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Diastereoselective synthesis of a novel lactam peptidomimetic exploiting vinylogous Mannich addition of 2-silyloxyfuran reagents

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Abstract

The total synthesis of a potential inhibitor of HIV-protease — the chiral nonracemic six-membered hydroxy lactam **6** — has been accomplished, that involves, as key reaction, the highly diastereoselective vinylogous Mannich addition of furan-based silyloxy diene **7** to glyceraldeyde imine **8**.

1. Introduction

In recent years, fruitful effort has been devoted to the design and construction of cyclic inhibitors of HIV-protease, whose structures mimic the extended conformation of protease substrates (transition-state dipeptide isosteres).[1] In particular, a number of six- and seven-membered candidates have been introduced (e.g. compounds **1**–**5**, Fig. 1), based on the known C_2-symmetric structure of the target protease homodimer, which exhibited potency in the micromolar–nanomolar inhibitory concentration range.[1a,b,f,g] Hence the search for a methodology aimed at the assembly of piperidinone-based units equipped with proper binding elements at the P1/P1′ and P2/P2′ subsites, and a required stereochemical arrangement becomes an attractive challenge, especially when the synthetic scheme is flexible and stereogovernable.

Among the existing techniques available for forging the requisite piperidinone scaffold, we chose the scantily exploited vinylogous version of a Mannich-type addition[2,3] as the leading carbon–carbon bond-forming manoeuvre to access chiral nonracemic hydroxylactam **6**, a potential candidate of an emerging progeny of HIV-protease inhibitors.[1a,c]

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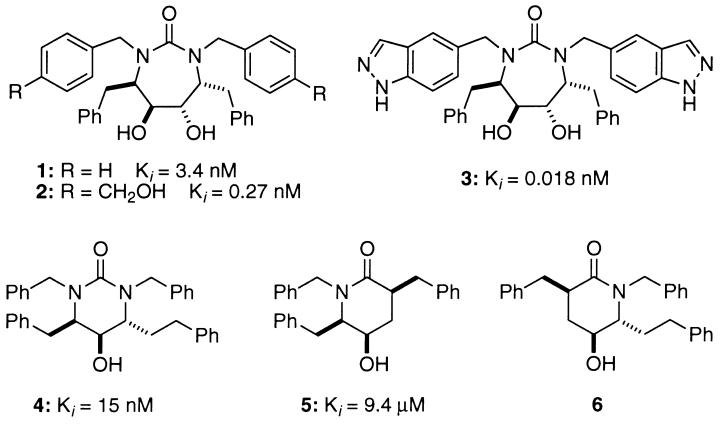
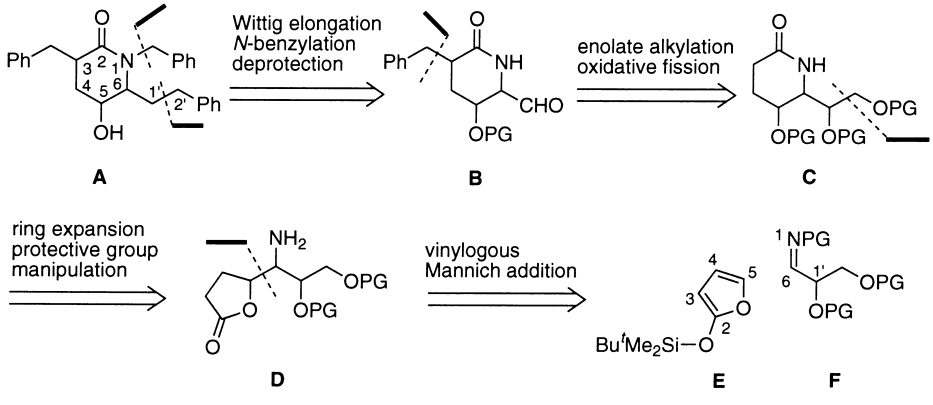


Figure 1.

Retrosynthetically, a generic piperidinone structure **A** (Scheme 1) is disconnected along the indicated bonds to identify lactam **B** as the immediate precursor. Aldehyde **B**, in turn, is traced to lactam **C** by stereoselective enolate alkylation, followed by oxidative fission of the diol side chain. The six-membered ring within **C** is formed by a γ-lactone to δ-lactam intramolecular annulation of substituted furanone **D**, which ultimately springs from furan-based silyloxy diene **E** and chiral nonracemic imine **F** by exploiting the vinylogous version of a Lewis acid-assisted Mannich reaction. Thus, the silyloxy diene unit **E** provides the C-2–C-5 portion of the piperidinone **A** (target numbering), and chiral imine **F** constitutes the chiral primer, while furnishing the N-1–C-6–C-1′ segment of the target compound.

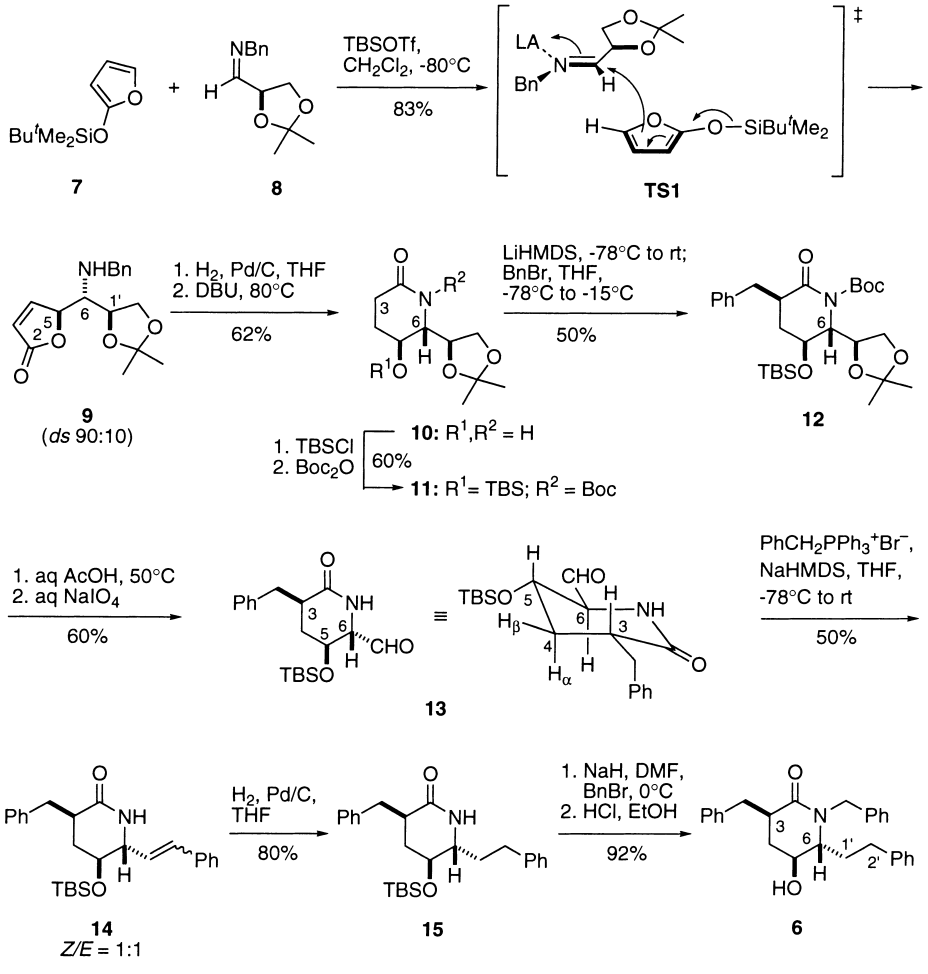


Scheme 1.

2. Results and discussion

The total synthesis of piperidinone **6** commenced with the regio- and diastereoselective addition of 2-(*tert*-butyldimethylsilyloxy)furan **7** to protected D-glyceraldehyde *N*-benzylimine **8**, a 3-carbon synthon readily available from the natural chiral pool (Scheme 2).[4] The key vinylogous coupling was carried out in the presence of 0.6 mol equiv. of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) as the Lewis acid catalyst (CH_2Cl_2, −80°C), leading to 5,6-*anti*–6,1′-*anti*-configured butenolide **9** in 83% yield and 80% diastereomeric excess.[5] The addition regiosense (attack at the remote C-5 position of furan **7**), as well as the simple diastereoselectivity (5,6-*anti*) of the vinylogous Mannich-type coupling may possibly

be governed by transition state **TS1**, where the indicated carbon–carbon bond-forming trajectory (*re* face of dienolate vs *si* face of imine) would seemingly be preferred, due to favorable stereoelectronic requirements. Whereas, for facial diastereoselection (6,1′-*anti*), a Felkin-type model clearly applies, resulting in a preferential attack of the nucleophile on the less demanding *si* face.



Scheme 2.

Catalytic hydrogenation of lactone **9** (Pd/C, THF) effected saturation of the butenolide double bond with concomitant removal of the amine benzyl group, providing an amino lactone intermediate (not shown), which underwent five-to-six-membered ring expansion upon treatment with neat 1,8-diazabicyclo[5:4:0]undec-7-ene (DBU) at 80°C. Lactam **10** was thus produced in 62% yield (over two stages), which was then subjected to sequential protection at the secondary hydroxyl (TBSCl, imidazole, DMF) and amide nitrogen (Boc_2O, DMAP, MeCN), to furnish the fully protected intermediate **11** in 60% yield.

Having established the piperidinone moiety, we next turned to implementation of the alkyl chains at the C-3 and C-6 positions. Thus, when **11** was treated with LiHMDS (THF, −78°C to room temperature), a lactam enolate was formed, which was stereoselectively benzylated (BnBr, −78 to −15°C) to afford the advanced intermediate **12** as the sole diastereoisomer in 50% yield. The *cis* relationship between the benzyl and the protected C-5 hydroxyl groups had not yet been proved at this point, because the ^1H

NMR data (i.e. coupling constants) had not allowed a firm stereochemical assignment (vide infra). The manipulation of the C-6 side chain began with acidic treatment of lactam **12** (70% aq. AcOH, 50°C) that produced concomitant removal of both the acetonide and the *N*-*tert*-butoxycarbonyl protecting groups. In the event, a diol intermediate was obtained (not shown), which was subjected to periodate oxidative fission to produce aldehyde **13** (60%), ready for the subsequent Wittig elongation.

The *cis* stereodisposition between the C-3 and C-5 substituents, as well as the C-5–C-6 *trans* relationship were now established based on careful inspection of its ^{1}H NMR spectrum, revealing diagnostic coupling constants for axially disposed H-3–H-4α and H-5–H-6 proton couples ($J_{3,4\alpha}$=12.0 Hz; $J_{5,6}$=9.2 Hz). Thus, as expected, the piperidinone substituents within **13** are located in thermodynamically stable *all*-equatorial conformation.

The coupling reaction between aldehyde **13** and benzylidene triphenylphosphorane allowed the preparation of 1:1 *E/Z* mixture **14** (50% yield), which was hydrogenated (Pd/C, THF) to furnish saturated lactam **15** in 80% yield. Clean *N*-benzylation of **15** (NaH, DMF; then BnBr, 0°C) followed by acidic removal of the TBS-ether protecting group (ethanolic HCl) completed the synthesis of the hydroxy piperidinone **6** in 92% yield.

In conclusion, furan-based silyloxy diene **7** readily engages in a Lewis acid-promoted vinylogous Mannich addition to chiral nonracemic imine **8** with a high chemical efficiency and diastereoselectivity. The chiral unsaturated lactone **9** so generated constitutes a valuable, functionality dense scaffold on which the constitutional and stereochemical elements of the target lactam **6** are implemented. No doubt, by varying the core substituents at the C-3, C-1′, and N-1 positions during the molecular assemblage, the prospect of creating diversified ensembles within this promising class of lactam peptidomimetics could soon be within our reach.[6]

3. Experimental

3.1. General procedures

Melting points were determined using an Electrothermal apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using a Bruker AC-300 spectrometer. Chemical shifts are quoted in parts per million (δ) relative to tetramethylsilane (0.0 ppm) or to the specific deuterated solvent as an internal standard, and coupling constants (*J*) are measured in hertz (Hz). Elemental analyses were performed by the Microanalytical Laboratory of the University of Sassari. All the solvents were dried according to common methods and distilled before use. All reactions were carried out in oven-dried glassware under a nitrogen or argon atmosphere unless otherwise noted. Analytical thin-layer chromatography was performed on 0.25 mm silica gel glass-backed plates (Merck Kieselgel 60 F_{254}). Flash chromatography was carried out on 32–63 μm silica gel (ICN Biomedicals), using the reported solvent mixtures. The compounds were visualized by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate and ammonium molybdate, followed by heating.

3.2. Materials

2-[(*tert*-Butyldimethylsilyl)oxy]furan **7** was prepared on a multigram scale from 2-furaldehyde (Aldrich) according to a reported procedure.[7] 2,3-*O*-Isopropylidene-D-glyceraldehyde *N*-benzylimine **8**

was obtained by reacting benzylamine (Aldrich) and 2,3-*O*-isopropylidene-D-glyceraldehyde (ex D-mannitol)[8] in dry diethyl ether at room temperature in the presence of anhydrous $MgSO_4$. The crude material so obtained was used in the subsequent coupling process.

3.3. 5-(N-Benzylamino)-6,7-O-isopropylidene-2,3,5-trideoxy-D-ribo-hept-2-enonic acid 1,4-lactone **9**

To a stirring solution of imine **8** (4.6 g, 20.6 mmol) in anhydrous CH_2Cl_2 (80 mL) under nitrogen atmosphere cooled to −80°C were sequentially added dienol ether **7** (4.1 g, 20.6 mmol) and TBSOTf (2.4 mL, 10.3 mmol), and the resulting mixture was allowed to react for 3 h at −80°C. The reaction was then quenched at the same temperature by addition of saturated aqueous $NaHCO_3$ and, after ambient temperature was reached, the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (2×15 mL), dried with $MgSO_4$, filtered, and concentrated to furnish an oily yellowish crude residue which was subjected to flash chromatographic purification on silica gel (hexanes:EtOAc, 60:40). Pure lactone **9** was obtained (5.2 g, 83%) as white crystals; mp 66–67°C; $[\alpha]_D^{20}$=−35.2 (c=0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J*=5.8, 1.6 Hz, 1H), 7.28 (m, 5H), 6.16 (dd, *J*=5.8, 2.1 Hz, 1H), 5.35 (app. quint, *J*=2.1 Hz, 1H), 4.07 (dd, *J*=8.3, 6.3 Hz, 1H), 3.95 (m, 1H), 3.7–3.9 (m, 4H), 3.08 (dd, *J*=7.5, 4.2 Hz, 1H), 1.39 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 154.3, 139.5, 128.1 (5C), 122.2, 109.6, 83.6, 75.5, 67.5, 61.2, 52.9, 26.5, 25.0. Anal. calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.04; H, 7.15; N, 4.50.

3.4. 5-Amino-6,7-O-isopropylidene-2,3,5-trideoxy-D-ribo-heptonic acid 1,5-lactam **10**

To a stirring solution of butenolide **9** (5.0 g, 16.5 mmol) in anhydrous THF (150 mL) was added 10% Pd on carbon (0.5 g) and a small amount of sodium acetate (120 mg) at room temperature. The reaction vessel was evacuated and thoroughly purged with hydrogen (four times), and the resulting heterogeneous mixture was allowed to stir under a balloon of hydrogen for 24 h at room temperature. After hydrogen evacuation, the catalyst was filtered off, and the filtrate concentrated to afford a crude oily residue that was subjected to flash chromatographic purification (EtOAc:MeOH, 90:10). A 2.7 g (75% yield) was obtained of a lactone intermediate as white crystals: mp 62–65°C; $[\alpha]_D^{20}$=+19.1 (c=0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (ddd, *J*=8.0, 7.3, 4.7 Hz, 1H), 4.07 (dd, *J*=7.7, 6.2 Hz, 1H), 3.99 (ddd, *J*=6.9, 6.2, 5.9 Hz, 1H), 3.88 (dd, *J*=7.7, 5.9 Hz, 1H), 3.24 (dd, *J*=6.9, 4.7 Hz, 1H), 2.54 (m, 2H), 2.21 (m, 2H), 2.01 (bs, 2H), 1.40 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 109.2, 81.0, 75.6, 66.4, 54.8, 28.5, 26.4, 25.0, 22.1. This intermediate (2.7 g, 12.5 mmol) was dissolved in 10 mL of DBU and the resulting solution warmed to 80°C and allowed to react for 4 h. The reaction mixture was concentrated under vacuum, leaving a brown crude residue that was purified by flash chromatography eluting with EtOAc:MeOH (75:25). Pure lactam **10** was obtained (2.2 g, 62% yield for the two steps from **9**) as a white crystalline solid: mp 110–113°C; $[\alpha]_D^{20}$=+22.3 (c=0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (bs, 1H), 4.50 (bs, 1H), 4.23 (app. quint, *J*=6.3 Hz, 1H), 4.06 (dd, *J*=8.4, 6.4 Hz, 1H), 3.79 (dd, *J*=8.4, 6.3 Hz, 1H), 3.75 (m, 1H), 3.42 (td, *J*=6.5, 1.4 Hz, 1H), 2.46 (dt, *J*=18.0, 5.8 Hz, 1H), 2.29 (ddd, *J*=18.0, 9.5, 6.3 Hz, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 109.5, 76.3, 65.8, 65.2, 59.4, 28.1, 27.4, 26.2, 24.8. Anal. calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.74; H, 8.02; N, 6.60.

3.5. 4-O-tert-Butyldimethylsilyl-5-(tert-butoxycarbonyl)amino-6,7-O-isopropylidene-2,3,5-trideoxy-D-ribo-heptonic acid 1,5-lactam **11**

A stirring solution of lactam **10** (2.0 g, 10.0 mmol) in dry DMF (50 mL) under nitrogen atmosphere was sequentially treated with TBSCl (2.1 g, 14.0 mmol) and imidazole (0.96 g, 14.0 mmol). The resulting mixture was warmed to 40°C and allowed to stir for 3 days, and during this period further quantities of TBSCl (3×1.4 g, 3×10.0 mmol) and imidazole (3×0.64 g, 3×10.0 mmol) were added in three sequential operations. The reaction mixture was then quenched with 5% aqueous citric acid and extracted with EtOAc (4×30 mL). The combined organic layers were washed with brine (2×20 mL), dried over $MgSO_4$, filtered, and concentrated to furnish a crude residue that was purified by flash chromatography (EtOAc:MeOH, 98:2). A monoprotected silylated intermediate (2.48 g, 8.0 mmol, 80%) was obtained as a white crystalline solid, which was then dissolved in 100 mL of MeCN. To this stirring solution were sequentially added Boc_2O (1.7 g, 8.0 mmol) and DMAP (46 mg, 0.4 mmol) and the resulting mixture warmed to 40°C. Further amounts of Boc_2O (3×1.7 g) and DMAP (3×46 mg) were added in three sequential operations over a period of 24 h, after which time the reaction mixture was concentrated under vacuum. The crude residue so obtained was subjected to flash chromatographic purification on silica gel (hexanes:EtOAc, 70:30) affording 2.4 g (60% yield for the two steps from **10**) of pure, fully protected lactam **11** as a colorless oil: $[\alpha]_D^{20}=-26.2$ (c=1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (app. quint, *J*=3.2 Hz, 1H), 4.27 (ddd, *J*=8.9, 3.1, 1.6 Hz, 1H), 4.02 (dd, *J*=8.5, 6.0 Hz, 1H), 3.96 (dd, *J*=8.5, 5.6 Hz, 1H), 3.88 (dt, *J*=8.9, 5.8 Hz, 1H), 2.73 (ddd, *J*=17.7, 10.3, 8.1 Hz, 1H), 2.42 (ddd, *J*=17.4, 7.4, 3.0 Hz, 1H), 2.15 (dddd, *J*=13.8, 10.4, 7.5, 2.9 Hz, 1H), 1.83 (m, 1H), 1.50 (s, 9H), 1.42 (s, 3H), 1.33 (s, 3H), 0.87 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 152.8, 109.5, 83.0, 76.9, 67.3, 64.2, 62.8, 29.9, 29.5, 27.8 (3C), 26.6, 25.5 (3C), 25.4, 17.7, −4.9, −5.1. Anal. calcd for $C_{21}H_{39}NO_6Si$: C, 58.71; H, 9.15; N, 3.26. Found: C, 58.75; H, 9.00; N, 3.30.

3.6. (3R,5S,6S,4′S)-3-Benzyl-5-[(tert-butyldimethylsilyl)oxy]-6-(2,2-dimethyldioxolan-4-yl)piperidin-2-one **12**

A 2 M solution of LiHMDS in THF (3.6 mL, 7.3 mmol) cooled to −78°C was injected by syringe into a stirred solution of piperidinone **11** (2.4 g, 5.6 mmol) in dry THF (80 mL). The resulting solution was stirred at this temperature for 30 min, warmed to room temperature for an additional 30 min, and again cooled to −78°C. The solution was then treated with benzyl bromide (1.2 mL, 9.5 mmol), and stirring was continued for 2 h at −78°C. The reaction mixture was allowed to warm to −15°C and then quenched with 5% aqueous citric acid. The mixture was extracted with CH_2Cl_2 (3×40 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the oily crude residue through flash chromatography on silica gel (hexanes:EtOAc, 85:15) furnished pure lactam **12** (1.5 g, 50% yield) along with 0.6 g (25%) of starting piperidinone **11**, which was recovered and subjected to the same alkylating reaction. Lactam **12**, colorless oil: $[\alpha]_D^{20}=-48.4$ (c=1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.19 (m, 3H), 4.35 (ddd, *J*=7.5, 3.0, 1.1 Hz, 1H), 4.28 (m, 1H), 4.01 (m, 2H), 3.90 (m, 1H), 3.45 (1/2 AB q, *J*=10.0 Hz, 1H), 2.67 (m, 1H), 2.63 (1/2 AB q, *J*=10.0 Hz, 1H), 2.10 (ddd, *J*=14.1, 7.9, 5.2 Hz, 1H), 1.62 (m, 1H), 1.53 (s, 9H), 1.40 (s, 3H), 1.31 (s, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 153.4, 139.7, 129.2 (2C), 128.4, 126.2 (2C), 109.8, 83.1, 76.3, 67.0, 65.4, 63.5, 41.8, 38.2, 32.4, 28.0 (3C), 26.6, 25.7 (3C), 25.4, 17.8, −4.5, −5.0. Anal. calcd for $C_{28}H_{45}NO_6Si$: C, 64.71; H, 8.73; N, 2.69. Found: C, 64.62; H, 8.91; N, 2.65.

3.7. (3R,5S,6S)-3-Benzyl-5-[(tert-butyldimethylsilyl)oxy]-6-formylpiperidin-2-one **13**

Piperidinone **12** (2.0 g, 3.9 mmol) was dissolved in 30 mL of 70% aqueous acetic acid and the resulting solution warmed to 50°C under stirring. The reaction mixture was allowed to stir at this temperature for 5 h and was then concentrated under vacuum, giving an oily residue (1.3 g) which was used as such in the subsequent reaction. The diol residue (1.3 g, 3.5 mmol) was dissolved in 30 mL of CH_2Cl_2 and treated with chromatography grade SiO_2 (2.0 g). To this heterogeneous mixture was added a 0.65 M aqueous solution of $NaIO_4$ (35 mL) dropwise and the resulting slurry stirred vigorously at room temperature for 20 min. The reaction mixture was filtered under suction and thoroughly washed with CH_2Cl_2. The filtrates were concentrated under vacuum to directly produce aldehyde **13** (0.8 g, 60% from **12**) as a yellowish glassy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.7 (s, 1H), 7.28 (m, 2H), 7.19 (m, 3H), 6.35 (bs, 1H), 3.92 (ddd, *J*=10.6, 9.3, 3.8 Hz, 1H), 3.80 (d, *J*=9.2 Hz, 1H), 3.28 (dd, *J*=13.7, 4.2 Hz, 1H), 2.84 (dd, *J*=13.7, 9.0 Hz, 1H), 2.58 (dddd, *J*=12.0, 9.0, 6.1, 4.2 Hz, 1H), 1.93 (ddd, *J*=12.9, 6.2, 3.8 Hz, 1H), 1.69 (app. quint, *J*=12.0 Hz, 1H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 171.8, 138.7, 129.1 (2C), 128.4, 126.4 (2C), 67.4, 66.5, 40.5, 37.1, 35.8, 25.5 (3C), 17.8, −4.2, −5.1. Anal. calcd for $C_{19}H_{29}NO_3Si$: C, 65.67; H, 8.41; N, 4.03. Found: C, 65.54; H, 8.60; N, 3.98.

3.8. (E/Z)-(3R,5S,6R)-3-Benzyl-5-[(tert-butyldimethylsilyl)oxy]-6-[(2-phenyl)ethen-1-yl]piperidin-2-one **14**

A 0.5 M solution of NaHMDS in THF (8.6 mL, 4.3 mmol) was injected dropwise by syringe to a solution of benzyl triphenylphosphonium (2.5 g, 5.8 mmol) in anhydrous THF (30 mL) at −40°C. The resulting red-orange solution was cooled to −78°C and treated with aldehyde **13** (0.8 g, 2.3 mmol) previously dissolved in 50 mL of dry THF. The reaction mixture was allowed to stir at −78°C for 30 min, and then it was slowly warmed to room temperature. After 16 h, the heterogeneous reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL), and extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, to provide an oily crude residue, which was purified by flash chromatography (hexanes:EtOAc, 60:40) furnishing a 1:1 mixture of *E/Z* alkenes **14** (485 mg, 50%) as a colorless oil. A portion of this olefin mixture was subjected to a further chromatographic purification, allowing characterization of the two geometric isomers.

E-**14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 6H), 7.22 (m, 4H), 6.55 (d, *J*=15.9 Hz, 1H), 6.03 (dd, *J*=15.9, 7.6 Hz, 1H), 5.67 (bs, 1H), 3.81 (app. t, *J*=7.9 Hz, 1H), 3.69 (ddd, *J*=10.7, 8.2, 3.5 Hz, 1H), 3.35 (dd, *J*=13.6, 4.0 Hz, 1H), 2.85 (dd, *J*=13.6, 9.1 Hz, 1H), 2.64 (dddd, *J*=11.6, 9.5, 5.7, 4.0 Hz, 1H), 1.88 (ddd, *J*=13.1, 5.8, 3.6 Hz, 1H), 1.66 (app. quint, *J*=12.3 Hz, 1H), 0.80 (s, 9H), −0.05 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 139.2, 135.9, 133.5, 129.2 (2C), 128.6 (2C), 128.3 (2C), 128.0, 127.7, 126.4 (2C), 126.2, 70.7, 62.6, 38.0, 37.1, 34.8, 25.6 (3C), 17.9, −4.6, −4.8.

Z-**14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1–7.4 (m, 10H), 6.72 (d, *J*=11.4 Hz, 1H), 5.64 (bs, 1H), 5.43 (dd, *J*=11.3, 10.1 Hz, 1H), 4.27 (app. t, *J*=9.2 Hz, 1H), 3.72 (ddd, *J*=11.3, 8.5, 3.6 Hz, 1H), 3.32 (dd, *J*=13.5, 3.8 Hz, 1H), 2.73 (dd, *J*=13.4, 9.3 Hz, 1H), 2.62 (m, 1H), 1.85 (ddd, *J*=13.0, 5.6, 3.6 Hz, 1H), 1.61 (app. quint, *J*=13.0 Hz, 1H), 0.78 (s, 9H), −0.04 (s, 3H), −0.05 (s, 3H).

3.9. (3R,5S,6R)-3-Benzyl-5-[(tert-butyldimethylsilyl)oxy]-6-[(2-phenyl)ethyl]piperidin-2-one **15**

A solution of olefin mixture **14** (421 mg, 1.0 mmol) in THF (30 mL) was subjected to catalytic hydrogenation with 10% Pd on carbon (100 mg), in the presence of NaOAc (100 mg) at room temperature for 24 h. The catalyst was then removed by filtration, and the filtrate was concentrated to give a

crude residue that was purified by flash chromatography on silica gel (hexanes:EtOAc, 60:40). Pure piperidinone **15** (340 mg, 80% yield) was obtained as a white solid: $[\alpha]_D^{20}$=+27.7 (c=0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 4H), 7.16 (m, 6H), 5.74 (bs, 1H), 3.57 (ddd, *J*=11.4, 8.3, 3.6 Hz, 1H), 3.34 (dd, *J*=13.5, 3.9 Hz, 1H), 3.13 (td, *J*=8.2, 2.4 Hz, 1H), 2.73 (dd, *J*=13.5, 9.4 Hz, 1H), 2.4–2.7 (m, 3H), 2.06 (dddd, *J*=16.9, 6.6, 6.6, 2.9 Hz, 1H), 1.81 (ddd, *J*=13.0, 5.8, 3.7 Hz, 1H), 1.67 (dddd, *J*=14.0, 9.5, 8.2, 5.6 Hz, 1H), 1.51 (app. quint, *J*=11.4 Hz, 1H), 0.82 (s, 9H), 0.05 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 141.0, 139.1, 129.2 (2C), 128.6 (2C), 128.4 (2C), 128.3 (2C), 126.3 (2C), 70.0, 59.0, 40.8, 37.2, 35.0, 34.6, 31.2, 25.7 (3C), 17.9, −4.1, −4.8. Anal. calcd for $C_{26}H_{37}NO_2Si$: C, 73.71; H, 8.80; N, 3.31. Found: C, 73.84; H, 8.17; N, 3.25.

*3.10. (3*R*,5*S*,6*R*)-1,3-Dibenzyl-5-hydroxy-6-[(2-phenyl)ethyl]piperidin-2-one **6***

To a stirring solution of piperidinone **15** (340 mg, 0.8 mmol) in dry DMF (15 mL) at room temperature was added NaH (96 mg, 2.4 mmol, 60% dispersion in mineral oil). After 30 min, the reaction mixture was cooled to 0°C and benzyl bromide was added (0.14 mL, 1.2 mmol). The temperature was allowed to raise to room temperature and the reaction was left stirring for 2 h before being quenched with water (15 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure providing an oily crude residue which was purified by flash chromatography (hexanes:EtOAc, 80:20). A solution of 390 mg (95% yield) of a *N*-benzylated pure intermediate was obtained, as a colorless, glassy solid: $[\alpha]_D^{20}$=−4.1 (c=0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 13H), 7.07 (m, 2H), 5.27 (d, *J*=14.8 Hz, 1H), 3.99 (d, *J*=15.0 Hz, 1H), 3.96 (dt, *J*=6.3, 4.0 Hz, 1H), 3.55 (dd, *J*=13.6, 3.7 Hz, 1H), 3.22 (app. quint, *J*=4.2 Hz, 1H), 2.83 (dd, *J*=13.5, 10.5 Hz, 1H), 2.4–2.7 (m, 3H), 1.98 (m, 2H), 1.80 (m, 1H), 1.63 (m, 1H), 0.80 (s, 9H), −0.04 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 140.8, 140.4, 137.2, 129.3 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.1 (2C), 127.1, 126.2, 125.9, 67.5, 62.8, 48.2, 39.8, 38.6, 32.9, 30.8, 29.6, 25.8 (3C), 18.0, −4.5, −4.9. This intermediate (390 mg, 0.76 mmol) was dissolved in a 1% ethanolic solution of HCl (25 mL) and the resulting mixture was stirred at room temperature for 5 h. After being concentrated, the reaction mixture was dissolved in a 1:1 THF:HCl solution (25 mL) and it was allowed to stir for an additional 3 h at room temperature. The reaction was concentrated furnishing a crude residue, from which pure piperidinone **6** (290 mg, 92% yield from **15**) was isolated by flash chromatographic purification (hexanes:EtOAc, 70:30) as a white glassy solid: $[\alpha]_D^{20}$=−18.0 (c=0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1–7.3 (m, 15H), 5.41 (d, *J*=14.6 Hz, 1H), 3.91 (dt, *J*=6.7, 4.4 Hz, 1H), 3.85 (d, *J*=14.9 Hz, 1H), 3.49 (dd, *J*=13.6, 4.1 Hz, 1H), 3.20 (app. quint, *J*=4.0 Hz, 1H), 2.84 (dd, *J*=13.3, 9.7 Hz, 1H), 2.5–2.7 (m, 3H), 2.32 (bs, 1H), 2.01 (m, 2H), 1.87 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 140.7, 140.3, 138.2, 129.5, 129.4 (2C), 128.8, 128.6 (2C), 128.4 (2C), 128.2 (4C), 127.4, 126.2 (2C), 67.2, 62.0, 47.9, 39.6, 38.1, 32.0, 31.1, 29.3. Anal. calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.04; H, 7.23; N, 3.60.

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