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New synthesis of (–)- and (+)-actinobolin from D-glucose

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Abstract—The total synthesis of (–)-actinobolin **2**, an antipode of the natural product starting from D-glucose is described. A three-component coupling reaction of a functionalized cyclohexenone (+)-**6**, derived from D-glucose by way of Ferrier's carbocyclization, with vinyl cuprate and an aldehyde (*R*)-**5** effectively constructed the carbon framework of **2** in a highly stereoselective manner. The formal synthesis of the natural enantiomer **1** from D-glucose was also achieved.

(+)-Actinobolin **1**, isolated from the culture broths of *Streptomyces* in 1959, has a broad antibacterial spectrum as well as moderate antitumor activity.[1] The structure elucidation study revealed that actinobolin has a highly oxygenated bicyclic γ-lactone (tetrahydroisochroman) framework with five contiguous chiral centers including an L-alanine residue.[2] Later, in 1979, a structurally related natural product, bactobolin was discovered and found to show more potent activities than actinobolin.[3] It has also been reported that they suppress antibody production and have a therapeutic effect on autoimmune encephalomyelitis.[4] Such interesting and challenging structures with potent biological properties have naturally received considerable attention from the synthetic community, and several reports on total syntheses[5] and chemical modification[6] of actinobolin and bactobolin have been described. We now report the new total synthesis of (–)-actinobolin **2**, the antipode of the natural product expected to show some biological activity, starting from D-glucose. The formal synthesis starting from D-glucose of natural enantiomer **1** is also presented.

Our retrosynthetic analysis for (–)-actinobolin **2** suggested that a bicyclic γ-lactone possessing an azide function **3** would be a promising intermediate for the total synthesis (Fig. 1). The γ-lactone **3** was expected to arise from cyclohexanone derivative **4**, which we

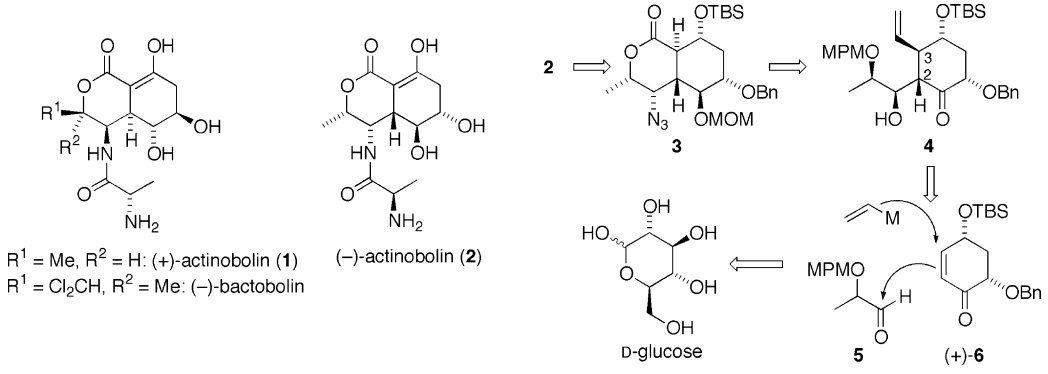

Figure 1. Structures of actinobolin and bactobolin, and retrosynthetic route to (–)-actinobolin. TBS = –SiMe$_2$(*t*-Bu), MPM = –CH$_2$C$_6$H$_4$(*p*-OMe), Bn = –CH$_2$Ph, MOM = –CH$_2$OMe.

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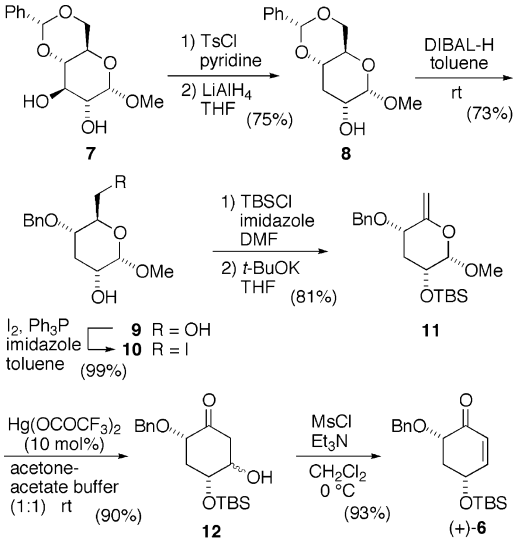
planned to prepare by way of a one-pot three-component coupling reaction[7] of cyclohexenone (+)-**6**, aldehyde **5** and a vinyl metal species. The cyclohexenone (+)-**6**, in turn, was envisioned to be synthesized in optically pure form starting from D-glucose utilizing a Ferrier's carbocyclization[8] as the key transformation.

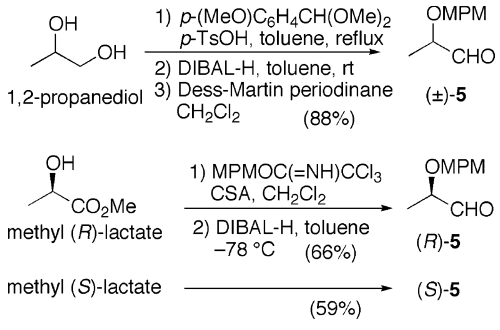
Synthesis of the cyclohexenone (+)-**6** commenced from 3-deoxy-D-glucose derivative[9] **8** prepared from commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **7** in two steps in 75% yield (Scheme 1). Reduction of **8** with DIBAL-H gave **9**[10] (73% yield), whose primary hydroxy group was selectively iodinated to afford **10** in 99% yield. After protection of the remaining hydroxy function as a TBS ether, the resulting compound was treated with *t*-BuOK to give 5-enopyranoside **11** in 81% yield. Catalytic Ferrier's carbocyclization[11] of **11** in acetone–acetate buffer[12] provided **12** as a mixture of diastereomers (α-OH:β-OH = ca. 1:10). β-Elimination of the mixture cleanly generated cyclohexenone (+)-**6** in 84% yield from **11**. The other requisite fragment, aldehyde **5** was synthesized from 1,2-propanediol, and methyl (*R*)- and (*S*)-lactates (Scheme 2). 1,2-Propanediol was converted into a *p*-methoxybenzylidene acetal derivative, whose treatment with DIBAL-H, followed by oxidation furnished racemic (±)-**5** in 88% overall yield. On the other hand, acid catalyzed *p*-methoxybenzylation of methyl (*R*)-lactate,[13] and subsequent reduction afforded (*R*)-**5** in 66% yield from methyl lactate. Similar treatment of (*S*)-lactate gave (*S*)-**5**.

With chiral cyclohexenone (+)-**6** and aldehydes **5** in hand, the crucial three-component coupling reaction was investigated using vinyl cuprate as the nucleophile (Scheme 3). Treatment of (+)-**6** with higher order vinyl cuprate in Et_2O at −78°C caused the stereoselective conjugate addition of the vinyl group to give an enolate intermediate **6′**, which was then reacted with racemic aldehyde (±)-**5** (excess amount) at −78°C, to provide **4** as the major isomer in 68% yield after chromatographic separation. When chiral aldehyde (*R*)-**5** was employed as the electrophile, the same diastereomer **4** was obtained in 85% yield. Interestingly, with another chiral aldehyde (*S*)-**5**, the aldol process was found to proceed much slower than the reaction with (*R*)-**5**, and a different diastereomer **13**, in which the stereochemistry of substituents at C-2 and C-3 were *cis*, was formed in 75% yield. The predominant formation of 1′,2′-*syn* isomers (**4** and **13**) suggested that the chelation control (chelation by the alkoxy and aldehyde oxygen in (*R*)- and (*S*)-**5**) should be an important factor in the aldol process. Reaction of chelated (*R*)-**5** and the intermediate enolate **6′** would proceed in a 'matched pair' manner (route *a* in Scheme 3) to give **4** smoothly, whereas combination of (*S*)-**5** and **6′** would be 'mismatched'. The steric repulsion between chelated (*S*)-**5** and **6′** (both routes *b* and *c*) rendered the aldol reaction sluggish, but gave 2,3-*cis*-adduct **13** stereoselectively via route *c*.[14]

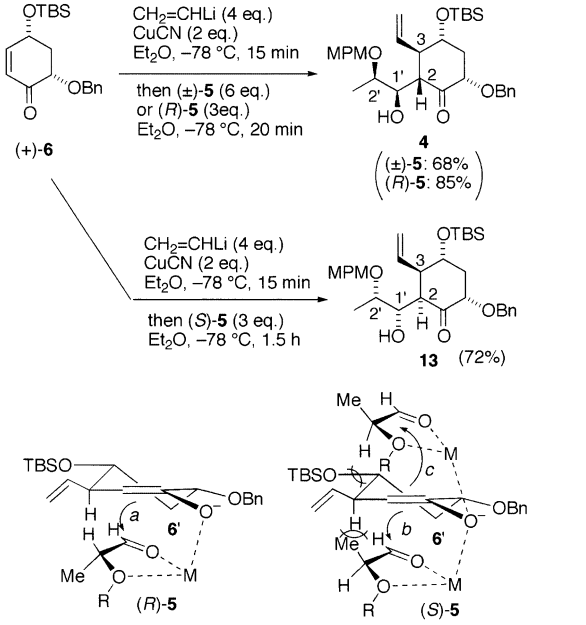
The stereoselective formation of three-components adduct **4** led us to use **4** as the precursor for the synthesis of (−)-actinobolin **2**. Conversion of **4** to **2** required the following transformations: (1) reduction of ketone carbonyl to β-alcohol; (2) introduction of a



Scheme 1.



Scheme 2.



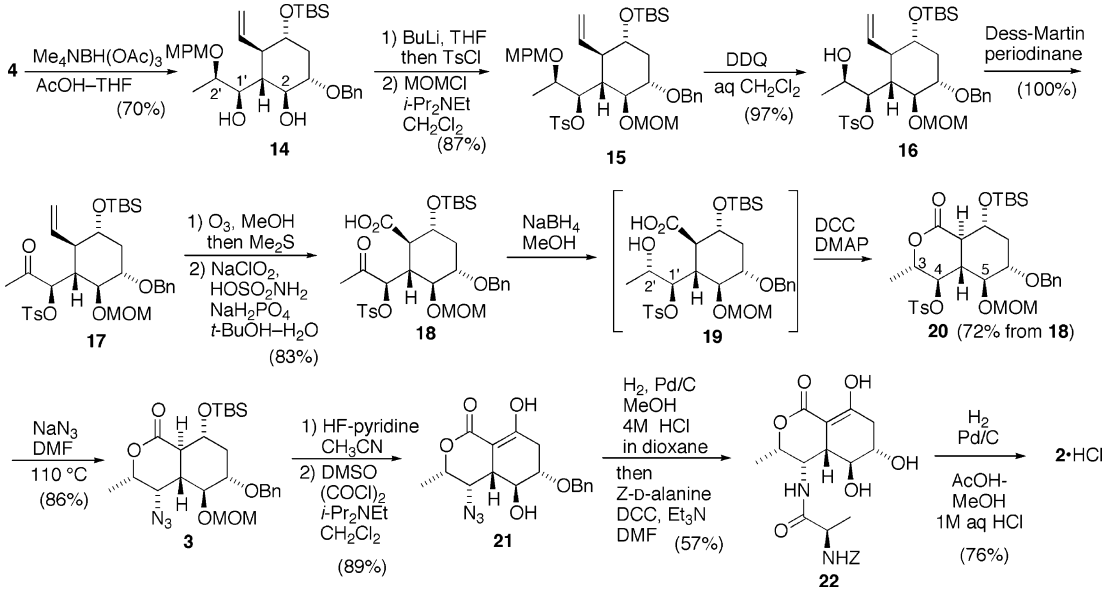
Scheme 3.

nitrogen function at C-1′ via S_N2 fashion; and (3) formation of γ-lactone with inversion of the configuration at C-2′ hydroxy group.

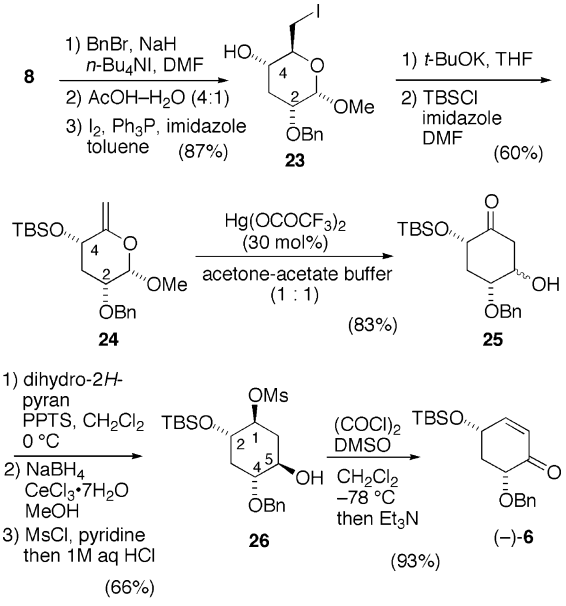
Treatment of **4** with $Me_4NBH(OAc)_3$[15] at room temperature stereoselectively reduced the carbonyl group to give desired *syn* diol **14** in 70% yield (Scheme 4). The hydroxy group at C-2 in **14** was anticipated to show less reactivity than that at C-1′ due to steric congestion. Indeed, reaction of **14** with BuLi (3 equiv.) at 0°C, followed by treatment with TsCl (2.8 equiv.) generated the 1′-OTs derivative, quantitatively. The remaining hydroxy function was then masked as a MOM ether to afford **15** in 87% yield.

The MPM protecting group was removed to give **16** (97% yield). Since attempted inversion of the hydroxy function in **16** by Mitsunobu reaction proved fruitless, we adopted an oxidation–reduction procedure. Dess–Martin oxidation of **16** afforded methyl ketone **17** in 100% yield. Reduction of the ketone **17** with various reducing reagents was attempted, however, the desired inverted alcohol could not be obtained as the major isomer. Fortunately, it was found that the stereoselective reduction successfully proceeded when carboxylic acid **18** was employed as the substrate. Thus, ozonolysis of **17**, followed by further oxidation with sodium chlorite afforded **18** in 83% yield. In this case, reduction of **18** with $NaBH_4$ in MeOH provided desired product **19** as the major isomer (**19**: its 2′-epimer = 82:18, 96% yield), and bicyclic compound **20** was obtained in 72% yield from **18** after lactonization followed by separation with silica gel chromatography.[16] Azidolysis of **20** with NaN_3 provided advanced intermediate **3** in 86% yield. Deprotection of the *O*-TBS moiety in **3**, followed by Swern oxidation afforded β-ketoester **21** in 89% yield. Interestingly, the methoxymethyl group was unexpectedly removed during the purification process with silica-gel chromatography. Hydrogenation of **21** in the presence of HCl reduced the azide function and removed the *O*-benzyl group to provide the amine hydrochloride, which, without isolation, was condensed with *N*-benzyloxycarbonyl-D-alanine (*Z*-D-alanine) in the presence of DCC to give protected actinobolin **22** in 57% yield. Finally, removal of benzyloxycarbonyl group by hydrogenolysis in MeOH–AcOH–1 M aq. HCl, followed by purification with Sephadex LH-20 (MeOH) furnished (−)-actinobolin hydrochloride (**2**·HCl) in 76% yield. The spectral (^1H and ^{13}C NMR) data of synthetic **2**·HCl were fully identical with those of natural (+)-actinobolin hydrochloride, kindly provided by Dr. Y. Nishimura, and the $[\alpha]_D$ value of the synthetic compound {$[\alpha]_D^{24}$ −47 (*c* 0.1, H_2O): lit.,[5f] $[\alpha]_D^{20}$ +48 (*c* 0.40, H_2O)} confirmed its unnatural absolute configuration.

Having established a new synthetic pathway to (−)-actinobolin from D-glucose, we turned our attention to the synthesis of the natural enantiomer **1**, also starting from D-glucose. For this purpose, compound **8** was again chosen as a building block, and its transformation into the enantiomer of (+)-**6** was investigated (Scheme 5). Benzylation of the hydroxy group in **8**, followed by acetal hydrolysis and selective iodination of the resulting primary alcohol afforded **23** in 87% overall yield. Treatment of **23** with base and subsequent *O*-silylation gave **24** in 60% yield. Catalytic Ferrier's carbocyclization of **24** in acetone–acetate buffer generated **25** as a diastereomeric mixture (α-OH: β-OH = ca. 6:1) in 83% yield. Protection of the hydroxy group in **25** as a THP ether and subsequent reduction of the ketone carbonyl, followed by *O*-methanesulfonylation and acidic workup afforded **26** as the major product in 66% yield. The observed large coupling constants in **26** ($J_{1,2}$ = 8.8, $J_{4,5}$ = 9.0 Hz) clearly showed that both OMs and OH groups were in the equatorial positions. Swern oxidation of **26** was accompanied by the β-elimination of the OMs group to furnish (−)-**6** in 93% yield. The



Scheme 4.



Scheme 5.

spectral data and the absolute value of $[\alpha]_D$ of (−)-**6** {$[\alpha]_D^{20}$ −22 (*c* 0.80, $CHCl_3$)} were fully identical with those of (+)-**6** {$[\alpha]_D^{23}$ +22 (*c* 0.94, $CHCl_3$)}, representing a formal synthesis of (+)-actinobolin **1**.

In summary, a new synthetic route to both (−)- and (+)-actinobolin starting from D-glucose has been established. This work demonstrated that the methodology involving the three-component coupling reaction on chiral cyclohexenones, derived from carbohydrates by way of Ferrier's carbocyclization, is effective for the chiral and stereoselective synthesis of natural products possessing highly oxygenated cyclohexane moieties.

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16. When 2′-epimer of **19** was subjected to the intramolecular Mitsunobu reaction (Ph_3P, diethyl azodicarboxylate, THF), a γ-lactone with retention of the 2′ stereochemistry (3-epimer of **20**) was formed in 80% yield. A similar phenomenon and mechanistic study on Mitsunobu reaction of hydroxycarboxylic acids with hindered alcohols have been reported, see: Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751–1753 and Ahn, C.; Deshong, P. *J. Org. Chem.* **2002**, *67*, 1754–1759.