Design and Synthesis of a Conformationally Restricted Trans Peptide Isostere Based on the Bioactive Conformations of Saquinavir and Nelfinavir

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The design and synthesis of a new peptide isostere which contains a *trans* alkene core is described. The key step involves a Wadsworth−Emmons reaction between chiral aldehyde (2*S*)-**9a** and chiral phosphonate **7** under base-sensitive conditions to give a chiral enone (2*R*)-**24a** which was reduced to afford the desired trans alkene isosteres (2*R*,5*R*)-**6a** and (2*R*,5*S*)-**6b** (Scheme 6). A potential application of this isostere in the synthesis of HIV protease inhibitors is also discussed.

Introduction

An important area of medicinal chemistry research is the design of metabolically stable peptide analogues (peptidomimetics) with an ability to either mimic or block the bioactivity of natural peptides.[1] The incorporation of conformationally restricted units, such as rings,[1−4] into a peptide sequence to force it to adopt a known, biologically active conformation is a good illustrative example of this process.

The isosteric replacement of a peptide bond represents another important and general tool in the design of peptidomimetics.[1,5] Examples of peptide bond replacements have been incorporated into oligopeptides to give specific inhibitors of proteolytic enzymes.[5−7] For example JG365 **1**,[6] a potent inhibitor of HIV protease, possesses a hydroxyethylamine (−CHOH−CH_2NH−) isostere in place of the scissile peptide bond (−CONH−) thus providing a nonhydrolyzable mimic of the tetrahedral transition state that would result from enzyme-catalyzed cleavage of its substrate.

We have previously reported the design and synthesis of an example of a cis-like conformationally restricted isostere **3a**[8a] that represents a combination of both of the aforementioned strategies in peptidomimetic design, i.e., isosteric replacement and conformational restriction. In these peptidomimetics a tetrazole ring was incorporated into positions 3 and 4 of a hydroxyethylamine isostere to force it to adopt a cis geometry as is shown in **2a** (Figure 1). This work was prompted by our continuing goal to produce a library of peptidomimetic core-structures that possess a well-defined conformation and/or reactivity[4,8] and also by a reported crystal structure of JG365 **1** bound to HIV-protease.[6] In this structure, the torsion angle, designated by τ in structure **1**, is 11.6°, a situation that resembles **2a** and hence is mimicked by **3a**.

We now report complementary work on some conformationally restricted peptidomimetics that mimic the alternative trans-like hydroxyethylamine geometry as depicted in **2b**. The idea depicted in **3b** was to incorporate a trans alkene into positions 3 and 4 of a hydroxyethylamine, rather than a tetrazole as in **3a**. We now demonstrate this idea with the preparation of model compounds of type **6** (Scheme 1).

The methodology developed for the preparation of these compounds is applicable to the synthesis of new HIV protease inhibitors based on the known conformations of saquinavir **4** and nelfinavir **5** as bound to HIV protease.[9,10]

Results and Discussion

The work presented here deals with the development of a general methodology for the preparation of the

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(9) Unlike JG365 **1**, the torsion angle designated by τ in the HIV-bound conformations of saquinavir **4** and nelfinavir **5** is much closer to a trans geometry, 155° and 153°, respectively (see Figure 1, and ref 10 below). This significant change in geometry, as compared to JG365 **1**, is thought to be due to an alternate mode of binding in which the *tert*-butyl amide and decahydroisoquinoline ring of **4** and **5** occupy the S2′ and S1′ subsites of the enzyme, respectively (For a definition of S2′, S1′ nomenclature, see Schechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157). An (*R*) configuration at the carbon bearing the hydroxyl group favors this mode of binding. For a more thorough discussion of HIV protease modes of binding, see Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359.

(10) Our determination of the torsion angles in saquinavir and nelfinavir was made using the relevant HIV protease/inhibitor complexes obtained from the Protein Data Bank (http://www.rcsb.org/pdb/), formerly Brookhaven Protein Database. Isolation of the three-dimensional structures of the inhibitors was achieved using Chem 3D software to strip away the surrounding protease structure.

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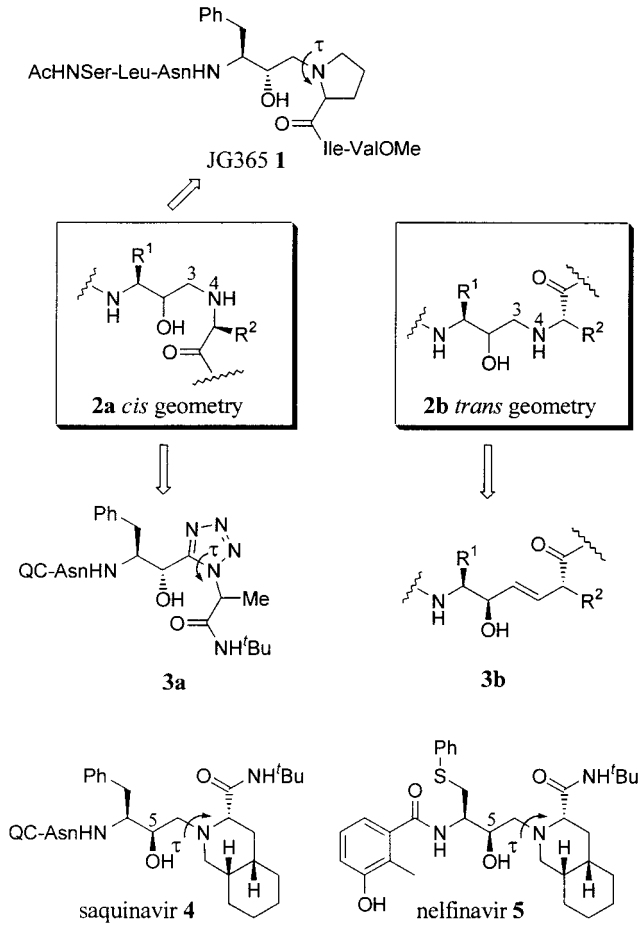
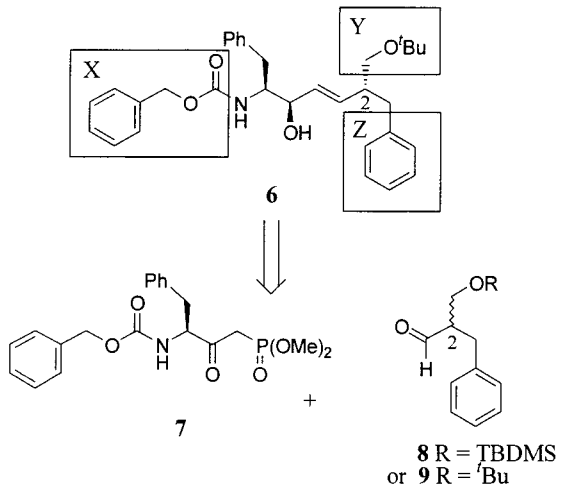


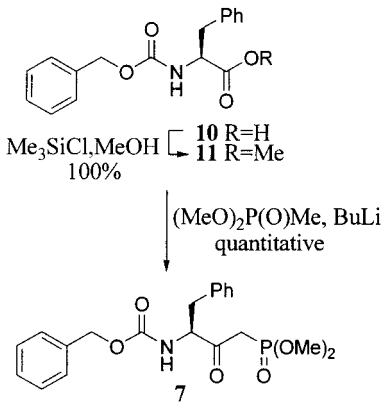
Figure 1.

Scheme 1

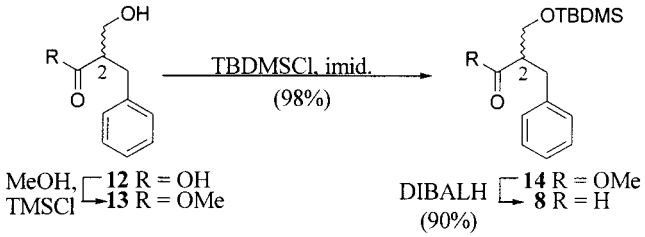


desired trans alkene systems. To expedite this, compound **6** was selected as the initial target. The decision to prepare the *tert*-butyl ether instead of the corresponding amide was made for several reasons including ease of synthesis and its steric similarity to the amide. In addition, the benzyl group at C-2 allows the commercially available hydrocinnamic acid to be used as a convenient starting material while still providing some of the steric properties of the cyclohexyl ring of the DIQ unit in saquinavir and nelfinavir. As our main goal was the development of a new methodology, the above compromises were deemed to be expedient.

Scheme 2



Scheme 3



The key step in the synthesis of **6** was a Wadsworth−Emmons reaction of phosphonate **7** with aldehydes **8** or **9** (Scheme 1). The reaction of a chiral aldehyde with a chiral phosphonate to afford a highly functionalized peptidomimetic is remarkably rare in the literature. Initial work involved reacting the anion derived from **7** with the racemic aldehyde **8**. The racemic aldehyde was used initially since it provides reference samples of both the (2*R*) and (2*S*) isomers of **6**. A sample of these compounds enriched in one isomer was also prepared using the (*S*)-isomer of **9** (see Scheme 6 and later for a discussion).

Synthesis of Starting Materials. The phosphonate **7** was prepared as detailed in Scheme 2. Treatment of CBZ-protected L-phenylalanine **10** with trimethylsilyl chloride (2.5 equiv) in dry methanol afforded the methyl ester **11** in quantitative yield. The ester **11** was then reacted with dimethyl methylphosphonate according to the general method of Deziel et al.[11] to afford the desired phosphonate **7** in excellent yield. The aldehyde **8** was prepared as shown in Scheme 3. *tert*-Butyldimethylsilyl (TBDMS) protection was used in these reactions to allow subsequent functionalization, for example, conversion into the *tert*-butyl ether of **6**. Compound **12**, prepared from hydrocinnamic acid using the method of Fincham et al.,[12] was doubly protected to give **14**. The conversion of intermediate **13** to **14** was carried out in the absence of solvent. Reduction of ester **14** with diisobutylaluminum hydride (DIBALH) gave the desired aldehyde **8**. The aldehyde proved to be unstable and was used in the subsequent Wadsworth−Emmons reactions without purification.

Next, the optically active aldehyde (2*S*)-**9a** was prepared. The key to its preparation involved using the

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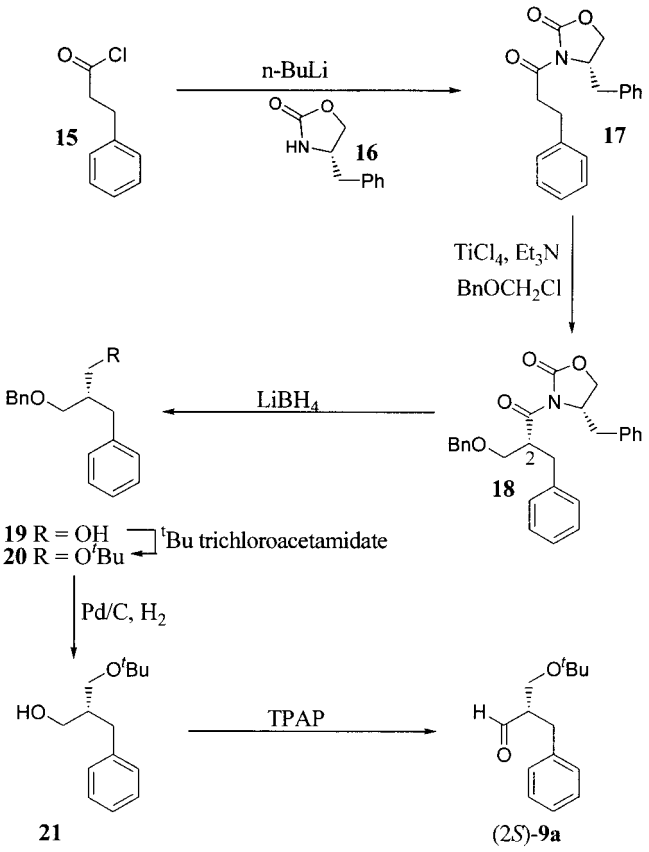
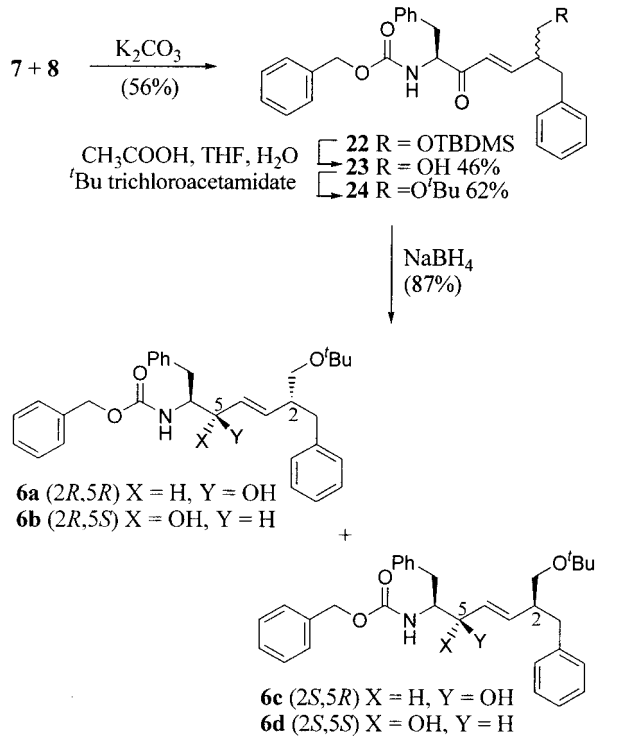
Scheme 4



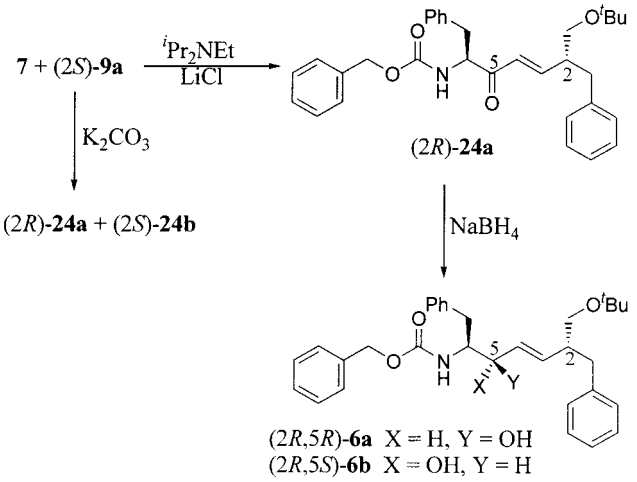
chiral oxazolidinone of **17** to control the introduction of a convenient precursor to the aldehyde moiety of **9a** (see Scheme 4). To this end, reaction of hydrocinnamoyl chloride **15** with the anion of (4*S*)-4-benzyl-2-oxazolidinone **16** afforded the key oxazolidinone **17**. Treatment of **17** with diisopropylethylamine, in the presence of titanium tetrachloride,[13b] followed by the addition of benzyl chloromethyl ether gave **18** and its C-2 epimer, de > 95% by ^{1}H NMR. The absolute configuration of the major isomer was assigned as depicted in **18** on the basis of well-established precedence in reactions of this type.[13] The oxazolidinone was then reductively cleaved, and the resulting alcohol **19** was protected as the *tert*-butyl ether **20** using *tert*-butyl trichloroacetamidate. In this case we decided to concern ourselves solely with the *tert*-butyl ether and accordingly introduced this group at an early stage in the synthesis. Catalytic hydrogenolysis of the benzyl group of **20** afforded the free alcohol **21** that was oxidized using tetra-*n*-propylammonium perruthenate and 4-methylmorpholine *N*-oxide[14] to give (2*S*)-**9a**. Again the aldehyde proved unstable and was used in the Wadsworth−Emmons reaction without purification.

Synthesis of Peptidomimetic 6. A Wadsworth−Emmons reaction of phosphonate **7** with aldehyde **8**, using K_2CO_3 as the base, afforded ketoalkene **22** in good yield (Scheme 5). Having confirmed that this key step was achievable, it remained to replace the silyl ether group with a *tert*-butyl ether, and to reduce the ketone to the desired hydroxyalkene **6**. To this end, the silyl

Scheme 5



Scheme 6



group of **22** was removed on treatment with acetic acid/water/THF (3:1:1) and the resulting alcohol **23** was treated with *tert*-butyl trichloroacetamidate to give **24**. Reduction of the ketoalkene **24** with $NaBH_4$ afforded the desired diastereomeric hydroxyalkenes **6a** − **6d** in a 2:1:2:1 ratio as determined by ^{1}H NMR. The configurations of the major isomers (**6a** and **6c**) were assigned (5*R*) on the basis of related work by Benedetti et al.[15] Column chromatography of the isomeric mixture afforded a pure sample of one of the minor isomers that was subsequently assigned as **6d**. See later for a justification of the structural assignments of all four isomers.

The reaction of (2*S*)-**9a** with phosphonate **7** (Scheme 6) was then attempted using K_2CO_3/CH_3CN, i.e., conditions identical to those used in the reaction of the

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racemic aldehyde (see Scheme 5). However, this resulted in formation of **24a** and **24b**, i.e., epimerization at C-2. In fact, the ^{1}H NMR spectrum of this product was identical to that of **24**, prepared using the racemic aldehyde, see Scheme 5. However, when more base-sensitive conditions were used (^{i}Pr$_2$NEt, LiCl, CH$_3$CN)[16] in the coupling of **7** and (2*S*)-**9a**, the desired Wadsworth−Emmons product (2*R*)-**24a** was produced in modest yield without epimerization at C-2 (determined by ^{1}H NMR). In fact we recommend these conditions be used in other Wadsworth−Emmons reactions of this aldehyde to avoid epimerization of the product alkene. With the Wadsworth−Emmons reaction in hand, all that remained was the reduction of ketoalkene **24** to afford the target compound **6**. Reduction using NaBH$_4$ afforded the desired (5*R*) alcohol **6a** in a 2:1 ratio with the corresponding (5*S*) alcohol **6b**. The absolute configurations of these two compounds were assigned as shown in Scheme 6; the C-2 configuration of both isomers is defined by the starting material (2*R*)-**24a** and, in addition, the major isomer **6a** was assigned the (5*R*)-configuration on the basis of the related work of Benedetti et al.[15] With the absolute configurations of these two compounds in hand it was possible to assign structures to all four isomers isolated in the racemic series (see Scheme 5). The (2*R*)-compounds, **6a** and **6b**, were clearly identified, thus establishing the identity of the second major isomer, **6c**. The remaining (2*S*)-stereoisomer (assigned **6d**) was isolated and fully characterized. A comparison of the ^{1}H NMR data obtained on this isomer, with the **6a**/**6b** mixture, revealed that the isolated minor isomer was not compound **6b**, thus identifying it as **6d.**

Conclusion

This paper describes the design and development of a general methodology for the synthesis of a trans peptide isostere with an application to the bioactive conformations of saquinavir and nelfinavir.[9] The key step in this methodology is the coupling of a chiral aldehyde (2*S*)-**9a** with a chiral phosphonate **7** under base-sensitive conditions to afford a chiral enone (2*R*)-**24a** with control of stereochemistry. We recommend that these conditions be used in similar Wadsworth−Emmons reactions to avoid epimerization of the product. We have established this general methodology and demonstrated its potential in the synthesis of HIV protease inhibitors based on the bioactive conformations of saquinavir and nelfinavir. Further work is now underway establishing the generality of this methodology and targeting specific compounds that more closely resemble saquinavir and nelfinavir, by modifying the terminal groups of the molecule and by introducing a bicyclic system to more closely resemble the DIQ unit of saquinavir and nelfinavir.

Experimental Section

Anhydrous solvents were obtained as follows: dichloromethane was distilled from CaH$_2$; tetrahydrofuran and toluene were distilled from sodium/benzophenone; hexane and cyclohexane were distilled from CaH$_2$; methanol and ethanol were distilled from the corresponding Mg alkoxide.

All air-sensitive reactions were carried out under a N$_2$ atmosphere. Silica gel 60 (230−400 mesh) was used for column chromatography. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shift is reported in parts per million using TMS as an internal reference for ^{1}H NMR and the solvent peak as an internal reference for ^{13}C NMR. Melting points are uncorrected.

Dimethyl [(3*S*)-4-Phenyl-3-[(benzyloxycarbonyl)amino]-2-oxobutyl]phosphonate (7). To a solution of the CBZ-protected phenylalanine **10** (9.24 g, 30.5 mmol) in dry methanol (300 mL) was added trimethylsilyl chloride (9.11 mL, 71.2 mmol). The reaction mixture was stirred for 18 h and then concentrated and placed under high vacuum for 8 h to afford the intermediate methyl ester **11** as a colorless oil in quantitative yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ, 3.09 (dd, 1H, J = 6.5, 13.8), 3.18 (dd, 1H, J = 6.0, 13.8), 3.73 (s, 3H), 4.66−4.74 (m, 1H), 5.12 (s, 2H), 5.40 (d, 1H, J = 7.8 Hz), 7.11−7.38 (m, 10H); ^{13}C NMR (75 MHz, CDCl$_3$): δ, 38.0, 52.1, 54.7, 66.8, 127.0, 127.9, 128.0, 128.4, 128.5, 129.1, 135.6, 155.5, 171.8.

A 1.6 M solution of n-BuLi in hexane (100 mL, 160 mmol) was added at −78 °C to a solution of dimethyl methylphosphonate (17.25 mL, 160 mmol) in dry THF (120 mL). After 1 h a solution of **11** (6.59 g, 21.0 mmol) in dry THF (80 mL) was added dropwise to the solution. The reaction mixture was stirred for 1 h at −78 °C after which time the coolant bath was removed and the reaction mixture was stirred for a further 1.5 h. The reaction mixture was then hydrolyzed with 10% aqueous acetic acid and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed successively with saturated NaHCO$_3$ solution (100 mL), water (100 mL), and saturated NaCl solution (100 mL) and then dried over MgSO$_4$. The yellow oil was purified by column chromatography on silica gel (hexane/EtOAc 1:1) to afford **7** as a colorless oil (quantitative). ^{1}H NMR (300 MHz, CDCl$_3$): δ, 2.97−3.30 (m, 4H), 3.70 (s, 3H), 3.73 (s 3H), 4.61−4.68 (m, 1H), 5.06 (s, 2H), 5.73 (d, 1H, J = 7.8 Hz), 7.13−7.37 (m, 10H); ^{13}C NMR (75 MHz, CDCl$_3$): δ, 36.9, 53.1, 61.5, 66.9, 126.9, 127.9, 128.4, 128.6, 129.2, 136.1, 155.8, 200.6.

Methyl (2*RS*)-3-Phenyl-2-(*tert*-butyldimethylsilyloxymethyl)propanoate (14). To a solution of **12** (6.56 g, 36.4 mmol) in dry methanol (250 mL) was added trimethylsilyl chloride (10.1 mL, 80.1 mmol). The reaction mixture was stirred for 16 h. The reaction mixture was concentrated under reduced pressure, and the resulting oil was purified by column chromatography on silica gel (hexane/EtOAc 2:1) to afford the intermediate hydroxyester **13** as a colorless oil (7.06 g, quantitative). ^{1}H NMR (300 MHz, CDCl$_3$): δ, 2.81−3.04 (m, 3H), 3.65 (s, 3/2H), 3.66 (s, 3/2H), 3.72 (s, 1H), 3.73 (s, 1H), 7.16−7.32 (m, 5H)); ^{13}C NMR (75 MHz, CDCl$_3$): δ, 34.2, 49.2, 51.7, 62.1, 126.3, 128.3, 128.7, 138.4, 174.9.

To the hydroxyester **13** (6.36 g, 32.7 mmol) were added *tert*-butyldimethylsilyl chloride (5.92 g, 39.2 mmol) and imidazole (5.33 g, 78.3 mmol), and the mixture was cooled in a cold water bath. A white solid rapidly precipitated. After stirring for 30 min, the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (2 × 70 mL) and EtOAc (70 mL). The combined organic layers were then washed with saturated ammonium chloride solution (30 mL) and saturated sodium chloride solution (30 mL) and dried over MgSO$_4$. The solvent was removed under reduced pressure to afford an oil which was purified by column chromatography on silica gel (hexane/EtOAc 9:1) to afford **14** as a colorless oil (10.0 g, 100%). ^{1}H NMR (300 MHz, CDCl$_3$): δ, 0.034 (s, 6H), 0.89 (s, 9H), 2.80−2.98 (m, 3H), 3.63 (s, 3H), 3.73−3.76 (m, 2H), 7.16−7.31 (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$): δ, 25.73, 34.14, 50.16, 51.43, 63.2, 126.3, 128.4, 128.9, 139.1, 221.0. HRMS (EI) calcd for C$_{13}$H$_{19}$O$_3$Si [M$^+$ − ^{t}Bu] 251.11035, found 251.11086.

(4*S*)-4-Benzyl-3-(3-phenyl-1-oxopropyl)-2-oxazolidinone (17). A 1.74 M solution of n-BuLi in hexane (12.2 mL, 21.3 mmol) was added dropwise to a solution of (4*S*)-4-benzyl-2-oxazolidinone **16**[17] (3.60 g, 20.3 mmol) in dry THF (20 mL). After 1 h, the acid chloride **15** (3.35 mL, 22.5 mmol) in dry THF (10 mL) was added dropwise at −78 °C. The reaction mixture was then allowed to warm to room temperature, and stirring was continued for 16 h.

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The reaction mixture was quenched with saturated aqueous NaCl (25 mL), and the resulting mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (4 × 40 mL), and the combined organic layers were dried over $MgSO_4$ and then concentrated to afford a yellow oil. Crystallization from hexane/EtOAc (4:1) **17** as white needles (4.62 g, 74%), mp 100−102 °C (lit.[17] 92−95 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 2.70−2.79 (m, 2H), 3.00−3.06 (m, 2H), 3.23−3.33 (m, 3H), 4.14−4.18 (m, 2H), 7.15−7.35 (m, 10H).

(4*S*)-4-Benzyl-3-[2-benzyloxymethyl-3-phenyl-1-oxopropyl]-2-oxazolidinone (18). $TiCl_4$ (0.15 mL, 1.36 mmol) was added to a solution of **17** (400 mg, 1.29 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. After stirring the reaction mixture for 5 min, diisopropylethylamine (0.225 mL, 1.29 mmol) was added, and the reaction mixture was stirred for 1 h. Benzyl chloromethyl ether (0.36 mL, 2.59 mmol) was added, and the reaction mixture was stirred at 0 °C for a further 5 h and then quenched with saturated aqueous NH_4Cl (4 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL) and diethyl ether (2 × 10 mL), and the combined organic layers were dried over $MgSO_4$ and then concentrated under reduced pressure. The yellow oil was purified by column chromatography (hexane/EtOAc 4:1) to afford **18** as a colorless oil (508 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 2.69 (dd, 1H, J = 9.3, 13.5 Hz), 2.89 (dd, 1H, J = 6.9, 13.8 Hz), 2.99 (dd, 1H, J = 8.4, 13.8 Hz), 3.19 (dd, 1H, J = 3.3, 13.5 Hz), 3.67 (dd, 1H, J = 4.8, 9.3 Hz), 3.83−3.93 (m, 2H), 4.03 (dd, 1H, J = 3.0, 9.0 Hz), 4.48−4.64 (m, 4H), 7.16−7.34 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 34.9, 37.3, 44.9, 54.9, 65.5, 70.3, 72.8, 126.2, 127.0, 127.3, 127.4, 128.1, 128.2, 128.6, 128.9, 129.2, 135.0, 137.9, 138.2, 152.8, 173.8. HRMS (EI) calcd for $C_{20}H_{20}NO_4$ [$M^+ - C_6H_5CH_2$] 338.13939, found 338.13923.

Benzyl (2*S*)-3-Phenyl-2-(hydroxymethyl)propyl Ether (19). To a solution of **18** (1.73 g, 4.03 mmol) in dry THF (20 mL) and methanol (0.17 mL) at 0 °C was added $LiBH_4$ (231 mg, 10.6 mmol). The reaction was stirred for 16 h and then quenched with 1 M aqueous sodium potassium tartrate (50 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 70 mL), and the combined organic layers were dried over $MgSO_4$ and then concentrated to afford a colorless oil which was purified by column chromatography (hexane/EtOAc 4:1) to afford **19** as a colorless oil (836 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 2.10−2.23 (m, 1H), 2.50−2.62 (m, 1H), 2.69 (d, 2H, J = 7.5 Hz), 3.51 (dd, 1H, J = 6.6, 9.0 Hz), 3.58−3.69 (m, 2H), 3.75 (dd, 1H, J = 3.9, 10.8 Hz), 4.51 (dd, 2H, J = 11.7, 15.6 Hz), 7.18−7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 34.4, 42.5, 65.3, 72.8, 73.4, 126.0, 127.6, 127.7, 128.3, 128.4, 129.0, 137.5, 139.9. HRMS (EI) calcd for $C_{17}H_{20}O_2$ [M^+] 256.14705, found 256.14633.

Benzyl (2*S*)-3-Phenyl-2-(*tert*-butyloxymethyl)propyl Ether (20). To a solution of **19** (416 mg, 1.62 mmol) in dry cyclohexane (3 mL) were added *tert*-butyl trichloroacetamidate (393 mg, 1.80 mmol) and $BF_3{\cdot}Et_2O$ (32 μL, 0.32 mmol). The reaction mixture was stirred for 16 h. Solid $NaHCO_3$ was added and, after stirring for 5 min, the reaction mixture was filtered through a short silica plug, eluting first with cyclohexane and then with CH_2Cl_2. Concentration of the cyclohexane fraction afforded **20** as a colorless oil (130 mg, 26%). Concentration of the CH_2Cl_2 fraction afforded a white solid/oil mixture that was further purified by column chromatography (hexane/EtOAc 4:1) to afford **20** as a colorless oil (187 mg, 37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.19 (s, 9H), 2.03−2.16 (m, 1H), 2.70 (d, 2H, J = 7.5 Hz), 3.34 (dd, 2H, J = 2.4, 5.4 Hz), 3.44 (dd, 2H, J = 1.5, 5.4 Hz), 4.48 (s, 2H), 7.20−7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 26.8, 27.5, 34.6, 41.8, 61.1, 69.9, 72.3, 72.9, 125.6, 127.3, 127.5, 128.0, 128.2, 129.2, 138.7, 140.6. HRMS (EI) calcd for $C_{17}H_{19}O_2$ [$M^+ - C_4H_8$] 255.13851, found 255.13866.

***tert*-Butyl (2*R*)-3-Phenyl-2-(hydroxymethyl)propyl Ether (21).** To a solution of **20** (175 mg, 0.56 mmol) in dry ethanol (2 mL) was added a catalytic amount of 10% Pd/C. The reaction flask was flushed with hydrogen, and the reaction mixture was stirred under a hydrogen atmosphere for 2 h. The reaction mixture was filtered through a short silica plug, washing with additional ethanol. The solvent was removed under reduced pressure to afford **21** as a colorless oil (126 mg, 100%).^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.18 (s, 9H), 2.01−2.13 (m, 1H), 2.62 (d, 2H, J = 7.8 Hz), 3.37 (dd, 2H, J = 7.5, 9.0 Hz), 3.55 (dd, 1H, J = 3.9, 9.0 Hz) 3.60 (dd, 1H, J = 6.9, 10.8 Hz), 3.66−3.76 (m, 2H), 7.17−7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 27.2, 34.4, 42.2, 65.0, 65.9, 73.2, 125.8, 128.1, 128.9, 140.0.

***tert*-Butyldimethylsilyl-(2*RS*,6*S*)-6-[*N*-(benzyloxycarbonyl)amino]-2-benzyl-5-oxo-7-phenyl-3-heptenyl Ether (22).** To a solution of **14** (3.0 g, 9.72 mmol) in dry toluene (75 mL) at −90 °C was added dropwise a 1.0 M solution of DIBALH in toluene (10.0 mL, 10 mmol). The reaction was stirred for 1.5 h at −80 to −90 °C and then quenched with saturated aqueous sodium potassium tartrate (30 mL). The reaction mixture was warmed to room temperature and extracted with diethyl ether (2 × 50 mL) and EtOAc (30 mL). The combined organic layers were dried over $MgSO_4$ and reduced to afford the aldehyde intermediate **8** as a colorless oil (2.36 g, 87%) which was used in the subsequent reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.036 (s, 3H), 0.043 (s, 3H), 0.894 (s, 9H), 2.62−2.72 (m, 1H), 2.83 (dd, 1H, J = 8.4, 14.1 Hz), 3.06 (dd, 1H, J = 6.0, 13.8 Hz)), 3.75 (dd, 1H, J = 5.4, 10.2 Hz), 3.90 (dd, 1H, J = 3.9, 10.2 Hz), 7.16−7.28 (m, 5H), 9.80 (d, 1H).

To a solution of phosphonate **7** (1.57 g, 4.16 mmol) and aldehyde **8** (1.15 g, 4.13 mmol) in dry ethanol (75 mL) was added anhyd potassium carbonate (575 mg, 4.16 mmol). The reaction was stirred for 24 h, filtered, and acidified with acetic acid. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (100 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (20 mL) and saturated aqueous sodium chloride (20 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a yellow oil that was purified by column chromatography (4:1 hexane/EtOAc) to afford **22** as a colorless oil (1.30 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 0.04 (s, 3/2 H), 0.05 (s, 3/2 H), 0.90 (s, 9/2 H), 0.91 (s, 9/2 H), 2.57−2.72 (m, 2H), 2.86−2.96 (m, 2H), 3.03−3.14 (m, 1H), 3.54−3.62 (m, 2H) 4.75−4.87 (m, 1H), 5.04−5.14 (m, 2H), 5.51 (d, 2h, J = 6.9 Hz), 6.06 (d, 1H, J = 15.6 Hz), 6.84−6.97 (m, 3H), 7.10−7.38 (m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, −5.5, 18.2, 25.8, 36.6,36.7, 37.8, 38.0, 47.0, 47.1, 58.5, 58.9, 64.1, 64.4, 66.6, 124.4, 126.0, 126.2, 126.8, 127.6, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 129.0, 129.2, 129.4, 129.7, 135.6, 136.4, 138.9, 139.0, 142.5, 150.1, 150.1, 155.4, 155.6, 196.0, 196.3. HRMS (FAB) calcd for $C_{34}H_{44}NO_4Si$ [MH^+] 558.3040, found 558.3051.

(2*RS*,6*S*)-6-[*N*-(Benzyloxycarbonyl)amino]-2-benzyl-5-oxo-7-phenyl-3-hepten-1-ol (23). The silyl ethers **22** was stirred in acetic acid/THF/H_2O (9 mL:3 mL:3 mL) for 72 h. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate followed by the addition of EtOAc (3 × 80 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford a colorless oil that was purified by column chromatography on silica gel (hexane/EtOAc 4:1) and dried under high vacuum to afford **23** as a viscous colorless oil (460 mg, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 2.60−3.09 (m, 3H), 3.50−3.68 (m, 2H) 4.77−4.90 (m, 1H), 5.04−5.13 (m, 2H), 5.49−5.53 (m, 2H), 6.06 (d, 1/2H, J = 16.2 Hz), 6.08 (d, 1/2H, J = 15.9 Hz), 6.77−6.89 (m, 1H), 6.93−7.37 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 13.9, 20.7, 36.3, 36.4, 37.3, 37.6, 46.8, 58.1, 58.8, 60.1, 63.8, 66.4, 126.0, 126.2, 126.5, 126.6, 127.6, 127.8, 128.0, 128.1, 128.6, 128.7, 129.1, 135.5, 136.1, 138.6, 149.7, 149.9, 155.5. HRMS (FAB) calcd for $C_{28}H_{30}NO_4$ [MH^+] 444.2175, found 444.2177.

***tert*-Butyl (2*RS*,6*S*)-6-[*N*-(Benzyloxycarbonyl)amino]-2-benzyl-5-oxo-7-phenyl-3-heptenyl Ether (24).** To a mixture of alcohols **23** (56 mg, 0.127 mmol) in dry cyclohexane (0.40 mL) were added *tert*-butyl trichloroacetamidate (30 mg, 0.138 mmol) and $BF_3{\cdot}Et_2O$ (1 drop). The reaction mixture was stirred for 16 h. Solid $NaHCO_3$ was added, and, after stirring for 5 min, the reaction mixture was filtered through a short silica plug, eluting first with CH_2Cl_2. Removal of the solvent

(17) Sanko Company Limited. Eur. Pat. 0383 635 A2, 1986.

afforded an oily residue that was purified by column chromatography (hexane/EtOAc 4:1) to afford **24** as a colorless oil (39 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.16 (s, 9/2H), 1.17 (s, 9/2H), 2.58−2.78 (m, 2H), 2.87−2.97 (m, 2H), 3.02−3.15 (m, 1H), 3.29−3.40 (m, 2H), 4.78−4.91 (m, 1H), 5.04−5.14 (m, 2H), 5.52 (d, 1H, J = 7.2 Hz), 6.04 (d, 1/2H, J = 16.2 Hz), 6.06 (d, 1/2H, J = 15.6 Hz), 6.85−6.99 (m, 3H), 7.13−7.40 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 27.3, 36.9, 37.0, 37.7, 37.8, 44.9, 45.0, 58.4, 58.7, 63.0, 66.5, 72.7, 126.1,126.6, 127.3, 127.5, 127.7, 127.8, 128.1, 128.3, 128.9, 129.3, 135.6, 136.3, 138.9, 139.0, 150.5, 155.3, 196.0, 196.2. HRMS (EI) calcd for $C_{32}H_{37}NO_4K$ [M + ^{39}K] 538.2360, found 538.2384.

***tert*-Butyl (2*R*,6*S*)-6-[*N*-(Benzyloxycarbonyl)amino]-2-benzyl-5-oxo-7-phenyl-3-heptenyl Ether ((2*R*)-24a).** To a solution of **21** (112 mg, 0.50 mmol) in dry CH_2Cl_2 (5 mL) were added crushed 4 Å molecular sieves and *N*-methylmorpholine *N*-oxide (89 mg, 0.76 mmol). After stirring for 5 min tetra-*n*-propylammonium perruthenate (catalytic amount) was added. The reaction mixture was stirred for 1 h. Additional *N*-methylmorpholine *N*-oxide (89 mg, 0.76 mmol) and tetra-*n*-propylammonium perruthenate (catalytic amount) were then added, and after stirring for an additional 1 h, the reaction mixture was passed through a short silica column, washed with additional CH_2Cl_2, and collected in fractions. The fractions containing the desired product (monitored by thin-layer chromatography, 2:1 hexane/EtOAc) were combined, and the solvent was removed under reduced pressure to afford the intermediate aldehyde (2*S*)-**9a** as a colorless oil (493 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.16 (s, 9H), 2.68−2.85 (m, 3H), 3.05 (dd, 1H, J = 6.0, 13.8 Hz), 3.50 (dd, 1H, J = 5.4, 8.7 Hz), 3.60 (dd, 1H, J = 4.5, 8.7 Hz), 7.18−7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 27.2, 31.5, 53.6, 59.2, 72.9, 126.2, 128.3, 128.9, 138.9, 203.8.

To a solution of phosphonate **7** (80 mg, 0.21 mmol) in dry acetonitrile (2 mL) were added LiCl (9 mg, 0.21 mmol) and diisopropylethylamine (31 μL, 0.18 mmol) followed by a solution of (2*S*)-**9a** (39 mg, 0.18 mmol) in dry acetonitrile (1 mL). The reaction was stirred for 72 h and then quenched with sat. $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford a yellow oil which was purified by column chromatography (4:1 hexane/EtOAc) to afford **24a** as a colorless oil (31 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.17 (s, 9H), 2.59−2.78 (m, 2H), 2.94 (td, 2H, J = 5.4, 12.9 Hz), 3.09 (dd, 1H, J = 6.0, 13.8), 3.30−3.40 (m, 2H), 4.80−4.87 (m, 1H), 5.06−5.16 (m, 2H), 5.56 (d, 1H, J = 7.8 Hz), 6.06 (d, 1H, J = 16.2 Hz), 6.91 (d, 1H, J = 8.4 Hz), 6.94−7.38 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 27.4, 37.2, 38.0, 45.2, 58.8, 63.2, 66.7, 72.9, 126.2, 126.8, 127.4, 127.9, 128.0, 128.2, 128.3, 128.4, 129.0, 129.5, 135.6, 139.1, 250.8, 155.5, 196.2, 215.2, 216.3. HRMS (FAB) calcd for $C_{32}H_{38}NO_4$ [M^+] 500.2801, found 500.2812.

***tert*-Butyl (2*RS*,5*RS*,6*S*)-6-[*N*-(Benzyloxycarbonyl)-amino]-2-benzyl-7-phenyl-3-hepten-5-ol (6a−d).** To a solution of **24** (32 mg, 0.064 mmol) in dry methanol (0.5 mL) at 0 °C was added $NaBH_4$ (2.3 mg, 0.06 mmol). The reaction mixture was stirred for 30 min, and then glacial acetic acid (1 drop) was added. The reaction mixture was partitioned between EtOAc (30 mL) and $NaHCO_3$ (10 mL). The aqueous layer was re-extracted with EtOAc (30 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to afford an oil which was purified by column chromatography (4:1 hexane/EtOAc) to afford the desired compounds as colorless oils in two fractions:

Fraction one was a pure sample of one of the minor isomers (**6d**) (5 mg, 16%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.14 (s, 9H), 2.47−2.56 (m, 2H), 2.64−2.78 (m, 1H), 2.81−2.93 (m, 2H), 3.24 (d, 2H, J = 6.0 Hz), 3.76−3.88 (m, 1H), 4.00−4.04 (m, 1H), 4.93−4.99 (m, 1H), 5.01 (s, 2H), 5.41 (dd, 1H, J = 6.6, 5.6 Hz), 5.57 (dd, 1H, J = 7.1, 15.5 Hz), 7.10−7.40 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 27.5, 37.4, 37.9, 44.6, 56.5, 64.1, 66.6, 74.6, 94.4, 105.3, 125.9, 126.4, 128.0, 128.1, 128.4, 128.5, 129.3, 130.5, 131.5, 135.1, 136.6, 138.1, 140.2. HRMS (FAB) calcd for $C_{32}H_{40}NO_4$ [MH^+] 502.2957, found 502.2980.

Fraction two was an inseparable mixture of the two major (**6a**, **6c**) and the remaining minor isomer (**6b**) (23 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.17 (s, ^{t}Bu, **6b**, **6c**), 1.19 (s, ^{t}Bu, **6a**), 2.37−2.64 (m, 2H), 2.81−3.04 (m, 1H), 3.24−3.38 (m, 2H), 3.91−3.99 (m, 1H), 4.12−4.15 (m, 1H), 4.57 (d, CH_2O^{t}Bu, J = 9.0, **6b**, **6c**) 4.71 (d, CH_2O^{t}Bu, J = 9.0, **6a**), 5.02 (s, CH_2(CBZ), **6a**), 5.04 (s, CH_2(CBZ), **6b**, **6c**), 5.32−5.67 (m, 2H), 7.10−7.40 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 27.5, 36.3, 36.6, 37.9, 44.9, 45.0, 56.6, 56.8, 64.3, 64.5, 66.7, 72.7, 73.0, 73.2, 125.9, 126.0, 126.3, 126.4, 127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 129.0, 129.1, 129.2, 129.3, 130.5, 131.5, 135.1, 136.6, 137.9, 138.1, 140.2, 140.5.

***tert*-Butyl (2*R*,5*RS*,6*S*)-6-[*N*-(Benzyloxycarbonyl)amino]-2-benzyl-7-phenyl-3-hepten-5-ol (6a, 6b).** To a solution of the ketoalkene (2*R*)-**24a** (29 mg, 0.06 mmol) in dry methanol (0.5 mL) at 0 °C was added $NaBH_4$ (3 mg, 0.08 mmol). The reaction mixture was stirred for 30 min, and then 10% aqueous acetic acid (3 drops) was added. The reaction mixture was partitioned between EtOAc (10 mL) and $NaHCO_3$ (10 mL). The aqueous layer was re-extracted with EtOAc (10 mL), and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to afford an oil which was purified by column chromatography (4:1 hexane/EtOAc) to afford an inseparable mixture (2:1, ^{1}H NMR) of the (2*R*,5*R*)-**6a** and (2*R*,5*S*)-**6b** isomers as a colorless oil (17.5 mg, 61%).

Major isomer (**6a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.17 (s, 9H), 2.37−2.68 (m, 4H), 2.81−3.04 (m, 2H), 3.24−3.38 (m, 2H), 3.92−4.20 (m, 1H), 4.72 (d, 1H, J = 8.7 Hz), 5.02 (s, 2H), 5.33 (d, 1H, J = 5.4 Hz), 5.52 (dd, 1H, J = 7.8, 15.6 Hz), 7.07−7.36 (m, 15H); Minor isomer (**6b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.19 (s, 9H), 2.37−2.68 (m, 4H), 2.81−3.04 (m, 2H), 3.24−3.38 (m, 2H), 3.92−4.20 (m, 1H), 4.57 (d, 1H, J = 9.0 Hz), 5.02 (s, 2H), 5.38 (d, 1H, J = 5.4 Hz), 5.63 (dd, 1H, J = 8.7, 15.3 Hz), 7.07−7.36 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.5, 36.3, 36.5, 37.9, 45.0, 45.3, 56.7, 56.8, 64.3, 64.6, 66.5, 66.7, 72.7, 73.0, 73.2, 73.4, 125.9, 126.0, 126.3, 126.4, 127.6, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 129.0, 129.1, 129.2, 130.4, 134.1, 134.8, 140.6. HRMS (EI) calcd for $C_{32}H_{39}NO_4Na$ [M + ^{23}Na] 524.2777, found 524.2772.

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Supporting Information Available: Copies of ^{1}H NMR spectra of **6a**−**d**, **7**, (2*S*)-**9a**, **11**, **14**, **18**−**24**, and (2*R*)-**24a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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