroxyl of 22,23-Dihydroavermectin B_1 Aglycone

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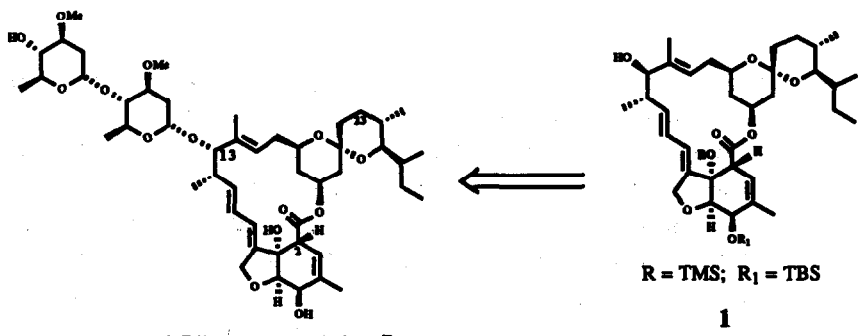
Abstract: The development of novel, mild inversion chemistry which facilitates the preparation of the 13-epi-22,23-dihydroavermectin B_1 aglycone 1 is described.

The avermectins and their analogues are highly functionalized naturally occurring 16-membered lactones which are widely used as potent antiparastic agents.[1] These structurally unique avermectins have an oleandrosyloleandrose subunit attached at the C_{13} position which appears to contribute to its high potency. Newer analogues of ivermectin (22,23-dihydroavermectin B_1) have been prepared by removal of the oleandrose substituent, providing 22,23-dihydroavermectin B_1 aglycone, and modification of the C_{13} position. Inversion of the stereochemistry at C_{13} has been found to improve the safety profile while maintaining good activity.[2] Consequently, considerable synthetic effort has been devoted to inverting the sterically congested C_{13} α-allyl-homoallylic hydroxy functionality of the avermectins.[2,3] The efficient inversion of the 13-α-hydroxy group, however, has proved to be a difficult synthetic transformation, complicated by the highly sensitive chemical functionalities present in this molecule. We now wish to report a mild, efficient inversion of the 13-position to prepare the 13-*epi*-22,23-dihydroavermectin B_1 aglycone 1 with cesium carboxylates (Scheme 1).



22,23-Dihydroavermectin B_1

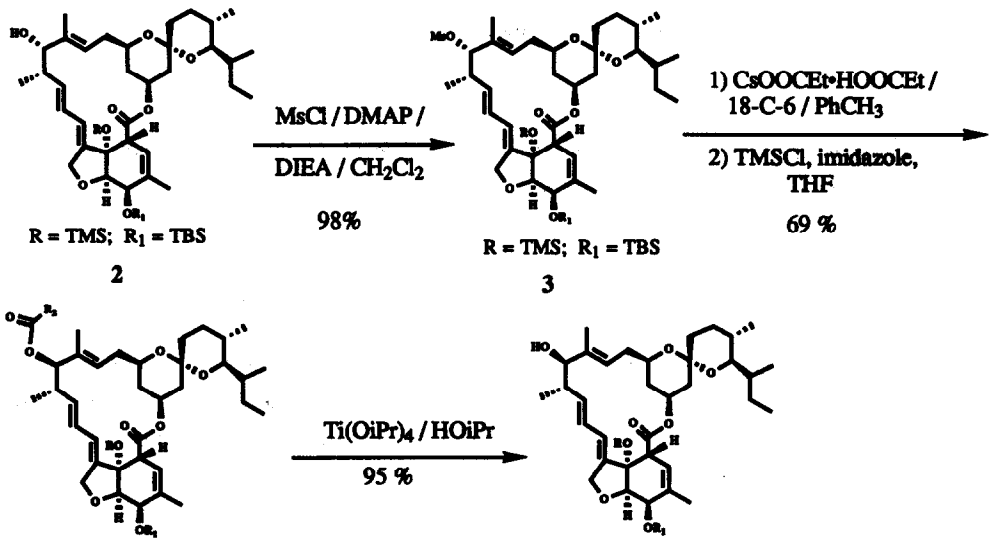
R = TMS; R_1 = TBS

1

The inversion of the C_{13}-hydroxy group has been previously reported by Mrozik[2a] and Jones[3]. A major drawback with the procedures was the lability of the tosylate leaving group. Also, the inversion processes used expensive, unavailable reagents and were not amenable to scale up.

The tosylate was replaced with the more stable mesylate 3; no displacement by chloride was observed as with tosyl chloride. At first, treatment of the aglycone 2[4] with triethylamine/mesyl chloride at -10 °C gave a complex mixture of products, along with some 13-α-mesylate 3. By changing the base to diisopropylethylamine a 65% yield of desired mesylate 3 was obtained after chromatography. Interestingly, addition of a pyridine base gave a significant enhancement of the mesylate formation.[5] After optimization an effective procedure was developed: compound 2 was treated with MsCl, a pyridine base (2,6-lutidine, DMAP or collidine), and diisopropylethylamine (1:2:2:3) in dichloromethane at -10 °C for 15 min to produce 3 in >98% yield.

Scheme 1



R = TMS; R_1 = TBS — **2**

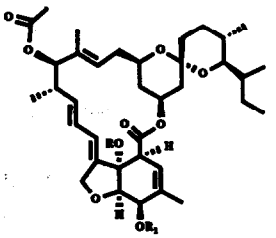
R = TMS; R_1 = TBS — **3**

4a: R = H; R_1 = TBS; R_2 = Me
4b: R = TMS; R_1 = TBS; R_2 = Me
4c: R = H; R_1 = TBS; R_2 = Et
4d: R = TMS; R_1 = TBS; R_2 = Et

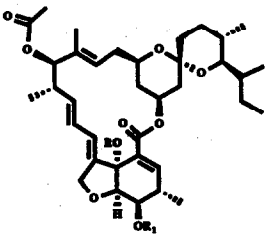
R = TMS; R_1 = TBS — **1**

Cesium carboxylates proved to be the most effective reagents for the inversion.[6] Compound 3 was treated with CsOAc/18-Crown-6 at 80 °C to provide a 50% combined yield of the 13-β-acetoxy compounds **4a** and **4b** in addition to two major impurities (>20%) **5** and **6**, which were generated by epimerization and isomerization, respectively, at the C-2 position.[7] Since the basicity of the reagent was causing the side reactions a buffered reagent was employed. Treatment of compound 2 with **cesium propionate•mono propionic acid**[8] (1.7 equiv)/18-C-6 (1.0 equiv) in toluene at 110 °C for 1.75 h produced the 13-β-propionates **4c** and **4d** with <5% of the C-2 impurities generated. In order to resilylate the 7-hydroxy group of **4c** the crude reaction mixture[9] was subjected directly to trimethylsilyl chloride/imidazole to give the 13-β-propionate **4d** in 69% isolated yield after column chromatography. To establish the buffering effect of the acid, an equivalent of acetic

acid was added to the cesium acetate reaction since commercially available cesium acetate does not contain free acetic acid. Again, <5% of the C-2 impurities were formed. Due to the expense of commercially available cesium propionate•propionic acid a new procedure was developed: 4 equiv of propionic acid, 1.08 equiv of cesium carbonate, and one equiv of 18-crown-6 were preheated in toluene at 105 °C for 2 h to form the buffered reagent. The mesylate **3** was then added and the reaction mixture was heated at 110 °C. The crude product was treated with TMSCl/imidazole to furnish the desired 13-β-propionate **4d** in 68% yield.[10]



5a: R = H; R_1 = TBS
5b: R = TMS; R_1 = TBS



6a: R = H; R_1 = TBS
6b: R = TMS; R_1 = TBS

The hydrolysis of the 13-β-carboxyl group of **4d** to the corresponding 13-β-hydroxyl compound **1** was a potential problem because of the sensitive functionality in the avermectin molecule. With this in mind a mild transesterification[11] was developed that cleanly produced the 13-β-alcohol **1**[12]. Treatment of compound **4d** with three equiv of titanium isopropoxide in isopropanol gave the 13-β-alcohol **1** in 95% yield with no detectable epimerimization at the C-2 position. This 13-β-alcohol **1** was recrystallized from acetonitrile/water (20:1) with 80% recovery. A second crop of **1** brought the combined recovery of >99 area%-pure material to >95%.

This highly effective and novel inversion process involving alcohol activation, buffered-cesium carboxylate displacement, and titanium-mediated transesterfication provides a non-chromatographic, large-scale process for the preparation of the crystalline 13-*epi*-22,23-dihydroavermectin B_1 aglycone **1** in ~67% overall yield.[13] The inversion methodology described herein clearly offers a mild entry into the 13-*epi*-analogues of the avermectins as well as other structurally complex secondary alcohols.

Acknowledgement. We would like to thank Raymond J. Cvetovich and Joseph S. Amato for supplying the 5-O-TBS-7-O-TMS-22,23-dihydroavermectin aglycone (**2**).

References and notes

1. (a) Blizzard, T.; Fisher, M. H.; Mrozik, H.; Shih, T. L. In *Recent Progress in the Chemical Synthesis of Antibiotics;* Lukacs, G.; Ohno, M.; Eds.; Springer: Berlin-Heidelberg, **1990**; pp 65-102. (b) Fisher, M. H.; Mrozik, H. In *Macrolide Antibiotics;* Omura, S. Ed.; Academic Press: New York **1984**; Chapter 14, pp 553-606. (c) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87-121.
2. (a) Mrozik, H.; Linn, B. O.; Eskola, P.; Lusi, A.; Matzuk, A.; Preiser, F. A.; Ostlind, D. A.; Schaeffer, J. M.; Fisher, M. H. *J. Med. Chem.* **1989**, *32*, 375-381. (b) Blizzard, T. A.; Margiatto, G. M.; Mrozik, H.;

Shoop, W. L.; Frankshun, R. A.; Fisher, M. H. *J. Med. Chem.* in press.

3. Jones, T. K.; Mrozik, H.; Fisher, M. H. *J. Org. Chem.* **1992**, *57*, 3248 and other methods cited therein.
4. The C_7 hydroxyl group of compound **2** was selectively protected as the trimethylsilyl ether using a procedure developed by Raymond J. Cvetovich, Joseph S. Amato, Richard F. Shuman, and Edward J. J. Grabowski, unpublished results.
5. The trialkylamine-pyridine combination is believed to operate through a different, hitherto, unexpected pathway. The mechanism of this mesylate formation is currently under investigation.
6. (a) Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, 1555. (b) Willis, L. C. *Tetrahedron Lett.* **1987**, *28*, 6705.
7. The structures of the C-2 impurities **5** and **6** were unambiguously confirmed using a combination of 1-D (^{1}H, 13C, NOEDS) and 2-D (COSY, HETCOR) NMR techniques.
8. The reagent was obtained from Aldrich Chemical Co.(cat.33,379-4) or Johnson Matthey Electronics (cat. 18865, Lot # H17D). Cesium propionate•propionic acid is less hygroscopic than cesium acetate.
9. The 18-crown-6 is easy to remove from the reaction mixture by the addition of hexanes which precipitate the 18-crown-6•cesium propionate as a solid. The reaction mixture was filtered and the filtrate was washed with 5% aqueous $NaHCO_3$ resulting in 18-crown-6-free product. The ^{1}H-NMR studies indicate that the solid contains 18-crown-6•cesium propionate.
10. No improvement was offered by alternative carboxylic acids: formic acid, methoxyacetic acid, valeric acid, decanoic acid, benzoic acid, 4-methoxybenzoic acid and 4-nitrobenzoic acid.
11. a) The original procedure required 0.5 equiv of $Ti(OR)_4$ reagent. However, three equiv of $Ti(OiPr)_4$ was required here due to the titanium complexation with other oxygens present in the molecule.
    b) Due to the acid-labile trimethylsilyloxy group, the work-up was changed from 1N HCl to 2% H_3PO_4; see Seebach, D.; Hungerbuher, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.
12. NMR Spectroscopy of 13-*epi*-22,23-dihydroavermectin B_1 aglycone **1**: Samples were prepared in $CDCl_3$.Proton and carbon-13 spectra were recorded on a Bruker AM-400 spectrometer at a frequency of 400.13 and 100.61 MHz respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton (δ=7.27 ppm) and relative to $CDCl_3$ for carbon-13 (δ=77.0 ppm). Coupling constants (J) were recorded in Hz: ^{1}H NMR, δ_H 5.84 (dd, J=14.9, 11.5, H_{10}), 5.65 (dt, J=11.5, 2.4, H_9), 5.47 (q, J=1.6, H_3), 5.33 (dd, J=14.9, 9.9, H_{11}), 5.29 (om, H_{15}), 4.79 (m, H_{19}), 4.68 (dd, J=14.3, 2.4, $C_{8a}H$), 4.57 (dd, J=14.3, 2.4, $C_{8a}H$), 4.39 (m, H_5), 3.80 (d, J=5.2, H_6), 3.77 (d, J=9.9, H_{13}), 3.62 (m, H_{17}), 3.23 (q, J=2.4, H_2), 3.17 (d, J=7.5, H_{25}), 2.43-2.25 (om, H_{20eq}, H_{12}, $C_{16}H_2$), 1.79 (s, $C_{4a}H_3$), 1.76 (om, H_{18eq}), 1.63-1.42 (om, H_{22}, H_{23}, H_{24}, H_{26}), 1.61 (s, $C_{14a}H_3$), 1.39 (m, $C_{27}H_2$), 1.17 (d, J=6.7, $C_{12}H_3$), 0.94-0.84 (om, $C_{28}H_3$, H_{18ax}), 0.94 (s, $(CH_3)_3C$), 0.86 (d, J=6.7, $C_{26a}H_3$), 0.68 (m, $C_{24a}H_3$), 0.140 (s, CH_3Si), 0.137 (s, CH_3Si), 0.12 (s, $(CH_3)_3Si$).
13. All new compounds were characterized by ^{1}H, ^{13}C, IR, and HR-MS or combustion analysis.

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