ORGANIC LETTERS

2008
Vol. 10, No. 22
5317−5319

Synthesis of β-Lactams Bearing Functionalized Side Chains from a Readily Available Precursor

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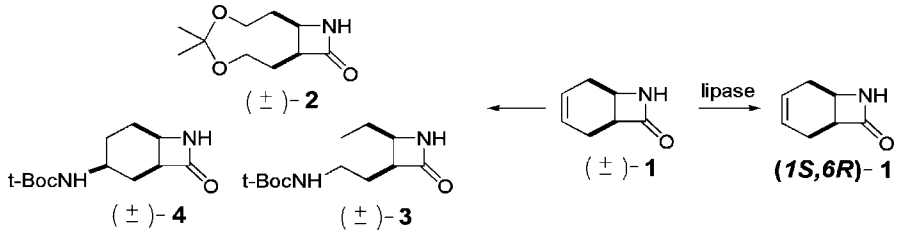
Received September 30, 2008

ABSTRACT

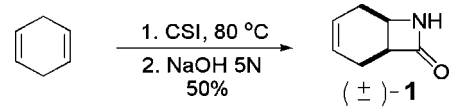


The reaction of chlorosulfonyl isocyanate (CSI) with alkenes provides β-lactams in quantity, and the products have frequently been used for ring-opening polymerization to generate nylon-3 materials. Prior uses of this approach have focused almost entirely on β-lactams with purely hydrocarbon substitutents. We show how a variety of β-lactams bearing protected polar substituents can be generated from CSI-derived building blocks.

β-Lactams can serve as precursors for the synthesis of polymers in the nylon-3 family via ring-opening polymerization (ROP).[1] We recently identified cationic nylon-3 copolymers that display antibacterial activity.[2] These random copolymers mimic the behavior of host-defense peptides,[3] which are natural oligomers that selectively disrupt bacterial membranes in preference to eukaryotic cell membranes. Described below is the synthesis of new β-lactams that will be useful for future efforts to refine the biological activity of nylon-3 polymers.

The development of random copolymers as antibacterial agents could be significant from a practical perspective because preparation of large quantities of these polymers should be straightforward, if the precurors are readily available. In contrast, stepwise chemical synthesis of peptides or other discrete oligomers with a defined subunit sequence is laborious. Reaction of chlorosulfonyl isocyanate (CSI) with alkenes is a well-established method for generating large quantities of β-lactams,[4] and this route has been popular for preparing ROP substrates. However, the intrinsic reactivity of CSI limits the types of alkenes that can be used for β-lactam formation; prior to our recent report[2a] CSI had been used largely to generate β-lactams with pure hydrocarbon appendages, as illustrated by the example in Scheme 1.[5] Our development of antibacterial nylon-3 derivatives hinged on extension of the CSI method to an alkene bearing a protected amino group. Because the resulting β-lactam proved to be

Scheme 1



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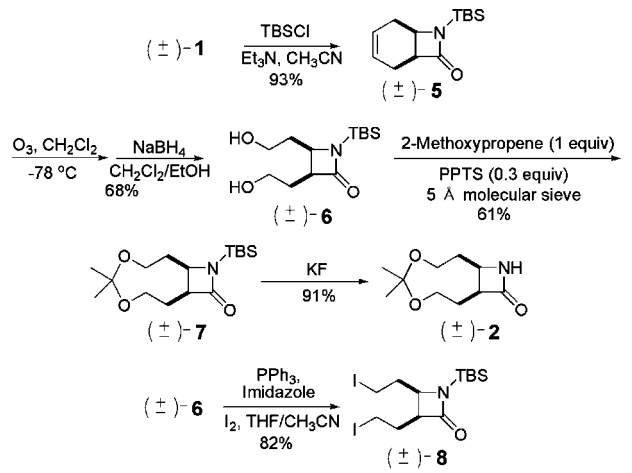
10.1021/ol802274x CCC: $40.75
Published on Web 10/29/2008

so valuable, we were motivated to explore other strategies for generating β-lactams bearing protected polar groups from CSI-derived products. Here we describe routes to several new β-lactams, derived from **1**, with appendages that contain protected amino or hydroxyl groups.

Scheme 2 illustrates the conversion of **1** to β-lactams that bear two side chains, one on each saturated ring carbon, with

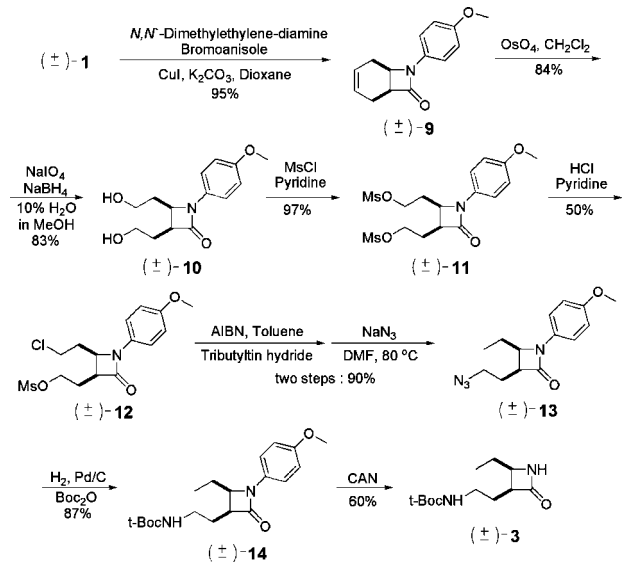
Scheme 2



cis stereochemistry. This route provides β-lactams in which both side chains bear the same functional group. After the lactam nitrogen has been protected with a silyl group[5] (**5**), the alkene can be oxidatively cleaved with ozone,[6] and a reductive workup provides dihydroxy β-lactam **6**. The hydroxyl groups can be protected by cyclic acetal formation. Removal of the silyl group then provides β-lactam **2**, which is suitable for ROP under standard anionic conditions. Alternatively, dihydroxy β-lactam **6** can be efficiently converted to diiodide[7] **8**, which could serve as a precursor for β-lactams bearing a variety of other polar group pairs in the side chains.

A variation on the route in Scheme 2, which is shown in Scheme 3, provides *cis*-disubstituted β-lactams in which the side chains are different. A silyl protecting group on the β-lactam nitrogen proved to be inadequate for this approach, but the p-methoxyphenyl (pMP) protecting group[8] was effective. In this route, oxidative alkene cleavage was achieved via OsO_4-mediated[9] dihydroxylation followed by reaction with $NaIO_4$ in the presence of $NaBH_4$,[10] to generate dihydroxy β-lactam **10**. This compound was readily con-

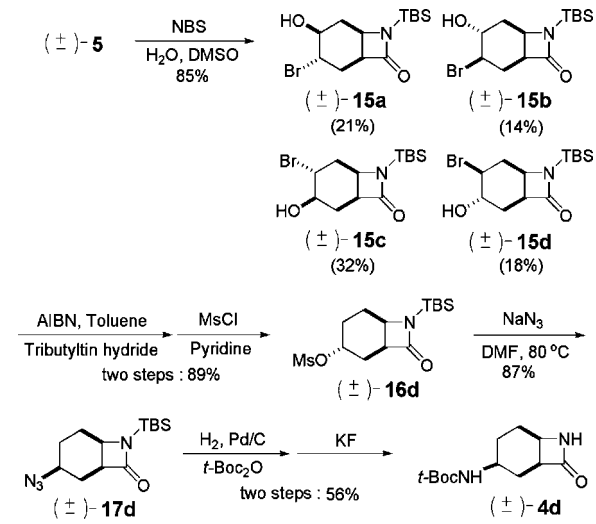
Scheme 3



verted to dimesylate **11**. Treatment of **11** with HCl provided monosubstituted product **12** in moderate yield. The identity of **12** was retrospectively established after two additional reactions, radical-mediated replacement of chlorine with hydrogen followed by displacement of mesylate with azide. This process yielded **13**, the structure of which was deduced from COSY data (Figure S1, Supporting Information). Reduction of the azide and in situ Boc protection provided **14**, which could be oxidatively deprotected[11] to generate **3**, a β-lactam that can participate in ROP reactions.

Scheme 4 shows a strategy for generating β-lactams that retain the *cis*-cyclohexyl constraint and bear polar substitution

Scheme 4



on the cyclohexyl ring. Treatment of racemic silyl-protected β-lactam **5** with *N*-bromosuccinimide in aqueous DMSO

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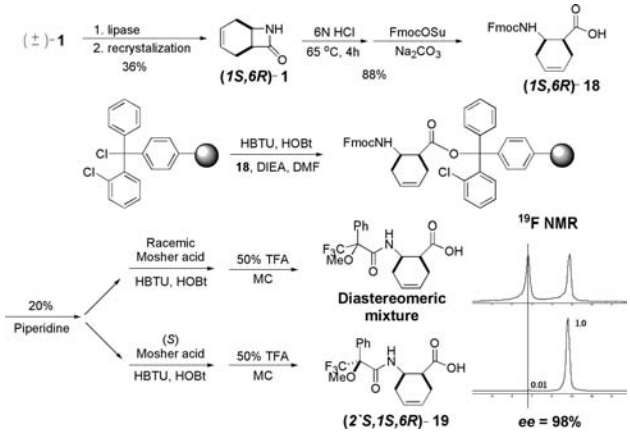
generated the four possible bromohydrin products,[12] **15a**−**d**. The structures of these bromohydrins were ultimately established by repeating this reaction with stereochemically pure (1*S*,6*R*)-**5** (the synthesis of which is described below) and isolating the products via chromatography. High-quality crystals could be grown for three of the stereochemically pure bromohydrins, **15a**, **15c** and **15d** (Figure S2, Supporting Information), and the crystal structures were obtained. Racemic **15d** was carried on via radical-mediated replacement of bromine with hydrogen followed by mesylation, to generate **16d**, which could be easily converted to azide **17d**. Reduction with in situ Boc protection of the amino group and subsequent silyl group removal yielded **4d**. Nylon-3 polymers containing constrained residues that bear a polar group may prove to have particularly interesting properties.

The synthetic routes outlined in Schemes 2−4 provide racemic β-lactams, which will be useful in some applications; the antibacterial nylon-3 polymers we have reported were generated from chiral but racemic β-lactams.[2] However, it would be valuable to have access to enantiopure β-lactam building blocks because some biomedical applications may require homochiral polymers. In addition, the ability to compare homochiral and heterochiral versions of a given polymer may prove useful for analyzing the mode of biological action. Enantiopure samples of β-lactams such as **2**, **3**, and **4d** can in principle be prepared from enantiopure **1**, and this key intermediate is available via enzymatic resolution.

Treatment of racemic **1** with a commercially available polymer-bound lipase[13] generates (1*S*,6*R*)-**1** (Scheme 5). The

Scheme 5



enantiopurity of this material was determined by hydrolysis to the β-amino acid, Fmoc protection, and conversion to the Mosher amide. As shown in Scheme 5 ^{19}F NMR-based comparison with the diastereomeric mixture of Mosher amides that is generated from racemic **1** indicates that enzymatic resolution provides a single enantiomer of **1** in 98% ee.[14] We assign the configuration of this isomer as (1*S*,6*R*)-**1** on the basis of ^{1}H NMR comparison of the enantioenriched Mosher amide and the diastereomeric mixture of Mosher amides generated from racemic **1** (Figure S3, Supporting Information). This assignment is consistent with the absolute configurations determined from crystallographic data for stereochemically pure **15a**, **15c**, and **15d**.

We have developed serviceable routes to β-lactams that bear side chain polar groups protected in ways that should be amenable to the synthesis of nylon-3 materials via anionic ring-opening polymerization. Recent work from our group has shown that such building blocks can lead to materials with very interesting biological activities,[2] but only one example of a polar-functionalized β-lactam was used in that study. The synthetic approaches developed here provide new β-lactams that are of interest as ROP substrates, and key intermediates in the routes we report should enable synthesis of additional β-lactams bearing a diverse range of side chain functionality. The β-lactams made available through the chemistry reported here include examples with two identical side chains, with two different side chains, and with a functionalized cyclic constraint. Because key intermediate **1** can be generated in highly enantioenriched form, all of these routes can potentially provide enantiopure β-lactams and thus homochiral nylon-3 polymers.

Acknowledgment. This work was supported in part by the Nanoscale Science and Engineering Center at UW-Madison (DMR-0425880) and the NSF Collaborative Research in Chemistry program (CHE-0404704). M.-r.L. was supported in part by Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2006-214-C00053). We thank Dr. Ilia Guzei at UW-Madison for solution of crystal structures. We thank Dr. Félix Freire at UW-Madison for helpful discussions.

Supporting Information Available: Experimental details and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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