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Enantioselective Synthesis of SB-203207

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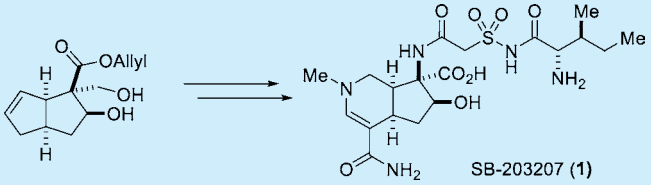
Supporting Information

ABSTRACT: Total synthesis of SB-203207 (**1**) was achieved, beginning with a desymmetrical C−H insertion reaction of a diazoester bearing our recently developed chiral auxiliary. Utilizing the optically active bicyclo[3.3.0]octane ring, four stereogenic centers were efficiently constructed in sequence. Finally, mild oxidation of **27** to carboxylic acid via a cyanohydrin intermediate and hydrolysis of cyanide to carboxyamide in the presence of the labile enamide group completed an efficient total synthesis of **1**.

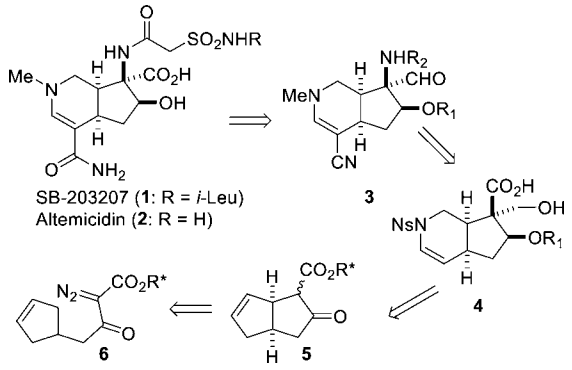


Nonproteinogenic α-disubstituted α-amino acid derivatives have recently attracted attention due to their potent biological activities, and they represent challenging structural targets for total synthesis.[1] However, few efficient methods are available for synthesizing complex α-amino acid derivatives bearing functional groups. Recently, researchers in the SmithKline Beecham group isolated SB-203207 (**1**) from a *Streptomyces* species[2] and showed that it inhibits isoleucyl *t*RNA synthetase with an IC_{50} value below 2 nM. Such inhibitors are promising candidates for the treatment of a variety of diseases, so an efficient and flexible synthesis of **1** is highly desirable.[3] Although a total synthesis of altemicidin (**2**), the core compound of **1**, was achieved by Kende and co-workers in 1995,[4] and the conversion of naturally occurring **2** to **1** was reported by the SmithKline Beecham group,[3] a total synthesis of **1** has not yet been reported.

During the course of our synthetic investigation of **2**, we reported a stereoselective synthesis of racemic intermediate **3** via a bicyclo[3.3.0]framework.[5] In an effort to develop an enantioselective synthesis of **1**, we focused on the stereoselective preparation of **5**. The heart of our synthetic plan is illustrated in Scheme 1. We aimed to introduce the highly polar leucenyl sulfonamide and vinylogous urea at a late stage in the synthesis.

Although we had previously synthesized racemic **3** through stereoselective introduction of a nitrogen atom and conversion to the azabicyclo[4.3.0] skeleton,[5] formation of the α-disubstituted α-amino acid moiety of **2** from **3** proved troublesome. However, we found an efficient oxidation method that yielded the carboxylic acid through cyanohydrin and acylcyanide intermediates. Some improvements of our previous synthetic procedures[5] were required for a large-scale preparation, and as reported herein we achieved an enantioselective total synthesis of **1**.

Scheme 1. Structure and Synthetic Strategy of SB-203207 (1)



As shown in Scheme 2, the construction of an optically active bicyclic[3.3.0]framework **12** was accomplished via an intramolecular C−H insertion reaction[6] in **11**. We have developed an efficient C−H insertion methodology using a combination of Rh_2(*S*-DOSP)$_4$[7] and a diazoester bearing our recently developed chiral auxiliary.[8] Although we had previously prepared the cyclization precursor **11** by the transesterification between the corresponding β-ketoester and the chiral alcohol **7**,[8c] its reproducibility was poor on a large scale. Thus, in our current approach, we started the synthesis with the condensation of **7** with α-bromoacetyl bromide. Because the preparation of diazoester **8** by the conventional diazotization

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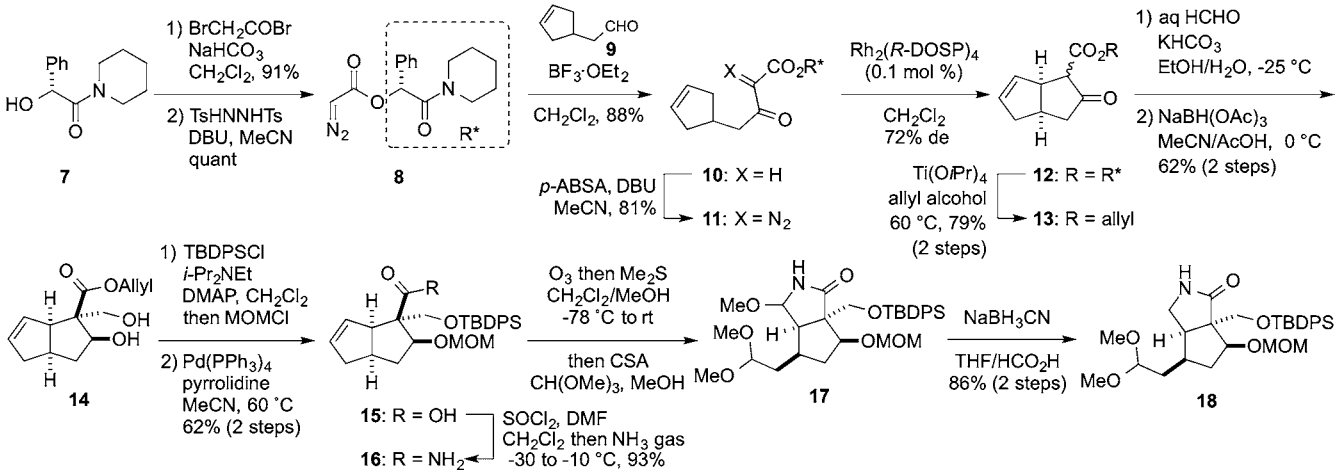
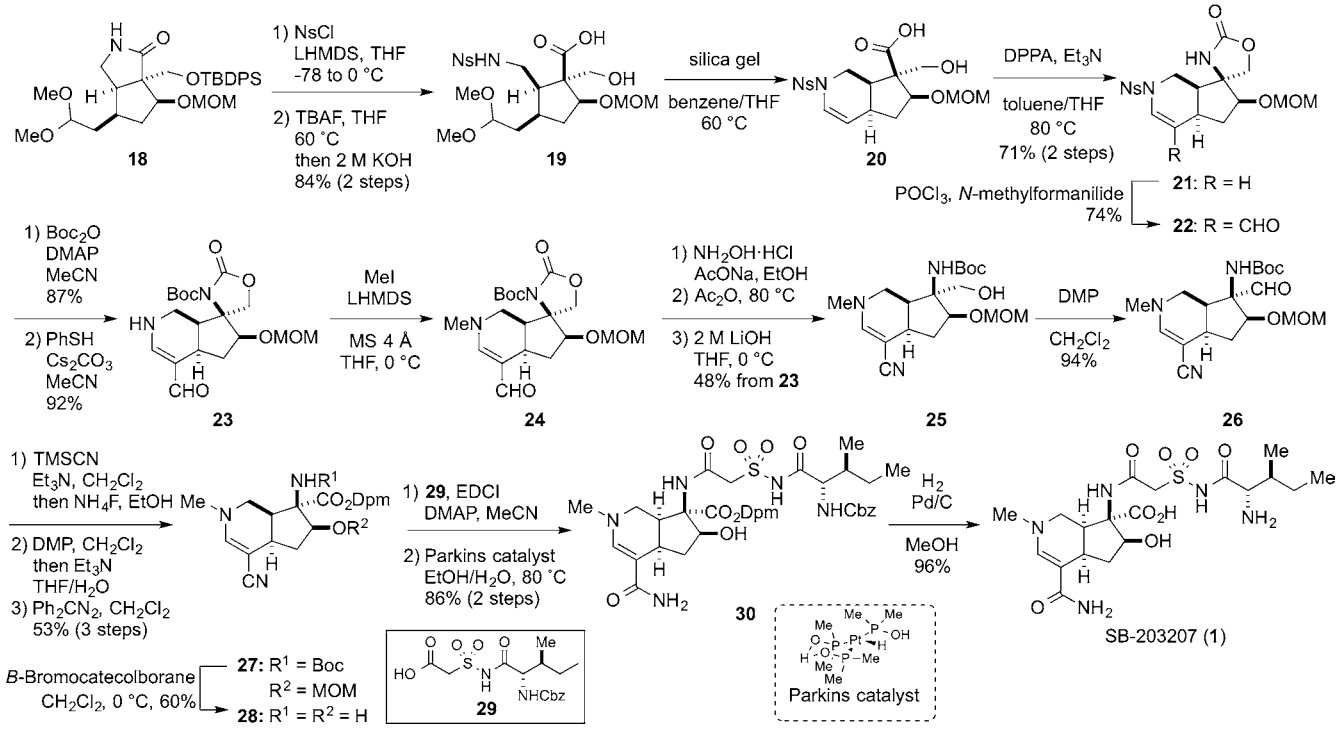
Scheme 2. Preparation of Lactam 18



Scheme 3. Total Synthesis of SB-203207 (1)



from a glycine derivative was also found to be difficult, we opted to use a novel diazotransfer method recently developed by our group.[9] Treatment of the α-bromoester with DBU in the presence of bis tosyl hydrazine proceeded smoothly to give **8** without the decomposition of the labile ester moiety. After the condensation of **8** and aldehyde **9** by means of a modified Roskamp reaction,[10] diazotransfer reaction of **10** provided the C−H insertion precursor **11**. Treatment of **11** with 0.1 mol % of Rh_2(*R*-DOSP)$_4$ resulted in the desired C−H insertion providing the optically active bicyclo[3.3.0]octane ring compound **12**. This transformation had the advantage of providing a one-step generation of the two chiral centers of the ring fusion. After the removal of the chiral auxiliary of **12** by transesterification,[11] stereoselective hydroxymethylation was achieved under careful temperature control.[12] On a large scale, epimerization of the α-position of the β-ketoester readily proceeded via retro-alkylation and alkylation. Subsequently, stereoselective reduction was carried out by treatment with NaBH(OAc)$_3$ through chelation with the primary hydroxyl group.[13] This was followed by one-step protection of the primary alcohol with TBDPS and the secondary alcohol with a MOM ether.

Incorporation of an amino functionality and the construction of the cyclic enamide from **15** were accomplished by using our racemic synthesis.[5] After the formation of amide **16** from allyl ester **15**, conversion to dimethyl acetal **17** was performed by ozonolysis and sequential treatment with methanol and HC(OMe)$_3$ in the presence of CSA.[14] After the selective reduction of the hemiaminal of **17** with NaBH$_3$CN, the incorporation of the Ns group[15] into lactam **18** was achieved by treatment with LHMDS and NsCl, as shown in Scheme 3. The TBDPS group was removed, and the lactam opening was performed by utilizing activation by Ns imide with the neighboring effect of the primary alcohol. Although a cyclic

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enamide formation from **19** had been carried out by treatment with CSA and quinolone in the previous synthesis,[5] the concomitant deprotection of the MOM ether occurred in a large-scale reaction. However, we found that heating in benzene in the presence of silica gel (anhydrous conditions) was suitable for this transformation, giving **20** in high yield. Next, the introduction of a nitrogen atom onto the quaternary carbon of **20** was performed by treatment with DPPA[16] to give **21**. After the incorporation of a C1 unit into enamide **22** via modified Vilsmeier reaction[17] and the protection of **22** with a Boc group, deprotection of the Ns group[18] and *N*-methylation afforded **24**. Conversion of aldehyde **24** to nitrile **25** was performed by treatment with hydroxylamine followed by the addition of acetic anhydride and base. Although the conversion to aldehyde **26** proceeded smoothly by hydrolysis of the oxazolidinone ring and DMP oxidation, further oxidation to the corresponding acid derivative was difficult. Non-nucleophilic oxidation reaction conditions were required because typical $NaOCl_2$-mediated Kraus oxidation,[19] as well as TEMPO[20]- or AZADO[21]-catalyzed oxidation, resulted in decomposition of the reactive cyanoenamide group.

After several attempts to convert aldehyde **26** to carboxylic acid, we found that the oxidation of the cyanohydrin intermediate was suitable. After the conversion to cyanohydrin,[22] Dess–Martin periodinane (DMP)-mediated oxidation provided acyl cyanide without the decomposition of the enamide group. After hydrolysis of acyl cyanide, the resulting carboxylic acid was protected by the reaction with diphenyldiazomethane[23] to give **27**. Simultaneous removal of the Boc and MOM groups by treatment with *B*-bromocatechol borane gave amino alcohol **28**. Incorporation of the side chain was carried out by treatment with **29**[3c24] in the presence of EDCI and DMAP. Conversion of the cyanoenamide derivative to carbamoylenamide was performed by treatment of catalytic quantities of Parkins catalyst.[25] The hydration reaction proceeded in high yield to provide **30** without loss of the functional group, due to the neutral reaction conditions. Finally, simultaneous cleavage of the Cbz and diphenylmethyl ester groups of **30** under hydrogenolysis conditions yielded SB-203207 (**1**), the spectral data of which (^{1}H NMR, ^{13}C NMR, IR, and HRMS) were in full agreement with those of the natural product.[2] Considering that the inhibitory activity is dependent on the nature of the amino acid residue in **1**,[3] this protocol should be useful for systematic investigation of the structure–activity relationship. Work along this line is underway in our laboratory.

In conclusion, we have accomplished an enantioselective total synthesis of SB-203207 (**1**). Our synthesis features a desymmetric C–H insertion reaction for the construction of the bicyclo[3.3.0] framework, stereoselective construction of sequential stereocenters, a novel conversion of aldehyde to carboxylic acid, and a nitrile hydrolysis-mediated vinylogous urea synthesis. Considering the easy incorporation of the side chain into **1**, this protocol is expected to provide ready access to a variety of derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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