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# Substrate-Controlled and Organocatalytic Asymmetric Synthesis of Carbocyclic Amino Acid Dipeptide Mimetics

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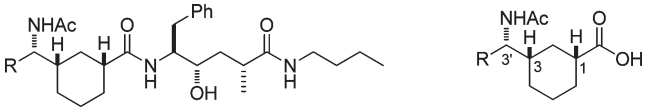


The asymmetric synthesis of a carbocyclic $\delta$-amino acid representing the $P_2/P_3$ subunit of a nonpeptidic truncated peptidomimetic molecule is described relying on two independent approaches.

## Introduction

The design and synthesis of peptidomimetic motifs as backbone components of peptide-based enzyme inhibitors has had a profound impact in the area of structure-based drug discovery.[1] Indeed, a number of high-profile and life-saving medicines such as anti-HIV agents are the result of such efforts.[2] Unmet medical needs related to Alzheimer's disease are also the subject of intense research efforts.[3] Thus, proteases involved in various phases of the disease progression have become the target of chemical intervention through the synthesis of so-called small molecule inhibitors.[4,5] Such proteases recognize a specific sequence in a natural peptide substrate, leading to cleavage and release of the amino and carboxyl components. Depending on their nature, these smaller peptides can trigger further interactions that may eventually be detrimental to the host. For example, the membrane-bound aspartic protease BACE1 ($\beta$-secretase) is known to cleave endoproteolytically the $\beta$-amyloid precursor protein (APP), as a first step in the release of a large ectodomain, which is the substrate of $\gamma$-secretase, eventually resulting in so-called amyloid plaque formation. Aspartic proteases such as BACE1 are ideal targets for inhibition by small molecules with the intention of developing an effective therapeutic agent.[6,7] The availability of structural data from the extracellular domain of BACE1 has greatly enhanced the design of potential inhibitors. Indeed, the first crystal structure of a BACE1-inhibitor complex comprising OM99-2 **A** (Figure 1), a potent heptapeptide inhibitor that harbors an unnatural $\delta$-amino-$\gamma$-hydroxy amino acid subunit as a hydroxyethylamino transition state mimic, was reported by the Tang and Ghosh groups in 2000.[8] Valuable insights gleaned from this structural information

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(2) For a recent review, see: (a) Ghosh, A. K.; Chapsal, B. D.; Weber, I. T.; Mitsuya, H. *Acc. Chem. Res.* **2008**, *41*, 78. (b) DeClerq, E. *Nat. Rev. Drug Discovery* **2007**, *6*, 1001. (c) *HIV Chemotherapy—A Critical Review*; Butera, S. T., Ed.; Caister Academic Press: Norfolk, U.K., 2005.

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(6) For example, see: (a) Stachel, J. S. *Drug Dev. Res.* **2009**, *70*, 101. (b) Jakob-Roente, R.; Jacobsen, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3030. (c) Silvestri, R. *Med. Res. Rev.* **2008**, *8*, 121. (d) Cole, S. L; Vassar, R. *Curr. Alzheimer Res.* **2008**, *5*, 100. (e) Ghosh, A. K.; Kumaragurubaran, N.; Hong, L.; Koelsch, G.; Tang, J. *Curr. Alzheimer Res.* **2008**, *5*, 12. (f) Hills, I. D.; Vacca, J. P. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 383. (g) Durham, T. B.; Shepherd, T. A. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 7761.

(7) For recent developments, see: (a) Iserloh, U.; Cumming, J. N.; Pan, J.; Wang, L. Y.; Stanford, A. W.; Kennedy, M. E.; Kuvelkar, R.; Chen, X.; Parker, E. M.; Strickland, C.; Voigt, J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 418. (b) Stauffer, S. R.; Stanton, M. G.; Gregro, A. R.; Steinbeiser, M. A.; Shaffer, J.-R.; Nantermet, P. G.; Barrow, J.-C.; Rittle, K. E.; Collasi, D.; Espeseth, A. A.; Lai, M.-T.; Pietrak, B. L.; Holloway, M. K.; Mcgaughey, G. B.; Munshi, S. K.; Hochman, J. H.; Simon, A. J.; Selnick, H. G.; Graham, S. L.; Vacca, J. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1788.

(8) (a) Hong, L.; Koelsch, G.; Lin, X.; Wu, W.; Terzyan, S.; Ghosh, A. K.; Zhang, X. C.; Tang, J. *Science* **2000**, *290*, 150. (b) Ghosh, A. K.; Tang, J. *Biochemistry*, **2002**, *41*, 10963 and references therein.

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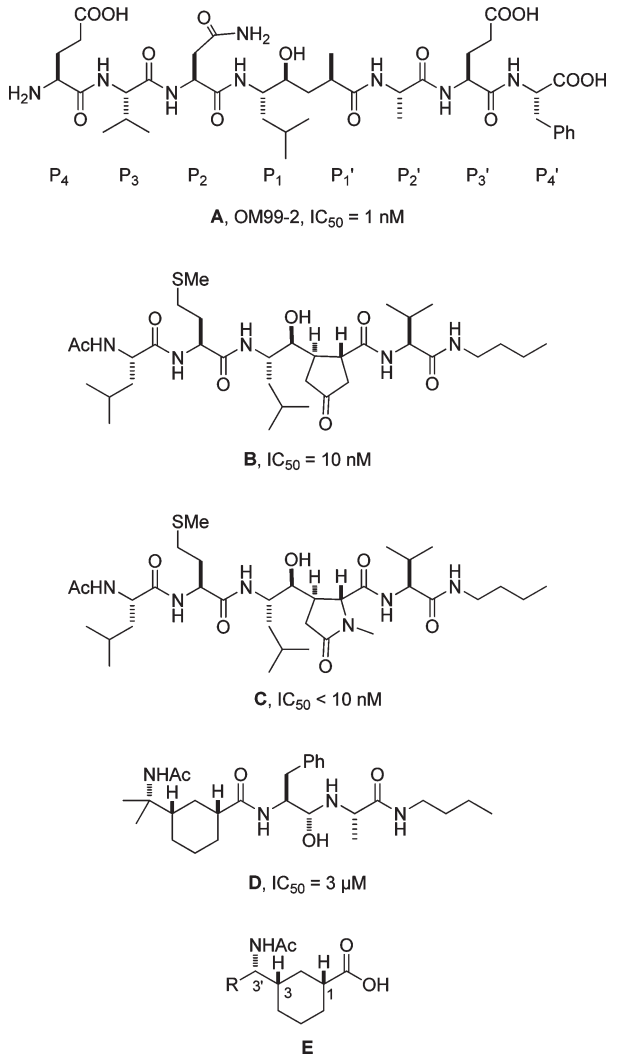


**FIGURE 1.** Tang–Ghosh BACE1 inhibitor OM99-2, and truncated peptidomimetics **B**–**C**.[10–12]

led to the design and synthesis of several other types of BACE1 inhibitors.[9]

In previous papers, we reported on the structure-based design, synthesis, and X-ray crystallographic studies of carbocyclic[10] (**B**) and heterocyclic[11,12] (**C**) $P_1/P_1'$ truncated variants of the Tang and Ghosh original 1nM BACE1 inhibitor **A** (Figure 1). Further refinement of these prototypical inhibitors led us to consider unnatural, minimally peptidic molecules in which the traditional $P_2/P_3$ dipeptide subunit in the Tang and Ghosh inhibitor was replaced by a cyclohexane spacer unit. Preliminary results with a prototypical molecule **D** resulted in low micromolar inhibitory activity against BACE1.[13] Despite the weak activity, a crystal structure of **D** in complex with BACE1, showed that it was indeed bound in the active site, although the orientation of the *N*-acetyl group was changed. In an effort to study the effect and the nature of the steric environment near the *N*-acetyl group, we considered the synthesis of carbocyclic amino acids represented by the generic structure **E** shown in Figure 1.

## Results

We report herein on the streocontrolled synthesis of 3-(1-aminoalkyl)-1-cyclohexane carboxylic acids in their enantiomerically enriched and pure forms. To the best of our knowledge, such carbocyclic $\delta$-amino acids with stereochemically defined substitutions are not known in the context of peptidomimetic design. In this regard, we also report on the incorporation of such constrained carbocyclic amino acids in prototypical molecules with reduced peptidic character as potential inhibitors of BACE1. We focused on compounds with the (1*R*,3*S*,3′*S*) configuration on the basis of previous precedents.[10–13] As a general strategy toward the synthesis of such stereodefined carbocyclic $\delta$-amino acids, we first relied on a resident-chirality-induced conjugate addition starting with chiral, nonracemic $\gamma$-*N*,*N*-dibenzyl $\alpha,\beta$-unsaturated amino acid esters[14] (Scheme 1).

The readily available enoates **1a**–**1d**[14] were subjected to conjugate addition in the presence of vinylmagnesium bromide and CuI, leading to the adducts **2a**–**2d** in modest yields.[14,15] Reduction of the esters to the corresponding alcohols with DIBAL-H, followed by oxidation under Swern conditions, afforded the aldehydes **3a**–**3d**. Treatment with bis-methylmercaptomethylene dimethyl phosphonate anion in the case of **3a** and **3b** led to the bis-methyl ketene dithioacetals **4a** and **4b** in 88% and 82% yields, respectively. In the case of **3c** and **3d**, it was beneficial to effect the extension with diethylphosphoryl dithiane to afford **4c** and **4d** in 97% and 78% yields, respectively. Cleavage of the ketene dithioacetal function in the presence of $CuSO_4$ in refluxing methanol gave the corresponding methyl esters **5a**–**5d** in yields varying between 62% and 75%. Formation of the potassium enolate with KHMDS and treatment with allyl bromide led to diastereomeric mixtures of the *C*-allyl esters **6a**–**6d** in 85–91% yields. Ring-closing metathesis in the presence of the Grubbs first generation catalyst[16] gave excellent yields of the corresponding 1,3-disubstituted 4-cyclohexene-1-carboxylate esters as mixtures of diastereomers. Upon heating these in a methanol solution containing NaOMe, epimerization took place to give a mixture of 3-substituted 4-cyclohexene-1-carboxylic acid esters **7a**–**7d** in which the 1,3-*cis*-isomers were predominant ( > 5:1 by NMR analysis). Trace amounts of carboxylic acids formed during the epimerization process were converted to the corresponding methyl esters **7a**–**7d** by treatment with diazomethane.

(9) See for example: Ghosh, A. K.; Gemma, S.; Tang, J. *Neurotherapeutics* **2008**, *5*, 399.
(10) Hanessian, S.; Yun, H.; Hou, Y.; Yang, G.; Bayrakdarian, M.; Therrien, E.; Moitessier, N.; Roggo, S.; Veenstra, S.; Tintelnot-Blomley, M.; Rondeau, J.-M.; Ostermeier, C.; Strauss, A.; Ramage, P.; Paganetti, P.; Neumann, U.; Betschart, C. *J. Med. Chem.* **2005**, *48*, 5175.
(11) Hanessian, S.; Yun, H.; Hou, Y.; Tintelnot-Blomley, M. *J. Org. Med. Chem.* **2005**, *70*, 6746.
(12) Hanessian, S.; Hou, Y.; Bayrakdarian, M.; Tintelnot-Blomley, M. *J. Org. Med. Chem.* **2005**, *70*, 6735.
(13) Hanessian, S.; Shao, Z.; Betschart, C.; Rondeau, J.-M.; Neumann, U.; Tintelnot-Blomley, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1924.
(14) Reetz, M. T.; Röhrig, D. *Angew. Chem.* **1989**, *28*, 1706.
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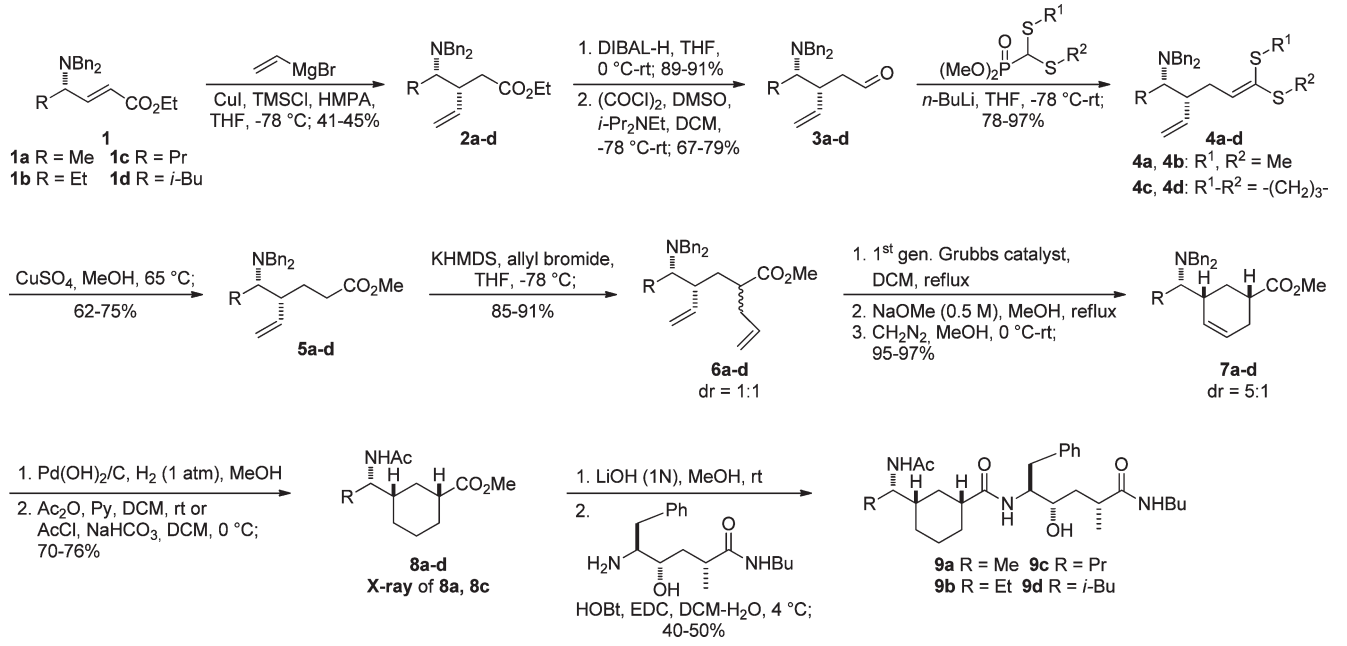
(16) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039. For an authoritative collection of relevant work see: (b) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1–3. (c) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (d) Schmidt, B.; Hermanns, J. *Top. Organomet. Chem.* **2004**, *7*, 223. (e) Connon, S. J.; Blechert, S. *Top. Organomet. Chem.* **2004**, *7*, 93.

**SCHEME 1. Synthesis of Carbocyclic Peptidomimetics 9a−d**

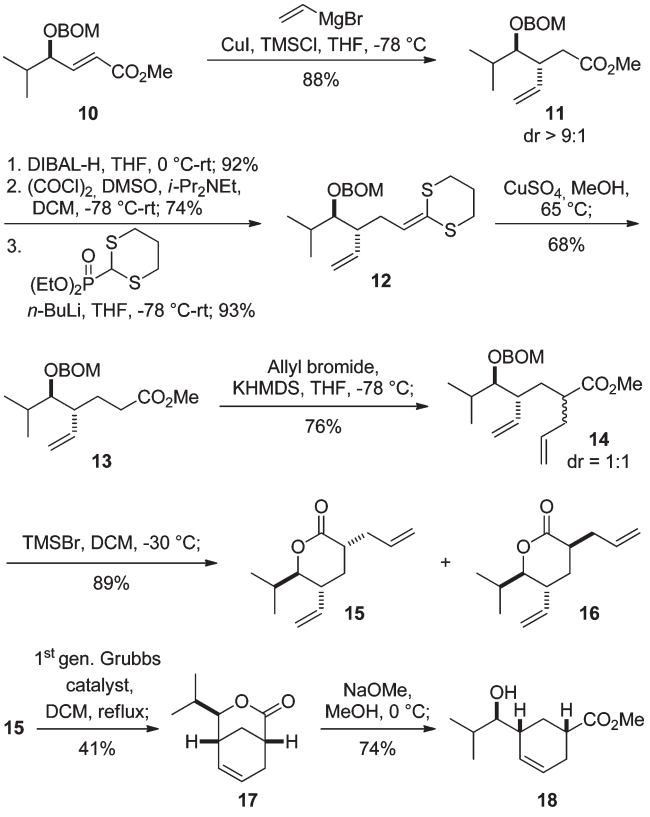



Hydrogenation of **7a** in the presence of $Pd(OH)_2$ in MeOH, followed by acetylation, gave **8a** as a crystalline white solid in 72% yield. A single crystal X-ray structure confirmed the assigned absolute stereochemistry.[17] Analogous treatment of **7b** followed by chromatographic purification gave **8b** in 72% yield as an amorphous white solid. The propyl analogue **8c** was obtained as a crystalline white solid in 76% yield, and its absolute stereochemistry was also confirmed by a single crystal X-ray analysis.[17] The isobutyl analogue **8d** was obtained as a colorless oil in 70% yield after chromatographic purification.

The individual *N*-acetyl carboxylic acids derived from crystalline samples of **8a** and **8c** were coupled with a hydroxyethylamine isostere equivalent[18] to give the prototypical inhibitor molecules **9a** and **9c** as diastereomerically pure products. Identical treatment of the diastereomerically enriched acids coming from **8b** and **8d** gave **9b** and **9d** after chromatographic purification in yields ranging between 40% and 50% and suitable for biological tests.

Since cuprate addition was unsuccessful in the case of the isopropyl analogue (Scheme 1, **1**, R = *i*-Pr), possibly due to steric reasons, we opted for an indirect approach. Thus, the *O*-benzyloxymethyl (*O*-BOM) enoate **10** was converted to the vinyl derivative **11** in excellent yield and selectivity (Scheme 2). Following the same protocol as for the *N*,*N*-dibenzylamino series, **11** was extended to the ketene dithioacetal **12** in excellent yield and then converted to **13**. Formation of the potassium enolate and treatment with allyl bromide at −78 °C led to a 1:1 mixture of *C*-allyl isomers (**14**). What was planned at this juncture was to cleave the BOM group and to introduce an azide group with inversion of configuration in order to attain the desired stereochemical orientation needed in the intended 3-(1-aminoalkyl)-1-cyclohexane carboxylic acid motif **E** after ring-closing metathesis. In the event, treatment of **14** with TMSBr to cleave the BOM group led to the *cis*- and *trans*-lactones **15** and **16** as a 1:1 mixture of diastereomers. When this mixture was subjected to ring-closing metathesis in the presence of the Grubbs first generation catalyst, the *cis*-bicylic lactone **17** was formed in 41% yield in addition to the recovery of the pure *trans*-allyl lactone **16** in a 45% yield. The

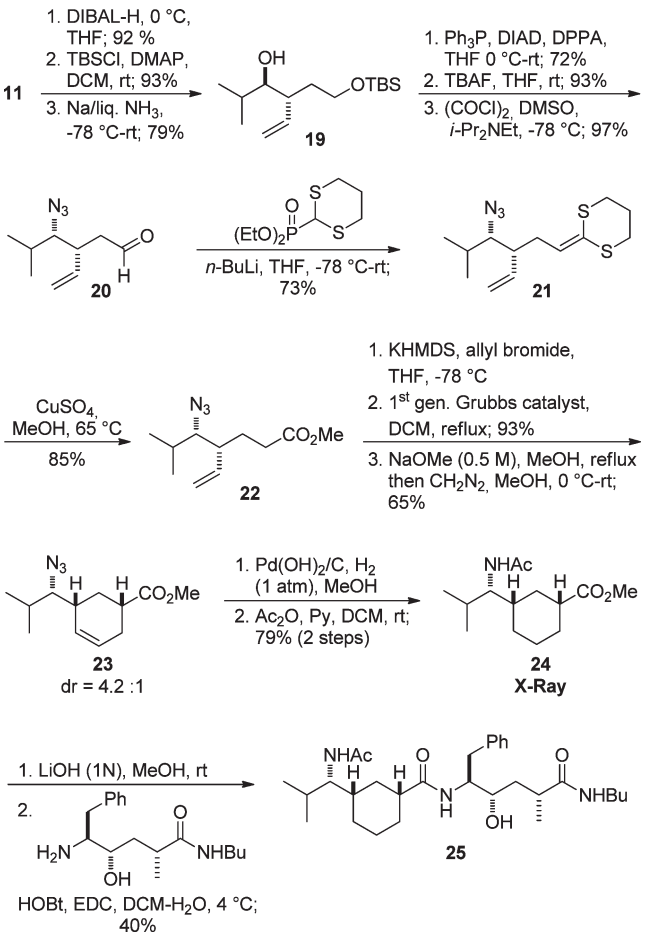
**SCHEME 2. Synthesis of Methyl Ester 18**




(17) See Supporting Information.

(18) (CAS no. 850426-30-1) Auberson, Y.; Glatthar, R.; Salter, R.; Simic, O.; Tintelnot-Blomley, M. Preparation of substituted spirocyclic lactams as inhibitors of proteinase BACE 1. WO2005035535.

**SCHEME 3. Synthesis of Carbocyclic Peptidomimetic 25**

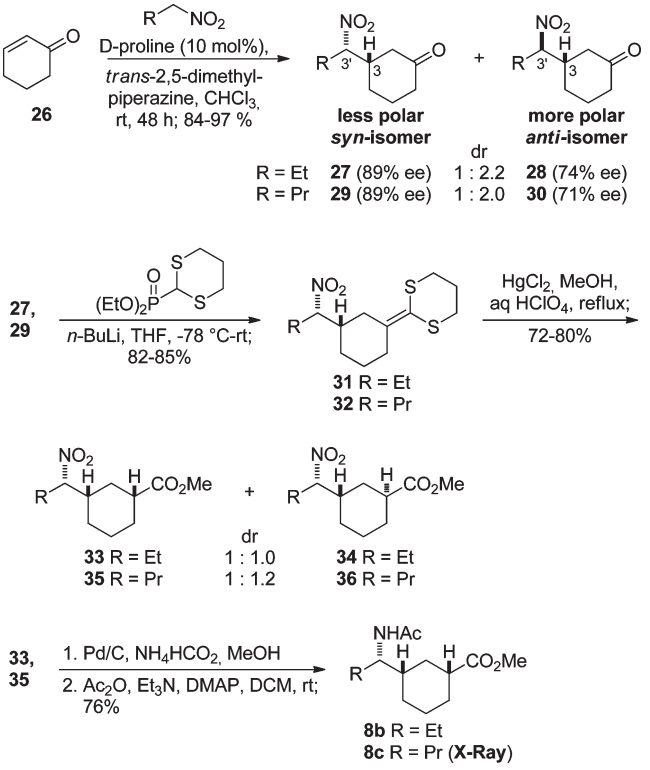



latter could be equilibrated to a 1:1 mixture of *cis*- and *trans*-lactones (**15** and **16**) in the presence of DBU in refluxing $CH_2Cl_2$. Methanolysis of **17** gave the methyl ester **18**. However, attempts to introduce an azide group under Mitsunobu conditions[19] resulted in unwanted byproduct due to elimination.

We then decided to introduce the azide group earlier in the sequence as shown in Scheme 3. Thus, the ester group in **11** was reduced, the resulting alcohol was protected as a TBS ether, and the BOM group was subsequently cleaved with Na in liquid ammonia to give **19**. Treatment under Mitsunobu conditions led to the corresponding azide with inversion of configuration. Cleavage of the TBS group and oxidation under Swern conditions gave aldehyde **20** in excellent overall yield. Extension to the ketene dithioacetal **21**, methanolysis to **22**, allylation of the potassium enolate, followed by ring-closing metathesis, and then NaOMe-induced equilibration of the mixture gave **23** as the major *cis*-isomer (>4:1, containing the minor diastereomer epimeric at C1). Reduction of the azide group and acetylation gave **24** as a crystalline solid whose structure and absolute stereochemistry was confirmed by single-crystal X-ray crystallography.[17] Following the previously established protocol, enantiomerically pure **24** was converted to the prototypical inhibitor **25**.

(19) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. C. *Org. React.* **1992**, *42*, 335. (c) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Baharaman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551.

**SCHEME 4. Organocatalytic Route to Carbocyclic Peptidomimetic 8b and 8c**




In an effort to shorten the synthetic sequence leading to compounds **8b** and **8c** as prototypes for the common 3-(3′-aminoalkyl)-1-cyclohexane carboxylic acid motif **E** (R = Et, Pr) shown in Figure 1, we explored a second approach based on an organocatalytic asymmetric conjugate addition of 1-nitroalkanes to 2-cycloalkenones previously developed in our laboratory (Scheme 4).[20,21] Addition of 1-nitropropane and 1-nitrobutane to 2-cyclohexenone **26** in the presence of 10 mol % of D-proline and a stoichiometric amount of *trans*-2,5-dimethylpiperazine in reagent grade $CHCl_3$ (containing 0.03% water or less) for 48 h gave, in each case, a separable mixture of isomers in 84−97% combined yield (Scheme 4). The chromatographically less polar *syn*-(3*S*,3′*S*)-propyl isomer **27** (89% ee) and the more polar *anti*-(3*S*,3′*R*)-propyl isomer **28** (74% ee), (1:2.2 ratio by $^1$H NMR and chiral HPLC, respectively) were individually characterized.[17]

A similar protocol with 1-nitrobutane gave the chromatographically less polar *syn*-(3*S*,3′*S*)-butyl isomer **29** (89% ee) and the more polar *anti*-(3*S*,3′*R*)-butyl isomer **30** (71% ee) in a product ratio of 1:2, respectively.

The individual *syn*-isomers **27** and **29** were each transformed to the corresponding ketene dithioacetals **31** and **32**. Methanolysis of **31** and **32** in the presence of $HgCl_2$ gave the methyl esters **33**, **34**, and **35**, **36**, respectively. Attempts to equilibrate the 1,3-*trans*-(1*S*)-isomers **34** and **36** to the desired 1,3-*cis*-(1*R*)-isomers without affecting the stereochemistry of the carbon center containing the nitro group were unsuccessful.

(20) (a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (b) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8*, 4787. (c) Hanessian, S.; Govindan, S.; Warrier, J. S. *Chirality* **2005**, *17*, 1.

(21) For a review on organocatalytic conjugate additions, see: Tsogoeva, S. *Eur. J. Org. Chem.* **2007**, 1701.

Reduction of **33** and **35** in the presence of 10% Pd/C and ammonium formate, followed by *N*-acetylation gave **8b** and **8c** respectively as diastereomeric mixtures in which the desired (1*R*,3*S*,3′*S*) component was present in a ratio of ~95:5 as measured by HPLC analysis of the original nitroalkane adducts **27** and **29**, respectively. A similar sequence of reactions with the chromatographically more polar *anti*-nitroketone isomers **28** and **30** was also achieved, although these "undesired" diastereomeric nitroalkyl esters were not pursued further in the context of our peptidomimetic BACE1 program.[10−13]

## Discussion

Conjugate additions of organocuprates to chiral nonracemic γ-alkoxy,[15a] γ-ureido,[15a] and γ-*N*,*N*-dibenzyl[14] substituted esters have been known to take place with a high level of 1,2-induction. Contrary to the γ-alkoxy series, the γ-*N*,*N*-dibenzyl counterparts afford *syn*-oriented substitution products as originally shown by Reetz and co-workers.[14] Therefore, the preponderance of the *syn*-oriented β-vinyl adducts **8a**−**d** was not unexpected. The robust *N*,*N*-dibenzyl group was highly compatible with the 2-step sequence of reactions involved in the one-carbon homologation by carbomethoxylation of the aldehydes via the ketene dialkyl dithioacetals **3a**−**d**. It was not surprising that the potassium enolate mediated allylation of acyclic **5** led to the *C*-allylated esters **6a**−**d** with virtually no selectivity compared to analogous systems, where the stereogenic center was adjacent to the enolate α-carbon atom.[15b,c] However, as anticipated, the desired 1,3-*cis*-substitution pattern was attained by a mild base-catalyzed equilibration after carbocyclization, favoring the thermodynamically more stable diequatorial isomers **7a**−**d** in ratios of 5:1. The subsequent steps involving reduction of the endocyclic double bond and the *N*,*N*-dibenzyl groups, followed by *N*-acetylation, proceeded uneventfully to give diasteromerically pure crystalline carbocycles in the case of **8a** and **8c**. Similar treatment gave the diastereomerically enriched carbocycles **8b** and **8d**, which were further converted to the intended peptidomimetics **9a**−**d**.

Conjugate addition of the mixed vinylcuprate to the enoate derived from the isopropyl analogue (Scheme 1, **1**, R = *i*-Pr) was unsuccessful and starting enoate was recovered, possibly due to steric reasons. Relying on the high 1,2-*anti*-selectivity in the conjugate addition of the corresponding γ-alkoxy enoates,[15a] we opted to start with compound **10**, which is readily available through diazotization of D-valine. The plan was to eventually displace the γ-hydroxyl group with a suitable source of nitrogen such as azide in an $S_N2$ fashion, thereby attaining the desired (*S*)-stereochemistry at C3′. The planned sequence was successfully implemented up to the stage of azide displacement, only to discover that the combination of two relatively bulky moieties flanking the hydroxyl group on the 1-hydroxy-isobutyl side chain presented major steric issues. This impasse was circumvented by effecting the $S_N2$ azide displacement earlier in the sequence, which led to the intended crystalline carbocyclic amino acid ester **24** in 18 steps starting with D-valine (Scheme 3). Despite the relative length of these sequences, a high level of stereochemical control was achieved as a result of a strong combination of internal induction and thermodynamic bias. The absolute configuration of **24** was confirmed by X-ray crystallography.

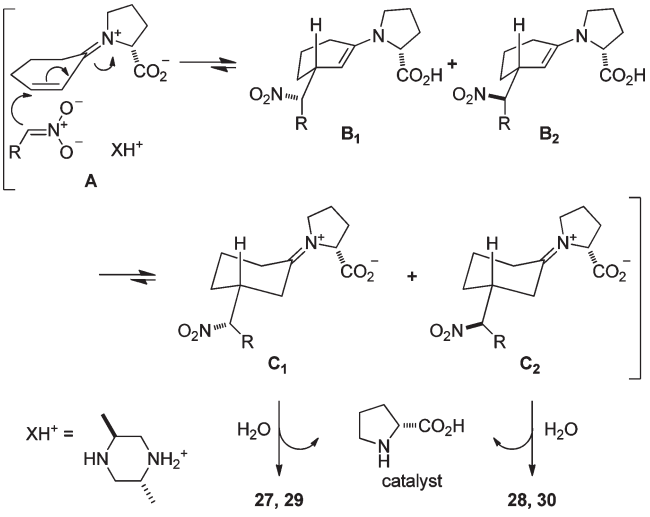



**FIGURE 2.** Proposed intermediates in the 1-nitroalkane addition to 2-cyclohexenone in the presence of D-proline as catalyst and *trans*-2,5-dimethylpiperazine as additive.

The first proline-catalyzed addition of 2-nitropropane to 2-cyclohexenone was reported by Yamaguchi and co-workers[22] in 1994, who achieved an ee of 59%, using rubidium L-prolinate as catalyst. In 2000, we reported on a substantial improvement in the enantioselective addition of 2-nitropropane to 2-cyclohexenone in the presence of 10 mol % of L-proline, in conjunction with *trans*-2,5-dimethylpiperazine as an additive.[20a] The reaction profile exhibited an unusual nonlinear effect, before reaching ee values ranging between 89% and 93%. Since then, the enantioselectivity of this reaction has been extended with *trans*-4,5-methano-L-proline as a catalyst to a maximun level of 99% ee.[20b]

We explored the feasibility of 1-nitroalkane additions to 2-cyclohexenones as an alternative approach to 3-(3′-aminoalkyl)-1-cyclohexane carboxylic acids exemplified by **E** (Figure 1). On the basis of our previous experience,[20a,b] it was expected that the proline-catalyzed conjugate addition of a 1-nitroalkane to 2-cyclohexenone would lead to a diastereomer in which the stereogenic center at C3 of the resulting 3-(3′-nitroalkyl)-1-cyclohexanone would be fixed as a result of the stereodifferentiating event during the approach of the nitronate anion at the azadienium carboxylate stage (Figure 2). However, the stereochemical fate of the carbon atom bearing the C3′-nitro group would be difficult to predict, since it could undergo proton-abstraction and reprotonation after the initial attack due to the acidity of the carbon atom. Although a priori there appears to be no stereochemical bias to favor one over another, the results show that the diastereomers with the C3′*S*-configuration as in the case of the propyl and butyl chains in **27** and **29**, respectively, are favored over the C3′*R*-counterparts in **28** and **30** as evidenced by the higher ee values (Scheme 4). Of the two possible iminium ions initially formed with 2-cyclohexenone, that with the proximal carboxylate group as in **A**[20c] (Figure 2) can undergo a *si*-face attack by the nitronate anion with its associated protonated bulky *trans*-2,5 dimethylpiperazinium

(22) (a) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223. (b) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett*. **1994**, *35*, 8233.

ion to give the corresponding enamines $\mathbf{B_1}$ and $\mathbf{B_2}$. Release of the D-proline, from hydrolysis of iminium ions $\mathbf{C_1}$ and $\mathbf{C_2}$ by water present in the reaction medium leads to the observed products **27** and **29**, respectively, in which the C3′*S*-configuration is favored (~95:5 ratio).

We have previously shown that, compared to other nitrogen bases, *trans*-2,5-dimethylpiperazine was the most effective additive with regard to enantioselectivity of the conjugate addition of 2-nitropropane to 2-cyclohexenone.[20a−c] Furthermore, chiral nonracemic 2,5-disubstituted dialkylpiperazines had no effect on the observed enantioselectivity.[20c]

In our original report,[20a] we had shown that the conjugate addition of 1-nitropropane to 2-cyclohexenone in the presence of 10 mol % of L-proline and *trans*-2,5-dimethylpiperazine as additive in $CHCl_3$ afforded a 80% yield of a 1:2 mixture of *ent*.**27** and *ent*.**28**. The diastereomeric excesses determined by $^{13}C$ NMR analysis of the corresponding ketals with (2*R*,3*R*)-2,3-butanediol were 85% and 72% for *ent*.**27** and *ent*.**28**, respectively. With *trans*-4,5-methano-L-proline as a catalyst, there was a measurable improvement in diastereoselectivity to 91% and 74%, respectively.[20b]

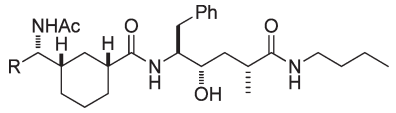
In the present study with D-proline, these results were independently confirmed by HPLC analysis on chiral columns. A priori, it is difficult to rationalize the preponderance of the *anti*-isomers **28** and **30** by a product ratio of 2:1 over the *syn*-counterparts **27** and **29**, respectively. The ratio appears to be a thermodynamic one under the reaction conditions. Nevertheless, it is interesting that the desired *syn*-(3*S*,3′*S*)-isomers **27** and **29** in the context of our intended carbocyclic amino acid motif **E** (Figure 1) were produced in an stereochemically enriched form of 89% ee corresponding to a ratio of ~95:5. In this regard, the modest enantiomeric excesses of the *anti*-(3*S*,3′*R*) isomers **28** and **30** (74% and 71%, respectively) were significantly better than the corresponding isomers with Maruoka's *N*-spiro chiral quaternary ammonium bromide phase transfer catalyst where an ee of 57% was reported for the same compounds.[23] However, the product ratios in Maruoka's study was highly in favor of the *syn*-isomer **27** (*syn*/*anti* 96:4, 91% ee and 57% ee, respectively).[23]

**Biological Results.** Compounds **9a**−**d** and **25** were tested for their inhibitory activities against BACE1, BACE2, and cathepsin D (Table 1). Although increasing the bulk of the alkyl group in the C3 appendage of the cyclohexane portion led to virtually no inhibitory activity against these enzymes, the isopropyl analogue **25** showed markedly higher potency on all three enzymes compared to the other congeners. One can speculate that in **25** the isopropyl group presents a preferred change in the conformation and in the pattern of interaction with these enzymes as described in detail in an SAR (structure−activity relationship) study of related analogues based on X-ray structural analysis with BACE1 in particular.[13]

## Conclusion

We have presented two conceptually and operationally different approaches to the stereocontrolled synthesis of novel dipeptide isosteres consisting of a novel 3-(3′-aminoalkyl)-1-cyclohexane-carboxylic acid motif. Despite the shorter synthetic route, the organocatalytic 1-nitroalkane conjugate addition reaction to 2-cyclohexenone leads to mixtures of diastereomers attaining ratios of ~95:5 for the (3*S*,3′*S*)-isomers **27** and **29**, which are the minor products, compared to the undesired (3*S*,3′*R*)-isomers **28** and **30**. Thus, the amino acid route is preferred as an entry into this new class of constrained 3-(3′-aminoalkyl)-1-cyclohexane carboxylic acids.[24] Incorporation of the congener with an isopropyl side chain such as **24** into a peptidomimetic construct has a led to compound **25** showing low micromolar inhibition of BACE1, BACE2, and cathepsin D in vitro. This was the basis for further design and synthesis toward selective and potent inhibitors of the enzyme BACE1.[13]

**TABLE 1. Enzyme Inhibitory Activity**




| | | IC$_{50}$ ($\mu$M) or % inhibition at 10 $\mu$M[a] | | |
|---|---|---|---|---|
| compound | R | BACE-1 | BACE-2 | CathD |
| **9a** | Me | 8% | 14% | 71% |
| **9b** | Et | 17% | 24% | 64% |
| **9c** | Pr | 15% | 80% | 84% |
| **9d** | *i*-Pr | 0.80 | 0.17 | 0.15 |
| **25** | *i*-Bu | 11% | 42% | 43% |

[a]For details of assays see ref 13.

## Experimental Section

**Ethyl (3*R*,4*S*)-4-(Dibenzylamino)-3-vinyl Pentanoate (2a).** To a suspension of copper iodide (9.525 g, 50 mmol) in THF (200 mL) at −78 °C was added vinylmagnesium bromide (100 mL, 100 mmol, 1 M in THF) dropwise during 1.5 h. After 30 min the TMSCl (25.3 mL, 200 mmol), ester **1a** (0.808 g, 2.5 mmol) in THF (20 mL), and HMPA (34.8 mL, 200 mmol) were added successively and stirred for additional 7 h at −78 °C. The reaction mixture was quenched with solution of ammonium hydroxide and ammonium chloride (1:1, 100 mL) and allowed to reach rt. The organic layer was extracted with ether (3 × 100 mL), dried over $Na_2SO_4$, and concentrated. The crude product was purified by flash chromatography (2.5% EtOAc in hexanes) to furnish **2a** (0.395 g, 45%) as pale yellow oil; $[\alpha]_D$ −49.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1735 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.38−7.28 (m, 10H), 5.80−5.60 (m, 1H), 5.00 (dd, $J$ = 17.0, 12.1 Hz, 2H), 4.10−4.00 (m, 2H), 3.79 (d, $J$ = 13.8 Hz, 2H), 3.50 (d, $J$ = 13.7 Hz, 2H), 2.80−2.60 (m, 2H), 2.35 (dd, $J$ = 4.2 Hz, 1H), 2.10 (dd, $J$ = 7 Hz, 1H), 1.20 (t, $J$ = 7.2 Hz, 3H), 1.00 (d, $J$ = 6.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.1, 140.6, 140.5 (2C), 129.4 (4C), 128.5 (4C), 127.2 (2C), 115.8, 60.6, 55.9, 54.3 (2C), 46.1, 38.7, 14.7, 10.5; MS (FAB) *m*/*z* 352 [ M + 1]$^+$; HRMS (FAB) calcd for $C_{23}H_{30}NO_2$ [M + 1]$^+$ 352.2276, found 352.2270.

**Ethyl (3*R*,4*S*)-4-(Dibenzylamino)-3-vinyl Hexanoate (2b).** To a suspension of copper iodide (11.43 g, 60 mmol) in THF (240 mL) at −78 °C was added vinylmagnesium bromide (120 mL, 120 mmol, 1 M in THF) dropwise during 1.5 h. After 30 min, the TMSCl (30.3 mL, 240 mmol), ester **1b** (1.000 g, 2.96 mmol) in THF (20 mL) and HMPA (41.7 mL, 240 mmol) were added successively and stirred for additional 7 h at −78 °C. The reaction was quenched with solution of ammonium hydroxide and ammonium chloride (1:1, 100 mL). After usual workup and

(23) Ooi, T.; Takada, S.; Fujioka, S.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5143.

(24) For the synthesis of conformationally constrained $\gamma$-amino acids, see: Guo, L.; Chi, Y.; Almeida, A. M.; Guzei, I. A.; Parker, B. K.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 16018.

column purification, ester **2b** (0.440 g) was isolated as pale yellow oil in 41% yield; $[\alpha]_D$ −35.19 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 1734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.10 (m, 10H), 5.80−5.70 (m, 1H), 5.00 (t, *J* = 10.2 Hz, 2H), 4.10−4.00 (m, 2H), 3.80 (d, *J* = 13.8 Hz, 2H), 3.40 (d, *J* = 13.7 Hz, 2H), 2.80−2.70 (m, 1H), 2.60−2.50 (m, 1H), 2.40 (q, *J* = 4.3 Hz, 1H), 2.30 (q, *J* = 4.3 Hz, 1H), 1.80−1.70 (m, 1H), 1.50−1.60 (m, 1H), 1.20 (t, *J* = 7.3 Hz, 3H), 1.00 (t, *J* = 7.3 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.3, 140.7 (2C), 139.2, 129.5 (4C), 128.6 (4C), 127.2 (2C), 116.3, 62.4, 60.5, 55.7 (2C), 42.7, 37.8, 19.4, 14.6, 13.1; MS (ESI) *m*/*z* 366.4 $[M+1]^+$; HRMS (ESI) calcd for $C_{24}H_{32}NO_2$ $[M + 1]^+$ 366.2428, found 366.2438

**Ethyl (3*R*,4*S*)-4-(Dibenzylamino)-3-vinyl Heptanoate (2c).** To a suspension of copper iodide (11.43 g, 60 mmol) in THF (240 mL) at −78 °C was added vinylmagnesium bromide (120 mL, 120 mmol, 1 M in THF) dropwise during 1.5 h. After 30 min, the TMSCl (30.3 mL, 240 mmol), ester **1c** (1.053 g, 3 mmol) in THF (20 mL) and HMPA (41.7 mL, 240 mmol) were added successively and stirred for additional 7 h at −78 °C. The reaction was quenched with solution of ammonium hydroxide and ammonium chloride (1:1, 100 mL). After usual workup and column purification, ester **2c** (0.510 g, 45%) was isolated as pale yellow oil; $[\alpha]_D$ −26.3 (*c* 1, $CHCl_3$); IR (neat) 1734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.27 (m, 10H), 5.95−5.80 (m, 1H), 5.10−5.05 (dd, *J* = 13.6, 4.9 Hz, 2H), 4.07−3.84 (m, 2H), 3.80 (d, *J* = 11.8 Hz, 2H), 3.45 (d, *J* = 11.9 Hz, 2H), 2.80−2.70 (m, 2H), 2.40−2.20 (m, 2H), 1.80−1.70 (m, 1H), 1.48−1.40 (m, 2H), 1.27−1.21 (m, 3H), 0.99 (t, *J* = 6.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.3, 140.7 (2C), 139.2, 129.5 (4C), 128.6 (4C), 127.3(2C), 116.4, 60.5, 60.2, 55.8 (2C), 43.1, 37.8, 28.8, 21.5, 14.8, 14.7; MS (ESI) *m*/*z* 380.2 $[M + 1]^+$; HRMS (FAB) calcd for $C_{25}H_{34}NO_2$ $[M + 1]^+$ 380.2584, found 380.2582.

**Ethyl (3*R*,4*S*)-4-(Dibenzylamino)-3-vinyl-6-methyl Heptanoate (2d).** To a suspension of copper iodide (11.43 g, 60 mmol) in THF (240 mL) at −78 °C was added vinylmagnesium bromide (120 mL, 120 mmol, 1 M in THF) dropwise during 1.5 h. After 30 min the TMSCl (30.3 mL, 240 mmol), ester **1d** (1.095 g, 3 mmol) in THF (20 mL), and HMPA (41.7 mL, 240 mmol) were added successively and stirred for additional 7 h at −78 °C. The reaction mixture was quenched with solution of ammonium hydroxide and ammonium chloride (1:1, 100 mL) and allowed to come to rt. The ester **2d** (0.495 g) was obtained as pale yellow oil in 42% yield after standard workup and purification; $[\alpha]_D$ −18.3 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.20 (m, 10H), 5.90−5.70 (m, 1H), 5.05 (bs, 1H), 5.00 (d, *J* = 3.1 Hz, 1H), 4.00−3.80 (m, 2H), 3.76 (d, *J* = 13.7 Hz, 2H), 3.40 (d, *J* = 13.7 Hz, 2H), 2.70 (bs, 2H), 2.40−2.30 (m, 2H), 1.80−1.60 (m, 1H), 1.50−1.40 (m, 2H), 1.10 (t, *J* = 7.3 Hz, 3H), 0.93 (d, *J* = 5.1 Hz, 3H), 0.89 (d, *J* = 5.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.2, 140.8 (2C), 139.0, 129.5 (4C), 128.6 (4C), 127.3 (2C), 116.5, 60.5, 58.0, 55.9 (2C), 42.9, 37.6, 35.6, 25.7, 24.2, 22.8, 14.6; MS (ESI) *m*/*z* 394.4 [ $M + 1]^+$; HRMS (FAB) calcd for $C_{26}H_{36}NO_2$ $[M + 1]^+$ 394.2741, found 394.2744.

**(3*R*,4*S*)-4-(Dibenzylamino)-3-vinyl Pentanal (3a).** To a solution of ester **2a** (0.500 g, 1.42 mmol) in THF (15 mL) at 0 °C was added DIBAL-H (2 mL, 3.0 mmol, 1.5 M in toluene) dropwise, and the mixture was allowed to come to rt during 2 h. The excess DIBAL-H was quenched with MeOH (3 mL) and diluted with Rochelle salt solution (15 mL) and EtOAc (50 mL) while stirring for 2 h. The organic layer was partitioned, washed with brine, dried ($Na_2SO_4$), and concentrated. The crude product was purified by flash chromatography (20% EtOAc in hexanes) to afford the corresponding alcohol (0.400 g, 91%) as a colorless oil; $[\alpha]_D$ − 65.45 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3330 $cm^{-1}$ ; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40 7.20 (m, 10 H), 5.70−5.60 (m, 1H), 5.13 (d, *J* = 10.2 Hz, 1H), 5.00 (d, *J* = 17.1 Hz, 1H), 3.78 (d, *J* = 13.8 Hz, 2H), 3.60−3.40 (m, 2H), 3.32 (d, *J* = 13.7 Hz, 2H), 2.60−2.55 (m, 1H), 2.25−2.20 (m, 1H), 1.80−1.70 (m, 1H), 1.40−1.30 (m, 1H), 1.30−1.20 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 142.4 (2C), 140.8, 129.4 (4C), 128.5 (4C), 127.2 (2C), 115.3, 61.6, 56.3, 54.1 (2C), 46.9, 35.4, 10.6; MS (ESI) *m*/*z* 310 $[M + 1]^+$; HRMS (FAB) calcd for $C_{21}H_{28}NO$ $[M + 1]^+$ 310.2165, found 310.2172.

To a stirring solution of oxalyl chloride (53 $\mu$L, 0.57 mmol) in $CH_2Cl_2$ (5 mL) at −78 °C was added DMSO (71 $\mu$L,1 mmol), and after 10 min the alcohol (0.150 g, 0.48 mmol) in $CH_2Cl_2$ (1 mL) was added and stirred for 30 min. After addition of triethylamine (278 $\mu$L, 2 mmol) the reaction mixture was stirred at −78 °C for 30 min, and then the dry ice bath was removed to allow the mixture to warm to rt during 30 min. The reaction mixture was quenched with water (2 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layer was washed with 10% citric acid solution (10 mL) and then with brine and dried over $Na_2SO_4$. After concentration, the residue was purified by silica gel column chromatography (10% EtOAc in hexanes) to furnish aldehyde **3a** (0.100 g, 67%) as a colorless viscous oil; $[\alpha]_D$ −39.25 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 1724 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.49 (s, 1H), 7.38−7.23 (m, 10H), 5.80−5.60 (m, 1H), 5.13 (d, *J* = 10.0 Hz, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 3.80 (d, *J* = 13.7 Hz, 2H), 3.31 (d, *J* = 13.7 Hz, 2H), 2.80−2.60 (m, 2H), 2.40 (dd, *J* = 4.3 Hz, 1H), 2.20 (dd, *J* = 6.4 Hz, 1H), 1.00 (d, *J* = 6.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 202.84, 140.50 (2C), 140.15, 129.40 (4C), 128.59 (4C), 127.33 (2C), 116.29, 55.92, 54.55 (2C), 46.69, 43.91, 10.70; MS (ESI) *m*/*z* 308.2 $[M + 1]^+$; HRMS (FAB) calcd for $C_{21}H_{26}NO$ $[M + 1]^+$ 308.2009, found 308.2119.

**(3*R*,4*S*)-4-(Dibenzylamino)-3-vinyl Hexanal (3b).** To a solution of ester **2b** (0.800 g, 2.19 mmol) in THF (25 mL) at 0 °C was added DIBALH (3 mL, 4.5 mmol, 1.5 M in toluene) dropwise, and the mixture was allowed to come to rt during 2 h. The excess DIBALH was quenched with MeOH (3 mL) and diluted with Rochelle salt solution (25 mL) and EtOAc (75 mL) while stirring for 2 h. The alcohol **37b** (0.635 g) was isolated as a colorless oil in 90% yield after standard workup and purification; $[\alpha]_D$ −52.2 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3362 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.25 (m, 10H), 5.80−5.70 (m, 1H), 5.10−5.00 (m, 2H), 3.80 (d, *J* = 13.8 Hz, 2H), 3.60−3.30 (m, 4H), 2.60−2.50 (m, 1H), 2.40−2.30 (m, 1H), 1.80−1.70 (m, 1H), 1.70−1.40 (m, 2H), 1.20−1.10 (m, 1H), 1.00 (t, *J* = 7.3 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 141.3, 140.9 (2C), 129.5 (4C), 128.5 (4C), 127.2 (2C), 116.0, 62.9, 61.7, 55.6 (2C), 43.7, 35.5, 19.7, 13.5; MS (FAB) *m*/*z* 324 $[M + 1]^+$; HRMS (FAB) calcd for $C_{22}H_{30}NO$ $[M + 1]^+$ 324.2327, found 324.2339.

To a stirring solution of oxalyl chloride (240 $\mu$L, 2.6 mmol) in $CH_2Cl_2$ (22 mL) at −78 °C was added DMSO (306 $\mu$L, 4.32 mmol), and after 10 min the alcohol **37b** (0.700 g, 2.16 mmol) in $CH_2Cl_2$ (3 mL) was added and stirred for 30 min. After addition of triethylamine (1.2 mL, 8.64 mmol) the reaction mixture was stirred at −78 °C for 30 min and then the dry ice bath was removed to allow the mixture to warm to rt during 30 min. The reaction mixture was quenched with water (5 mL). After usual workup and column purification, aldehyde **3b** (0.500 g, 72%) was characterized as colorless viscous oil; $[\alpha]_D$ −33.6 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1723 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.30 (bs, 1H), 7.30−7.20 (m, 10H), 5.90−5.70 (m, 1H), 5.10−5.00 (m, 2H), 3.80 (d, *J* = 13.7 Hz, 2H), 3.45 (d, *J* = 13.7 Hz, 2H), 2.90−2.80 (m, 1H), 2.60−2.50 (m, 1H), 2.50−2.40 (m, 2H), 1.90−1.70 (m, 1H), 1.60−1.40 (m, 1H), 1.00 (t, *J* = 7.3 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 202.7, 140.6 (2C), 138.7, 129.5 (4C), 128.6 (4C), 127.4 (2C), 116.8, 62.3, 55.9 (2C), 46.5, 40.3, 19.3, 13.1; MS (ESI) *m*/*z* 322.3 $[M + 1]^+$; HRMS (FAB) calcd for $C_{22}H_{27}NO$ 321.2092, found 321.2119.

**(3*R*,4*S*)-4-(Dibenzylamino)-3-vinyl Heptanal (3c).** To a solution of ester **2c** (0.510 g, 1.35 mmol) in THF (14 mL) at 0 °C was added DIBALH (1.8 mL, 2.7 mmol, 1.5 M in toluene) dropwise, and the mixture was allowed to come to rt during 2 h. The excess DIBALH was quenched with MeOH (3 mL) and diluted with

Rochelle salt solution (25 mL) and EtOAc (75 mL) while stirring for 2 h. The alcohol **37c** (0.405 g, 89%) was isolated as a colorless oil after standard workup and purification; $[\alpha]_D$ −41.5 (*c* 1, $CHCl_3$); IR (neat) 3350 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.39−7.26(m, 10H), 5.80−5.70 (m, 1H), 5.01 (m, 2H), 3.80 (d, $J$ = 13.5 Hz, 2H), 3.49−3.44 (m, 4H), 2.56−2.54 (m, 1H), 2.54−2.20 (m, 1H), 1.80−1.60 (m, 4H), 1.60−1.10 (m, 3H), 0.88 (t, $J$ = 7.1 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 141.5, 141.1 (2C), 129.7 (4C), 128.7 (4C), 127.4 (2C), 116.1, 61.5, 60.9, 55.6 (2C), 44.1, 35.5, 29.5, 22.1, 15.1; MS (ESI) $m/z$ 338.2 $[M + 1]^+$; HRMS (FAB) calcd for $C_{23}H_{32}NO$ $[M + 1]^+$ 338.2478, found 338.2476.

To a stirring solution of oxalyl chloride (147 $\mu$L, 1.6 mmol) in $CH_2Cl_2$ (15 mL) at −78 °C was added DMSO (302 $\mu$L, 4.26 mmol), and after 10 min the alcohol **37c** (0.480 g, 1.42 mmol) in $CH_2Cl_2$ (5 mL) was added and stirred for 30 min. After addition of *i*-$Pr_2NEt$ (987 $\mu$L, 5.68 mmol) the reaction mixture was stirred at −78 °C for 30 min, and then the dry ice bath was removed to allow the mixture to warm to rt during 30 min. The reaction mixture was quenched with water (5 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The organic layer was washed with 10% citric acid solution (20 mL), washed with brine, and dried over $Na_2SO_4$. After concentration, the residue was purified by normal silica gel column chromatography (10% EtOAc in hexane) to furnish aldehyde **3c** (0.376 g, 79%) as colorless viscous oil; $[\alpha]_D$ −24.9 (*c* 1.1, $CHCl_3$); IR (neat) 1723 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.34 (t, $J$ = 1.5 Hz, 1H), 7.39−7.24 (m, 10H), 5.84−5.75 (m, 1H), 5.09 (t, $J$ = 1.5 Hz, 1H), 5.06 (d, $J$ = 9.6 Hz, 1H), 3.80 (d, $J$ = 13.5 Hz, 2H), 3.40 (d, $J$ = 13.5 Hz, 2H), 2.67−2.64 (m, 1H), 2.48 (m, 1H), 2.46 (d, $J$ = 5.4 Hz, 2H), 1.70−1.60 (m, 1H), 1.52−1.44 (m, 3H), 0.99 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 202.6, 140.8 (2C), 138.9, 129.7 (4C), 128.7 (4C), 127.5 (2C), 116.8, 60.0, 56.0 (2C), 46.5, 40.7, 28.8, 21.5, 14.9; MS (ESI) $m/z$ 336.2 $[M + 1]^+$; HRMS (FAB) calcd for $C_{23}H_{30}NO$ $[M + 1]^+$ 336.2322, found 336.2320

**(3*R*,4*S*)-4-(Dibenzylamino)-3-vinyl-6-methyl Heptanal (3d).** To a solution of ester **2d** (1.200 g, 3.05 mmol) in THF (30 mL) at 0 °C was added DIBALH (4 mL, 6 mmol, 1.5 M in toluene) dropwise, and the mixture was allowed to come to rt during 2 h. The excess DIBALH was quenched with MeOH (5 mL) and diluted with Rochelle salt solution (15 mL) and EtOAc (50 mL) while stirring for 2 h. After standard workup and purification, the product was isolated as desired alcohol **37d** (0.965 g) as a colorless oil in 90% yield; $[\alpha]_D$ −40.36 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3328 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.20 (m, 10H), 5.80−5.60 (m, 1H), 5.20−5.10 (d, $J$ = 10 Hz, 1H), 5.00 (bs, 1H), 3.80 (d, $J$ = 13.7 Hz, 2H), 3.40 (d, $J$ = 13.8 Hz, 2H), 3.40−3.20 (bs, 2H), 2.60 (bs, 1H), 2.25 (bs, 1H), 1.80−1.00 (m, 5H), 0.91 (d, $J$ = 6.4 Hz, 3H), 0.85 (d, $J$ = 6.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 141.2, 141.1 (2C), 129.6 (4C), 128.5 (4C), 127.3 (2C), 116.3, 61.7, 58.7, 55.7 (2C), 43.9, 36.1, 35.5, 25.9, 23.9, 23.1; MS (FAB) $m/z$ 352 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{24}H_{34}NO$ $[M + 1]$ 352.2640, found 352.2649.

To a stirring solution of oxalyl chloride (406 $\mu$L, 4.44 mmol) in $CH_2Cl_2$ (40 mL) at −78 °C was added DMSO (524 $\mu$L, 7.4 mmol), and after 10 min the alcohol **37d** (1.3 g, 3.7 mmol) in $CH_2Cl_2$ (10 mL) was added and stirred for 30 min. After addition of triethylamine (2.3 mL, 16 mmol) the reaction mixture was stirred at −78 °C for 30 min, and then the dry ice bath was removed to allow the mixture to warm to rt during 30 min. The reaction mixture was quenched by adding water (10 mL) and extracted with $CH_2Cl_2$ (3 × 30 mL). After usual workup, the crude product was purified by normal silica gel column chromatography with 10% EtOAc in hexane to furnish aldehyde **3d** (0.943 g, 73%) as colorless viscous oil; $[\alpha]_D$ −15.7 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1723 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.27 (bs, 1H), 7.34−7.25 (m, 10H), 5.90−5.75 (m, 1H), 5.10−5.00 (m, 2H), 3.75 (d, $J$ = 13.8 Hz, 2H), 3.38 (d, $J$ = 13.8 Hz, 2H), 2.80 (bs, 1H), 2.70 (bs, 1H), 2.50−2.40 (m, 2H), 1.90−1.70 (m, 1H), 1.47−1.44 (m, 2H), 0.95 (t, $J$ = 6.3 Hz, 6H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 202.5, 140.7 (2C), 138.6, 129.6 (4C), 128.7 (4C), 127.4 (2C), 116.9, 57.9, 56.0 (2C), 46.4, 40.4, 35.4, 25.7, 24.3, 22.7; MS (ESI) $m/z$ 350.4 $[M + 1]^+$; HRMS (FAB) calcd for $C_{24}H_{31}NO$ 349.2405, found 349.2396.

**(2*S*,3*R*)-*N*,*N*-Dibenzyl-6,6-bis(methylthio)-3-vinylhex-5-en-2-amine (4a).** To a stirring solution of bis-methyl mercaptomethanphosphonate (0.476 g, 2.2 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (1.56 mL, 2.5 mmol, 1.6 M in hexane) dropwise during 15 min. After 1 h, aldehyde **3a** (0.614 g, 2 mmol) in THF (5 mL) was added and stirred for 15 min at −78 °C, and then the cooling bath was removed. The reaction was quenched after 1 h by adding water (3 mL) and extracted with EtOAc (40 mL). The organic phase was washed with brine, dried ($Na_2SO_4$), and concentrated. The purification of crude product over silica gel column chromatography (5% EtOAc in hexanes) furnished ketene dithioacetal **4a** (0.698 g, 88%) as a transparent oil; $[\alpha]_D$ −38.5 (*c* 1, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.21 (m, 10H), 5.80−5.60 (m, 2H), 5.07 (d, $J$ = 10.2 Hz, 1H), 4.90 (d, $J$ = 16.2 Hz, 1H), 3.75 (d, $J$ = 13.7 Hz, 2H), 3.30 (d, $J$ = 13.8 Hz, 2H), 2.70−2.60 (m, 1H), 2.50−2.40 (m, 1H), 2.30−2.20 (m, 5H), 2.10 (s, 3H), 1.01 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 141.9,140.8 (2C), 133.3, 132.9, 129.4 (4C), 128.5 (4C), 127.1(2C), 115.2, 55.7, 53.9 (2C), 49.8, 33.8, 17.3, 17.2, 10.5; MS (ESI) $m/z$ 398.2 $[M+1]^+$ ; HRMS (FAB) calcd for $C_{24}H_{31}NS_2$ $[M + 1]^+$ 397.1931, found 397.1930.

**(3*S*,4*R*)-*N*,*N*-Dibenzyl-7,7-bis(methylthio)-4-vinylhept-6-en-3-amine (4b).** To a stirring solution of bis-methyl mercaptomethanphosphonate (0.367 g, 1.7 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (1.2 mL, 1.8 mmol, 1.6 M in hexane) dropwise during 15 min. After 1 h, aldehyde **3b** (0.500 g, 1.55 mmol) in THF (5 mL) was added and stirred for 15 min at −78 °C, and then the cooling bath was removed. The reaction was quenched after 1 h by adding water (3 mL). After usual extraction with EtOAc and silica gel column purification, a compound characterized as ketene dithioacetal **4b** (0.520 g) was produced in 82% yield as a transparent oil; $[\alpha]_D$ −49.3 (*c* 1.025, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 7.40−7.20 (m, 10H), 5.70−5.60 (m, 2H), 5.00 (q, $J$ = 8.0 Hz, 2H), 3.80 (d, $J$ = 17.2 Hz, 2H), 3.50 (d, $J$ = 17.1 Hz, 2H), 2.60−2.50 (m, 2H), 2.40−2.20 (m, 5H), 2.20 (s, 3H), 1.80−1.70 (m, 1H), 1.50−1.40 (m, 1H), 1.00 (t, $J$ = 7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 140.9, 140.9 (2C), 134.2, 132.7, 129.5 (4C), 128.5 (4C), 127.2 (2C), 115.9, 62.8, 55.5 (2C), 47.0, 33.6, 19.9, 17.4, 17.3, 13.4; MS ($m/z$) $m/z$ 412.3 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{25}H_{34}NS_2$ $[M + 1]^+$ 412.2132, found 412.2125.

**(3*R*,4*S*)-3-(2-(1,3-Dithian-2-ylidene)ethyl)-*N*,*N*-dibenzylhept-1-en-4-amine (4c).** To a stirring solution of 2-phosphoryl 1,3-dithiane (0.384 g, 1.5 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (1 mL, 1.6 mmol, 1.6 M in hexane) dropwise during 15 min. After 1 h, aldehyde **3c** (0.380 g, 1.13 mmol) in THF (5 mL) was added and stirred for 15 min at −78 °C, and then the cooling bath was removed. The reaction mixture was quenched after 1 h by adding water (5 mL) and extracted with EtOAc (40 mL). The organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated. The purification of crude product over silica gel column chromatography using 5% EtOAc in hexane as mobile phase furnished ketene dithioacetal **4c** (0.480 g, 97%) as a transparent oil; $[\alpha]_D$ −46.2 (*c* 1, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 7.42−7.24 (m, 10H), 5.74−5.72 (m, 2H), 5.06 (d, $J$ = 13.5 Hz, 1H), 5.01 (d, $J$ = 18.1 Hz, 1H), 3.79 (d, $J$ = 13.5 Hz, 2H), 3.54 (d, $J$ = 13.2 Hz, 2H), 2.87−2.82 (m, 4H), 2.65−2.60 (m, 1H), 2.31−2.25 (m, 2H), 2.20−2.14 (m, 3H), 1.65−1.55 (m, 1H), 1.40−1.37 (m, 3H), 0.92 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 140.9 (2C), 140.8, 133.9, 129.6 (4C), 128.6 (4C), 127.3 (2C), 126.0, 116.1, 60.7, 55.5 (2C), 47.0, 32.6, 30.9, 30.2, 29.5, 25.8, 21.8, 14.9; MS (ESI) $m/z$ 438.2 $[M + 1]^+$; HRMS (FAB) calcd for $C_{27}H_{36}NS_2$ $[M + 1]^+$ 438.2284, found 438.2286

**(3*R*,4*S*)-3-(2-(1,3-Dithian-2-ylidene)ethyl)-*N*,*N*-dibenzyl-6-methylhept-1-en-4-amine (4d).** To a stirring solution of 2-phosphoryl 1,3 dithiane (0.256 g, 1 mmol) in THF (10 mL) at −78 °C was added n-BuLi (625 μL, 1 mmol, 1.6 M in hexane) dropwise during 15 min. After 1 h, aldehyde **3d** (0.349 g, 1 mmol) in THF (5 mL) was added and stirred for 15 min at −78 °C, and then the cooling bath was removed. The reaction mixture was quenched after 1 h by adding water (3 mL) and extracted with EtOAc (40 mL). The organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated. The purification of crude product over silica gel column chromatography using 5% EtOAc in hexane as mobile phase furnished ketene dithioacetal **4d** (0.351 g) in 78% yield as a transparent oil; $[\alpha]_D$ −40.36 (*c* 1.1, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 5.80 (q, *J* = 8.1 Hz, 1H), 5.60 (t, *J* = 7.2 Hz, 1H), 5.00 (q, *J* = 16.1,12.2 Hz, 2H), 3.70 (d, *J* = 13.7 Hz, 2H), 3.45 (d, *J* = 13.8 Hz, 2H), 2.80−2.70 (m, 4H), 2.70−2.60 (m, 1H), 2.40−2.30 (m, 1H), 2.30−2.20 (m, 1H), 2.10−2.00 (m, 3H), 1.80−1.60 (m, 1H), 1.50−1.40 (m, 1H), 1.40−1.30 (m, 1H), 0.88 (d, *J* = 7.1 Hz, 3H), 0.82 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 141.0, 140.6, 133.8 (2C), 129.6 (4C), 128.6 (4C), 127.6 (2C), 126.1, 116.3, 58.6, 55.6 (2C), 46.9, 36.3, 32.5, 30.9, 30.1, 25.8, 25.7, 23.8, 23.1; MS (ESI) *m*/*z* 452.4 $[M + 1]^+$; HRMS (FAB) calcd for $C_{28}H_{38}NS_2$ $[M + 1]^+$ 452.2440, found 452. 2446.

**Methyl (4*R*,5S)-5-(Dibenzylamino)-4-vinyl Hexanoate (5a).** Ketene dithioacetal **4a** (0.102 g, 0.256 mmol) was taken in a methanolic solution of copper sulfate pentahydrate (5 mL, 0.2 M) and heated at 65 °C for 2 h. After concentration, the reaction mixture was diluted with EtOAc (20 mL) and water (2 mL) and partitioned. The organic phase was concentrated, and usual purification over silica gel column chromatography eluting 2.5% EtOAc in hexanes furnished ester **5a** (0.056 g, 62%) as a colorless oil; $[\alpha]_D$ −66.9 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 1739 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.39−7.20 (m, 10H), 5.60−5.50 (m, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 4.90 (d, *J* = 16.0 Hz, 1H), 3.75 (d, *J* = 13.8 Hz, 2H), 3.62 (s, 3H), 3.25 (d, *J* = 13.7 Hz, 2H), 2.70−2.50 (m, 1H), 2.40−2.20 (m, 1H), 2.20−2.00 (m, 2H), 1.90−1.70 (m, 1H), 1.40−1.30 (m, 1H), 1.00 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 174.8, 141.7, 140.8 (2C), 129.4 (4C), 128.5 (4C), 127.1 (2C), 115.7, 56.1, 53.9 (2C), 51.9, 49.5, 32.3, 27.5, 10.4; MS (FAB) *m*/*z* 352 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{23}H_{30}NO_2$ $[M + 1]^+$ 352.2295, found 352.2288.

**Methyl (4*R*,5*S*)-5-(Dibenzylamino)-4-vinyl Heptanoate (5b).** Ketene dithioacetal **4b** (0.500 g, 1.22 mmol) was taken in a methanolic solution of copper sulfate pentahydrate (12 mL, 0.2 M) and heated at 65 °C for 2 h. After concentration, the reaction mixture was diluted with EtOAc (20 mL) and water (2 mL) and partitioned. The organic phase was concentrated, and usual purification over silica gel column chromatography eluting with 2.5% EtOAc in hexane furnished ester **5b** (0.300 g, 67%) as a colorless oil; $[\alpha]_D$ −62.9 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1739 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 5.70−5.50 (m, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 4.95 (d, *J* = 17.1 Hz, 1H), 3.73 (d, *J* = 13.7 Hz, 2H), 3.60 (s, 3H), 3.50 (d, *J* = 13.8 Hz, 2H), 2.60−2.40 (m, 1H), 2.20−2.10 (m, 2H), 2.10−1.90 (m, 1H), 1.80−1.50 (m, 3H), 1.50−1.30 (m, 1H), 0.98 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 174.7, 140.9 (2C), 140.8, 129.5 (4C), 128.5 (4C), 127.2 (2C), 116.3, 62.6, 55.4 (2C), 51.7, 46.7, 32.4, 27.4, 19.8, 13.5; MS (FAB) *m*/*z* 366 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{24}H_{32}NO_2$ $[M + 1]^+$ 366.2433, found 366.2427.

**Methyl (4*R*,5*S*)-5-(Dibenzylamino)-4-vinyl Octanoate (5c).** Ketene dithioacetal (**4c**). (0.480 g, 1.09 mmol) was taken in a methanolic solution of copper sulfate pentahydrate (60 mL, 0.2 M solution) and heated at 65 °C for 2 h. After concentration in vacuo, the reaction mixture was diluted with EtOAc (40 mL) and water (2 mL) and partitioned. The organic phase was concentrated, and usual purification over silica gel column chromatography eluting with 3% EtOAc in hexane furnished ester **5c** (0.310 g, 75%) as a colorless oil; $[\alpha]_D$ −47.5 (*c* 1, $CHCl_3$); IR (neat) 1739 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.41−7.21 (m, 10H), 5.68−5.62 (m, 1H), 5.08 (d, *J* = 13.8 Hz, 1H), 5.00 (d, *J* = 18.3 Hz, 1H), 3.78 (d, *J* = 13.1 Hz, 2H), 3.66 (s, 3H), 3.47 (d, *J* = 13.2 Hz, 2H), 2.58 (t, *J* = 6.3 Hz, 1H), 2.18−2.13 (m, 2H), 2.10−1.95 (m, 1H), 1.68−1.55 (m, 3H), 1.40−1.37 (m, 3H), 0.93 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 174.8, 140.9 (2C), 140.8, 129.5 (4C), 128.5 (4C), 127.2 (2C), 116.3, 60.6, 55.4 (2C), 51.8, 47.1, 32.4, 29.5, 27.4, 21.9, 14.9; MS (ESI) *m*/*z* 380.2 $[M + 1]^+$; HRMS (FAB) calcd for $C_{25}H_{34}NO_2$ $[M + 1]^+$ 380.2584, found 380.2588.

**Methyl (4*R*,5*S*)-5-(Dibenzylamino)-4-vinyl-6-methyl Heptanoate (5d).** Ketene dithioacetal **4d** (0.900 g, 1.99 mmol) was taken in a methanolic solution of copper sulfate pentahydrate (20 mL, 0.2 M solution) and heated at 65 °C for 2 h. After concentration in vacuo, the reaction mixture was diluted with EtOAc (40 mL) and water (2 mL) and partitioned. The organic phase was concentrated, and usual purification over silica gel column chromatography eluting with 2% EtOAc in hexane furnished ester **5d** (0.493 g, 63%) as a colorless oil; $[\alpha]_D$ −40.38 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 1740 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.40−7.22 (m, 10H), 5.80−5.60 (m, 1H), 5.10 (d, *J* = 8.2 Hz, 1H), 5.00 (d, *J* = 14.3 Hz, 1H), 3.74 (d, *J* = 13.7 Hz, 2H), 3.64 (s, 3H), 3.44 (d, *J* = 13.8 Hz, 2H), 2.70−2.60 (m, 1H), 2.20−2.00 (m, 2H), 2.00−1.90 (m, 1H), 1.70−1.50 (m, 3H), 1.50−1.40 (m, 1H), 1.30−1.20 (m, 1H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.82 (d, *J* = 6.3 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 174.7, 141.0 (2C), 140.6, 129.5 (4C), 128.5 (4C), 127.2 (2C), 116.6, 58.4, 55.6 (2C), 51.7, 46.9, 36.3, 32.4, 27.4, 25.9, 23.8, 23.1; MS (FAB) *m*/*z* 394 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{26}H_{36}NO_2$ $[M + 1]$ 394.2746, found 394.2758.

**Diastereomeric Mixture of Methyl (4*R*,5*S*,2*R*/*S*)-5-(Dibenzylamino)-4-vinyl-2-allyl Hexanoate (6a).** The ester was azeotroped twice with benzene prior to use. To a solution of ester **5a** (0.190 g, 0.541 mmol) in THF (10 mL) at −78 °C was added KHMDS (2.7 mL, 1.35 mmol, 0.5 M in toluene) dropwise while stirring for 15 min. Allyl bromide (235 μL, 2.7 mmol) was added, and after 10 min of reaction the mixture was quenched by adding saturated $NH_4Cl$ solution (2 mL) and allowed to reach rt. Usual workup and silica gel column purification (4% EtOAc in hexanes) afforded ester **6a** (0.190 g, 90%, dr = 1:1) as a transparent oil; $[\alpha]_D$ −59.1 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1735 $cm^{-1}$; $^1$H NMR ($CDCl_3$) δ 7.39−7.20 (m, 10H), 5.80−5.50 (m, 2H), 5.20−4.80 (m, 4H), 3.80 (dd, *J* = 6.1 Hz, 2H), 3.65 (s, 1.5 H), 3.57 (s, 1.5H), 3.30 (d, *J* = 13.8 Hz, 2H), 2.80−2.00 (m, 5H), 1.80−1.10 (m, 2H), 1.10−1.00 (m, 3H); $^{13}$C NMR ($CDCl_3$) δ 176.7, 141.8, 140.8 (2C), 135.8, 129.4 (4C), 128.5 (4C), 127.2 (2C), 117.3, 115.8, 56.3, 54.1 (2C), 51.7, 48.2, 43.3, 38.1, 34.7, 10.6; second set 176.5, 141.6, 140.7 (2C), 135.7, 129.4 (4C), 128.5 (4C), 127.1(2C), 117.2, 115.5, 56.2, 53.8 (2C), 51.7, 48.1, 43.3, 36.0, 34.0, 10.3; MS (FAB) *m*/*z* 392 $[M + 1]^+$; HRMS (FAB) calcd for $C_{26}H_{34}NO_2$ $[M + 1]^+$ 392.2589, found 392.2587.

**Diastereomeric Mixture of Methyl (4*R*,5*S*,2*R*/*S*)-5-(Dibenzylamino)-4-vinyl-2-allyl Heptanoate (6b).** To a solution of ester **5b** (0.190 g, 0.52 mmol) in THF (25 mL) at −78 °C was added KHMDS (2.6 mL, 1.3 mmol, 0.5 M in toluene) dropwise while stirring for 15 min. Allyl bromide (226 μL, 2.6 mmol) was added, and after10 min the mixture was processed as described above for **6a**. Silica gel column purification with 4% EtOAc in hexane afforded ester **6b** (0.180 g, 85%) as a transparent oil; $[\alpha]_D$ −52.3 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 5.70−5.50 (m, 2H), 5.10−4.90 (m, 4H), 3.80−3.70 (m, 2H), 3.65 (s, 1.5H), 3.59 (s, 1.5H), 3.50−3.40 (m, 2H), 2.60−2.00 (m, 5H), 1.80−1.30 (m, 4H), 0.97−0.92 (m, 3H); two sets of carbon $^{13}$C NMR ($CDCl_3$) δ 176.5, 140.9 (2C), 135.8 (2C), 129.5 (4C), 128.5 (4C), 127.2 (2C), 117.2, 116.5, 63.3, 55.2(2C), 51.7, 45.2, 43.7, 37.9, 34.5. 19.9, 13.6; second set 176.6, 140.9, 140.5, 135.8 (2C), 129.5 (4C), 128.5 (4C), 127.1 (2C), 117.0, 116.0, 62.5, 55.8 (2C), 51.6, 44.9, 43.4, 36.7, 34.4, 19.5, 13.3; MS (FAB) *m*/*z*

406 $[M + 1]^+$; HRMS (FAB) calcd for $C_{27}H_{36}NO_2$ $[M + 1]^+$ 406.2746, found 406.2730.

**Diastereomeric Mixture of Methyl (4*R*,5*S*,2*R*/*S*)-5-(Dibenzylamino)-4-vinyl-2-allyl Octanoate (6c).** To a solution of ester **5c** (0.200 g, 0.52 mmol) in THF (26 mL) at −78 °C was added KHMDS (2.6 mL, 1.3 mmol, 0.5 M in toluene) dropwise while stirring for 10 min. Allyl bromide (227 μL, 2.63 mmol) was added, and after 10 min the mixture was processed as described for **6a**. Silica gel column purification with 2% EtOAc in hexane afforded ester **6c** (0.200 g, 91%, dr = 1:1) as a transparent oil; $[\alpha]_D$ −33.6 (*c* 1.2,$CHCl_3$); IR (neat) 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.40−7.23 (m, 10H), 5.80−5.50 (m, 2H), 5.02−4.96 (m, 4H), 3.80−3.70 (m, 2H), 3.67 (s, 1.5H), 3.60 (s, 1.5H), 3.51−3.41 (m, 2H), 2.65−2.00 (m, 5H), 1.65−1.20 (m, 6H), 0.96 (m, 3H); $^{13}C$ NMR ($CDCl_3$) δ 176.6, 140.9 (2C), 140.5, 135.9, 129.5 (4C), 128.6 (4C), 127.3 (2C), 117.2, 116.3, 61.4, 55.8 (2C), 51.7, 45.5, 43.6, 37.9, 34.5, 29.6, 22.1, 14.9; other set 176.5, 140.8 (2C), 140.5, 135.8, 129.5 (4C), 128.5 (4C), 127.1 (2C), 117.0, 116.1, 60.6, 55.2 (2C), 51.6, 45.4, 43.4, 36.7, 34.4, 29.0, 22.0, 14.9; MS (ESI) *m*/*z* 420.3 $[M + 1]^+$; HRMS (FAB) calcd for $C_{28}H_{38}NO_2$ $[M + 1]^+$ 420.2897, found 420.2895.

**Diastereomeric Mixture of Methyl (4*R*,5*S*,2*R*/*S*)-5-(Dibenzylamino)-4-vinyl-2-allyl-7-methyl Octanoate (6d).** To a solution of ester **5d** (0.290 g, 0.73 mmol) in THF (37 mL) at −78 °C was added KHMDS (3.6 mL, 1.8 mmol, 0.5 M in toluene) dropwise while stirring for 15 min. Allyl bromide (317 μL, 3.6 mmol) was added, and after 10 min the mixture was processed as described for **6a**. Silica gel column purification with 4% EtOAc in hexane afforded ester **6d** (0.280 g, 88%, dr = 1:1) as a transparent oil; $[\alpha]_D$ −24.5 (*c* 1, $CHCl_3$); IR ($CDCl_3$) 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 5.80−5.50 (m, 2H), 5.20−4.90 (m, 4H), 3.74 (t, *J* = 13.2 Hz, 2H), 3.65 (s, 1.5H), 3.59 (s, 1.5H), 3.50 (d, *J* = 13.2 Hz, 1H), 3.42 (d, *J* = 13.1 Hz, 1H), 2.70−2.60 (m, 1H), 2.50−2.20 (m, 1H), 2.20−2.00 (m, 3H), 1.80−1.50 (m, 2H), 1.50−1.40 (m, 2H), 1.40−1.20 (m, 1H), 0.90−0.78 (m, 6H); $^{13}C$ NMR ($CDCl_3$) δ 176.5, 176.4, 141.0, 140.7, 140.4, 135.9, 135.8, 129.6, 129.5, 128.6, 128.5, 127.3, 127.2, 117.2, 117.0, 116.8, 116.3, 59.4, 58.1, 55.9, 55.5, 51.7, 51.5, 45.3, 45.3, 43.7, 43.5, 37.9, 36.9, 36.5, 35.9, 34.6, 34.5, 26.0, 25.8, 24.1, 23.6, 23.3, 22.9; MS (FAB) *m*/*z* 434 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{29}H_{40}NO_2$ $[M + 1]^+$ 434.3059, found 434.3045.

**(1*S*)-Methoxycarbonyl-[5*R*-(1*S*-dibenzylaminoethyl)]-3-cyclohexene (7a) and the (1*R*) Epimer.** To a solution of ester **6a** (0.190 g, 0.485 mmol) in $CH_2Cl_2$ (100 mL) was added Grubbs first generation catalyst (8 mg, 0.0097 mmol), and the mixture was refluxed for 1 h. After concentration, the crude product was purified by silica gel column with a Florisil pad at the top to furnish the product **7a** as a mixture of isomers (0.170 g, 96%). This product was refluxed for 48 h with sodium methoxide in methanol (0.5 M, 5 mL), and the solution was cooled to rt. The reaction mixture was neutralized with Amberlite resin and filtered, and the organic layer was concentrated, taken up in MeOH (2 mL), and titrated with diazomethane. After concentration and passing through small pad of silica gel, **7a** and its 1-epimer (dr = 5.5:1) were isolated in quantitative yield; $[\alpha]_D$ +24.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.35−7.21 (m, 10 H), 6.20 (d, *J* = 5 Hz, 1H), 5.60 (m, 1H), 3.82−3.78 (d, *J* = 13.8 Hz, 2H), 3.67 (s, 3H), 3.37−3.34 (d, *J* = 13.8 Hz, 2H), 2.60−2.50 (m, 1H), 2.50−2.40 (m, 1H), 2.40−2.20 (m, 2H), 2.20−2.10 (m, 1H), 2.00−1.90 (m, 1H), 1.20−1.00 (m, 1H), 1.05 (d, *J* = 7.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 176.9, 140.7, 130.5, 129.3 (4C), 129.1, 128.6 (4C), 127.2 (2C), 124.9, 57.5, 54.3 (2C), 52.1, 40.5, 39.4, 30.3, 28.1, 10.2; MS (FAB) *m*/*z* 364 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{24}H_{30}NO_2$ $[M + 1]$ 364.2276, found 364.2269.

**(1*S*)-Methoxycarbonyl-[3*R*-(1*S*-dibenzylaminopropyl)]-4-cyclohexene (7b) and the (1*R*) Epimer.** To a solution of ester **6b** (0.170 g, 0.419 mmol) in $CH_2Cl_2$ (80 mL) was added Grubbs first generation catalyst (17 mg, 0.020 mmol), and the mixture was refluxed for 1 h. After concentration the residue was purified by silica gel column with a Florisil pad at the top to furnish a thick gum (0.150 g, 95%). This product was treated as described above. After concentration and passing through a small pad of silica gel, **7b** and its 1-epimer, (dr = 5:1) were isolated in quantitative yield; $[\alpha]_D$ −38.7 ( *c* 1, $CHCl_3$); IR ($CHCl_3$) 1734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.40−7.20 (m, 10H), 5.80−5.60 (m, 2H), 3.80−3.70 (m, 5H), 3.60 (d, *J* = 13.8 Hz, 2H), 2.70−2.60 (m, 2H), 2.50−2.40 (m, 1H), 2.30−2.10 (m, 2H), 2.00−1.90 (m, 1H), 1.80−1.60 (m, 2H), 1.50−1.40 (m, 1H), 0.95 (t, *J* = 7.1 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 176.8, 140.8, 130.8 (2C), 129.4 (4C), 128.5 (4C), 127.1 (2C), 125.7, 63.3, 55.1 (2C), 52.1, 40.6, 37.5, 29.9, 28.4, 19.7, 13.3; MS (FAB) *m*/*z* 378 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{25}H_{32}NO_2$ $[M + 1]^+$ 378.2433, found 378.2422.

**(1*S*)-Methoxycarbonyl-[3*R*-(1*S*-dibenzylaminobutyl)]-4-cyclohexene (7c) and the (1*R*) Epimer.** To a solution of ester **6c** (0.200 g, 0.47 mmol) in $CH_2Cl_2$ (80 mL) was added Grubbs first generation catalyst (0.020 g, 0.024 mmol), and the mixture was stirred for 2 h at rt. After concentration the crude was purified by silica gel column with a Florisil pad at the top to furnish a thick gum (0.176 g, 96%). This product was treated as described above. After concentration and passing through small pad of silica gel, **7c** and its 1-epimer (dr = 5:1) were isolated in quantitative yield; $[\alpha]_D$ −29.2 ( *c* 1, $CHCl_3$); IR (neat) 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.40−7.21 (m, 10H), 5.74 (d, *J* = 9.7 Hz, 1H), 5.67−5.64 (m, 1H), 3.72 (s, 3H), 3.65 (d, *J* = 13.5 Hz, 4H), 2.63−2.49 (m, 2H), 2.30−2.10 (m, 2H), 2.00−1.80 (m, 1H), 1.70−1.60 (m, 2H), 1.40−1.20 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 176.1, 140.1 (2C), 130.1, 128.7 (4C), 127.7 (4C), 126.4 (2C), 126.3, 60.4, 54.3 (2C), 51.3, 39.8, 36.8, 29.2, 28.6, 27.6, 20.8, 14.0; MS (ESI) *m*/*z* 392.2 $[M + 1]^+$; HRMS (ESI) calcd for $C_{26}H_{34}NO_2$ $[M + 1]^+$ 392.2584, found 392.2599.

**(1*S*)-Methoxycarbonyl-[3*R*-(1*S*-dibenzylaminoisobutyl)]-4-cyclohexene and the (1*R*) Epimer (7d).** To a solution of ester **6d** (0.220 g, 0.50 mmol) in $CH_2Cl_2$ (100 mL) was added Grubbs first generation catalyst (0.021 g, 0.025 mmol), and the mixture was refluxed for 1 h. After concentration the crude was purified by silica gel column with a Florisil pad at the top to furnish a thick gum (0.198 g, 97%). After concentration and passing through a small pad of silica gel, **7d** and its 1-epimer (dr = 5.1:1) were isolated in quantitative yield; $[\alpha]_D$ −30.5 ( *c* 1, $CHCl_3$); IR ($CHCl_3$) 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.40−7.10 (m, 10H), 5.80−5.60 (m, 2H), 3.80−3.75 (m, 4H), 3.70−3.50 (m, 3H), 2.70−2.60 (m, 3H), 2.40−2.20 (m, 2H), 2.00−2.60 (m, 3H), 1.60−1.40 (m, 1H), 1.40−1.10 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 176.9, 141.0 (2C), 130.9, 129.5 (4C), 128.5 (4C), 127.2 (2C), 125.9, 58.8, 55.0 (2C), 52.1, 40.6, 37.4, 36.3, 29.9, 28.4, 25.4, 23.6, 22.9; MS (FAB) *m*/*z* 406 $[M + 1]^+$ ; HRMS (FAB) calcd for $C_{27}H_{36}NO_2$ 406.2746, found 406.2760.

**(1*S*)-Methoxycarbonyl-[3*S*-(1*S*-acetamidoethyl)]-cyclohexane (8a).** To a solution of **7a** (0.040 g, 0.11 mmol) in MeOH (10 mL) was added $Pd(OH)_2/C$ (0.080 g). After three times evacuation, the flask was filled with hydrogen and stirred under 1 atm hydrogen pressure for 5 h. The reaction mixture was filtered through a pad of Celite and concentrated. The crude amine was taken in a mixture of $CH_2Cl_2$ and saturated $NaHCO_3$ (1:1, 4 mL) at 0 °C, acetyl chloride (150 μL) was added, and the mixture was stirred for 1 h and allowed to come to rt during an additional 1 h. The reaction mixture was diluted with $CH_2Cl_2$ (20 mL), and the organic phase was separated and concentrated. The crude reaction mixture was purified by silica gel chromatography (10% MeOH in EtOAc) to give **8a** (0.018 g, 72%) as a white solid. (X-ray provided, see Supporting Information). Recrystallization from EtOAc−hexanes gave colorless crystals, mp 110−111 °C; $[\alpha]_D$ −31.8 (*c* 1,$CHCl_3$); IR ($CHCl_3$) 3275,1734, 1653 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.20 (m, 1H), 4.00−3.80 (m, 1H), 3.60 (s, 3H), 2.30 (m, 1H), 2.00−1.80 (m, 5H), 1.80−1.70 (m, 1H),

1.70−1.60 (m, 1H), 1.60−1.40 (m, 1H), 1.40−1.20 (m, 4H), 1.10 (d, $J = 6.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.6, 169.7, 52.0, 49.4, 43.5, 42.4, 31.2, 29.2, 28.6, 25.6, 23.9, 17.8; MS (FAB) 228 [M + 1]$^+$ ; HRMS (FAB) calcd for $C_{12}H_{21}O_3N$ 227.1521, found 227.1525.

**(1*S*)-Methoxycarbonyl-[3*S*-(1*S*-acetamidopropyl)]-cyclohexane (8b).** To a solution of **7b** (0.080 g, 0.212 mmol) in MeOH (8 mL) was added $Pd(OH)_2/C$ (160 mg), and the mixture was stirred for 2 h under hydrogen pressure (1 atm). After filtration through small pad of Celite, the organic layer was concentrated and taken in $CH_2Cl_2$ (1.5 mL). Pyridine (51 $\mu$L, 0.63 mmol) and acetic anhydride (59 $\mu$L, 0.63 mmol) were added while stirring for 12 h at rt. The reaction mixture was processed as described for **8a**. Purification by silica gel chromatography (65% EtOAc in hexane) furnished **8b** (0.037 g, 72%) as a white solid; $[\alpha]_D$ −36.1 (*c* 0.285, $CHCl_3$); IR (neat) 3285, 1739, 1648 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.20−5.18 (d, $J = 8.5$ Hz, 1H), 3.79−3.73 (m, 1H), 3.66 (s, 3H), 2.30 (t, $J = 12.1$ Hz, 1H), 2.00 (s, 3H), 1.92 (d, $J = 11.5$ Hz, 2H), 1.87 (d, $J = 12.1$ Hz, 1H), 1.71 (d, $J = 12.7$ Hz, 1H), 1.63−1.55 (m, 1H), 1.47−1.36 (m, 1H), 1.33−1.13 (m, 4H), 1.00−0.94 (m, 1H), 0.89 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.6, 170.2, 55.2, 51.9, 43.6, 41.3, 32.1, 29.2, 27.9, 25.6, 24.9, 23.9, 11.0; MS (FAB) *m*/*z* 242 [M + 1]$^+$; HRMS (FAB) calcd for $C_{13}H_{23}NO_3$ 241.1677, found 241.1672.

**(1*S*)-Methoxycarbonyl-[3*S*-(1*S*-acetamidopropyl)]-cyclohexane (8c).** To a solution of **7c** (0.090 g, 0.23 mmol) in MeOH (9 mL) was added $Pd(OH)_2/C$ (180 mg), and the mixture was stirred for 2 h under hydrogen pressure (1 atm). After filtration through a small pad of Celite, the organic layer was concentrated and taken in $CH_2Cl_2$ (1.5 mL). Pyridine (55 $\mu$L, 0.69 mmol) and acetic anhydride (65 $\mu$L, 0.69 mmol) were added while stirring for 12 h at rt. The reaction mixture was processed as described for **8a**. Purification by silica gel chromatography (65% EtOAc in hexane) furnished **8c** (0.045 g, 76%) as a white solid. (X-ray provided, see Supporting Information.) Recrystallization from EtOAc−hexanes gave colorless crystals, mp 138−139 °C; $[\alpha]_D$ −38.8 (*c* 1, $CHCl_3$); IR (neat) 3285, 1734, 1641 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.20−5.10 (bs, 1H), 3.88−3.86 (m, 1H), 3.68 (s, 3H), 2.31−2.28 (m, 1H), 2.01 (s, 3H), 1.97−1.94 (m, 2H), 1.89−1.85 (m, 1H), 1.75−1.50 (m, 3H), 1.50−1.10 (m, 7H), 0.90 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.8, 169.4, 52.7, 51.2, 42.8, 40.9, 33.5, 31.2, 28.4, 27.2, 24.8, 23.2, 19.1, 13.6; MS (ESI) *m*/*z* 256.1 [M + 1]$^+$; HRMS (FAB) calcd for $C_{14}H_{26}NO_3$ 256.1834, found 256.1828.

**(1*S*)-Methoxycarbonyl-[5*S*-(1*S*-acetamidoisobutyl)]-cyclohexane (8d).** To a solution of **7d** (0.080 g, 0.197 mmol) in MeOH (10 mL) was added $Pd(OH)_2/C$ (0.160 g), and the mixture was stirred for 2 h under hydrogen pressure (1 atm). After filtration through a small pad of Celite, the organic layer was concentrated and taken in $CH_2Cl_2$ (2 mL). Pyridine (48 $\mu$L, 0.59 mmol) and acetic anhydride (55 $\mu$L, 0.59 mmol) were added while stirring for 12 h at rt. The reaction mixture was processed as described for **8a**. After concentration, the residue was purified by silica gel chromatography (70% EtOAc in hexane) to furnish **8d** (0.037 g, 70%) as a transparent oil; $[\alpha]_D$ −54.8 (*c* 1.1, $CHCl_3$); IR (neat) 3284, 1737, 1647 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.15−5.12 (d, $J = 9.4$ Hz, 1H), 3.98−3.93 (m, 1H), 3.68 (s, 3H), 2.34−2.28 (t, $J = 3.5$ Hz, 1H), 2.00 (s, 3H), 1.96 (d, $J = 11.5$ Hz, 2H), 1.85 (d, $J = 11.5$ Hz, 1H), 1.80−1.20 (m, 9H), 1.00−0.80 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.9, 169.3, 51.3, 50.9, 42.8, 41.4, 40.5, 31.1, 28.5, 27.2, 24.8, 24.6, 23.3, 23.2, 21.4; MS (ESI) *m*/*z* 270.1 [M + 1]$^+$; HRMS (FAB) calcd for $C_{15}H_{28}NO_3$ [M + 1]$^+$ 270.1991, found 270.1991.

**(1*R*,3*S*)-3-[(*S*)-1-Acetamidoethyl)]-*N*-[(2*S*,3*S*,5*R*)-6-(butylamino)-3-hydroxy-5-methyl-6-oxo-1-phenylhexan-2-yl)]cyclohexanecarboxamide (9a).** To a solution of **8a** (6.2 mg, 0.0273 mmol) in MeOH (1 mL) was added lithium hydroxide solution (100 $\mu$L, 1 N solution in water), and the mixture was stirred for 12 h at rt. The reaction mixture was diluted with EtOAc (10 mL) and neutralized with dilute HCl, washed with brine, dried ($Na_2SO_4$), and concentrated. The crude product was used directly for coupling without purification. To a solution of Boc-protected amine (16 mg, 0.0408 mmol) in $CH_2Cl_2$ (1 mL) was added TMSI (27 $\mu$L, 0.195 mmol) at rt for 30 min. The reaction mixture was quenched with $Na_2S_2O_3$ solution and extracted with EtOAc. The organic layer was washed with $NaHCO_3$ solution and brine, dried ($Na_2SO_4$), and concentrated. It was used immediately without purification. The acid and amine were taken in a mixed solvent ($CH_2Cl_2-H_2O$, 1:1; 1 mL), HOBt (6 mg, 0.0408 mmol) and EDC (8 mg, 0.0408 mmol) were added, and the mixture was stirred at 4 °C for 24 h. The reaction mixture was diluted with EtOAc (10 mL), washed with dilute HCl, $NaHCO_3$, and brine, and dried ($Na_2SO_4$). After concentration, the crude product was purified by silica gel chromatography (5% MeOH in $CH_2Cl_2$) to give **9a** (5 mg, 40%) as a white solid; $[\alpha]_D$ −27.8 (*c* 0.205, MeOH); $^1$H NMR (MeOD) $\delta$ 7.27−7.15 (m, 5H), 4.06−4.04 (m, 1H), 3.70−3.66 (m, 1H), 3.56−3.53 (m, 1H), 3.12 (t, $J = 7.0$ Hz, 2H), 2.93 (dd, $J = 5.8$, 5.6 Hz, 1H), 2.74 (dd, $J = 9.5$ Hz, 1H), 2.57−2.54 (m, 1H), 2.20−2.15 (m, 1H), 1.92 (s, 3H), 1.90−1.80 (m, 1H), 1.80−1.65 (m, 3H), 1.60−1.50 (m, 1H), 1.50−1.30 (m, 9H), 1.07 (d, $J = 7.0$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 1.00−0.97 (m, 1H), 0.93 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (MeOD) $\delta$ 178.9, 178.7, 172.4, 140.1, 130.3 (2C), 129.2 (2C), 127.2, 70.9, 55.9, 50.6, 46.2, 43.4, 39.9, 39.0, 38.6, 37.9, 32.9, 32.5, 30.5, 29.3, 26.3, 22.6, 21.1, 18.5, 17.7, 14.1; MS (ESI) *m*/*z* 510.5 [ M + Na]$^+$; HRMS (FAB) calcd for $C_{28}H_{45}N_3O_4$ 487.3410, found 487.3402

**(1*R*,3*S*)-3-[(*S*)-1-Acetamidopropyl)]-*N*-[(2*S*,3*S*,5*R*)-6-(butylamino)-3-hydroxy-5-methyl-6-oxo-1-phenylhexan-2-yl)]cyclohexanecarboxamide (9b).** To a solution of **8b** (8 mg, 0.0332 mmol) in MeOH (1 mL) was added LiOH solution (100 $\mu$L, 1 N solution in water), and the mixture was stirred for 12 h at rt. The reaction mixture was diluted with EtOAc (10 mL) and neutralized with dilute HCl, washed with brine, dried ($Na_2SO_4$), and concentrated. The crude product was used directly for coupling without purification. To a solution of Boc-protected amine (26 mg, 0.0664 mmol) in $CH_2Cl_2$ (1 mL) was added TMSI (38 $\mu$L, 0.26 mmol) at rt for 30 min.. The reaction mixture was processed as described for **9a**. The acid and amine were taken in a mixed solvent ($CH_2Cl_2-H_2O$, 1:1, 1 mL), HOBt (9 mg, 0.065 mmol) and EDC (13 mg, 0.066 mmol) were added, and the mixture was stirred at 4 °C for 24 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with dilute HCl, $NaHCO_3$, and brine, and dried ($Na_2SO_4$). After concentration, the crude product was purified by silica gel chromatography (5% MeOH in $CH_2Cl_2$) to give **9b** (8 mg, 50%) as white solid; $[\alpha]_D$ −24 (*c* 0.22, MeOH); $^1$H NMR (MeOD) $\delta$ 7.26−7.16 (m, 5H), 4.04−4.03 (m, 1H), 3.54 (t, $J = 4.0$ Hz, 2H), 3.12 (t, $J = 7.1$ Hz, 2H), 2.73 (dd, $J = 5.8$, 5.7 Hz, 1H), 2.73 (dd, $J = 9.4$, 9.3 Hz, 1H), 2.57−2.52 (m, 1H), 2.15−2.10 (m, 1H), 1.95 (s, 3H), 1.85−1.75 (m, 1H), 1.75−1.60 (m, 3H), 1.60−1.50 (m, 2H), 1.50−1.40 (m, 4H), 1.40−1.20 (m, 7H), 1.08 (d, $J = 6.9$ Hz, 2H), 1.05−0.99 (m, 1H), 0.93 (t, $J = 7.2$ Hz, 3H), 0.87 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (MeOD) $\delta$ 177.9, 177.7, 172.1, 139.2, 129.3 (2C), 128.3 (2C), 126.2, 69.9, 55.6, 54.9, 45.4, 41.3, 39.0, 38.1, 37.7, 37.0, 32.6, 31.6, 29.6, 27.8, 25.4, 24.4, 21.5, 20.0, 17.5, 13.0, 9.8; MS (ESI) *m*/*z* 502.2 [M + 1]$^+$; HRMS (FAB) calcd for $C_{29}H_{48}N_3O_4$ [M + 1]$^+$ 502.3567, found 502.3599.

**(1*R*,3*S*)-3-[(*S*)-1-Acetamidobutyl)]-*N*-[(2*S*,3*S*,5*R*)-6-(butylamino)-3-hydroxy-5-methyl-6-oxo-1-phenylhexan-2-yl)]cyclohexanecarboxamide (9c).** To a solution of **8c** (10 mg, 0.039 mmol) in MeOH (1 mL) was added LiOH solution (150 $\mu$L, 1 N solution in water), and the mixture was stirred for 12 h at rt. The reaction mixture was diluted with EtOAc (10 mL), neutralized with dilute HCl, washed with brine, dried ($Na_2SO_4$), and concentrated. The crude product was used directly for coupling

without purification. To a solution of Boc-protected amine (16 mg, 0.039 mmol) in $CH_2Cl_2$ (1 mL) was added TMSI (22 $\mu$L) at rt for 30 min. The reaction mixture was processed as described for **9a**. The acid and amine were taken in a mixed solvent ($CH_2Cl_2-H_2O$, 1:1, 1 mL), HOBt (5.3 mg, 0.039 mmol) and EDC (7.5 mg, 0.039 mmol) were added, and the mixture was stirred at 4 °C for 24 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with dilute HCl, $NaHCO_3$, and brine, and dried ($Na_2SO_4$). After concentration, the crude product was purified by silica gel chromatography (5% MeOH in $CH_2Cl_2$) to give **9c** (8 mg, 40%) as white solid; $[\alpha]_D$ −50 (*c* 0.25, MeOH:$CHCl_3$[1:1]); IR (neat) 3315, 1648, 1630 $cm^{-1}$; $^1H$ NMR (MeOD−$CDCl_3$ [5:1]) $\delta$ 8.11 (s, 1H), 7.59−7.48 (m,4H), 4.38 (t, $J$ = 6.7 Hz, 1H), 3.97 (bs,1H), 3.86 (m, 1H), 3.44 (t, $J$ = 7.1 Hz, 2H), 3.22 (dd, $J$ = 5.7, 6.0 Hz, 1H), 3.00 (dd, $J$ = 9.3, 9.2 Hz, 1H), 2.85−2.80 (m, 1H), 2.55 (s, 1H), 2.50−2.40 (m, 1H), 2.28 (s, 3H), 2.20−2.10 (m, 1H), 2.05−1.95 (m, 3H), 1.90 (d, $J$ = 12.5 Hz, 1H), 1.80−1.50 (m, 12H), 1.40 (d, $J$ = 6.8 Hz, 4H), 1.25 (t, $J$ = 7.0 Hz, 6H); $^{13}C$ NMR (MeOD−$CDCl_3$ [5:1]) $\delta$ 177.2, 177.0, 171.2, 138.2, 128.6 (2C), 127.6 (2C), 125.6, 68.9, 53.9, 52.9, 44.6, 40.8, 38.3, 37.5, 36.8, 36.5, 32.9, 31.7, 30.8, 29.3, 28.8, 27.1, 24.7, 21.1, 19.4, 18.7, 16.8, 12.8, 12.6; MS (ESI) $m/z$ 516 $[M + 1]^+$; HRMS (FAB) calcd for $C_{30}H_{50}N_3O_4$ $[M + 1]^+$ 516.3723, found 516.3720.

**(1*R*,3*S*)-3-[(*S*)-1-Acetamido-3-methylbutyl)]-*N*-[(2*S*,3*S*,5*R*)-6-(butylamino)-3-hydroxy-5-methyl-6-oxo-1-phenylhexan-2-yl)]-cyclohexanecarboxamide (9d).** To a solution of **8d** (10 mg, 0.037 mmol) in MeOH (1 mL) was added LiOH solution (100 $\mu$L, 1 N solution in water), and the mixture was stirred for 12 h at rt. The reaction mixture was diluted with EtOAc (10 mL) and neutralized with dilute HCl, washed with brine, dried ($Na_2SO_4$), and concentrated. The crude product was used directly for coupling without purification. To a solution of Boc-protected amine (15 mg, 0.038 mmol) in $CH_2Cl_2$ (1 mL) was added TMSI (27 $\mu$L, 0.195 mmol) at rt for 30 min. The reaction mixture was processed as described for **9a**. The acid and amine were taken in a solution of cosolvent ($CH_2Cl_2-H_2O$, 1:1, 1 mL), HOBt (5 mg, 0.037 mmol) and EDC (7 mg, 0.041 mmol) were added, and the mixture was stirred at 4 °C for 24 h. The reaction mixture was diluted with EtOAc (10 mL), washed with dilute HCl, $NaHCO_3$, and brine, and dried ($Na_2SO_4$). After concentration, the crude product was purified by silica gel chromatography (5% MeOH in $CH_2Cl_2$) to give **9d** (7 mg, 40%) as a white solid; $[\alpha]_D$ −52.8 (*c* 0.25, MeOH); $^1H$ NMR (MeOD) $\delta$ 7.20−7.00 (d, $J$ = 10.0 Hz, 1H), 6.68−6.60 (m, 4H), 4.40 (bs, 1H), 3.92−3.85 (m, 1H), 3.70−3.80 (m, 1H), 3.45−3.40 (m, 1H), 3.13 (t, $J$ = 6.0 Hz, 2H), 2.93 (dd, $J$ = 4.8, 4.7 Hz, 1H), 2.81 (dd, $J$ = 7.9, 8.1 Hz, 1H), 2.65−2.62 (m, 1H), 2.35−2.30 (m, 1H), 2.12 (s, 3H), 2.12−2.00 (m, 1H), 1.93−1.89 (m, 3H), 1.79−1.77 (m, 2H), 1.70−1.51 (m, 11H), 1.37 (d, $J$ = 5.9 Hz, 3H), 1.32−1.24 (m, 6H), 1.20 (d, $J$ = 5.5 Hz, 3H); $^{13}C$ NMR (MeOD) $\delta$ 178.9, 178.8, 172.8, 140.1, 130.3 (2C), 129.3 (2C), 127.3, 70.8, 55.9, 52.8, 46.4, 43.3, 41.8, 39.9, 39.1, 38.6, 37.9, 33.5, 32.6, 30.7, 28.8, 26.4, 26.2, 24.0, 22.5, 22.0, 21.1, 18.6, 14.1; MS (ESI) $m/z$ 530.4 $[M + 1]^+$; HRMS (FAB) calcd for $C_{31}H_{52}N_3O_4$ 530.3880, found 530.3892.

**Methyl (3*R*,4*R*)-4-(Benzyloxymethoxy)-5-methyl-3-vinyl Hexanoate (11).** To a suspension of copper(I) iodide (5.71 g, 30 mmol) in THF (100 mL) at −78 °C was added vinylmagnesium bromide (60 mL, 1 M solution in THF) dropwise during 20 min, and the mixture was stirred for 45 min. The unsaturated ester **10** (1.39 g, 5 mmol) in THF (20 mL) was added, followed by TMSCl (11.4 mL, 90 mmol) while stirring for 4 h. The reaction mixture was quenched with $NH_4OH-NH_4Cl$ solution (1:1, 100 mL) and allowed to come to rt. The organic layer was separated, washed with satd $NH_4Cl$ solution and brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by silica gel column chromatography using 5% EtOAc in hexanes to furnish the major isomer **11** (1.35 g, dr = 9:1) as a colorless oil in 88% yield; $[\alpha]_D$ + 2.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.37−7.28 (m, 5H), 5.79−5.70 (m, 1H), 5.05 (dd, $J$ = 17.2, 11.8 Hz, 2H), 4.80 (dd, $J$ = 6.9 Hz, 2H), 4.67 (s, 2H), 3.66 (s, 3H), 3.31−3.29 (m, 1H), 2.86−2.84 (m, 1H), 2.74 (dd, $J$ = 4.1, 4.2 Hz, 1H), 2.37 (dd, $J$ = 9.8 Hz, 1H), 1.91−1.86 (m, 1H), 0.99 (d, $J$ = 7.0 Hz, 3H), 0.97 (d, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.6, 139.1, 138.2, 128.8 (2C), 128.1 (2C), 128.07, 116.8, 96.9, 87.1, 70.6, 51.8, 44.1, 36.4, 31.0, 20.6, 17.3; MS (ESI) $m/z$ 329.3 $[M + Na]^+$; HRMS (FAB) calcd for $C_{18}H_{27}O_4$ $[M + 1]^+$ 307.1904, found 307.1906.

**2-((3*R*,4*R*)-4-(Benzyloxymethoxy)-5-methyl-3-vinylhexylidene-1,3-dithiane (12).** To a solution of ester **11** (0.612 g, 2 mmol) in THF (20 mL) at 0 °C was added DIBAL-H (3 mL, 4.5 mmol, 1.5 M in toluene), and the mixture was stirred for 2 h. The reaction mixture was quenched with MeOH (5 mL) followed by addition of Rochelle salt solution (15 mL) and EtOAc (50 mL) while stirring for 2 h. The organic layer was partitioned, washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by passing through a small pad silica gel using 15% EtOAc in hexanes as eluent to give the alcohol (0.511 g, 92%) as a colorless viscous oil; $[\alpha]_D$ −7.2 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3416 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.37−7.28 (m, 5H), 5.77−5.67 (m, 1H), 5.13−5.07 (m, 2H), 4.84 (d, $J$ = 2.4 Hz, 2H), 4.70 (s, 2H), 3.75−3.69 (m, 1H), 3.64−3.58 (m, 1H), 3.29−3.26 (m, 1H), 2.49−2.42 (m, 1H), 2.00−1.89 (m, 2H), 1.65−1.54 (m, 2H), 0.98 (d, $J$ = 6.9 Hz, 3H), 0.94 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 140.4, 138.3, 128.8 (2C), 128.2 (2C), 128.1, 116.6, 97.0, 88.2, 70.6, 61.4, 44.8, 33.3, 30.9, 20.7, 17.5; MS (ESI) $m/z$ 279.2 $[M + 1]^+$; HRMS (ESI) calcd for $C_{17}H_{26}O_3Na$ $[M + 23]^+$ 301.1774, found 301.1779.

To a stirring solution of oxalyl chloride (92 $\mu$L, 1.0 mmol) in $CH_2Cl_2$ (8 mL) at −78 °C was added DMSO (212 $\mu$L, 3 mmol), and after 10 min the alcohol (0.260 g, 0.93 mmol) in $CH_2Cl_2$ (2 mL) was added and stirred for 30 min. After addition of *i*-$Pr_2NEt$ (695 $\mu$L, 4 mmol) the reaction mixture was stirred at −78 °C for 30 min, and then the dry ice bath was removed to allow the mixture to warm to rt during 30 min. The reaction mixture was quenched with water (2 mL) and extracted with C $H_2Cl_2$ (3 × 10 mL). The organic layer was washed with 10% citric acid solution (10 mL), washed with brine, and dried over $Na_2SO_4$. After concentration, the residue was purified by silica gel chromatography (9% EtOAc in hexanes) to furnish the corresponding aldehyde (0.190 g, 74%) as colorless viscous oil; $[\alpha]_D$ −3.6 (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 1725 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.70 (t, $J$ = 2.1 Hz, 1H), 7.39−7.28 (m, 5H), 5.80−5.70 (m, 1H), 5.15 (d, $J$ = 16.0 Hz, 1H), 5.09 (d, $J$ = 8.9 Hz, 1H), 4.77 (d, $J$ = 3.2 Hz, 2H), 4.65 (d, $J$ = 1.7 Hz, 2H), 3.31 (dd, $J$ = 4.0, 4.1 Hz, 1H), 2.98−2.95 (m, 1H), 2.72 (dd, $J$ = 2.0, 5.0 Hz, 1H), 2.69−2.44 (m, 1H), 1.93−1.88 (m, 1H), 0.99 (d, $J$ = 7.0 Hz, 3H), 0.98 (d, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 202.5, 139.2, 138.2, 128.8 (2C), 128.1 (3C), 117.0, 96.9, 87.3, 70.7, 45.5, 42.2, 30.9, 20.5, 17.2; MS (ESI) $m/z$ 279.2 $[M + 3]^+$; HRMS (FAB) calcd for $C_{17}H_{25}O_3$ $[M + 1]^+$ 277.1798, found 277.1796.

To a stirring solution of 2-phosphoryl 1,3-dithiane (0.180 g, 0.7 mmol) in THF (8 mL) at −78 °C was added *n*-BuLi (500 $\mu$L, 0.8 mmol, 1.6 M in hexane) dropwise during 15 min. After 1 h, the aldehyde (0.190 g, 0.68 mmol) in THF (2 mL) was added, the mixture was stirred for 15 min at −78 °C, and the cooling bath was removed. The reaction mixture was quenched after 1 h by adding water (3 mL) and extracted with EtOAc (40 mL). The organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated. The purification of crude product over silica gel column chromatography using 10% EtOAc in hexanes furnished ketene dithioacetal **12** (0.240 g) in 93% yield as a transparent oil; $[\alpha]_D$ + 30.6 (*c* 1, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 7.37−7.28 (m, 5H), 5.96 (t, $J$ = 7.2 Hz, 1H), 5.69−5.62 (m, 1H), 5.06 (s, 1H), 5.06 (d, $J$ = 7.8 Hz, 1H), 4.83 (s, 2H), 4.71 (s, 2H), 3.28 (dd, $J$ = 4.1, 4.2 Hz, 1H), 2.84 (q, $J$ = 6.1 Hz, 4H),

2.68−2.63 (m, 1H), 2.36−2.15 (m, 4H), 1.92−1.91 (m, 1H), 0.98 (d, $J$ = 6.9 Hz, 3H), 0.95 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 139.8, 138.4, 133.5, 128.8 (2C), 128.2 (2C), 128.0, 126.5, 116.7, 96.9, 87.5, 70.6, 47.7, 31.0, 30.9, 30.7, 30.1, 25.7, 20.9, 17.4; MS (ESI) $m/z$ 381.3 $[M + 3]^+$; HRMS (FAB) calcd for $C_{21}H_{31}O_2S_2$ $[M + 1]^+$ 379.1760, found 379.1758.

**Methyl (5*R*,4*R*)-5-(*O*-Benzyloxymethoxy)-4-vinyl-6-methyl Heptanoate (13).** Ketene dithioacetal **12** (0.225 g, 0.59 mmol) was dissolved in a methanolic solution of copper sulfate pentahydrate (10 mL, 0.2 M solution) and heated at 65 °C for 2 h. After concentration, the reaction mixture was diluted with EtOAc (40 mL) and water (2 mL). The organic phase was concentrated, and usual purification over silica gel chromatography eluting with 4% EtOAc in hexanes furnished **13** (0.130 g, 68%) as a colorless oil; $[\alpha]_D$ + 1.4 ($c$ 1, $CHCl_3$); IR ($CHCl_3$) 1739 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.37−7.28 (m, 5H), 5.64−5.55 (m, 1H), 5.10 (d, $J$ = 10.1 Hz, 1H), 5.08 (d, $J$ = 17.0 Hz, 1H), 4.83 (s, 2H), 4.69 (s, 2H), 3.66 (s, 3H), 3.24 (dd, $J$ = 4.4, 4.3 Hz, 1H), 2.43−2.41 (m, 1H), 2.39−2.35 (m, 2H), 2.21−2.08 (m, 1H), 1.93−1.89 (m, 1H), 1.59−1.54 (m, 1H), 0.98 (d, $J$ = 6.9 Hz, 3H), 0.95 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.6, 139.7, 138.4, 128.8 (2C), 128.2 (2C), 128.0, 117.2, 97.0, 87.9, 70.6, 51.8, 47.7, 32.5, 31.0, 25.4, 20.7, 17.3; MS (ESI) $m/z$ 343.3 $[M + Na]^+$; HRMS (FAB) calcd for $C_{19}H_{29}O_4$ $[M + 1]^+$ 321.2060, found 321.2062.

**Diastereomeric Mixture of Methyl (5*R*,4*R*,2*R*,*S*)-5-(*O*-Benzyloxymethoxy)-4-vinyl-2-allyl-6-methyl Heptanoate (14).** To a solution of ester **13** (0.130 g, 0.40 mmol) in THF (20 mL) at −78 °C was added KHMDS (2 mL, 1 mmol, 0.5 M in toluene) dropwise while stirring for 15 min. Allyl bromide (173 $\mu$L, 2 mmol) was added and the reaction was followed by TLC after 15 min. The mixture was quenched by adding saturated $NH_4Cl$ solution (5 mL) and allowed to reach rt. Usual workup and purification by silica gel chromatography (5% EtOAc in hexanes) afforded ester **14** (0.110 g, 76%, dr = 1:1) as a transparent oil; $[\alpha]_D$ −1.45 ($c$ 1.1,$CHCl_3$); IR (neat) 1739 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.39−7.28 (m, 5H), 5.77−5.55 (m, 2H), 5.11−4.99 (m, 4H), 4.84−4.74 (m, 2H), 4.75−4.60 (m, 2H), 3.68 (s, 1.7H), 3.62 (s, 1.3H), 3.24−3.18 (m, 1H), 2.70−2.50 (m, 1H), 2.50−2.25 (m, 3H), 2.10−2.00 (m.0.5H), 1.95−1.80 (m, 1.5H), 1.75−1.60 (m, 0.5H), 1.50−1.30 (m, 0.5H), 1.00−0.80 (m, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.3, 140.0, 138.4, 135.8, 128.8 (2C), 128.1 (2C), 128.0, 117.2, 97.1, 88.6, 70.5, 51.7, 45.8, 43.4, 38.0, 32.0, 31.1, 20.8, 20.4, 17.9; for 2-epimer 176.6, 139.8, 138.3, 135.7, 128.8 (2C), 128.1 (2C), 128.0, 117.2, 117.1, 116.9, 97.1, 88.1, 70.6, 51.7, 46.3, 43.7, 36.1, 31.9, 30.9, 17.4; MS (ESI) $m/z$ 383.4 $[M + Na]^+$; HRMS (FAB) calcd for $C_{22}H_{33}O_4$ $[M + 1]^+$ 361.2373, found 361.2370.

**(3*R*,5*R*,6*R*)-3-Allyl-6-isopropyl-5-vinyltetrahydro-2*H*-pyran-2-one (15) and (3*S*,5*R*,6*R*)-3-Allyl-6-isopropyl-5-vinyltetrahydro-2*H*-pyran-2-one (16).** To a solution of ester **14** (0.110 g, 0.30 mmol) in $CH_2Cl_2$ (6 mL) at −78 °C was added TMSBr (1.2 mL, 9 mmol). The reaction mixture was warmed to −30 °C while stirring for 1 h, then quenched by adding $NH_4Cl$ solution, and allowed to come to rt. The organic layer was diluted with $CH_2Cl_2$ (25 mL), partitioned, dried ($Na_2SO_4$), and concentrated. The crude product was purified by silica gel chromatography (6% EtOAc in hexane) to give a mixture of lactones **15** and **16** (0.056 g, 89%) as a colorless gum; $[\alpha]_D$ + 73.4 ($c$ 1, $CHCl_3$); IR (neat) 1734 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.95−5.50 (m, 2H), 5.25−5.00 (m, 4H), 4.00 (dd, $J$ = 8.4, 2.0 Hz, 1H), 2.75−2.25 (m, 4H), 2.00−1.50 (m, 3H), 1.07 (dd, $J$ = 6.9,6.7 Hz, 3H), 0.92 (dd, $J$ = 6.9, 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.4, 137.5, 135.3, 118.2, 117.8, 88.6, 41.9, 40.6, 36.3, 32.6, 30.2, 20.2, 14.5; second set- 175.4, 137.7, 135.6, 117.9, 117.4, 85.2, 39.7, 37.5, 35.6, 30.7, 29.7, 20.3, 14.7; MS (ESI) $m/z$ 209.1 $[M + 1]^+$; HRMS (FAB) calcd for $C_{13}H_{21}O_2$ $[M + 1]^+$ 209.1536, found 209.1531.

**(1*R*,4*R*,5*R*)-4-Isopropyl-3-oxabicyclo[3.3.1]non-6-en-2-one (17).** To a solution of lactones **15** and **16** (0.055 g, 0.26 mmol) in $CH_2Cl_2$ (20 mL) was added first generation Grubbs catalyst (17 mg, 0.0206 mmol), and the mixture was refluxed for 12 h. After concentration, the crude product along with starting material was purified by silica gel chromatography (12% EtOAc in hexanes) to furnish the bicyclic lactone, **17** (0.025 g, 41%). Diene **16** was recovered (45%), and recycled by refluxing DBU in $CH_2Cl_2$); $[\alpha]_D$ +76.4 ($c$ 1.2,$CHCl_3$); IR ($CHCl_3$) 1731 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.89−5.85 (m, 1H), 5.82−5.77 (m, 1H), 3.86 (d, $J$ = 9.7 Hz, 1H), 2.92−2.89 (m, 1H), 2.50 (bs, 1H), 2.49−2.44 (m, 1H), 2.37−2.32 (m, 1H), 2.11 (d, $J$ = 10.8 Hz, 1H), 2.08−1.92 (m, 1H), 1.75 (dd, $J$ = 7.9, 4.0 Hz, 1H), 1.15 (d, $J$ = 6.6 Hz, 3H), 0.94 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.9, 129.3, 127.9, 89.9, 35.7, 32.5, 31.7, 29.1, 22.5, 20.4, 19.5; MS (ESI) $m/z$ 181.1 $[M + 1]^+$; HRMS (FAB) calcd for $C_{11}H_{17}O_2$ $[M + 1]^+$ 181.1223, found 181.1225.

**(1*S*)-Methoxycarbonyl-[3*R*-(1*R*-hydroxy-2-methylpropyl)]-4-cyclohexene (18).** Bicyclic lactone **17** (0.025 g) was dissolved in a methanolic solution of sodium methoxide (0.5 M, 2 mL) at 0 °C and stirred for 30 min. The solution was diluted with $CHCl_3$ (10 mL), neutralized with Amberlite resin, and filtered. After concentration, **18** (0.022 g, 74%) was isolated as a colorless oil; $[\alpha]_D$ −1.5 ($c$ 1, $CHCl_3$); IR (neat) 3478, 1736 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.92−5.90 (m, 1H), 5.55 (d, $J$ = 10.1 Hz, 1H), 3.71 (s, 3H), 3.23 (dd, $J$ = 7.9, 4.0 Hz, 1H), 2.75−2.50 (m, 2H), 2.45−2.25 (m, 2H), 2.20−2.00 (m, 1H), 1.90−1.75 (m, 1H), 1.70−1.50 (m, 1H), 1.00 (d, $J$ = 6.6 Hz, 3H), 0.93 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.5, 129.7, 128.9, 79.9, 52.1, 39.8, 39.4, 30.6, 28.2, 25.4, 19.6, 19.1; MS (ESI) $m/z$ 213.2 $[M + 1]^+$; HRMS (FAB) calcd for $C_{12}H_{21}O_3$ $[M + 1]^+$ 213.1485, found 213.1484.

**(4*R*,3*R*)-1-*tert*-Butyldimethylsilyloxy-4-hydroxy-3-vinyl-5-methyl Hexanol (19).** To a solution of alcohol resulting from the reduction of **11** (2.2 g, 7.91 mmol) in $CH_2Cl_2$ (80 mL) were added DMAP (2.89 g, 23.73 mmol) and TBSCl (1.31 g, 8.7 mmol) while stirring for 30 min at rt. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL), washed with dilute HCl solution (1 N) and brine, dried over $Na_2SO_4$, and concentrated. The residue was passed through a small pad of silica gel to furnish TBS ether **19** (2.9 g, 93%) as a transparent oil; $[\alpha]_D$ + 3.8 ($c$ 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 7.38−7.28 (m, 5H), 5.70−5.63 (m, 1H), 5.07 (s, 1H), 5.03 (d, $J$ = 7.4 Hz, 1H), 4.83 (d, $J$ = 3.9 Hz, 2H), 4.69 (s, 2H), 3.69−3.64 (m, 1H), 3.57−3.52 (m, 1H), 3.25 (t, $J$ = 5.5 Hz, 1H), 2.47−2.44 (m, 1H), 1.95−1.89 (m, 2H), 1.48−1.46 (m, 1H), 0.97 (t, $J$ = 6.8 Hz, 6H), 0.92 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.6, 139.8, 128.8 (2C), 128.2 (2C), 128.0, 116.3, 96.9, 88.4, 70.5, 61.5, 43.9, 32.9, 31.0, 26.3 (3C), 20.7, 18.7, 18.0, −4.8 (2C); MS (ESI) $m/z$ 393.3 $[M + 1]^+$; HRMS (ESI) calcd for $C_{23}H_{40}O_3SiNa$ $[M + 23]^+$ 415.2638, found 415.2640.

Sodium (0.704 g, 30.6 g atom) was placed in three neck round-bottom flask, and liquid ammonia (~ 250 mL) was condensed at −78 °C while the solution became greenish blue. The TBS ether (1 g, 2.55 mmol) in THF (7 mL) was added while stirring for 1 h. The cooling bath was removed, and $NH_3$ was refluxed at rt for 2 h. The reaction mixture was quenched with careful addition of solid $NH_4Cl$ until it became colorless, and excess $NH_3$ was removed by a stream of $N_2$. The residue was extracted with ether (75 mL × 3) and purified by silica gel chromatography using 4% EtOAc in hexanes to afford alcohol **19** (0.55 g, 79%) as a colorless oil; $[\alpha]_D$ +0.7 ($c$ 1, $CHCl_3$); IR ($CHCl_3$) 3437 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 5.74−5.67 (m, 1H), 5.09 (s, 1H), 5.05 (d, $J$ = 5.6 Hz, 1H), 3.77−3.72 (m, 1H), 3.63−3.57 (m, 1H), 3.28−3.25 (dd, $J$ = 4.8 Hz, 1H), 2.39−2.36 (m, 1H), 1.86−1.78 (m, 2H), 1.67−1.60 (m, 1H), 0.97 (d, $J$ = 6.9 Hz, 3H), 0.92 (s, 9H), 0.90 (d, $J$ = 5.5 Hz, 3H), 0.08 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 140.4, 116.0, 78.9, 61.4, 45.1, 33.3, 30.8, 26.3 (3C), 20.5, 18.6, 16.3, −5.0 (2C); MS (ESI) $m/z$ 273.1 $[M + 1]^+$; HRMS (FAB) calcd for $C_{15}H_{33}O_2Si$ $[M + 1]^+$ 273.2244, found 273.2240.

**(4*S*,3*R*)-4-Azido-3-vinyl-5-methyl Hexanal (20).** To a solution of alcohol **19** (0.51 g, 1.87 mmol) in THF (19 mL) at 0 °C was added triphenylphosphine (2.454 g, 9.37 mmol), and the mixture

was stirred for a minute. DIAD (1.85 mL, 9.37 mmol) was added dropwise, and a white precipitate appeared while stirring for 5 min. DPPA (2.018 mL, 9.37 mmol) was added dropwise at 0 °C, and the reaction mixture was allowed to come to rt and stirred for 24 h. After concentration, the residue was purified by silica gel chromatography using 5% EtOAc in hexanes to give azide **20** (0.40 g, 72%) as a colorless transparent oil; $[\alpha]_D$ −39.6 (*c* 1.25, $CHCl_3$); IR (neat) 2099 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.72−5.50 (m, 1H), 5.18 (dd, $J$ = 10.3, 1.9 Hz, 1H), 5.12 (dd, $J$ = 15.7, 1.4 Hz, 1H), 3.68−3.66 (m, 1H), 3.60−3.59 (m, 1H), 2.96 (q, $J$ = 4.4 Hz, 1H), 2.60−2.50 (m, 1H), 1.80−1.75 (m, 1H), 1.75−1.50 (m, 2H), 1.02 (d, $J$ = 6.7 Hz, 3H), 0.98 (d, $J$ = 6.6 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 137.5, 118.1, 74.2, 60.6, 43.1, 35.8, 31.3, 26.3 (3C), 20.2, 19.6, 18.6, −4.9 (2C); MS (ESI) $m/z$ 298.1 $[M + 1]^+$; HRMS (FAB) calcd for $C_{15}H_{32}N_3OSi$ $[M + 1]^+$ 298.2309, found 298.2306.

To a solution of the above TBS ether (0.400 g, 1.35 mmol) in THF (15 mL) was added $Bu_4NF$ (1.35 mL, 1.35 mmol, 1 M in THF), and the mixture was stirred for 2 h at rt. After concentration, the residue was purified by chromatography using 20% EtOAc in hexanes to furnish the corresponding alcohol (0.230 g, 93%) as a colorless oil; $[\alpha]_D$ −63.18 (*c* 1.1, $CHCl_3$); IR (neat) 3341, 2097 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.71−5.62 (m, 1H), 5.19 (dd, $J$ = 17.6, 7.6 Hz, 2H), 3.76−3.70 (m, 1H), 3.69−3.61 (m, 1H), 2.94 (dd, $J$ = 4.6, 4.2 Hz, 1H), 2.61−2.54 (m, 1H), 1.85−1.60 (m, 4H), 1.02 (d, $J$ = 6.4 Hz, 3H), 0.96 (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 137.4, 118.4, 74.3, 60.8, 43.7, 35.7, 31.3, 20.1, 19.7; MS (ESI) $m/z$ 187.2 $[M - N_2 + MeOH]^+$; HRMS (FAB) calcd for $C_9H_{18}N_3O$ $[M + 1]^+$ 184.1444, found 184.1441.

To a solution of oxalyl chloride (138 $\mu$L, 1.5 mmol) in $CH_2Cl_2$ (10 mL) at −78 °C was added DMSO (289 $\mu$L, 4.08 mmol) dropwise, and the mixture was stirred for 15 min. The alcohol (0.250 g, 1.36 mmol) in $CH_2Cl_2$ (5 mL) was added while stirring for 30 min, and then *i*-$Pr_2NEt$ (945 $\mu$L, 5.44 mmol) was added. After 30 min the cooling bath was removed and allowed to come to rt during 30 min. The reaction mixture was quenched with water (5 mL), extracted with $CH_2Cl_2$ (50 mL), and washed with 10% citric acid solution and brine. The organic layer was dried ($Na_2SO_4$), concentrated, and purified by silica gel chromatography with 4% EtOAc in hexanes to give aldehyde **20** (0.240 g, 97%) as a transparent viscous oil; $[\alpha]_D$ −38.9 (*c* 1, $CHCl_3$); IR (neat) 2100, 1726 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 9.76 (t, $J$ = 1.6 Hz, 1H), 5.79−5.70 (m, 1H), 5.19 (t, $J$ = 8.3 Hz, 2H), 3.05−2.98 (m, 2H), 2.67 (d, $J$ = 5.1 Hz, 2H), 1.86−1.81 (m, 1H), 1.07 (d, $J$ = 6.6 Hz, 3H), 1.02 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 201.3, 135.8, 118.9, 72.9, 47.0, 40.8, 31.5, 19.9 (2C); HRMS (FAB) calcd for $C_9H_{16}N_3O$ $[M + 1]^+$ 182.1288, found 182.1286.

**2-[(3*R*,4*S*)-4-Azido-5-methyl-3-vinylhexylidene)]-1,3-dithiane (21).** To a solution of 2-phosphoryl 1,3-dithiane (0.371 g, 1.45 mmol) in THF (15 mL) at −78 °C was added n-BuLi (0.9 mL, 1.45 mmol, 1.6 M in hexane), and the mixture was stirred for 1 h. The aldehyde **20** (0.240 g, 1.32 mmol) in THF (5 mL) was added while stirring for 15 min. The cooling bath was removed, and stirring was continued for 30 min. The reaction mixture was quenched with $NH_4Cl$ solution (5 mL) extracted with ether (50 mL), and the organic layer was concentrated and purified by silica gel chromatography (2% EtOAc in hexanes) to afford ketene dithioacetal **21** (0.276 g, 73%) as a pale yellow oil; $[\alpha]_D$ −1.36 (*c* 1.1, $CHCl_3$); IR (neat) 2099 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.90 (t, $J$ = 7.3 Hz, 1H), 5.71−5.65 (m, 1H), 5.13 (dd, $J$ = 17.1, 10.4 Hz, 2H), 2.97 (dd, $J$ = 4.1, 4.2 Hz, 1H), 2.92−2.85 (m, 4H), 2.55−2.50 (m, 1H), 2.44−2.42 (m, 1H), 2.35−2.30 (m, 1H), 2.16−2.14 (m, 2H), 1.87−1.82 (m, 1H), 1.05 (d, $J$ = 6.7 Hz, 3H), 0.95 (d, $J$ = 6.8 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 137.1, 131.3, 128.1, 118.1, 73.1, 46.4, 33.0, 31.6, 30.7, 29.9, 25.5, 20.2, 19.7; MS (ESI) $m/z$ 288.1 $[M - N_2 + MeOH]^+$; HRMS (FAB) calcd for $C_{13}H_{22}N_3S_2$ $[M + 1]^+$ 284.1250, found 284.1250.

**Methyl (5*S*,4*R*)-5-Azido-4-vinyl-6-methyl Heptanoate (22).** Ketene dithioacetal **21** (0.220 g, 0.77 mmol) was dissolved in a methanolic solution of $CuSO_4$ (30 mL, 0.2 M) and heated at 65 °C for 2.5 h. After concentration, the residue was diluted with EtOAc (40 mL) and water (5 mL). The organic layer was concentrated and purified by column (3% EtOAc in hexanes) to give ester **22** (0.150 g, 85%) as a colorless viscous oil; $[\alpha]_D$ −63.8 (*c* 1.25, $CHCl_3$); IR (neat) 2100, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.63−5.56 (m, 1H), 5.18 (dd, $J$ = 10.3, 1.0 Hz, 1H), 5.12 (d, $J$ = 17.2 Hz, 1H), 3.69 (s, 3H), 2.97 (dd, $J$ = 4.5, 4.6 Hz, 1H), 2.39−2.27 (m, 3H), 1.87−1.73 (m, 3H), 1.04 (d, $J$ = 6.6 Hz, 3H), 0.98 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 174.2, 136.9, 118.9, 74.0, 52.0, 46.6, 31.9, 31.3, 27.9, 20.2, 19.3; MS (ESI) $m/z$ 198.1 $[M - N_2 + 1]^+$; HRMS (FAB) calcd for $C_{11}H_{20}N_3O_2$ $[M + 1]^+$ 226.1550, found 226.1544.

**(1*S*)-Methoxycarbonyl-[3*S*-(1*S*-azido-2-methylpropyl)]-4-cyclohexene (23) and the (1*R*)-Epimer.** To a solution of ester **22** (0.150 g, 0.66 mmol) in THF (30 mL) at −78 °C was added KHMDS (3.3 mL, 1.65 mmol, 0.5 M in toluene) solution while stirring for 5 min. Allyl bromide (285 $\mu$L, 3.3 mmol) was added, and the reaction was followed by TLC (ca. 5 min). The reaction mixture was quenched with water (7 mL) and allowed to come to rt. The organic layer was extracted with EtOAc (50 mL), dried ($Na_2SO_4$), and concentrated. The crude product was purified by silica gel chromatography (2% EtOAc in hexanes) to furnish allylation product (0.115 g, 65%, dr = 1:1) as a colorless oil; $[\alpha]_D$ −54.2 (*c* 1, $CHCl_3$); IR (neat) 2100, 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.79−5.56 (m, 2H), 5.25−5.00 (m, 4H), 3.73 (s, 1.5H), 3.70 (s, 1.5H), 2.99−2.80 (m, 1H), 2.70−2.50 (m, 1H), 2.50−2.25 (m, 3H), 2.00−1.80 (m, 2H), 1.70−1.50 (m, 1H), 1.10−0.95 (m, 6H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.1, 137.1, 135.3, 119.1, 117.6, 74.4, 51.8, 45.4, 43.0, 37.8, 34.7, 31.3, 20.2, 19.1; another set of carbons 176.1, 137.0, 135.3, 118.3, 117.5, 73.3, 51.8, 44.8, 43.0, 36.4, 34.5, 31.2, 20.1, 19.6; MS (ESI) $m/z$ 238.1 $[M - N_2 + 1]^+$; HRMS (FAB) calcd for $C_{14}H_{24}N_3O_2$ $[M + 1]^+$ 266.1863, found 266.1861.

To a solution of the above product (0.029 g, 0.11 mmol) in $CH_2Cl_2$ (20 mL) was added Grubbs second generation catalyst (13 mg, 0.0153 mmol), and the mixture was stirred for 3 h at rt. After concentration, the residue was purified by silica gel chromatography (3% EtOAc in hexanes) to give the corresponding cyclohexene (0.024 g, 93%) as a colorless gum. The epimeric mixture of products was dissolved in a methanolic solution of NaOMe (0.5 M, 3 mL), and the mixture was refluxed for 48 h. After cooling, the reaction mixture was neutralized with Amberlite resin and diluted with $CHCl_3$ (15 mL), and filtered, and the organic layer was concentrated, dissolved in MeOH (5 mL), and then treated with excess diazomethane at 0 °C. After 1 h, the solution was concentrated, and the oily residue was passed through a small pad of silica gel to furnish nonseparable equilibrated product **23** (dr = 4.2:1) in almost quantitative yield; $[\alpha]_D$ +68.6 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2099, 1737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.87−5.82 (m, 1H), 5.78−5.73 (m, 1H), 3.72 (s, 3H), 2.89 (t, $J$ = 6.3 Hz, 1H), 2.70−2.59 (m, 1H), 2.49−2.40 (bs, 1H), 2.35−2.20 (m, 2H), 2.10−2.00 (m, 2H), 1.51 (q, $J$ = 11.5 Hz, 1H), 1.04 (d, $J$ = 6.8 Hz, 3H), 0.99 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.2, 127.8, 127.4, 74.2, 52.2, 39.9, 38.6, 30.6, 30.0, 28.2, 20.9, 17.8; MS (ESI) $m/z$ 241.0 $[M - N_2 + MeOH]^+$; HRMS (ESI) calcd for $C_{12}H_{19}N_3O_2Na$ $[M + 23]^+$ 260.1369, found 260.1376..

**(1*S*)-Methoxycarbonyl-[3*S*-(1*S*-acetamido-2-methylpropyl)]-cyclohexane (24).** To a solution of **23** (0.040 g, 0.168 mmol) in MeOH (12 mL) was added $Pd(OH)_2/C$ (0.080 g, 20 wt %), and the suspension was stirred for 3 h under hydrogen pressure (1 atm). After filtration through small pad of Celite, the organic layer was concentrated, and the residue was taken up in $CH_2Cl_2$ (2 mL). Pyridine (41 $\mu$L, 0.504 mmol) and acetic anhydride (48 $\mu$L, 0.504 mmol) were added while stirring for 12 h at rt.

The reaction mixture was diluted with $CH_2Cl_2$ (12 mL), washed with dilute HCl solution and brine, and dried ($Na_2SO_4$). After concentration, the residue was purified by silica gel chromatography (80% EtOAc in hexanes) to furnish amide **24** (0.034 g, 79%) as a white crystalline solid. (X-ray provided. See Supporting Information.) Recrystallization from EtOAc and hexanes gave colorless crystals, mp 122−124 °C; $[\alpha]_D$ −9.0 (*c* 0.5, $CHCl_3$) ; IR ($CHCl_3$) 3290, 1735, 1648 $cm^{-1}$ ; $^1H$ NMR ($CDCl_3$) $\delta$ 5.10 (d, $J$ = 6.5 Hz, 1H), 3.66 (s, 3H), 2.36 (t, $J$ = 3.5 Hz, 1H), 2.02 (s, 3H), 1.98−1.81 (m, 2H), 1.75−1.72 (m, 2H), 1.70−1.67 (m, 3H), 1.60−1.40 (m, 1H), 1.40−1.20 (m, 3H), 0.93 (d, $J$ = 6.7 Hz, 3H), 0.85 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 176.5, 170.4, 58.5, 52.0, 43.7, 39.4, 33.2, 29.1 (2C), 27.6, 25.5, 23.8, 20.5, 17.7; MS (ESI) $m/z$ 256.1 $[M + 1]^+$; HRMS (FAB) calcd for $C_{14}H_{26}NO_3$ 256.1834, found 256.1866.

**(1*R*,3*S*)-3-[(*S*)-1-Acetamido-2-methylpropyl)]-*N*-[(2*S*,3*S*,5*R*)-6-(butylamino)-3-hydroxy-5-methyl-6-oxo-1-phenylhexan-2-yl)]-cyclohexanecarboxamide (25).** To a solution of **24** (7 mg, 0.027 mmol) in MeOH (1 mL) was added LiOH solution (100 $\mu$L, 1 N solution in water) and then stirred for 12 h at rt. The reaction mixture was diluted with EtOAc (10 mL), neutralized with dilute HCl, washed with brine, dried ($Na_2SO_4$), and concentrated. The crude product was used directly for coupling without purification. To a solution of Boc-protected amine (15 mg, 0.038 mmol) in $CH_2Cl_2$ (1 mL) was added TMSI (27 $\mu$L, 0.195 mmol) at rt for 30 min. The reaction mixture was quenched with $Na_2S_2O_3$ solution and extracted with EtOAc. The organic layer was washed with $NHCO_3$ solution and brine, dried ($Na_2SO_4$), and concentrated. It was used immediately without purification. The acid and amine were dissolved in a mixed solvent ($CH_2Cl_2$−$H_2O$, 1:1, 1 mL), and HOBt (5.5 mg, 0.041 mmol) and EDC (7.9 mg, 0.041 mmol) were added and stirred at 4 °C for 24 h. The reaction mixture was diluted with EtOAc (10 mL), washed with dilute HCl, $NaHCO_3$, and brine, and dried ($Na_2SO_4$). After concentration, the crude product was purified by silica gel chromatography (5% MeOH in $CH_2Cl_2$) to give amide **25** (6.5 mg, 40%) as a white solid; $[\alpha]_D$ −36.4 (*c* 0.25, MeOH); IR ($CHCl_3$) 3308, 1629 $cm^{-1}$; $^1H$ NMR (MeOD) $\delta$ 7.59 (d, $J$ = 10.1 Hz, 1H), 7.28−7.22 (m, 3H), 7.19−7.15 (m, 1H), 4.09−4.04 (bs, 1H), 3.57−3.55 (m, 1H), 3.48−3.47 (m, 1H), 3.33−3.32 (exchangeable 4H), 3.14 (t, $J$ = 7.1 Hz, 2H), 2.92 (dd, $J$ = 5.4, 5.5 Hz, 1H), 2.74 (dd, $J$ = 9.8, 9.8 Hz, 1H), 2.59−2.54 (m, 1H), 2.20−2.18 (m, 1H), 1.98 (s, 3H), 1.84−1.70 (m, 5H), 1.51−1.28 (m, 10H), 1.10 (d, $J$ = 7.0 Hz, 3H), 0.94 (t, $J$ = 7.2 Hz, 4H), 0.91 (d, $J$ = 6.7 Hz, 3H), 0.86 (d, $J$ = 6.7 Hz, 3H); $^{13}C$ NMR (MeOD) $\delta$ 177.9, 177.7, 172.4, 139.1, 129.3 (2C), 128.3 (2C), 126.2, 78.5, 70.0, 60.5, 58.9, 54.8, 45.3, 38.9, 38.8, 38.0, 37.6, 36.9, 33.5, 31.6, 29.4, 28.7, 27.5, 25.3, 21.4, 20.1, 19.8, 19.5, 17.6, 16.6, 13.5, 13.1; MS (ESI) $m/z$ 516 $[M + 1]^+$; HRMS (FAB) calcd for $C_{30}H_{50}N_3O_4$ 516.3723 $[M + 1]^+$, found 516.3736.

**(3*S*)-[(1*S*-Nitropropyl)]cyclohexanone (27) and (3*S*)-[(1*R*-Nitropropyl)]cyclohexanone (28).** A mixture of 2-cyclohexene-1-one **26** (0.100 mL, 1.04 mmol), 1-nitropropane (0.195 mL, 2.18 mmol), 2,5-dimethylpiperazine (0.120 g, 1.04 mmol), and a catalytic amount of D-proline (12 mg, 10 mol %) was stirred in reagent grade chloroform (8 mL) for 48 h at rt. The reaction mixture was diluted with $CH_2Cl_2$ and washed with aqueous HCl (3%). The organic phase was dried ($MgSO_4$), filtered, and evaporated, and the residue was purified by chromatography (EtOAc−hexanes 1:4) to obtain a 1:2.2 diastereomeric mixture of **27** and **28** as a colorless oil (0.162 g, 84%). A portion of the crude product was separated by column chromatography for characterization. For the less polar *syn*-isomer **27**: $[\alpha]_D$ −26 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 1542, 1714 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.31 (m, 1H), 2.54−2.40 (m, 2H), 2.37−2.24 (m, 2H) 2.16−2.08 (m, 2H), 2.03−1.78 (m, 3H), 1.72−1.60 (m, 1H), 1.55−1.45 (m, 1H), 0.97 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 208.32, 93.86, 43.52, 41.16, 40.59, 27.13, 23.83, 23.74, 9.89; MS (FAB) $m/z$ 186 $[M + 1]^+$, ee = 89%. The enantiomeric excess of the less polar *syn*-isomer was determined by RP-HPLC analysis with a CHIRALPAK AD-RH column (see Supporting Information). For the more polar *anti*-isomer **28**: $[\alpha]^{20}_D$ +15°(*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 1542, 1714, $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.36 (m, 1H), 2.45−2.34 (m, 2H), 2.32−2.20 (m, 3H), 2.17−2.08 (m, 1H), 2.05−1.95 (m, 2H), 1.86−1.78 (m, 1H),1.73−1.61 (m, 1H), 1.50−1.36 (m, 1H), 0.97 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 208.33, 93.87, 43.02, 40.98, 40.53, 27.33, 24.09, 23.73,10.01; MS (FAB) $m/z$ 186 $[M+1]^+$, ee = 74%. The enantiomeric excess of the more polar isomer was determined by RP-HPLC analysis with CHIRALPAK AD-RH column (see Supporting Information).

**(3*S*)-[(1*S*-Nitrobutyl)]cyclohexanone (29) and (3*S*)-[(1*R*-Nitrobutyl)]cyclohexanone (30).** A mixture of 2-cyclohexene-1-one (0.100 mL, 1.04 mmol), 1-nitrobutane (0.220 mL, 2.08 mmol), 2,5-dimethylpiperazine (0.120 g, 1.04 mmol), and a catalytic amount of D-proline (12 mg, 10 mol %) was stirred in reagent grade chloroform (8 mL) for 48 h at rt. The reaction mixture was diluted with $CH_2Cl_2$ and washed with aqueous HCl (3%). The organic phase was dried ($MgSO_4$), filtered, evaporated, and chromatographed (EtOAc−hexanes, 1:4) to obtain a 1:2 diastereomeric mixture of **29** and **30** as a colorless oils (0.200 g, 97%). A portion of the crude product was separated by silica gel chromatography for characterization. For the less polar *syn*-isomer **29**: $[\alpha]_D$ −18 (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 1548, 1717, $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.42−4.36 (m, 1H), 2.54−2.40 (m, 2H), 2.35−2.24 (m, 2H), 2.16−2.06 (m, 2H) 2.05−1.84 (m, 2H), 1.73−1.44 (m, 3H), 1.40−1.24 (m, 2H), 0.96 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 208.26, 92.11, 44.56, 41.36, 40.57, 32.32, 27.07, 23.83, 18.72, 13.01; MS (FAB) $m/z$ 200 $[M + 1]^+$, ee = 89%. The enantiomeric excess of the less polar isomer was determined by RP-HPLC analysis with a CHIRALPAK AD-RH column (see Supporting Information). For the more polar *anti*-isomer **30**: $[\alpha]^{20}_D$ + 20° ( *c* 0.1, $CHCl_3$); IR ($CHCl_3$) 1548, 1717, $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.48−4.43 (m, 1H), 2.48−2.37 (m, 2H), 2.33−2.20 (m, 3H), 2.19−2.11 (m, 1 H), 2.10−1.98 (m, 2H), 1.76−1.62 (m, 2H), 1.52−1.20 (m, 3H), 0.98 (t, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 209.52, 93.25, 44.17, 42.37, 41.75, 33.50, 28.58, 25.29, 20.05, 14.25; MS (FAB) $m/z$ 200 $[M + 1]^+$, ee = 71%. The enantiomeric excess of the more polar isomer was determined by RP-HPLC analysis with a CHIRALPAK AD-RH column (see Supporting Information).

**Diastereomeric Mixture of 2-{(3*S*)-[(1*S*)-Nitropropyl]cyclohexylidene}-1,3-dithiane (31) and the (1*R*) Epimer.** To a stirring solution of [1,3]dithian-2-yl-phosphonic acid diethyl ester (0.097 g, 0.378 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (0.258 mL, 0.412 mmol, 1.6 M in hexane) dropwise during 15 min. After 1 h **27** (0.07 g, 0.378 mmol) in THF (1 mL) was added, and the mixture was stirred for 15 min at −78 °C and then allowed to warm to rt. The reaction mixture was quenched after 1 h by adding a saturated solution of $NH_4Cl$ (2 mL) and extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine, dried, and concentrated, and the residue was purified by silica gel chromatography (5% EtOAc in hexanes) to give **31** as a colorless oil (0.092 g, 85%); $[\alpha]_D$ −0.91 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1547 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.33−4.25 (m, 1H), 3.09−2.88 (m, 5H), 2.16−1.66 (m, 9H), 1.40−1.26 (m, 2H), 0.98 (t, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 140.04, 94.19, 40.96, 33.57, 31.12, 29.93, 29.85, 28.57, 24.78, 24.61, 24.29, 10.00; MS (FAB) $m/z$ 288 $[M + 1]^+$; HRMS (FAB) calcd for $C_{13}H_{22}NO_2S_2$ $[M + 1]^+$ 288.1086, found 288.1082.

**Diastereomeric Mixture of 2-{(3*S*)-[(1*S*)-Nitrobutyl]cyclohexylidene}-1,3-dithiane (32) and the (1*R*) Epimer.** To a stirring solution of [1,3]dithian-2-yl-phosphonic acid diethyl ester (0.129 g, 0.502 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (0.48 mL, 0.552 mmol, 1.6 M in hexane) dropwise during 15 min.

After 1 h, ketone **29** (0.100 g, 0.502 mmol) in THF (1 mL) was added and stirred for 15 min at −78 °C, and then cooling bath was removed. The reaction mixture was quenched after 1 h by adding a saturated solution of $NH_4Cl$ (2 mL) and extracted with EtOAc (3 × 10 mL). The organic phase was washed with brine, dried over $Na_2SO_4$, and concentrated. The purification of crude product by column chromatography (5% EtOAc in hexanes) furnished ketene dithioacetal **32** as a colorless oil (0.124 g, 82%); $[\alpha]_D$ −1.3 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1547 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.30 (m, 1H), 3.0 (m, 1H), 2.67−2.56 (m, 3H), 1.99−1.73 (m, 9H), 1.41−1.28 (m, 6H), 0.95 (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR $\delta$ 140.66, 119.54, 93.20, 41.92, 34.36, 33.61, 31.88, 30.60, 29.28, 25.52, 25.37, 19.66, 13.91; MS (FAB) *m*/*z* 302 $[M + 1]^+$; HRMS (FAB) calcd for $C_{14}H_{24}NO_2S_2$ $[M + 1]^+$ 302.1243, found 302.1241.

**Diastereomeric Mixture of (1*S*)-Methoxycarbonyl-[3*S*-(3′*S*)-1-nitropropyl]-cyclohexane (33), (1*R*)-Methoxycarbonyl-[3*S*-(3′*S*)-1-nitropropyl]-cyclohexane (34), and Their (3′*R*)-1-Nitropropyl Epimers.** A solution of **31** (0.09 g, 0.313 mmol), mercuric chloride (0.591 g, 1.25 mmol), methanol (6 mL), and perchloric acid (0.132 mL of a 70% aqueous solution, 0.939 mmol) was heated at reflux for 2 h. After cooling and filtration, the reaction mixture was neutralized with a saturated solution of $NaHCO_3$ and extracted with dichloromethane. The combined organic extracts were washed with brine, dried, and concentrated, and the residue was purified by silica gel chromatography (EtOAc−hexanes 1:4) to give a 1:1 mixture of ester **33** and **34** as a colorless oil (0.057 g, 80%). A portion of the crude product was separated by chromatography for characterization. For **33** (0.027 g): $[\alpha]_D$ −9.0 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1549, 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.21 (m, 1H), 3.68 (s, 3H), 2.34 (m, 1H), 2.18−1.84 (m, 6H), 1.65−1.58 (m, 1H), 1.33−1.04 (m, 4H), 0.94 (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 175.91, 96.03, 52.17, 43.07, 31.36, 29.06, 28.93, 25.05, 24.39, 10.79; MS (FAB) *m*/*z* 288 $[M + 1]^+$; HRMS (FAB) calcd for $C_{11}H_{19}NO_4$ $[M + 1]^+$ 229.1314 found 229.1309.

**Diastereomeric Mixture of (1*S*)-Methoxycarbonyl-[3*S*-(3′*S*)-1-nitrobutyl]-cyclohexane (35), (1*R*)-Methoxycarbonyl-[3*S*-(3′*S*)-1-nitrobutyl]-cyclohexane (36), and Their (3′*R*)-1-Nitropropyl or Butyl Isomers.** A solution of **32** (0.120 g, 0.398 mmol), mercuric chloride (0.752 g, 1.59 mmol), methanol (7 mL), and perchloric acid (0.17 mL of a 70% aqueous solution, 1.19 mmol) was heated at reflux for 2 h. After cooling and filtration, the reaction mixture was neutralized with saturated solution of $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic extract were washed with brine, dried ($Na_2SO_4$), and concentrated to give a 1:1 diasteriomeric mixture of the ester **35** and **36** as a colorless oil (0.069 g, 72%). A portion of the crude product was separated by column chromatography for characterization. For **35** (0.32 g): $[\alpha]_D$ −13.7 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1548, 1733 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.27 (m, 1H), 3.68 (s, 3H), 2.34 (m, 1H), 2.03−1.56 (m, 7H), 1.33−1.15 (m, 1H), 0.94 (t, $J = 7.3$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 175.76, 94.16, 52.02, 43.04, 40.90, 32.95, 31.38, 28.96, 28.91, 25.03, 19.57, 13.76; MS (FAB) *m*/*z* 244 $[M + 1]^+$; HRMS (FAB) calcd for $C_{12}H_{22}NO_4$ $[M + 1]^+$ 244.1543, found 244.1538.

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**Supporting Information Available:** Complete crystallographic data for compounds **8a**, **8c**, **24**; copies of $^1H$ and $^{13}C$ NMR spectra for all the new compounds; chiral RP-HPLC chromatograms of compounds **27**−**30** This material is available free of charge via the Internet at http://pubs.acs.org.