Organic Process Research & Development

Article

pubs.acs.org/OPRD

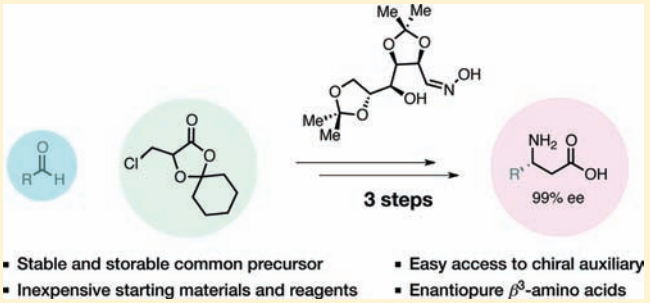
Enantioselective, Chromatography-Free Synthesis of β^3-Amino Acids with Natural and Unnatural Side Chains

Thibaud Gerfaud, Ying-Ling Chiang, Imants Kreituss, Justin A. Russak, and Jeffrey W. Bode*

Laboratorium für Organische Chemie, Department of Chemistry and Applied Biosciences, ETH−Zürich, Wolfgang Pauli Strasse 10, 8093 Zürich, Switzerland

Supporting Information

ABSTRACT: β^3-Amino acids are key components of some pharmaceuticals, excellent surrogates for metabolically labile α-amino acids, and building blocks for chiral heterocycles. Unfortunately they are not easily accessible in enantiomerically pure form, especially when possessing unnatural side chains. A flexible, chromatography-free process for the synthesis of enantiopure β^3-amino acids possessing natural and unnatural side chains is described. The procedure uses inexpensive starting materials and reagents and offers a good alternative to the hazardous and expensive Arndt−Eistert homologation of enantiopure α-amino acids. Its utility has been demonstrated with the preparative scale synthesis of two valuable β^3-amino acids possessing unnatural side chains.



INTRODUCTION

β-Amino acids are a fascinating and important class of unnatural amino acids with diverse applications. They are present in a wide range of natural products[1] (Jasplakinolide) and are key components of some pharmaceuticals such as Sitagliptin,[2] developed at Merck, or Otamixaban,[3] under development at Sanofi-Aventis (Figure 1). They are also the basic units of a rapidly growing class of oligomeric peptides and are widely regarded as excellent surrogates for metabolically labile α-amino acids.[4] Considerable efforts are currently underway to use β-amino acids for the formation of peptides with secondary, tertiary, and even quaternary structures and to design and identify structures with biological and catalytic properties.[5] The individual β-amino acid monomers are also highly sought as the basic building blocks of chiral heterocycles.

Unlike peptides consisting of natural α-amino acids, which are widely available in enantiomerically pure form at a nominal cost, each enantiopure β-amino acid monomer must be synthesized from a suitable chiral starting material or by asymmetric synthesis.[6] A method able to rapidly and efficiently provide β^3-amino acids with natural and unnatural side chains from simple and commercially available starting materials would thus be of primary interest for exploratory work. β^3-Amino acid monomers containing naturally occurring side chains are now widely available by homologation of the corresponding natural α-amino acids.[7] Although this chemistry is both expensive and hazardous, as it requires large quantities of toxic diazomethane and enantiopure, suitably protected starting materials, it has been executed on large scale with specialized facilities. For β-amino acids containing unnatural side chains, asymmetric enamine or enamide transfer hydrogenation is attractive from an industrial point of view but requires high hydrogen pressures and proprietary ligands.[8] Many other methods have been reported, but no general approach has emerged; the various routes are usually not amenable to scale-up or diversity in side-chain functionality and have to be optimized for each substrate.[9] For 3-aryl substituted β^3-amino acids, enzymatic resolution provides access to a number of derivatives, but this approach does not appear to give satisfactory results for aliphatic or functionalized side chains.[10] In some high volume cases, directed evolution of enzymes can offer an efficient and economically viable alternative to classical chemical approaches for the large scale production of pharmaceuticals containing β-amino acids residues.[11] Unfortunately, this solution is not general and requires intensive optimization for a given substrate. Other types of β-amino acids, particularly β^2-amino acids, are even more difficult to prepare.[12]

We have recently disclosed a unified approach to β^2-, $\beta^{2,3}$-, and β^3-amino acids featuring a chiral auxiliary mediated cycloaddition followed by a redox neutral fragmentation of the resulting cycloadduct to give the enantiopure β-amino acids (Scheme 1).[13] This approach has proven to be useful for the gram scale preparation of β-amino acids, with the side chain derived from the corresponding aldehyde. Particularly in cases where the corresponding α-amino acids are not available, this route provides a reliable and predictable alternative to the Arndt−Eistert homologation. A number of β-amino acids possessing aliphatic or protected functional groups side chains have been synthesized under one standard set of reaction conditions. This method is of particular interest because the

Received: March 14, 2012
Published: March 30, 2012

   dx.doi.org/10.1021/op300069n | Org. Process Res. Dev. 2012, 16, 687−696

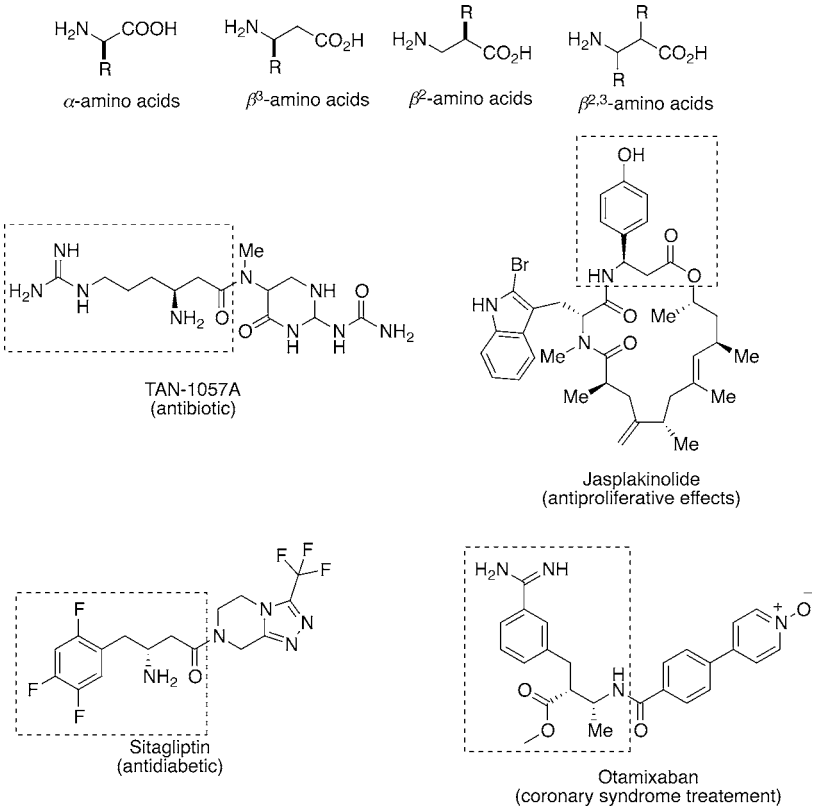
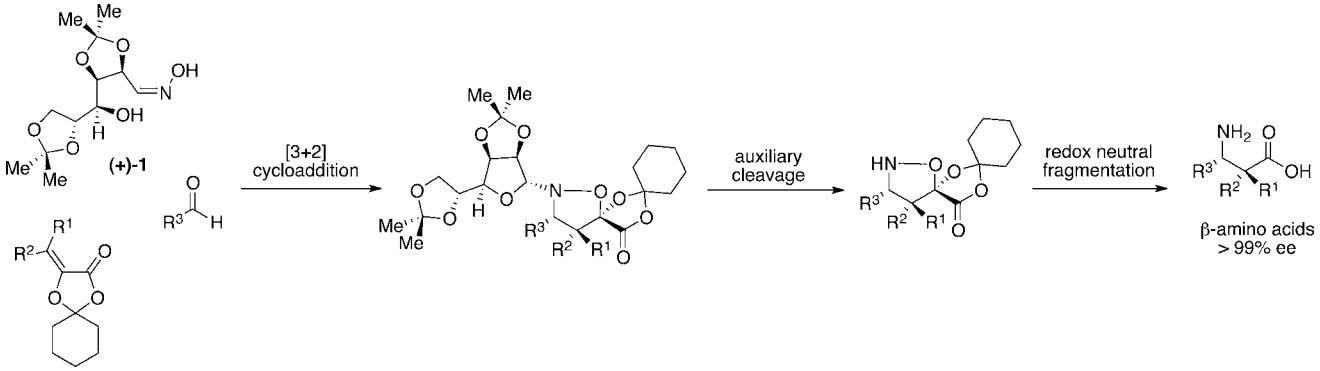


Figure 1. Structure and occurrence of β-amino acids.

Scheme 1. Diastereoselective [3 + 2] Cycloaddition/Redox Neutral Fragmentation Approach for the Synthesis of Enantiopure β-Amino Acids



products are obtained in enantiomerically pure form, both configurations are accessible by simply switching the chiral auxiliary for its enantiomer, and the use of dangerous or toxic reagents is not necessary.

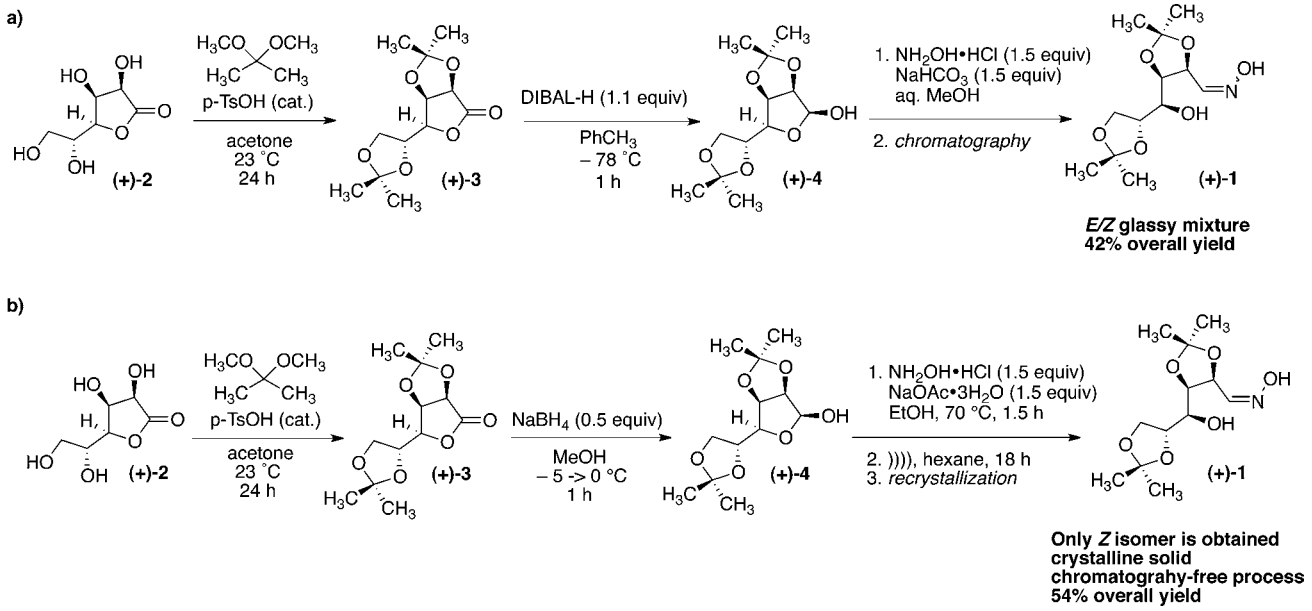
The successful development of this approach for β^3-amino acid synthesis required a large-scale preparation of L- and D-gulose-derived chiral auxiliaries and a practical synthesis of cyclohexylidene acrylate **5**. These needs led us to re-evaluate the chiral auxiliary synthesis, which was difficult to execute on large scale because of the physical properties of the products, use of expensive reagents, and requirement for chromatography. The acrylate, as well, was both cumbersome to prepare on scale and subject to degradation during storage. In this report we provide the full details of our optimized synthesis of the chiral auxiliaries **1** and an alternative approach to acrylate **5** featuring an in situ generation from chloride **10**. The application of these methods to the preparative scale synthesis of two valuable β^3-amino acids that we have not previously reported is also described.

RESULTS AND DISCUSSION

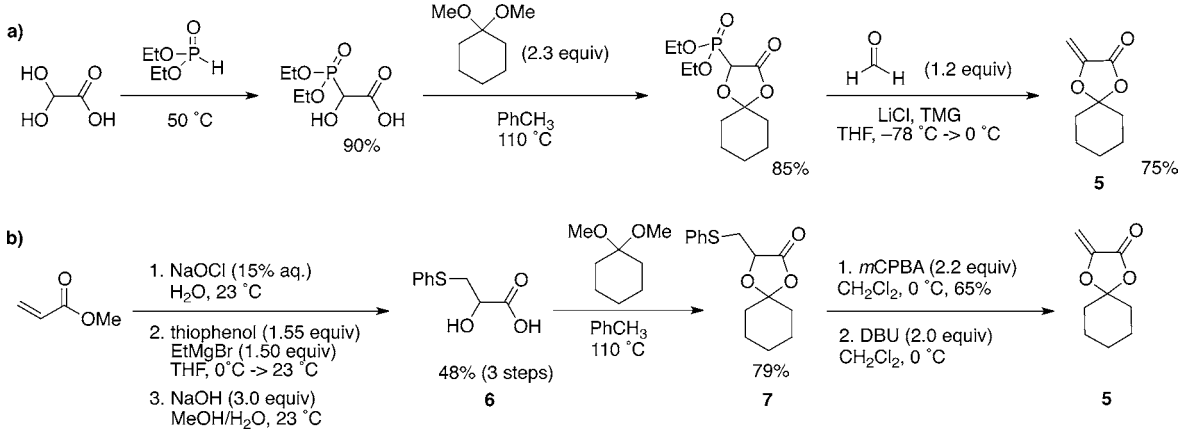
Improved Synthesis of Gulose-Derived Auxiliaries. Our approach to the synthesis of β^3-amino acids relies on a diastereoselective [3 + 2] nitrone cycloaddition to introduce and control the stereochemistry of the resulting isoxazolidine. Our early work in this area was based on the 1977 report by Vasella and co-workers using the easily prepared D-mannose-derived auxiliaries.[14] This chiral auxiliary, however, had three insurmountable problems: (1) it gave the pseudounnatural configuration in the resulting β^3-amino acids and the enantiomer, L-mannose, is available only in small quantities and at great cost; (2) many of the cycloadditions gave only

dx.doi.org/10.1021/op300069n | Org. Process Res. Dev. 2012, 16, 687−696

Scheme 2. Preparation of the Chiral Auxiliary by Rohloff (a) and Improved Procedure (b)



Scheme 3. First Approaches to the Required Acrylate via Horner–Wadsworth–Emmons Reaction (a) or Using a Sulfone As Leaving Group (b)



modest diastereoselectivity; and (3) enrichement of the major diastereoisomer by recrystallization was difficult.

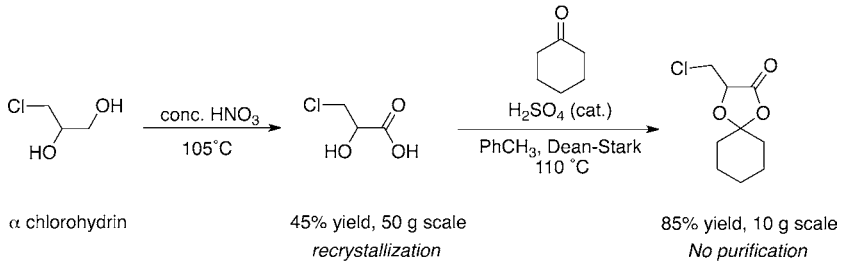
In the course of their total synthesis of (+)-negamycin, Kibayashi and co-workers have reported the use of D-gulose-derived oxime as a convenient surrogate for L-mannose.[15] We became interested in this approach because both D- and L-gulose are commercially available at a reasonable price in the form of their gulonic acid-1,4-lactone, which could be converted to the chiral auxiliaries in three steps.[16] Our first investigations on the use of these chiral auxiliaries in the nitrone cycloaddition were plagued by difficulties in the crystallization of both starting chiral auxiliary and obtained isoxazolidines. We reasoned that the cyclohexylidene protecting groups employed by Kibayashi could disminish the ability of the isoxazolidine to crystallize, and by analogy to the mannose-derived products, we anticipated that switching the cyclohexylidene protecting groups for acetonide would improve their properties. Following procedures by Rohloff and Schwartz[17] and Tamura and Sakamoto,[14f] we prepared 2,3:5,6-*O*-diisopropylidene-gulose oxime ((+)-**1**) in three steps: D-gulonic acid-1,4-lactone ((+)-**2**) was protected as its diisopropylidene derivative (+)-**3**, reduced to the lactol (+)-**4** using DIBAL-H, and converted to a glassy 6:5 *E*/*Z* mixture of gulose-derived oximes in 42% overall yield (Scheme 2a). The use of these gulose-derived auxiliaries in the nitrone cycloaddition gave excellent results. Not only were higher diastereoselectivities obtained in comparison with the D-mannose-derived auxiliaries (even in the cases of less bulky, aliphatic side chains), but the cycloadducts were more easily crystallized, facilitating the enrichment and purification of the major diastereomer.

The synthesis of **1** up to 100 g scale posed several problems: (1) it involved an expensive DIBAL-H reduction, requiring cryogenic temperatures, and a time-consuming and solvent-intensive workup; (2) the final product, a glassy mixture of *E* and *Z* oximes, was difficult to both purify and handle; and (3) column chromatography was required and residual solvent was difficult to remove from the resulting syrup.

To improve the synthesis of the chiral auxiliary, we first developed a reduction of (+)-**3** to (+)-**4** using $NaBH_4$ in methanol as an inexpensive alternative to DIBAL-H. This also simplified the reaction workup and obviated the need for column chromatography. Additionally, the final crude glassy

dx.doi.org/10.1021/op300069n | Org. Process Res. Dev. 2012, 16, 687–696

Scheme 4. Synthesis of Acrylate Precursor 10



mixture of *E*/*Z* oximes can be converted exclusively into the *Z*-isomer (+)-**1** by overnight sonication in hexane, providing a white solid powder which can be further recrystallized into a white crystalline solid (Scheme 2b). The D-gulose auxiliary (+)-**1** and L-gulose auxiliary (−)-**1** are both obtained in the same range of yields and are stable and storable as solids for long periods of time. This chromatography-free protocol is scalable, practical, reliable, and commonly used in our laboratory on a 50−100 g scale.[18] On scale, the use of sonication might be problematic, but the implementation of a dynamic crystallization process to enrich the mixture with the *Z*-isomer using a sonication loop to control crystal growth could be envisionned as an alternative.

Improved Synthesis of the Acrylate. Another obstacle to the cost-effective scale-up of our approach to β^3-amino acids was the synthesis and stability of the requisite acrylate **5**. In our first generation synthesis, **5** was prepared from the corresponding phosphonate[19] via an Horner−Wadsworth−Emmons reaction, but on scale it had a propensity to polymerize, rendering its handling and storage difficult (Scheme 3a). Even stabilized with hydroquinone, **5** could usually not be stored more than 1 week at −20 °C. To avoid the storage and handling of **5**, we sought to identify a precursor that could be used to generate the desired acrylate in situ.

On the basis of reports from Roush,[20] we initially investigated the use of sulfones as leaving groups for acrylate formation (Scheme 3b). The requisite starting material could be prepared by a 5-step sequence: first, the hydroxy acid **6** is obtained via a low-yielding epoxidation of methyl acrylate, followed by nucleophilic ring opening with magnesium thiophenolate and final saponification of the methyl ester. Second, the dimethyl acetal of cyclohexanone was prepared and then transacetalized with **6**. Oxidation of thioether **7** to the corresponding sulfone with *m*CPBA followed by elimination with DBU yielded the desired acrylate **5**. In addition to a long linear sequence, this protocol suffered from other notable disadvantages such as expensive reagents (Grignard reagent), low yields, and several chromatographic purifications. Elimination of the sulfone with DBU to generate the acrylate always led to partial cleavage of the acetal, preventing its use as an in situ precursor to **5**.

As an alternative we sought to explore the synthesis and reactivity of dioxolanone **10**, which was known to eliminate to the corresponding acrylate upon exposure to a mild base.[21] This precursor was promising because (1) the necessary 3-chloro-2-hydroxypropanoic acid (**9**) can be obtained from α-chlorohydrin (**8**), an inexpensive and widely accessible starting material;[22] (2) oxidation of α-chlorohydrin can be performed with nitric acid (another inexpensive reagent) and the product purified by recrystallization; (3) acetal formation with cyclohexanone is carried out with a catalytic amount of sulfuric acid and should not require additional purification. It remained to be determined, however, if the dioxolanone product **10** would be stable to storage and amenable to an in situ generation of the acrylate under conditions compatible with the nitrone cycloaddition.

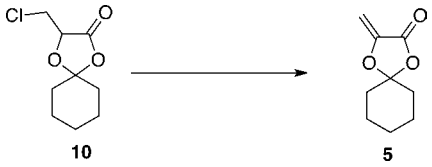
The synthesis of **10** began with the oxidation of α-chlorohydrin with nitric acid (Scheme 4). The previously reported procedure[23] was found to be convenient on small scale (<10 g), but upon scale-up, its highly exothermic nature and the strong gas evolution was difficult to control. A reverse addition protocol was implemented to avoid those issues (see the Supporting Information for a detailed procedure). After quenching, extraction with ethyl acetate and recrystallization provide **9** as a white crystalline solid. Using this method, the oxidation could be routinely performed in our laboratory on a 50 g scale (450 mmol) and has been executed by our research partners on a kilogram scale.

With this material in hand, we turned our attention to the acetal formation. The use of 5 mol % of concentrated sulfuric acid proved to be sufficient to catalyze the acetal formation in refluxing toluene with removal of the water (Dean−Stark trap). To ensure complete conversion and simple purification of the product, we decided to use a slight excess of the hydroxy acid **9** (1.2 equiv). Once water had been distilled off (usually 10−12 h), the crude reaction mixture was neutralized and washed with saturated aqueous sodium bicarbonate to remove the excess **9**, affording the desired acetal **10** in good yield (>80%) and in sufficient purity to be used as such for the next step (acrylate formation and [3 + 2] cycloaddition).

In our previous work, the cycloaddition was performed in toluene at 110 °C. To devise a one-pot procedure, we first screened different bases in this solvent. No reaction was observed in toluene using triethylamine or DIPEA, even under reflux, whereas the use of DBU led to partial cleavage of the acetal (Table 1). Switching to a more polar solvent such as chloroform gave superior results. Although no reaction was observed at room temperature with triethylamine, under reflux clean formation of the acrylate took place and no hydrolysis or polymerization of the acrylate was observed. Having identified a suitable base for acrylate generation, we concentrated our efforts on finding a procedure where acrylate formation and [3 + 2] cycloaddition could be telescoped, and which would avoid the use of chloroform as a solvent, which is prohibitive on large scale because of its toxicity (suspected carcinogen), environmental impact, and cost. To avoid the use of molecular sieves or other dehydrating agents (mandatory for clean nitrone formation), we decided to screen other solvents possessing the following properties: (1) a boiling point above 100 °C (required for the cycloaddition with sterically hindered

dx.doi.org/10.1021/op300069n | Org. Process Res. Dev. 2012, 16, 687−696

Table 1. Optimization of Acrylate Formation



10 5

entry	base (equiv)	solvent	temp (°C)	time (h)	result
1	Et_3N (2)	toluene	23	10	no reaction
2	Et_3N (2)	toluene	110	10	no reaction
3	DIPEA (2)	toluene	110	10	no reaction
4	DBU (2)	toluene	110	10	no acrylate formation, partial acetal cleavage[a]
5	Et_3N (2)	$CHCl_3$	23	10	no reaction
6	DIPEA (2)	$CHCl_3$	65	10	no reaction
7	Et_3N (2)	$CHCl_3$	65	10	clean acrylate formation
8	DBU (2)	$CHCl_3$	65	10	acrylate formation and partial acetal cleavage[a]
9	Et_3N (2)	CPME	100	18	45% starting material:55% acrylate
10	Et_3N (2)	*n*-propyl acetate	100	18	clean acrylate formation, 100% conversion

[a]After workup, cyclohexanone was observed by ^1H NMR.

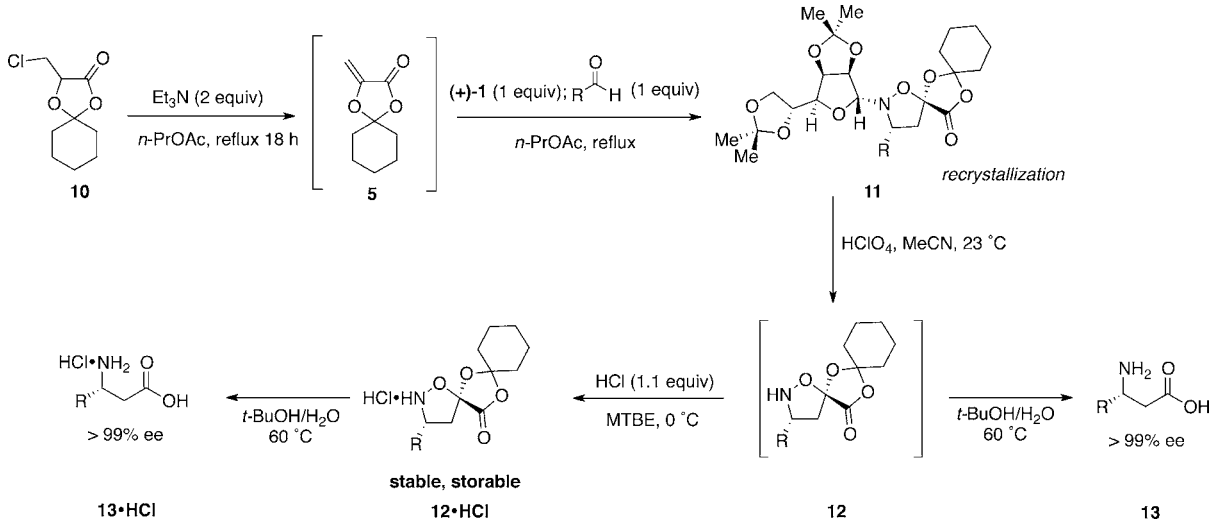
aldehydes), (2) immiscible with water (in order to use a Dean–Stark trap to remove water), (3) capable of forming an azeotrope with water, (4) a low heat of vaporization, (5) a polarity sufficient for chloride elimination, (6) environmentally more friendly, and (7) low toxicity. Cyclopentyl methyl ether (CPME) and *n*-propyl acetate fullfilled these criteria and were thus tested in this transformation (Table 1, entries 9 and 10). Both solvents exhibited clean and exclusive formation of the acrylate upon heating at 100 °C, but *n*-propyl acetate proved to be superior in terms of conversion. The telescoped procedure was thus performed as follows: the acrylate precursor was heated under reflux in the presence of 2 equiv of triethylamine in *n*-propylacetate for 18 h, the mixture was cooled to 23 °C, the aldehyde and the oxime chiral auxiliary were added, and the mixture was heated under reflux with removal of the water (Dean–Stark trap). After workup, the desired cycloadducts were obtained with good to excellent levels of diastereoselectivity, and recrystallization of the crude reaction mixture afforded the diastereomerically pure cycloadducts **11**, avoiding purification by column chromatography.

This protocol has been routinely applied for cycloadditions with many different aldehydes on both milligram and gram scales.[13] The one-pot sequential formation of the acrylate followed by the cycloaddition proved to be superior; in the purely one-pot procedure, some hydrolysis of the acetal was observed, even in the presence of molecular sieves.

Removal of the chiral auxiliary with aqueous perchloric acid in CH_3CN proceeded cleanly, affording after neutralisation with $NaHCO_3$ the corresponding isoxazolidines **12** in good yield and very good purity. As reported previously, these mild conditions are also tolerant of protected functionalised side chains.[13] The isoxazolidines can be precipitated as their HCl salt and stored as such. Attempts to store the free isoxazolidines led to slow decomposition in many cases. Furthermore, the isoxazolidine·HCl salts can be used directly in the redox neutral fragmentation. On scale, the use of perchloric acid could become problematic because of its strong oxidizing nature.[24] As an alternative, TFA/DCM (1:1) is also effective for chiral auxiliary removal, but these conditions are less tolerant to protected side chains and thus less interesting from the perspective of a flexible and general process. After evaporation of the TFA/DCM mixture, the isoxazolidine·TFA salts obtained were found to be less stable than their HCl counterparts. If the isoxazolidines do not need to be stored, the isoxazolidine free base can be directly submitted to fragmentation to give the β^3-amino acids **13** in high yields (Scheme 5).[25]

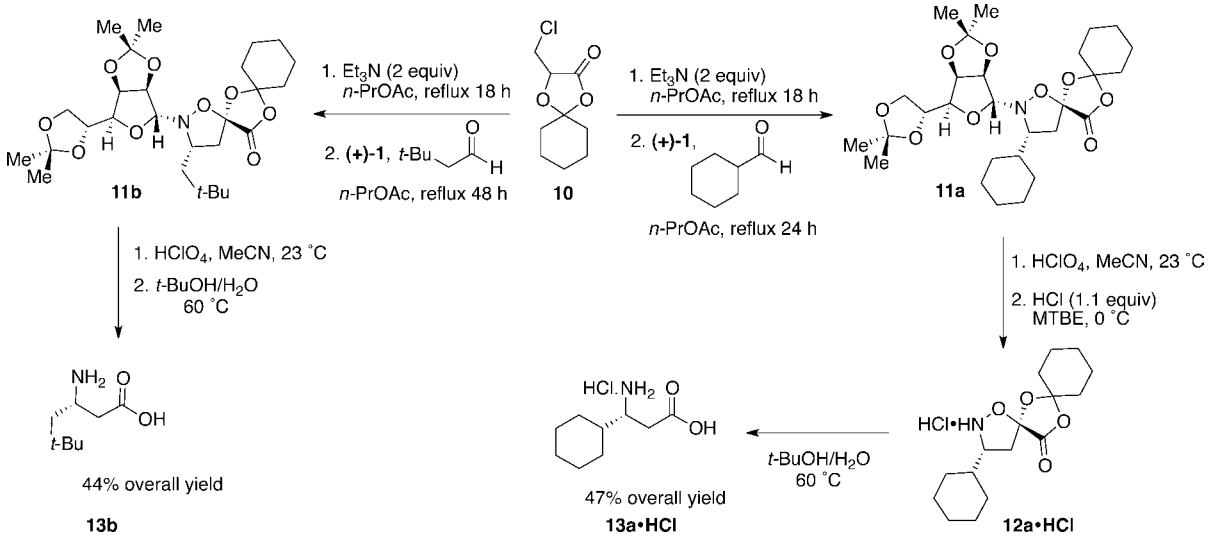
Simply warming the salts in a 1:1 *t*-BuOH/H_2O mixture at 60 °C for 24–36 h affords the corresponding enantiopure β^3-amino acids salts **13**·HCl (Scheme 5). For further scale-up of this process, the recovery of the chiral auxiliary would be an advantage. In some cases, we have found that the cleavage of the auxiliary can be performed using hydroxylamine buffered by sodium acetate. These mild conditions are generally tolerant to protected side chains and allowed in many cases >70% recovery of the chiral auxiliary. The major limitation of this approach is the necessary chromatographic purification to separate the free

Scheme 5. In Situ Acrylate Generation, [3 + 2] Nitrone Cycloaddition, Chiral Auxiliary Cleavage, and Redox Neutral Fragmentation Sequence for the Synthesis of β^3-Amino Acids



dx.doi.org/10.1021/op300069n | Org. Process Res. Dev. 2012, 16, 687–696

Scheme 6. Preparation of (*R*)-3-Amino-3-cyclohexylpropanoic Acid Hydrochloride (13a·HCl) and (*S*)-3-Amino-5,5-dimethylhexanoic Acid (13b)



isoxazolidine from the recovered chiral auxiliary. For our purpose, and regarding the easy access to the chiral auxiliary, this option was not investigated but could be implemented in specific cases for large scale applications.

To demonstrate the utility and reliability of our method, we have applied this procedure to the synthesis of two valuable β^3-amino acids possessing unnatural side chains. (Scheme 6)

The one-pot acrylate formation/cycloaddition sequence using the acrylate precursor **10** and cyclohexylcarboxaldehyde furnished crude **11a** in 24 h (dr 91:9:0:0), which was recrystallized from hexane to afford diastereomerically pure **11a** (as determined by ^{1}H NMR) in 64% yield. Cleavage of the chiral auxiliary with perchloric acid in acetonitrile afforded the corresponding free isoxazolidine **12a**, which was precipitated as its HCl salt **12a**·HCl in 82% yield. (*R*)-3-Amino-3-cyclohexylpropanoic acid hydrochloride (**13a**·HCl) was obtained after fragmentation in 1:1 *t*-BuOH/H_2O at 60 °C for 36 h and simple trituration with EtOAc in 90% yield and 99% ee (47% overall from **10**). Crude **11b** was obtained by the one-pot acrylate formation/cycloaddition sequence between the acrylate precursor **10** and 3,3-dimethylbutanal for 48 h (dr 77:13:10:0, the longer reaction time is attributed to the increased steric hindrance of the aldehyde). Two successive recrystallizations from 9:1 hexane/EtOAc were necessary to give diastereomerically pure **11b** (as determined by ^{1}H NMR) in 52% yield. Cleavage of the chiral auxiliary with perchloric acid in acetonitrile furnished free isoxazolidine **12b**,[25] which was directly submitted to fragmentation in 1:1 *t*-BuOH/H_2O at 60 °C for 36 h and trituration with EtOAc, affording (*S*)-3-amino-5,5-dimethylhexanoic acid (**13b**) in 86% yield and 99% ee (44% overall from **10**).

CONCLUSION

We have developed a flexible, enantioselective, and chromatography-free protocol for the synthesis of β^3-amino acids. This method features the in situ generation of an acrylate from a stable and storable precursor, a diastereoselective nitrone [3 + 2] cycloaddition, and a redox-neutral fragmentation. We have also provided a scalable, chromatography-free synthesis of the chiral auxiliary from either enantiomer of commercially available gulonic acid γ-lactone. We believe that this approach is highly suitable for the multigram-scale synthesis of a wide range of β^3-amino acids possessing unnatural side chains, has a potential for further scale-up, and offers a good alternative to the hazardous and expensive Arndt–Eistert homologation of enantiopure α-amino acids. Its utility has been demonstrated with the synthesis of (*R*)-3-amino-3-cyclohexylpropanoic acid hydrochloride and (*S*)-3-amino-5,5-dimethylhexanoic acid. These revised protocols will also be useful for the other β^3-amino acids that we have prepared using this chiral auxiliary and nitrone cycloaddition.[13]

EXPERIMENTAL SECTION

General. Chemicals were purchased from Acros, Aldrich, or BioBlocks Inc. and used without further purification unless otherwise stated. Flash column chromatography was performed on Silicycle Silica Flash F60 (230–400 Mesh) using a forced flow of 0.3–0.5 bar. Thin layer chromatography was performed on aluminium backed plates precoated with silica gel (Merck, Silica Gel 60 F254) and were visualized by fluorescence quenching under UV light or by staining with phosphomolybdic acid. ^{1}H NMR and ^{13}C NMR were measured on VARIAN Mercury 300 MHz, 75 MHz or Bruker Avance 400 MHz, 100 MHz instruments, respectively. Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks, and coupling constants are reported in hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectrometric measurements were performed by the mass spectrometry service of the LOC at the ETHZ on Agilent 1200 (LC) and Bruker maXis for ESI-Q-TOF instruments. Optical rotation measurements were performed using a Jasco P-2000 Polarimeter, operating at the sodium D line with a 100 mm path length cell, and were reported as $[\alpha]^T_D$ (concentration (g/100 mL), solvent). Infrared (IR) data was obtained on a JASCO FT-IR-4100 spectrometer with only major peaks being reported. SFC (supercritical fluid chromatography) was performed on a JASCO liquid chromatography unit. Daicel Chiralcel columns (0.46 cm × 25 cm) were used. See the Supporting Information for details of chromatographic conditions. Melting points were

dx.doi.org/10.1021/op300069n | Org. Process Res. Dev. 2012, 16, 687–696

measured on an Electrothermal Mel-Temp melting point apparatus and are uncorrected.

2,3:5,6-*O*-Diisopropylidene-D-gulono-lactone ((+)-3). A 1 L round-bottomed flask equipped with a Teflon-coated magnetic stir bar is charged with acetone (560.0 mL) and dimethoxypropane (140.0 mL; 1.130 mol; 4.00 equiv). D-Gulonic acid-1,4-lactone (51.1 g, 0.287 mol; 1.00 equiv) and *p*-toluenesulfonic acid monohydrate (5.4 g; 28.8 mmol; 0.10 equiv) are added. After being stirred at 23 °C for 24 h, the reaction is quenched by adding $NaHCO_3$ (7.2 g; 86.2 mmol; 0.30 equiv) and stirred for an additional 1 h (**Caution: CO_2 releases**). The solvent is concentrated by rotary evaporation; the resultant brown solid is taken up in water (500 mL) and extracted with EtOAc (3 × 300 mL). The combined organic layers are washed with saturated brine (500 mL) and dried with Na_2SO_4. The solvent is concentrated by rotary evaporation to yield an off-white solid (74.3 g, 99% crude yield). The crude solid is dissolved in a minimal amount of refluxing EtOAc (ca. 65 mL), and hexane (ca. 15 mL) is added dropwise until a cloudy solution is obtained. An additional portion of EtOAc (ca. 15 mL) is added until the solution turns clear again. The solution is cooled to 23 °C while the crystals are formed and placed at 4 °C overnight. The crystals are collected and washed with a chilled mixture of EtOAc and hexane (1:1) to afford the title compound (45.1 g) as white needle-shaped crystals. The filtrate is concentrated and recrystallized in a similar manner from EtOAc (ca. 20 mL) and hexane (40 mL) to provide additional product (6.3 g) as white needle-shaped crystals, for a combined mass of 51.4 g (69% yield). Mp = 150−152 °C; $[\alpha]^{21}_D$ = −78.4 (*c* 0.99 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (d, *J* = 5.5 Hz, 1H), 4.74 (dd, *J* = 3.0, 5.5 Hz, 1H), 4.46−4.41 (m, 2H), 4.21 (dd, *J* = 6.5, 9.0 Hz, 1H), 3.82 (dd, *J* = 6.5, 9.0 Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.1, 114.8, 110.6, 81.0, 76.2, 75.9, 75.4, 65.3, 26.9, 26.8, 26.0, 25.3.

2,3:5,6-*O*-Diisopropylidene-D-gulofuranose ((+)-4). Caution! This procedure should be carried out in an efficient fume hood due to the evolution of hydrogen gas during the reaction. A 1 L round-bottomed flask equipped with a Teflon-coated magnetic stir bar and an internal thermometer is charged with methanol (800.0 mL). (+)-3 (51.0 g, 0.198 mol, 1.00 equiv) is added and the flask is placed in a sodium chloride/ice bath. When the internal temperature reaches −5 °C, sodium borohydride (3.75 g, 99.0 mmol, 0.50 equiv) is added in 6 portions each, 15 min apart. After addition of sodium borohydride, the mixture is stirred for an additional 30 min until TLC shows the completion of the reaction. The reaction is quenched by the addition of water (20 mL), and stirred for 30 min until no bubble releases, then allowed to warm to room temperature. Methanol is removed by rotary evaporation; the crude residue is taken up in water (500 mL), and extracted with EtOAc (3 × 400 mL). The combined organic layers are washed with saturated brine and dried with Na_2SO_4. The solvent is concentrated by rotary evaporation to yield the title compound 3 as a white solid (45.6 g, 89% crude yield) which is exclusively the β−isomer. The crude product is sufficiently pure to be used directly for the next step. An analytical sample is obtained by recrystallization (1.5 g crude product is recrystallized from EtOAc (ca. 5 mL) and hexane (ca. 15 mL) to give 1.1 g of pure product). Mp = 119−120 °C; $[\alpha]^{21}_D$ = −2.7 (*c* 0.97 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (d, *J* = 2.0 Hz, 1H), 4.69 (dd, *J* = 4.0, 6.0 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 1H), 4.38−4.34 (m, 1H), 4.21 (dd, *J* = 6.5, 8.5 Hz, 1H), 4.12 (dd, *J* = 3.5, 8.5 Hz, 1H), 3.72 (dd, *J* = 7.5, 8.5 Hz, 1H), 3.06 (d, *J* = 2.0 Hz, 1H), 1.44 (s, 6H), 1.38 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.0, 109.9, 101.5, 85.8, 82.4, 80.0, 75.7, 66.2, 26.9, 26.1, 25.6, 24.9.

2,3:5,6-*O*-Diisopropylidene-D-gulose Oxime ((+)-1). Caution! Nonaqueous mixtures of hydroxylamine can be explosive. A 1 L round-bottomed flask equipped with a Teflon-coated magnetic stir bar is charged with absolute EtOH (250.0 mL). Crude (+)-**4** (44.1 g; 0.170 mol; 1.00 equiv) is added, and the flask is placed in an oil bath. While the mixture is stirred, hydroxylamine hydrochloride (17.7 g; 0.255 mol; 1.50 equiv) and sodium acetate trihydrate (34.7 g; 0.255 mol; 1.50 equiv) are added in one portion. The suspension is heated to 70 °C and stirred for 2 h. The solution is cooled to 23 °C, and 600 mL of saturated aqueous $NaHCO_3$ is added over 1 h (**Caution: CO_2 releases, upon scale-up the use of phosphate buffers to quench the reaction might be preferred.**) Ethanol is removed by rotary evaporation, and the residue is extracted with EtOAc (3 × 400 mL). The combined organic layers are washed with brine, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude oil is treated with a minimal amount of hexane (ca. 4 mL) and then sonicated overnight, turning into a white solid. The trace amount of hexanes is removed under high vacuum to afford (+)-**1** as a white powder (46.3 g, 99% crude yield) that is exclusively *Z*-isomer. The crude solid (46.3 g) is dissolved in a minimal amount of refluxing EtOAc (ca. 30 mL), and hexane (ca. 90 mL) is added dropwise until a cloudy solution is obtained. The solution is cooled to room temperature while the crystals are formed and placed at 4 °C overnight. The crystals are collected and washed with a cold mixture of 1:2 EtOAc/hexane to afford compound (+)-**1** (41.3 g, 88% yield) as white crystals. Mp = 117−119 °C; $[\alpha]^{21}_D$ = +172.8 (*c* 1.1 in $CHCl_3$). This compound is in equilibrium in solution with its closed hydroxylamine form. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.13 (d, *J* = 4.0 Hz, 1H), 5.25 (dd, *J* = 4.0, 7.5 Hz, 1H), 4.32−4.23 (m, 3H), 4.12 (dd, *J* = 6.5, 8.5 Hz, 1H), 3.58 (t, *J* = 8.5 Hz, 1H), 3.39 (t, *J* = 6.5 Hz, 1H), 1.56 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 110.2, 109.8, 78.6, 78.1, 72.8, 70.9, 66.4, 26.5, 26.3, 25.6, 24.8.

3-Chloro-2-hydroxypropanoic Acid [1713-85-5] (9). Caution! Nitrogen oxides are highly toxic. This procedure should be carried out in a well-ventilated hood. A 1 L two-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a reflux condenser, and an addition funnel is charged with 3-chloro-1,2-propanediol (50.0 g; 0.452 mol; 1.00 equiv). The top of the condenser is fitted with a vacuum adapter and some tubing to ensure that the gases formed during the reaction will be bubbled through 2.0 L of a 3.0 N NaOH aqueous solution cooled at 0 °C. The addition funnel is charged with nitric acid (155.0 mL of a 65% aqueous solution) and sealed with a septum. The flask and its contents are heated to 80 °C with an oil bath, and a small portion (10−15 mL) of concentrated nitric acid is added with vigorous stirring to initiate the reaction. As the reaction begins, a large amount of dark orange-brown vapors appears. Stirring is continued, and the addition of nitric acid is resumed after the initial exothermic reaction subsides (usually within 15 min). The remaining nitric acid is added in 20−30-mL aliquots over 30−60 min so that nitrogen oxides are continually evolved but the reaction does not become violent. After completion of the addition, the temperature of the oil bath is increased to 105 °C, and the mixture is stirred for 3 h. During this time, nitrogen is flushed

dx.doi.org/10.1021/op300069n | *Org. Process Res. Dev.* 2012, 16, 687−696

in the reaction mixture via a needle through the septum of the addition funnel to ensure that all acidic vapors are bubbled through the basic NaOH solution. Then the reaction mixture is cooled to 23 °C, and 35.0 g of $NaHCO_3$ dissolved in 300 mL of H_2O is slowly added to partially neutralize the nitric acid. The aqueous layer is saturated with NaCl and extracted with EtOAc (7 × 250 mL). The combined organic layers are dried with Na_2SO_4. EtOAc is evaporated by rotary evaporation, the temperature of the water bath is increased to 60 °C, and the remaining nitric acid is evaporated to yield a yellow solid. The crude solid is dissolved in a minimal amount of refluxing chloroform (ca. 200 mL, 5 mL per gram). At this point, some solid may not dissolve in chloroform, and in this case the hot solution is filtered. The filtrate is cooled to room temperature while the crystals are formed and placed at 4 °C overnight. The crystals are collected and washed with cold chloroform to afford **9** (25.3 g; 45% yield) as white needle-shaped crystals. Mp 75 °C; IR (neat, cm^{-1}) ν 3443, 3405, 1915, 1613, 1224, 1737, 1427, 1100, 713; ^1H NMR (CD_3OD, 400 MHz) δ 4.45 (t, J = 4.2 Hz, 1H), 3.84 (d, J = 4.4 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.8, 70.4, 46.2; HRMS (m/z, ES) calcd for $C_3H_4ClO_3$ 122.9854, found 122.9860.

5-Chloromethyl-2,2-pentamethylene-1,3-dioxolan-4-one (10). A 500 mL round-bottomed flask equipped with a Teflon-coated magnetic stir bar is charged with **9** (10.0 g; 80.6 mmol; 1.20 equiv), cyclohexanone (7.1 g; 72.6 mmol; 1.00 equiv), and toluene (134.0 mL). Then concentrated sulfuric acid (200 μL; 3.8 mmol; 0.05 equiv) is added, and the flask equipped with a Dean−Stark trap and a reflux condenser. The flask and its contents are heated under reflux for 20 h while water is removed by azeotropic distillation. The reaction mixture is cooled to 23 °C, and the solvent is evaporated by rotary evaporation. The crude oil is dissolved in EtOAc (300 mL), and the organic layer is washed with a saturated aqueous $NaHCO_3$ solution (2 × 200 mL) and saturated brine (200 mL) and dried with Na_2SO_4. The solvent is removed by rotary evaporation to afford **10** (12.6 g, 76% yield) as pale brown oil. IR (neat, cm^{-1}) ν 2938, 2862, 1791, 1602, 1556, 1450, 1371, 1212, 1155, 1117, 1072, 940, 909; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.73 (t, J = 3.5 Hz, 1H), 3.85 (d, J = 3.3 Hz, 2H), 2.01−1.81 (m, 3H), 1.81−1.64 (m, 5H), 1.58−1.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 112.5, 74.1, 42.7, 36.1, 36.0, 24.4, 23.0, 22.9; HRMS (m/z, ES) calcd for $C_9H_{13}ClNaO_3$ 227.0445, found 227.0444.

General Procedure for the Cycloaddition. A round-bottomed flask equipped with a Teflon-coated magnetic stir bar and a reflux condenser is charged with **10** (1.00 equiv) and dry *n*-propylacetate (0.5 M). Triethylamine (2.00 equiv) is added, and the flask is heated under reflux for 18 h. The reaction mixture is cooled to 23 °C, and (+)-**1** (1.00 equiv) and the requisite aldehyde (1.00 equiv) are added. A Dean−Stark trap is fitted on the flask, and the reaction mixture heated under reflux for an additional 24−48 h. The course of the reaction is monitored by TLC until complete disappearence of the acrylate. The reaction mixture is cooled to 23 °C and diluted with EtOAc. The organic layer is washed with aqueous 1 N HCl and brine, dried over Na_2SO_4, and evaporated to dryness. The crude product is recrystallized 2 times to afford the pure cycloadduct **11**.

11a. Obtained according to the general procedure 1 from 10.0 g of **10** (48.8 mmol) with a cycloaddition time of 24 h. Recrystallization from pure hexane (100 mL) afforded **11a** as a white solid (16.8 g, 64% yield, single cycloadduct). Mp = 131−132 °C; $[\alpha]^{26}_D$ = −16.4 (c 1.0 in $CHCl_3$); IR (neat, cm^{-1}) ν 2937, 1799, 1449, 1371, 1249, 1207, 1116, 1072, 847; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, J = 6.1 Hz, 1H), 4.69−4.62 (m, 2H), 4.35 (dt, J = 8.4, 6.6 Hz, 1H), 4.20 (dd, J = 8.5, 6.9 Hz, 1H), 4.05 (dd, J = 8.5, 3.8 Hz, 1H), 3.73 (dd, J = 8.6, 6.4 Hz, 1H), 3.56−3.46 (m, 1H), 2.76 (dd, J = 14.0, 8.0 Hz, 1H), 2.36 (d, J = 15.0 Hz, 1H), 2.09−0.95 (m, 33H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 112.9, 111.5, 109.7, 105.9, 96.7, 84.3, 84.2, 80.2, 75.6, 66.0, 65.8, 38.6, 37.6, 36.9, 36.4, 31.1, 30.0, 26.6, 26.4, 26.1, 25.8, 25.6, 25.2, 24.9, 24.3, 23.0, 22.9; HRMS (m/z, ES) calcd for $C_{28}H_{44}NO_9$ 538.3011, found 538.3009.

11b. Obtained according to the general procedure from 10.0 g of **10** (48.8 mmol) with a cycloaddition time of 48 h. Two successive recrystallizations from 9:1 hexane/EtOAc (100 mL) afforded **11b** as a white solid (13.3 g, 52% yield, single cycloadduct). Mp = 132−133 °C; $[\alpha]^{26}_D$ = −7.4 (c 0.9 in $CHCl_3$); IR (neat, cm^{-1}) ν 2944, 1799, 1452, 1374, 1200, 1155, 1071, 1033, 990, 923, 848; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, J = 6.1 Hz, 1H), 4.69 (s, 1H), 4.65 (dd, J = 6.0, 4.0 Hz, 1H), 4.37 (dd, J = 15.3, 6.9 Hz, 1H), 4.21 (dd, J = 8.4, 6.9 Hz, 1H), 4.06 (dd, J = 8.4, 3.9 Hz, 1H), 3.91 (q, J = 5.8 Hz, 1H), 3.70 (dd, J = 8.4, 7.0 Hz, 1H), 2.96 (dd, J = 13.6, 7.5 Hz, 1H), 2.12 (dd, J = 13.6, 1.7 Hz, 1H), 1.98−1.60 (m, 9H), 1.52−1.42 (m, 6H), 1.39 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 112.8, 111.7, 109.7, 105.7, 97.2, 84.6, 84.3, 80.2, 75.6, 66.0, 58.0, 47.8, 42.8, 37.6, 36.4, 30.5, 29.8 (3C), 26.6, 26.1, 25.2, 25.0, 24.3, 23.0, 22.9; HRMS (m/z, ES) calcd for $C_{27}H_{44}NO_9$ ($[M + H]^+$) 526.3011, found 526.3005.

General Procedure for Chiral Auxiliary Cleavage Affording the Stable Isoxazolidine Hydrochloride Salt 12·HCl. Caution! Perchloric acid is a strong oxidizing agent that reacts violently with metals and is potentially explosive at high concentrations. A round-bottomed flask equipped with a Teflon-coated magnetic stir bar is charged with **11** (1.00 equiv) and acetonitrile (0.1 M). Perchloric acid (70% w/w solution in H_2O, 2.50 equiv) is added, and the flask is stirred at 23 °C for 4−8 h. The reaction mixture is quenched by the careful addition of saturated aqueous $NaHCO_3$ (**Caution: CO_2 releases**), and acetonitrile is evaporated under vacuum. The aqueous layer is extracted with EtOAc, and the organic layer is washed with saturated brine and dried over Na_2SO_4. The solvent is evaporated by rotary evaporation to afford a pale yellow oil. This oil is dissolved in MTBE (0.1 M) and cooled at 0 °C, and a solution of HCl in diethyl ether (2 M solution, 1.10 equiv) is slowly added over 1 h. After completion of the addition, the flask is placed in the refrigerator at 4 °C overnight. The solid is collected by filtration and washed with MTBE to afford **12**·HCl.

12a·HCl. Obtained according to the general procedure from 16.0 g of **11a** (29.7 mmol) with a reaction time of 6 h. White solid (8.1 g, 82% yield). Mp 141−142 °C; $[\alpha]^{26}_D$ = +29.1 (c 0.9 in $CHCl_3$); IR (neat, cm^{-1}) ν 2921, 2853, 2415, 1808, 1442, 1284, 1244, 1194, 1104, 1085, 942; ^1H NMR (400 MHz, CD_3OD) δ 3.89 (dd, J = 17.6, 10.1 Hz, 1H), 3.18 (dd, J = 14.4, 7.5 Hz, 1H), 2.56 (dd, J = 14.4, 10.5 Hz, 1H), 1.97−1.01 (m, 21H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.2, 113.2, 107.0, 66.8, 38.5, 38.4, 36.8, 35.2, 30.2, 29.4, 25.2, 25.0, 24.7, 23.6, 22.6, 22.5; HRMS (m/z, ES) calcd for $C_{16}H_{26}NO_4$ 296.1856, found 296.1861.

General Procedure for the Redox Neutral Fragmentation Affording the β^3-Amino Acid HCl Salt 13·HCl. A round-bottomed flask equipped with a Teflon-coated magnetic

dx.doi.org/10.1021/op300069n | Org. Process Res. Dev. 2012, 16, 687−696

stir bar is charged with the isoxazolidine hydrochloride salt (1.00 equiv) and a 1:1 mixture of *t*-BuOH/H_2O (0.1 M). The reaction mixture is stirred at 60 °C for 36 h. The reaction mixture is evaporated to dryness under vacuum to afford a solid. The solid is triturated with acetone, collected by filtration, and washed with acetone to afford **13**·HCl.

(*R*)-3-Amino-3-cyclohexylpropanoic Acid Hydrochloride 13a·HCl. Obtained according to the general procedure from 5.5 g of **12a**·HCl (16.7 mmol) with a reaction time of 36 h. White solid (3.1 g, 90% yield). Mp 231−232 °C;[26] $[\alpha]^{26}_D$ = +49.3 (*c* 0.1 in H_2O); IR (neat, cm^{-1}) ν 2917, 2852, 1709, 1586, 1505, 1418, 1386, 1236, 1193, 1164; ^1H NMR (400 MHz, DMSO-d_6) δ 12.71 (brs, 1H), 8.02 (brs, 2H), 3.25 (dd, *J* = 11.6, 5.6 Hz, 1H), 2.65 (dd, *J* = 17.3, 5.2 Hz, 1H), 2.53 (dd, *J* = 17.3, 7.2 Hz, 1H), 1.77−1.53 (m, 6H), 1.25−0.93 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 52.3, 34.7, 28.4 (2C), 28.0, 26.0, 25.9 (2C); HRMS (*m*/*z*, ES) calcd for $C_9H_{18}NO_2$ ($[M - Cl]^+$) 172.1332, found 172.1329.

General Procedure for Chiral Auxiliary Cleavage and Redox Neutral Fragmentation Affording the β^3-Amino Acid 13. A round-bottomed flask equipped with a Teflon-coated magnetic stir bar is charged with **11** (1.00 equiv) and acetonitrile (0.1 M). Perchloric acid (70% w/w solution in H_2O, 2.5 equiv) is added, and the flask is stirred at 23 °C for 4−8 h. The reaction mixture is quenched by the careful addition of saturated aqueous $NaHCO_3$, and acetonitrile is evaporated under vacuum. The aqueous layer is extracted with EtOAc, and the organic layer is washed with saturated brine and dried over Na_2SO_4. The solvent is evaporated by rotary evaporation to afford an oil. A round-bottomed flask equipped with a Teflon-coated magnetic stir bar is charged with this oil and a 1:1 mixture of *t*-BuOH/H_2O (0.1 M). The reaction mixture is stirred at 60 °C for 36 h. The reaction mixture is evaporated to dryness under vacuum to afford a solid. The solid is triturated with EtOAc, collected by filtration, and washed with EtOAc to afford **13**.

(*S*)-3-Amino-5,5-dimethylhexanoic Acid 13b. Obtained according to the general procedure from 13.0 g of **11b** (24.7 mmol) with a reaction time of 36 h. White solid (3.4 g, 86% yield). Mp 203−204 °C; $[\alpha]^{26}_D$ = +27.5 (*c* 1.1 in H_2O); IR (neat, cm^{-1}) ν 2954, 1645, 1544, 1466, 1393, 1309, 1251, 1213, 1150, 1089; ^1H NMR (400 MHz, CD_3OD) δ 3.48−3.37 (m, 1H), 2.53 (dd, *J* = 16.9, 3.6 Hz, 1H), 2.31 (dd, *J* = 16.9, 9.4 Hz, 1H), 1.62−1.45 (m, 2H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.4, 46.7, 46.5, 39.8, 29.6, 28.6 (3C); HRMS (*m*/*z*, ES) calcd for $C_8H_{18}NO_2$ ($[M + H]^+$) 160.1332, found 160.1331.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all synthesized compounds. Procedures and SFC spectra for ee determination of the final β^3-amino acids. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

bode@org.chem.ethz.ch

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the David and Lucille Packard Foundation (fellowship to J.W.B), the Arnold and Mable Beckman Foundation, and ETH-Zürich. We thank Dr. Stefan Abele (Actelion Pharmaceuticals) for helpful suggestions.

■ REFERENCES

(1) (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117−128. (b) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M. I. *Curr. Med. Chem.* **2002**, *9*, 811−822.

(2) Hansen, K. B.; Balsells, J.; Dreher, S.; Hsiao, Y.; Kubryk, M.; Palucki, M.; Rivera, N.; Steinhuebel, D.; Armstrong, J. D.; Askin, D.; Grabowski, E. J. J. *Org. Process Res. Dev.* **2005**, *9*, 634−639.

(3) Sakai, T.; Kawamoto, Y.; Tomioka, K. *J. Org. Chem.* **2006**, *71*, 4706−4709.

(4) (a) Seebach, D.; L. Matthews, J. *Chem. Commun.* **1997**, *21*, 2015−2022. (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232.

(5) (a) Qiu, J. X.; Petersson, E. J.; Matthews, E. E.; Schepartz, A. *J. Am. Chem. Soc.* **2006**, *128*, 11338−11339. (b) Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. *Nat. Chem. Biol.* **2007**, *3*, 252−262.

(6) For selected examples, see: (a) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543−554. (b) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y. K.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918−9919. (c) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952−4953. (d) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048−6049. (e) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gomez-Bengoa, E.; Garcia, J. S. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188−9189. (f) Chi, Y.; English, E. P.; Pomerantz, W. C.; Horne, W. S.; Joyce, L. A.; Alexander, L. R.; Fleming, W. S.; Hopkins, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6050−6055. (g) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700−3701. (h) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588−9589. (i) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609−611. (j) Matsumura, K.; Zhang, X.; Hori, K.; Murayama, T.; Ohmiya, T.; Shimizu, H.; Saito, T.; Sayo, N. *Org. Process Res. Dev.* **2011**, *15*, 1130−1137.

(7) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913−941.

(8) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385−1393.

(9) For reviews see: (a) Juaristi, E.; Soloshonok, V. *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Wiley: New York, 2005. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035.

(10) For a recent example, see: Grayson, J. I.; Roos, J.; Osswald, S. *Org. Process Res. Dev.* **2011**, *15*, 1201−1206.

(11) Savile, C. K.; Janey, J. M.; Mundorff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. J. *Science* **2010**, *329*, 305−309.

(12) Lelais, G.; Seebach, D. *Biopolymers* **2004**, *76*, 206−243.

(13) Yu, S. Y.; Ishida, H.; Juarez-Garcia, M. E; Bode, J. W. *Chem. Sci.* **2010**, *1*, 637−641.

(14) (a) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273−1295. (b) Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33−58. For selected applications of carbohydrate-derived chiral auxiliaries for the synthesis of hydroxylamines and isoxazolidines, see: (c) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103−6106. (d) Lantos, I.; Flisak, J.; Liu, L.; Matsuoka, R.; W; Stevenson, D.; Tubman, K.; Tucker, L.; Zhang, W.-Y.; Adams, J.; Sorenson, M; Garigipati, R.; Erhardt, K.; Ross, S. *J. Org. Chem.* **1997**, *62*, 5385−5391. (e) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054−3056. (f) Mita, N.; Tamura, O.; Ishibashi, H.; Sakamoto, M. *Org. Lett.* **2002**, *4*, 1111−

1114. (g) Topić, D.; Aschwanden, P.; Fässler, R.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 5329−5330. (h) Ritter, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 936−938. (i) Gao, Z.-X.; Wang, M.; Wang, S.; Yao, Z.-J. *Org. Lett.* **2009**, *11*, 3678−3681.
(15) (a) Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647−4648. (b) Kasahara, K.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 2225−2233.
(16) D- and L-Gulono lactones are derived, respectively, from D-xylose and L-ascorbic acid. They are available from Carbosynth for 1200 and 2500 USD/kg (catalog price).
(17) Rohloff, J. C.; Alfredson, T. V.; Schwartz, M. A. *Tetrahedron Lett.* **1994**, *35*, 1011−1014.
(18) D- and L-Gulose oxime chiral auxiliaries are commercially available from BioBlocks, Inc.
(19) Huchler, G.; Rall, W.; Ries, U. U.S. Patent 2008045705, 2008.
(20) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380−3387.
(21) Likhterov, V. R.; Etlis, V. S.; Ternoskoi, L. A. *Khim. Geterotsikl. Soedin.* **1985**, 1316−1318.
(22) For example, α-chlorohydrin [CAS 96-24-2] is available from Acros for 53.70 USD/liter.
(23) (a) Hope, D. B.; Walti, M. *J. Chem. Soc. C* **1970**, 2475−2478. (b) Wisniewski, K. *Org. Prep. Proced. Int.* **1999**, *31*, 211−214.
(24) Harris, E. M. *CRC Handbook of Laboratory Safety*, 4th ed.; Furr, A. K., Ed.; CRC Press: Boca Raton, 1995; Section 4.6.2.4, Perchloric Acid, p 308.
(25) Isoxazolidine·HCl salts can be stored in the absence of water at room temperature. The free base form is stable in the absence of water during the evaporation of the solvent used for the workup (EtOAc, 30 °C) and can be stored for 24 h at 4 °C before being submitted to fragmentation. The free base oxidizes slowly to the isoxazoline.
(26) Nejman, M.; Sliwinska, A.; Zwierzak, A. *Tetrahedron* **2005**, *61*, 8536−8541.