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Synthesis of chiral iodo-*N,O*-acetonide aminal scaffolds via an efficient cascade reaction of amino acid-derived epoxides

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ABSTRACT

Novel amino acid-derived iodo-*N,O*-acetonide aminals were developed as chiral, non-epimerizable scaffolds to facilitate complex molecule synthesis. These scaffolds are readily prepared from commercially available amino acid derivatives in ⩽6 steps, contain an orthogonally-protected β-hydroxy amine moiety, and feature a directly reactive alkyl-iodide group for facile substitution chemistry. Further, a novel ring opening/cyclization cascade reaction was developed to prepare these compounds efficiently (59–72%) from readily available epoxide derivatives.

Nature's set of biological building blocks (i.e., amino acids, monosaccharides, etc.), while diverse, all share common chemical characteristics. Perhaps their most critical, from a synthetic point of view, are the diverse functionality and innate chirality they possess, which oftentimes template their assembly and facilitate reactions to occur via defined stereochemical (i.e., enantio- or diastereoselective) paths. In this manner, biological systems exploit these chemical scaffolds to routinely construct molecules of varying size, function, and structural complexity.

Since amino acids are among the most functionalized, easily manipulated, and inexpensive members of Nature's chiral pool, these biomolecules are ideal for generating customized chiral platforms as synthons for complex molecule construction. Examples of enantiomerically-pure scaffolds, both bio-inspired[1] and completely synthetic,[2] in asymmetric synthesis are plentiful. Yet, we believe a substantial need for broadly-applicable advanced synthons exists due to the structural and stereochemical diversity in targets currently being pursued. Further, the templates in current use are oftentimes narrow in scope, or are plagued with structural shortcomings that can limit their utility. For example, Garner's aldehyde,[1a] a widely-utilized serine-based scaffold, contains a lone asymmetric center that is readily epimerizable when reagents are used that promote enolization.[3]

Several key characteristics must be present in order for a scaffold molecule, no matter how structurally elegant, to find application(s) as a potential platform for complex molecule construction. First, it should contain a functionalized, homochiral structure overlapping many common motifs in target molecules. Second, it should be either commercially available or prepared readily and efficiently in a minimum number of steps. Third, it should feature orthogonal protection/reactivity that facilitates subsequent (often diastereoselective) reaction chemistry.

As such, we set out to design and efficiently construct chiral multifunctionalized, orthogonally protected amino acid-based scaffolds containing isolated groups accessible individually based upon the reaction conditions. Our initial efforts toward preparing scaffolds that feature these characteristics began with *N*-Boc-L-leucine (**1**). We selected this amino acid substrate since its *i*-butyl side chain affords keen solubility in organic solvents, which facilitate rapid and efficient purification of its various derivatives by standard silica gel-based chromatography.

Our synthetic routes toward various scaffold molecules are displayed in Scheme 1. We initially prepared three distinct scaffold molecules that met our design criteria (vide supra), compounds **4**, **6**, and **7a**. All three arise from known[4] epoxide derived amino acid **3a**. This key intermediate is prepared in four straight-forward steps ((1) esterification, (2) ester reduction to the primary alcohol, (3) alcohol oxidation to the aldehyde (**2a**), and (4) Corey-Chaykovsky epoxidation) from commercially available **1**. Of note, the epoxidation of **2a** occurs diastereoselectively, whereby the desired epoxide (**3a**) is favored (by a 7:1 ratio), and easily separated from its epimer by flash chromatography in our hands, consistent with the results of Konno and co-workers.[4b] Treatment of epoxide **3a** with TMSCl in pyridine/dichloromethane[5] and an equivalent of KCl gives protected chlorohydrin **4**, albeit in poor (20%) yield. This poor yield, coupled with the poor reactivity **4** displayed toward nucleophiles in our hands, prompted us to explore the analogous protected iodohydrin (**6**). This compound was made in two steps (from **3a**) using PPh_3 and molecular iodine to generate iodohydrin **5**, followed by standard TMS protection. Additionally, we prepared this compound in high yield in a single step by treating **3a** with TMSI (generated in-situ)

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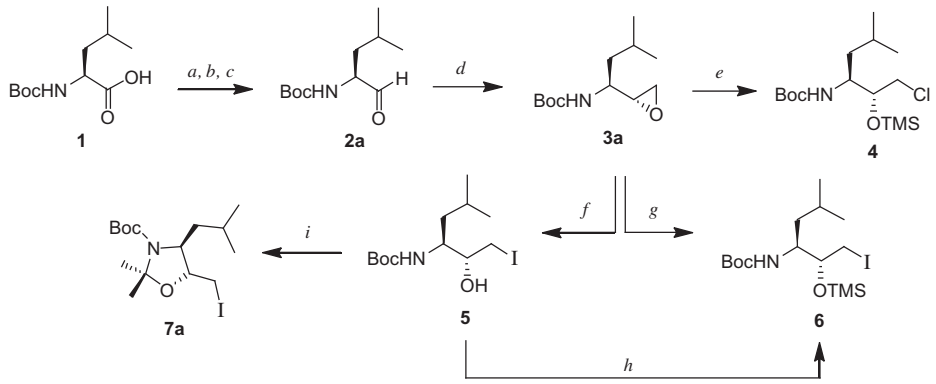


Scheme 1. Reagents and conditions: (a) CH_3I, $NaHCO_3$, DMF; (b) $NaBH_4$, $CaCl_2$, THF/EtOH; (c) $Py{\cdot}SO_3$, NEt_3, CH_2Cl_2/DMSO, 82% (3-step); (d) $SO(CH_3)_3I$, NaH, DMSO, 60% (d.r. = 7:1); (e) TMSCl, KCl, pyr./CH_2Cl_2, 20%; (f) PPh_3, I_2, CH_2Cl_2, 82%; (g) TMSCl, LiI, pyr./CH_2Cl_2, 87%; (h) TMSCl, imidazole, DMF, 81%; (i) 2,2-DMP, *p*-TsOH, $MgSO_4$, $PhCH_3$, 75 °C, 81%.

in the presence of pyridine. A major limitation with **6** is the acidic N–H of the Boc group. This could preclude the use of strong bases or nucleophiles in subsequent reaction chemistry, greatly limiting its utility as a template or scaffold. Alternative amine protecting groups could be screened to solve this problem, albeit at the likely expense of adding steps to the synthesis. However, the other major problem with **6**, akin to **4**, was that substitution reactions were either sluggish or extremely low-yielding. This was especially the case when sterically large nucleophiles were used, suggesting the size of the proximal *i*-butyl and TMS groups hinder these reactions.

Scaffold **7a** was prepared in good yield by warming iodohydrin **5** with 2,2-dimethoxypropane (2,2-DMP) in the presence of *p*-toluenesulfonic acid. We believe this chiral, multifunctionalized, orthogonally protected/reactive iodo-*N,O*-acetonide aminal to be an ideal scaffold for complex molecule synthesis (Fig. 1).

We have streamlined the construction of this structurally unique class of molecules by developing a novel cascade reaction to prepare the iodo-*N,O*-acetonide aminal core directly from a suitably functionalized epoxide (Scheme 2).[6] This reaction involves the treatment of readily available α-amino acid-derived epoxides (e.g., **3a**–**d**) with lithium iodide, 2,2-dimethoxypropane, catalytic *p*-TsOH, and magnesium sulfate in warm toluene to give the desired iodo-*N,O*-acetonide aminals (**7a**–**d**) in good (59–72%) yield (Scheme 3). This cascade reaction likely begins by protonation of the epoxide, and subsequent nucleophilic addition of iodide. The iodo-alcohol products of this first step (in the case of the *i*-butyl series, **5**) have been confirmed by independent synthesis and by isolating small amounts from the reactions. However, this transient intermediate immediately reacts with 2,2-dimethoxypropane, a reagent and cosolvent in this reaction. Condensation and evaporation of methanol from this second step is facilitated by heat (75 °C), and trace amounts of water are scavenged by $MgSO_4$. The product, iodo-aminal **7**, is isolated and purified by flash chromatography following standard reaction work-up.

We have also begun to demonstrate the scope and utility of these scaffolds. In this vein, we have expanded this methodology

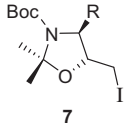
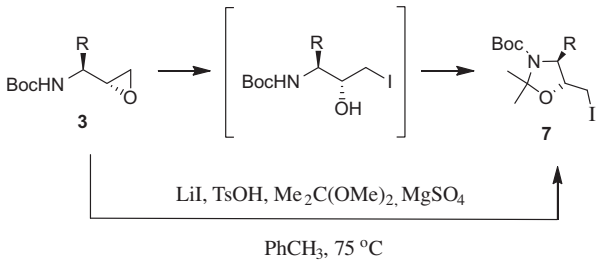
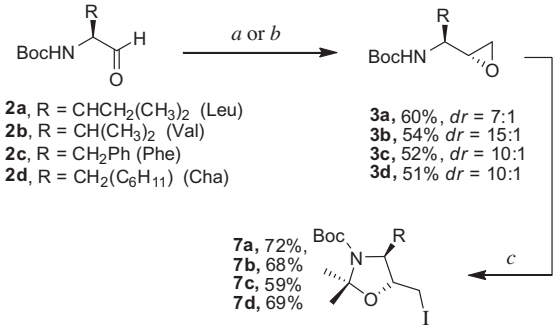


Figure 1. The functionality contained within these iodo-*N,O*-acetonide aminal scaffolds include (1) an orthogonally protected β-hydroxy amine moiety with contiguous asymmetric centers, (2) an 'R group' of an amino acid, and (3) a leaving group for substitution reactions with nucleophiles.



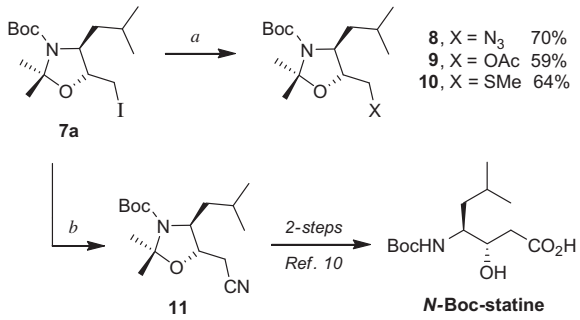
Scheme 2. Overview of the cascade reaction developed to generate iodo-*N,O*-acetonide aminals (**7**) directly from amino acid-derived epoxides (**3**).



Scheme 3. Reagents and conditions: (a) $SO(CH_3)_3I$, NaH, DMSO; (b) (1) Ph_3PCH_3I, KHMDS, THF/DMSO, −78 °C to rt, (2) *m*-CPBA, CH_2Cl_2; (c) LiI, 2,2-DMP, *p*-TsOH, $MgSO_4$, $PhCH_3$, 75 °C.

to other amino acids using a modular approach since the chemistry is not vastly dependent upon the 'R groups' of the various residues (except for isolated cases in which residues contain either labile or difficult to protect 'R groups', for example, Arg, His, PhGly, etc.). Scheme 3 illustrates our initial exploration into various natural and unnatural amino acid derivatives featuring nonpolar side chains; *N*-Boc protected leucine (Leu), valine (Val), phenylalanine (Phe), and cyclohexylalanine (Cha).

The Corey–Chaykovsky epoxidation of aldehydes **2** gave moderate yields and good diastereoselectivity[7] of each entry with the lone exception of **2c**. Not only were the yields of **3c** consistently poor (⩽20%) using this epoxidation methodology, but a 1:1 mixture of diastereomers was obtained. Thus, to generate sufficient quantities of **3c** we used a 2-step protocol involving Wittig olefination followed by a diastereoselective epoxidation using *m*-CPBA.[4a,8] We



Scheme 4. Reagents and conditions: (a) X^-, DMSO, 50 °C; (b) KCN, DMSO, 50 °C, 69%.

are currently investigating the precise mechanism(s) of diastereofacial selectivity in these epoxidation reactions computationally and using synthetic model systems.

In all cases, epoxides **3a–d** were smoothly and directly converted to the desired iodo-*N,O*-acetonide aminals **7a–d** by way of the novel cascade process in good (59–72%) yields.[9] These scaffolds are readily soluble in organic solvents, amenable to long-term (6–12 months) storage at −10 °C, and can be prepared on multigram scale. Not unexpectedly, the ^{1}H NMR spectra of **7** at 25 °C display the distinct *N*-Boc rotamers (ca. 1:1 ratio) present at this temperature. Variable temperature experiments revealed those conformationally-sensitive nuclei to cleanly coalesce at 45–50 °C. In this vein, the corresponding carbon nuclei display extensively broadened signals in the ^{13}C NMR spectra, which are characteristic of molecules containing analogous functionality.[10]

The reactive alkyl iodide contained within scaffolds **7a–d** offers an attractive site for a wide variety of substitution reactions under mild conditions. Scheme 4 illustrates this utility, as scaffold **7a** was successfully treated with a variety of nucleophiles with differing basicity and functionality. The yields of these substitution reactions were good (59–70%), and each was accomplished by simply dissolving the reagents in warm DMSO for 12 h followed by straight-forward work-up and purification.

We envision widespread application for functionalized chiral templates of this nature (**7**–**11**), most notably for rapid/efficient access to highly sought after peptide-derived natural products and/or biologically relevant molecules. For instance, this technology affords expedited access to nitrile **11**, which Yuste and co-workers[10] used to prepare the *N*-Boc protected form of statine, a β-hydroxy-γ-amino acid widely used as a linchpin component of peptidomimetic aspartic protease inhibitors. Further, the azide group within **8** represents a synthetic handle for 'click' chemistry with terminal acetylenes. This methodology has found widespread use as a bioconjugation strategy due to its high yields, functional group tolerance, and robust 1,2,3-triazole products.

In summary, we present a family of amino acid-derived iodo-*N,O*-acetonide aminal synthetic scaffolds containing non-epimerizable contiguous asymmetric centers and introduce a novel epoxide opening/cyclization cascade reaction to efficiently prepare them. These platforms are attractive substrates for complex molecule synthesis due to their orthogonal protection motif, inherent chirality, and ability to directly undergo substitution chemistry with an array of nucleophiles. We are currently expanding this methodology to various other amino acid derivatives and utilizing these scaffolds to construct biologically active peptide-derived natural products and lipophilic non-natural β-, and γ-peptides for therapeutic use in disorders of the central nervous system. The results of these investigations will be presented in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization data for compounds **4**–**6**, **7a**–**d**, and **8**–**11**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.049.

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9. *Representative procedure for the cascade reaction of epoxides* **3** *to iodo-N,O-acetonide aminals* **7**. To a solution of **3b** (0.100 g, 0.465 mmol) in dry toluene (5 mL) was added LiI (0.156 g, 1.16 mmol), $TsOH{\cdot}H_2O$ (0.035 g, 0.186 mmol), 2,2-dimethoxypropane (2.8 mL), and anhydrous $MgSO_4$ (0.279 g, 2.33 mmol) was added. The reaction was heated to 75 °C and allowed to stir for 6 h. The reaction was then allowed to cool to room temperature and filtered. The filtrate was evaporated, and the residue dissolved in methylene chloride and washed with saturated aqueous sodium bicarbonate, water, and brine. The solution was then dried with magnesium sulfate and filtered. The crude product was purified via column chromatography (12:1 hexanes:EtOAc) to afford **7b** (121 mg, 68%) as a colorless solid. $[\alpha]_D$ −4.1 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (700 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.7 Hz, 6H), 1.48 (s, 9H), 1.52 (s, 3H), 1.64 (s, 3H), 2.07 (br, 1H), 3.25 (d, *J* = 5.9 Hz, 2H), 3.81 (br, 1H), 4.11 (m, *J* = 6.6 Hz, 1H). ^{13}C NMR (175 MHz, 50 °C, $CDCl_3$) δ 9.8, 18.4, 19.2, 27.8, 28.4, 30.0, 31.5, 67.1, 77.8, 80.1, 94.6, 152.3. MS (ESI) for $C_{14}H_{26}INO_3$ $(M+Na)^+$ 406.09, found 406.13.
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