Stereoselective Synthesis of All Four Isomers of Coronamic Acid: A General Approach to 3-Methanoamino Acids

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Abstract: A general approach to the synthesis of enantiomerically enriched 3-methanoamino acids is presented where the cyclopropyl unit was introduced by a stereoselective cyclopropanation using a D-glucose-derived chiral auxiliary. This methodology was applied to the synthesis of the four stereoisomers of coronamic acid **14**, **17**, **20**, and **22**. Starting with the readily available allylic alcohol **5**, β-D-glucopyranoses (*E*)-**6** and (*Z*)-**7** have been selectively prepared using trichloroacetimidate **2**. These olefins were cyclopropanated with very high diastereoselectivities using Et_2Zn/CH_2I_2 (≥98% de) and Et_2Zn/CH_2ICl (≥97% de) in yields greater than 90%. After cleavage of the chiral auxiliary by ring contraction of the 2-*O*-triflyl derivative of cyclopropanes **8** and **9**, cyclopropylmethanols (−)-**10** and (+)-**11** have been transformed to all four isomeric protected amino acids by selective protecting group manipulations, oxidation of primary alcohols, and Curtius rearrangement.

Introduction

Since the first synthesis of 1-aminocyclopropane-1-carboxylic acid (ACC, Figure 1) in 1922,[1] over 40 different methodologies have been reported for the preparation of 3-methanoamino acids.[2] Considerable efforts were directed toward the synthesis of ACC[3] when it was found that this unsubstituted methanoamino acid was the biosynthetic precursor to the plant hormone ethylene[4] responsible for fruit ripening.[5] Naturally occurring and synthetic 3-methanoamino acids are also of major biological interest. Inhibitors of EFE (ethylene-forming enzyme),[6] aminotransferase,[7] tryptophane hydrolase,[8] Dopa decarboxylase,[9] histidine decarboxylase,[10] and carboxypeptidase[11] are found among this unique class of cyclopropyl amino acids. Moreover, *N*-substituted derivatives have fungicide properties while 2-amino-5-phosphonopentanoic acid analogs (AP5) are competitive antagonists of the complex receptor *N*-methyl-D-aspartate.[12]

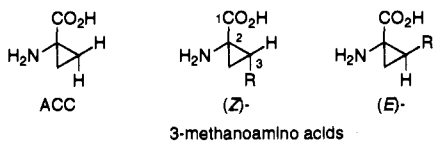

Figure 1.

Conformationally constrained peptidomimetics could also be synthesized by incorporating 3-methanoamino acids unit into a peptidic chain. This manipulation has a strong effect on the biological activity of the new peptide analog. The rigidity of the cyclopropane allows only two angles $x_1 = 0°$ and ±150° for the side chain corresponding to (*E*)- and (*Z*)-configurations of the cyclopropyl unit. This analogy to dehydroamino acids favors small ϕ and ψ angles which leads to compact, folded peptide conformations.[13,14] Furthermore, the rate of peptide hydrolysis is strongly reduced as a consequence of steric constraints introduced by the cyclopropane. This prevents proteolytic degradation and enhances the bioavailability of the peptide.[15] Cyclopropylamino acids with two stereogenic centers present four possible stereoisomers which could all be incorporated into a peptidic chain to produce four different peptidomimetic diastereomers. This allows the study of a very wide range of potentially bioactive derivatives, and it is not unusual

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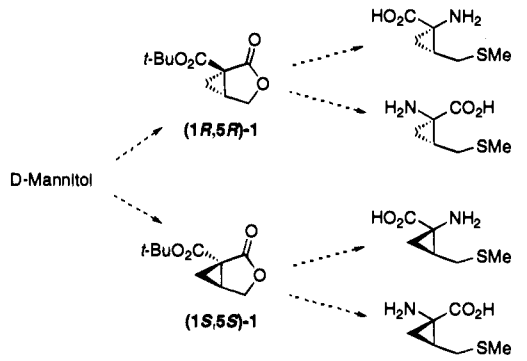
to find one of the four peptidomimetics to be more potent. Substitution of Phe by the four stereoisomers of cyclo-Phe[16] in [D-Ala^2,Leu^5,Phe^4]-enkephalin showed that the (*E*)-isomers displayed reduced activities in the mice vas deferens (MVD) and guinea pigs ileum (GPI) muscle assays.[17] Conversely, the (*Z*)-isomers showed stronger muscle binding affinities.[13] Also using cyclo-Phe, a series of dipeptides [(*E*)-cyclo-Phe-X-OR] where X = Phe, Leu and R = H, Me were synthesized and among those the diastereomer [(2*R*,3*S*)-(*E*)-cyclo-Phe-Phe-OMe] was found to be the best inhibitor of chymotrypsin.[18] Analogs of CCK (26−33) containing (*E*)-cyclo-Phe and (*Z*)-cyclo-Phe showed different binding affinities for the CCK-A and CCK-B receptors.[19] More recently, Burgess has replaced Met by the four stereoisomers of cyclo-Met in the anti-opiate neuropeptide [Phe-Met-Arg-Phe-NH_2];[20] these four pepidomimetics presented similar bioactivities, but one of them, [Phe-(2*S*,3*R*)-cyclo-Met-Arg-Phe-NH_2], was shown to have a bias toward a γ-turn structure in DMSO.[21c] These few examples clearly show that *the access to the four stereoisomers of 3-methanoamino acids in high optical purity is mandatory for a complete peptidomimetic biological investigation.* But, as it was recently pointed out by Burgess,[2c] the lack of powerful methodology for the synthesis of optically pure cyclopropyl amino acids is still the major obstacle in the development of this fascinating field of bioorganic chemistry.

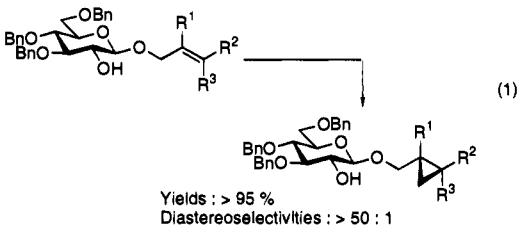
The first approach used for the synthesis of enantiomerically pure 3-methanoamino acids was based on the resolution of racemic materials.[21] More recently, several efforts were directed toward the diastereoselective control using chiral auxiliaries in the cyclopropanation reaction.[3b,18,22] Some of these methodologies appeared to be very efficient for the synthesis of 3-methanoamino acids with high optical purity, but none of them were found to be general for obtaining all four stereoisomers. Burgess has developed the first general strategy for the asymmetric synthesis of all four stereoisomers of 3-methanomethionine starting from the enantiomerically pure synthons (1*R*,5*R*)-**1** and (1*S*,5*S*)-**1** (Scheme 1).[23] Even though this methodology involves lengthy sequences, it appeared to be very efficient and was

Scheme 1



therefore applied to the preparation of cyclo-Arg, cyclo-Glu, cyclo-Gln, cyclo-Lys, and carnosadine.[2c]

We recently reported that a β-D-glucopyranose derivative can be used as an extremely efficient chiral auxiliary for the stereoselective cyclopropanation of allylic alcohols (eq 1).[24] This methodology was found to be general for a wide variety of olefins and it was anticipated that this approach could be used as the key step to generate 3-methanoamino acids.



(1)

This paper describes the development of the first general approach for the enantioselective synthesis of all four stereoisomers of 3-methanoamino acids using our chiral auxiliary and a suitably substituted allylic alcohol. It focuses on the optimization of the key cyclopropanation reaction and all the subsequent functional group manipulations to produce protected (−)- and (+)-coronamic acid and (−)- and (+)-*allo*-coronamic acid (Figure 2).[25,26]

(+)-Coronamic acid is a constituent of the vivotoxin coronatine[27] produced by *Pseudomonas syringae*, pv *atropurpurea*, which induces the chlorosis of Italian rye-grass leaves,[28] expands

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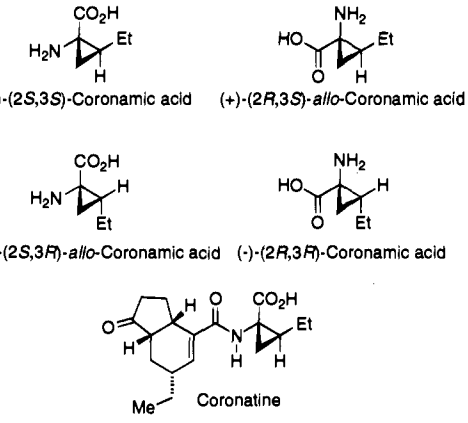


Figure 2.

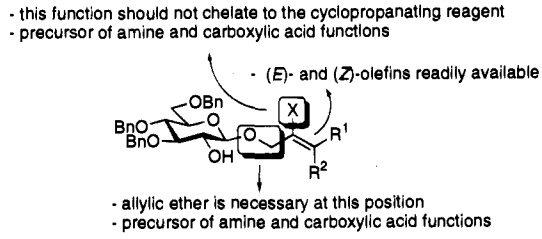


Figure 3.

potato cells, and inhibits wheat root elongation.[29] Biosynthetic studies have shown that coronamic acid originates from L-*allo*-isoleucine and from L-isoleucine.[30] Among the four possible stereoisomers of 3-ethyl-3-methanoamino acid, (+)-*allo*-coronamic acid was found to be one of the most powerful competitive inhibitor of the ethylene biosynthesis. It produces 1-butene under the action of EFE.[31]

Results and Discussion

The general cyclopropanation methodology involving the glucose-derived auxiliary has certain limitations with regard to the structure of the allylic aglycon. The olefinic precursor of the cyclopropane α-amino acid should be compatible with the previously optimized glycosylation, cyclopropanation, and deglycosylation reactions. Figure 3 represents the structural requirements for this allylic alcohol.

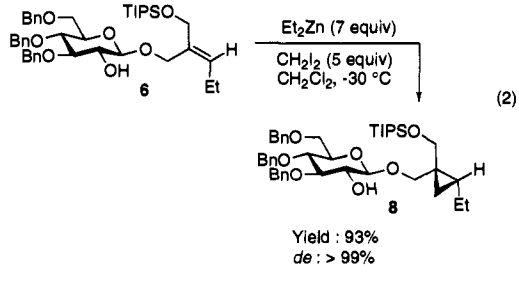
To ensure the efficiency of the key cyclopropanation step, the use of an allylic alcohol that is very similar to the systems described earlier is preferable.[24a-e] Consequently, the glycosidic linkage must come from a primary allylic alcohol[32] and the X functional group should not participate during the cyclopropanation process. Furthermore, X should not be an electron-withdrawing group such as an ester or an amide since these groups would deactivate the olefin in the cyclopropanation. Obviously, it should be easily transformed to either an amine and a carboxylic acid, and since we are interested in the synthesis of (*E*)- and (*Z*)-isomers of 3-methanoamino acids, both geometrical isomers of the olefin should be readily accessible. These structural limitations dictate the retrosynthetic analysis shown in Scheme 2. This strategy relies on the fact that both functional groups (amine and carboxylic acid) can potentially evolve from a primary alcohol. The monoprotection and the careful protecting group interconversion of these two alcohols set the absolute configuration at the C-2 center and ensure the control of the relative stereochemistry. In this fashion, (*E*)- and (*Z*)-amino acids are accessible *from the same cyclopropylmethanol derivative*. The diastereoselective cyclopropanation of the (*E*)- or (*Z*)-olefin using the β-D-glucopyranose-derived chiral auxiliary will set the absolute stereochemistry at the C-3 position. A bulky silyl ether was chosen as the protecting group for the primary alcohol (the X group) to prevent any undesired complexation of the silyl ether with the zinc reagent during the cyclopropanation reaction.[33] As we can see from the retrosynthetic analysis, this sequence is extremely convergent since it provides routes to *the four stereoisomers of coronamic acid from the same chiral auxiliary*.

Synthesis of Optically Pure Cyclopropylmethanol. The feasibility and practicality of the approach presented in Scheme 2 is ultimately based on the ease with which monoprotected 2-alkylidene-1,3-propanediols can be obtianed. We have recently developed a stereoselective route to this class of compounds that features a novel S_N2' Mitsunobu reaction. This approach provides full control of the double-bond geometry and differentiation of the two oxygenated positions (Scheme 3).[34] (*E*)-α,β-Unsaturated ester **4** was isolated in 85% yield when 2-substituted methyl acrylate **3**[35] was submitted to Mitsunobu conditions at −40 °C. The *p*-Nitrobenzoate was then cleaved to afford the allylic alcohol **5** in 87% yield.

Both (*E*)- and (*Z*)-allyl glucosides could be prepared by starting with the alcohol **5** simply by modifing the reaction sequence (Scheme 4). In this manner, the synthesis of monoprotected (*E*)-1,3-propanediol is not necessary.

The (*E*)-isomer **6** was obtained in an overall yield of 78% from alcohol **5** by a Schmidt glycosylation[36] of the trichloroacetamidate **2**[24d] and subsequent reduction of the ester group and monoprotection of the resulting primary alcohol. Similarly, the analogous (*Z*)-allyl glucopyranose was also obtained from the alcohol **5** in four steps. Protection of the primary alcohol as a triisopropylsilyl ether followed by a DIBAL-H reduction of the ester produced the desired glycosylation precursor in 93% yield (two steps). Treatment of this monoprotected 1,3-diol and trichloroacetimidate **2** with $BF_3{\cdot}OEt_2$ at −30 °C followed by cleavage of the acetate under standard conditions afforded the desired glycosylation product **7** in excellent yield (79%, two steps). When this glycosylation was carried out at −78 °C, the glucopyranoside was obtained in less than 40% yield. The low reactivity of the allylic alcohol due to the steric hindrance of the bulky triisopropylsilyl group accounts for this observation.

With these glucopyranosides in hand, the key cyclopropanation reactions were performed using the optimized cyclopropanation conditions that have been reported recently (eq 2).[24e]



(2)

Diastereomerically pure (>99% de[37]) cyclopropane **8** was easily

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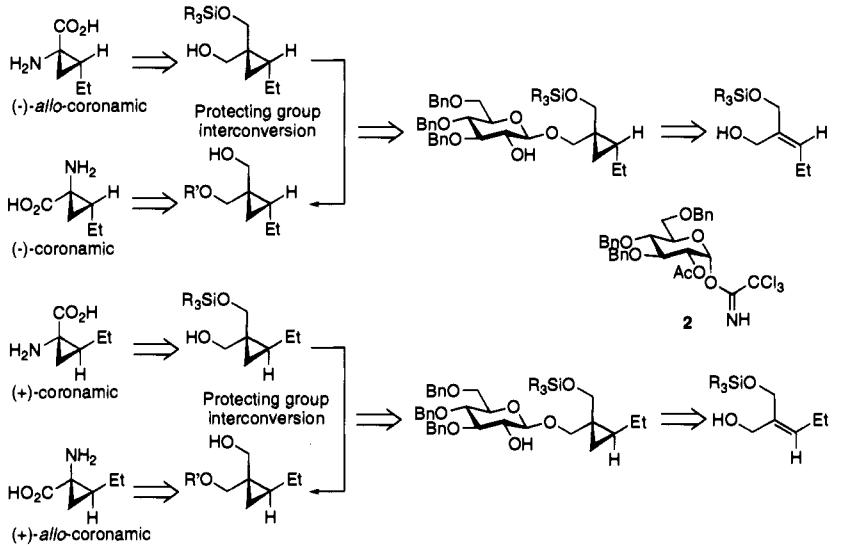
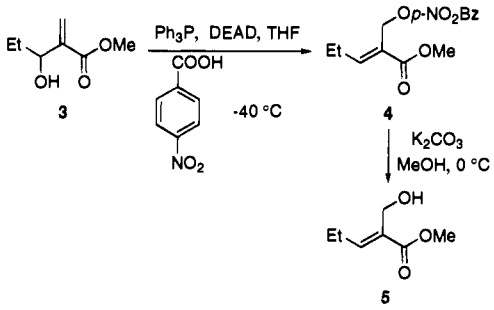
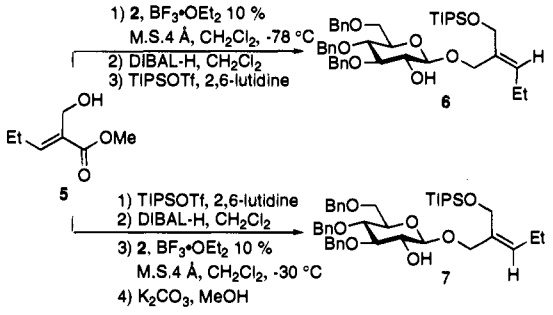
Scheme 2



Scheme 3



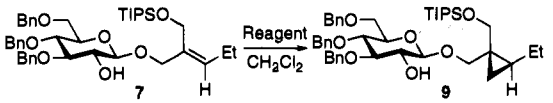
Scheme 4



obtained in 93% yield when glycoside **6** was treated with $ZnEt_2$ (7 equiv) and CH_2I_2 (5 equiv) in CH_2Cl_2 at −30 °C. HPLC analysis of the crude reaction mixture showed that a >100:1 mixture of diastereomers was obtained. Traces of the minor diastereomer detected by HPLC could be easily removed by flash chromatography.[38]

The cyclopropanation of the (*Z*)-isomer **7** was conducted following the same conditions as those described for **6**. Surprisingly, the reaction was very sluggish and cyclopropane **9** and its diastereomer were obtained in only 65% yield and as a 20:1 mixture (Table 1, entry 1). Previous studies on the cyclopropanation of the (*E*)-isomer **6**[25e] have shown that slow reactions usually produce much lower diastereomeric ratios. We believe that more than one reactive species could be involved in the cyclopropanation and that low reaction rates favor the cyclopropanation by a "less selective" iodomethylzinc species generated after a certain time.[39] As expected, high yield and a low diastereoselectivity were observed if the reaction was carried out at 0 °C (entry 2).[40] *All the reactions performed on this compound, under various conditions, clearly showed that this olefin was by far less reactive than those studied previously.* This problem of reactivity was circumvented by using $ClCH_2I$ instead of CH_2I_2 to generate the more reactive chloromethylzinc reagent.[41] In previous studies, the use of the chloromethylzinc carbenoid with the carbohydrate auxiliary had generally led to lower diastereoselectivities and appearance of numerous side products that were not usually observed with the analogous iodomethylzinc reagent. Cyclopropane **9** was obtained in good yield with a 25:1 diastereomeric ratio, when **7** was treated with

Table 1. Cyclopropanation of Glucopyranose 7 under Various Conditions



entry	reagent (equiv)	temp (°C)	time	yield[a]	de[c]
1	Et_2Zn (7) CH_2I_2 (5)	−20	18 h	65%	20:1
2	Et_2Zn (7) CH_2I_2 (5)	0	2 h	>95%	3:1
3	Et_2Zn (7) CH_2ICl (5)	−20	40 min	>95%	25:1
4	Et_2Zn (4) CH_2ICl (4)	−60	18 h	98%[b]	66:1

[a] Determined by ^1H NMR and based on unreacted starting material. [b] Isolated yield of pure product after chromatography on silica gel. [c] Determined by HPLC of the crude product.

(34) (a) Charette, A. B.; Côté, B. *Tetrahedron Lett.* **1993**, *34*, 6833−6836. (b) Charette, A. B.; Côté, B.; Monroc, S.; Prescott, S. *J. Org. Chem.* **1995**, *60*, 6888−6894.

(35) Obtained on a 50 g scale from methyl acrylate and propionaldehyde using the Baylis−Hillman reaction (cat. DABCO, neat, 5 days): (a) Baylis, A. B.; Hillman, N. E. *German Patent* **2** 155 113, **1972**; *Chem. Abstr.* **1972**, *77*, 34 174. See also: (b) Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849−3859. (c) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1843−1846.

(36) (a) Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257−1270. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235.

(37) The minor stereoisomer was undetectable by HPLC.

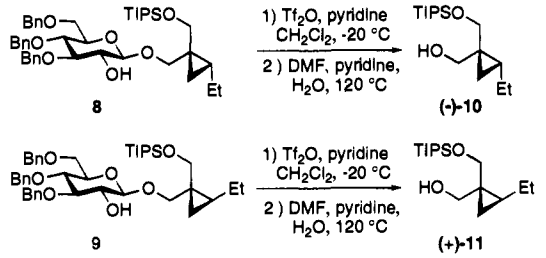
(38) At this point, the absolute stereochemistry of the major diastereomer was assumed to be that shown in eq 2. This is consistent with the previously observed diastereofacial selectivities in the cyclopropanation of other substrates (see ref 24a−e).

(39) Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.*, in press.

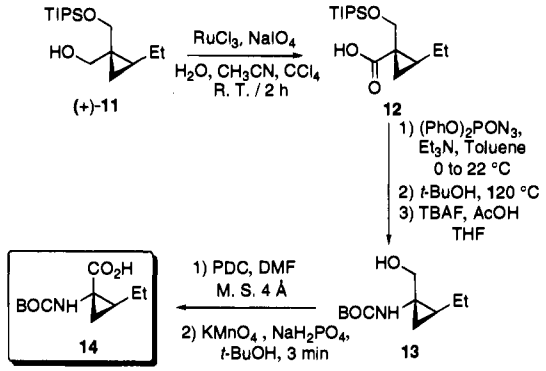
(40) This variation of selectivity at higher temperature was also observed with glucopyranose **6** even if the ratio was still very good (40:1 at 0 °C).

(41) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974−6981.

Scheme 5



Scheme 6



Et_2Zn (7 equiv) and CH_2ICl (5 equiv) at −20 °C (entry 3). The only parameter that led to significantly improved selectivities was varying the temperature (entry 4). To the best of our knowledge, this is the lowest temperature at which a Simmons–Smith cyclopropanation has been conducted. After further optimization, cyclopropane **9** was isolated in quantitative yield and as a 66:1 mixture of diastereomers (entry 4).

The chiral auxiliary was finally removed using the ring contraction procedure that was developed in our laboratories for the rearrangement of 2-*O*-[[(trifluoromethyl)sulfonyl]oxy]-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside.[24c] Cyclopropylmethanols (−)-**10** and (+)-**11** were produced in 75% and 80% yield, respectively, when the glycosides **8** and **9** were submitted to the very mild basic conditions necessary to induce the hetero-Wagner–Meerwein rearrangement (Scheme 5). With these two key intermediates in hand, the synthesis of the four stereoisomers of coronamic acid could then be completed using straightforward transformations.

Synthesis of (+)-Coronamic Acid. The differentiation of the two oxygenated positions of cyclopropylmethanol (+)-**11** is the key control element for the selective synthesis of (+)-coronamic acid and (+)-*allo*-coronamic acid. The sequence presented in Scheme 6 begins with the oxidation of the primary alcohol with ruthenium oxide[42] under the Sharpless conditions to afford carboxylic acid **12** in 83% yield. Jones' reagent was found to be ineffective for this transformation since the oxidation stopped at the aldehyde. The use of more vigorous conditions led to extensive decomposition. Carboxylic acid **12** was then converted into the corresponding acyl azide in the presence of diphenylphosphoryl azide (DPPA)[43] and Et_3N in toluene at 0 °C. This intermediate was purified by a short-path filtration on silica gel and then directly submitted to the Curtius rearrangement in refluxing *tert*-butyl alcohol. Alcohol **13** was isolated after cleavage of the triisopropylsilyl group in 75% yield for the three steps. Usually, the Curtius rearrangement with DPPA does not require isolation of the acyl azide. But when this procedure was used for **12**, a significant amount of silyl ether cleavage was observed and typical yields obtained for this transformation were not greater than 50%. If necessary, the isocyanate could also be isolated if the Curtius rearrangement was carried out without a nucleophile.[44]

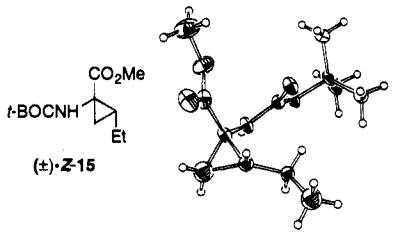


Figure 4.

The final oxidation to produce the protected (+)-coronamic acid was also problematic. As in the oxidation of **11**, Jones' reagent was inefficient for the oxidation of the amino alcohol **13** to the carboxylic acid **14**. When alcohol **13** was submitted to the ruthenium-catalyzed oxidation, we were surprised to isolate two very similar acids in a 2:1 ratio (>80% yield). These two compounds were treated with CH_2N_2, and the resulting methyl esters were separated by chromatography. ^{1}H-NMR analysis indicated that both compounds were possibly diastereomers, the minor being produced by the epimerization of one center. This hypothesis was confirmed when the minor isomer (*Z*)-**15** was crystallized and its structure unambiguously established by X-ray crystallographic analysis (Figure 4).[45,46]

A more efficient procedure for the oxidation of the primary alcohol to complete the synthesis of *N*-BOC coronamic acid was sought. A two-step oxidation sequence proved to be successful. The aldehyde was initially obtained upon treatment with PDC in DMF,[47] and the second oxidation could be smoothly accomplished in 85% yield with $KMnO_4$ under the Masamune's conditions.[48,49] The absolute configuration of **14** was established by comparing its optical rotation ($[\alpha]_D = +32.1°$ (*c* 0.7, MeOH)) with the literature value[21b] ($[\alpha]_D = +33.3°$ (*c* 1.1, MeOH)). The stereochemistry is in agreement with the sense of induction generally observed in the cyclopropanation involving the β-D-glucopyranoside's chiral auxiliary.

Synthesis of (+)-*allo*-Coronamic Acid. It was shown in the retrosynthetic analysis that both the (*E*)- and (*Z*)-isomers

(42) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

(43) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.

(44) The addition of *t*-BuOH on the isocyanate could be done at room temperature with CuCl; however, the isolated yield was only of 55%: Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131–132.

(45) The sample for the X-ray crystallographic study was obtained when carrying the sequence on racemic material. The acids were treated with a solution of CH_2N_2 in ether and separated by flash chromatography (10% ethyl acetate/hexanes). Alternatively, we found that the absolute configuration at *C*-3 was retained if the $RuO_4/NaIO_4$ oxidation was carried out on enantiomerically enriched material. This was demonstrated by ^{1}H NMR analysis of the Mosher's esters derived from the chromatographically separable alcohols (*E*)- and (*Z*)-**13** obtained by reduction of the mixture of acids **14** and **15** (1. DIBAL; 2. $NaBH_4$).

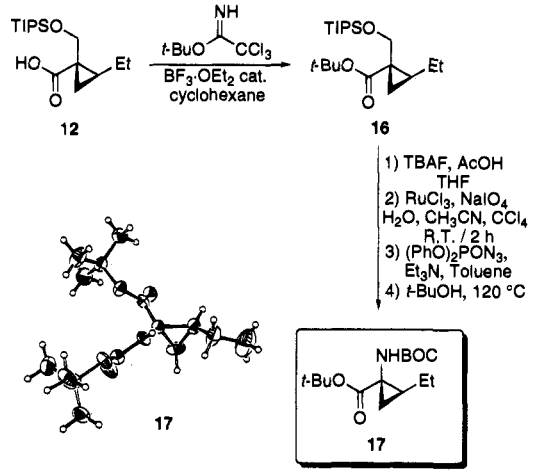
(46) The opening of the cyclopropane may come from the generation of a cyclopropyl carbinyl radical which is postulated to be an intermediate during the oxidation of alcohols by transition metals. The rigorous explanation of this fascinating phenomena remains uncelar and is still under investigation.

(47) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402. Even if this procedure was known to oxidize primary alcohols to acids, only a small amount of **14** (<10%) was observed by TLC. For a good example of oxidation of amino alcohols to carboxylic acids with PDC, DMF, and M.S., see: Beaulieu, P. L.; Duceppe, J.-S.; Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196–4204.

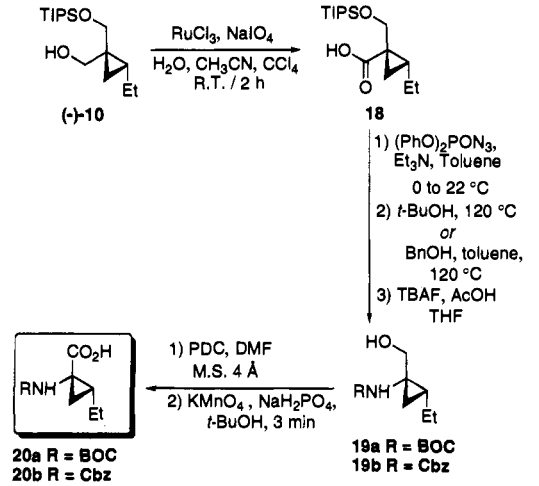
(48) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537–4540.

(49) The formation of the (*Z*)-isomer (*ca.* 7%) was also observed in this two-step procedure. This minor contaminant was completely removed by chromatography of the corresponding methyl ester derivatives (CH_2N_2, ether, 0 °C). We have not determined if this epimerization occurs in the PDC or in the $KMnO_4$ step, but no erosion in the enantiomeric purity of the major product could be detected.

Scheme 7



Scheme 8



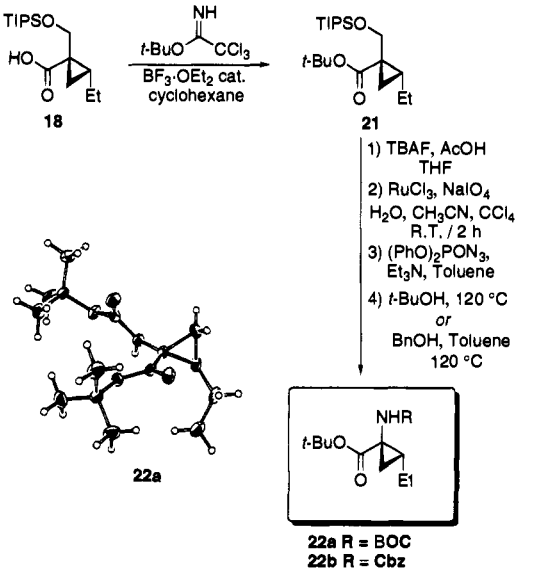
were accessible from the same intermediate (Scheme 2). The strategy leading to the (+)-*allo*-coronamic acid involved a simple interconversion of protecting groups. This sequence, illustrated in Scheme 7, was realized starting with *tert*-butyl ester of carboxylic acid **16** obtained in 90% yield from the corresponding carboxylic acid **12**.[50]

Primary alcohol **16** was then deprotected with TBAF/AcOH and then oxidized with $RuCl_3/NaIO_4$. The resulting carboxylic acid was treated with DPPA/Et_3N to generate the corresponding acyl azide. Finally, the acyl azide was heated to reflux in *tert*-butyl alcohol to produce the protected amino acid **17** in 45% overall yield from **12** (five steps). The absolute and relative configuration of the *N*-BOC *tert*-butyl ester of (+)-*allo*-coronamic acid was unambiguously established by X-ray crystallography.

Synthesis of (−)-*allo*-Coronamic Acid. *N*-BOC-protected (−)-*allo*-coronamic acid was prepared by the same general strategy that was shown previously (Scheme 8). Cyclopropylmethanol (−)-**10** was oxidized to carboxylic acid **18** with ruthenium oxide in 91% yield. Curtius rearrangement and trapping of the isocyanate with *tert*-butyl alcohol produced the corresponding BOC-protected amine. The triisopropylsilyl group was then cleaved under standard conditions to produce the amino alcohol **19a** in an excellent yield of 91% (three steps). The Curtius reaction was also conducted with benzyl alcohol, and the CBz protecting group was introduced to generate the

(50) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483−2486.

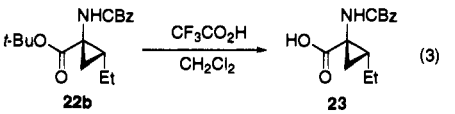
Scheme 9



amino alcohol **19b** in 93% yield. Finally, protected *N*-BOC **20a** and *N*-CBz **20b** amino acids of (−)-*allo*-coronamic acid were obtained in 90% and 94% yields after oxidation of the primary alcohols **19a** and **19b**.[51] The availability of having a *N*-BOC as well as a *N*-CBz group on the amine presents a strong advantage for peptide synthesis as this introduces more flexibility for the selective manipulation of protecting groups. The relative stereochemistry was confirmed by comparing the ^1H NMR spectrum of **20a** with that of the (*E*)-isomer **14** and the absolute configuration was assumed to be (2*S*,3*R*) from the X-ray crystal structure obtained in the synthesis of (−)-coronamic acid (*vide infra*) since the amino acids **20** and **22** come from the same intermediate.

Synthesis of (−)-Coronamic Acid. The synthesis of protected (−)-coronamic acid was achieved by following the sequence described for (+)-*allo*-coronamic acid (Scheme 9). In addition to the *N*-BOC, the *N*-CBz protecting group was also introduced after the Curtius rearrangement and the amino acids **22a** and **22b** were isolated in overall yields of 46% and 59%, respectively, from **18** (five steps). The absolute and relative stereochemistry of **22a** was established by single crystal X-ray structure analysis.

It is also possible to unveil the carboxylic acid under acidic conditions. For example, amino acid **22b** produced the free acid in an excellent yield of 98% when treated with TFA (eq 3). Furthermore, it has been shown that 3-methanoamino acids were resistant to hydrogenolysis conditions (5% PD/C), thus allowing the selective cleavage of the CBz protecting group.[2a]



Summary

We have shown that the four stereoisomers of protected coronamic acid could be synthesized using a very convergent sequence starting from the readily available intermediate **5**. Optically pure cyclopropylmethanols (−)-**10** and (+)-**11** could be selectively transformed into (*E*)- and (*Z*)-isomers of the corresponding amino acid by simple, high-yielding functional group manipulations. All four cyclopropyl units were introduced by highly diastereoselective reactions using the chiral

(51) No epimerization was observed in this series.

auxiliary derived from D-glucose and zinc carbenoid reagent generated either from Et_2Zn/CH_2I_2 (≥98% de) or Et_2Zn/CH_2ICl (97% de). So far, we have found that there is no limitation to this general strategy since a wide variety of allylic alcohols can be prepared by the S_N2' Mitsunobu reaction and cyclopropanated by this method.

Furthermore, we have recently reported that a dioxaborolane derived from *N,N,N',N'*-tetramethyltartardiamide could be used as a chiral controller for the enantioselective cyclopropanation of allylic alcohols.[52] Substitution of the chiral auxiliary by this new promoter would shorten the overall sequence by two steps (glycosylation and deglycosylation) since we have shown that the cyclopropanations of monoprotected 2-alkylidene-1,3-propanediols is very effective with this chiral ligand (90–93% ee).

Finally, the application of this methodology to other 3-methanoamino acids is currently under investigation and will be reported in due course.

Experimental Section

General Procedure. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Unless otherwise noted, all nonaqueous reactions were performed under an oxygen-free atmosphere of nitrogen with rigid exclusion of moisture from reagents and glassware. Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium ammonium molybdate, ethanolic phosphomolybdic acid, aqueous potassium permanganate, or aqueous chromic acid. Liquid chromatography was performed using a force flow (flash chromatography) of the indicated solvent system on EM Reagents Silica Gel 60 (230–400 mesh). Preparative TLC was performed using Whatman Silica gel C8 TLC plates (PLK5F). Infrared spectra were recorded on a Perkin Elmer 781 and 1330 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded in deuteriochloroform, unless otherwise noted, on a Varian VXR-300, Bruker AMX-300, or Bruker ARX-400 spectrometer. Chemical shifts are reported in parts per million on the δ scale from an internal standard of residual chloroform (7.265 ppm) or tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and br = broad), coupling constant in hertz, integration, and assignment. ^{13}C NMR spectra were recorded in deuteriochloroform, unless otherwise noted, on a Varian VXR-300, Bruker AMX-300, or Bruker ARX-400 spectrometer. Chemical shifts are reported in parts per million from the central peak of deuteriochloroform (76.9 ppm) on the δ scale. All spectra were obtained with complete proton decoupling, and COSY/HETCOR experience, when required, was used to ensure assignment. Optical rotations were determined with a Jasco DIP-360 and Perkin-Elmer 241 polarimeters at 589 nm and, unless otherwise stated, at 20 °C (room temperature). Data are reported as follows: $[\alpha]_\lambda$, concentration (*c* g/100 mL), and solvent. High-resolution mass spectra (HRMS) were recorded on a MS-50 Kratos spectrometer. Combustion analyses were performed by Galbraith Laboratories (Knoxville, TN). Analytical gas chromatography (GLC) was carried out on a Hewlett Packard 5890 series II gas chromatograph equipped with a split mode capillary injector and a flame ionization detector. The following fused silica capillary columns were employed: 0.32 mm × 30 DB-1, DB-1701, DB-WAX, Cyclodex-B (J and W Associates), 0.32 mm × 30 m GT-A, B-PH, B-DA (Chiraldex). Unless otherwise noted, injector and detector temperatures were 250 °C and the split was 30:1. Data are reported as follows: column type, oven temperature, carrier pressure, and retention time (t_r). High-performance liquid chromatography (HPLC) was conducted using a Waters 600E pumping system with a Waters 486 UV detector, Waters 410 RI detector, and the following stationary phases: 4 μm silica gel NOVA-PAK (8 × 200 mm), 5 μm silica gel Partisil-5 (5 × 240 mm), normal phase Chiralcel OD and OJ. Data are reported as follows: column type, eluent, flow rate, and retention time (t_r). When necessary, solvents and reagents were dried prior to use as follows: ether, tetrahydrofuran, benzene, and toluene were stored over and distilled from sodium benzophenone ketyl; dichloromethane, triethylamine, pyridine, and hexane were distilled over calcium hydride. Unless otherwise stated, the reagents were purchased from Aldrich Chemical Co., Alfa, Lancaster, and Fluka and used as received. Trifluoromethanesulfonic anhydride was distilled two times over P_2O_5.

Methyl (*E*)-2-[[(4-Nitrobenzoyl)oxy]methyl]-2-pentenoate (4). To a solution of allylic alcohol **3**[35] (8.42 g, 58.4 mmol) in dry THF (500 mL) was added triphenylphosphine (20 g, 76 mmol) and *p*-nitrobenzoic acid (12.7 g, 76 mmol). The clear resulting solution was placed at −40 °C, and diethyl azodicarboxylate (DEAD) (12 mL, 76 mmol) was added over a period of 10 min. The reaction was then slowly warmed to −30 °C over 1 h and kept at this temperature until TLC analysis showed the complete consumption of starting material (1 h). The −30 °C bath was replaced by an ice bath, and after 15 min at 0 °C, the solution was concentrated under reduced pressure (bath <30 °C). The residue was dissolved in ether (300 mL), and the organic layer was successively washed with H_2O (20 mL) and 1.0 M aqueous NaOH (2 × 20 mL). The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Subsequent preadsorption of the residue on silica gel and flash chromatography (7–20% EtOAc/hexanes) produced the desired *p*-nitrobenzoate (14.4 g, 84%) as a slightly yellow solid that can be recrystallized from MeOH at 0 °C or from ether/hexane: mp 53–54.5 °C; R_f 0.22 (10% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (dt, J = 9, 2 Hz, 2H, $H_{arom.}$), 8.11 (dt, J = 9, 2 Hz, 2H, $H_{arom.}$), 7.09 (t, J = 8 Hz, 1H, CH_3CH_2CH), 5.09 (s, 2H, CH_2O-*p*-NO_2Bz), 3.74 (s, 3H, CO_2CH_3), 2.36 (qn, J = 8 Hz, 2H, CH_3CH_2), 1.06 (t, J = 8 Hz, 3H, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 164.2, 151.6, 150.4, 135.3, 130.6, 125.8, 123.3, 59.1, 51.8, 22.1, 13.0; IR (KBr) 2970, 1720, 1610, 1525, 1265, 1100, 950, 710 cm^{-1}; HRMS calcd for $C_{14}H_{16}NO_6$ 294.0978, found 294.0946.

Methyl (*E*)-2-(Hydroxymethyl)-2-pentenoate (5). The *p*-nitrobenzoate **4** (3.5 g, 11.9 mmol) was dissolved in dry methanol (120 mL), and the solution was cooled to 0 °C. After 15 min of stirring, K_2CO_3 (3.3 g, 24 mmol) was added in one portion and the reaction was kept at 0 °C until the TLC analysis showed the complete consumption of the starting material (1 h). The solution was poured into a dropping funnel containing ether (300 mL) and saturated aqueous NaCl (50 mL). The minimum amount of H_2O to dissolve K_2CO_3 was then added. The aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic layers were washed with saturated aqueous NaCl (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated using a rotary evaporator at *atmospheric pressure*, in a bath at 50–60 °C. The residue was purified by flash chromatography (20–30% EtOAc/hexane) to produce alcohol **5** (1.5 g, 87%) as a volatile colorless liquid: R_f 0.2 (20% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (t, J = 8 Hz, 1H, CH=C), 4.27 (s, 2H, CH_2OH), 3.71 (s, 3H, CO_2CH_3), 2.79 (s, 1H, CH_2OH), 2.24 (q, J = 8 Hz, 2H, CH_2CH_3), 1.01 (t, J = 8 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 147.2, 130.3, 56.7, 51.6, 21.5, 13.1; IR (neat) 3440 (v. br), 2990, 2970, 2890, 1710, 1640, 1430, 1305, 1275, 1220, 1140, 1075, 1005, 745 cm^{-1}; HRMS (FAB) calcd for $C_7H_{12}O_3$ 144.0787, found 144.0773.

2'-[[(Triisopropylsilyl)oxy]methyl]-(*E*)-2'-pentenyl 3,4,6-Tri-*O*-benzyl-β-D-glucopyranose (6). To a solution of trichloroacetimidate **2** (11.2 g, 17.6 mmol), alcohol **5** (2.54 g, 17.6 mmol), and 4 Å molecular sieves (*ca.* 2 g) in CH_2Cl_2 (180 mL) at −78 °C was added a 0.2 M solution of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (8.5 mL). The reaction was stirred for 1.5 h at −78 °C and 15 min at 0 °C, and $NaHCO_3$ (*ca.* 2 g) and H_2O (20 mL) were added. The mixture was poured into ether (250 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Subsequent flash chromatography (15–20% EtOAc/hexane) produced the desired glucopyranose **6** (8.66 g, 87%) as a viscous colorless oil: R_f 0.3 (20%

(52) (a) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651–2652. (b) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1994**, *60*, 1081–1083.

EtOAc/hexane): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.23 (m, 15H, Ph), 7.04 (t, J = 8 Hz, 1H, C=C*H*), 5.05 (t, J = 9 Hz, 1H, C*H*OAc), 4.85 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.84 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.73 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.70 (d, J = 12 Hz, 1H, C*H*$_2$Ph), 4.65−4.60 (m, 3H, C*H*$_2$Ph, C*H*$_2$C=CHEt, C*H*O$C_7H_{11}O_2$), 4.49−4.42 (m, 2H, C*H*$_2$Ph, C*H*$_2$C=CHEt), 3.81−3.70 (m, 7H, C*H*OBn, C*H*$_2$OBn, CO_2CH_3), 3.55−3.52 (m, 1H, C*H*CH$_2$OBn), 2.33 (q, J = 8 Hz, 2H, C*H*$_2$CH$_3$), 1.98 (s, 3H, OAC), 1.08 (t, J = 8 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 166.9, 149.9, 137.9, 137.9, 137.7, 128.1, 128.0, 128.0, 128.0, 128.0, 127.6, 127.5, 127.3, 127.2, 127.2, 99.5, 82.7, 77.7, 74.9, 74.6, 73.1, 72.8, 68.4, 61.8, 51.3, 21.6, 20.4, 12.9; IR (neat) 3060, 3030, 2970 (br), 2870, 1750, 1715, 1650, 1490, 1450, 1430, 1370, 1230 (br), 1060 (br), 730, 690 cm^{-1}. To a solution of the glucopyranoside (8.66 g) in CH_2Cl_2 (140 mL) at −78 °C was added a 1.0 M solution of DIBAL-H in hexane (84 mL, 84 mmol) over 25 min. The solution was warmed slowly to −50 °C over a period of 1.5 h, and the acetone/CO_2 bath was replaced by an ice bath followed by the careful addition of 0.5 M aqueous Rochelle's salt until the evolution of the gas stopped. The resulting mixture was diluted with 0.5 M aqueous Rochelle's salt (500 mL) and ether (150 mL). The heterogenous solution was stirred vigorously until the two layers became clear, and then the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was dissolved with CH_2Cl_2 (140 mL), and the solution was cooled to 0 °C. To this clear solution was added 2,6-lutidine (2.45 mL, 21 mmol) followed by triisopropylsilyl trifluoromethanesulfonate (4.14 mL, 15.4 mmol). When TLC analysis showed the complete consumption of starting material, saturated aqueous $NaHCO_3$ (10 mL) was added and the solution was diluted with ether (200 mL). The organic layer was extracted with ether (2 × 50 mL), and the combined organic layers were washed with 5% aqueous HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (8% EtOAc/hexane) to produce glucopyranoside **6** (8.87 g, 90%) as a viscous colorless oil: R_f 0.25 (10% EtOAc/hexane); $[\alpha]_D$ −12.2° (*c* 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.20 (m, 15H, Ph), 5.77 (t, J = 8 Hz, 1H, C=C*H*), 5.01 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.89 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.86 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.67 (d, J = 12 Hz, 1H, C*H*$_2$Ph), 4.59 (d, J = 12 Hz, 2H, C*H*$_2$Ph), 4.44 (d, J = 12 Hz, 1H, C*H*$_2$C=CHEt), 4.38 (d, J = 12 Hz, 1H, C*H*$_2$C=CHEt), 4.36−4.25 (m, 3H, C*H*$_2$C=CHEt, C*H*O$C_{15}H_{31}SiO_2$), 3.81−3.73 (m, 2H, C*H*$_2$OBn), 3.66−3.62 (m, 3H, C*H*OBn, C*H*OH), 3.56−3.49 (m, 1H, C*H*CH$_2$OBn), 2.57 (s, 1H, CHO*H*), 2.18 (q, J = 8 Hz, 2H, C*H*$_2$CH$_3$), 1.24−1.09 (m, 21H, Si(*i*-Pr)$_3$), 1.01 (t, J = 8 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.1, 138.1, 133.2, 132.5, 128.2, 128.2, 128.2, 127.8, 127.6, 127.6, 127.5, 127.4, 100.9, 84.5, 77.4, 75.1, 74.9, 74.9, 74.6, 73.4, 68.8, 65.4, 63.7, 20.5, 17.9, 14.2, 11.9; IR (neat) 3460, 3030, 2940, 2870, 1610, 1590, 1495, 1450, 1360, 1110, 1060, 880, 730, 690 cm^{-1}.

2′-[[(Triisopropylsilyl)oxy]methyl]-(*Z*)-2′-pentenyl 3,4,6-Tri-*O*-benzyl-β-D-glucopyranose (7). Alcohol **5** (2.0 g, 13.8 mmol) was dissolved in CH_2Cl_2 (150 mL), and the solution was cooled to 0 °C. To this clear solution was added 2,6-lutidine (2.4 mL, 20.7 mmol) followed by TIPSOTf (4.5 mL, 16.6 mmol). The ice bath was removed, and when TLC analysis showed the complete consumption of the starting material, the reaction was diluted with ether (150 mL) and quenched with H_2O. The organic layer was washed with 10% aqueous HCl (3 × 30 mL), saturated aqueous $NaHCO_3$ (30 mL), and saturated aqueous NaCl (30 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered on a short plug of silica gel using 2% EtOAc/hexane as the eluent in order to eliminate the methyl *p*-nitrobenzoate. The resulting colorless oil was dissolved in CH_2Cl_2 (150 mL), the solution was cooled to −78 °C, and a 1.0 M solution of DIBAL-H in hexane (147 mL, 147 mmol) was added over a period of 15 min. The solution was stirred at −78 °C until TLC analysis showed the complete consumption of starting material. Then the reaction was slowly quenched with 0.5 M aqueous Rochelle's salt and diluted with ether (100 mL). The solution was allowed to warm to room temperature and was then diluted with 0.5 M aqueous Rochelle's salt (150 mL). The heterogenous solution was vigorously stirred until the two layers were completely clear. The organic layer was washed with saturated aqueous NaCl (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue can be purified either by distillation using Kugelrohr (90 °C at 0.4 mmHg) or by flash chromatography (6% EtOAc/hexane) to produce 2-[[(triisopropylsilyl)oxy]methyl]-2-(*Z*)-pentenol (3.5 g, 93%): R_f 0.31 (10% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (t, J = 7 Hz, 1H, CH$_3$CH$_2$C*H*), 4.42 (s, 2H, CH$_2$O), 4.15 (s, 2H, CH$_2$O), 2.67 (s, (br), 1H, OH), 2.01 (qt, J = 8 Hz, 2H, CH$_3$C*H*$_2$), 1.10−1.02 (m, 21H, isopropyl), 0.96 (t, J = 8 Hz, 3H, C*H*$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 130.4, 67.1, 61.3, 20.7, 17.9, 14.0, 11.8; IR (neat) 3350 (br), 2940, 2860, 1460, 1070, 870, 790, 670 cm^{-1}; HRMS calcd for $C_{15}H_{33}O_2Si$ 273.2251, found 273.2250. To a solution of this alcohol (3.5 g, 12.8 mmol), trichloroacetimidate **2** (8.6 g, 13.5 mmol), and 4 Å molecular sieves (*ca.* 1 g) in CH_2Cl_2 (70 mL) at −78 °C was added freshly distilled BF_3·OEt_2 (157 μL, 1.28 mmol). The acetone/CO_2 bath was immediately replaced by a bath at −30 °C, and the reaction was stirred for 4 h at that temperature. The reaction was quenched with solid $NaHCO_3$ (*ca.* 1 g) and diluted with ether (300 mL). The resulting mixture was then poured into a dropping funnel containing H_2O (50 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was allowed to crystallize and then CH_2Cl_2 (100 mL) was added. The resulting suspension was stirred for 15 min at −78 °C, and the mixture was rapidly filtered to eliminate the major part of the residual trichloroacetamide. This crystallization can be repeated if necessary. The solution was concentrated under reduced pressure, and the residue purified by flash chromatography (7% EtOAc/hexane) to produce the desired glucopyranoside (*ca.* 9 g). The resulting viscous oil was dissolved in MeOH (30 mL), and K_2CO_3 (1 g) was added in one portion. The reaction was stirred at room temperature until TLC analysis showed the complete consumption of starting material (16 h). The solution was poured into a dropping funnel containing ether (300 mL) and H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with saturated aqueous NaCl (3 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatrography (6%−10% EtOAc/hexane) to produce glucopyranoside **7** (7.1 g, 79%) as a viscous colorless oil: R_f 0.25 (10% EtOAc/hexane); $[\alpha]_D$ −15.9° (*c* 1.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.19 (m, 15H, Ph), 5.58 (t, J = 7 Hz, 1H, C=C*H*), 5.02 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.88 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.86 (d, J = 11 Hz, 1H, C*H*$_2$Ph), 4.66 (d, J = 12 Hz, 1H, C*H*$_2$Ph), 4.58 (d, J = 12 Hz, 2H, C*H*$_2$Ph), 4.48 (d, J = 12 Hz, 1H, C*H*$_2$C=CHEt), 4.39 (s, 2H, C*H*$_2$C=CHEt), 4.35 (d, J = 7 Hz, 1H, C*H*O$C_{15}H_{31}SiO_2$), 4.24 (d, J = 12 Hz, 1H, C*H*$_2$C=CHEt), 3.81−3.72 (m, 2H, C*H*$_2$OBn), 3.66−3.63 (m, 3H, C*H*OBn, C*H*OH), 3.53−3.50 (m, 1H, C*H*CH$_2$OBn), 2.75 (s, (br), 1H, CHO*H*), 2.14 (q, J = 7 Hz, 2H, C*H*$_2$CH$_3$), 1.23−1.07 (m, 21H, Si(*i*-Pr)$_3$), 1.02 (t, J = 8 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.0, 133.9, 132.9, 132.8, 128.1, 128.1, 127.8, 127.7, 127.5, 127.5, 127.3, 127.3, 101.5, 84.4, 75.0, 74.8, 74.6, 73.3, 71.5, 68.8, 58.9, 20.6, 17.8, 14.0, 11.8; IR (neat) 3480 (br), 3080, 3040, 2950, 2880, 1500, 1450, 1360, 1100 (br), 880, 730, 690 cm^{-1}.

(2′*R*,3′*R*)-2′-[[(Triisopropylsilyl)oxy]methyl]-2′,3′-methanopentyl 3,4,6-Tri-*O*-benzyl-β-D-glucopyranose (8). To a solution of glucopyranoside **6** (8.25 g, 11.7 mmol) in CH_2Cl_2 (120 mL) cooled to −30 °C was added in one portion diethylzinc (8.4 mL, 81.9 mmol). After 10 min of stirring, diiodomethane (4.7 mL, 58.5 mmol) was added to the solution over a period of 1 min. When TLC analysis (15% EtOAc/hexane) no longer showed any evolution (10 h), the cloudy solution was slowly poured in a stirring mixture of ether (200 mL) and saturated aqueous NH_4Cl (50 mL) at 0 °C. To this solution was added a minimum amount of 10% aqueous HCl to dissolve the white precipitate. The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with 0.05 M aqueous Na_2SO_3 (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product of the reaction was analyzed by HPLC to obtain a diastereomeric ratio of >100:1 (4 μm silica gel NOVA-PAK, 8 mm ×

20 cm; 8% EtOAc/hexane; flow rate 1 mL/min, T_r (major) 15.7 min, T_r (minor) 20.4 min).[53] The residue was purified by flash chromatography (6% EtOAc/hexane) to produce glucopyranoside **8** (7.8 g, 93%) as a viscous colorless oil. After the chromatography, the HPLC and ^{1}H NMR analyses indicated the presence of only one diastereomer: R_f 0.3 (10% EtOAc/hexane); $[\alpha]_D$ −11.7° (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.21 (m, 15H, Ph), 5.02 (d, J = 11 Hz, 1H, CH_2Ph), 4.89 (d, J = 11 Hz, 1H, CH_2Ph), 4.86 (d, J = 11 Hz, 1H, CH_2Ph), 4.65 (d, J = 12 Hz, 1H, CH_2Ph), 4.60 (d, J = 11 Hz, 1H, CH_2Ph), 4.58 (d, J = 12 Hz, 1H, CH_2Ph), 4.36 (d, J = 7 Hz, 1H, $CHOC_{16}H_{33}SiO_2$), 3.95 (d, J = 11 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.82−3.72 (m, 4H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$, CH_2OBn), 3.66−3.59 (m, 3H, $CHOBn$, $CHOH$), 3.50 (d, J = 10 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.52−3.49 (m, 1H, $CHCH_2OBn$), 2.53 (s, 1H, $CHOH$), 1.53−1.36 (m, 2H, CH_2CH_3), 1.17−1.05 (m, 21H, Si(*i*-Pr)$_3$), 1.02 (t, J = 7 Hz, 3H, CH_2CH_3), 0.81−0.76 (m, 1H, $CH_{cyclopro.}$), 0.71 (dd, J = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 0.23 (t, J = 5 Hz, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.2, 138.1, 128.2, 128.2, 128.2, 127.8, 127.8, 127.6, 127.5, 127.4, 127.4, 102.5, 84.4, 77.5, 75.2, 74.9, 74.9, 74.8, 73.4, 69.6, 68.9, 67.4, 26.4, 22.8, 22.0, 17.9, 14.7, 14.2, 11.9; IR (neat) 3460 (br), 3020, 2940, 2860, 1490, 1450, 1360, 1100 (v. br), 875, 780, 740, 690 cm^{-1}.

(2′*R*,3′*S*)-2′-[[(Triisopropylsilyl)oxy]methyl]-2′,3′-methanopentyl 3,4,6-Tri-*O*-benzyl-β-D-glucopyranose (9). To a solution of glucopyranose 7 (7.1 g, 10.07 mmol) in CH_2Cl_2 (150 mL) at −30 °C was added diethylzinc (4.13 mL, 40.3 mmol). The solution was stirred for 15 min at −30 °C and cooled to −78 °C, and chloroiodomethane (2.93 mL, 40.3 mmol) was added over 30 s. The bath was slowly warmed to −60 °C, and the reaction was kept between −60 and −50 °C until the TLC analysis showed that >95% of the starting material had been consumed (16 h). The solution was warmed to −30 °C and kept at this temperature for 1 h. The reaction was then diluted with ether and quenched with saturated aqueous NH_4Cl. The resulting mixture was poured into a mixture of ether (300 mL) and H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude product was analyzed by HPLC to obtain a 66:1 diastereomeric ratio (4 μm silica gel NOVA-PAK (8 mm × 20 cm; 7% EtOAc/hexane; flow rate 1 mL/min, T_r (major) 26.0 min, T_r (minor) 30.7 min).[54] The residue was then purified by flash chromatography (7−10% EtOAc/hexane) to produce glucopyranoside **9** (7.13 g, 98%), which was contaminated with *ca.* 1% of the unseparable diastereomeric glycoside: R_f 0.30 (10% EtOAc/hexane); $[\alpha]_D$ −2.5° (*c* 3.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.15 (m, 15H, Ph), 4.97 (d, J = 11 Hz, 1H, CH_2Ph), 4.83 (d, J = 11 Hz, 1H, CH_2Ph), 4.82 (d, J = 11 Hz, 1H, CH_2Ph), 4.59 (d, J = 12 Hz, 1H, CH_2Ph), 4.53 (d, J = 11 Hz, 1H, CH_2Ph), 4.52 (d, J = 12 Hz, 1H, CH_2Ph), 4.31 (d, J = 7 Hz, 1H, $CHOC_{16}H_{33}SiO_2$), 3.95 (d, J = 10 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.83 (d, J = 11 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.74−3.66 (m, 3H, CH_2OBn, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.61−3.54 (m, 3H, $CHOBn$, $CHOH$), 3.45−3.43 (m, 1H, $CHCH_2OBn$), 3.36 (d, J = 10 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 2.52 (s (br), 1H, $CHOH$), 1.53−1.46 (m, 1H, CH_2CH_3), 1.32−1.25 (m, 1H, CH_2CH_3), 1.15−1.03 (m, 21H, Si(*i*-Pr)$_3$), 0.99 (t, J = 7 Hz, 3H, CH_2CH_3), 0.74−0.67 (m, 1H, $CH_{cyclopro.}$), 0.64 (dd, J = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 0.22 (t, J = 5 Hz, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.1, 128.2, 128.2, 128.1, 127.8, 127.5, 127.4, 127.4, 102.0, 84.4, 77.4, 75.0, 75.0, 74.8, 74.8, 73.8, 73.3, 68.9, 62.9, 26.2, 23.2, 21.7, 17.9, 17.9, 14.7, 14.2, 11.8; IR (neat) 3450 (br), 3050, 3020, 2920, 2850, 1450, 1350, 1050 (br), 900, 720, 690 cm^{-1}.

(53) An authentic 1:1 diastereomeric mixture was synthesized by the glycosylation reaction using racemic cyclopropylmethanol **10** and glycoside **2** (the ^{1}H NMR spectra of the 1:1 mixture and of the enriched material are included in the supporting information). The detection limit of the minor diastereomer is at least 1% under these conditions.

(54) An authentic 1:1 diastereomeric mixture was prepared from racemic cyclopropylmethanol **11** and glycoside **2** (the ^{1}H NMR spectra of the 1:1 mixture of the enriched material are included in the supporting information). In this case, both diastereomers were unseparable by flash chromatography but separable by HPLC.

(2*R*,3*R*)-2-[[(Triisopropylsilyl)oxy]methyl]-2,3-methanopentan-1-ol ((−)-10). To a solution of cyclopropyl **8** (6.25 g, 8.69 mmol) in CH_2Cl_2 (175 mL) at −20 °C was added pyridine (4.2 mL, 52.1 mmol) in one portion followed by triflic anhydride (2.1 mL, 13.0 mmol) over 10 min. The reaction was stirred at −20 °C for 40 min, and an additional amount of triflic anhydride (0.8 mL, 4.3 mmol) was added. The reaction was then allowed to warm to room temperature over 2 h, recool to 0 °C, and then quenched with saturated aqueous $NaHCO_3$. This mixture was diluted with ether (300 mL) and H_2O (100 mL), and the layers were separated. The aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with H_2O (4 × 50 mL), a saturated aqueous solution of $NaHCO_3$ (50 mL), and brine (50 mL) and then dried over $MgSO_4$. The solution was concentrated under reduced pressure (bath at <30 °C), and the residue was filtered on a short plug of silica gel (5% EtOAc/hexane + 0.5% pyridine). The triflate was immediately dissolved in DMF (100 mL) and pyridine (7 mL) was added followed by H_2O (12.5 mL). The resulting homogenous solution was placed in an oil bath that had been previously heated to 120 °C. The reaction was stirred at 110 °C (internal temperature) for 5−10 min and was then cooled to room temperature. The solution was then poured in a separating funnel containing a mixture of ether (300 mL), ethyl acetate (300 mL), and H_2O (200 mL), and the layers were separated. The aqueous layer was extracted with 50% ether/EtOAc (2 × 200 mL). The combined organic layers were washed with H_2O (4 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (4% EtOAc/hexane) to afford cyclopropylmethanol (−)-**10** (1.81 g, 75% from **8**): R_f 0.25 (5% EtOAc/hexane); $[\alpha]_D$ −19.2° (*c* 1.4, $CHCl_3$); RMN ^{1}H (300 MHz, $CDCl_3$) δ 3.80 (d, J = 11 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.76 (d, J = 10 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.65 (d, J = 11 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.53 (d, J = 10 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.00 (s (br), 1H, CH_2OH), 1.53−1.33 (m, 2H, CH_2CH_3), 1.15−1.03 (m, 21H, Si(*i*-Pr)$_3$), 1.00 (t, J = 7 Hz, 3H, CH_2CH_3), 0.79−0.70 (m, 1H, $CH_{cyclopro.}$), 0.52 (dd, J = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 0.19 (t, J = 5 Hz, 1H, $CH_{2cyclopro.}$); RMN ^{13}C (75 MHz, $CDCl_3$) δ 72.8, 66.0, 27.7, 24.8, 22.3, 17.8, 14.4, 14.3, 11.7; IR (neat) 3460 (br), 2960, 2880, 1465, 1390, 1250, 1090, 1060, 1010, 880, 810, 680 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{35}O_2Si$ 287.2406, found 287.2406.

(2*R*,3*S*)-2-[[(Triisopropylsilyl)oxy]methyl]-2,3-methanopentan-1-ol ((+)-11). The reaction was performed by following the procedure described for (−)-**10**. The residue was purified by flash chromatography (6−8% EtOAc/hexane) to afford cyclopropylmethanol (+)-**10** (2.11 g, 80% from **9**): R_f 0.35 (10% EtOAc/hexane); $[\alpha]_D$ −3.77° (*c* 3.4, $CHCl_3$); RMN ^{1}H (300 MHz, $CDCl_3$) δ 3.96 (d, J = 10 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.69 (d, J = 10 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.63 (d, J = 11 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 3.36 (d, J = 11 Hz, 1H, $CH_2C(CH_{2cyclopro.})CH_{cyclopro.}$), 2.97 (s (br), 1H, CH_2OH), 1.46−1.26 (m, 2H, CH_2CH_3), 1.15−1.03 (m, 21H, Si (*i*-Pr)$_3$), 0.99 (t, J = 7 Hz, 3H, CH_2CH_3), 0.87−0.77 (m, 1H, $CH_{cyclopro.}$), 0.55 (dd, J = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 0.07 (t, J = 5 Hz, 1H, $CH_{2cyclopro.}$); RMN ^{13}C (100 MHz, $CDCl_3$) δ 71.3, 67.0, 27.7, 24.5, 22.2, 17.8, 17.6, 14.4, 14.2, 11.7; IR (neat) 3400 (br), 2920, 2860, 1460, 1380, 1080, 1060, 875, 800, 670 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{35}O_2Si$ 287.2406, found 287.2406.

(2*S*,3*S*)-2-[[(Triisopropylsilyl)oxy]methyl]-2,3-methanopentanoic Acid (12). The alcohol (+)-**11** (2.0 g, 6.98 mmol) was oxidized by following the procedure described for **18**. Filtration on silica gel (5−10% EtOAc/hexane + 1% AcOH) afforded the pure acid **12** (1.74 g, 83%): R_f 0.5 (10% EtOAc/hexane + 1% AcOH); $[\alpha]_D$ +9.94° (*c* 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (d, J = 11 Hz, 1H, CH_2OTIPS), 3.91 (d, J = 11 Hz, 1H, CH_2OTIPS), 1.63−1.54 (m, 2H, CH_2CH_3), 1.44−1.36 (m, 2H, $CH_{cyclopro.}$, $CH_{2cyclopro.}$), 1.17−1.02 (m, 24H, Si(*i*-Pr)$_3$, CH_2CH_3), 0.69 (dd, J = 7, 4 Hz, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 61.8, 29.6, 29.2, 21.9, 19.7, 17.8, 13.9, 11.8; IR (neat) 2940, 2860, 1690, 1460, 1425, 1380, 1250, 1090, 870, 790, 670 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{33}SiO_3$ 301.2199, found 301.2185.

(2*S*,3*S*)-2-(*N*-(*tert*-Butoxycarbonyl)amino)-2,3-methanopentan-1-ol (13). The amino alcohol **13** was prepared using the procedure described for **19a** (scale of 702 mg, 2.34 mmol). Subsequent flash chromatography (30% EtOAc/hexane) produced the desired alcohol **13**

as a colorless oil that was free of **19** by ^1H and ^{13}C NMR (380 mg, 75%): R_f 0.3 (30% EtOAc/hexane); $[\alpha]_D$ +21.3° (*c* 1.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (s (br), 1H, N*H*BOC), 3.73−3.61 (s (br), 1H, CH_2OH), 3.72 (d, J = 11 Hz, 1H, CH_2OH), 3.62 (d, J = 11 Hz, 1H, CH_2OH), 1.61−1.52 (m, 1H, CH_2CH_3), 1.40 (s, 9H, *t*-Bu), 1.34−1.21 (m, 1H, CH_2CH_3), 1.07−0.98 (m, 1H, $CH_{2cyclopro.}$), 0.99 (t, J = 7 Hz, 3H, CH_2CH_3), 0.84 (dd, J = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 0.46 (t, J = 6 Hz, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 79.8, 66.5, 38.4, 28.6, 28.2, 22.5, 18.5, 13.8; IR (neat) 3300 (br), 2950, 2910, 2860, 1670, 1480, 1355, 1240, 1155, 1010, 905, 770, 720 cm^{-1}; HMRS (Fab) calcd for $C_{11}H_{22}NO_3$ 216.1599, found 216.1607.

(2*S*,3*S*)-2-(*N*-(*tert*-Butoxycarbonyl)amino)-2,3-methanopentanoic Acid (14). Method A. To a mixture of alcohol **13** (29 mg, 0.13 mmol) in a mixture of CCl_4 (400 μL), CH_3CN (400 μL), and H_2O (500 μL) were added $NaIO_4$ (87 mg, 0.41 mmol) $RuCl_3$ (4 mg). The mixture was stirred at room temperature for 2 h, and the reaction mixture was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. TLC analysis of the crude mixture indicated the presence of acids **14** and **15** (R_f 0.2 and 0.25 (40% EtOAc/hexanes)).

Method B. The acid **14** was synthesized using the procedure described for **20a** (scale of 270 mg, 1.25 mmol). Recrystallization from 5% ether/hexanes produced the acid **14** (271 mg, 95%), which is slightly contaminated with 7% of the (*Z*)-isomer. This mixture was treated with diazomethane, and the methyl ester of the minor isomer was removed by flash chromatography (10% EtOAc/hexane). The major methyl ester was subsequently hydrolyzed upon treatment with 40% aqueous KOH (50 equiv) in methanol (90% overall yield): mp 125−126 °C; R_f 0.3 (25% EtOAc/hexane + 1% AcOH); $[\alpha]_D$ +33.1° (*c* 0.7, MeOH), lit.[22b] $[\alpha]_D$ +33.3° (*c* 1.1, MeOH); ^1H NMR (400 MHz, C_6D_6 + 1 drop of DMSO, 70 °C) δ 5.88 (s (br), 1H, N*H*BOC), 1.79−1.62 (m, 2H, CH_2CH_3), 1.52 (dd, J = 8, 5 Hz, 1H, $CH_{2cyclopro.}$), 1.48 (s, 9H, *t*-Bu), 1.41−1.32 (m, 1H, $CH_{cyclopro.}$), 1.18 (dd, J = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 1.01 (t, J = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, C_6D_6 + 1 drop of DMSO)[55] δ 174.5, 156.3, 79.2, 78.5, 33.3, 32.8, 28.6, 23.0, 20.9, 13.8, 13.7; IR (KBr) 3250, 3090, 2970, 2930, 2870, 2680, 2560, 2480, 1685, 1640, 1400, 1360, 1300, 1190, 1155, 1050, 935, 850, 770, 660 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{20}NO_4$ 230.1392, found 230.1399.

***tert*-Butyl (2*S*,3*S*)-2-[[(Triisopropylsilyl)oxy]methyl]-2,3-methanopentanoate (16).** The title compound was prepared using the procedure described for **21** (scale of 669 mg, 2.23 mmol). The crude *tert*-butyl ester (755 mg, >90%) produced was used directly in the next step without further purification. An analytically pure sample was obtained by flash chromatography (2% EtOAc/hexane): R_f 0.6 (2% EtOAc/hexane); $[\alpha]_D$ +15.78° (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (d, J = 11 Hz, 1H, CH_2OTIPS), 3.95 (d, J = 11 Hz, 1H, CH_2OTIPS), 1.62−1.52 (m, 1H, CH_2CH_3), 1.49−1.40 (m, 1H, $CH_{cyclopro.}$), 1.42 (s, 9H, *t*-Bu), 1.38−1.29 (m, 1H, CH_2CH_3), 1.18 (dd, J = 9, 4 Hz, 1H, $CH_{2cyclopro.}$); 1.14−1.03 (m, 21H, Si(*i*-Pr)$_3$), 1.01 (t, J = 7 Hz, 3H, CH_2CH_3), 0.61 (dd, J = 7, 4 Hz, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 79.8, 61.7, 31.0, 28.1, 27.9, 22.1, 18.6, 17.9, 14.0, 12.0; IR (neat) 2940, 2870, 1715, 1460, 1370, 1250, 1150, 1090, 880, 680 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{41}SiO_3$ 357.2825, found 357.2806.

***tert*-Butyl (2*R*,3*S*)-2-[*N*-(*tert*-Butoxycarbonyl)amino]-2,3-methanopentanoate (17).** The amino acid **17** was prepared using the procedure described for **22a**. Subsequent flash chromatography (60:35:5 hexanes/$CHCl_3$/EtOAc) produced the amino acid **17** (232 mg, 45% from **12**) as a white solid. The amino acid can also be recrystallized from 10% ether/hexane: mp 119−120 °C; R_f 0.3 (5% EtOAc/hexane); $[\alpha]_D$ +35.5° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO, 90 °C) δ 6.74 (bs, 1H, N*H*BOC), 1.62−1.47 (m, 2H, CH_2CH_3, $CH_{cyclopro.}$), 1.41 (s, 9H, *t*-Bu), 1.40 (s, 9H, *t*-Bu), 1.25 (dd, J = 9, 5 Hz, 1H, $CH_{cyclopro.}$), 1.20−1.09 (m, 1H, CH_2CH_3), 0.97 (t, J = 7 Hz, 3H, CH_2CH_3), 0.67 (dd, J = 7, 5 Hz, 1H, $CH_{cyclopro.}$); ^{13}C NMR (100 MHz, C_6D_6) δ 172.3, 156.2, 80.3, 78.8, 39.3, 29.7, 28.4, 28.0, 22.5, 21.6, 13.5; IR (KBr) 3350, 2980, 2940, 2880, 1700, 1510, 1450, 1365, 1250, 1160 (br), 1070, 1020, 850, 760, 650 cm^{-1}.

(2*S*,3*R*)-2-[[(Triisopropylsilyl)oxy]methyl]-2,3-methanopentanoic Acid (18). To a solution of alcohol (−)-**10** (1.78 g, 6.21 mmol) in a mixture of CH_3CN (17 mL), CCl_4 (17 mL) and H_2O (26 mL) was added $NaIO_4$ (5.3 g, 24.8 mmol). The solution was vigorously stirred at room temperature, and $RuCl_3 \cdot xH_2O$ (39 mg, 0.19 mmol) was added in one portion. After 2 h, the solution was diluted with CH_2Cl_2 (60 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The black residue was filtered on a short plug of silica gel (5% EtOAc/hexane + 1% AcOH) to produce the acid **18** (1.7 g, 91%) as a slightly purplish oil: R_f 0.5 (10% EtOAc/hexane + 1% AcOH); $[\alpha]_D$ −27.25° (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (d, J = 10 Hz, 1H, CH_2OTIPS), 3.87 (d, J = 10 Hz, 1H, CH_2OTIPS), 1.65−1.45 (m, 2H, CH_2CH_3), 1.36−1.26 (m, 1H, $CH_{cyclopro.}$), 1.19 (dd, J = 7, 4 Hz, 1H, $CH_{2cyclopro.}$), 1.15−1.01 (m, 22H, Si(*i*-Pr)$_3$), $CH_{2cyclopro.}$), 0.94 (t, J = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 64.9, 30.2, 28.8, 20.5, 17.8, 17.1, 13.6, 11.8; IR (neat) 2980, 2870, 1700, 1460, 1430, 1310, 1260, 1200, 1110, 1070, 880, 680 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{33}SiO_3$ 301.2199, found 301.2188.

(2*S*,3*R*)-2-(*N*-(*tert*-Butoxycarbonyl)amino)-2,3-methanopentan-1-ol (19a). To a solution of acid **18** (349 mg, 1.16 mmol) in toluene (10 mL) at 0 °C was added triethylamine (645 μL, 4.64 mmol) followed by diphenylphosphoryl azide (500 μL, 2.32 mmol). The ice bath was removed, and after 1.5 h of stirring at room temperature, the reaction was diluted with ether (50 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure.[56] The residue was purified by flash chromatography (1% EtOAc/hexane) to afford the acyl azide (362 mg, 96%). The azide was immediately dissolved in dry *tert*-butyl alcohol (10 mL), and the solution was heated under reflux (120 °C) for 24 h or until the isocyanate had completely disappeared by TLC (R_f 0.9, 5% EtOAc/hexane). The *tert*-butyl alcohol was evaporated under reduced pressure, the residue was dissolved in dry THF (7 mL), and glacial acetic acid (66 μL, 1.16 mmol) was added followed by a 1.0 M solution of TBAF in THF (2.3 mL, 2.32 mmol). The reaction was stirred 2 h at room temperature or until TLC analysis showed the complete consumption of the starting materials. Then 10 mL of saturated aqueous $NaHCO_3$ was added, and the reaction was diluted with ether (50 mL). The aqueous layer was extracted twice with 50% EtOAc/ether (25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (30% EtOAc/hexane) to produce the alcohol **19a** (227 mg, 91%): R_f 0.2 (20% EtOAc/hexane); $[\alpha]_D$ −29.1° (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 1H, N*H*BOC), 3.68 (d, J = 11 Hz, 1H, CH_2OH), 3.47 (d, J = 11 Hz, 1H, CH_2OH), 3.69−3.45 (s (br), 1H, CH_2OH), 1.66−1.50 (m, 1H, CH_2CH_3), 1.45 (s, 9H, *t*-Bu), 1.34−1.20 (m, 1H, CH_2CH_3), 1.03 (t, J = 7 Hz, 3H, CH_2CH_3), 1.06−0.86 (m, 2H, $CH_{cyclopro.}$, $CH_{2cyclopro.}$), 0.40 (t, J = 5 Hz, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 80.1, 71.0, 39.4, 28.2, 25.5, 21.5, 18.1, 13.8; IR (near) 3420 (br), 2960, 2930, 2870, 1690, 1500 (br), 1385, 1365, 1250, 1165, 1060, 1040, 855, 775 cm^{-1}.

(2*S*,3*R*)-2-(*N*-Benzyloxycarbonyl)amino)-2,3-methanopentan-1-ol (19b). To a solution of acid **18** (173 mg, 0.576 mmol) in toluene (5 mL) at 0 °C was added triethylamine (320 μL, 2.3 mmol) followed by diphenylphosphoryl azide (250 μL, 1.15 mmol). The ice bath was removed, and the solution was stirred for 2 h at room temperature. The reaction mixture was then diluted with ether and H_2O. The layers were separated, and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure.[54] The residue was purified by flash chromatography (1% EtOAc/hexane) to afford the desired acyl azide (180 mg, 95%) which was immediately dissolved in a solution of benzyl alcohol (120 μL) in dry toluene (4 mL). The clear solution was heated under reflux (120 °C) for 24 h or until TLC analysis showed complete consumption of the starting isocyanate (R_f > 0.9, 5% EtOAc/hexane). The solution

(55) Rotameric isomer was included in this listing.

(56) This intermediate is thermally unstable and should not be heated over 40 °C.

was concentrated under reduced pressure, the residue was dissolved in dry THF (4 mL), and glacial acetic acid (33 μL, 0.576 mmol) was added followed by a 1.0 M solution to TBAF in THF (1.15 mL, 1.15 mmol). The reaction was stirred for 5 h at room temperature or until TLC analysis showed the complete consumption of the starting material. Saturated aqueous $NaHCO_3$ (10 mL) was added followed by ether (50 mL). The aqueous layer was extracted with 50% EtOAc/ether (2 × 25 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The solid residue was recrystallized from 10% ether/hexane to produce alcohol **19b** (133 mg, 93%): mp 86−86.5 °C; R_f 0.2 (30% EtOAc/hexane); $[\alpha]_D$ −17.1° (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.28 (m, 5H, Ph), 5.40 (s (br), 1H, N*H*CBz), 5.12 (d, *J* = 12 Hz, 1H, CH_2Ph), 5.06 (d, *J* = 12 Hz, 1H, CH_2Ph), 3.64 (d, *J* = 11 Hz, 1H, CH_2OH), 3.50 (d, *J* = 11 Hz, 1H, CH_2OH), 3.32 (s (br), 1H, CH_2OH), 1.58−1.47 (m, 1H, CH_2CH_3), 1.27−1.18 (m, 1H, CH_2CH_3), 1.06−0.92 (m, 2H, $CH_{cyclopro.}$, $CH_{2cyclopro.}$), 1.00 (t, *J* = 7 Hz, 3H, CH_2CH_3), 0.45 (t (br), *J* = 5 Hz, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 136.0, 128.4, 128.0, 128.0, 69.9, 66.9, 39.4, 25.1, 21.4, 17.6, 13.7; IR (KBr) 3330 (br), 3080, 3030, 3010, 2960, 2930, 2870, 1695, 1525, 1465, 1450, 1260, 1085, 1020, 730, 690 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{20}NO_3$ 250.1443, found 250.1453.

(2*S*,3*R*)-2-(*N*-(*tert*-Butoxycarbonyl)amino)-2,3-methanopentanoic Acid (20a). To a solution of alcohol **19a** (223 mg, 1.03 mmol) in DMF (10 mL) was added freshly activated 4 Å molecular sieves (*ca.* 1 g) followed by PDC (1.9 g, 5.18 mmol). After 40 min of stirring at room temperature, the solution was diluted with ether (10 mL) and stirred vigorously. The mixture was filtered on Celite (further washed with a mixture of ether/CH_2Cl_2/H_2O), and the solution was concentrated under vacuum (30 °C at 0.5 mmHg). The layers were separated, and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic layers were washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting colorless oil was immediately dissolved in a mixture of *tert*-butyl alcohol (6 mL) and 5% aqueous NaH_2PO_4 (4 mL). To this solution was added in one portion a 1.0 M aqueous solution of $KMnO_4$ (6.2 mL, 6.2 mmol). The reaction mixture was stirred for 3 min at room temperature and then quenched with saturated aqueous $NaHSO_3$ (*ca.* 2 mL). The solution was then diluted with CH_2Cl_2 and H_2O. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL). Between each extraction, the aqueous layer was progressively acidified to pH 3. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting solid was recrystallized from 10% ether/hexanes to produce the acid **20a** (212 mg, 90%): mp 129−129.5 °C; R_f 0.3 (25% EtOAc/hexane containing 1% AcOH); $[\alpha]_D$ −31.6° (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6 + 1 drop of DMSO-d_6, 70 °C) δ 4.93 (s (br), 1H, N*H*BOC), 1.77−1.69 (m, 1H, $CH_{cyclopro.}$), 1.64 (dd, *J* = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 1.61−1.44 (m, 1H, CH_2CH_3), 1.46 (s, 9H, *t*-Bu), 1.17−1.06 (m, 1H, CH_2CH_3), 0.83 (t, *J* = 7 Hz, 3H, CH_2CH_3), 0.66−0.64 (m, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (75 MHz, acetone-d_6 + 1 drop of DMSO-d_6) δ 175.8, 157.2, 79.7, 78.9, 38.8, 30.2, 28.7, 22.7, 22.2, 13.9; IR (KBr) 3390, 3100, 2980, 2960, 2940, 2880, 1700 (br), 1510, 1450, 1365, 1250, 1165, 1090, 950, 785 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.73; H, 8.61; N, 6.19.

(2*S*,3*R*)-2-(*N*-(Benzyloxycarbonyl)amino)-2,3-methanopentanoic Acid (20b). The title compound was prepared by the procedure given for **20a** (scale of 127 mg, 0.509 mmol). Analytically pure amino acid **20b** was obtained after a recrystallization from 10% ether/hexanes (126 mg, 94%): mp 111−111.5 °C; R_f 0.4 (30% EtOAc/hexane); $[\alpha]_D$ −22.6° (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz recorded at 70 °C, C_6D_6 + drop of DMSO-d_6) δ 7.27−7.03 (m, 5H, Ph), 5.49 (s (br), 1H, N*H*CBz), 5.14 (d, *J* = 13 Hz, 1H, CH_2Ph), 5.09 (d, *J* = 13 Hz, 1H, CH_2Ph), 1.80−1.73 (m, 1H, $CH_{cyclopro.}$), 1.68 (dd, *J* = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 1.56−1.45 (m, 1H, CH_2CH_3), 1.15−1.04 (m, 1H, CH_2CH_3), 0.83 (t, *J* = 7 Hz, 3H, CH_2CH_3), 0.76−0.72 (m, 1H, $CH_{2cyclopro.}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 158.5, 156.9, 136.0, 128.3, 128.0, 127.5, 67.3, 66.9, 38.0, 31.0, 24.0, 23.5, 21.4, 13.3; IR (KBr) 3350, 3030, 2960, 2880, 1710, 1520, 1450, 1330, 1285, 1250, 1100, 930, 780, 740, 690 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.72; H, 6.51; N, 5.18.

***tert*-Butyl (2*S*,3*R*)-2-[[(Triisopropylsilyl)oxy]methyl]-2,3-methanopentanoate (21).** To a solution of acid **18** (817 mg, 2.72 mmol) in cyclohexane (7.8 mL) at 0 °C, was added *tert*-butyloxy trichloroacetimidate (1.19 g, 5.44 mmol) followed by BF_3·OEt_2 (50 μL, 0.41 mmol). The ice bath was removed, and the solution was stirred at room temperature for 1.5 h and then quenched with $NaHCO_3$. The solution was diluted with hexane and filtered on a small plug (*ca.* 2 in.) of silica gel. The silica gel was then washed with an additional portion of 10% EtOAc/hexane (75 mL). The crude product was used directly in the next step without further purification. An analytically pure sample was obtained by flash chromatography (5% EtOAc/hexane): R_f 0.3 (2% EtOAc/hexane); $[\alpha]_D$ −4.9° (*c* 3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.22 (d, *J* = 10 Hz, 1H, CH_2OTIPS), 3.44 (d, *J* = 10 Hz, 1H, CH_2OTIPS), 1.53−1.36 (m, 2H, CH_2CH_3), 1.43 (s, 9H, CO_2*t*-Bu), 1.24−0.99 (m, 23H, Si(*i*-Pr)$_3$, $CH_{cyclopro.}$, $CH_{2cyclopro.}$), 0.96−0.89 (m, 1H, $CH_{2cyclopro.}$), 0.91 (t, *J* = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 79.9, 65.4, 31.9, 28.0, 26.4, 20.7, 17.9, 16.3, 13.8, 11.9; IR (neat) 2960, 2940, 2870, 1730, 1465, 1395, 1370, 1320, 1250, 1150, 1100, 880, 680 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{41}SiO_3$ 357.2825, found 357.2834.

***tert*-Butyl (2*R*,3*R*)-2-(*N*-(*tert*-Butoxycarbonyl)amino)-2,3-methanopentanoate (22a).** To a solution of cyclopropane **21** (*ca.* 780 mg, 2.19 mmol) in dry THF (10 mL) was added glacial acetic acid (125 μL, 2.19 mmol) followed by a 1.0 M solution of TBAF in THF (4.37 mL, 4.37 mmol). The reaction was stirred for 5 h at room temperature or until the TLC analysis showed the complete consumption of the starting material.[57] Saturated aqueous $NaHCO_3$ (5 mL) was then added, and the reaction mixture was diluted with ether (25 mL). The aqueous layer was extracted twice with 50% EtOAc/ether (25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure (volatile). The resulting oil was immediately dissolved in a mixture of CH_3CN (7.5 mL), CCl_4 (7.5 mL), and H_2O (10 mL). $NaIO_4$ (1.87 g, 8.76 mmol) was then added followed by $RuCl_3$·xH_2O (14 mg, 0.066 mmol). After 2 h of stirring at room temperature, the solution was diluted with CH_2Cl_2 (25 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The dark residue was filtered on a short plug of silica gel that was washed several times with 30% EtOAc/hexane containing 1% of AcOH. To a solution of the acid in toluene (20 mL) at 0 °C was added triethylamine (1.11 mL, 8 mmol) followed by diphenylphosphoryl azide (862 μL, 4 mmol). The ice bath was removed, and the reaction mixture was stirred for an additional 3 h at room temperature. Ether (50 mL) and H_2O (10 mL) were then added. The layers were separated, and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure.[56] The residue was purified by flash chromatography (3% EtOAc/hexane) to afford the desired acyl azide (390 mg, 60%) as a colorless oil. The *N*-BOC amino acid derivative was prepared by heating a solution of the azide (182 mg, 0.76 mmol) in dry *tert*-butyl alcohol (7 mL) at 120 °C for 48 h or until the isocyanate had completely disappeared (R_f > 0.9, 10% EtOAc/hexane). The *tert*-butyl alcohol was evaporated under reduced pressure, and the residue was purified by flash chromatography (8% EtOAc/hexane) to produce the protected amino acid **22a** (165 mg, 76%) as a white solid. This compound can also be crystallized from 10% Et_2O/hexane: mp 68.5−69 °C; R_f 0.25 (8% EtOAc/hexane); $[\alpha]_D$ −4.5° (*c* 2.3, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6, 70 °C) δ 4.61 (s, 1H, N*H*BOC), 1.64−1.52 (m, 2H, CH_2CH_3), 1.44−1.39 (m, 1H, $CH_{2cyclopro.}$), 1.44 (s, 9H, *t*-Bu), 1.40 (s, 9H, *t*-Bu), 1.14−1.06 (m, 1H, $CH_{cyclopro.}$), 0.97 (dd, *J* = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 0.92 (t, *J* = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 155.7, 80.6, 79.1, 39.2, 32.1, 28.1, 27.8, 22.01, 20.1, 13.4; IR (neat) 3380, 2980, 2960, 2880, 1720,

(57) Sometimes an additional 0.5 equiv of TBAF is necessary for complete conversion.

1500 (br), 1370, 1250, 1150, 1110, 1050, 850 cm^{-1}. Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 63.24; H, 9.79; N, 4.99.

***tert*-Butyl (2*R*,3*R*)-2-(*N*-(Benzyloxycarbonyl)amino)-2,3-methanopentanoate (22b).** To a solution of the above acyl azide (207 mg, 0.865 mmol) (see procedure for **22a**) in dry toluene (5 mL) was added benzyl alcohol (180 μL, 1.73 mmol). The resulting solution was heated under reflux (120 °C) for 24 h or until TLC analysis showed the complete consumption of the isocyanate (R_f > 0.9, 10% EtOAc/hexane). The volatiles were then evaporated under reduced pressure, and the residue was purified by flash chromatography (8% EtOAc/hexane) to produce the protected amino acid **22b** (270 mg, 98%) as a colorless oil: R_f 0.25 (8% EtOAc/hexane); $[\alpha]_D$ −8.19° (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6, 70 °C) δ 7.27−7.24 (m, 2H, C_6H_5), 7.15−7.04 (m, 3H, C_6H_5), 5.08 (d, *J* = 12 Hz, 1H, CH_2Ph), 5.05 (d, *J* = 12 Hz, 1H, CH_2Ph), 4.85 (s, 1H, NHCBz), 1.61−1.51 (m, 2H, CH_2CH_3), 1.40 (dd, *J* = 8, 5 Hz, 1H, $CH_{2cyclopro.}$), 1.33 (s, 9H, *t*-Bu), 1.17−1.08 (m, 1H, $CH_{cyclopro.}$), 0.98 (dd, *J* = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 0.91 (t, *J* = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 156.3, 136.4, 128.3, 127.9, 127.8, 81.1, 66.5, 39.3, 32.7, 27.8, 22.4, 20.2, 13.4; IR (near) 3360 (br), 2980, 2940, 2880, 1730, 1520 (br), 1460, 1400, 1370, 1350, 1250 (br), 1160, 1050, 850, 740, 700 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{26}NO_4$ 320.1862, found 320.1844.

(2*R*,3*R*)-2-(*N*-(Benzyloxycarbonyl)amino)-2,3-methanopentanoic Acid (23). To a solution of *tert*-butyl ester **22b** (94 mg, 0.294 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (1 mL). The reaction was stirred for 2 h at room temperature. The solution was then diluted with CH_2Cl_2 and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (25% EtOAc/hexane containing 1% AcOH) to produce the amino acid **23** (77 mg, 98%) as a colorless viscous oil: R_f 0.4 (30% EtOAc/hexane + 1% AcOH); $[\alpha]_D$ −29.0° (*c* 2.5, MeOH); ^{1}H NMR (400 MHz, C_6D_6/1 drop DMSO-d_6, 70 °C) δ 9.93 (s (br), 1H, CO_2H), 7.26−7.03 (m, 5H, Ph), 6.02 (s (br), 1H, NHCBz), 5.08 (s, 2H, CH_2Ph), 1.77−1.58 (m, 2H, CH_2CH_3), 1.50 (dd, *J* = 8, 5 Hz, 1H, $CH_{2cyclopro.}$), 1.39−1.29 (m, 1H, $CH_{cyclopro.}$), 1.14 (dd, *J* = 9, 5 Hz, 1H, $CH_{2cyclopro.}$), 0.95 (t, *J* = 7.Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 156.5, 136.0, 128.3, 128.2, 127.9, 66.7, 38.4, 34.2, 29.5, 20.2, 13.3; IR (neat) 3030, 2960, 2930, 2870, 2570, 1700, 1510, 1450, 1400, 1340, 1250, 1100, 1020, 900, 735, 690 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1250.

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Supporting Information Available: ^{1}H NMR spectra of compounds **8** and **9** as well as their authentic 1:1 diastereomeric mixtures (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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