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# THE DIASTEREOSELECTIVE SYNTHESIS OF (+)-ACTINOBOLIN FROM D-GLUCOSE [1]

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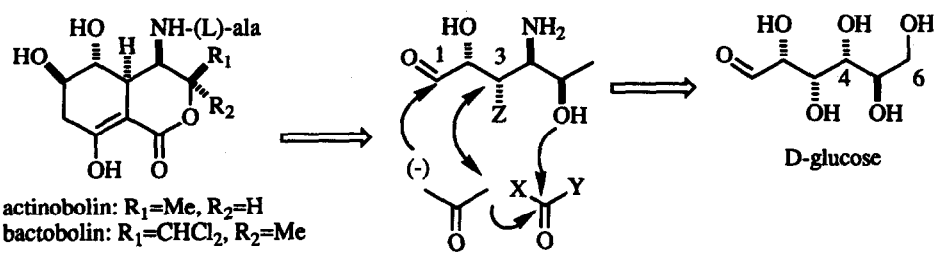
*Key Words: actinobolin; bactobolin; [3+3] annulation; 4,6-dideoxy-4-galactosamine; diastereoselective synthesis*

***Abstract:*** *The carbocyclic ring of actinobolin was constructed by a [3+3] annulation of a D-galactosamine derivative with 3-phenylthio-2-(trimethylsilylmethyl)propene. Formation of the lactone and acylation with L-alanine according to literature precedent gave (+)-actinobolin.*

The bacterial metabolites actinobolin[2] and bactobolin[3] are broad spectrum antibiotics which also display significant antitumor activity. The synthesis of these compounds has attracted considerable interest recently.[4] Our approach to the synthesis of these natural products envisioned the [3+3] annulation of an appositely functionalized hexanal with an acetone or an acetoacetate synthon to form the carbocyclic ring (see Scheme I). One advantage of this disconnection lies in the possibility of employing a hexose derivative to introduce 4 of the 5 stereogenic centers present in the target structures with the correct absolute configuration. Consideration of the aldehyde structure required for an actinobolin synthesis reveals a possible correlation with D-glucose via conversion of the 4-hydroxy group into an amino group with inversion of stereochemistry and deoxygenation at C-6.

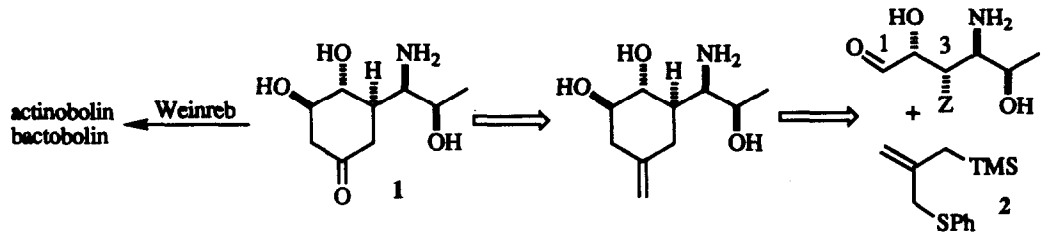
**Scheme I**




Weinreb has previously demonstrated[4i] that suitably protected derivatives of **1** could be efficiently converted into both actinobolin and bactobolin. Therefore, our initial goal was to prepare an intermediate analogous to **1** by a [3+3] annulation onto a galactosamine derivative (see Scheme II). Both of the C-C bonds resulting from annulation must be formed stereoselectivly. Considerable literature precedent[5] suggests that the desired stereochemistry at C-1 should result from an α-chelation controlled addition to the aldehyde group. On the other hand, the desired stereochemistry at C-3 could, in principle, result from a nucleophilic substitution

(with inversion of configuration) by an enolate, or equivalent, with a derivative bearing a suitably configured leaving group at C-3. However, our concern with the viability of the latter process under either inter- or intramolecular conditions led us to develop a free radical based protocol for the formation of this C-C bond. We have described[6] the preparation of 3-hydroxy-1-methylenecyclohexanes from 3-hydroxyaldehydes via a [3+3] annulation process involving sequential two electron and one electron allylation with 3-phenylthio-2-(trimethylsilylmethyl)propene (2) (see Scheme II).

**Scheme II**




The aldehyde required for annulation with **2** was prepared from the readily available **3**[7] (see Scheme III). The glucoside **3** was converted into the 4,6-dideoxy-4-azidogalactoside **4** ($[\alpha]_D$ = -37.1; *c*=0.76, $CHCl_3$) in 65% overall yield in analogy with the published procedure.[8] The azide **4** was reduced[9] to the corresponding amine which was converted into the ethyl carbamate **5**. Acetolysis of the glycoside followed by mild[10] hydrolysis of the resulting anomeric acetate provided a mixture of hemiacetals **6**. Reduction with $NaBH_4$ gave an acylcic triol[11] which regioselectively formed the cyclic carbamate **7** upon treatment with KH. Persilylation of **7** followed by selective hydrolysis gave the primary alcohol **8** which was oxidized to the desired aldhyde **9**.

The aldehyde **9** smoothly coupled with **2**[6] in the presence of $TiCl_4$ to give the alcohol **10**[12] together with up to 10% of the debenzylated **11**. Although separable, the mixture of **10** and **11** was, in practice, subjected to $BBr_3$ to give **11** in 65-70% yield from **9**. After considerable experimentation we settled on the cyclic thiocarbamate **12** as the substrate for radical cyclization.[13] Conversion of diol **11** into the corresponding acetonide followed by hydrolysis of the silyl groups and treatment with $Im_2C{=}S$ gave **12**. Photolysis (Rayonette, 300 nm) of a mixture of **12** and $(Me_3Sn)_2$ in the presence of benzophenone[14] induced 6-endo-trig radical cyclization[6] to give **13** ($[\alpha]_D$ = 10.1; *c*=0.68, $CHCl_3$).[15]

The conversion of **13** into actinobolin was guided by Weinreb's synthetic route.[4e,4i] Treatment of **13** with (4-methylphenyl)methylsulfonyl chloride (PMS-Cl)[4b,16] followed by ozonolysis of the exocyclic methylene group gave ketone **14**. The cyclic carbamate of **14** was hydrolyzed by treatment with methoxide to give the corresponding alcohol[4e,4i] which was cyclized to **15** [17]($[\alpha]_D$ = 5.2; *c*=0.23, $CHCl_3$) via intramolecular acylation in analogy to Weinreb's procedure.[4e,4i]

The preparation of **15** constitutes a formal synthesis of actinobolin. The efficient conversion of both racemic[4i] and optically active[4b,18] **15** into (+)-actinobolin hydrochloride has been previously reported.

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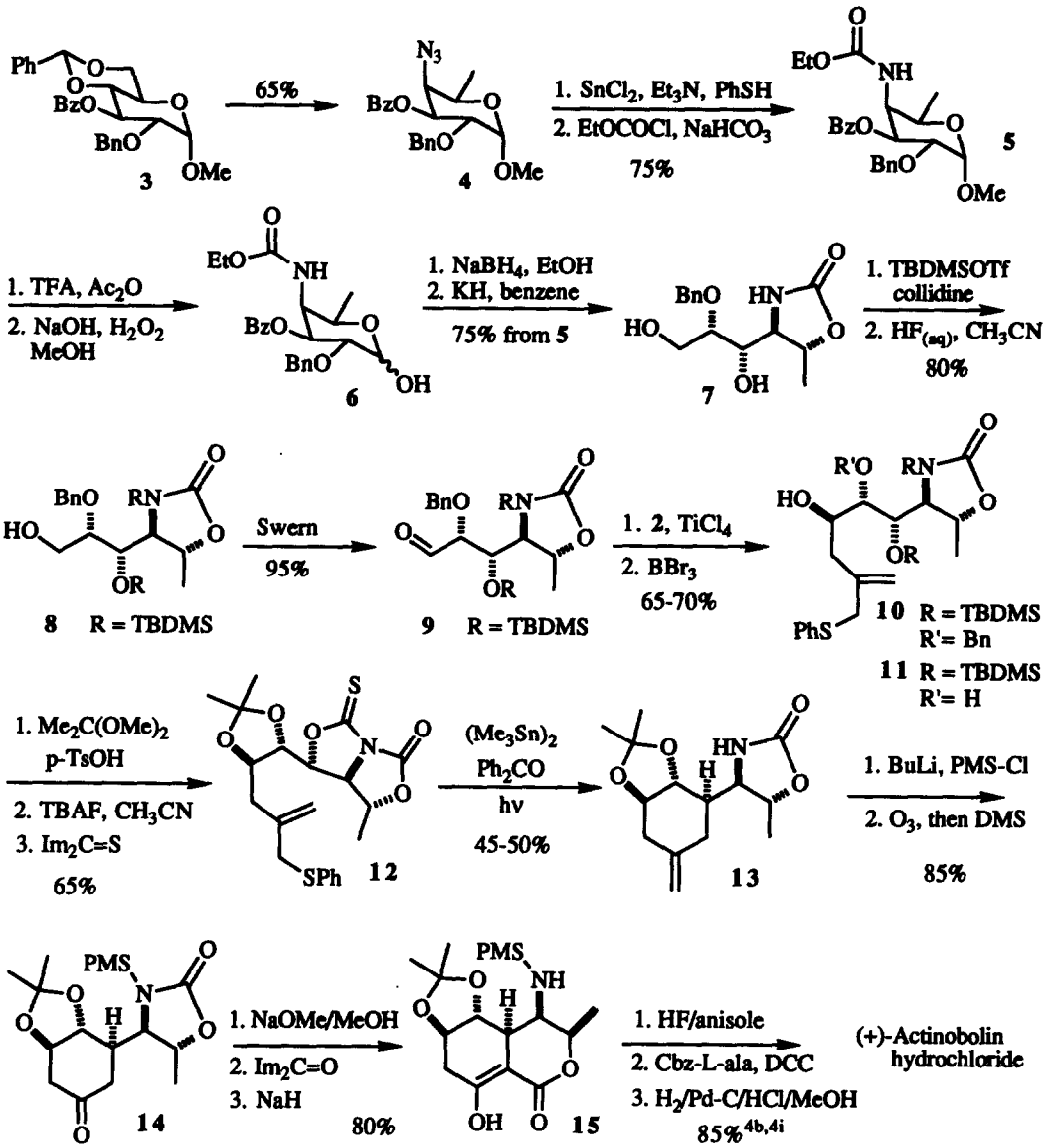
**Scheme III**

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7. Prepared from methyl 4,6-O-benzylidene-α-D-glucopyranoside by selective 2-O-benzylation (1. $Bu_2SnO$, benzene, reflux; 2. BnBr, $CH_3CN$, reflux; 72% (plus 12% of the 3-O-benzyl derivative); cf. Haque, M. E.; Kikuchi, T.; Yoshimoto, K.; Tsuda, Y. *Chem. Pharm. Bull.*, **1985**, *33*, 2255) followed by benzolyation (BzCl, pyridine, r.t.; 90%) in 65% overall yield.
8. Paulsen, H.; Lorentzen, J. P. *Carbohydr. Res.*, **1985**, *140*, 155. This procedure uses the 3-O-acetyl derivative corresponding to **3**; we obtained better yields (especially for azide displacement) with **3**. The route involves: i) hydrolysis (TFA, MeOH, $H_2O$, reflux; 90%); ii) bismesylation (MsCl, pyridine, 3-5 °C; 95%); iii) selective reduction at C-6 (1. NaI, EtCOMe, reflux; 2. Zn, ether, HOAc, r.t.; 85%); iv) displacement with azide ($NaN_3$, DMF, reflux; 90%). Cf. Stevens, C.L.; Blumbergs, P.; Ottenbach, D.H. *J. Org. Chem.*, **1966**, *31*, 2817.
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10. The compound was susceptible to elimination of the benzoate. Alkaline hydrogen peroxide has been used to hydrolyze base sensitive esters: (a) Corey, E. J., *et. al. J. Am. Chem. Soc.*, **1978**, *100*, 4620. (b) Woodward, R. B., *et. al. J. Am. Chem. Soc.*, **1981**, *103*, 3213.
11. The benzoyl group migrates to the C-1 position and is hydrolysed under the reaction conditions.
12. Only a single diastereomer of **10** was detected and we assign the stereochemistry as shown on the basis of analogy to known examples.[6] This assignment is confirmed by conversion of **10** into the known **15**[4e,4i].
13. Cyclic thiocarbonates have been used to initiate radical cyclization: Ziegler, F. E.; Metcalf, C. A., III; Shulte, G. *Tetrahedron Lett.*, **1992**, *33*, 3117. We are unaware of any examples of the use of cyclic thiocarbamates for this purpose.
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15. No stereoisomers of **13** were detected in the reaction mixture. The higher stereoselectivity of this reaction compared to those in our model study was expected due to geometric constraints imposed by the acetonide.
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17. Both **15** and its hydroxyketone precursor had spectral (ms, ir, $^1H$ and $^{13}C$ nmr) properties which agreed favorably with those reported for the corresponding racemic materials.[4i]
18. The diol corresponding to hydrolysis of the acetonide group in **15** was used.


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