JOC The Journal of Organic Chemistry

Article

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Ugi and Passerini Reactions of Biocatalytically Derived Chiral Aldehydes: Application to the Synthesis of Bicyclic Pyrrolidines and of Antiviral Agent Telaprevir

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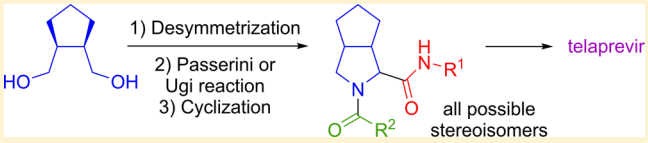
Supporting Information

ABSTRACT: Lipase mediated desymmetrization of a *meso*-diol (1,2-cyclopentanedimethanol) allows the synthesis of both enantiomers of some chiral aldehydes, whose behavior in Passerini and Ugi reactions has been explored. Exploiting these two complementary multicomponent reactions and coupling them with a subsequent cyclization process, we observed that 6 out of all 8 possible stereoisomers of peptidomimetic pyrrolidines can be obtained in good yields. The potential of these protocols has been proved by the development of a new efficient synthesis of antiviral drug telaprevir.

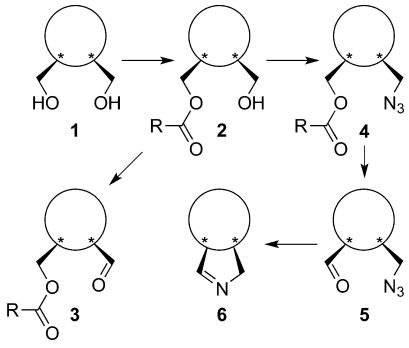


INTRODUCTION

Isocyanide-based multicomponent reactions (IMCRs) have become very popular in recent years especially in the diversity-oriented synthesis[1] of libraries of drug candidates.[2] Although the advantages of high step- and atom-economy associated with these methodologies should make them also well suited to target-oriented synthesis, their exploitation in the total synthesis of active pharmaceutical ingredients (APIs) has been much less explored,[3−6] probably because the literature reports typically deal with the synthesis of racemic substances from simple commercially available building blocks. The "real" drugs often call for chiral, enantiomerically pure, components, (wrongly) perceived as too complex to be used in multicomponent chemistries. Biocatalysis[7,8] is a "green" and efficient methodology to prepare chiral building blocks. Our group has been active for nearly 30 years in this field and recently reported on the utilization of biocatalytically derived building blocks in diastereoselective isocyanide-based multicomponent reactions.[9−11]

In particular, monoesters **2** derived from desymmetrization[7,8] of *meso* or prochiral diols **1** are quite interesting, being convertible into aldehydes **3** and **5** (through the azide **4**) or into cyclic imines **6** (through intramolecular Staudinger−Aza−Wittig[12] reaction) (Scheme 1). In addition, the complementarity of enzymatic monoacylation/monohydrolysis and the intrinsic stereodivergency of these building blocks gives access to both enantiomeric series. Cyclic imines **6** have been subjected to Ugi−Joullié tricomponent reactions, which are often stereoconservative (proceeding with no epimerization) and diastereoselective.[11,13] However, the use of aldehydes **3** or **5** as starting components in IMCRs is unprecedented. We will therefore describe herein our latest results in this field, culminated in a new synthesis of important antiviral drug telaprevir.

Scheme 1. Enzymatically Derived Chiral Building Blocks for IMCRs



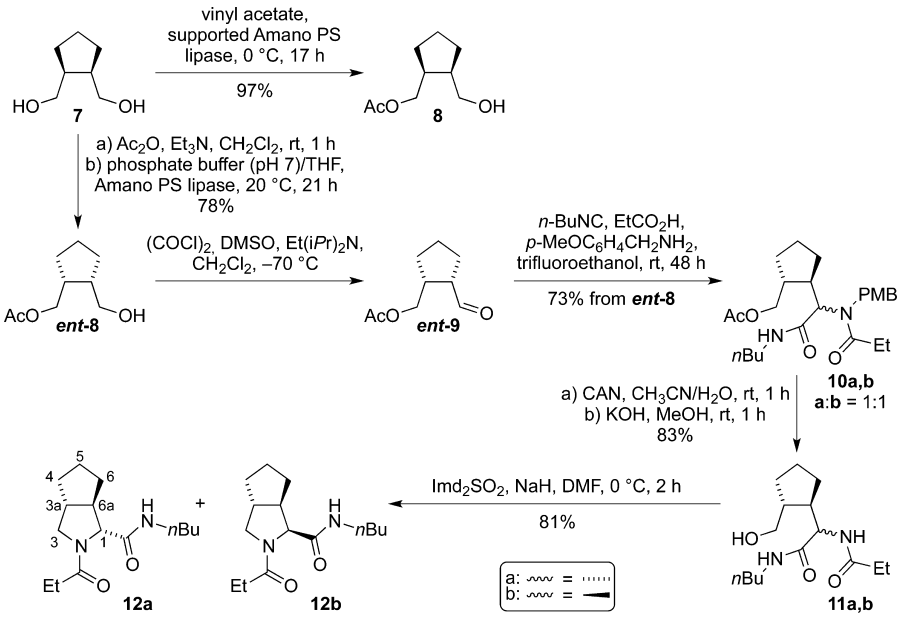
RESULTS AND DISCUSSION

We chose as the *meso*-diol for our studies the known cyclopentane derivative **7** (Scheme 2),[14,15] which was best prepared by reduction of *cis*-1,2-cyclopentanedicarboxylic anhydride.[16−18] From this diol, we obtained in high enantiomeric excess (e.e.) both enantiomers of monoacetate **8** by using either an enzymatic acetylation or the complementary enzymatic monohydrolysis of the diacetate of **7**. After optimization, both enantiomers could be obtained in high e.e. (97% for **8** and 95% for *ent*-**8**). It is worth noting that, although both monohydrolysis[19−21] and monoacetylation[20] have been already reported with other enzymes, in our hands the e.e. values were not fully satisfactory, and we had to test various enzymes and conditions before obtaining the best results. In

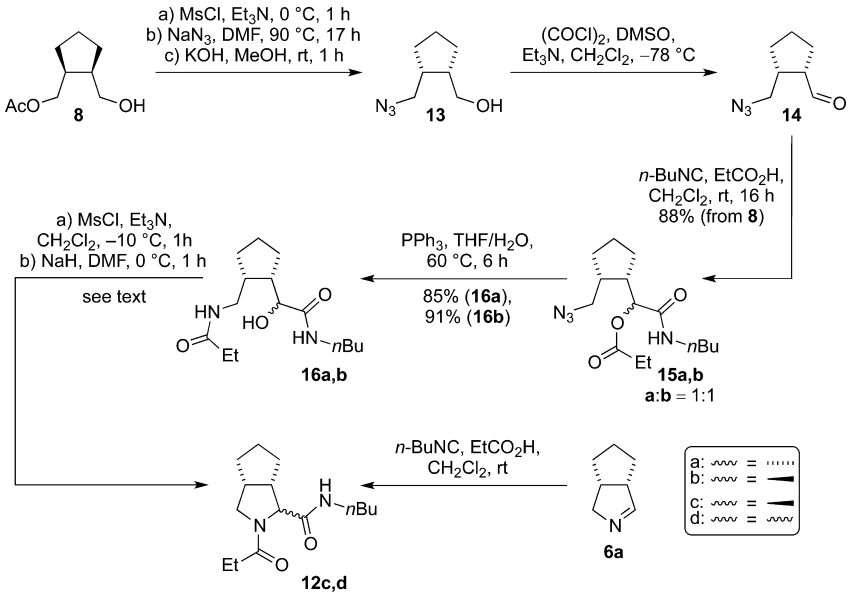
Received: December 15, 2014
Published: March 11, 2015

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

Scheme 2. Ugi Approach to *trans*-Fused Bicyclic Pyrrolidines



Scheme 3. Passerini Approach to *cis*-Fused Bicyclic Pyrrolidines



particular, monoacetylation of **7** was best carried out by Amano PS lipase supported on Celite.[22]

The following studies were carried out on the (1*R*,2*S*) isomer *ent*-**8**. Oxidation to the aldehyde *ent*-**9** was carried out under Swern conditions. This aldehyde was found to be rather sensitive to epimerization and afforded the more stable *trans* isomer. However, by using *N*,*N*-diisopropylethylamine as the base and performing a rapid workup at pH 4 (in order to remove all the base before evaporation) we were able to obtain diastereomerically pure *ent*-**9**. The stereochemical integrity was checked by BH_3 reduction followed by GC analysis. Because of this lability, the crude aldehyde was directly submitted to a model Ugi reaction[23,24] with *n*-butyl isocyanide, propionic acid, and *p*-methoxybenzylamine (PMB-NH_2). The reaction proceeded in good yield but with poor diastereoselectivity, affording a 1:1 mixture of the two diastereomers **10a,b**. We later demonstrated (after conversion into **12a,b**) that they were not the expected *cis* compounds, but the *trans* ones instead (a thorough discussion on the relative configuration is reported after discussion of the Passerini approach).

Since only two diastereomers were detected, epimerization on carbon **6a** (**12a,b**) was complete. We can rule out that the epimerization occurred during oxidation because the stereochemical integrity of *ent*-**9** was demonstrated by GC-MS analysis on the crude Swern product (after reduction to the corresponding alcohol by means of BH_3) before submitting it to the Ugi reaction. In addition, it should be noted that incubation of aldehyde *ent*-**9** in the same solvent with a tertiary amine (triethylamine) for 48 h led to only partial epimerization. Therefore, we think that this complete epimerization is due to the imine−enamine equilibrium and not to simple base mediated deprotonation of the aldehyde.[25] This result is in agreement with the pioneering work by Kelly,[26] who noticed partial epimerization of α-chiral aldehydes during Ugi reactions.

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

In our case, complete conversion into *trans* isomers indicates that they should be much more stable.

Adducts **10a,b** could be useful intermediates for preparing heterocycles through S_N2 cyclizations.[27] By removing the *p*-methoxybenzyl group and the acetate, we obtained chromatographically separable alcohols **11a,b**. Then, substitution of the OH group by one of the two secondary amides to give either a six-membered or a five-membered ring was attempted both on the diastereomeric mixture or on the isolated isomers. Initial experiments, involving the formation of a mesylate followed by base treatment, were unsuccessful. We eventually found that 1,1′-sulfonyl diimidazole in combination with NaH[28−30] was able to promote the desired cyclization. Interestingly, only pyrrolidines were formed in good yields and no loss of stereochemical integrity was observed (each isomer afforded a single product). Separation of the diastereomers was easier at this level, and therefore, under a synthetic point of view, it was more convenient to carry out the whole synthesis on the mixture. Even though the *trans* bicyclic derivatives **12a,b** are quite strained and therefore less thermodinamically stable than the corresponding *cis* ones (**12c,d**, Scheme 3), we did not observe any epimerization: this is due to the lack of an electron withdrawing group bound to the stereogenic center, which makes the deprotonation, responsible for the epimerization, unlikely.

In conclusion this synthetic protocol was able to afford the final adducts **12a,b** in good overall yields and is complementary to the synthesis of pyrrolidines through the Ugi−Joullié reaction of bicyclic imines, which affords *cis*-fused products instead.[11,13] Since monoacetate **8** is available as well, all four *trans*-fused pyrrolidines can be prepared.

In order to gain access to the *cis*-fused series as well, we turned our attention to the Passerini reaction,[23,24] which was expected to be less troublesome in terms of epimerization.[31] In this case, we chose to start from azidoaldehyde **14** instead of acetoxyaldehyde **9**. Passerini reactions of aldehyde **9** would afford doubly acylated diols, where the two ester moieties were expected to be difficult to differentiate, on the basis of preliminary experiments carried out by us on similar adducts. An alternative strategy would involve the hydrolysis of both esters to give a diol, followed by double substitution of the corresponding dimesylate by ammonia or a synthetic equivalent of it, to give a pyrrolidine. However, in our hands this approach was found to be inefficient due to the easy formation of a tetrahydrofuran. Therefore, we decided to differentiate the two arms before the Passerini step, converting monoacetate **8** into azidoaldehyde **14** (Scheme 3) through a straightforward procedure, already applied by us in similar cases.[11]

Pleasingly, azidoaldehyde **14** underwent a model Passerini reaction with *n*-butyl isocyanide and propionic acid in high yield and, most importantly, with no epimerization at all. The whole sequence from monoacetate **8** to compounds **15a,b** can be carried out without any intermediate purification and with an excellent overall yield (88%). Unfortunately, adducts **15** were obtained as a nearly 1:1 separable diastereomeric mixture. In order to obtain pyrrolidines **12** from these adducts, we carried out a two-step protocol involving (a) azide reduction with concomitant acyl migration; (b) S_N2 cyclization of the resulting secondary amide onto the secondary alcohol. Starting from **15a**, both steps worked out in excellent yields to give pyrrolidine **12c** as a single isomer.

The first stage resembles the PADAM (Passerini−amine deprotection−acyl migration) protocol, where the acyl group introduced onto the aldehyde oxygen during the Passerini reaction undergoes a subsequent *O*- to *N*-acyl migration to give peptidomimetic structure. This protocol was first introduced by us starting from *α*-aminoaldehydes[32] and was recently extended to *β*-aminoaldehydes.[33] Now, aldehyde **14** is equivalent to a *γ*-aminoaldehyde, and therefore, the results reported here further extend the scope of the strategy. As far as the cyclization step is concerned, in this instance 1,1′-sulfonyl diimidazole worked poorly, and the best cyclization yields were obtained by mesylation of the alcohol followed by base-mediated cyclization. Under these conditions, the yield of **12c** from **16a** was 91%.

However, when we repeated the cyclization on epimer **16b**, we surprisingly obtained a 2.7:1 mixture of **12c** (major) and **12d** (minor). Clearly, while **16a** reacts in a stereospecific manner (most likely with complete inversion of configuration), **16b** gives a nonstereospecific transformation. The reaction of **16b** is also slower, and some unreacted mesylate of **16b** is recovered. Therefore, a possible explanation is that, because cyclization of the mesylate of **16b** is sluggish, there is enough time for it to equilibrate to **16a**, which, by contrast, reacts faster. The equilibration may take place through base-mediated enolization. Thus, a mixture of **16a** and **16b** could be cyclized to give mostly **12c**, which was isolated in pure diastereomeric form in 73% yield! Also a small amount (10%) of **12d** was obtained. This means that **12c** can be produced in a stereoconvergent way with an overall yield of 55% from monoacetate **8**.

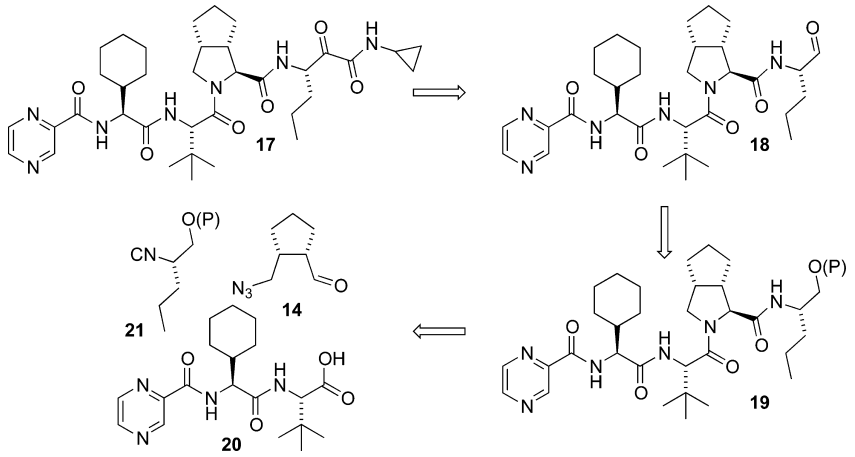
The relative and absolute configuration of adduct **12c**, obtained through the Passerini route described in Scheme 3, was unambiguously established by comparison with the major product obtained through the Ugi−Joullié reaction of cyclic imine **6a**, prepared as previously described,[34] with propionic acid and *n*-butyl isocyanide. This reaction afforded, as a major product, compound **12c**, that was identical (NMR, TLC, and $[\alpha]_D$) to the one obtained from **16a**. The Ugi−Joullié reaction also gave a small amount of all-*cis* compound **12d** (d.r. = 92:8). This was identical (NMR and TLC) to the minor adduct obtained from **16b** (as described above, **16b** afforded a mixture of **12c** and **12d**). The Ugi−Joullié reactions on **6a** were already demonstrated to afford preferentially, with high d.r., the *trans* adducts.[13] Since isomers **12a** and **12b**, obtained through the Ugi route described in Scheme 2, were clearly different from **12c** and **12d** (NMR and TLC), although having spectroscopic and MS data consistent with the same constitutional formula, the **3a−6a** relative configuration must necessarily be *trans*.

The **1−6a** relative configuration of **12a** and **12b** was established by the values of J_{1-6a} at ^{1}H NMR. This value is larger (9.9 Hz) for all-*trans* isomer **12a** than for the **1−6a** *cis*-epimer **12b** (7.8 Hz.). Moreover, in **12b** there is a large NOE between ***H*-1** and ***H*-6a**, which is not possible in **12a**. To further corroborate these assumptions, we carried out a minimization using ChemBio3D Ultra (CambridgeSoft)(PM3). These bicyclic systems were found to be quite rigid: apart from conformations deriving from rotation of the single bonds outside the ring, only one significant conformation of the bicyclic system was found. The calculated dihedral angles (***H*-1−*H*-6a**) for the four isomers are −159.3° (**12a**), −36.2° (**12b**), 122.7° (**12c**), and 12.7° (**12d**), which are consistent with the experimental *J* values.

In conclusion, the complementarity of Ugi and Passerini reactions and the availability of both **8** and *ent*-**8** allowed us to prepare in good yields 6 out of 8 possible stereoisomers of

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

Scheme 4. Initially Planned Retrosynthesis of Telaprevir 17



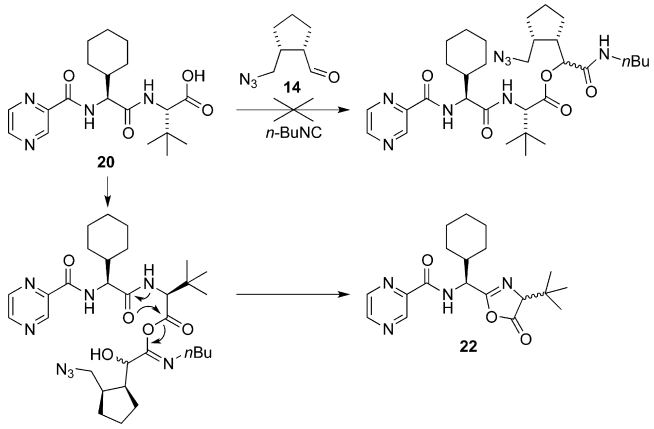
pyrrolidines **12**, the remaining two, namely, **12d** and *ent*-**12d**, being accessible only in low yield. The number of steps from desymmetrized monoacetates **8** or *ent*-**8**, is comparable, for both routes, to an alternative approach to pyrrolidines, previously demonstrated by us on similar substrates, where monoacetates are first converted into pyrrolines, followed by the Ugi–Joullié multicomponent reaction.[11] Moreover, the here described approaches are stereochemically more versatile since 6 stereoisomers (instead of 2) may be obtained. Finally, the procedure herein avoids the intermediacy of pyrrolines, which are sometimes not easily manipulated due to their tendency to polymerize.

As a first application of this methodology, we decided to develop a new efficient synthesis of an important API, telaprevir **17** (Scheme 4). This compound is one of the most innovative drugs launched during the last 10 years.[35,36] It is indeed one of the two first specific drugs directed against hepatitis C, a severe and widely distributed disease. Approximately 170 million people worldwide are chronic carriers of this virus (2% of the world's population). The biological target of telaprevir is a specific viral serine protease, and it is effective for genotype 1 of the virus. Although the treatment of HCV with antiviral drugs is still quite expensive, it is anticipated that the advent of generic drugs will strongly lower the cost, making this drug available to a larger population, especially in less-developed countries. For this purpose, cost-effective syntheses of this active principle are needed, and multicomponent reactions can be a good way to achieve this goal, as already demonstrated by Ruijter and others.[5]

The planned retrosynthesis is shown in Scheme 4. Telaprevir can be obtained through a Passerini reaction on aldehyde **18**, which derives from protected alcohol **19**. We wanted to prepare intermediate **19** in a very convergent way, employing the same strategy above-described for the simple model **12c**, which has the same absolute and relative configuration of our target. Compound **19** could be in principle obtained in just two linear steps after the Passerini reaction of peptide **20**[5] with azidoaldehyde **14** and a suitably protected isocyanide **21** derived from L-α-aminopentanoic acid. In order to check the feasibility of this approach, we initially used *n*-butyl isocyanide as a simplified model for **21**.

However, the reaction of peptide **20** with aldehyde **14** and *n*-butyl isocyanide failed to give the expected Passerini product. Under the typical Passerini conditions, **20** was nearly completely converted into the corresponding oxazolone **22** (Scheme 5).

Scheme 5. Attempted Passerini Reaction Employing Acid 20

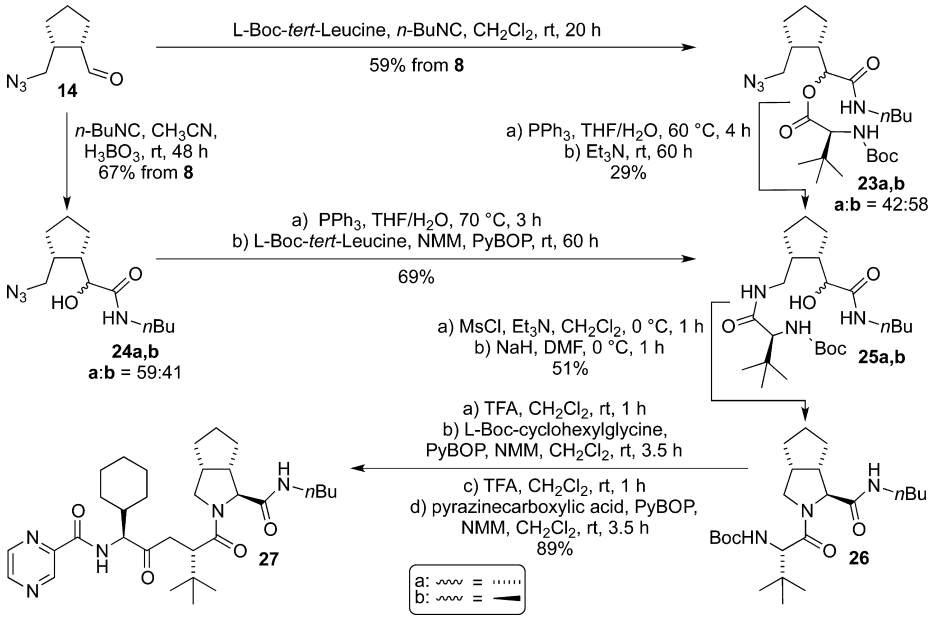


We think that α-addition to the isocyanide takes place normally, to give the usual intermediate. However, at this level, the activated acyl group is attached by the oxygen of the amide bond between cyclohexylglycine and *tert*-leucine. This reaction is evidently faster than the usual acyl migration onto the free hydroxy group. Formation of this type of oxazolones is a well-known problem encountered during the coupling of peptide acids.[37] However, these compounds are not isolated since they can still react with amines to give amides, their intermediate formation being deemed responsible of racemization/epimerization of the obtained coupling product. In this case, the absence of a good nucleophile like an amine makes this adduct stable enough to be isolated.

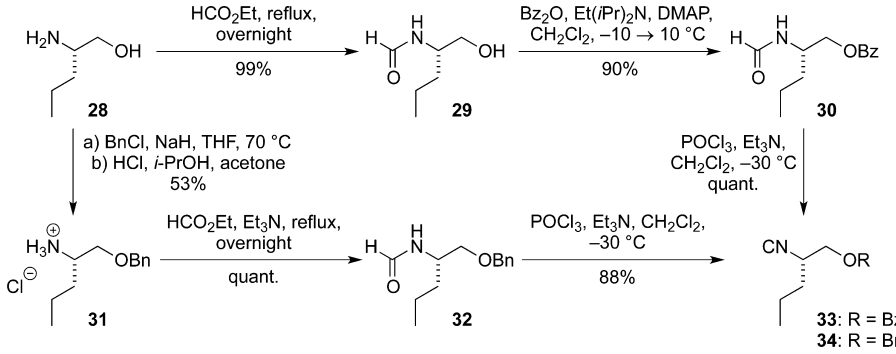
It is interesting to note that the behavior of acid **20** is specific for the Passerini reaction since it can be used as input in Ugi–Joullié reactions without any problems, as reported by Ruijter et al.[5] and confirmed by us as well. Thus, we had to redesign our synthesis, employing as the carboxylic component Boc protected L-*tert*-leucine, with the intention to add later the other fragments (Scheme 6). The Passerini reaction of **22** with aldehyde **14** (prepared once again by Swern oxidation of alcohol **13**) proceeded in good (unoptimized) yield to give **23a,b** (**a**/**b** 42:58). However, the next Staudinger-acyl migration protocol turned out to be troublesome. Probably

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411–3428

Scheme 6. Synthesis of Model Peptide 27



Scheme 7. Synthesis of α-Aminopentanol Derived Isocyanides



because of the steric bulk of the acyl residue, migration was sluggish and required the addition of a base, and the yield was unacceptably low.

Thus, we decided to shift to the route depicted on the left (Scheme 6), which involves the same number of steps and is based on a "truncated" Passerini reaction followed by azide reduction and acylation. Among the various reported methods for performing "truncated" Passerini,[31] the best results were obtained using boric acid.[38,39] The resulting alcohols **24a,b** were then straightforwardly converted into **25a,b** in good yield, proving that this second pathway was definitely more efficient. This time, the **a**/**b** diastereomeric ratio was 59:41, therefore slightly favoring the correct isomer for telaprevir synthesis. Anyway, the final cyclization was carried out on the diastereomeric mixture, being confident in the stereoconvergent conversion into **26**. Actually this isomer was isolated in good yield, whereas only traces of the epimer could be detected. Finally, the complete peptide chain was smoothly installed to afford **27**. We found out that a stepwise introduction of the remaining two fragments was more efficient because of the partial epimerization observed when the preassembled dipeptide was directly used.

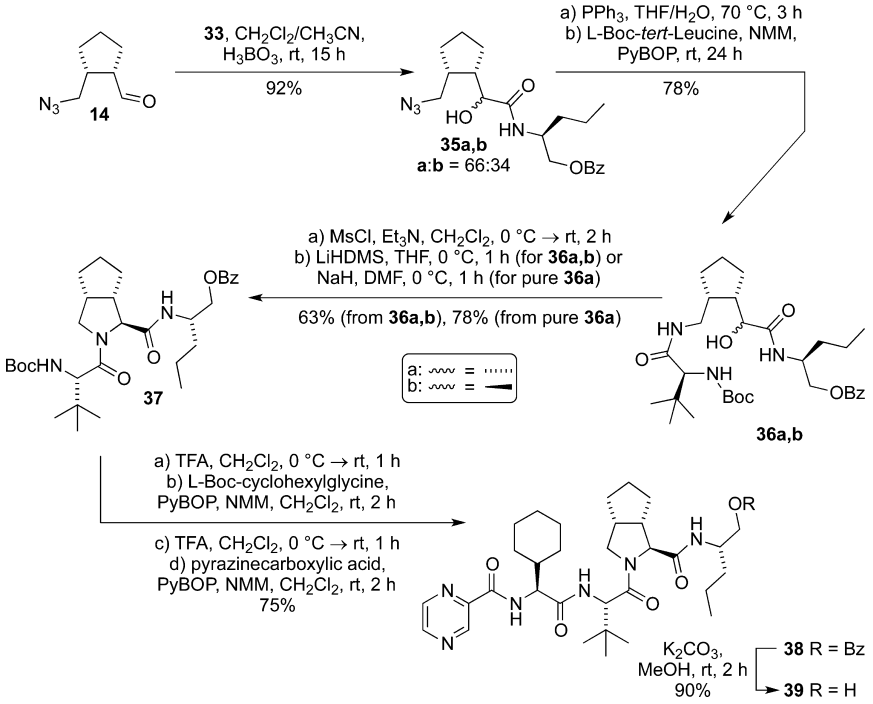
Having proved on model compounds that the key intermediate could be accessed by the truncated Passerini protocol, we moved on to apply it to the synthesis of telaprevir. Toward this goal, we needed chiral, enantiomerically pure, protected isocyanides **33** or **34** that were prepared starting from commercially available L-α-aminopentanol **28** (Scheme 7).

In the case of **33**, we introduced first the formyl group and then the benzoyl protection, whereas for **34** it was better to introduce first the benzyl ether and then to formylate the amine. In both cases, dehydration gave in high yields the required isocyanides.

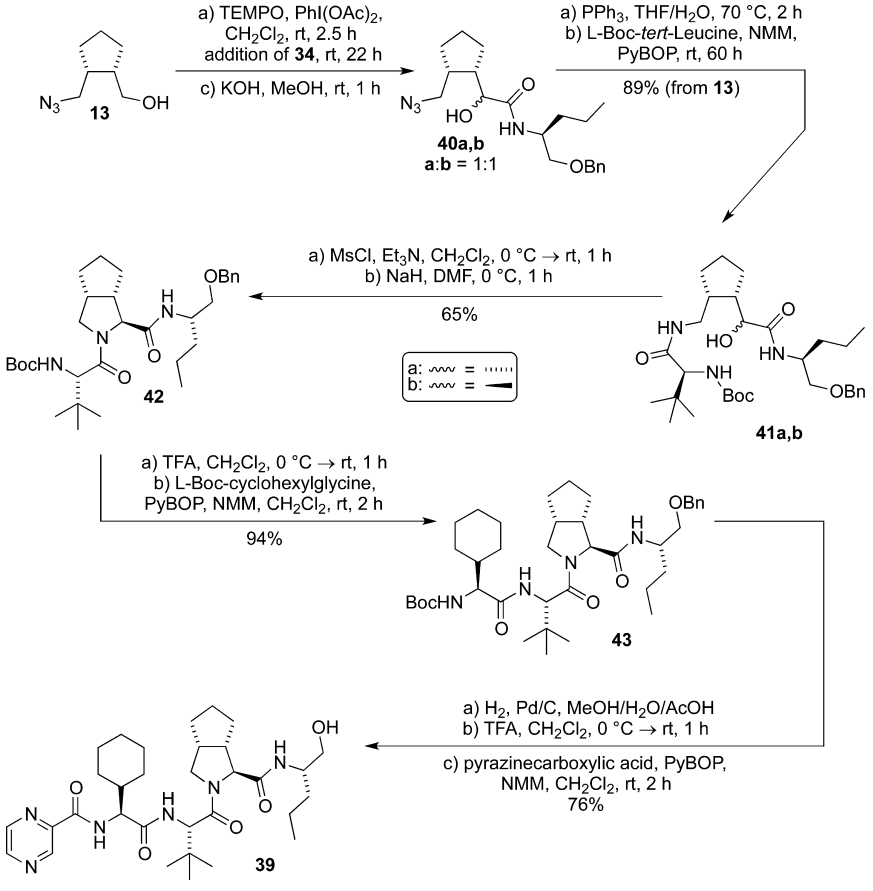
We first employed isocyanide **33** (Scheme 8). The synthesis proceeded even better than that for the model compound. Actually, the truncated Passerini not only gave a nearly quantitative yield (after solvent optimization) but also turned out to be more diastereoselective, giving a 2:1 mixture of **35a** and **35b**. After the introduction of protected L-*tert*-leucine, cyclization was also in this case stereoconvergent. However, while the cyclization of the mesylate of pure **36a** gave good results under the usual conditions (NaH, DMF), in the case of **36a,b** we needed to optimize the reaction, finding that the best conditions involved lithium hexamethyldisilazide (LiHMDS) in THF. Under these conditions, only isomer **37** was isolated in 63% yield along with 12% of the unreacted mesylate derived from **36b**. Attempts to obtain a complete conversion increasing the reaction times or the amount of base failed, due to fragility of the benzoate under basic conditions. Pyrrolidine **37** was

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

Scheme 8. Synthesis of Key Intermediate 40 through the "Benzoate" Route



Scheme 9. Synthesis of Key Intermediate 40 through the "Benzyl" Route

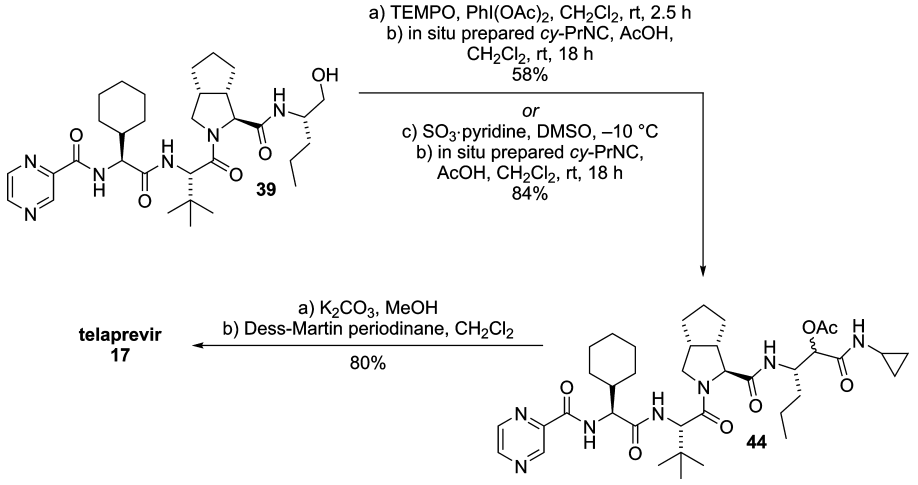


finally converted into alcohol **39** by sequential acylations and deprotection.

The incomplete conversion into the cyclization product prompted us to explore an alternative route to **39**, using the more robust benzyl protection and hence isocyanide **34** (Scheme 9). Moreover, we thought that the synthesis of azidoaldehyde **14** through Swern oxidation at −78 °C could not have been ideal for large scale production.

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

Scheme 10. Completion of Telaprevir Synthesis



Recently, various methods for the one-pot conversion of alcohols into Passerini adducts by *in situ* oxidation have been reported. The reagents used are *o*-iodoxybenzoic acid (IBX),[40−42] Dess−Martin periodinane,[5] or dioxygen in the presence of suitable catalysts.[43] However, none of these conditions seemed suitable in our case: IBX is poorly soluble and reported to be shock sensitive,[44] Dess−Martin periodinane is quite expensive and its reactions are typically slow, and the catalytic oxidation with dioxygen requires an excess of isocyanide. Therefore, we searched for a stoichiometric oxidant that would be commercially available, safe, affordable, and compatible with a subsequent one-pot Passerini reaction. We eventually found out that iodosobenzene diacetate (DIB) in the presence of the catalytic TEMPO radical (2,2,6,6-tetramethyl-1-piperidinyloxy)[45] was ideal for our purposes. This reagent is commercially available, not expensive, and safe.[46] The oxidation reaction of **13** is fast enough (2.5 h), and it works very well in the same solvent that is appropriate for the Passerini reaction (CH_2Cl_2), allowing an easy one-pot procedure. The presence of acetic acid as an oxidation byproduct does not allow one to perform a truncated Passerini, but the acetyl group can be easily removed, without any intermediate workup, after the MCR. In this way, crude alcohols **40a,b** were obtained in quantitative yield from alcohol **13**.

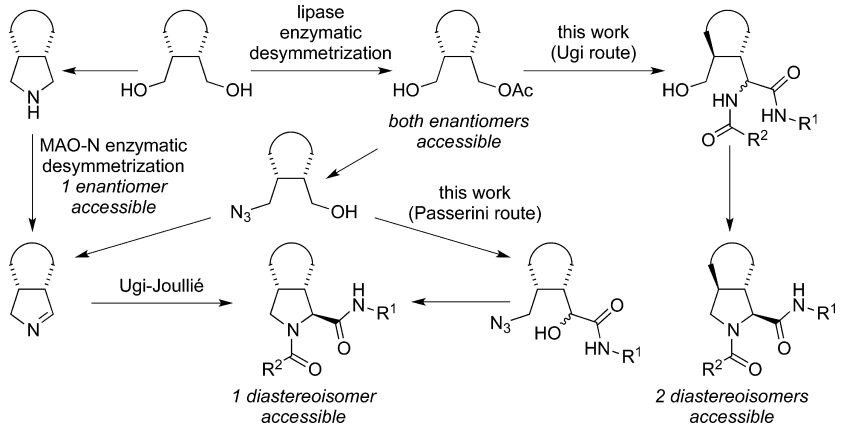
The crude mixture was pure enough to be used directly for the ensuing step to give **41a,b**. Finally, cyclization afforded pure diastereomer **42** in 65% yield (58% overall yield from azidoalcohol **13**!). It is worth noting that the cyclization yield was higher compared to that of the "benzoate" route, despite the lower diastereoselectivity of the Passerini reaction. Equilibration of the two mesylates, leading stereoconvergently to **42**, was more efficient in this case, thanks to the higher stability of the benzyl protecting group under basic conditions. Pyrrolidine **42** was finally converted into alcohol **39**. This time, we preferred to remove the benzyl protection before installing the piperazine fragment. The overall yield of **39** from azido alcohol **13** was 41%, compared to 34% with the "benzoate" route. Both pathways are efficient, but the "benzyl" route is in our opinion better also because of the higher operational simplicity.

To complete the synthesis of telaprevir, alcohol **39** had to be oxidized and subjected to a Passerini reaction with cyclopropyl isocyanide. We first chose to use the "one-pot" oxidation-Passerini using DIB and catalytic TEMPO.[47] However, the relative volatility of cyclopropyl isocyanide and its unpleasant smell makes its purification troublesome. This prompted us to explore the possibility to prepare the isocyanide *in situ* as well. In the literature, we could find very few examples of this strategy,[48,49] but none of them seemed suited for our purposes. After various attempts, we found that the method of choice employed the *in situ* prepared Burgess reagent.[50] The crude isocyanide solution obtained in this way can be directly used without the need of troublesome purification operations. We believe that the here reported method for the generation of a crude isocyanide to be directly used without any purification may find widely application in IMCRs. In this way, we were able to obtain Passerini adduct **44** (Scheme 10) through *in situ* generation of both the aldehyde (from the alcohol) and the isocyanide (from the formamide). However, the yield turned out to be only moderate. Therefore, we searched for other oxidation methods, again avoiding those requiring expensive or unsafe reagents. We eventually found that an excellent overall yield (84%) of the two steps (oxidation-Passerini) could be achieved by using the Parikh−Doering method,[51] although in this case a brief extractive workup of the intermediate aldehyde had to be performed prior to treatment with the *in situ* generated isocyanide. The two-step conversion of Passerini adduct **44** into telaprevir was finally carried out as previously described.[5]

In conclusion, we were able to set up a convenient synthesis of telaprevir, also amenable for upscaling, from desymmetrized monoacetate **8**. The overall yield from this biocatalytically derived chiral building block is a remarkable 26.4%. From the stereochemical point of view, all three stereogenic centers are fully controlled thanks to the enantioselective enzymatic desymmetrization and to the stereoconvergent cyclization step that overcomes the low diastereoselectivity of the Passerini reaction. Although the synthetic pathway is longer and less convergent than the one reported by Ruijter and others,[5] all steps are operationally simple and employ inexpensive reagents. Furthermore, the biocatalytic step makes use of a cheap and commercially available lipase, avoiding the preparation and maintenance of a specific bacterial culture to produce the needed proprietary MAO-N enzyme (MonoAmine Oxidase). Finally, this synthetic approach allowed us to deeply explore the behavior of chiral aldehydes derived from enzymatic desymmetrization of *meso*-diols in Passerini and Ugi reactions, and our findings (including the capability to obtain all possible

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

Scheme 11. Comparison of the Various Strategies for the Stereocontrolled Synthesis of Bicyclic Pyrrolidines



stereoisomers of a given pyrrolidine) can be important for the preparations of other heterocycles and other biologically active peptidomimetics. Scheme 11 reviews the four alternative strategies based on IMCRs to access chiral pyrrolidines. They are the desymmetrization of *meso*-pyrrolidines followed by the Ugi–Joullié reaction;[13] the desymmetrization of *meso*-diols followed by conversion into both enantiomers of pyrrolines and again by the Ugi–Joullié reaction;[11] and the Ugi and Passerini approaches described in this article. Studies directed to the application of IMCRs to aldehydes derived from other desymmetrized *meso*-diols are in progress.

EXPERIMENTAL SECTION

General Experimental Methods. NMR spectra were taken at r.t. in $CDCl_3$ or in d_6-DMSO at 300 MHz (^{1}H), and 75 MHz (^{13}C), using, as internal standard, TMS (^{1}H NMR in $CDCl_3$; 0.000 ppm) or the central peak of DMSO (^{1}H NMR in d_6-DMSO; 2.506 ppm) or the central peak of $CDCl_3$ (^{13}C in $CDCl_3$; 77.02 ppm), or the central peak of DMSO (^{13}C in d_6-DMSO; 39.43 ppm). Chemical shifts are reported in ppm (δ scale). Peak assignments were made with the aid of gCOSY and gHSQC experiments. In an ABX system, the proton A is considered upfield and B downfield. NMR spectra of *N*-acylpyrrolidines and of Ugi adducts have always been recorded at various temperatures. At temperatures ≤40 °C, two sets of signals are often detected because of the presence of a mixture of rotamers at the tertiary amide (*M* = major, *m* = minor). At high temperature (120 °C), coalescence is observed, demonstrating that the two sets of signals are due to conformers (and not to diastereomers or different products). However, since at 120 °C several signals become broad, we preferred to report and describe here the spectra recorded at low temperatures.[52]

IR spectra were recorded as solid, oil, or foamy samples, with the ATR (attenuated total reflectance) technique or as $CHCl_3$ solutions. TLC analyses were carried out on silica gel plates and viewed at UV (λ = 254 or 360 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming). R_f values were measured after an elution of 7–9 cm. HRMS was performed by employing electron impact ionization; the analyzer is a trisector magnetic Sector (electrostatic/magnetic/electrostatic EBE mass spectrometer). GC-MS analyses were performed on column HP-1, 0.33 μm, 0.201 mm i.d., and 12 m. Analysis conditions are as follows: solvent delay 2 min, mass range 33–600, injector temperature 250 °C, detector temperature 280 °C, MS temperature around 170 °C, starting temperature 50 or 70 °C, starting time 2 min, temperature gradient 20 °C/min, final temperature 260 °C, flux through column 1.0 mL/min, split ratio 100:1, sample concentration 1 mg/mL, and amount injected 1 μL. Column chromatography was done with the "flash" methodology by using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. All reactions employing dry solvents were carried out under nitrogen.

(*1S,2R*)-2-(Hydroxymethyl)cyclopentyl)methyl Acetate 8. *Supportation of Amano PS Lipase.* It was supported on Celite following the same procedure already described by us for pig pancreatic lipase (SPPL-4).[22] (1 g of this supported enzyme corresponds to 0.23 g of original lipase.) To a solution of *meso*-diol 7 (5.00 g, 38.4 mmol, 87% purity by GC) (obtained by $LiAlH_4$ reduction of *cis*-cyclopentane-1,2-dicarboxylic anhydride)[16−18] in vinyl acetate (190 mL) cooled to 0 °C, freshly activated powered 3 Å molecular sieves (0.50 g) and supported Amano PS (3.25 g) were added. The reaction mixture was stirred at 0 °C for 17 h, then filtered through a sintered funnel, and washed with CH_2Cl_2 (100 mL). The filtrate was concentrated, and the residue was eluted from a column of silica gel with PE–Et_2O (from 2:1 to 1:3) to give **8** (6.39 g, 97%, e.e. = 97%) as an oil. R_f = 0.56 (PE–Et_2O 1:2). $[\alpha]_D$ +7.30 (c = 2.13, $CHCl_3$). Lit. for (1*R*,2*S*) enantiomer: −8.2.[21] ^{1}H NMR ($CDCl_3$, 25 °C): δ = 4.03 and 4.12 (AB part of an ABX system, J_{AB} = 11.0, J_{AX} = 6.9, J_{BX} = 7.4 Hz, 2 H, CH_2OAc), 3.56 and 3.66 (AB part of an ABX system, J_{AB} = 10.9, J_{AX} = 6.8, J_{BX} = 7.5 Hz, 2 H, CH_2OH), 2.35 (hexuplet, 1 H, J = 7.2 Hz, C*H*), 2.23 (hexuplet, 1 H, J = 7.4 Hz, C*H*), 2.07 (s, 3 H, CH_3), 1.98 (br s, 1H, O*H*), 1.36–1.87 (m, 6 H, 3 CH_2). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 171.2 (*C*O), 65.2 (CH_2), 63.2 (CH_2), 44.0 (*C*H), 39.7 (*C*H), 28.8 (CH_2), 27.9 (CH_2), 23.0 (CH_2), 21.0 (CH_3). IR (ATR): ν = 3415, 2953, 2873, 1736, 1716, 1453, 1392, 1367, 1236, 1029, 971 cm^{-1}. GC-MS (initial temp: 70 °C): R_t = 5.77 min; m/z 129 (M^+ − 43, 7.0%), 112 (7.5), 111 (23), 97 (7.3), 94 (22), 93 (14), 91 (6.1), 83 (11), 82 (61), 81 (69), 80 (12), 79 (44), 77 (5.5), 70 (14), 69 (7.0), 68 (25), 67 (79), 66 (5.6), 61 (17), 57 (13), 55 (14), 54 (14), 53 (8.5), 44 (11), 43 (100), 41 (22), 39 (11). HRMS (EI) m/z: $[M]^+$ Calcd for $C_9H_{16}O_3$ 172.1099; found, 172.1101.

(*1R,2S*)-2-(Hydroxymethyl)cyclopentyl)methyl Acetate *ent*-8. A solution of *meso*-diol 7 (1.99 g, 15.4 mmol) in dry CH_2Cl_2 (30 mL) at room temperature was treated with triethylamine (8.5 mL, 61.5 mmol), 4-dimethylaminopyridine (0.38 g, 3.1 mmol), and acetic anhydride (3.6 mL, 38.4 mmol). The mixture was stirred at room temperature for 1 h, then it was treated with saturated aq $NaHCO_3$ solution (80 mL), and extracted with CH_2Cl_2 (100 + 50 +50 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with PE–Et_2O (from 3:1 to 2:1) to give the diacetate[19−21] (3.20 g, 97%) as an oil. A suspension of this diacetate (2.61 g, 12.18 mmol) in THF (8.7 mL) was treated with 1 M pH 7 phosphate buffer (K_2HPO_4/KH_2PO_4) (87 mL), at 20 °C, and then with Amano PS lipase (550 mg). The suspension was stirred at 20 °C for 21 h. The mixture was saturated with NaCl, diluted with AcOEt, and filtered through a Celite cake, washing thoroughly with AcOEt. The phases were separated and the organic phase dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with PE–Et_2O (1:1 to 1:2) to give *ent*-**8** (1.68 g, 80%, e.e. 95%) as an

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

oil. $[\alpha]_D$ −7.20 (c = 2.27, $CHCl_3$). Lit.: −8.2.[21] The other spectroscopic data were identical to those of enantiomer **8**.

Determination of e.e. Values of 8 and *ent*-8. A solution of monoacetate **8** (4.0 mg, 23.8 μmol) in dry CH_2Cl_2 (1 mL) was cooled to 0 °C and treated with DMAP (5.8 mg, 47.6 μmol) and (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (6.7 μL, 35.7 μmol). The mixture was allowed to reach room temperature for 50 min, then it was concentrated. The crude was purified by preparative TLC (PE−Et_2O 2:1) to give the corresponding Mosher ester as an oil (7 mg, 0.025 mmol, 76%). ^1H NMR analysis allowed determination of e.e. values through integration of CH_2OCO signals.

(2*S*,1′*R*,2′*R*) and (2*R*,1′*R*,2′*R*) 2-(2-(Acetoxymethyl)-cyclopentyl)-*N*-butyl-2-(*N*-(4-methoxybenzyl)propionamido)-acetamides 10a,b. To a solution of DMSO (0.62 mL, 8.70 mmol) in dry CH_2Cl_2 (20 mL), at −70 °C under nitrogen atmosphere, a solution of oxalyl chloride in dry CH_2Cl_2 (1.43 M, 4.5 mL) was added. The solution was stirred for approximately 10 min, until effervescence ceased. A solution of *ent*-**8** (0.60 g, 3.48 mmol) in dry CH_2Cl_2 (10 + 4 mL) was added dropwise, and the solution was stirred for 10 min at −70 °C. *N*,*N*-Diisopropylethylamine (2.80 mL, 16.35 mmol) was then added, and the solution was stirred for 2 h at −70 °C and 1.5 h at −50 °C. After this time, the reaction mixture was poured into a mixture of 5% aq $(NH_4)H_2PO_4$ (70 mL) and 1 M HCl (5 mL) (final pH 4) and extracted with CH_2Cl_2 (100 + 30 mL). The organic layer was washed with saturated aq $NaHCO_3$ solution (20 mL), water (2 × 20 mL), and brine (20 mL), dried (Na_2SO_4), and concentrated. The resulting crude aldehyde *ent*-**9** was at once taken up in trifluoroethanol (7 mL) and treated with freshly activated 4 Å powdered molecular sieves (87 mg), *p*-methoxybenzylamine (644 μL, 4.93 mmol), propionic acid (315 μL, 4.22 mmol), and *n*-butylisocyanide (441 μL, 4.22 mmol). The reaction mixture was stirred at room temperature for 48 h, then the molecular sieves were filtered away and the solvent evaporated. The residue was eluted from a column of silica gel with PE−AcOEt (4:1 → 1:1) to give **10a,b** (1.14 g, 73%) as a 54:46 mixture of diastereoisomers (HPLC analysis; Synergi Hydro-RP 150 × 3 mm, 4 μm, temp 21 °C, flow = 0.4 mL/min, mobile phase H_2O/CH_3CN from 90:10 to 0:100 in 30 min. R_t (**a**) = 20.52 min, (**b**) = 21.08 min). Note that the relative configuration has not been assigned at this level. Therefore, we do not know if **10a** is the precursor of **11a** or of **11b**. R_f = 0.18 (PE−Et_2O 1:2) (the two diastereomers were not separated); ^1H NMR ($CDCl_3$, 25 °C): δ = 7.04 (*a*+*b*) (dd, *J* = 8.4 (o), 4.8 (m) Hz, 2 H, Ar*H*), 6.82 (*a*+*b*) (dd, *J* = 8.4 (o), 2.7 (m) Hz, 2 H, Ar*H*), 6.50 (*a*+*b*) (broad s, 1 H, N*H*), 4.68 and 4.53 (*a*+*b*) (AB syst., *J* = 17.1 Hz, 2 H, CH_2-PMB), 4.61−4.46 (*a*+*b*) (m, 1 H, C*H*-N), 4.04 and 4.90 (*a*) (AB part of ABX syst., J_{AB} = 12.9, J_{AX} = 4.8, J_{BX} = 7.2 Hz, 1 H, CH_2-OAc), 3.87 and 3.70 (*b*) (AB part of ABX syst., J_{AB} = 10.8, J_{AX} = 4.5, J_{BX} = 8.4 Hz, 1 H, CH_2-OAc), 3.79 (*a*) (s, 1.5 H, OMe), 3.78 (*b*) (s, 1.5 H, OMe), 3.23−2.97 (*a*+*b*) (m, 2 H, CH_2NH), 2.57 (*a*+*b*) (center of m, 1 H, *H*-1), 2.47−2.19 (*a*+*b*) (m, 2 H, $COCH_2CH_3$), 2.06 (*a*) (s, 1.5 H, $COCH_3$), 2.02 (*b*) (s, 1.5 H, $COCH_3$), 1.91 (*a*+*b*) (center of m, 1 H, *H*-2), 1.87−1.45 (*a*+*b*) (m, 6 H, *H*-3, *H*-4, *H*-5), 1.50−1.38 (*a*+*b*) (m, 2 H, CH_2CH_2NH), 1.34−1.25 (*a*+*b*) (m, 2 H, $CH_2CH_2CH_2NH$), 1.10 (*a*) (t, *J* = 7.5 Hz, 1.5 H, $COCH_2CH_3$), 1.09 (*b*) (t, *J* = 7.5 Hz, 1.5 H, $COCH_2CH_3$), 0.91 (*a*+*b*) (t, *J* = 7.2 Hz, 3 H, $CH_3CH_2CH_2CH_2NH$). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 176.7 and 176.6 (*a*+*b*) (*C*O), 171.2 and 171.1 (*a*+*b*) (*C*=O), 170.1 and 169.9 (*a*+*b*) (*C*=O), 158.8 (*a*+*b*) (Cq), 129.2 and 129.1 (*a*+*b*) (Cq), 127.7, 127.4, 114.0, and 113.9 (*a*+*b*) (aromatic CH), 67.3 (*a*+*b*) (CH_2−OAc), 62.7 (*a*+*b*) (CH−N), 55.3 (*a*+*b*) (OMe), 48.9 (*a*+*b*) (CH_2−PMB), 41.9 (*a*) (*C*-2), 40.3 (*b*) (*C*-1), 39.8 and 39.7 (*a*+*b*) (*C*-2), 39.0 (*a*+*b*) (CH_2NH), 31.4 (*a*+*b*) (CH_2CH_2NH), 29.8, 29.6, 29.4, and 29.3 (*a*+*b*) (*C*-3 and *C*-5), 27.52 and 27.48 (*a*+*b*) ($COCH_2CH_3$), 24.5 and 24.2 (*a*+*b*) (*C*-4), 21.1 and 21.0 (*a*+*b*) ($COCH_3$), 20.1 (*a*+*b*) ($CH_2CH_2CH_2NH$), 13.8 (*a*+*b*) ($CH_3CH_2CH_2CH_2NH$), 9.6 and 9.5 (*a*+*b*) ($COCH_2CH_3$). IR (ATR): ν = 3312, 2955, 2872, 1737, 1675, 1625, 1586, 1540, 1513, 1462, 1416, 1364, 1303, 1232, 1175, 1110, 1080, 1031, 973, 808, 738, 605 cm^{-1}. HRMS (EI) *m*/*z*: $[M]^+$ Calcd for $C_{25}H_{38}N_2O_5$ 446.2781; found, 446.2780.

(2*S*,1′*R*,2′*R*) and (2*R*,1′*R*,2′*R*) *N*-Butyl-2-(2-(hydroxymethyl)-cyclopentyl)-2-(propionamido)acetamides 11a and 11b. To a solution of **10a,b** (0.60 g, 1.34 mmol) in CH_3CN-H_2O (3:1, 16 mL) at room temperature was added CAN (ceric ammonium nitrate) (2.95 g, 5.37 mmol). The reaction mixture was stirred at room temperature for 1 h, then diluted with H_2O (25 mL). After evaporation of most of the CH_3CN, the aqueous phase was extracted with AcOEt (100 + 40 mL), washed with saturated aq Na_2CO_3 (25 mL) and with brine (25 mL), dried (Na_2SO_4), and concentrated. This crude was taken up in MeOH (8 mL) and added, at room temperature, with KOH (0.11 g, 2.01 mmol). The reaction mixture was stirred at room temperature for 1 h, then treated with saturated aq NH_4Cl solution (30 mL). After evaporation of most of the MeOH, the pH was adjusted to 5−6 by the addition of 1 M HCl solution, and the aqueous phase was extracted with AcOEt (100 + 50 mL), washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with PE−AcOEt (1:1 → 0:1) containing 1% of MeOH to give **11a,b** (315 mg, 83%) as a mixture of diastereoisomers. Analytical samples of pure diastereomers were obtained by careful chromatography with AcOEt−MeOH 99:1.

***11a* (White Solid).** R_f = 0.26 (AcOEt−MeOH 99:1). Mp = 164.5−167.0 °C. $[\alpha]_D$ +19.9 (*c* = 1.22, MeOH). ^1H NMR (DMSO-d_6, 40 °C): δ = 7.84 (t, *J* = 5.4 Hz, 1 H, N*H*Bu), 7.71 (d, *J* = 8.4 Hz, 1 H, N*H*-CH), 4.58 (t, *J* = 4.8 Hz, 1 H, O*H*), 4.07 (t, *J* = 8.4 Hz, 1 H, NH−C*H*), 3.35−3.16 (m, 2 H, CH_2OH), 3.15−2.92 (m, 2 H, NHCH_2), 2.12 (m, 2 H, CH_2 of Et), 1.84 (center of m, 2 H, *H*-2, *H* −1), 1.64−1.22 (m, 10 H, *H*-3, *H*-4, *H*-5, 2 CH_2 of Bu), 0.99 (t, *J* = 7.5 Hz, 3 H, $COCH_2CH_3$), 0.87 (t, *J* = 6.9 Hz, 3 H, CH_3 of Bu). ^{13}C NMR (DMSO-d_6, 40 °C): δ = 172.4, 170.9 (*C*O), 64.6 (CH_2−OH), 55.9 (*C*H-NH), 43.7 and 43.5 (*C*-1 and *C*-2), 37.9 (CH_2NH), 30.9 (CH_2CH_2NH), 29.4 and 29.0 (*C*-3 and *C*-5), 28.2 ($COCH_2CH_3$), 24.2 (*C*-4), 19.3 ($CH_2CH_2CH_2$NH), 13.4 ($CH_3CH_2CH_2CH_2$NH), 9.7 ($COCH_2CH_3$). IR (ATR): ν = 3396, 3281, 3096, 2936, 2869, 1633, 1541, 1462, 1367, 1340, 1275, 1229, 1179, 1152, 1121, 1056, 1023, 947, 892, 783, 711, 636 cm^{-1}. HRMS (EI) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{28}N_2O_3$ 284.2100; found, 284.2096.

***11b* (White Solid).** R_f = 0.33 (AcOEt−MeOH 99:1). Mp = 187.0−189.9 °C; $[\alpha]_D$ −29.80 (*c* = 1.00, MeOH). ^1H NMR (DMSO-d_6, 40 °C): δ = 7.80 (t, *J* = 5.4 Hz, 1 H, N*H*Bu), 7.69 (d, *J* = 8.7 Hz, 1 H, N*H*-CH), 4.35 (t, *J* = 4.9 Hz, 1 H, O*H*), 4.26 (dd, *J* = 8.7, 6.9 Hz, 1 H, NH−C*H*), 3.33 (dt, *J* = 10.2 (d), 4.9 (t) Hz, 1 H, CH_2−OH), 3.18 (ddd, *J* = 10.2, 7.2, 4.9 Hz, 1 H, CH_2−OH), 3.04 (m center, 2 H, NH−CH_2), 2.15 (m, 2 H, CH_2CO), 1.89 (quintuplet, *J* = 6.9 Hz, 1 H, *H*-1), 1.83−1.74 (m, 1 H, *H*-2), 1.66−1.21 (m, 10 H, *H*-3, *H*-4, *H*-5, 2 CH_2 of Bu), 0.99 (t, *J* = 7.5 Hz, 3 H, $COCH_2CH_3$), 0.87 (t, *J* = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR (DMSO-d_6, 40 °C): δ = 172.6, 170.9 (CO), 63.7 (CH_2−OH), 54.3 (CH-NH), 43.6 (*C*-1), 42.8 (*C*-2), 37.9 (CH_2NH), 30.9 (CH_2CH_2NH), 29.0 and 28.1 (*C*-3 and *C*-5), 28.2 ($COCH_2CH_3$), 23.8 (*C*-4), 19.3 ($CH_2CH_2CH_2$NH), 13.4 ($CH_3CH_2CH_2CH_2$NH), 9.8 ($COCH_2CH_3$). IR (ATR): ν = 3404, 3280, 3096, 2958, 2936, 2863, 1631, 1540, 1461, 1387, 1365, 1314, 1277, 1231, 1212, 1152, 1118, 1073, 1058, 1025, 950, 917, 897, 864, 788, 721, 633 cm^{-1}. HRMS (EI) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{28}N_2O_3$ 284.2100; found, 284.2097.

(1*R*,3a*R*,6a*R*)- and (1*S*,3a*R*,6a*R*)-*N*-Butyl-2-propionyloctahydrocyclopenta[*c*]pyrrole-1-carboxamides 12a and 12b. To a solution of **11a,b** (100 mg, 0.35 mmol) in dry DMF (1.5 mL) at 0 °C, 1,1′-sulfonyldiimidazole (0.104 g, 0.53 mmol) and sodium hydride (60%, dispersion in mineral oil, 21 mg, 0.52 mmol) were added. The mixture is stirred for 2 h at 0 °C, then treated with saturated aq NH_4Cl solution (15 mL) and extracted with AcOEt (50 mL × 2). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with AcOEt−MeOH 99:1 to give **12a** (37 mg) and **12b** (39 mg) (81% overall yield). Cyclization carried out on separated **11a** and **11b** showed that **11a** gives **12a**, whereas **11b** gives **12b**.

***12a* (Oil).** R_f = 0.21 (AcOEt−MeOH 99:1). $[\alpha]_D$ +77.40 (*c* = 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 25 °C) (82:18 mixture of rotamers *M* and *m*): δ = 6.43 (*M*) (br t, *J* = 5.1 Hz, 1 H, N*H*Bu), 6.06 (*m*) (br t, *J* = 5.1 Hz, 1 H, N*H*Bu), 4.18 (*m*) (dd, *J* = 10.8, 6.0 Hz, 1 H, *H*-3), 3.83 (*m*) (d, *J* = 9.9 Hz, *H*-1), 3.78 (*M*) (d, *J* = 10.2 Hz, 1 H, *H*-1), 3.64 (*M*)

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

(dd, J = 9.3, 6.3 Hz, *H*-3), 3.38−3.17 (*M*+*m*) (m, 2 H, NHCH_2), 3.19 (*M*) (dd, J = 9.3, 11.1 Hz, 1 H, *H*-3), 2.93 (*m*) (t, J = 10.5 Hz, 1 H, *H*-3), 2.30 (*M*+*m*) (q, J = 7.5 Hz, 2 H, CH_2CO), 2.32−2.20 (*M*) (m, 1 H, *H*-6a), 2.19−2.06 (*M*+*m*) (m, 2 H, *H*-4 or *H*-6), 1.97−1.68 (m, 3 H, *H*-4 or *H*-6 (*M*+*m*), *H*-6a (*m*), *H*-3a (M)), 1.55−1.23 (*M*+*m*) (m, 6 H, 2 CH_2 of Bu, *H*-5), 1.13 (*M*+*m*) (t, J = 7.5 Hz, 3 H, COCH$_2$CH_3), 0.93 (*m*) (t, J = 7.2 Hz, 3 H, CH_3 of Bu), 0.92 (*M*) (t, J = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 25 °C) (82:18 mixture of rotamers *M* and *m*): δ = 174.8 (*m*) (*C*O), 173.6 (*M*) (*C*O), 171.7 (*m*) (*C*O), 171.1 (*M*) (*C*O), 64.3 (*m*) (*C*-1), 62.5 (*M*) (*C*-1), 59.0 (*m*) (*C*-6a), 54.6 (*M*) (*C*-6a), 50.3 (*M*) (*C*-3a), 50.1 (*M*) (*C*-3), 49.5 (*m*) (*C*-3a), 48.9 (*m*) (*C*-3), 39.3 (*M*) (CH$_2$NH), 39.1 (*m*) (CH$_2$NH), 31.6 (*m*) (CH$_2$CH$_2$NH), 31.5 (*M*) (CH$_2$CH$_2$NH), 28.0 (*M*+*m*) (COCH$_2$CH$_3$), 28.3, 24.2, and 23.7 (*M*) (*C*-4, *C*-5 and *C*-6), 26.8, 24.5, and 23.8 (*m*) (*C*-4, *C*-5 and *C*-6), 20.0 (*M*+*m*) (CH$_2$CH$_2$CH$_2$NH), 13.73 (*M*) (COCH$_2$CH$_3$), 13.67 (*m*) (COCH$_2$CH$_3$), 9.0 (*M*) (CH$_3$CH$_2$CH$_2$CH$_2$NH), 8.9 (*m*) (CH$_3$CH$_2$CH$_2$CH$_2$NH). GC-MS (initial temp: 70 °C): R_t = 10.03 min; *m*/*z* 266 (M^+, 1.7%), 167 (24), 166 (50), 111 (9.5), 110 (100), 81 (9.2), 68 (58), 57 (14), 41 (8.6). IR (ATR): ν = 3294, 3096, 2956, 2934, 2871, 1643, 1558, 1460, 1432, 1374, 1310, 1244, 1204, 1181, 1164, 1150, 1115, 1078, 1021, 985, 945, 915, 811, 745, 691, 616 cm^{-1}. HRMS (EI) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{26}N_2O_2$ 266.1994; found, 266.1988.

12b *(White Solid).* R_f = 0.41 (AcOEt−MeOH 99:1). Mp 113.3−114.7 °C. $[\alpha]_D$ +1.44 (c = 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 25 °C) (68:32 mixture of rotamers *M* and *m*): δ = 6.35 (*M*) (br t, J = 5.1 Hz, 1H, N*H*Bu), 6.11 (*m*) (br t, J = 5.1 Hz, 1H, N*H*Bu), 4.38 (*M*) (d, J = 7.8 Hz, 1H, *H*-1), 4.27 (*m*) (d, J = 7.8 Hz, 1 H, *H*-1), 3.82 (*m*) (dd, J = 11.1, 6.6 Hz, 1 H, *H*-3), 3.68 (*M*) (dd, J = 9.3, 6.9 Hz, 1 H, *H*-3), 3.32−3.12 (*M*+*m*) (m, 2 H, NH−CH_2), 2.97 (*M*+*m*) (dd, J = 9.3, 10.5 Hz, 1 H, *H*-3), 2.57 (*M*) (qt, J = 11.8 (q), 5.9 (t) Hz, 1 H, *H*-3a), 2.31 (*M*+*m*) (center of m, 2 H CH_2CO), 2.20 (*m*) (center of m, *H*-6a), 2.15−1.65 (m, 5 H, *H*-4 and *H*-6 (M+m), *H*-6a (*M*), *H*-3a (*m*)), 1.56−1.41 (*M*+*m*) (m, 2 H, *H*-5), 1.38−1.19 (*M*+*m*) (m, 2 H, CH_2 of Bu), 1.13 (*M*) (t, J = 7.5 Hz, 3 H, COCH$_2$CH_3), 1.12 (*m*) (t, J = 7.5 Hz, 3 H, COCH$_2$CH_3), 0.93 (*m*) (t, J = 7.2 Hz, 3 H, CH_3 of Bu), 0.87 (*M*) (t, J = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 25 °C) (68:32 mixture of rotamers *M* and *m*): δ = 174.2 (*m*) (*C*O), 173.5 (*M*) (*C*O), 169.5 (*M*) (*C*O), 169.0 (*m*) (*C*O), 61.5 (*m*) (*C*-1), 58.9 (*M*) (*C*-1), 54.7 (*m*) (*C*-6a), 53.1 (*M*) (*C*-6a), 49.2 (*M*) (*C*-3), 48.1 (*m*) (*C*-3), 47.7 (*M*) (*C*-3a), 46.2 (*m*) (*C*-3a), 39.1 (*m*) (CH$_2$NH), 39.0 (*M*) (CH$_2$NH), 31.8 (*m*) (CH$_2$CH$_2$NH), 31.6 (*M*) (CH$_2$CH$_2$NH), 27.9 (*M*) (COCH$_2$CH$_3$), 27.6 (*m*) (COCH$_2$CH$_3$), 27.5 and 24.4 (*m*) (*C*-4 and *C*-6), 27.4 and 24.3 (*M*) (*C*-4 and *C*-6), 22.9 (*m*) (CH$_2$CH$_2$CH$_2$NH), 22.0 (*M*) (CH$_2$CH$_2$CH$_2$NH), 20.01 (*m*) (*C*-5), 20.00 (*M*) (*C*-5), 13.7 (*M*) (COCH$_2$CH$_3$), 13.6 (*m*) (COCH$_2$CH$_3$), 8.9 (*m*) (CH$_3$CH$_2$CH$_2$CH$_2$NH), 8.7 (*M*) (CH$_3$CH$_2$CH$_2$CH$_2$NH). GC-MS (initial temp: 70 °C): R_t = 9.98 min. *m*/*z*: 266 (M^+, 1.8%), 166 (54), 111 (8.9), 110 (100), 81 (8.6), 57 (11), 41 (6.7). IR (ATR): ν = 3397, 3281, 3096, 2936, 2869, 1633, 1542, 1462, 1371, 1340, 1313, 1276, 1229, 1180, 1152, 1121, 1057, 1023, 947, 893, 784, 712, 637 cm^{-1}. HRMS (EI) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{26}N_2O_2$ 266.1994; found, 266.1982.

((*1S,2R*)-2-(Azidomethyl)cyclopentyl)methanol 13. A solution of monoacetate **8** (5.75 g, 33.4 mmol) in dry CH_2Cl_2 (80 mL) was cooled to 0 °C and treated with Et_3N (6.0 mL, 43.4 mmol) and methanesulfonyl chloride (3.1 mL, 40.1 mmol). The mixture was allowed to reach room temperature, kept for 1 h at this temperature, then quenched with saturated aq NH_4Cl solution (60 mL) and extracted with CH_2Cl_2 (50 + 100 mL). The combined organic phases were washed with water (60 mL), brine (60 mL), dried (Na_2SO_4), and concentrated to give the crude mesylate (8.35 g) as an oil. R_f = 0.51 (PE−CH_2Cl_2−Et_2O 2:2:1). It was taken up in dry DMF (60 mL), treated with NaN_3 (5.42 g, 83.4 mmol), stirred for 17 h at 90 °C, then diluted with H_2O (100 mL) and extracted with Et_2O (200 + 100 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. This crude azido acetate (6.42 g) was taken up in MeOH (60 mL) at room temperature and added with a 1 M solution of KOH in MeOH (48.5 mL, 48.5 mmol). The reaction mixture was stirred at room temperature for 1 h, then treated with saturated aq NH_4Cl solution (60 mL). After evaporation of most of the MeOH, the pH was adjusted to 5−6 by the addition of 1 M HCl solution, and then the remaining aqueous phase was extracted with AcOEt (2 × 150 mL), washed with brine (40 mL), dried (Na_2SO_4), and concentrated to give crude azidoalcohol **13** (4.92 g, 95% from **8**). This crude product could be used in the next step without further purification. An analytical sample was purified by flash chromatography eluting with 3:1 PE−Et_2O to give **13** as an oil. R_f = 0.20 (PE−Et_2O 3:1). $[\alpha]_D$ +2.69 (c = 1.45, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 3.54−3.67 (m, 2 H, CH_2OH), 3.29 and 3.45 (AB part of an ABX system, J_{AB} = 12.3, J_{AX} = 6.9; J_{BX} = 7.8 Hz, 2 H, CH_2N$_3$), 2.28 (hexuplet, J = 7.2 Hz, *H*-1 or *H*-2), 2.22 (center of m, 1 H, *H*-1 or *H*-2), 1.31−1.90 (m, 7 H). ^{13}C NMR ($CDCl_3$, 25 °C): δ = 63.1 (CH$_2$), 52.6 (CH$_2$), 44.0 (CH), 40.9 (CH), 29.7 (CH$_2$), 27.8 (CH$_2$), 23.1 (CH$_2$). IR ($CHCl_3$): ν = 3673, 3613, 3497, 3040, 2947, 2871, 2391, 2097, 1601, 1446, 1216, 1011, 926, 658 cm^{-1}. GC-MS (initial temp: 70 °C): R_t = 5.44 min; *m*/*z* 126 (M^+ − 29, 1.8%), 96 (10), 95 (5.3), 86 (5.1), 82 (19), 81 (41), 80 (10), 79 (29), 77 (5.7), 70 (9.7), 69 (25), 68 (23), 67 (100), 66 (9.0), 65 (7.8), 59 (68), 57 (20), 56 (73), 55 (25), 54 (37), 53 (21), 46 (15), 43 (18), 42 (14), 41 (84), 40 (8.0), 39 (40). Elemental analysis: found C, 54.3; H, 8.5; N, 26.95%. $C_7H_{13}N_3O$ requires C, 54.17; H, 8.44; N, 27.08%.

(*2R,1′S,2′R*)- and (*2S,1′S,2′R*)-2-(2-(Azidomethyl)-cyclopentyl)-*N*-butyl-2-(propionyloxy)acetamides 15a and 15b. To a solution of DMSO (0.57 mL, 8.05 mmol) in dry CH_2Cl_2 (20 mL), at −78 °C under nitrogen atmosphere, a solution of oxalyl chloride in dry CH_2Cl_2 (1.43 M, 4.70 mL) was added. The solution was stirred for approximately 10 min, until effervescence ceased. A solution of crude **13** (0.50 g, 3.22 mmol) in dry CH_2Cl_2 (2 × 5 mL) was added dropwise, and the solution was stirred for 10 min at −78 °C. Triethylamine (2.10 mL, 15.13 mmol) was then added, and the solution was stirred for 1 h at the same temperature. After this time, the reaction mixture was poured into a mixture of 5% aq $(NH_4)H_2PO_4$ (100 mL) and 1 M HCl (5 mL) (final pH 4) and extracted with Et_2O (2 × 100 mL). The organic layer was washed with saturated aq $NaHCO_3$ solution (80 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and coevaporated with CH_2Cl_2 to have a final solution of crude **14** in ca. 1 mL of CH_2Cl_2. It was diluted with another 6 mL of CH_2Cl_2 and treated, at r.t., with propionic acid (286 μL, 3.86 mmol) and *n*-butylisocyanide (401 μL, 3.86 mmol). The reaction mixture was stirred at room temperature for 16 h, then concentrated. The residue was eluted from a column of silica gel with PE−Et_2O (3:1 → 1:1) to give **15a,b** (938 mg, 88% from **8**) as a 47:53 mixture by NMR analysis. For synthetic purposes, the mixture was used for the next steps. However, through careful chromatography with PE−Et_2O, it was possible to obtain pure analytical samples of the two diastereomers.

15a *(Oil).* R_f = 0.25 (PE−Et_2O 2:1). $[\alpha]_D$ +35.20 (c = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 5.95 (br t, J = 6.0 Hz, 1 H, N*H*Bu), 5.20 (d, J = 6.3 Hz, 1 H, C*H*OCOEt), 3.45 and 3.19 (AB part of a ABX syst., J_{AB} = 12.3, J_{AX} = 6.9, J_{BX} = 8.1 Hz, 2 H, CH_2N$_3$), 3.26 (dt, J = 7.2, 6.0 Hz, 2 H, NH−CH_2), 2.54 (quintuplet, J = 7.2 Hz, 1 H, *H*-1), 2.44 (q, J = 7.5 Hz, 2 H, CH_2CO), 2.33 (sextuplet, J = 6.9 Hz, 1 H, *H*-2), 1.87−1.43 (m, 8 H, *H*-3, *H*-4, *H*-5, CH_2 of Bu), 1.37−1.26 (m, 2 H, CH_2 of Bu), 1.19 (t, J = 7.5 Hz, 3 H, COCH$_2$CH_3), 0.92 (t, J = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 173.4, 169.3 (*C*O), 74.1 (*C*H-NH), 52.1 (CH$_2$−N$_3$), 43.5 (*C*-1), 41.0 (*C*-2), 39.0 (CH$_2$NH), 31.6 (CH$_2$CH$_2$NH), 30.0, 26.2, and 22.7 (*C*-3, *C*-4 and *C*-5), 27.8 (CO*C*H$_2$CH$_3$), 20.0 (CH$_2$CH$_2$CH$_2$NH), 13.7 (CH$_3$CH$_2$CH$_2$CH$_2$NH), 9.0 (COCH$_2$CH$_3$). GC-MS (initial temp: 70 °C): R_t = 10.19 min; *m*/*z* 281 (M^+ − 28, 1.6%), 187 (19), 132 (5.3), 131 (75), 130 (13), 126 (31), 110 (16), 109 (11), 108 (14), 100 (13), 96 (7.7), 82 (7.5), 81 (22), 80 (8.3), 79 (9.0), 74 (7.9), 67 (9.8), 59 (8.9), 58 (8.0), 57 (100), 56 (8.7), 55 (7.0), 41 (18). IR (ATR): ν = 3311, 2959, 2874, 2093, 1744, 1652, 1535, 1459, 1358, 1267, 1168, 1082, 1024, 898, 807, 665 cm^{-1}. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{26}N_4O_3$ 310.2005; found, 310.2009.

15b *(White Solid).* R_f = 0.19 (PE−Et_2O 2:1). Mp = 58.1−59.9 °C. $[\alpha]_D$ −25.10 (c = 1.14, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 5.97 (br t, J = 2.5 Hz, 1 H, N*H*Bu), 4.91 (d, J = 9.3 Hz, 1 H, C*H*OCOEt),

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

3.32 and 3.10 (AB part of an ABX syst., J_{AB} = 12.3, J_{AX} = 6.0, J_{BX} = 8.4 Hz, 2 H, CH_2N_3), 3.27 (dt, J = 7.2, 2.7 Hz, 1 H, NH−CH_2), 3.25 (dt, J = 7.2, 2.1 Hz, 1 H, NH−CH_2), 2.52 (center of m, 1 H, *H*-1), 2.43 (q, J = 7.5 Hz, 2 H, CH_2CO), 2.34 (center of m, 1 H, *H*-2), 1.87−1.56 (m, 5 H, *H*-3, *H*-4, 1 *H*-5), 1.45 (center of m, 2 H, CH_2 of Bu), 1.44−1.27 (m, 3 H, 1 *H*-5 and CH_2 of Bu), 1.18 (t, J = 7.5 Hz, 3 H, $COCH_2CH_3$), 0.92 (t, J = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 173.7, 169.2 (*C*O), 74.7 (*C*H-NH), 51.9 (CH_2−N_3), 43.8 (*C*-1), 40.0 (*C*-2), 39.0 (CH_2NH), 31.5 (CH_2CH_2NH), 29.2, 26.5, and 22.2 (*C*-3, *C*-4 and *C*-5), 27.5 ($COCH_2CH_3$), 20.0 ($CH_2CH_2CH_2$NH), 13.7 ($CH_3CH_2CH_2CH_2$NH), 9.0 ($COCH_2CH_3$). GC-MS (initial temp: 70 °C): R_t = 10.22 min; m/z 265 (M^+ − 44, 2.0%), 187 (5.8), 131 (35), 130 (6.1), 126 (13), 110 (8.1), 108 (7.1), 100 (8.5), 82 (5.6), 81 (17), 80 (5.8), 79 (6.8), 74 (5.7), 67 (8.6), 59 (7.9), 58 (8.0), 57 (100), 56 (7.8), 55 (7.5), 41 (21). IR (ATR): ν = 3306, 3099, 2955, 2872, 2090, 1739, 1652, 1560, 1459, 1443, 1420, 1369, 1353, 1330, 1262, 1179, 1117, 1086, 1065, 1038, 1025, 979, 941, 907, 876, 832, 814, 752, 693, 652, 611 cm^{-1}. HRMS (EI): m/z $[M]^+$ calcd for $C_{15}H_{26}N_4O_3$ 310.2005; found, 310.2009.

(*2R,1′S,2′R*)-*N*-Butyl-2-(hydroxy)-2-(2-(propionamidomethyl)cyclopentyl)acetamides 16a. A stirred solution of **15a** (227 mg, 0.73 mmol) in THF (4 mL) at 60 °C was treated with triphenylphosphine (211 mg, 0.81 mmol) and, after 1 h, with H_2O (0.4 mL). The reaction mixture was stirred at 60 °C for 6 h, then concentrated. The residue was eluted from a column of silica gel with CH_2Cl_2−MeOH (25:1 → 10:1) to give **16a** (177 mg, 85%) as an amorphous solid. R_f = 0.32 (CH_2Cl_2−MeOH 20:1). $[\alpha]_D$ +24.30 (c = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 7.32 (br t, J = 4.8 Hz, 1 H, N*H*COEt), 7.09 (br t, J = 5.7 Hz, 1 H, N*H*-Bu), 4.90 (d, J = 5.7 Hz, 1 H, O*H*), 4.18 (t, J = 5.4 Hz, 1 H, C*H*OH), 3.48 (ddd, J = 13.8, 8.4, 5.7 Hz, 1 H, C*H*H-NHCOEt), 3.30 (dt, J = 13.2 (d), 6.9 (t) Hz, 1 H, NHC*H*$_2$-Pr), 3.23 (dt, J = 13.2 (d), 6.9 (t) Hz, 1 H, NHC*H*$_2$-Pr), 3.11 (dt, J = 13.8 (d), 4.8 (t) Hz, 1 H, C*H*H-NHCOEt), 2.26 (center of m, 2 H, *H*-1 and *H*-2), 2.18 (q, J = 7.5 Hz, 2 H, CH_2CO), 1.83−1.29 (m, 10 H, *H*-3, *H*-4, *H*-5, 2 CH_2 of Bu), 1.12 (t, J = 7.5 Hz, 3 H, $COCH_2CH_3$), 0.93 (t, J = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 174.8, 174.7 (*C*O), 71.1 (*C*H−OH), 45.9, 40.9 (*C*-1 and *C*-2), 41.1 (CH_2NHCOEt), 38.9 (Pr-CH_2NH), 31.55 (CH_2CH_2NH), 31.48, 25.2, and 22.7 (*C*-3, *C*-4 and *C*-5), 29.7 ($COCH_2CH_3$), 20.0 ($CH_2CH_2CH_2$NH), 13.7 ($CH_3CH_2CH_2CH_2$NH), 9.9 ($COCH_2CH_3$). GC-MS (initial temp: 70 °C): R_t = 11.17 min; m/z 284 (M^+, 8.0%), 184 (40), 156 (11), 155 (30), 154 (7.3), 131 (29), 128 (13), 126 (21), 111 (21), 110 (49), 100 (16), 98 (7.3), 94 (5.8), 93 (11), 91 (6.1), 87 (43), 86 (15), 81 (13), 79 (7.2), 75 (5.2), 74 (100), 72 (5.1), 70 (5.8), 69 (5.5), 67 (14), 59 (5.2), 58 (9.7), 57 (62), 56 (10), 55 (14), 44 (12), 43 (7.5), 41 (25), 39 (6.0). IR (ATR): ν = 3370, 3309, 2957, 2939, 2907, 2871, 1642, 1622, 1539, 1453, 1430, 1371, 1313, 1281, 1250, 1223, 1169, 1143, 1091, 1064, 972, 932, 904, 870, 793, 729, 707, 692, 619 cm^{-1}. HRMS (EI): m/z $[M]^+$ calcd for $C_{15}H_{28}N_2O_3$ 284.2100; found, 284.2090.

(*2R,1′S,2′R*)-*N*-Butyl-2-(hydroxy)-2-(2-(propionamidomethyl)cyclopentyl)acetamides 16b. The title compound was prepared from **15b** in 91% yield following the same procedure employed for **16a**. White solid. R_f = 0.32 (CH_2Cl_2−MeOH 20:1). Mp 154.2−160.0 °C; $[\alpha]_D$ −42.44 (c = 0.6, MeOH). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 6.73 (br t, J = 5.7 Hz, 1 H, N*H*-Bu), 6.46 (br t, J = 4.8 Hz, 1 H, N*H*COEt), 4.63 (d, J = 5.4 Hz, 1 H, O*H*), 4.00 (dd, J = 9.3, 5.4 Hz, 1 H, C*H*−OH), 3.28 (center of m, 3 H, 1H of CH_2-NHCOEt and NHC*H*$_2$-Pr), 3.07 (dt, J = 12.6 (d), 6.3 (t) Hz, 1 H, 1H of C*H*$_2$-NHCOEt), 2.30−2.06 (m, 2 H, *H*-1 and *H*-2), 2.20 (q, J = 7.5 Hz, 2 H, CH_2 of Et), 1.79−1.45 (m, 8 H, *H*-3, *H*-4, *H*-5, CH_2 of Bu), 1.43−1.29 (m, 2 H, CH_2 of Bu), 1.14 (t, J = 7.5 Hz, 3 H, $COCH_2CH_3$), 0.93 (t, J = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 174.4, 173.8 (*C*O), 73.0 (*C*H−OH), 47.7, 41.2 (*C*-1 and *C*-2), 40.1 (CH_2NHCOEt), 38.9 (Pr-CH_2NH), 31.6 (CH_2CH_2NH), 29.9, 26.9, and 22.5 (C-3, *C*-4 and *C*-5), 29.7 ($COCH_2CH_3$), 20.1 ($CH_2CH_2CH_2$NH), 13.7 ($CH_3CH_2CH_2CH_2$NH), 9.8 ($COCH_2CH_3$). GC-MS (initial temp: 70 °C): R_t = 11.25 min; m/z 284 (M^+, 5.6%), 210 (6.2), 185 (9.5), 184 (78), 182 (7.4), 156 (8.3), 155 (23), 154 (13), 131 (52), 128 (21), 126 (19), 111 (34), 110 (86), 100 (20), 98 (11), 94 (6.0), 93 (17), 87 (34), 86 (15), 81 (18), 79 (9.6), 77 (5.3), 75 (5.2), 74 (100), 72 (7.4), 70 (7.6), 69 (7.0), 67 (19), 59 (7.1), 58 (12), 57 (86), 56 (15), 55 (19), 53 (5.7), 44 (13), 43 (11), 42 (5.0), 41 (33), 39 (7.2). IR (ATR): ν = 3410, 3324, 3299, 2955, 2872, 2318, 1647, 1625, 1533, 1465, 1454, 1431, 1371, 1341, 1310, 1260, 1227, 1175, 1154, 1110, 1096, 1061, 1037, 903, 731, 699, 655 cm^{-1}. HRMS (EI): m/z $[M]^+$ calcd for $C_{15}H_{28}N_2O_3$ 284.2100; found, 284.2090.

(*1S,3aR,6aS*)-*N*-Butyl-2-propionyloctahydrocyclopenta[*c*]-pyrrole-1-carboxamides 12c. *a. From Pure **16a**.* A solution of **16a** (146 mg, 0.51 mmol) in dry CH_2Cl_2 (5 mL) was cooled to −10 °C and treated with Et_3N (98 μL, 0.71 mmol) and methanesulfonyl chloride (50 μL, 0.65 mmol). The mixture was allowed to reach room temperature during 1 h, and then it was treated with saturated aq NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (50 + 25 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give the crude mesylate (182 mg, quant. yield) as an amorphous solid. It was taken up in dry DMF (4 mL), cooled to 0 °C, and treated with sodium hydride (60% dispersion in mineral oil, 32 mg, 0.80 mmol). The mixture was stirred for 1 h at 0 °C and then treated with saturated aq NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (40 mL × 2). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with AcOEt−MeOH (100:2) to give **12c** (125 mg, 91%) as an oil.

*b. From the Diastereomeric Mixture of **16a** and **16b**.* A 47:53 mixture of **15a,b** (938 mg, 3.02 mmol) was converted into **16a,b** (755 mg, 88%) as described above for the pure diastereomers. Then this mixture was treated exactly under the same conditions employed for the conversion of pure **16a** into **12c** affording, after chromatography, **12c** (504 mg, 71%) plus **12d** (70 mg, 10%).

R_f = 0.52 (AcOEt). $[\alpha]_D$ −116.10 (c = 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C) (84:16 mixture of rotamers *M* and *m*): δ = 6.83 (*M*) (br t, J = 5.1 Hz, 1H, N*H*Bu), 5.97 (*m*) (br t, J = 5.1 Hz, 1 H, N*H*Bu), 4.41 (*M*) (d, J = 1.8 Hz, 1 H, *H*-1), 4.11 (*m*) (d, J = 1.8 Hz, 1 H, *H*-1), 3.66 (*M*) (dd, J = 10.8, 8.4 Hz, 1 H, *H*-3), 3.57 (*m*) (dd, J = 12.6, 6.0 Hz, *H*-3), 3.28−3.12 (*M*+*m*) (m, NH−C*H*$_2$, 3 H, *H*-3), 3.01 (*M*) (tdd, J = 8.4 (d), 7.2 (d), 1.8 (t) Hz, 1 H, *H*-6a), 2.87 (*M*) (ddt, J = 12.3 (d), 8.1 (t), 4.5 (d) Hz, 1 H, *H*-3a), 2.78 (*m*) (center of m, 1 H, *H*-6a), 2.65 (*m*) (center of m, 1 H, *H*-3a), 2.32 (*M*+*m*) (app. octuplet, J = 7.5 Hz, 2 H, C*H*$_2$ of Et), 2.02−1.80 (*M*+*m*) (m, 2 H, 1 H of *H*-4, 1 H of *H*-6), 1.76−1.53 (*M*+*m*) (m, 2 H, *H*-5), 1.53−1.25 (*M*+*m*) (m, 6 H, 1 H of *H*-4, 1 H of *H*-6, 2 CH_2 of Bu), 1.14 (*M*) (t, J = 7.5 Hz, 3 H, $COCH_2CH_3$), 1.13 (*m*) (t, J = 7.5 Hz, 3 H, $COCH_2CH_3$), 0.93 (*m*) (t, J = 7.2 Hz, 3 H, CH_3 of Bu), 0.90 (*M*) (t, J = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 29 °C) (84:16 mixture of rotamers *M* and *m*): δ = 173.7 (*m*) (*C*O), 173.5 (*M*) (*C*O), 171.7 (*M*) (*C*O), 171.3 (*m*) (*C*O), 68.1 (*m*) (*C*-1), 66.1 (*M*) (*C*-1), 53.4 (*M*) (CH_2-3), 52.4 (*m*) (CH_2-3), 50.3 (*m*) (*C*-6a), 44.7 (*M*) (*C*-6a), 42.9 (*M*) (*C*-3a), 40.5 (*m*) (*C*-3a), 39.1 (*m*+*M*) (CH_2NH), 32.8 and 31.6 (*m*) (*C*-4 and *C*-6), 32.5 and 32.2 (*M*) (*C*-4 and *C*-6), 31.5 (*M*+*m*) (CH_2CH_2NH), 27.9 (*M*) ($COCH_2CH_3$), 27.8 (*m*) ($COCH_2CH_3$), 25.7 (*M*) (*C*-5), 25.5 (*m*) (*C*-5), 20.0 (*M*+*m*) ($CH_2CH_2CH_2$NH), 13.7 (*M*+*m*) ($COCH_2CH_3$), 9.1 (*m*) ($CH_3CH_2CH_2CH_2$NH), 8.9 (*M*) ($CH_3CH_2CH_2CH_2$NH). GC-MS (initial temp: 70 °C): R_t = 9.76 min. m/z 266 (M^+, 1.3%), 167 (8.9), 166 (32), 111 (8.9), 110 (100), 81 (5.2), 57 (8.6), 41 (6.2). IR (ATR): ν = 3297, 3083, 2956, 2872, 1626, 1545, 1462, 1424, 1377, 1308, 1230, 1154, 1080, 1024, 811, 751, 664 cm^{-1}. HRMS (EI): m/z $[M]^+$ Calcd for $C_{15}H_{26}N_2O_2$ 266.1994; found, 266.1987.

(*1R,3aR,6aS*)-*N*-Butyl-2-propionyloctahydrocyclopenta[*c*]-pyrrole-1-carboxamides 12d. A solution of **16b** (120 mg, 0.42 mmol) in dry CH_2Cl_2 (4 mL) was cooled to 0 °C and treated with Et_3N (81 μL, 0.58 mmol) and methanesulfonyl chloride (42 μL, 0.54 mmol). The mixture was allowed to reach room temperature for 1 h, then it was treated with saturated aq NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (50 + 25 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give the crude mesylate. It was taken up in dry DMF (4 mL) at 0 °C, and sodium hydride (60% dispersion in mineral oil, 27 mg, 0.68 mmol) was added. The mixture was stirred for 3 h at 0 °C, then treated with saturated aq NH_4Cl solution (30 mL) and extracted with

DOI: 10.1021/jo502829j
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AcOEt (40 mL × 2). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with AcOEt−MeOH (100:2 → 100:5) to give first **12c** (57 mg, 51%) as an oil and then **12d** (21 mg, 19%) as an oil. R_f = 0.40 (AcOEt); $[\alpha]_D$ +87.43 (c = 0.72, $CHCl_3$). ^1H NMR ($CDCl_3$, 29 °C) (64:36 mixture of rotamers *M* and *m*): δ = 6.09 (*m*) (br t, J = 5.1 Hz, 1 H, N*H*Bu), 5.90 (*M*) (br t, J = 5.1 Hz, 1 H, N*H*Bu), 4.51 (*M*) (d, J = 9.0 Hz, 1 H, *H*-1), 4.45 (*m*) (d, J = 9.0 Hz, 1 H, *H*-1), 4.28 (*m*) (dd, J = 12.0, 9.0 Hz, 1 H, *H*-3), 3.78 (*M*) (dd, J = 10.5, 9.0 Hz, 1 H, *H*-3), 3.38−3.17 (*M*+*m*) (m, 3 H, NH−C*H*$_2$, *H*-3 (*M*)), 3.06 (*m*) (quintuplet, J = 8.7 Hz, 1 H, *H*-6a), 3.01−2.60 (*M*+*m*) (m, 3 H, *H*-3 (*m*), *H*-3 (*m*), *H*-7), 2.32 (*M*) (q, J = 7.5 Hz, 2 H, C*H*$_2$ of Et), 2.22 (*m*) (q, J = 7.5 Hz, 2 H, C*H*$_2$ of Et), 1.92−1.25 (*M*+*m*) (m, 10 H, *H*-4, *H*-6, *H*-5, 2 C*H*$_2$ of Bu), 1.13 (*M*) (t, J = 7.5 Hz, 3 H, COCH$_2$C*H*$_3$), 1.10 (*m*) (t, J = 7.5 Hz, 3 H, COCH$_2$C*H*$_3$), 0.92 (*m*) (t, J = 7.2 Hz, 3 H, C*H*$_3$ of Bu), 0.91 (*M*) (t, J = 7.2 Hz, 3 H, C*H*$_3$ of Bu). ^{13}C NMR ($CDCl_3$, 29 °C) (64:36 mixture of rotamers *M* and *m*): δ = 173.8 (*m*) (CO), 172.7 (*M*) (CO), 170.7 (*m*) (CO), 170.4 (*M*) (CO), 64.8 (*m*) (CH-1), 63.6 (*M*) (CH-1), 52.8 (*M*) (CH$_2$-3), 52.1 (*m*) (CH$_2$-3), 48.1 (*m*) (CH-6a), 45.5 (*M*) (CH-6a), 43.9 (*M*) (CH-3a), 41.9 (*m*) (CH-3a), 39.1 (*m*+*M*) (CH$_2$NH), 31.6 (*M*+*m*) (CH$_2$CH$_2$NH), 29.7, 27.8, and 26.6 (*M*) (CH$_2$-4, CH$_2$-5 and CH$_2$-6), 29.4, 27.8, and 26.2 (*m*) (CH$_2$-4, CH$_2$-5 and CH$_2$-6), 27.7 (*M*) (COCH$_2$CH$_3$), 26.9 (*m*) (COCH$_2$CH$_3$), 20.1 (*M*+*m*) (CH$_2$CH$_2$CH$_2$NH), 13.7 (*M*+*m*) (COCH$_2$CH$_3$), 9.0 (*m*) (CH$_3$CH$_2$CH$_2$CH$_2$NH), 8.9 (*M*) (CH$_3$CH$_2$CH$_2$CH$_2$NH). GC-MS (initial temp. 70 °C): R_t = 10.17 min. *m*/*z*: 266 (M^+, 0.9%), 167 (6.9), 166 (29), 111 (8.3), 110 (100), 57 (7.9), 41 (5.1). IR (ATR): ν = 3290, 3079, 2956, 2935, 2872, 1625, 1548, 1463, 1428, 1376, 1310, 1219, 1152, 1082, 1027, 981, 811, 736, 646 cm^{-1}. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{26}N_2O_2$ 266.1994; found, 266.1990.

(*2R,1′S,2′R*)- and (*2S,1′S,2′R*)-2-(2-(Azidomethyl)-cyclopentyl)-2-((*S*)(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)oxy)-*N*-butylacetamides 23a and 23b. To a stirred solution of crude aldehyde **14** (prepared as described for the synthesis of **15a,b**) (2 mL, 0.50 mmol, of a 0.25 M solution in CH_2Cl_2), L-Boc-*tert*-leucine (127 mg, 0.55 mmol) and *n*-butylisocyanide (58 μL, 0.55 mmol) were added. The reaction mixture was stirred at room temperature for 20 h, then concentrated. The residue was eluted from a column of silica gel with PE−Et_2O (3:1 → 1:1) to give **23a,b** (as an oil, 137 mg, 59% from **8**) as a mixture of diastereoisomers (**a**/**b** = 42:58, by NMR analysis). Analytical samples of **23a** and **23b** could be obtained by repeated chromatography. The relative configuration was determined by independent conversion of **23a** into **25a**.

***23a** (Oil).* R_f = 0.61 (PE−Et_2O 1:1). $[\alpha]_D$ +1.58 (c = 0.72, $CHCl_3$). ^1H NMR ($CDCl_3$, 29 °C): δ = 6.90 (br s, 1 H, N*H*Bu), 5.08 (d, J = 8.1 Hz, 1 H, C*H*O), 5.02 (br d, J = 7.5 Hz, 1 H, NHBoc), 3.94 (d, J = 7.5 Hz, 1 H, C*H*NHBoc), 3.74 and 3.17 (AB part of an ABX system, J_{AB} = 12.0, J_{AX} = 9.3, J_{BX} = 5.4 Hz, 2 H, C*H*$_2$N$_3$), 3.37 (center of m, 1 H, NHC*H*H−Pr), 3.02 (center of m, 1 H, NHC*H*H−Pr), 2.35−2.53 (m, 2 H, *H*-1, *H*-2), 1.87−1.45 (m, 8 H, *H*-3, *H*-4, *H*-5, C*H*$_2$ of Bu), 1.43 (s, 9 H, Boc), 1.32 (hexuplet, J = 7.2 Hz, 2 H, C*H*$_2$CH$_3$ of Bu), 1.04 (s, 9 H, *t*Bu), 0.91 (t, J = 7.2 Hz, 3 H, C*H*$_3$ of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 171.8 (CO), 169.1 (CO), 156.3 (CO), 80.7 (Cq), 75.3 (CH−O), 62.8 (CHNHBoc), 51.7 (CH$_2$N$_3$), 44.3 (CH-1), 40.9 (CH-2), 39.0 (NHCH$_2$Pr), 33.3 (Cq), 31.4 (NHCH$_2$CH$_2$CH$_2$CH$_3$), 29.5, 27.8, and 22.4 (CH$_2$-3, CH$_2$-4, CH$_2$-5), 28.2 (Boc), 26.7 (*t*Bu), 20.0 (NHCH$_2$CH$_2$CH$_2$CH$_3$), 13.7 (NHCH$_2$CH$_2$CH$_2$CH$_3$). IR (ATR): ν = 3327, 2961, 2874, 2095, 1750, 1692, 1657, 1526, 1456, 1392, 1366, 1314, 1250, 1206, 1160, 1066, 1033, 1009, 912, 862, 791, 738, 628 cm^{-1}. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{23}H_{42}N_5O_5$ 468.3186; found, 468.3186.

***23b** (Oil).* R_f = 0.51 (PE−Et_2O 1:1). $[\alpha]_D$ −46.70 (c = 0.57, $CHCl_3$). ^1H NMR ($CDCl_3$, 29 °C): δ = 6.42 (br s, 1 H, N*H*Bu), 5.02 (d, J = 8.1 Hz, 1 H, N*H*Boc), 4.97 (br d, J = 8.1 Hz, 1 H, C*H*-O), 4.02 (d, J = 8.1 Hz, 1 H, C*H*NHBoc), 3.44 and 3.10 (AB part of an ABX system, J_{AB} = 12.0, J_{AX}= 9.3, J_{BX} = 5.1 Hz, 2 H, C*H*$_2$N$_3$), 3.25 (center of m, 2 H, NHC*H*$_2$-Pr), 2.56 (dq, J = 10.5, 7.2 Hz, 1 H, *H*-1), 2.34 (center of m, 1 H, *H*-2), 1.83−1.43 (m, 8 H, *H*-3, *H*-4, *H*-5, CH$_2$ of Bu), 1.46 (s, 9 H, Boc), 1.33 (hexuplet, J = 7.2 Hz, 2 H, C*H*$_2$CH$_3$ of Bu), 1.05 (s, 9 H, *t*Bu), 0.91 (t, J = 7.2 Hz, 3 H, C*H*$_3$ of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 171.0 (CO), 168.7 (CO), 156.3 (CO), 80.5 (Cq), 75.6 (CH−O), 62.6 (CHNHBoc), 51.8 (CH$_2$N$_3$), 43.7 (CH-1), 39.9 (CH-2), 39.1 (NHCH$_2$Pr), 33.8 (Cq), 31.4 (NHCH$_2$CH$_2$CH$_2$CH$_3$), 29.3, 26.8, and 22.3 (CH$_2$-3, CH$_2$-4, CH$_2$-5), 28.3 (Boc), 26.8 (*t*Bu), 20.0 (NHCH$_2$CH$_2$CH$_2$CH$_3$), 13.7 (NHCH$_2$CH$_2$CH$_2$CH$_3$). IR (ATR): ν = 3313, 2961, 2874, 2095, 1720, 1660, 1500, 1456, 1392, 1366, 1248, 1210, 1160, 1062, 1035, 1008, 975, 861, 756, 665, 615 cm^{-1}; HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{23}H_{42}N_5O_5$ 468.3186; found, 468.3186.

(*2R,1′S,2′R*)- and (*2S,1′S,2′R*)-2-(2-(Azidomethyl)-cyclopentyl)-*N*-butyl-2-hydroxyacetamides 24a and 24b. To a stirred solution of crude aldehyde **14** (prepared as described for the synthesis of **15a,b**) (1.2 mL, 0.70 mmol, of a 0.6 M solution in CH_2Cl_2) and *n*-butylisocyanide (88 μL, 0.84 mmol) in dry CH_3CN (0.6 mL) was added boric acid (52 mg, 0.84 mmol). The reaction mixture was stirred at room temperature for 48 h, then concentrated. The residue was eluted from a column of silica gel with PE−AcOEt (2:1 → 1:1) to give **24a,b** (119 mg, 67% from **8**) as a mixture of diastereoisomers (**a**/**b** = 59:41, by NMR analysis). By repeated chromatography, it was possible to obtain an analytical sample of **24a**. The relative configuration was determined by independent conversion of **24a** into **25a**.

***24a** (White Solid).* R_f = 0.73 (PE−AcOEt 1:1). Mp = 54.1−55.4 °C. $[\alpha]_D$ +63.10 (c = 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$, 29 °C): δ = 6.62 (br s, 1 H, NH), 4.31 (br m, 1 H, C*H*OH), 3.59 (br m, 1 H, CHO*H*), 3.52 (AB part of ABX syst., J_{AB} = 12.3, J_{AX} = 7.2, J_{BX} = 6.0 Hz, 2 H, C*H*$_2$N$_3$), 3.28 (app. nonuplet, J = 6.6 Hz, 2 H, C*H*$_2$NH), 2.48 (dq, J = 8.4, 2.7 Hz, 1 H, *H*-1), 2.31 (hexuplet, J = 7.5 Hz, 1 H, *H*-2), 1.77 (center of m, 2 H, 1 *H*-3 and 1 *H*-4), 1.63−1.29 (m, 8 H, 1 *H*-3, 1 *H*-4, *H*-5, 2 C*H*$_2$ of Bu), 0.93 (t, J = 7.2 Hz, 3 H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 173.2 (CO), 71.2 (CHOH), 52.8 (CH$_2$N$_3$), 44.2 (CH-1), 41.6 (CH-2), 38.9 (CH$_2$NH), 31.6 (CH$_2$CH$_2$NH), 30.4, 23.8, and 23.6 (CH$_2$-3, CH$_2$-4 and CH$_2$-5), 20.0 (CH$_2$CH$_2$CH$_2$NH), 13.7 (CH$_3$). IR ($CHCl_3$): ν = 3674, 3602, 3413, 2958, 2871, 2402, 2099, 1659, 1514, 1251, 1195, 1110, 1030, 919, 830, 657 cm^{-1}. GC-MS (initial temp: 70 °C): R_t = 9.55 min. *m*/*z*: 254 (M^+, 0.1%), 131 (28), 130 (14), 127 (8.4), 126 (100), 111 (5.3), 109 (11), 108 (5.4), 100 (14), 98 (6.6), 97 (8.0), 96 (8.2), 82 (8.4), 81 (40), 80 (6.5), 79 (16), 74 (14), 72 (5.8), 70 (5.8), 69 (13), 68 (7.5), 67 (19), 59 (27), 58 (19), 57 (41), 56 (15), 55 (18), 54 (5.1), 53 (8.1), 46 (8.6), 44 (9.4), 43 (7.4), 42 (8.9), 41 (40), 39 (9.6). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{22}N_4O_2$ 254.1743; found, 254.1744.

(*2R,1′S,2′R*)- and (*2S,1′S,2′R*)-2-(2-(((*S*)(2-((*tert*-Butoxycarbonyl)amino)-3,3-dimethylbutanoyl)amino)methyl)-cyclopentyl)-*N*-butyl-2-hydroxyacetamides 25a and 25b. *Method A.* To a stirred solution of **23a,b** (40 mg, 85 μmol) in dry THF (1 mL) at 60 °C triphenylphosphine (25 mg, 95 μmol) was added. After 1 h, H_2O (10 μL) was added, and stirring was continued for 4 h. After this time, the solution was cooled to room temperature and treated with Et_3N (2.5 μL, 18 μmol). The reaction mixture was stirred at room temperature for 60 h, then concentrated. The crude product was eluted from a column of silica gel with 1:3 PE−AcOEt to give **25a,b** (11 mg, 29%) as an amorphous solid.

Method B. To a stirred solution of **24a,b** (100 mg, 0.39 mmol) in dry THF (3 mL) at 70 °C, triphenylphosphine (113 mg, 0.43 mmol) was added. After 2 h, H_2O (0.14 mL) was added, and stirring was continued for 3 h. After this time, the solution was cooled to room temperature and treated with *N*-methylmorpholine (NMM) (108 μL, 0.98 mmol), L-Boc-*tert*-leucine (99 mg, 0.43 mmol) and PyBOP ((benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate) (224 mg, 0.43 mmol). The reaction mixture was stirred at room temperature for 60 h, then treated with saturated aq NH_4Cl solution (15 mL), and most of the THF was evaporated. The aqueous phase was extracted with AcOEt (30 mL × 2), washed with saturated aq $NaHCO_3$ solution (30 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with 1:1 PE−AcOEt with 1% MeOH to give **25a,b** (119 mg, 69%) as an amorphous solid. By repeated chromatography, it was

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

possible to obtain an analytical sample of pure **25a**, whose relative configuration was established through independent conversion into **26**.

25a *(White Foam).* $[\alpha]_D$= +29.9 (*c* = 1.14, $CHCl_3$). ^1H NMR ($CDCl_3$, 29 °C): δ = 7.01 (br s, 1 H, NHCH$_2$CH), 6.92 (br t, *J* = 5.7 Hz, 1 H, N*H*Bu), 5.50 (br d, *J* = 9.0 Hz, 1 H, N*H*Boc), 4.64 (d, *J* = 5.1 Hz, 1 H, OH), 4.20 (t, *J* = 4.2 Hz, 1 H, C*H*OH), 3.76 (d, *J* = 9.0 Hz, 1 H, C*H*NHBoc), 3.51 (quintuplet, *J* = 6.3 Hz, 1 H, 1H of NHCH_2CH), 3.16−3.36 (m, 3 H, 1H of NHCH_2CH, NHCH_2-Pr), 2.33 (center of m, 1 H, *H*-1), 2.24 (center of m, 1 H, *H*-2), 1.77−1.28 (m, 10 H, *H*-3, *H*-4, *H*-5, 2 CH_2 of Bu), 1.41 (s, 9 H, Boc), 0.99 (s, 9 H, *t*Bu), 0.92 (t, *J* = 7.2 Hz, 3 H, Ci_3 of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 174.5 (CO), 171.1 (CO), 156.2 (CO), 79.9 (Cq), 71.3 (CHOH), 62.9 (CHNHBoc), 44.4 (CH-1), 41.6 (CH-2), 40.3 (NHCH_2CH), 38.9 (NHCH_2−Pr), 34.2 (Cq), 31.6 (CH_2 of Bu), 30.7, 24.6, and 23.4 (CH_2-3, CH_2-4, CH_2-5), 28.3 (CH_3 of Boc), 26.6 (CH_3 of *t*Bu), 20.0 (CH_2 of Bu), 13.8 (CH_3 of Bu). IR ($CHCl_3$): ν = 3676, 3609, 3426, 2959, 2870, 2393, 1658, 1494, 1367, 1244, 1159, 1068, 907, 661 cm^{-1}. HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{23}H_{43}N_3O_5$ 441.3203; found, 441.3204.

(*1S,3aR,6aS*)-*N*-Butyl-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)octahydrocyclopenta[*c*]pyrrole-1-carboxamide 26. A solution of **25a,b** (83 mg, 0.19 mmol) in dry CH_2Cl_2 (2 mL) was cooled to 0 °C and treated with Et_3N (68 μL, 0.49 mmol) and methanesulfonyl chloride (35 μL, 0.45 mmol). The mixture was allowed to reach room temperature for 2 h, then it was quenched with a saturated aq NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (20 mL × 2). The organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give the crude mesylates (110 mg, **a**/**b** ratio = 58:42) as an amorphous solid. The crude product was taken up in dry DMF (1 mL), cooled at 0 °C, and added with sodium hydride (60% dispersion in mineral oil, 12 mg, 0.30 mmol). After 1 h, the solution was quenched with saturated aq NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (20 mL × 2). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with PE−AcOEt (2:1 → 1:1) to give **26** (41 mg, 51%) as an oil (R_f = 0.66 (PE−AcOEt 1:1)). Further elution gave a mixture of the epimer of **26** and of its mesylate, in 43:57 ratio (15 mg, 9% and 12%, respectively) (R_f = 0.42 (PE−AcOEt 1:1). **26**: $[\alpha]_D$ −93.50 (*c* = 1.28, $CHCl_3$). ^1H NMR ($CDCl_3$, 29 °C): δ = 6.81 (br s, 1 H, N*H*Bu), 5.20 (br d, *J* = 10.1 Hz, 1 H, N*H*Boc), 4.41 (d, *J* = 2.7 Hz, 1 H, *H*-1), 4.31 (d, *J* = 10.1 Hz, 1 H, C*H*NHBoc), 3.78−3.67 (m, 2 H, *H*-3), 3.20 (q, *J* = 7.2 Hz, 2 H, NHCH_2-Pr), 3.03 (center of m, 1 H, *H*-6a), 2.82 (center of m, 1 H, *H*-3a), 1.96−1.81 (m, 2 H, 1 H of *H*-4 and 1 H of *H*-6), 1.74−1.26 (m, 8 H, 1 H of *H*-4, 1 H of *H*-6, *H*-5, 2 CH_2 of Bu), 1.42 (s, 9 H, Boc), 0.98 (s, 9 H, *t*Bu), 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 171.6 (CO), 170.9 (CO), 155.7 (CO), 79.6 (Cq), 66.2 (CH-1), 58.1 (CHNHBoc), 54.3 (CH_2-3), 44.7 (CH-6a), 43.1 (CH-3a), 39.1 (NHCH_2Pr), 35.3 (Cq), 32.3, 31.9 (CH_2-4, CH_2-6), 31.6 (NHCH_2CH_2CH_2CH$_3$), 28.2 (Boc), 26.3 (*t*Bu), 25.5 (CH_2-5), 20.1 (NHCH_2CH_2CH$_2$CH$_3$), 13.7 (NHCH_2CH_2CH$_2$CH$_3$). IR (ATR): ν = 3327, 2956, 2871, 1716, 1683, 1623, 1495, 1437, 1366, 1324, 1230, 1167, 1060, 1006, 889, 857, 753, 664 cm^{-1}. GC-MS (initial temp: 70 °C): R_t = 12.33 min. *m*/*z*: 423 (M$^+$, 0.2%), 158 (5.0), 130 (14), 111 (8.5), 110 (100), 86 (12), 57 (18), 41 (7.2). HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{23}H_{41}N_3O_4$ 423.3097; found, 423.3095.

(*1S,3aR,6aS*)-*N*-Butyl-2-((*S*)-2-((*S*)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-octahydrocyclopenta[*c*]pyrrole-1-carboxamide 27. To a cooled (0 °C) solution of **26** (84 mg, 200 μmol) in CH_2Cl_2 (2 mL) was added dropwise CF_3CO_2H (1 mL). The solution was allowed to reach room temperature during 1 h, then it was concentrated. The solution of the crude trifluoroacetate salt in dry CH_2Cl_2 (2 mL) was treated with *N*-methylmorpholine (NMM) (152 μL, 1.4 mmol), L-Boc-cyclohexylglycine (56 mg, 220 μmol) and PyBOP ((benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate) (124 mg, 240 μmol). The reaction mixture was stirred at room temperature for 3.5 h, then treated with saturated aq NH_4Cl solution (15 mL) and extracted with AcOEt (50 mL × 2), washed with saturated aq $NaHCO_3$ solution (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated. The crude was filtered from a short column of silica gel with PE−AcOEt (2:1 → 3:2) to give the coupling product (101 mg) as an amorphous solid. R_f = 0.62 (PE−AcOEt 1:1). To a cooled (0 °C) solution of the coupling product in CH_2Cl_2 (2 mL) was added dropwise CF_3CO_2H (1 mL). The solution was allowed to reach room temperature in 1 h, then it was concentrated. The solution of the crude trifluoroacetate salt in dry CH_2Cl_2 (2 mL) was treated with NMM (139 μL, 1.24 mmol), pyrazinecarboxylic acid (24 mg, 190 μmol), and PyBOP ((benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate) (112 mg, 220 μmol). The reaction mixture was stirred at room temperature for 2 h, then treated with saturated aq NH_4Cl solution (15 mL) and extracted with AcOEt (50 + 30 mL), washed with saturated aq $NaHCO_3$ solution (20 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. The crude was eluted from a column of silica gel with PE−AcOEt (1:2 → 1:4) to give coupling product **27** (102 mg, 89% from **26**) as an amorphous solid. R_f = 0.28 (PE−AcOEt 1:1). $[\alpha]_D$ −49.50 (*c* = 1.2, MeOH). ^1H NMR ($CDCl_3$, 29 °C): δ = 9.43 (d, *J* = 1.5 Hz, 1 H, H ortho to CO), 8.76 (d, *J* = 2.5 Hz, 1 H, H meta to CO), 8.56 (dd, *J* = 2.5, 1.5 Hz, 1 H, H para to CO), 8.35 (br d, *J* = 9.0 Hz, 1 H, N*H* of cyclohexyl-Gly), 6.76 (br d, *J* = 9.6 Hz, 1 H, N*H* of *t*Leu), 6.68 (br t, *J* = 5.4 Hz, 1 H, N*H*Bu), 4.74 (d, *J* = 9.6 Hz, 1 H, C*H* of *t*Leu), 4.56 (dd, *J* = 9.0, 6.9 Hz, 1 H, C*H* of cyclohexyl-Gly), 4.44 (d, *J* = 2.7 Hz, 1 H, *H*-1), 3.73 (center of m, 2 H, *H*-3), 3.21 (qd, *J* = 6.9, 2.4 Hz, 2 H, NHCH_2-Pr), 3.06 (tdd, *J* = 8.4, 5.7, 2.7 Hz, 1 H, *H*-6a), 2.85 (center of m, 1 H, *H*-3a), 1.91 (center of m, 3 H, C*H* of cyclohexyl-Gly, 1H of CH_2-4, 1H of CH_2-6), 1.76−1.01 (m, 18 H, 10H of cyclohexyl-Gly, CH_2-5, 1H of CH_2-4, 1H of CH_2-6, 2 CH_2 of Bu), 0.97 (s, 9 H, *t*Bu), 0.89 (t, *J* = 7.2 Hz, 3 H, CH_3 of Bu). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 170.7, 170.6, and 162.9 (4 CO), 147.4 (aromatic CH ortho to N and meta to CO), 144.5 (aromatic CH ortho to CO), 144.1 (Cq), 142.7 (aromatic CH ortho to N and para to CO), 66.2 (CH-1), 57.9 (CHNH of cyclohexyl-Gly), 56.6 (CHNH of *t*Leu), 54.6 (CH_2-3), 44.6 (CH-6a), 43.0 (CH-3a), 41.2 (CH of cyclohexyl), 39.2 (NHCH_2−Pr), 35.7 (Cq), 32.5, 32.3 (CH_2-4, CH_2-6), 31.6 (NHCH_2CH_2CH_2CH$_3$), 29.6, 28.7, 26.0, 25.9, 25.8, 25.6 (5 CH_2 of cyclohexyl, CH_2-5), 26.4 (*t*Bu), 20.1 (NHCH_2CH_2CH_2CH$_3$), 13.7 (CH_3 of Bu). IR (ATR): ν = 3320, 2931, 2869, 1656, 1621, 1521, 1446, 1340, 1301, 1232, 1158, 1051, 1020, 843, 756, 739 cm^{-1}. HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{31}H_{49}N_6O_4$ 569.3815; found, 569.3818.

(*S*)-*N*-(1-Hydroxypentan-2-yl)formamide 29. A solution of L-norvalinol **28** (14.90 g, 144.4 mmol) in ethyl formate (75 mL) was refluxed until the complete disappearance of **28**, monitoring the reaction by GC. Ethyl formate was evaporated under reduced pressure, and the residue was purified by crystallization from AcOEt to give **29** (13.30 g, 70%) as a colorless low-melting solid. GC method (HP-1 column, 30 m long, 0.3 mm wide, flow 1 mL/min) (120 °C for 3 min, from 120 to 190 °C at 10 °C/min; from 190 to 250 °C at 30 °C/min): R_t (**28**) = 3.4 min, R_t (**29**) = 6.1 min. The analytical and spectroscopical data were identical to those already reported.[5]

(*S*)-2-Formamidopentyl Benzoate 30. A solution of **29** (4.30 g, 32.8 mmol) in dichloromethane (43 mL) was cooled to −15 °C, and *N*,*N*-di*iso*propylethylamine (6.8 mL, 39.7 mmol) and 4-dimethylaminopyridine (0.20 g, 1.6 mmol) were consecutively added keeping the temperature below −10 °C. Afterward, benzoic anhydride (7.40 g, 32.7 mmol) was added in small portions keeping the temperature below −10 °C. After complete addition, the mixture was stirred overnight at −10 °C. After complete conversion (monitoring by GC using the method detailed in the previous reaction, R_t = 12.8 min), the mixture was cooled to room temperature and quenched with water and saturated aq $NaHCO_3$ solution. The phases were separated, and the organic phase was dried (Na_2SO_4) and filtered. The solution obtained was concentrated under vacuum, and the residue was crystallized from diisopropyl ether to afford **30** (6.96 g, 90%) as a white solid. R_f = 0.61 (CH_2Cl_2−MeOH 10:1 with 1% AcOH). Mp = 68.7−70.0 °C. $[\alpha]_D$ −45.80 (*c* = 2, $CHCl_3$). ^1H NMR ($CDCl_3$, 29 °C) (78:22 mixture of rotamers *M* and *m*): δ = 8.22 (*M*) (br s, 1 H, CHO), 8.12 (*m*) (d, *J* = 11.8 Hz, 1 H, CHO), 8.05−7.97 (*M*+*m*) (m, 4 H, aromatic H), 7.60−7.52 (*M*+*m*) (m, 2 H, aromatic H), 7.48−7.39 (*M*+*m*) (m, 4 H,

DOI: 10.1021/jo502829j
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aromatic H), 5.76 (*M*+*m*) (br m, 2 H, NH), 4.50−4.33 (*M*) (m, 2 H, C*H*NH, CH_2O), 4.32 and 4.23 (*m*) (AB part of ABX syst., J_{AB} = 11.4, J_{AX} = 7.5, J_{BX} = 4.2 Hz, 2 H, CH_2O), 3.76 (*m*) (center of m, 1 H, C*H*NH), 1.68−1.30 (*M*+*m*) (m, 8 H, CH_2CH_2CH_3), 0.97 (*m*) (t, *J* = 7.2 Hz, 3 H, CH_2CH_2CH_3), 0.96 (*M*) (t, *J* = 7.2 Hz, 3 H, CH_2CH_2CH_3). ^{13}C NMR (CDCl_3, 29 °C): δ = 171.2, 166.2 (*m*) (2 *C*O), 166.6 (*M*) (2 *C*O), 164.1 (*m*) (*C*HO), 160.9 (*M*) (*C*HO), 133.4 (*m*) and 133.5 (*M*) (aromatic *C*H), 129.64 (*M*) and 129.59 (*m*) (aromatic *C*H), 128.54 (*m*) and 128.47 (*M*) (aromatic *C*H), 77.2 (*M*+*m*) (*C*O), 67.1 (*m*) and 66.3 (*M*) (*C*H_2O), 51.5 (*m*) and 47.1 (*M*) (*C*HNH), 34.0 (*m*) and 33.7 (*M*) (*C*H_2CH_2CH_3), 19.1 (*M*) and 18.9 (*m*) (CH_2*C*H_2CH_3), 13.8 (*M*) and 13.7 (*m*) (CH_2CH_2*C*H_3). IR (ATR): ν = 3379, 3068, 2955, 2870, 1712, 1657, 1603, 1541, 1465, 1388, 1316, 1284, 1263, 1230, 1176, 1145, 1124, 1097, 1070, 1027, 975, 764, 738, 704, 686, 677 cm^{-1}. GC-MS (initial temp: 70 °C): R_t = 9.17 min. *m*/*z*: 235 (M^+, 0.1%), 113 (23), 106 (5.3), 105 (63), 101 (6.2), 100 (100), 99 (5.5), 85 (7.5), 77 (33), 72 (7.9), 70 (9.1), 58 (20), 55 (5.4), 51 (9.0), 46 (11). HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_3$ 236.1287; found, 236.1288.

(*S*)-2-Isocyanopentyl Benzoate 33. A solution of **30** (37.00 g, 157.9 mmol) in dichloromethane (740 mL) was cooled to −40 °C. Triethylamine (73.16 g, 723.0 mmol) and $POCl_3$ (36.18 g, 236.0 mmol) were successively added, keeping the temperature below −30 °C. After 2 h, the mixture was warmed to room temperature and quenched with saturated aq $NaHCO_3$ solution. The phases were separated, the organic phase was dried (Na_2SO_4), and the solvent was concentrated under vacuum to give isocyanide **33** (quantitative yield) as an orange oil. R_f = 0.84 (PE−AcOEt 2:1). $[\alpha]_D$ +19.50 (*c* = 2, $CHCl_3$). ^{1}H NMR (CDCl_3, 29 °C): δ = 8.12−8.00 (m, 2 H, aromatic H ortho to CO), 7.59 (tt, *J* = 7.5, 1.2 Hz, 1 H, aromatic H para to CO), 7.51−7.42 (m, 2 H, aromatic H meta to CO), 4.44 (dd, *J* = 11.1, 2.1 Hz, 1H, CH*H*O), 4.33 (dd, *J* = 11.1, 7.2 Hz, 1H, CH*H*O), 3.94 (br m, 1 H, *C*HNC), 1.83−1.41 (m, 4 H, CH_2CH_2CH_3), 0.99 (t, *J* = 6.5 Hz, 3 H, CH_2CH_2CH_3). ^{13}C NMR (CDCl_3, 29 °C): δ = 165.9 (*C*O), 157.3 (*C*N-), 133.4 (aromatic *C*H), 129.7 (2 aromatic *C*H), 128.4 (2 aromatic *C*H), 65.3 (*C*H_2O), 53.5 (*C*H-NC), 33.4 (*C*H_2CH_2CH_3), 18.7 (CH_2*C*H_2CH_3), 13.3 (CH_2CH_2*C*H_3). IR ($CHCl_3$): ν = 3933, 3608, 2970, 2891, 2873, 2143, 1721, 1601, 1416, 1389, 1311, 1253, 1239, 1110, 1097, 1066, 1025, 894, 718, 659 cm^{-1}. GC-MS (initial temp: 70 °C): R_t = 7.68 min. *m*/*z*: 216 (M^+, 14%), 160 (23), 148 (7.2), 146 (16), 106 (8.4), 105 (100), 77 (47), 51 (14), 41 (7.1). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{15}NO_2$ 217.1103; found, 217.1109.

(*S*)-1-(Benzyloxy)pentan-2-amine Hydrochloride 31. To a solution of L-norvalinol **28** (5.00 g, 56.1 mmol) in dry THF (60 mL), sodium hydride (60% dispersion in mineral oil, 2.24 g, 56.0 mmol) was added in small portions. The mixture was refluxed, and benzyl chloride (5.7 mL, 49.5 mmol) was added. After complete addition, the mixture was stirred overnight at 70 °C, then cooled to room temperature, quenched with water, and most of the THF was evaporated. The aqueous phase was extracted with CH_2Cl_2 and washed with 1 M HCl (3 times). Then, the aqueous phase was brought to pH 12 by the addition of 10% NaOH solution and extracted with CH_2Cl_2 (3 times). The organic phase was dried (Na_2SO_4) and concentrated. The residue was dissolved in isopropanol, and a solution of HCl in isopropanol was added until pH 2. Then, isopropanol was evaporated under reduced pressure and the residue taken up with acetone. The white solid obtained was filtered and dried to give **31** (6.80 g, 53%). R_f = 0.30 (CH_2Cl_2−MeOH 20:1). Mp 155.3−156.4 °C. $[\alpha]_D$ +9.13 (*c* = 2, MeOH). ^{1}H NMR (DMSO-d_6, 25 °C): δ = 9.19 (br m, 3 H, NH_3), 7.64−7.60 (m, 2 H, aromatic H), 7.44−7.38 (m, 3 H, aromatic H), 4.19 (s, 2 H, CH_2Ph), 3.75 and 3.60 (AB syst., *J* = 12.3 Hz, 2 H, *C*H_2OBn), 2.97 (br s, 1 H, *C*HCH$_2$OBn), 1.69−1.61 (m, 2 H, *C*H_2CH_2CH_3), 1.45−1.18 (m, 2 H, CH_2*C*H_2CH_3), 0.85 (t, *J* = 7.2 Hz, 3 H, CH_2CH_2*C*H_3). ^{13}C NMR (DMSO-d_6, 25 °C): δ = 132.0 (Cq), 130.1 (2 aromatic *C*H), 128.6 (aromatic *C*H), 128.4 (2 aromatic *C*H), 58.21 (*C*H_2Ph), 57.9 (*C*H_2OBn), 47.4 (*C*HNH$_2$), 28.9 (*C*H_2CH_2CH_3), 18.2 (CH_2*C*H_2CH_3), 13.6 (CH_2CH_2*C*H_3). IR (ATR): ν = 3307, 3060, 3044, 2962, 2939, 2897, 2871, 2831, 2639, 1823, 1542, 1501, 1458, 1449, 1437, 1426, 1358, 1335, 1304, 1282, 1229, 1215, 1139, 1098, 1082, 1055, 1039, 1033, 1020, 1003, 993, 936, 925, 898, 887, 813, 801, 746, 702, 636, 619 cm^{-1}. Elemental analysis: found, C, 62.4; H, 8.9; N, 6.0%. $C_{12}H_{20}ClNO$ requires C, 62.73; H, 8.77; N, 6.10%.

(*S*)-(((2-Isocyanopentyl)oxy)methyl)benzene 34. To a solution of **31** (500 mg, 2.17 mmol) in ethyl formate (5 mL), Et_3N (0.67 mL, 4.34 mmol) was added. The mixture was refluxed overnight. Then, ethyl formate was evaporated under reduced pressure, and the residue was washed with water and brine. The organic phase was dried (Na_2SO_4) and concentrated to give formamide **32** as an oil. R_f = 0.27 (PE−AcOEt 1:1). A solution of **32** (1.14 g, 5.1 mmol) in dichloromethane (25 mL) was cooled to −30 °C. Triethylamine (3.3 mL, 23.8 mmol) and $POCl_3$ (0.72 mL, 7.7 mmol) were successively added, keeping the temperature below −30 °C. After 40 min, the mixture was warmed to room temperature and quenched with saturated aq $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (50 mL × 2). The organic phase was dried (Na_2SO_4), and the solvent was concentrated under vacuum. The residue was eluted from a column of silica gel with PE−Et_2O (5:1) to give **34** (925 mg, 88%) as an oil. R_f = 0.53 (PE−Et_2O 5:1). $[\alpha]_D$ −16.40 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (CDCl_3, 29 °C): δ = 7.42−7.28 (m, 5 H, aromatic H), 4.59 (s, 2 H, CH_2Ph), 3.72 (center of m, 1 H, *C*HCN), 3.61−3.45 (m, 2 H, CHCH_2O), 1.69−1.35 (m, 4 H, *C*H_2CH_2CH_3), 0.95 (t, *J* = 7.2 Hz, 3 H, CH_2CH_2CH_3). ^{13}C NMR (CDCl_3, 29 °C): δ = 137.4 (*C*N), 128.5 (2 aromatic *C*H), 127.9 (aromatic *C*H), 127.7 (2 aromatic *C*H), 73.4 (*C*H_2Ph), 71.5 (CH*C*H_2O), 54.5 (*C*H-NC), 33.5 (*C*H_2CH_2CH_3), 18.8 (CH_2*C*H_2CH_3), 13.4 (CH_2CH_2*C*H_3). IR (ATR): ν = 3031, 2961, 2873, 2139, 1739, 1497, 1454, 1364, 1253, 1205, 1105, 1028, 955, 909, 795, 736, 697 cm^{-1}; GC-MS (initial temp: 70 °C): R_t = 7.17 min. *m*/*z*: 203 (M^+, 7.0%), 202 (45), 146 (8.3), 144 (8.9), 134 (9.4), 117 (6.8), 107 (8.8), 105 (12), 92 (9.3), 91 (100), 79 (6.5), 77 (7.3), 65 (15), 55 (5.9), 54 (14), 42 (5.7), 41 (7.6), 39 (6.8). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{17}NO$ 203.1310; found, 203.1308.

(*2R,1′S,2′R*)- and (*2S,1′S,2′R*)-2-(2-(Azidomethyl)-cyclopentyl)-*N*-((*S*)-1-(benzoyloxy)pent-2-yl)-2-hydroxyacetamides 35a and 35b. To a stirred solution of crude aldehyde **14** (prepared as described for the synthesis of **15a,b**) (0.4 mL, 1.2 mmol, of a 2.92 M solution in CH_2Cl_2) and isocyanide **33** (300 mg, 1.4 mmol) in dry CH_3CN (0.5 mL) was added boric acid (85 mg, 1.4 mmol). The reaction mixture was stirred at room temperature for 15 h, then concentrated. The residue was eluted from a column of silica gel with PE−AcOEt (3:1 → 2:1) to give **35a,b** (431 mg, 92% combined yield) as a mixture of diastereoisomers. HPLC analysis: Gemini C6-Phenyl 150 × 3 mm, 3 μm, temp 22 °C, flow = 0.5 mL/min, mobile phase H_2O/CH_3CN = 50:50. R_t = 11.92 min. (**b**), 13.46 min (**a**). **a**/**b** ratio = 66.3:33.7. **35a**: R_f = 0.34 (PE−AcOEt 3:1); **35b**, R_f = 0.23 (PE−AcOEt 3:1). Although the main synthesis was carried out on the diastereomeric mixture, an analytical sample of **35a** (white solid) could be obtained by repeated chromatography. Mp = 136.2−137.8 °C. $[\alpha]_D$ +19.5 (*c* = 2, $CHCl_3$). ^{1}H NMR (CDCl_3, 29 °C): δ = 8.05−8.02 (m, 2 H, 2 aromatic H ortho to CO), 7.57 (tt, *J* = 7.4, 1.4 Hz, 1 H, aromatic H para to CO), 7.45 (center of m, 2 H, 2 aromatic H meta to CO), 6.64 (br d, *J* = 7.5 Hz, 1 H, NH), 4.39−4.27 (m, 4 H, C*H*NH, C*H*OH, CH_2OBz), 3.51 and 3.50 (AB part of an ABX syst., 2 H, J_{AB} = 12.6, J_{AX} = 9.6, J_{BX} = 3.3 Hz, 2 H, C$H_2$$N_3$), 3.30 (center of m, 1 H, OH), 2.45 (dq, *J* = 8.4, 2.7 Hz, 1 H, *H*-1), 2.29 (center of m, 1 H, *H*-2), 1.79−1.33 (m, 10 H, CH_2-3, CH_2-4, CH_2-5, 2 CH_2 of Pr), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR (CDCl_3, 29 °C): δ = 173.0 and 166.6 (2 *C*O), 133.2 (aromatic *C*H para to CO), 129.8 (Cq), 129.7 (2 aromatic *C*H ortho to CO), 128.4 (2 aromatic *C*H meta to CO), 71.4 (*C*HOH), 66.4 (*C*H_2OBz), 52.8 (*C*$H_2$$N_3$), 48.1 (*C*HNH), 44.4 (*C*H-1), 41.6 (*C*H-2), 33.8 (*C*H_2 of Pr), 30.3 (*C*H_2-4), 23.8 and 23.4 (*C*H_2-3, *C*H_2-5), 19.1 (*C*H_2 of Pr), 13.9 (*C*H_3 of Pr). IR (AR): ν = 3441, 3291, 2955, 2935, 2866, 2192, 2095, 1688, 1642, 1603, 1584, 1522, 1457, 1450, 1389, 1342, 1322, 1290, 1181, 1164, 1131, 1077, 1043, 1026, 1002, 965, 932, 896, 848, 806, 743, 709, 687, 679, 629 cm^{-1}. GC-MS (initial temp: 70 °C): R_t = 12.04 min. *m*/*z*: 342 (M^+ − 46, 1.6%), 208 (13), 207 (100), 179 (16), 177 (9.4), 109 (5.5), 108 (6.1), 106 (5.3), 105 (50), 81 (26), 79 (7.3), 77 (27), 67 (11), 54

DOI: 10.1021/jo502829j
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(6.3), 53 (6.6), 51 (5.4), 44 (6.4), 42 (5.3), 41 (18). HRMS (EI): m/z $[M + H]^+$ calcd for $C_{20}H_{29}N_4O_4$ 389.2189; found, 389.2199.

(*2R,1′S,2′R*)-*N*-((*S*)-1-(Benzoyloxy)pent-2-yl)-2-(2-(((*S*)(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)amino)-methyl)cyclopentyl)-2-hydroxyacetamide 36a. To a stirred solution of **35a** (163 mg, 0.42 mmol) in dry THF (4 mL) at 70 °C triphenylphosphine (121 mg, 0.46 mmol) was added. After 1 h, H_2O (160 μL) was added, and stirring was continued for 2 h. Then, the solution was cooled to room temperature, treated with *N*-methylmorpholine (NMM) (184 μL, 1.67 mmol), L-Boc-*tert*-leucine (107 mg, 0.46 mmol), and PyBOP ((benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate) (241 mg, 0.46 mmol). The reaction mixture was stirred at room temperature for 24 h, then quenched with a saturated aq NH_4Cl solution (40 mL), and most of the THF was evaporated. The aqueous phase was extracted with AcOEt (80 + 50 mL), washed with saturated aq $NaHCO_3$ solution (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with 1:1 PE−AcOEt to give **36a** (188 mg, 78%) as an amorphous solid. R_f = 0.46 (PE−AcOEt 1:1). $[\alpha]_D$ +8.47 (c = 1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 8.06−8.01 (m, 2H, 2 aromatic H ortho to CO), 7.57 (tt, J = 7.2, 1.5 Hz, 1 H, aromatic H para to CO), 7.44 (center of m, 2 H, 2 aromatic H meta to CO), 6.96−6.85 (br m, 2 H, N*H*CH and N*H*CH_2), 5.46 (br d, J = 9.0 Hz, 1 H, NHBoc), 4.48 (d, J = 5.1 Hz, 1 H, OH), 4.39−4.27 (m, 3 H, C*H*NH, CH_2OBz), 4.22 (t, J = 5.1 Hz, 1 H, C*H*OH), 3.73 (d, J = 9.0 Hz, 1 H, C*H*NHBoc), 3.49 (dt, J = 13.5 (d), J = 6.3 (t) Hz, 1H, NHC*H*H), 3.22 (dt, J = 13.5 (d), J = 5.1 (t) Hz, 1H, NHC*H*H), 2.29 (center of m, 1 H, *H*-1), 2.19 (center of m, 1 H, *H*-2), 1.68−1.34 (m, 10 H, CH_2-3, CH_2-4, CH_2-5, 2 CH_2 of Pr), 1.41 (s, 9 H, Boc), 0.99 (s, 9 H, *t*Bu), 0.94 (t, J = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 174.3, 171.1, 166.5, and 156.2 (4 CO), 133.1 (aromatic CH para to CO), 129.8 (Cq), 129.7 (2 aromatic CH ortho to CO), 128.4 (2 aromatic CH meta to CO), 79.9 (Cq), 71.4 (CHOH), 66.4 (CH_2OBz), 62.9 (CHNHBoc), 48.1 (CHNH), 44.6 (CH-1), 41.5 (CH-2), 40.3 ($NHCH_2$), 34.1 (CH_2 of Pr), 33.6 (Cq), 30.7 and 23.3 (CH_2-3, CH_2-5), 28.3 (Boc), 26.6 (*t*Bu), 24.6 (CH_2-4), 19.1 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR ($CHCl_3$): ν = 3675, 3607, 3424, 2961, 2870, 2391, 1706, 1662, 1601, 1494, 1367, 1315, 1244, 1164, 1113, 1069, 917, 657 cm^{-1}. HRMS (EI): m/z $[M]^+$ calcd for $C_{31}H_{49}N_3O_7$ 575.3571; found, 575.3577.

(*1S,3aR,6aS*)-*N*-((*S*)-1-(Benzoyloxy)pent-2-yl)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-octahydrocyclopenta[*c*]pyrrole-1-carboxamide 37. *Method A (from Pure **36a**).* A solution of **36a** (99 mg, 0.17 mmol) in dry CH_2Cl_2 (2 mL) was cooled to 0 °C and treated with Et_3N (62 μL, 0.44 mmol) and methanesulfonyl chloride (32 μL, 0.41 mmol). The mixture was allowed to reach room temperature during 1 h, then was quenched with a saturated aq NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (50 + 25 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give the crude mesylate (120 mg, quant. yield) as an amorphous solid. It was taken up in dry DMF (1.8 mL) at 0 °C, and sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol) was added. The mixture was stirred for 1 h at 0 °C, then treated with saturated aq NH_4Cl solution (15 mL) and extracted with CH_2Cl_2 (40 mL × 2). The combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with PE−AcOEt (4:1 → 3:1) to give **37** (79 mg, 78%) as an amorphous solid.

*Method B (from **35a,b**).* A 66.3:33.7 mixture of **35a,b** (306 mg, 0.788 mmol) was converted into **36a,b** (67:33 ratio by NMR) (355 mg, 0.617 mmol, 78%) following the same procedure described for pure **36a**. It was taken up in dry CH_2Cl_2 (7 mL), cooled to 0 °C, and treated with Et_3N (222 μL, 1.65 mmol) and methanesulfonyl chloride (115 μL, 0.147 mmol). The mixture was allowed to reach room temperature during 1 h, then was quenched with a saturated aq NH_4Cl solution (40 mL) and extracted with CH_2Cl_2 (70 + 35 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give the crude mesylates as a diastereomeric mixture (430 mg) and as an amorphous solid. This mesylate was taken up in dry THF (8 mL) and treated with a freshly prepared (from hexamethyldisilazane and 1.6 M *n*BuLi in hexanes) 0.4 M solution of lithium hexamethyldisilazide (LiHMDS) in THF−hexanes (1.54 mL, 0.617 mmol). The solution was stirred at 0 °C for 1 h and then treated with saturated aq NH_4Cl solution (30 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was eluted from a column of silica gel with PE−AcOEt (4:1 → 3:1) to give **37** (216 mg, 63%) as an amorphous solid. The epimer of **37** was not detected, whereas we could isolate 13% of unreacted mesylate of **36b**.

R_f = 0.65 (PE−AcOEt 2:1). $[\alpha]_D$ −24.2 (c = 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 8.09−8.05 (m, 2H, aromatic H ortho to CO), 7.57 (tt, J = 7.5, 1.2 Hz, 1 H, aromatic H para to CO), 7.48−7.42 (m, 2 H, aromatic H meta to CO), 6.85 (br d, J = 8.1 Hz, 1 H, N*H*CH), 5.22 (br d, J = 9.9 Hz, 1 H, N*H*Boc), 4.42−4.26 (m, 5 H, *H*-1, C*H*NHBoc, NHC*H*, CH_2OBz), 3.78−3.67 (m, 2 H, *H*-3), 2.95 (center of m, 1 H, *H*-6a), 2.80 (center of m, 1 H, *H*-3a), 1.89−1.75 (m, 2 H, 1 H of *H*-4 and 1 H of *H*-6), 1.72−1.33 (m, 8 H, 1 H of *H*-4, 1 H of *H*-6, *H*-5, 2 CH_2 of Pr), 1.42 (s, 9 H, Boc), 0.99 (s, 9 H, *t*Bu), 0.91 (t, 3 H, J = 7.2 Hz, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 171.8, 170.9, 166.4, and 155.8 (4 CO), 133.1 (aromatic CH para to CO), 129.9 (Cq), 129.7 (2 aromatic CH ortho to CO), 128.4 (2 aromatic CH meta to CO), 79.6 (Cq), 66.4 (CH-1), 66.2 (CH_2OBz), 58.2 (CHNHBoc), 54.3 (CH_2-3), 48.1 (CHNH), 44.7 (CH-6a), 43.1 (CH-3a), 35.3 (Cq), 33.9 (CH_2 of Pr), 32.1 and 31.8 (CH_2-4, CH_2-6), 28.3 (Boc), 26.3 (*t*Bu), 25.4 (CH_2-5), 19.1 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR ($CHCl_3$): ν = 3970, 3675, 3618, 3425, 3311, 3004, 2957, 2871, 2397, 1705, 1676, 1618, 1492, 1430, 1367, 1316, 1266, 1164, 1111, 1065, 920, 659 cm^{-1}. HRMS (EI): m/z $[M]^+$ calcd for $C_{31}H_{47}N_3O_6$ 557.3465; found, 557.3459.

(*1S,3aR,6aS*)-*N*-((*S*)-1-(benzoyloxy)pent-2-yl)-2-((*S*)-2-((*S*)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)octahydrocyclopenta[*c*]pyrrole-1-carboxamide 38. The title compound was prepared from **37** following the same procedure used to convert **26** into **27**. The crude was purified by flash chromatography eluting with 1:2 PE−AcOEt to give **3** (69 mg, 75% from **37**) as an amorphous solid. R_f = 0.40 (PE−AcOEt 1:2). $[\alpha]_D$ −52.67 (c = 0.96, EtOH). ^{1}H NMR ($CDCl_3$, 40 °C): δ = 9.43 (d, J = 1.5 Hz, 1 H, aromatic H ortho to CO), 8.76 (d, J = 2.5 Hz, 1H, aromatic H ortho to N and meta to CO), 8.55 (dd, J = 2.5, 1.5 Hz, 1H, aromatic H ortho to N and para to CO), 8.36 (br d, J = 9.3 Hz, 1H, NH of cyclohexyl-Gly), 8.06 (center of m, 2 H, aromatic H ortho to CO), 7.59 (tt, J = 7.5, 2.1 Hz, 1H, aromatic H para to CO), 7.45 (center of m, 2 H, aromatic H meta to CO), 6.85 (br d, J = 8.1 Hz, 1H, N*H*CH), 6.75 (br d, J = 9.6 Hz, 1H, NH of *t*Leu), 4.76 (d, J = 9.6 Hz, 1H, C*H* of *t*Leu), 4.55 (dd, J = 9.0, 6.9 Hz, 1H, C*H* of cyclohexyl-Gly), 4.42 (d, J = 2.4 Hz, 1H, *H*-1), 4.39−4.29 (m, 3 H, NHC*H*, CH_2OBz), 3.78−3.67 (m, 2 H, *H*-3), 2.94 (tdd, J = 8.1, 5.4, 2.7 Hz, 1H, *H*-6a), 2.83 (center of m, 1H, *H*-3a), 1.85 (center of m, 3 H, C*H* of cyclohexyl-Gly, 1H of CH_2-4, 1H of CH_2-6), 1.74−1.25 (m, 12 H, 4H of cyclohexyl-Gly, CH_2-5, 1H of CH_2-4, 1H of CH_2-6, 2 CH_2 of Pr), 1.25−0.94 (m, 6H, CH_2 of cyclohexyl-Gly), 0.98 (s, 9 H, *t*Bu), 0.89 (t, J = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 40 °C): δ = 170.7, 170.6, 170.5, 166.5, and 162.9 (5 CO), 147.4 (aromatic CH ortho to N and meta to CO), 144.5 (aromatic CH ortho to CO), 144.1 (Cq), 142.7 (aromatic CH ortho to N and para to CO), 133.2 (aromatic CH of Bz), 129.8 (Cq), 129.7 (2 aromatic CH of Bz), 128.4 (2 aromatic CH of Bz), 66.3 (CH-1 and CH_2OBz), 58.0 (CHNH of cyclohexyl-Gly), 56.6 (CHNH of *t*Leu), 54.6 (CH_2-3), 48.1 (NHCH), 44.9 (CH-6a), 43.0 (CH-3a), 41.2 (CH of cyclohexyl), 35.7 (Cq), 33.9 (CH_2-5), 32.4, 32.2 (CH_2-4, CH_2-6), 29.6 (CH_2 of Pr), 28.7, 26.0, 25.9, 25.8, 25.6 (5 CH_2 of cyclohexyl), 26.4 (*t*Bu), 19.1 (CH_2 of Pr), 13.8 (CH_3 of Pr). IR (ATR): ν = 3319, 2930, 2869, 1659, 1619, 1581, 1519, 1448, 1399, 1369, 1315, 1271, 1158, 1111, 1071, 1050, 1020, 847, 807, 776, 711, 687 cm^{-1}. HRMS (EI): m/z $[M]^+$ calcd for $C_{39}H_{54}N_6O_6$ 702.4105; found, 702.4100.

**(*1S,3aR,6aS*)-2-((*S*)-2-((*S*)-2-Cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-*N*-((*S*)-1-hydroxypent-2-yl)octahydrocyclopenta[c]pyrrole-1-carboxa-

DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428

mide 39. *Method A.* To a solution of **38** (59 mg, 0.08 mmol) in MeOH (2 mL) at room temperature, potassium carbonate (14 mg, 0.10 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, then treated with a saturated aq NH_4Cl solution and extracted with AcOEt. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography eluting with AcOEt-PE (5:1 → 100:0) to give **39** (43 mg, 90%) as an amorphous solid.

Method B. A solution of compound **43** (84 mg, 0.12 mmol) in MeOH/H_2O/AcOH (4 mL:400 μL:80 μL) was treated with 10% Pd/C (24 mg) and hydrogenated at 1 atm and room temperature for 18 h. After filtration of the catalyst and evaporation of the solvent, the crude was taken up in CH_2Cl_2 (2 mL), cooled (0 °C), and treated with CF_3CO_2H (1 mL). The solution was allowed to reach room temperature during 1 h and then concentrated. The solution of the crude trifluoroacetate salt in dry CH_2Cl_2 (4 mL) was treated with *N*-methylmorpholine (NMM) (95 μL, 0.86 mmol), pyrazinecarboxylic acid (17 mg, 0.13 mmol), and PyBOP ((benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate) (77 mg, 0.21 mmol). The reaction mixture was stirred at room temperature for 14 h, then treated with a saturated aq NH_4Cl solution and extracted with AcOEt, washed with saturated aq $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated. The crude was purified by flash chromatography eluting with AcOEt−MeOH 99:1 to give the coupling product **39** (56 mg, 76% from **43**) as an amorphous solid.

$[\alpha]_D$ −59.64 (*c* = 1.00, MeOH). ^{1}H NMR (a mixture of conformers *M*/*m* in 8:1 ratio was observed. Only the signals of the major one are reported) (DMSO-d_6, 29 °C): δ = 9.19 (d, *J* = 1.5 Hz, 1H, aromatic H ortho to CO), 8.90 (d, *J* = 2.4 Hz, 1H, aromatic H ortho to N and meta to CO), 8.76 (dd, *J* = 2.4, 1.5 Hz, 1H, aromatic H ortho to N and para to CO), 8.49 (br d, *J* = 9.0 Hz, 1H, NH of cyclohexyl-Gly), 8.22 (br d, *J* = 9.0 Hz, 1H, NH of *t*Leu), 7.53 (br d, *J* = 8.7 Hz, 1H, NHCH), 4.68 (dd, *J* = 9.0, 6.3 Hz, 1H, CH of cyclohexyl-Gly), 4.56 (t, *J* = 5.4 Hz, 1H, OH), 4.54 (d, *J* = 8.1 Hz, 1H, CH of *t*Leu), 4.18 (d, *J* = 3.3 Hz, 1H, *H*-1), 3.78 and 3.64 (AB part of ABX syst., J_{AB} = 10.5, J_{AX} = 7.8, J_{BX} = 3.6 Hz, 2 H, *H*-3), 3.67 (center of m, 1 H, NHCH), 3.34−3.17 (m, 2 H, CH_2OH), 2.68 (center of m, 1H, *H*-3a), 2.52 (center of m, 1H, *H*-6a), 1.82−0.91 (m, 21 H, CH and 10 CH_2 of cyclohexyl-Gly, CH_2-4, CH_2-5, CH_2-6, 2 CH_2 of Pr), 0.93 (s, 9 H, *t*Bu), 0.82 (t, *J* = 6.6 Hz, 3 H, CH_3 of Pr). ^{13}C NMR (DMSO-d_6, 29 °C): δ = 171.2, 170.3, 168.9, and 161.9 (4 CO), 147.8 (aromatic CH ortho to N and meta to CO), 144.0 (Cq), 143.4 (2 aromatic CH of pyrazine), 65.5 (CH-1), 63.4 (CH_2−OH), 56.3 (CHNH of cyclohexyl-Gly and CHNH of *t*Leu), 54.2 (CH_2-3), 49.9 (NHCH), 46.9 (CH-6a), 42.3 (CH-3a), 40.3 (CH of cyclohexyl), 35.9 (Cq), 33.1, 32.2, 31.9, 29.0, 27.9, 25.7, 25.6, 25.5, 24.7 (CH_2-5, CH_2-4, CH_2-6, CH_2 of Pr, 5 CH_2 of cyclohexyl), 26.3 (*t*Bu), 18.3 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR (ATR): ν = 3319, 2930, 2869, 1656, 1619, 1579, 1520, 1444, 1399, 1369, 1300, 1273, 1204, 1158, 1098, 1051, 1019, 868, 809, 776 cm^{-1}. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{32}H_{50}N_6O_5$ 598.3843; found, 598.3824.

(2*R*,1′*S*,2′*R*)- and (2*S*,1′*S*,2′*R*)-2-(2-(Azidomethyl)-cyclopentyl)-*N*-((*S*)-1-(benzyloxy)pent-2-yl)-2-hydroxyacetamides 40a and 40b. To a solution of alcohol **13** (400 mg, 2.58 mmol) and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) (40 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL), (diacetoxyiodo)benzene (912 mg, 2.82 mmol) was added. After complete reaction (monitored by TLC, 2.5 h), isocyanide **34** (572 mg, 2.82 mmol) in dry CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred at room temperature for 22 h, then concentrated. The residue was dissolved in MeOH (8 mL) at room temperature and treated with KOH (144 mg, 5.16 mmol). The reaction mixture was stirred at room temperature for 1 h, then treated with saturated aq NH_4Cl solution (100 mL) and extracted with CH_2Cl_2 (160 + 100 mL), dried (Na_2SO_4), and concentrated. The crude product was filtered from a short silica column (1:1 PE−AcOEt) to give a mixture of **40a** and **40b** (1.05 g, **a**/**b** ratio = 1:1). The synthesis was continued on the unseparated mixture. However, analytical samples of **40a** and **40b** were obtained by flash chromatography eluting with PE−AcOEt (3:1 → 1:2). The relative configuration was demonstrated by independent conversion of **40a** into **42**.

40a *(Amorphous Solid).* R_f = 0.41 (AcOEt−PE 1:3). $[\alpha]_D$ +16.02 (*c* = 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 7.39−7.26 (m, 5 H, aromatic H of Bn), 6.55 (br d, *J* = 9.0 Hz, 1 H, NH), 4.52 and 4.49 (AB syst., *J* = 12.3 Hz, 2 H, CH_2Ph), 4.30 (dd, *J* = 4.8, 2.4 Hz, 1 H, CHOH), 4.11 (center of m, 1 H, CHNH), 3.51 and 3.49 (AB part of ABX syst., J_{AB} = 12.6, J_{AX} = 7.8, J_{BX} = 6.0 Hz, 2 H, CH_2N_3), 3.48 and 3.47 (AB part of ABX syst., J_{AB} = 9.6, J_{AX} = 3.9, J_{BX} = 3.9 Hz, 2 H, CH_2OBn), 3.41 (d, *J* = 4.8 Hz, 1 H, OH), 2.41 (dq, *J* = 8.1, 2.4 Hz, 1 H, *H*-1), 2.29 (center of m, 1 H, *H*-2), 1.83−1.67 (m, 2 H, 1 H of CH_2-3, 1 H of CH_2-4), 1.63−1.41 (m, 6 H, 1 H of CH_2-3, 1 H of CH_2-4, CH_2-5, CH_2 of Pr), 1.39−1.26 (m, 2 H, CH_2 of Pr), 0.92 (t, *J* = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 172.9 (CO), 138.0 (Cq), 128.4 (2 aromatic CH), 127.7 (aromatic CH), 127.7 (2 aromatic CH), 73.2 (CH_2Ph), 71.6 (CH_2OBn), 71.1 (CHOH), 52.9 (CH_2N_3), 48.7 (CHNH), 44.3 (CH-1), 41.8 (CH-2), 33.9 (CH_2-5), 30.5 (CH_2-3), 23.9 (CH_2 of Pr), 23.7 (CH_2-4), 19.3 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR (ATR): ν = 3361, 3271, 2957, 2936, 2863, 2799, 2082, 1637, 1527, 1497, 1475, 1467, 1451, 1411, 1363, 1336, 1310, 1283, 1270, 1217, 1207, 1151, 1118, 1100, 1076, 1047, 1029, 1018, 992, 963, 951, 925, 915, 906, 806, 743, 700 cm^{-1}. HRMS (EI): *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{31}N_4O_3$ 375.2396; found, 375.2388.

40b *(White Solid).* R_f = 0.20 (AcOEt−PE 1:3). Mp = 44.2−45.8 °C. $[\alpha]_D$ −72.20 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 7.38−7.26 (m, 5 H, aromatic H of Bn), 6.51 (br d, *J* = 9.0 Hz, 1 H, NH), 4.52 and 4.49 (AB syst., *J* = 12.0 Hz, 2 H, CH_2Ph), 4.11 (center of m, 1 H, CHNH), 3.96 (dd, *J* = 8.4, 5.7 Hz, 1 H, CHOH), 3.52 and 3.23 (AB part of ABX syst., J_{AB} = 12.3, J_{AX} = 6.9, J_{BX} = 7.2 Hz, 2 H, CH_2N_3), 3.49 and 3.47 (AB part of ABX syst., J_{AB} = 9.6, J_{AX} = 3.9, J_{BX} = 4.2 Hz, 2 H, CH_2OBn), 3.36 (d, *J* = 5.7 Hz, 1 H, OH), 2.34 (m, 1 H, *H*-2), 2.18 (center of m, 1 H, *H*-1), 1.81−1.46 (m, 8 H, CH_2-3, CH_2-4, CH_2-5, CH_2 of Pr), 1.39−1.24 (m, 2 H, CH_2 of Pr), 0.92 (t, *J* = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 172.8 (CO), 138.0 (Cq), 128.4 (2 aromatic CH), 127.8 (aromatic CH), 127.7 (2 aromatic CH), 73.2 (CH_2Ph), 73.0 (CHOH), 71.5 (CH_2OBn), 52.4 (CH_2N_3), 48.5 (CHNH), 47.2 (CH-1), 40.2 (CH-2), 33.9, 29.4, 26.9, 22.8 (CH_2-3, CH_2-4, CH_2-5, CH_2 of Pr), 19.3 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR (ATR): ν = 3295, 3065, 3032, 2935, 2897, 2862, 2087, 1634, 1551, 1496, 1455, 1361, 1314, 1263, 1235, 1206, 1135, 1103, 1086, 1061, 1028, 1001, 987, 968, 900, 866, 819, 780, 746, 697 cm^{-1}. HRMS (EI): *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{31}N_4O_3$ 375.2396; found, 375.2391.

(2*R*,1′*S*,2′*R*)-*N*-((*S*)-1-(Benzyloxy)pent-2-yl)-2-(2-(((*S*)(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)amino)methyl)-cyclopentyl)-2-hydroxyacetamides 41a,b. To a stirred solution of **40a,b** (966 mg, 2.58 mmol) in dry THF (24 mL) at 70 °C triphenylphosphine (740 mg, 2.82 mmol) was added. After 3 h, H_2O (980 μL) was added, and stirring was continued for 2 h. Then, the solution was cooled to room temperature, treated with *N*-methylmorpholine (NMM) (1.41 μL, 12.88 mmol), L-Boc-*tert*-leucine (654 mg, 2.82 mmol), and PyBOP ((benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate) (1.474 mg, 2.82 mmol). The reaction mixture was stirred at room temperature for 60 h, then quenched with a saturated aq NH_4Cl solution (50 mL), and most of the THF was evaporated. The aqueous phase was extracted with AcOEt (80 + 50 mL), and the organic phase was dried (Na_2SO_4) and concentrated. The crude product was eluted from a column of silica gel with PE−AcOEt (1:1 → 1:2) to give **41a,b** (1.286 g, 89%, **a**/**b** ratio = 47:53 by NMR analysis) as an amorphous solid. The synthesis was continued on the unseparated mixture. However, analytical samples of **41a** and **41b** were obtained by flash chromatography eluting with PE−AcOEt (3:1 → 1:2). The relative configuration was demonstrated by conversion of **41a** into **42**.

41a *(Amorphous Solid).* R_f = 0.54 (PE−AcOEt 1:1). $[\alpha]_D$ +5.80 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 7.38−7.26 (m, 5 H, aromatic H of Bn), 7.00 (br t, *J* = 4.8 Hz, 1 H, NHCH$_2$), 6.80 (br d, *J* = 9.0 Hz, 1 H, NHCH), 5.50 (br d, *J* = 9.0 Hz, 1 H, NHBoc), 4.52 and 4.48 (AB syst, *J* = 12.0 Hz, 2 H, CH_2Ph), 4.43 (br d, *J* = 4.8 Hz, 1 H, OH), 4.20 (dd, *J* = 4.8, 3.6 Hz, 1 H, CHOH), 4.09 (center of m, 1 H, NHCH), 3.75 (d, *J* = 9.0 Hz, 1 H, CHNHBoc), 3.56−3.46 (m, 1H, NHCHH), 3.48 and 3.45 (AB part of ABX syst., J_{AB} = 9.6, J_{AX} = 4.2, J_{BX} = 4.2 Hz, 2 H, CH_2OBn), 3.26 (dt, *J* = 13.8 (d), 5.1 (t) Hz, 1H,

DOI: 10.1021/jo502829j
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NHC*H*H), 2.35−2.18 (m, m, *H*-1, *H*-2), 1.83−1.25 (m, 10 H, CH_2-3, CH_2-4, CH_2-5, 2 CH_2 of Pr), 1.41 (s, 9 H, Boc), 0.99 (s, 9 H, *t*Bu), 0.90 (t, J = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 173.9, 171.0, and 156.2 (3 *C*O), 138.1 (Cq), 128.4 and 127.7 (5 aromatic *C*H of Bn), 79.8 (Cq), 73.1 (CH_2Ph), 71.7 (CH_2OBn), 71.3 (*C*HOH), 62.8 (*C*HNHBoc), 48.6 (*C*HNH), 44.6 (*C*H-1), 41.6 (*C*H-2), 40.3 (NHCH_2), 34.3 (CH_2 of Pr), 33.8 (Cq), 30.8, 24.5, and 23.5 (CH_2-3, CH_2-4, CH_2-5), 28.3 (Boc), 26.6 (*t*Bu), 19.2 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR ($CHCl_3$): ν = 3308, 2957, 2870, 1697, 1642, 1498, 1454, 1365, 1313, 1245, 1166, 1111, 1068, 1029, 1008, 909, 861, 749, 697, 665 cm^{-1}. HRMS (EI): m/z [M]$^+$ calcd for $C_{31}H_{51}N_3O_6$ 561.3778; found, 561.3762.

41b *(Amorphous Solid).* R_f = 0.38 (PE−AcOEt 1:1). $[\alpha]_D$ −38.96 (c = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 7.38−7.26 (m, 5 H, aromatic H of Bn), 6.68 (br s, 1 H, N*H*CH_2), 6.42 (br d, J = 9.0 Hz, 1 H, N*H*CH), 5.28 (br d, J = 9.0 Hz, 1 H, NHBoc), 4.52 and 4.48 (AB syst, J = 12.0 Hz, 2 H, CH_2Ph), 4.17−4.06 (m, 2 H, NHC*H*, OH), 3.96 (dd, J = 9.6, 5.1 Hz, 1 H, *C*HOH), 3.79 (d, J = 9.0 Hz, 1 H, *C*HNHBoc), 3.48 and 3.46 (AB part of ABX syst., J_{AB} = 9.6, J_{AX} = 3.9, J_{BX} = 4.2 Hz, 2 H, CH_2OBn), 3.46 (ddd, J = 13.5, 6.6, 4.5 Hz, 1H, NHC*H*H), 3.15 (dt, J = 13.5 (d), 6.6 (t) Hz, 1H, NHC*H*H), 2.25 (center of m, 1 H, *H*-2), 2.08 (m, 1 H, *H*-1), 1.77−1.25 (m, 10 H, CH_2-3, CH_2-4, CH_2-5, 2 CH_2 of Pr), 1.43 (s, 9 H, Boc), 0.98 (s, 9 H, *t*Bu), 0.91 (t, J = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 173.1, 171.2, 155.8 (3 *C*O), 138.0 (Cq), 128.4 (2 aromatic *C*H), 127.7 (3 aromatic *C*H), 79.6 (Cq), 73.2 (CH_2Ph), 73.1 (*C*HOH), 71.5 (CH_2OBn), 62.5 (*C*HNHBoc), 48.6 (*C*HNH), 47.8 (*C*H-1), 41.2 (*C*H-2), 39.8 (NHCH_2), 34.6 (Cq), 33.9 (CH_2 of Pr), 29.7, 26.9, and 22.5 (CH_2-3, CH_2-4, CH_2-5), 28.3 (Boc), 26.6 (*t*Bu), 19.3 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR ($CHCl_3$): ν = 3307, 2957, 2872, 1697, 1646, 1498, 1454, 1391, 1366, 1314, 1235, 1167, 1094, 1066, 1029, 1007, 907, 860, 751, 697, 665 cm^{-1}. HRMS (EI): m/z [M]$^+$ calcd for $C_{31}H_{51}N_3O_6$ 561.3778; found, 561.3762.

(*1S,3aR,6aS*)-*N*-((*S*)-1-(Benzyloxy)pent-2-yl)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-octahydrocyclopenta[*c*]pyrrole-1-carboxamide 42. A solution of **41a,b** (500 mg, 0.90 mmol) in dry CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with Et_3N (440 μL, 3.20 mmol) and methanesulfonyl chloride (210 μL, 2.70 mmol). The mixture was allowed to reach room temperature in 1 h, then was quenched with a saturated aq NH_4Cl solution (70 mL) and extracted with CH_2Cl_2 (70 + 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to give the crude mesylates (559 mg) as an amorphous solid. R_f (**a**) = 0.59, and R_f (**b**) = 0.49 (PE−AcOEt 1:1). To a solution of these crude mesylates in dry DMF (10 mL) at 0 °C, sodium hydride (60% of a dispersion in mineral oil, 85 mg, 2.12 mmol) was added. The mixture was stirred for 1 h at 0 °C, then treated with saturated aq NH_4Cl solution (75 mL) and extracted with CH_2Cl_2 (80 mL × 2). The combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was eluted from a column of silica gel with PE−AcOEt (4:1 → 3:1) to give **42** (315 mg, 65%) as an amorphous solid and an unseparable mixture of its epimer and the mesylate of **41b** in 94:6 ratio (30 mg). R_f = 0.48 (PE−AcOEt 3:1). $[\alpha]_D$ −85.20 (c = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 7.37−7.25 (m, 5 H, aromatic H of Bn), 6.69 (br d, J = 8.7 Hz, 1 H, N*H*CH), 4.54−4.48 (AB syst., J = 12.0 Hz, 2 H, CH_2Ph), 4.40 (d, J = 2.7 Hz, 1 H, *H*-1), 4.30 (br d, J = 10.2 Hz, 1 H, N*H*Boc), 4.03 (center of m, 1 H, NHC*H*), 3.77−3.66 (m, 2H, *H*-3), 3.46 and 3.44 (AB part of ABX syst., J_{AB} = 9.6, J_{AX} =3.9, J_{BX} =4.2 Hz, 2 H, CH_2OBn), 2.99 (tdd, J = 8.1, 6.0, 2.7 Hz, 1 H, *H*-6a), 2.81 (center of m, 1 H, *H*-3a), 1.95−1.80 (m, 2 H, 1 H of *H*-4 and 1 H of *H*-6), 1.75−1.25 (m, 8 H, 1 H of *H*-4, 1 H of *H*-6, *H*-5, 2 CH_2 of Pr), 1.42 (s, 9 H, Boc), 0.98 (s, 9 H, *t*Bu), 0.87 (t, J = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 171.7, 170.6, and 155.8 (3 *C*O), 138.2 (Cq), 128.3 (2 aromatic *C*H of Bn), 127.6 (3 aromatic *C*H of Bn), 79.6 (Cq), 73.1 (CH_2Ph), 71.38 (CH_2OBn), 66.4 (*C*H-1), 58.2 (*C*HNHBoc), 54.2 (CH_2-3), 48.9 (*C*HNH), 44.8 (*C*H-6a), 43.1 (*C*H-3a), 35.3 (Cq), 34.1 (CH_2 of Pr), 32.3 and 31.9 (CH_2-4, CH_2-6), 28.3 (Boc), 26.3 (*t*Bu), 25.5 (CH_2-5), 19.2 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR (ATR): ν = 3314, 2956, 2870, 1711, 1677, 1624, 1496, 1437, 1391, 1365, 1325, 1233, 1167, 1099, 1060, 1028, 1007, 911, 856, 733, 698 cm^{-1}. HRMS (EI): m/z [M]$^+$ calcd for $C_{31}H_{49}N_3O_5$ 543.3672; found, 543.3676.

(*1S,3aR,6aS*)-*N*-((*S*)-1-(Benzyloxy)pent-2-yl)-2-((*S*)-2-cyclohexyl-2-((*tert*-butoxycarbonyl)amino)acetamido)-3,3-dimethylbutanoyl)octahydrocyclopenta[*c*]pyrrole-1-carboxamide 43. To a solution of **42** (198 mg, 0.36 mmol) in CH_2Cl_2 (2 mL), cooled to 0 °C, CF_3CO_2H (1 mL) was added dropwise. The solution was allowed to reach room temperature during 1 h, then concentrated. The solution of the crude trifluoroacetate salt in dry CH_2Cl_2 (4 mL) was treated with *N*-methylmorpholine (NMM) (280 μL, 2.55 mmol), L-Boc-cyclohexylglycine (103 mg, 0.40 mmol), and PyBOP ((benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate) (227 mg, 0.44 mmol). The reaction mixture was stirred at room temperature for 2 h, then treated with saturated aq NH_4Cl solution (25 mL) and extracted with AcOEt (50 + 25 mL), washed with saturated aq $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated. The crude was purified by flash chromatography eluting with 2:1 PE−AcOEt to give **43** (218 mg, 94%) as an amorphous solid. R_f = 0.45 (PE−AcOEt 2:1). $[\alpha]_D$ −76.97 (c = 1.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 29 °C): δ = 7.38−7.26 (m, 5 H, aromatic H), 6.63 (br d, J = 9.0 Hz, 1 H, N*H*CH), 6.45 (br d, J = 9.6 Hz, 1 H, NH of *t*Bu-Leu), 5.06 (br d, J = 8.7 Hz, 1 H, NHBoc), 4.69 (d, J = 9.6 Hz, 1H, *C*H of *t*Leu), 4.54 and 4.49 (AB syst., J = 12.0 Hz, 2 H, CH_2Ph), 4.39 (d, J = 2.4 Hz, 1H, *H*-1), 4.03 (center of m, 1H, NHC*H*), 3.90 (br t, J = 7.5 Hz, 1H, *C*H of cyclohexyl-Gly), 3.73−3.66 (m, 2 H, *H*-3), 3.46 and 3.44 (AB part of ABX syst., J_{AB} = 9.3, J_{AX} = 3.9, J_{BX} = 4.2 Hz, 2 H, CH_2OBn), 2.99 (tdd, J = 8.1, 5.7, 2.4 Hz, 1 H, *H*-6a), 2.82 (center of m, 1H, *H*-7), 1.89 (center of m, 2 H, 1H of CH_2-4, 1H of CH_2-6), 1.76−1.10 (m, 19 H, 11 H of cyclohexyl-Gly, CH_2-5, 1H of CH_2-4, 1H of CH_2-6, 2 CH_2 of Pr), 1.44 (s, 9 H, Boc), 0.98 (s, 9 H, *t*Bu), 0.87 (t, J = 7.2 Hz, 3 H, CH_3 of Pr). ^{13}C NMR ($CDCl_3$, 29 °C): δ = 171.3, 170.6, 170.4, and 155.7 (4 *C*O), 138.2 (aromatic Cq), 128.3 (2 aromatic *C*H of Bn), 127.60 (aromatic *C*H of Bn), 127.58 (2 aromatic *C*H of Bn), 79.8 (Cq of Boc), 73.0 (CH_2Ph), 71.3 (CH_2OBn), 66.3 (*C*H-1), 59.6 (*C*HNH of cyclohexyl-Gly), 56.4 (*C*HNH of *t*Leu), 54.4 (CH_2-3), 48.9 (NHCH), 44.6 (*C*H-6a), 42.9 (*C*H-3a), 40.8 (CH of cyclohexyl), 35.6 (Cq), 34.1 (CH_2-5), 32.5, 32.3 (CH_2-4, CH_2-6), 29.6, 28.5, 26.1, 25.9, 25.8, 25.6 (CH_2 of Pr and 5 CH_2 of cyclohexyl), 28.3 (Boc), 26.3 (*t*Bu), 19.2 (CH_2 of Pr), 13.9 (CH_3 of Pr). IR (ATR): ν = 3309, 2932, 2870, 2322, 1703, 1679, 1652, 1609, 1525, 1448, 1390, 1365, 1334, 1286, 1252, 1232, 1167, 1096, 1056, 1039, 1018, 993, 959, 925, 875, 844, 800, 745, 700, 635 cm^{-1}. HRMS (EI): m/z [M]$^+$ calcd for $C_{39}H_{62}N_4O_6$ 682.4669; found, 682.4654.

(*1S,3aR,6aS*)-*N*-((*2SR,3S*)-2-Acetoxy-1-(cyclopropylamino)-1-oxohexan-3-yl)-2-((*S*)-2-((*S*)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-octahydrocyclopenta[*c*]pyrrole-1-carboxamides 44. *In Situ Preparation of Cyclopropyl Isocyanide.* To a solution of chlorosulfonyl isocyanate (21.93 g, 154.95 mmol) in CH_2Cl_2 (39 mL) a solution of MeOH (6.6 mL, 162.69 mmol) in CH_2Cl_2 (39 mL) was added at 0 °C in about 1 h. When the addition was complete, the reaction mixture was warmed to 20 °C and stirred for 30 min at the same temperature, then concentrated under vacuum to give the sulfamoyl chloride intermediate as a colorless solid, which was taken up in toluene (305 mL) and warmed at 40 °C. This solution was added dropwise, in about 1 h, to a solution of Et_3N (48.6 mL, 348.6 mmol) in toluene (105 mL) keeping the temperature between 25 and 30 °C. After complete addition, the suspension was cooled at 0 °C and after 1 h filtered to give 53 g of the crude Burgess reagent containing 42% w/w of triethylamine hydrochloride by ^{1}H NMR. A solution of *N*-cyclopropylformamide (956 mg, 11.2 mmol) in CH_2Cl_2 (6 mL) was treated with the above-described crude Burgess reagent (4.67 g,11.24 mmoL). The reaction was monitored by GC, and complete conversion was achieved in about 2 h. This CH_2Cl_2 solution containing cyclopropyl isocyanide was used as such immediately in the following Passerini reaction.

Synthesis of ***44.*** Alcohol **39** (4.48 g, 7.48 mmol) was dissolved in CH_2Cl_2 (25 mL), and DMSO (19 mL) and triethylamine (5.22 mL, 37.3 mmol) were added. The mixture was cooled to −10 °C, and a

DOI: 10.1021/jo502829j
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solution of SO_3·pyridine complex (5.82 g, 36.6 mmol) in DMSO (18 mL) was added dropwise, keeping the temperature between −12 and −10 °C. After complete reaction (monitoring by HPLC), the reaction mixture was diluted with CH_2Cl_2 and washed with water, then with 0.1 N HCl, then water again. The organic layer was dried (Na_2SO_4) and evaporated. The residue was taken up in CH_2Cl_2 (7 mL) and added dropwise at 0 °C to the solution of crude cyclopropyl isocyanide (11.2 mmol) freshly prepared as described above. To the resulting reaction mixture, AcOH (0.64 mL, 11.2 mmol) was then added at 0 °C. After 10 min, the reaction mixture was warmed to room temperature and stirred at the same temperature for 18 h. The reaction was diluted with CH_2Cl_2, then quenched adding saturated aq $NaHCO_3$ solution. After phase separation, the CH_2Cl_2 solution was washed with a saturated aq $NaHCO_3$ solution, followed by water. The organic phase was dried (Na_2SO_4) and concentrated. The crude was purified by flash chromatography eluting with *n*-hexane-AcOEt (60:40 → 0:100) to give **44** (4.55 g, 84%) as a colorless solid and as a diastereomeric mixture. The physical and spectral data were in agreement with those reported in the literature.[5]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of all 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.

■ ACKNOWLEDGMENTS

We thank Chemessentia for funding, Dr. Katharine Powles for her precious help in improving the manuscript, Mr. Andrea Galatini for collaboration in NMR analyses, and Mitsubishi Italia for the kind gift of the Amano PS enzyme.

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DOI: 10.1021/jo502829j
J. Org. Chem. 2015, 80, 3411−3428