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Synthesis of (-)-Bactobolin from D-Glucose and from (+)-Actinobolin

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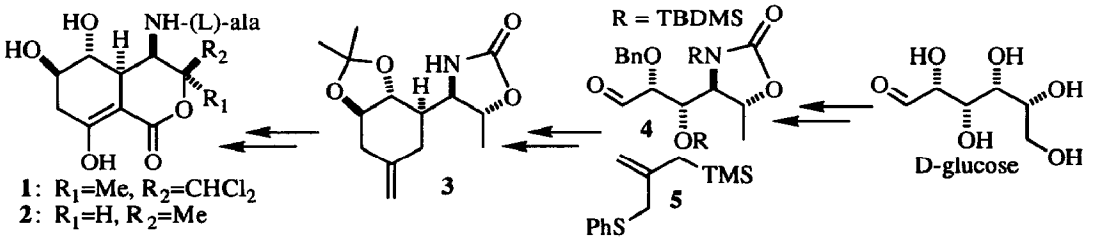
Abstract: The preparation of (-)-**16** from (+)-**3** constitutes a formal enantiospecific synthesis of (-)-bactobolin from D-glucose. The key transformation involves the diastereoselective addition of $LiCHCl_2$ to **7** in the presence of $CeCl_3$. The synthesis of (+)-**3** from (+)-actinobolin sulfate is reported and illustrates the conversion of (+)-actinobolin into (-)-bactobolin.

Bactobolin (**1**),[1] a metabolite of *Pseudomonas yoshidomiensis*, is a broad spectrum antibiotic and has significant antitumor activity.[2] Bactobolin is a close structural analogue to actinobolin (**2**)[3] but is much more potent in bioactivity.[2] These compounds have attracted considerable synthetic interest and several syntheses of the actinobolin skeleton have been reported.[4,5] Despite the structural similarities between **1** and **2**, to date only the elegant route of Weinreb *et al.* has successfully produced bactobolin.[6,7] A unique feature of Weinreb's synthesis of bactobolin (and actinobolin)[6] is the late stage introduction of the lactone carbonyl group by intramolecular acylation. We prepared **3** ($[\alpha]_D$ = 19°; *c*=0.23, MeOH) by [3+3] annulation[8] of the D-glucose derived aldehyde **4** with 3-phenylthio-2-(trimethylsilylmethyl)-propene (**5**) and followed the intramolecular acylation strategy for the conversion of (+)-**3** into actinobolin (Scheme 1).[5] We now report the extension of our synthetic scheme to include bactobolin by the preparation of (+)-**3** from actinobolin and the efficient conversion of (+)-**3** into (-)-**16**.

Scheme 1

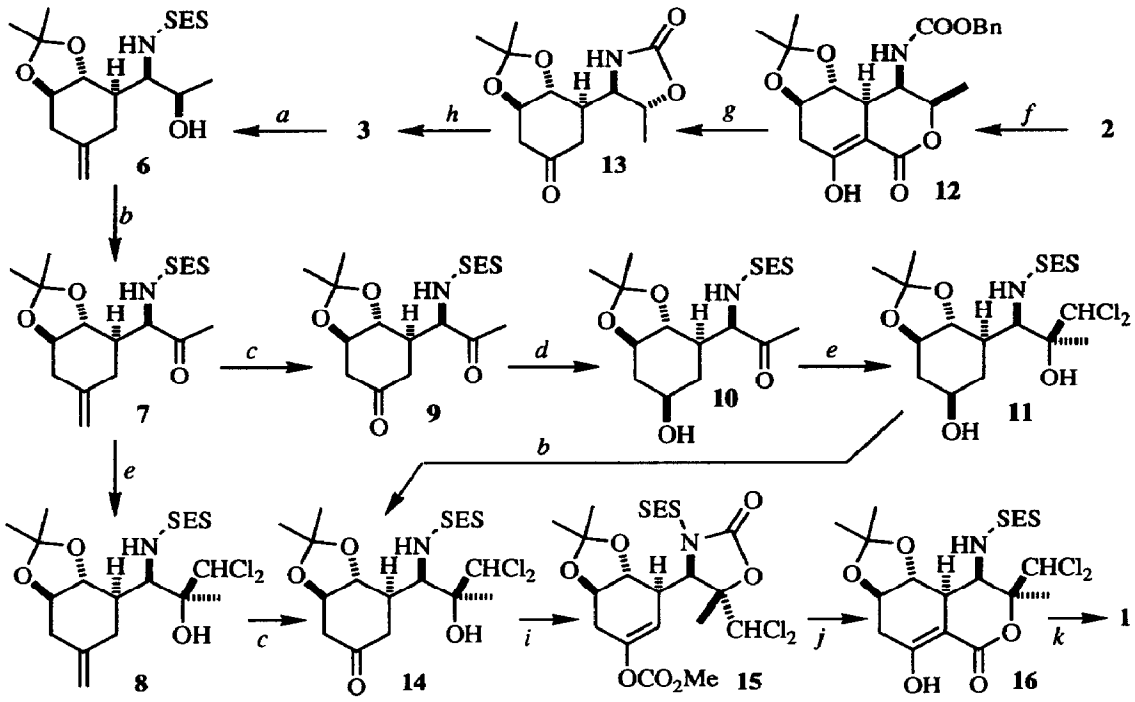


The most direct route to bactobolin from **3** would involve incorporation of the dichloromethyl substituent before oxidation of the methylene group. Treatment of (+)-**3** with BuLi and 2-(trimethylsilyl)ethanesulfonyl chloride (SES-Cl)[9] followed by hydrolysis gave **6** which was converted into the methyl ketone **7** by oxidation

(Scheme 2). Our initial attempts to effect addition of $LiCHCl_2$ with[6] or without[7a] added $CeCl_3$ to the ketone group in **7** were unsuccessful. Other workers have observed that this reaction is particularly sensitive to subtle changes in the substrate structure.[6,7a] Weinreb established[6] that the hydroxyl group in (±)-**10** was crucial for efficient conversion into **1**. Since the amount of **7** was limited, we decided to proceed to bactobolin by the known[6] route via **10** to conserve synthetic material.

The preparation of **10** from **3** was facilitated by using a route that obviated the need for a protecting group strategy (Scheme 2). Ozonolysis of **7** gave the dione **9**. Reaction of **9** with $NaBH_4$ under our previously developed conditions (50% MeOH in CH_2Cl_2, -78 °C, 0.5 h)[10] resulted in the chemoselective and stereoselective reduction of the cyclohexanone carbonyl in the presence of the methyl ketone to give the desired (-)-**10** ($[\alpha]_D$ = -44.6°; *c*=0.56, $CHCl_3$) in 72% yield (92% based on consumed **9**) along with recovered **9** (22%).[11,12] The spectroscopic properties of (-)-**11** (MS, IR, ^1H and ^{13}C NMR) of agreed closely with those previously reported for (±)-**11**.[4h] Unfortunately, we were unable to reproduce the reported[4h] addition of $LiCHCl_2$ to **10** on the necessary 10-20 mg scale.

Scheme 2



a) BuLi, SES-Cl; NaOMe, MeOH (94%). *b*) CrO_3, pyr. (91%). *c*) O_3; DMS (91%). *d*) $NaBH_4$, MeOH, CH_2Cl_2, -78 °C (92%). *e*) $LiCHCl_2$,$CeCl_3$ (see text). *f*) PhNCS; $H^{(+)}$; Cbz-Cl; DMP, acetone, $H^{(+)}$ (52%; cf. ref. 14). *g*) $NH_4OH_{(aq)}$ (57%). *h*) CH_2Br_2, Zn, $TiCl_4$ (74%). *i*) MeO_2CCl, TEA, 4-pyrrolidinopyridine (91%). *j*) NaOMe, MeOH (67%). *k*) Bu_4NF; HCl, MeOH; Cbz-(L)-ala, DCC; H_2/Pd-C (see ref. 4h).

To obtain additional material, we prepared **12** from actinobolin[13] according to the known procedure[14] (Scheme 2). Following a lead from the structure elucidation of acinobolin,[15] refluxing a solution of **12** in aqueous NH_4OH resulted in hydrolysis of the lactone ring with subsequent decarboxylation and formation of the oxazolidone to give **13**. Olefination[16] of **13** gave **3** ($[\alpha]_D = 20°$; *c*=0.50, MeOH) which was identical to that previously synthesized from D-glucose. Both **7** and **10** were prepared from semi-synthetic **3** as shown in Scheme 2. Under optimized conditions,[17] the reaction of **7** with $LiCHCl_2/CeCl_3$ gave **8** as 7.5:1 mixture (^1H NMR) of stereoisomers in 44% yield along with recovered **7** (42%). Similar treatment of **10** gave **11** as a single stereoisomer (30%) along with recovered **10** (40%). The stereoselectivity presumably results from a chelation controlled addition and is consistent with previous observations.[6,7a] Ozonolysis of **8** gave **14** which was identical to the product obtained from oxidation of **11**. Spectral data for **11** and **14** were consistent with those reported for the corresponding racemic materials.[4h]

In our hands, treatment of **14** with MeO_2CCl gave the enol carbonate **15** in excellent yield.[18,19] Completion of the bactobolin skeleton was effected by cyclization of **15** with NaOMe to give (-)-**16** ($[\alpha]_D$ = -26°; *c*=0.60, $CHCl_3$); spectroscopic data (IR, MS, ^1H and ^{13}C NMR) agreed closely with that for (±)-**16**.[4h] The efficient transformation of (±)-**16** into bactobolin has been described.[4h] Thus the preparation of (-)-**16** from (+)-**3** constitutes a formal enantiospecific[20] synthesis of bactobolin from D-glucose. Similarly, the preparation of (+)-**3** from **2** demonstrates the conversion of (+)-actinobolin into (-)-bactobolin.

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11. No stereoisomers of **10** were detected in the reaction mixture.
12. Increasing the reaction time to 1 h did not improve the yield of **10**; however, diol (ca. 10%) was detected in the reaction mixture. The direct conversion of **7** into **10** was attempted by using $NaBH_4$ rather than DMS for reductive work-up of the ozonolysis reaction. The reduction of hydroperoxide with $NaBH_4$ to give **9** was not sufficiently rapid at -78 °C to be efficacious. For example, after 0.5 h, the yield of **10** was <50% while after 1 h diol could be detected along with **9** and **10** (1:2, respectively).
13. We thank the Parke-Davis Pharmaceutical Research Divison of Warner-Lambert Co. for a generous gift of actinobolin sulfate.
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17. The reactions conditions were optimized and calibrated using $PhCH_2CH(NHSES)COCH_3$ as the substrate [prepared from phenylalanine: a) Dakin, H. D.; West, R. *J. Biol. Chem.*, **1928**, *78*, 91; b) Toyoda, T.; Suyama, T.; Kanao, S. *Yakugaku Zasshi*, **1963**, *83*, 856 (*Chem. Abstr.*, **1964**, *60*, 1832e)]. The protocol used was slightly modified from that reported[4h] to accommodate a smaller scale. We obtained better reproducibility using MeLi (1.0 M in ether) as the base to generate $LiCHCl_2$. MeLi was added to a solution of CH_2Cl_2 (0.25 mL) in THF (0.30 mL) at -100 to -110 °C (bath). After stirring for 30 min., ether (3.2 mL) was added dropwise to the resulting white suspension and then anhydrous $CeCl_3$ (1.05 equiv. relative to MeLi) was added via a side arm. After stirring for 1 h, a solution of the substrate in CH_2Cl_2 (1 mL) was added dropwise. After stirring for 2 h, MeOH (1 mL) was added dropwise and, after warming to -78 °C over several min., the mixture was diluted with EtOAC, washed with brine, dried over $MgSO_4$, concentrated, and fractionated by medium pressure chromatography. Reactions were conducted with 0.05-0.08 mmol of substrate. A 70-80% yield was obtained with the model substrate using 8 equiv. of $LiCH_2Cl_2$; 25-35 equiv. of $LiCH_2Cl_2$ were required for reactions of **7** and **10**.
18. Under these conditions, the formation of the ketone corresponding to **15** was reported although this product was not characterized.[4h]
19. IR ν_{max}: 1793, 1761, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.80 (1H, s, $CHCl_2$), 5.37 (1H, t, J = 0.5 Hz, C=CH), 4.90 (1H, d, J = 1 Hz, CH-N), 3.82 (3H, s, OMe), 3.79 (2H, m, 2 x CH-O), 3.57 (2H, m, CH_2S), 2.94 (1H, m, CH-C=C), 2.68 and 2.55 (each 1H, m, CH_2-C=C), 1.76 (3H, s, Me), 1.46 (6H, s, 2 x Me), 1.13 (2H, m, CH_2-Si), 0.08 (9H, s, SiMe); ^{13}C NMR ($CDCl_3$) δ: 153.3, 151.5, 149.8, 112.1, 111.5, 86.5, 76.4, 75.5, 74.8, 58.7, 55.5, 51.8, 40.4, 32.5, 27.2, 26.7, 15.7, 9.3, -2.1; LRMS (CI, NH_3) m/z: 591, 593 (M+18).
20. We use this term to describe a diastereoselective synthesis of a specific enantiomer as opposed to a diastereoselective synthesis of a racemate or an enantioselective synthesis (cf. Ward, R. S. *Chem. Br.*, **1991**, *27*, 803).

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