Total synthesis of the potent immunosuppressant (−)-Pironetin

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Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday
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Abstract
A convergent and efficient total synthesis of (−)-pironetin, a compound that shows plant growth regulatory activity, and is immunosuppressive as well as having remarkable antitumoral activity, is described. The synthesis required 19 steps from N-propionyl oxazolidinone (S)-9 and produced the desired product in 11% overall yield.

Keywords: Immunosuppressive activity, antitumoral activity, unsaturated lactone, total synthesis

Introduction
The potent immunosuppressor pironetin¹ (1) was isolated independently by two research groups from Streptomyces sp. NK-10958 and from the fermentation broths of Streptomyces prunicolor PA-48153 (Figure 1). Pironetin shows plant growth regulatory activity as well as immunosuppressive and antitumor activities.² Three The mode of action of pironetin is different from those established for the immunosuppressants cyclosporin A (CsA) and FK506, which inhibit T cell activation.⁴ Pironetin showed suppressive effects on the responses of T and B lymphocytes to mitogens.

Figure 1
In a recent paper, the Osada group reported that the α,β-unsaturated lactone, the chirality at the C7–position and the terminal portion of the alkyl chain are important for microtubule inhibitory activity of pironetins.\(^3\) The relative and absolute configurations of pironetin were proposed by means of spectral methods and further confirmed by total synthesis.\(^5\)–\(^7\)

(—)-Pironetin was isolated in very small amounts. Attracted by its potent cytotoxicity, and to provide material for more extensive biological evaluation, along with access to promising novel analogues, we have undertaken its total synthesis.\(^5\)–\(^7\) We have recently described an efficient total synthesis of pironetin.\(^7\) In this paper we wish to describe an improvement of this synthesis, which might give access to additional derivatives with potential relevance to biological studies, along with unsuccessful approaches.

**Results and Discussion**

Our disconnection, summarized in Scheme 1, involved cleavage of the C4-C5 bond to give aldehyde 2 and N-butanoyloxazolidinone 3.\(^8\) Aldehyde 2 is further dissected in a straightforward manner by cleavage of the C11-C12 bond, which is viewed as arising from a coupling of vinylic species 4 with tosylate 5a, iodide 5b or bromide 5c. Fragment C5-C11 (5) may be further dissected to give 6, available from β-ketoimide 7 and aldehyde 8.
Scheme 1. Retrosynthetic analysis of pironetin.

Our first approach to fragment C5-C11 started with the aldol reaction between the (Z)-boron enolate of N-propionyl oxazolidinone (R)-9 with propionaldehyde to give aldol adduct 10 in 82% yield and >99:1 diastereoselectivity (Scheme 2).\textsuperscript{9,10}
Scheme 2. First approach to fragment C5-C11.

Treatment of 10 with SO₃-pyr in a mixture of DMSO/CH₂Cl₂ gave β-ketoimide 7 in 96% yield. Treatment of β-ketoimide 7 with Sn(OTf)₂ and Et₃N in CH₂Cl₂ followed by addition of aldehyde 8 gave aldol adduct 6 with a modest diastereoselectivity (86:14) in only 50% yield. Attempts to improve yields and diastereoselectivities for this transformation failed. The next step involved reduction of the ketone function in 6 with Me₄NHB(OAc)₃ in CH₃CN/CH₃CO₂H to provide diol 11, together with lactone 12 and chiral auxiliary 13, a mixture which was difficult to...
separate by silica gel column chromatography. We were able to isolate only small amounts of lactone 12, and its formation proved that the reduction proceeded with the desired stereochemistry. Coupling constants between H1–H2 (10.3 Hz), H2–H3 (4.4 Hz) and H3–H4 (4.6 Hz), confirmed the relative stereochemistry for lactone 12.

In view of these disappointing results, we decided to use another strategy for the synthesis of fragment C5-C11, which is based in the use of two consecutive asymmetric aldol reactions (Scheme 3). Synthesis of aldehyde 16 began with asymmetric aldol addition of the boron enolate derived from N-propionyloxazolidinone (S)-9 with aldehyde 8 to give aldol adduct 14 in 87% yield (ds >95:5) (Scheme 3). Exchange of the oxazolidinone auxiliary in aldol 14 with N,O-dimethylhydroxylamine in the presence of Me3Al in THF at 0 °C was followed by silylation with TBSOTf and 2,6-lutidine in CH2Cl2 at 0 °C to give the Weinreb amide 15 (81%, 2 steps). Aldehyde 16 was prepared in 92% yield by reduction of 15 with DIBAL-H in toluene at 0 °C.

Scheme 3. Preparation of aldehyde 16.

Aldol adduct 17 was obtained in a good overall yield following treatment of the boron enolate generated from oxazolidinone (R)-9 with aldehyde 16 (84%, >95:5 diastereoselectivity) (Scheme 4). At this point, the relative stereochemistry for aldol adduct 17 was determined after conversion to the the same lactone 12 prepared before (Scheme 4). Formation of lactone 12 was accomplished after a three-step sequence (56% overall yield) that involved treatment of aldol 17 with HF/H2O/CH3CN, cleavage of the oxazolidinone auxiliary with H2O2/LiOH, and treatment of the carboxylic acid 18 in refluxing benzene.
Methylation of 17 with Me$_3$OBF$_4$ in the presence of a proton sponge at ambient temperature, provided 19 in 60% isolated yield (Scheme 5). As this reaction proved to be difficult to reproduce on a larger scale, we decided to promote the conversion of 17 to the corresponding primary alcohol. Treatment of 17 with LiBH$_4$ in THF/MeOH at 0 °C provided 1,3-diol 20 in 89% yield (Scheme 5). The next steps involved tosylation of the primary OH-function in 20 to provide tosylate 21 (95% yield) followed by methylation with Me$_3$OBF$_4$ in the presence of a proton sponge at ambient temperature, providing 5a in 89% isolated yield (Scheme 5).
In order to introduce the remaining 3 carbon atoms of the pironetin side chain, we first promoted a model study involving coupling between tosylate 22 and the corresponding Grignard and cuprate reagents derived from (E)-1-bromo-1-propene (4a) (Schemes 6 and 7). Treatment of (E)-1-bromo-1-propene (4a) with Mg\(^0\) in THF led to the Grignard reagent 4b (Scheme 6). Reaction of (E)-1-bromo-1-propene with \(^t\)BuLi in THF followed by addition of CuCN provided the expected cuprate 4c (Scheme 6). Reaction of tosylate 22 with Grignard reagent 4b gave coupled product 23 in 35% yield. We were not able to get better yields for this reaction. Treatment of tosylate 22 with cuprate 4c led to 23 in 84% yield (Scheme 6).

**Scheme 6.** Model studies with Grignard and cuprate reagents.

We next moved to the real system (Scheme 7). Treatment of tosylate 5a with Grignard reagent 4b gave bromide 5c in good yields as the sole product, together with starting material. Treatment of tosylate 5a with cuprate 4c (50 equivalents) led to a mixture of primary alcohol 24 (60%) and the desired product 25 in only 15% yield. Confirmation that alcohol 24 has been formed in this reaction came from treatment of aldol adduct 19 with LiBH\(_4\) and MeOH in THF providing the same alcohol 24 in excellent yields. Bromide 5c also proved to be unreactive under these conditions with both 4b and 4c. In spite of a series of experimental modifications we were not able to improve the yields for the formation of 25.

After examining several different attempts to couple C12 vinyl cuprates, C11 tosylates and bromides, we turned our attention to the use of a Suzuki coupling approach employing an alkyl...
iodide with vinyl bromides and vinyl iodides. Alkyl iodide 5b was prepared after a four-step sequence starting with diol 20 (Scheme 8). Selective silylation of diol 20, followed by methylation with Me3OBF4 in the presence of a proton sponge at ambient temperature, gave 27 (84% overall yield). Selective removal of the TBS primary group with a solution of HF-pyridine in THF and treatment of the resulting primary alcohol 24 with PPh3, I2 and imidazole gave iodide 5b in 83% overall yield for the two-step sequence.

Scheme 7. Coupling studies.

Scheme 8. Preparation of alkyl iodide 5b.
As before, we first did a model study for this coupling (Scheme 9). This was achieved through the use of a Pd-catalyzed coupling of an intermediate boronate derived from alkyl iodide 29 with vinyl bromide 4a (Scheme 9). Treatment of alkyl iodide 28 with tBuLi in Et₂O at –78 °C, followed by addition of 9-MeO-9-BBN, gave a boronate intermediate. Addition of vinyl bromide 4a in the presence of Pd(dppf)Cl₂, AsPh₃, K₂CO₃ and water in DMF gave coupled product 23 in 74% yield.

Scheme 9. Model studies involving Suzuki coupling.

As this worked well, we tried this coupling using iodide 5b (Scheme 10). Treatment of alkyl iodide 5b with tBuLi in Et₂O at –78 °C followed by addition of 9-MeO-9-BBN, and vinyl bromide 4a in the presence of Pd(dppf)Cl₂, AsPh₃, K₂CO₃ and water in DMF provided only product 29, formed by I/H exchange. We tried the coupling with vinyl iodides 30a and 30b as well, but always isolated only 29, with no signals for the desired product.

Scheme 10. Attempts to promote the Suzuki coupling in the real system.
Due to the difficulties in installing the \((E)\)-double bond using these approaches, we abandoned these strategies and altered our synthetic route. At this point, we were attracted to a study by Smith and Beumel,\(^{20}\) who reported the displacement of tosylates by means of the lithium acetylide-ethylenediamine complex to give alkynes in good yields. On the basis of this precedent, we focused our attention on this synthetic strategy.\(^{21}\)

We were very pleased to find that treatment of tosylate 5a with 5 equivalents of lithium acetylide in DMSO at room temperature produced acetylene 31 in 82% yield, together with elimination product 32 in 13% yield (Scheme 11). After treatment of 31 with \(^n\)BuLi and quenching with methyl iodide we were able to isolate the corresponding alkyne.\(^{22}\)

![Scheme 11. Preparation of aldehyde 2.](attachment:image.png)

Deduction of the alkyne proceeded smoothly with Na and liquid NH\(_3\) providing control for the \((E)\)-geometry of the C12–C13 double bond with concomitant removal of the PMB group at C5, giving primary alcohol 33 in 49% yield for the three-step sequence from 5a (Scheme 11).\(^{23}\) TPAP oxidation of 33 under the standard conditions gave the desired aldehyde 2 in 94% yield.\(^{24}\)

Asymmetric aldol addition of the boron enolate derived from N-butanoyloxazolidinone 3 with aldehyde 2 gave aldol adduct 34 in 90% yield (ds >95:5) (Scheme 12). However, all our attempts to prepare the Weinreb amide derivative by treatment of aldol adduct 34 with MeONHMe.HCl and Me\(_3\)Al in THF failed and we decided to prepare primary alcohol 35. Silylation of aldol 34 with TBSOTf and 2,6-lutidine was followed by treatment with LiBH\(_4\) in THF/MeOH to provide alcohol 35 (87% yield, 2 steps).
Scheme 12. Preparation of alcohol 35.

In order to introduce the (Z)-double bond, we prepared phosphonate 36 using two different approaches. The first one involved treatment of o-cresol with PCl$_3$ in the presence of imidazole in CH$_2$Cl$_2$ as solvent, followed by a sequence involving reaction with water and treatment with ethyl 2-bromoacetate in the presence of Et$_3$N to give 36 in 70% over two steps (Scheme 13).$^{25}$

Scheme 13. Preparation of phosphonate 36.

The second approach to phosphonate 36 started with treatment of ethyl 2-(diethoxyphosphoryl)acetate with PCl$_5$ under reflux, to give ethyl 2-(chlorophosphonyl)acetate, which, after treatment with o-cresol and Et$_3$N in benzene at 0 °C, gave ethyl 2-((bis(o-tolyloxy))phosphoryl)acetate (36) in 75% yield over two steps (Scheme 13).$^{25}$

Primary alcohol 35 was treated with TPAP$^{24}$ to provide the aldehyde, which reacted with β-ketophosphonate 36 in the presence of NaH in THF to give (Z)-α,β-unsaturated ester 37 (Z:E >95:05) in 84% yield over two steps (Scheme 14). The (Z)-geometry for ester 37 was confirmed
by coupling constant analysis. Ester 37 was most efficiently converted to (−)-pironetin (1) after treatment with 1% HCl/EtOH at ambient temperature (89% yield). 1-7

Scheme 14. Completion of the synthesis of pironetin.

The spectroscopic and physical data for synthetic 1 [1H and 13C NMR, IR, [α]20D, Rf] were identical in all respects with the published data. 1-4 In summary, a convergent and efficient total synthesis of (−)-pironetin has been accomplished. The synthesis required 19 steps from oxazolidinone (S)-9 and produced the desired product in 11% overall yield. This approach compares very well with other published routes, being one of the shortest approaches to (−)-pironetin. As a result, the route presented here is, in principle, readily applicable for the preparation of additional analogues of pironetin. 26

Experimental Section

General Procedure. All reactions were carried out under an atmosphere of argon or nitrogen in flame-dried glassware with magnetic stirring. Dichloromethane, triethylamine, 2,6-lutidine, diisopropylamine, dimethylformamide and N-methylpyrrolidone were distilled from CaH2. Dimethyl sulfoxide was distilled under reduced pressure from calcium hydride and stored over molecular sieves. THF and toluene were distilled from sodium/benzophenone ketyl. Oxalyl chloride was distilled immediately prior to use. MeOH was distilled from Mg(OMe)2. Petrol refers to the fraction boiling between 40-60 °C. Purification of reaction products was carried out by flash chromatography using silica-gel (230-400 mesh). Analytical thin layer chromatography was performed on silica gel 60 and GF (5-40-μm thickness) plates. Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain or
phosphomolybdic acid followed by heating or I₂ staining. ¹H-NMR spectra were taken in CDCl₃ at 300 MHz or at 500 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm) unless otherwise indicated. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, ap t = apparent triplet, m = multiplet, br = broad, td = triplet of doublets, quint d = quintet of doublets, coupling constant(s) in Hz; integration). Proton-decoupled ¹³C-NMR spectra were taken in CDCl₃ at 75 MHz spectrometer and are recorded in ppm.

(S)-3-((2S,3R)-5-(4-Methoxybenzyloxy)-3-hydroxy-2-methylpentanoyl)-4-benzylloxazolidin-2-one (14). Di-n-butylborol trifluoromethanesulfonate (0.78 mL, 3.15 mmol) was added to a solution of (S)-4-benzyl-3-propionyloxazolidin-2-one 14 (0.61 g, 2.62 mmol) in 7 mL of CH₂Cl₂ at such a rate to maintain the internal temperature below +3 °C (type K thermocouple thermometer). Triethylamine (0.48 mL, 3.41 mmol) was then added dropwise (internal temperature below +4 °C). The resulting yellow solution was then cooled to −78 °C and aldehyde 8 (0.56 g, 2.89 mmol) in 6 mL of CH₂Cl₂ was added slowly (internal temperature below −70 °C). After 20 min, the solution was warmed to 0 °C and stirred at that temperature for 1 h. The reaction was quenched by the addition of 3 mL of pH 7.0 aqueous phosphate buffer solution and 9 mL of MeOH (internal temperature below +10 °C, bath temperature = -10 °C). A solution of 12 mL of MeOH and 8 mL of 30% aqueous H₂O₂ was added carefully (internal temperature below +10 °C) and the resulting yellow solution was stirred at 0 °C for 1 h. The volatiles were removed at aspirator pressure and the residue was extracted with three 15 mL portions of Et₂O. The combined organic extracts were washed with 20 mL of saturated aqueous NaHCO₃ and 20 mL of brine. The organic solution was dried over anhydrous MgSO₄ and purified by flash column chromatography (30% EtOAc/hexanes) to give 0.974 g of the syn aldol adduct 14 as a colorless oil (87% yield, >95:5 diastereoselectivity). Rf 0.34 (50% EtOAc/hexanes); [α]D +51.5° (c 1.15, CH₂Cl₂); IR νmax (film, cm⁻¹) 3489, 3031, 2938, 2866, 1774, 1691, 1609, 1511, 1454, 1243, 1207, 1104; ¹H NMR (500 MHz, CDCl₃) δ 7.28 (m, 7H), 6.87 (d, J 8.5 Hz, 2H), 4.58 (ddd, J 12.8, 7.0 and 3.4 Hz, 1H), 4.44 (s, 2H), 4.18 (m, 3H), 3.80 (m, 1H), 3.80 (s, 3H), 3.68 (m, 1H), 3.63 (m, 1H), 3.34 (br s, 1H), 3.25 (dd, J 13.4 and 3.1 Hz, 1H), 2.78 (dd, J 13.4 and 9.5 Hz, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.28 (d, J 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 176.6, 159.2, 153.1, 135.1, 130.2, 129.4, 129.3, 129.0, 127.4, 113.8, 72.9, 70.5, 68.1, 66.1, 55.3 (55.278), 55.3 (55.271), 42.5, 37.8, 33.7, 11.1; Anal. calcd. for C₂₄H₂₉NO₆: C 67.43, H 6.84, N 3.28; Found: C 67.21, H 6.88, N 3.35; HRMS calcd. for C₂₄H₂₉NO₆: 427.1995; found: 427.1994.

(2S,3R)-5-(4-Methoxybenzyloxy)-3-hydroxy-N-methoxy-N,2-dimethylpentanamide. To a suspension of N,O-dimethylhydroxylamine hydrochloride (0.401 g, 4.11 mmol) in 4 mL of THF at 0 °C was added 2.1 mL (4.15 mmol) of a 2.0 M solution of trimethylaluminum in toluene (gas evolution). The resulting solution was stirred at ambient temperature for 30 min, and then cooled to -15 °C. A solution of β-hydroxy imide 14 (0.585 mg, 1.37 mmol) in 3 mL of THF was added by cannula and the resulting mixture was stirred at 0 °C for 2 h. This solution was transferred by cannula to a well-stirred mixture of 15 mL of CH₂Cl₂ and 30 mL of 0.5 N aq. HCl. After the
mixture was stirred at 0 °C for 1 h, the organic phase was separated. The aqueous phase was extracted with three 25 mL portions of CH₂Cl₂. The combined organic extracts were dried over anhydrous MgSO₄, filtered, concentrated and purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give the desired Weinreb amide (0.254 g, 91%) as a colorless oil: \( R_f 0.23 \) (50% EtOAc/hexanes); \( [\alpha]_D^2 +4.48^\circ \) (c 1.26, CH₂Cl₂); IR \( \nu_{\text{max}} \) (film, cm\(^{-1}\)) 3440, 2934, 2868, 1747, 1634, 1514, 1462, 1175, 1086; \( ^1H \) NMR (500 MHz, CDCl₃) \( \delta \) 7.25 (d, 2H, \( J \) 8.8 Hz), 6.87 (d, \( J \) 8.5 Hz, 2H), 4.45 (s, 2H), 4.03 (dt, \( J \) 9.2 and 3.7 Hz, 1H), 3.93 (s, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.64 (m, 1H), 3.18 (s, 3H), 2.91 (br s, 1H), 1.82 (m, 1H), 1.68 (m, 1H), 1.19 (d, \( J \) 7.0 Hz, 3H); \( ^13C \) NMR (125 MHz, CDCl₃) \( \delta \) 177.8, 159.1, 130.3, 129.3, 113.7, 72.8, 70.4, 68.0, 61.5, 55.2, 39.5, 34.0, 31.9, 11.2.

(2S,3R)-5-(4-Methoxybenzyl oxygen)-3-(tert-Butyldimethylsilyloxy)-N-methoxy-N,2-dimethylpentanamide (15). To a solution of the previously prepared Weinreb amide (0.743 g, 2.39 mmol) and 2,6-lutidine (0.38 mL, 3.34 mmol) in CH₂Cl₂ (5 mL) at 0 °C, TBSOTf (0.69 mL, 2.87 mmol) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C before it was diluted with CH₂Cl₂ (10 mL) and saturated aqueous NaHCO₃ solution (10 mL). The organic layer was separated, and the aqueous layer was further extracted with CH₂Cl₂ (2 x 15 mL). All the organic layers were combined and dried with MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (15% EtOAc/hexanes) to give the desired product 15 (0.82 g, 89%) as a colorless oil: \( R_f 0.39 \) (30% EtOAc/hexanes); \( [\alpha]_D^2 +4.27^\circ \) (c 1.17, EtOH); IR \( \nu_{\text{max}} \) (film, cm\(^{-1}\)) 3488, 2954, 2862, 1658, 1616, 1503, 1461, 1379, 1299, 1249, 1175, 1100; \( ^1H \) NMR (500 MHz, CDCl₃) \( \delta \) 7.24 (d, \( J \) 8.8 Hz, 2H), 6.86 (d, \( J \) 8.5 Hz, 2H), 4.42 (d, \( J \) 11.7 Hz, 1H), 4.39 (d, \( J \) 11.7 Hz, 1H), 4.02 (dt, \( J \) 7.8 and 5.0 Hz, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 3.56 (dt, \( J \) 9.0 and 7.1 Hz, 1H), 3.49 (dt, \( J \) 9.3 and 7.0 Hz, 1H), 3.14 (s, 3H), 1.83 (m, 2H), 1.13 (d, \( J \) 7.1 Hz, 3H), 0.88 (s, 9H), 0.054 (s, 3H), 0.042 (s, 3H); \( ^13C \) NMR (125 MHz, CDCl₃) \( \delta \) 176.6, 159.0, 130.6, 129.3, 115.9, 130.6, 129.3, 113.7, 113.3, 112.5, 66.2, 61.2, 55.2, 41.2, 35.4, 32.0, 25.9, 18.0, 14.5, -4.4, -4.5; Anal. calcd. for C₂₂H₃₉NO₅Si: C 62.08, H 9.24, N 3.29; found: C 61.93, H 9.31, N 3.38; HRMS calcd. for C₂₂H₃₉NO₅Si: 425.2597; found: 425.2598.

(2S,3R)-5-(4-Methoxybenzyl oxy)-3-(tert-Butyldimethylsilyloxy)-2-methylpentanal (16). To a stirred solution of Weinreb amide 15 (0.587 g, 1.39 mmol) in toluene (5 mL) at 0 °C was added DIBAL-H (1.0 M solution in toluene, 0.49 mL, 2.77 mmol). After 30 minutes at 0 °C, EtOAc (3.0 mL) was added followed by aqueous sodium tartrate (0.5 M, 5.0 mL) and the solution was warmed to ambient temperature and stirred for 30 min. Additional sodium tartrate (0.5 M, 5.0 mL) was added and the organic layer was diluted with CH₂Cl₂ (10 mL). The aqueous layer was further extracted with CH₂Cl₂ (2 x 15 mL). The aqueous layer was combined and dried with MgSO₄, filtered, and concentrated in vacuo to give aldehyde 16 (0.465 g, 92%) as a colorless oil: \( R_f 0.47 \) (20% EtOAc/hexanes); \( [\alpha]_D^2 +44.7^\circ \) (c 1.00, CH₂Cl₂); IR \( \nu_{\text{max}} \) (film, cm\(^{-1}\)) 2953, 2850, 2711, 1773, 1614, 1583, 1511, 1459, 1366, 1299, 1248, 1171; \( ^1H \) NMR (300 MHz, C₆D₆) \( \delta \) 9.61 (s, 1H), 7.20 (d, \( J \) 8.4 Hz, 2H), 6.81 (d, \( J \) 8.0 Hz, 2H), 4.28 (m, 1H), 4.30 (d, \( J \) 11.7 Hz, 1H), 4.24 (d, \( J \) 11.7 Hz, 1H), 3.33 (dt, \( J \) 9.5 and 6.4 Hz, 1H), 3.29 (s, 3H),
3.24 (dt, J 9.5 and 5.7 Hz, 1H), 2.15 (ddd, J 14.1, 7.0 and 3.5 Hz, 1H), 1.67 (q, J 6.2 Hz, 2H), 0.97 (d, J 7.0 Hz, 3H), 0.90 (s, 9H), 0.036 (s, 3H), 0.008 (s, 3H); 13C NMR (75 MHz, CD6D) δ 203.9, 160.3, 131.4, 129.9, 114.6, 73.2, 66.6, 55.1, 51.9, 35.4, 26.3, 18.5, 8.0, -4.1, -4.3;

Anal. calcd. for C20H34O4Si: C 65.53, H 9.35; found: C 65.79, H 9.3; HRMS calcd. for C20H34O4Si (M+-H2O): 348.2121; found: 348.2145.

(R)-3-((2R,3S,4R,5R)-7-(4-Methoxybenzoyloxy)-5-(tert-Butyldimethylsilyloxy)-3-hydroxy-2,4-dimethylheptanoyl)-4-benzoxazolidin-2-one (17).

Di-n-butylboryltrifluoromethanesulfonate (0.53 mL, 2.14 mmol) was added to a solution of (R)-4-benzyl-3-propionyloxazolidin-2-one 9 (0.415 g, 1.78 mmol) in 7 mL of CH2Cl2 at such a rate to maintain the internal temperature below +3 °C (type K thermocouple thermometer). Diisopropylethylamine (0.40 mL, 2.31 mmol) was then added dropwise (internal temperature below +4 °C). The resulting yellow solution was then cooled to –78 °C and aldehyde 16 (0.50 g, 1.37 mmol) in 2 mL of CH2Cl2 was added slowly (internal temperature below –70 °C). After 20 min, the solution was warmed to 0 °C and stirred at that temperature for 1 h. The reaction was quenched by the addition of 3 mL of pH 7.0 aqueous phosphate buffer solution and 9 mL of MeOH (internal temperature below +10 °C, bath temperature = -10 °C). A solution of 12 mL of MeOH and 8 mL of 30% aqueous H2O2 was added carefully (internal temperature below +10 °C) and the resulting yellow solution was stirred at 0 °C for 1 h. The volatiles were removed at aspirator pressure and the residue was extracted with three 15 mL portions of Et2O. The combined organic extracts were washed with 20 mL of saturated aqueous NaHCO3 and 20 mL of brine. The organic solution was dried over anhydrous MgSO4 and purified by flash column chromatography (35% EtOAc/hexanes) to give 0.69 g of the aldol adduct 17 as a colorless oil (84% yield, >95:5 diastereoselectivity). Rf 0.44 (30% EtOAc/hexanes); IR νmax (film, cm⁻¹) 3463, 3036, 2928, 2856, 1784, 1701, 1608, 1511, 1454, 1387, 1294, 1243, 1212; 1H NMR (300 MHz, CDCl3) δ 7.27 (m, 7H), 6.87 (d, J 8.8 Hz, 2H), 4.67 (m, 1H), 4.44 (d, J 11.7 Hz, 1H), 4.38 (d, J 11.7 Hz, 1H), 4.27 (br s, 1H), 4.17 (m, 2H), 4.05 (dt, J 9.1 and 3.2 Hz, 1H), 4.01 (dt, J 10.2 and 1.7 Hz, 1H), 3.86 (qd, J 6.8 and 1.6 Hz, 1H), 3.80 (s, 3H), 3.49 (m, 2H), 3.35 (dd, J 13.2 and 3.3 Hz, 1H), 2.74 (dd, J 13.4 and 9.7 Hz, 1H), 1.83 (m, 3H), 1.20 (d, J 7.0 Hz, 3H), 0.88 (s, 9H), 0.86 (d, J 7.0 Hz, 3H), 0.12 (s, 3H), 0.065 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 176.0, 159.2, 153.3, 135.6, 130.5, 129.5, 129.3, 129.0, 127.3, 113.8, 73.4, 73.0, 72.5, 66.6, 66.1, 55.8, 55.2, 40.6, 39.7, 37.6, 31.9, 25.7, 17.8, 12.1, 8.2, -4.6, -5.1.

(3R,4S,5R,6R)-6-(2-(4-Methoxybenzoyloxy)ethyl)-4-hydroxy-3,5-dimethyl-tetrahydropyran-2-one (12). To a solution of 235 mg (0.393 mmol) of aldol adduct 17 in 4 mL of acetonitrile at 0 °C was added 4.2 mL of freshly prepared HF solution (stock solution prepared from 0.50 mL of aqueous HF, 8.6 mL of CH3CN, and 0.90 mL of H2O). After a total reaction time of 6 h, the solution was poured into 10 mL each of CH2Cl2 and saturated aqueous NaHCO3. The aqueous layer was extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were dried over anhydrous MgSO4, filtered, and concentrated in vacuo to afford a yellow oil (0.18 g, 0372 mmol). This product was used immediately without further purification. To a solution of the yellow oil in 6 mL of THF at 0 °C were added immediately without further purification.
and 0.043 g of LiOH (0.744 mmol, 0.2 M in H₂O). The mixture was stirred for 15 min at 0 °C and was quenched with 5 mL of aqueous 1.5 M Na₂SO₃. After 5 min, the reaction mixture was poured into 30 mL each of CH₂Cl₂ and H₂O. The aqueous layer was acidified to pH 3.0 with aqueous 0.1 M HCl and was extracted with CH₂Cl₂ (3 x 10 mL). The CH₂Cl₂ layers were dried over anhydrous MgSO₄, filtered, and concentrated in vacuo to give carboxylic acid 18 (0.085 g, 70% over two steps).

A solution of carboxylic acid 18 (85 mg) in 5 mL of benzene was maintained under reflux for 6 h. The solvent was removed under reduced pressure and the resulting yellow oil was purified by flash column chromatography (45% EtOAc/hexanes) to give 63 mg of lactone 12 as a colorless oil (56% yield over 3 steps).

Rf 0.21 (50% EtOAc/hexanes); [α]D +66.6° (c 1.05, CH₂Cl₂); IR νmax (film, cm⁻¹) 3432, 2916, 2848, 1716, 1612, 1516, 1464, 1361, 1299, 1253, 1099; 1H NMR (500 MHz, C₆D₆) δ 7.19 (d, J 8.5 Hz, 2H), 6.80 (d, J 8.5 Hz, 1H), 4.28 (d, J 11.6 Hz, 1H), 4.23 (d, J 11.6 Hz, 1H), 4.08 (ddd, J 9.3, 4.6 and 2.4 Hz, 1H), 3.47 (td, J 9.1 and 4.5 Hz, 1H), 3.31 (m, 1H), 3.28 (s, 3H), 2.99 (dd, J 10.4 and 4.4 Hz, 1H), 2.15 (qd, J 10.4 and 7.1 Hz, 1H), 1.73 (m, 1H), 1.46 (m, 1H), 1.39 (m, 1H), 1.34 (br s, 1H), 1.23 (d, J 6.8 Hz, 3H), 0.59 (d, J 7.1 Hz, 3H); 13C NMR (75 MHz, C₆D₆) δ 172.1, 159.9, 131.0, 129.5, 114.1, 75.8, 73.5, 72.9, 65.8, 54.6, 39.8, 33.4, 33.1, 14.1, 14.3; MS (m/z) 308 (4), 203 (4), 176 (43), 157 (74), 121 (100), 109 (10), 91 (10), 69 (28), 57 (19), 41 (9); HRMS calcd. for C₁₇H₄₅O₅: 308.1624; found: 308.1624.

(R)-3-((2R,3S,4R,5R)-7-(4-Methoxybenzyloxy)-5-(tert-Butyldimethylsilyloxy)-3-methoxy-2,4-dimethylheptanoyl)-4-benzyloxazolidin-2-one (19). To a solution of aldol 17 (0.090 g, 0.15 mmol) in CH₂Cl₂ (5 mL) at ambient temperature under argon were added proton sponge (0.161 g, 0.75 mmol) and Me₃OBF₄ (0.111 g, 0.752 mmol), and the heterogeneous reaction mixture was stirred with protection from light for 48 h. The light brown reaction mixture was poured into CH₂Cl₂ (10 mL) and was washed with cold aqueous 1 M HCl (2 x 5 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography (15% EtOAc/hexanes) afforded 0.055 g (60%) of 19 as a clear oil: Rf 0.65 (10% EtOAc/hexanes); 1H NMR (300 MHz, CDCl₃) δ 7.28 (m, 7H), 6.87 (d, J 8.8 Hz, 2H), 4.56 (m, 1H), 4.44 (d, J 11.7 Hz, 1H), 4.38 (d, J 11.7 Hz, 1H), 4.15 (dt, J 9.0 and 2.0 Hz, 1H), 4.12 (m, 2H), 3.95 (qd, J 6.8 and 2.8 Hz, 1H), 3.80 (s, 3H), 3.60 (dd, J 9.1 and 2.9 Hz, 1H), 3.38 (m, 3H), 3.35 (s, 3H), 2.78 (dd, J 13.4 and 9.7 Hz, 1H), 1.82 (m, 2H), 1.58 (m, 1H), 1.19 (d, J 6.6 Hz, 3H), 0.87 (s, 3H), 0.86 (d, J 7.0 Hz, 3H), 0.057 (s, 3H), 0.046 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 176.5, 135.6, 129.5, 129.2, 129.0, 127.4, 113.9, 82.9, 72.6, 69.1, 67.1, 65.9, 59.7, 56.1, 55.2, 41.1, 40.2, 37.6, 35.9, 29.6, 25.9, 18.2, 9.6, 9.0, -3.6, -4.6.

(2S,3R,4R,5R)-7-(4-Methoxybenzyloxy)-5-(tert-Butyldimethylsilyloxy)-2,4-dimethylheptane-1,3-diol (20). To a solution of aldol 17 (110 mg, 0.184 mmol) and MeOH (8 µL, 0.184 mmol) in THF (1.0 mL) at 0 °C was slowly added a 1.0 M solution of LiBH₄ in THF (0.1 mL, 0.184 mmol) (gas evolution). After stirring for 1 h at 0 °C the reaction was quenched by the addition of 1.5 mL of 1.0 M aqueous sodium potassium tartrate solution and stirred for an additional 10 min. The mixture was then diluted with 5 mL of CH₂Cl₂ and 1.5 mL of 1.0 M aqueous sodium potassium tartrate solution. The layers were separated and the aqueous layer was...
extracted with two 5 mL portions of CH₂Cl₂. The combined organic extracts were washed with 5 mL of brine, dried over anhydrous MgSO₄, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (25% EtOAc/hexanes) to give diol 20 (0.072 g, 89%) as a viscous oil. \( R_f \) 0.50 (50% EtOAc/hexanes); [\( \alpha \)\]D +31.4° (c 1.11, CH₂Cl₂); IR \( \nu_{\text{max}} \) (film, cm⁻¹) 3421, 2956, 2929, 2858, 1721, 1612, 1514, 1465, 1382, 1361, 1300, 1250, 1175, 1087; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.25 (d, \( J \) 8.8 Hz, 2H), 6.88 (d, \( J \) 8.5 Hz, 2H), 4.56 (br s, 1H), 4.45 (d, \( J \) 11.5 Hz, 1H), 4.39 (d, \( J \) 11.5 Hz, 1H), 3.97 (dt, \( J \) 9.0 and 3.2 Hz, 1H), 3.93 (dd, \( J \) 10.3 and 1.7 Hz, 2H), 3.81 (s, 3H), 3.79 (dd, \( J \) 10.5 and 3.6 Hz, 1H), 3.67 (dd, \( J \) 10.6 and 5.5 Hz, 1H), 3.53 (m, 2H), 2.81 (br s, 1H), 1.91 (m, 1H), 1.85 (m, 2H), 1.65 (m, 1H), 0.95 (d, \( J \) 6.8 Hz, 3H), 0.89 (s, 9H), 0.73 (d, \( J \) 7.1 Hz, 3H), 0.12 (s, 3H), 0.066 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 159.2, 130.5, 129.3, 113.8, 76.3, 75.1, 72.6, 68.0, 66.6, 55.3, 39.7, 36.2, 31.0, 25.7, 17.8, 13.5, 8.3, -4.4, -5.1; HRMS calcd. for C₂₃H₄₂O₅Si: 426.2802; found: 426.1554.

(2\(^S\),3\(^R\),4\(^R\),5\(^R\))-7-(4-Methoxybenzyloxy)-5-(tert-Butyldimethylsilyloxy)-3-hydroxy-2,4-dimethylheptyl 4-methylbenzenesulfonate (21).

To a solution of diol 20 (0.036 g, 0.082 mmol) in CH₂Cl₂ (1 mL) were added \( p \)-toluenesulfonyl chloride (0.017 g, 0.090 mmol), triethylamine (114 \( \mu \)L, 0.82 mmol), and 4-(dimethylamino)pyridine (0.002 g). The mixture was stirred for 2 h at 25 °C and then diluted with ethyl acetate (2 mL). The organic layer was washed with brine, dried, and concentrated. The crude product was chromatographed on silica gel (15% EtOAc/hexanes) to afford tosylate 21 (0.043 g, 89%) as a colorless oil. \( R_f \) 0.69 (50% EtOAc/hexanes); [\( \alpha \)\]D +19.9° (c 1.00, EtOH); IR \( \nu_{\text{max}} \) (film, cm⁻¹) 3465, 2956, 2929, 2858, 1721, 1612, 1514, 1465, 1361, 1300, 1246, 1175, 1099; \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.79 (d, \( J \) 8.4 Hz, 2H), 7.32 (d, \( J \) 7.7 Hz, 2H), 7.25 (d, \( J \) 8.8 Hz, 2H), 6.88 (d, \( J \) 8.8 Hz, 2H), 4.44 (d, \( J \) 11.3 Hz, 1H), 4.38 (d, \( J \) 11.3 Hz, 1H), 4.14 (br s, 1H), 4.09 (dd, \( J \) 9.5 and 7.3 Hz, 1H), 3.93 (m, 2H), 3.81 (s, 3H), 3.68 (dd, \( J \) 10.1 and 1.3 Hz, 2H), 3.50 (m, 2H), 2.43 (s, 3H), 1.81 (m, 4H), 0.86 (s, 9H), 0.83 (d, \( J \) 6.6 Hz, 3H), 0.68 (d, \( J \) 7.0 Hz, 3H), 0.084 (s, 3H), 0.046 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 159.2, 144.5, 133.3, 130.5, 129.7, 129.3, 113.7, 74.8, 73.7, 72.5, 72.0, 66.5, 55.3, 39.4, 35.4, 31.1, 25.7, 21.6, 17.8, 13.3, 8.23, -4.46, -5.12; Anal. calcd. for C₃₀H₄₈O₇SSi: C 62.04, H 8.33; Found: C 61.89, H 8.41; HRMS calcd. for C₃₀H₄₈O₇SSi: 580.2890; found: 580.2881.

(2\(^S\),3\(^R\),4\(^R\),5\(^R\))-7-(4-Methoxybenzyloxy)-5-(tert-Butyldimethylsilyloxy)-3-methoxy-2,4-dimethylheptyl 4-methylbenzenesulfonate (5a).

To a solution of tosylate 21 (0.176 g, 0.30 mmol) in CH₂Cl₂ (3 mL) at ambient temperature under argon were added proton sponge (0.382 g, 1.78 mmol) and Me₃OBF₄ (0.219 g, 1.48 mmol), and the heterogeneous reaction mixture was stirred with protection from light for 12 h. The light brown reaction mixture was poured into CH₂Cl₂ (10 mL) and was washed with cold aqueous 1 M HCl (2 x 10 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography (15% EtOAc/hexanes) afforded 0.160 g (89%) of 5a as a clear oil: \( R_f \) 0.56 (30% EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.80 (d, \( J \) 8.3 Hz, 2H), 7.34 (d, \( J \) 8.0 Hz, 2H), 7.24 (d, \( J \) 8.6 Hz, 2H), 6.86 (d, \( J \) 8.8 Hz, 2H), 4.43 (d, \( J \) 11.5 Hz, 1H), 4.38 (d, \( J \) 11.5 Hz, 1H), 4.06 (m, 1H), 4.04 (ap d, \( J \) 8.6 Hz, 1H), 3.96 (dd, \( J \) 9.3 and 6.4 Hz, 1H), 3.80 (s,
3H), 3.40 (m, 2H), 3.32 (s, 3H), 3.25 (dd, J 9.5 and 1.7 Hz, 1H), 2.45 (s, 3H), 2.00 (m, 1H), 1.81 (m, 1H), 0.87 (s, 9H), 0.76 (d, J 6.9 Hz, 3H), 0.67 (d, J 6.9 Hz, 3H), 0.061 (s, 3H), 0.054 (s, 3H); 13C NMR (125 MHz, CDCl 3) δ 159.0, 144.7, 133.2, 130.5, 129.8, 129.1, 127.9, 113.7, 80.4, 72.7, 72.6, 69.2, 67.0, 60.8, 55.2, 40.2, 35.6, 35.1, 26.0, 21.6, 18.3, 9.3, 9.1, -3.35 -4.2.

2-Methyl-3-phenylpropyl 4-methylbenzenesulfonate (22). To a solution of 2-methyl-3-phenylpropan-1-ol (1.37 g, 9.13 mmol) in CH 2Cl 2 (30 mL) were added p-toluenesulfonyl chloride (2.61 g, 13.7 mmol), triethyl amine (12.7 mL, 91.33 mmol), and 4-(dimethylamino)pyridine (0.112 g). The mixture was stirred for 12 h at 25 °C and then diluted with ethyl acetate (2 mL). The organic layer was washed with brine, dried, and concentrated. The crude product was chromatographed on silica gel (2% EtOAc/hexanes) to afford tosylate 21 (2.64 g, 95%) as a colorless oil. Rf 0.62 (50% EtOAc/hexanes); IR ν max (film, cm⁻¹) 3066, 3028, 2966, 2930, 2737, 2583, 2527, 2284, 1919, 1814, 1740, 1658, 1597, 1497, 1453, 1361, 1293; 1H NMR (300 MHz, CDCl 3) δ 7.78 (d, J 8.4 Hz, 2H), 7.34 (d, J 8.1 Hz, 2H), 7.21 (m, 2H), 7.05 (m, 3H), 3.89 (dd, J 9.3 and 5.7 Hz, 1H), 3.84 (dd, J 9.3 and 5.7 Hz, 1H), 2.68 (dd, J 13.6 and 6.6 Hz, 1H), 2.46 (s, 3H), 2.40 (dd, J 13.5 and 7.7 Hz, 1H), 2.07 (m, 1H), 0.89 (d, J 6.6 Hz, 3H); 13C NMR (75 MHz, CDCl 3) δ 144.7, 139.2, 133.3, 129.8, 129.1, 128.3, 127.9, 113.7, 80.4, 72.7, 72.6, 69.2, 67.0, 60.8, 55.2, 40.2, 35.6, 35.1, 26.0, 21.6, 18.3, 9.3, 9.1, -3.35 -4.2.

1-(3-iodo-2-methylpropyl)benzene (28). To a solution of triphenylphosphine (1.54 g, 5.86 mmol) in CH 2Cl 2 (30 mL), at 0 °C, were added imidazole (0.399 g, 5.86 mmol) and iodine (1.49 g, 5.86 mmol). The resulting solution was stirred at 0 °C for 10 min, and then a solution of 2-methyl-3-phenylpropan-1-ol (1.27 g, 4.88 mmol) in CH 2Cl 2 (1 mL) was added. After the mixture was stirred for 2 h at ambient temperature, the solvent was removed. Purification by flash column chromatography on silica gel (5% EtOAc/hexanes) gave iodide 28 (1.98 g, 90%) as a colorless oil: R f 0.38 (hexanes); IR ν max (film, cm⁻¹) 3085, 3060, 3022, 2960, 2924, 2842, 1945, 1876, 1801, 1603, 1491, 1453, 1373, 1311, 1269; 1H NMR (300 MHz, CDCl 3) δ 7.29 (m, 2H), 7.20 (m, 3H), 3.22 (dd, J 9.5 and 4.8 Hz, 1H), 3.11 (dd, J 9.5 and 5.5 Hz, 1H), 2.67 (dd, J 13.5 and 7.3 Hz, 1H), 2.58 (dd, J 13.4 and 6.8 Hz, 1H), 1.74 (m, 1H), 1.01 (d, J 6.6 Hz, 3H); 13C NMR (75 MHz, CDCl 3) δ 139.8, 129.1, 128.4, 126.2, 42.5, 36.7, 20.7, 17.1.

(E)-1-(2-methylhex-4-enyl)benzene (23). Procedure 1: A solution of (E)-propenyl-magnesium bromide (2.47 mmol) was added dropwise to a solution of 22 (0.150 g, 0.49 mmol) and recrystallized CuI (0.188 g, 0.99 mmol) in dry THF (1 mL) at -40 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to 0 °C, stirred for 12 h at this temperature, quenched with methanol (0.5 mL) and concentrated in vacuo. The residue was diluted with ether (10 mL) and filtered through a short pad of silica gel. Evaporation of ether and purification by flash column chromatography on silica gel (5% EtOAc/hexanes) gave iodide 28 (1.98 g, 90%) as a colorless oil: Rf 0.38 (hexanes); IR ν max (film, cm⁻¹) 3085, 3060, 3022, 2960, 2924, 1945, 1876, 1801, 1603, 1491, 1453, 1373, 1311, 1269; 1H NMR (300 MHz, CDCl 3) δ 7.29 (m, 2H), 7.20 (m, 3H), 3.22 (dd, J 9.5 and 4.8 Hz, 1H), 3.11 (dd, J 9.5 and 5.5 Hz, 1H), 2.67 (dd, J 13.5 and 7.3 Hz, 1H), 2.58 (dd, J 13.4 and 6.8 Hz, 1H), 1.74 (m, 1H), 1.01 (d, J 6.6 Hz, 3H); 13C NMR (75 MHz, CDCl 3) δ 139.8, 129.1, 128.4, 126.2, 42.5, 36.7, 20.7, 17.1.

(E)-1-(2-methylhex-4-enyl)benzene (23). Procedure 2: t-Butyllithium (21.7 equiv, 1.6M in pentane) was added to a solution of trans-1-bromo-1-propene (10.3 equiv) in dry THF (5 mL) at -78 °C. After 30 min, a pale yellow solution was warmed to 23 °C for 1 h, recooled to -78 °C, and added to a gray suspension of copper (I) cyanide (5.15 equiv) in THF (3 mL) at -78 °C. The resulting white suspension was stirred for 1 h
at −40 °C to −50 °C, during which time it became a gray, then black, suspension and then dark green-yellow solution. A solution of tosylate 22 (1.0 equiv) in THF (0.5 mL) was added, and the black-green solution was warmed to 0 °C. After 30 min, 1:1 saturated aqueous NH₄Cl-10% NH₄OH (1 mL) was added, and the mixture was warmed to 23 °C with vigorous stirring. After 20 min, water (3 mL) and Et₂O (3 mL) were added, the aqueous portion was extracted with Et₂O (2 x 5 mL), and the combined organic fractions were dried (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography on silica gel (1% EtOAc/hexanes) gave 23 (84%).

\[ R_f \] 0.67 (hexanes); \( ^1H \) NMR (300 MHz, CDCl₃) \( \delta \) 7.27 (m, 2H), 7.16 (m, 3H), 5.43 (m, 2H), 2.65 (dd, \( J \) 13.4 and 6.0 Hz, 1H), 2.34 (dd, \( J \) 13.4 and 8.1 Hz, 1H), 2.03 (m, 1H), 1.85 (m, 1H), 1.76 (m, 1H), 1.67 (m, 3H), 0.84 (d, \( J \) 6.6 Hz, 3H).

\( (2S,3R,4R,5R)-7-(4-Methoxybenzoyloxy)-1,5-bis(tert-Butyldimethylsilyloxy)-2,4-dimethylheptan-3-ol (26). \) To a stirred solution of diol 20 (0.444 g, 1.04 mmol) in CH₂Cl₂ (5 mL) at ambient temperature were added imidazole (0.103 g, 1.56 mmol), tert-butyldimethylsilyl chloride (0.182 g, 1.25 mmol), and DMAP (0.012 g, 10mol%) and stirring was continued for 12 h. The reaction mixture was partitioned between EtOAc and H₂O, and then the organic layer was washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated. Purification of the crude product on silica gel (5% EtOAc/hexanes) gave 26 (0.528 g, 95%) as a viscous oil: \( R_f \) 0.69 (20% EtOAc/hexanes); [\( \alpha \)]D +18.8° (c 1.06, CH₂Cl₂); IR \( \nu \) max (film, cm⁻¹) 3494, 2959, 2859, 1734, 1615, 1516, 1463, 1385, 1363, 1250, 1173; \( ^1H \) NMR (300 MHz, CDCl₃) \( \delta \) 7.26 (d, \( J \) 8.4 Hz, 2H), 6.88 (d, \( J \) 8.8 Hz, 2H), 4.45 (d, \( J \) 11.7 Hz, 1H), 4.39 (d, \( J \) 11.3 Hz, 1H), 4.05 (dt, \( J \) 6.2 and 2.6 Hz, 1H), 3.91 (br s, 1H), 3.80 (s, 3H), 3.77 (br s, 1H), 3.68 (dd, \( J \) 9.9 and 6.0 Hz, 1H), 3.58 (dd, \( J \) 9.9 and 5.9 Hz, 1H), 3.51 (m, 2H), 1.84 (q, \( J \) 6.5 Hz, 2H), 1.76 (m, 1H), 1.68 (m, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.85 (d, \( J \) 6.6 Hz, 3H), 0.73 (d, \( J \) 7.0 Hz, 3H), 0.11 (s, 3H), 0.059 (s, 9H); \( ^13C \) NMR (75 MHz, CDCl₃) \( \delta \) 159.1, 130.6, 129.2, 113.7, 73.2, 73.1, 72.5, 67.4, 66.9, 55.2, 39.9, 37.4, 32.3, 25.9, 25.8, 18.3, 18.0, 12.3, 8.6, -4.9, -5.4, -5.5; Anal. calcd. for C₂₉H₅₆O₅Si₂: C 64.39, H 10.43; Found: C 64.11, H 10.25; HRMS calcd. for C₂₉H₅₆O₅Si₂: 540.3666; found: 540.3663.

\( 1-(((3R,4R,5R,6S)-3,7-bis(tert-Butyldimethylsilyloxy)-5-methoxy-4,6-dimethylheptyl oxy)methyl)-4-methoxybenzene (27). \) To a solution of alcohol 26 (0.664 g, 1.23 mmol) in CH₂Cl₂ (6 mL) at ambient temperature under argon were added proton sponge (2.108 g, 9.84 mmol) and Me₃OBF₄ (1.273 g, 8.61 mmol), and the heterogeneous reaction mixture was stirred with protection from light for 12 h. The light brown reaction mixture was poured into CH₂Cl₂ (10 mL) and was washed with cold aqueous 1 M HCl (2 x 10 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and evaporated. Purification by flash chromatography (5% EtOAc/hexanes) afforded 0.60 g (88%) of 27 as a clear oil: \( R_f \) 0.50 (EtOAc/hexanes 10%); [\( \alpha \)]D +4.54° (c 1.10, CH₂Cl₂); IR \( \nu \) max (film, cm⁻¹) 2950, 2927, 2855, 1615, 1586, 1514, 1462, 1390, 1361, 1307, 1253, 1074; \( ^1H \) NMR (500 MHz, CDCl₃) \( \delta \) 7.26 (d, \( J \) 8.7 Hz, 2H), 6.87 (d, \( J \) 8.8 Hz, 2H), 4.44 (d, \( J \) 11.4 Hz, 1H), 4.40 (d, \( J \) 11.4 Hz, 1H), 4.11 (ddd, \( J \) 8.1, 5.5 and 1.4 Hz, 1H), 3.80 (s, 3H), 3.55 (t, \( J \) 9.4 Hz, 1H), 3.47 (dd, \( J \) 9.5 and 6.0 Hz, 1H), 3.46 (s, 3H), 3.43 (m, 3H), 1.84 (m, 2H), 1.80 (m, 1H), 1.51 (m, 1H), 0.90 (s, 9H), 0.88 (s, 9H),
0.73 (d, J 6.6 Hz, 3H), 0.73 (d, J 6.93 Hz, 3H), 0.080 (s, 3H), 0.072 (s, 3H), 0.050 (s, 3H), 0.046 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 159.1, 130.7, 129.1, 113.7, 80.4, 72.6, 69.3, 67.3, 66.0, 60.7, 55.2, 40.4, 37.8, 35.9, 26.0, 25.9, 18.29, 18.26, 9.5, 9.3, -3.3, -4.2, -5.3, -5.4; HRMS calcd. for C\(_{30}\)H\(_{58}\)O\(_5\)Si\(_2\): 554.3822; found: 554.3829.

\((2S,3R,4R,5R)-7-(4-Methoxybenzyloxy)-5-(tert-butyldimethylsilyloxy)-3-methoxy-2,4-dimethylheptan-1-ol\) (24). Procedure 1. To a solution of 73 mg (0.104 mmol) of the imide 19 and 11 \(\mu\)L (0.26 mmol) of MeOH in 1 ml of THF at 0 °C was slowly added 0.13 mL (0.26 mmol) of a 1.0 M solution of LiBH\(_4\) in THF (gas evolution). After stirring for 1 h at 0 °C the reaction was quenched by the addition of 1.5 mL of 1.0 M aqueous sodium potassium tartrate solution and stirred for an additional 10 min. The mixture was then diluted with 5 mL of CH\(_2\)Cl\(_2\) and 1.5 mL of 1.0 M aqueous sodium potassium tartrate solution. The layers were separated and the aqueous layer was extracted with two 5 mL portions of CH\(_2\)Cl\(_2\). The combined organic extracts were washed with 5 mL of brine, dried over anhydrous MgSO\(_4\), and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (25% EtOAc/hexanes) to give the desired product 24 (39 mg, 84% over two steps) as a viscous oil. \(R_f\) 0.49 (50% EtOAc/hexanes).

Procedure 2. To a solution of 27 (0.457 g, 0.824 mmol) in freshly distilled THF (9 mL) in a plastic vial was added pyridine (2 mL). The reaction mixture was cooled to 0 °C and HF·Pyridine (70:30, 7.1 mL) was added dropwise. After the addition was complete the reaction was let to warm to ambient temperature and stirred for 24 h, and then transferred directly to a pipette column loaded with silica gel. Elution (20% EtOAc/hexanes) gave 24 (0.356 mg, 98% yield) as a colorless oil: IR \(\nu\)max (film, \(\text{cm}^{-1}\)) 3438, 2928, 2860, 2064, 1996, 1882, 1728, 1613, 1585, 1510, 1460, 1361, 1305; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.26 (d, J 8.8 Hz, 2H), 6.87 (d, J 8.8 Hz, 2H), 4.56 (br s, 1H), 4.45 (d, J 11.7 Hz, 1H), 4.39 (d, J 11.4 Hz, 1H), 4.11 (ddd, J 7.7, 5.9 and 1.8 Hz, 1H), 3.80 (s, 3H), 3.79 (dd, J 10.5 and 3.6 Hz, 1H), 3.67 (dd, J 10.6 and 5.5 Hz, 1H), 3.45 (s, 3H), 3.43 (m, 2H), 3.36 (dd, J 11.7 and 9.5 Hz, 1H), 1.84 (m, 3H), 1.62 (m, 1H), 0.88 (s, 9H), 0.86 (d, J 7.0 Hz, 3H), 0.76 (d, J 7.0 Hz, 3H), 0.079 (s, 3H), 0.074 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 159.1, 130.6, 129.2, 113.7, 82.6, 72.6, 69.4, 67.1, 66.7, 60.2, 55.2, 40.2, 37.3, 35.7, 26.0, 18.3, 10.0, 9.6, -3.4, -4.2.

\((3R,4R,5S,6R)-1-(4-Methoxybenzyloxy)-7-iodo-5-methoxy-4,6-dimethylheptan-3-yloxy)(tert-butyl)dimethylsilane\) (5b). To a solution of triphenylphosphine (0.164 g, 0.63 mmol) in CH\(_2\)Cl\(_2\) (1.0 mL), at 0 °C, were added imidazole (0.117 g, 1.72 mmol) and iodine (0.159 g, 0.63 mmol). The resulting solution was stirred at 0 °C for 10 min, and then a solution of alcohol 28 (0.056 g, 0.2 mmol) in CH\(_2\)Cl\(_2\) (1 mL) was added. After the mixture was stirred for 16 h at ambient temperature, the solvent was removed. Purification by flash column chromatography on silica gel (5% EtOAc/hexanes) gave iodide 5b (0.058 g, 83%) as a colorless oil: \(R_f\) 0.49 (10% EtOAc/hexanes); IR \(\nu\)max (film, \(\text{cm}^{-1}\)) 2957, 2922, 2860, 1613, 1516, 1460, 1299, 1253, 1173, 1087; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.26 (d, J 8.5 Hz, 2H), 6.87 (d, J 8.8 Hz, 2H), 4.45 (d, J 11.7 Hz, 1H), 4.39 (d, J 11.4 Hz, 1H), 4.13 (ddd, J 7.9, 5.9 and 1.6 Hz, 1H), 3.82 (s, 3H), 3.53 (s, 3H), 3.43 (m, 2H), 3.31 (dd, J 10.5 and 5.9 Hz, 1H), 3.23 (dd, J 9.6 and 6.6 Hz, 1H), 1.97 (m,
1H), 1.85 (m, 2H), 1.53 (m, 1H), 0.94 (d, J 7.0 Hz, 3H), 0.90 (s, 9H), 0.72 (d, J 7.0 Hz, 3H), 0.11 (s, 3H), 0.085 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 150.1, 130.6, 129.1, 113.7, 83.2, 72.6, 69.3, 67.1, 61.4, 51.2, 41.0, 39.4, 35.8, 26.0, 18.3, 13.6, 13.5, 9.3, -3.3,-4.1.

((3R,4R,5S,6R)-1-(4-Methoxybenzyloxy)-7-bromo-5-methoxy-4,6-dimethylheptan-3-yloxy)(tert-butyl)dimethylsilane (5c). 

Rf 0.48 (10% EtOAc/hexanes); IR νmax (film, cm⁻¹) 2960, 2925, 2870, 1615, 1514, 1460, 1300, 1253, 1178, 1100; 1H NMR (300 MHz, CDCl3) δ 7.27 (d, J 8.4 Hz, 2H), 6.87 (d, J 8.4 Hz, 2H), 4.45 (d, J 11.7 Hz, 1H), 4.39 (d, J 11.3 Hz, 1H), 4.13 (ddd, J 8.0, 5.8 and 1.7 Hz, 1H), 3.80 (s, 3H), 3.52 (s, 3H), 3.45 (m, 5H), 2.02 (m, 1H), 1.85 (m, 2H), 1.54 (m, 1H), 0.93 (d, J 7.0 Hz, 3H), 0.89 (s, 9H), 0.73 (d, J 7.0 Hz, 3H), 0.10 (s, 3H), 0.081 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 159.1, 130.6, 129.1, 113.7, 81.9, 72.6, 69.3, 67.1, 61.3, 55.3, 40.8, 38.8, 38.4, 35.8, 26.0, 18.3, 12.2, 9.3, -3.3,-4.2.

((3R,4R,5R)-1-(4-Methoxybenzyloxy)-5-methoxy-4,6-dimethylheptan-3-yloxy)(tert-butyl)dimethylsilane (29). 

Rf 0.52 (10% EtOAc/hexanes); IR νmax (film, cm⁻¹) 2956, 2929, 2853, 1705, 1612, 1514, 1465, 1365, 1178; 1H NMR (500 MHz, C6D6) δ 7.26 (d, J 8.8 Hz, 2H), 6.87 (d, J 8.8 Hz, 2H), 4.44 (d, J 11.7 Hz, 1H), 4.39 (d, J 11.4 Hz, 1H), 4.10-4.14 (m, 1H), 3.80 (s, 3H), 3.51 (s, 3H), 3.46 (s, 3H), 3.43 (m, 5H), 2.98 (dd, J 9.1 and 2.2 Hz, 1H), 1.82 (m, 3H), 1.45 (m, 1H), 1.02 (d, J 7.0 Hz, 3H), 0.88 (s, 9H), 0.82 (d, J 7.0 Hz, 3H), 0.75 (d, J 7.0 Hz, 3H), 0.075 (s, 3H), 0.069 (s, 3H); 13C NMR (75 MHz, C6D6) δ 159.1, 130.7, 129.1, 113.7, 86.6, 72.6, 69.4, 67.2, 61.2, 55.2, 40.9, 35.9, 29.8, 26.0, 18.3, 9.6, -3.4,-4.3. HRMS calcd. for C24H44O4Si: 424.3009; found: 424.3004.

tert-Butyl((3R,4R,5R,6S)-5-methoxy-1-(4-methoxyphenoxy)-4,6-dimethylnon-8-yn-3-yloxy)dimethylsilane (31). 

To a suspension of lithium acetylide-ethylenediamine complex (1.30 g, 12.7 mmol) in dry DMSO (10 mL) was slowly added a solution of 5a (1.51 g, 2.54 mmol) in dry DMSO (5 mL) at ambient temperature. Stirring was maintained at ambient temperature for 16 h, and then Et2O (10 mL), and saturated aqueous NH4Cl (10 mL) were cautiously added to the brownish reaction mixture. The aqueous layer was extracted with Et2O (3 x 10 mL), and the Et2O extracts were washed with brine (2 x 50 mL) and dried over MgSO4. Filtration and concentration under vacuum yielded a pale-yellow oil, which was purified by filtration over a plug of silica gel (5% EtOAc/hexanes) to give 31 (0.93 g, 82%). Rf 0.56 (10% EtOAc/hexanes); [α]D²⁰ = + 10.5 (c 1.43, CHCl3); IR νmax (film, cm⁻¹) 3308, 2954, 2927, 2859, 1742, 1616, 1510, 1467, 1382, 1303, 1245; 1H NMR (500 MHz, C6D6) δ 7.26 (d, J 8.8 Hz, 2H), 6.87 (d, J 8.8 Hz, 2H), 4.44 (d, J 11.7 Hz, 1H), 4.39 (d, J 11.7 Hz, 1H), 4.10-4.14 (m, 1H), 3.80 (s, 3H), 3.51 (s, 3H), 3.39-3.60 (m, 3H), 2.29 (ddd, J 16.7, 8.8 and 2.5 Hz, 1H), 2.19 (ddd, J 16.7, 6.6 and 2.5 Hz, 1H), 1.98 (t, J 2.5 Hz, 1H), 1.78-1.94 (m, 3H), 1.48-1.60 (m, 1H), 0.88 (s, 9H), 0.86 (d, J 6.9 Hz, 3H), 0.74 (d, J 7.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H); 13C NMR (75 MHz, C6D6) δ 159.1, 130.6, 129.1, 113.7, 83.9, 82.7, 72.6, 69.4, 67.2, 61.3, 55.2, 40.8, 35.9, 35.3, 26.0, 24.1, 18.3, 12.8, 9.3, -3.2,-4.2; HRMS calcd. for C26H44O4Si: 448.3008; found: 448.3004.

tert-Butyl((3R,4R,5R,6S)-5-methoxy-1-(4-methoxyphenoxy)-4,6-dimethyldec-8-yn-3-yloxy)dimethylsilane. To a cold (−78 °C), stirred solution of 1-alkyne 31 (0.35 g, 0.78 mmol) in
THF (4 mL) was added \(n\)-BuLi (0.4 mL, 2.14 M in hexanes, 0.86 mmol). The solution was allowed to warm to room temperature before adding methyl iodide (0.5 mL, 7.8 mmol). The reaction mixture was stirred at ambient temperature for 16 h. The mixture was cooled to 0 °C and quenched with saturated aqueous NH\(_4\)Cl (10 mL). The aqueous layer was extracted with Et\(_2\)O (3 x 10 mL), and the Et\(_2\)O extracts were washed with brine (2 x 50 mL) and dried over MgSO\(_4\). Filtration and concentration under vacuum yielded a pale-yellow oil used in the next step without further purification. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.08 (s, 3H), 0.10 (s, 3H), 0.74 (d, \(J \approx 7.0 \text{ Hz}\), 3H), 0.83 (d, \(J \approx 6.6 \text{ Hz}\), 3H), 0.90 (s, 9H), 1.09–1.37 (m, 2H), 1.77 (t, \(J \approx 2.4 \text{ Hz}\), 1H), 1.82–1.90 (m, 4H), 2.10–2.19 (m, 2H), 3.41–3.50 (m, 1H), 3.51 (s, 3H), 3.75 (br t, \(J \approx 6.0 \text{ Hz}\), 2H), 3.80 (s, 3H), 4.13 (br t, \(J \approx 6.4 \text{ Hz}\), 1H) 4.39 (d, \(J \approx 11.8 \text{ Hz}\), 1H), 4.45 (d, \(J \approx 11.7 \text{ Hz}\), 1H), 6.86 (d, \(J \approx 8.4 \text{ Hz}\), 2H), 7.26 (d, \(J \approx 8.3 \text{ Hz}\), 2H).

(3R,4R,5R,6S,E)-3-(tert-Butyldimethylsilyloxy)-5-methoxy-4,6-dimethyldec-8-en-1-ol (33).

To a vigorously stirred –78 ºC solution of ammonia (3 mL) in THF (3 mL) were added the previously prepared alkyne (0.27 g, 0.58 mmol) and several small pieces of lithium wire. The reaction mixture was monitored by TLC analysis. When the reaction was judged complete (6 h) the ammonia was allowed to evaporate and solid NH\(_4\)Cl was added in several small portions until the reaction mixture became colorless. The solution was transferred to a separatory funnel and shaken with saturated aqueous NH\(_4\)Cl. The organic phase was removed and the aqueous layer extracted with Et\(_2\)O (3 x 5 mL). The combined organics were washed with brine (10 mL), dried over MgSO\(_4\) and concentrated. The residue was purified by flash chromatography (20% EtOAc/hexanes) to provide the desired alcohol 33 as a colorless oil (0.15 g, 60 % yield over two steps). \(R_f\) 0.18 (20 % EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.30-5.49 (m, 2H), 4.11 (ddd, \(J \approx 7.75, 5.64 \text{ and } 2.13 \text{ Hz}\), 1H), 3.66-3.71 (m, 2H), 3.48 (s, 3H), 3.16 (dd, \(J \approx 9.1 \text{ and } 1.8 \text{ Hz}\), 1H), 2.13 (m, 1H), 2.01 (m, 1H), 1.78 (m, 2H), 1.66 (dd, \(J \approx 5.8 \text{ and } 0.5 \text{ Hz}\), 3H), 1.58-1.71 (m, 2H), 0.88 (s, 9H), 0.82 (d, \(J \approx 6.71 \text{ Hz}\), 3H), 0.76 (d, \(J \approx 7.02 \text{ Hz}\), 3H), 0.10 (s, 3H), 0.09 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 130.4, 126.4, 84.4, 49.6, 60.8, 60.0, 40.6, 38.5, 38.4, 35.5, 25.9, 18.2, 17.9, 12.8, 10.0, -3.5, -4.0.

Ethyl 2-((bis(o-tolyloxy))phosphoryl)acetate (36). Procedure 1. To a solution of imidazole (2.4 g, 35.3 mmol) in CH\(_2\)Cl\(_2\) (23 mL) was added PCl\(_3\) (1.0 mL, 11.77 mmol) followed by o-cresol (2.47 g, 35.3 mmol) at 0 ºC. After the mixture was stirred for 30 min, water (0.2 mL, 11.77 mmol) was added. The salt was filtered and treated with ethyl 2-bromoacetate (1.52 g) and triethylamine (1.93 mL) at 0 ºC. The resulting mixture was stirred for 1 h at ambient temperature, partitioned between CH\(_2\)Cl\(_2\) (10 mL) and H\(_2\)O (10 mL), and then the organic layer was washed with saturated aqueous solution of NaHCO\(_3\) (10 mL), brine, dried over anhydrous MgSO\(_4\), filtered, and evaporated. Purification of the crude product on silica gel (5% EtOAc/hexanes) gave phosphonate 36 (2.86 g, 70%) as a colorless oil.

Procedure 2. PCl\(_5\) (11.6 g, 55.7 mmol) was added to ethyl 2-(diethoxyphosphoryl)acetate (5.0 g, 22.3 mmol) at 0 ºC. When the exothermic reaction was completed, the mixture was heated at 75 ºC for 10 h. Distillation removed P(O)Cl\(_3\) and excess PCl\(_3\) and yielded the dichloride (4.45 g, 3 mmHg/105-110 ºC), which was dissolved in benzene (30 mL) and treated with a solution of o-
cresol (4.69 g, 43.4 mmol) in benzene (10 mL) and Et3N (6.1 mL, 43.4 mmol) at 0 °C. After stirring for 1 h at 25 °C, the mixture was filtered. The filtrate was diluted with EtOAc (20 mL), washed successively with 1 N NaOH (20 mL x 3), saturated NH4Cl, and brine, dried (MgSO4), and concentrated to give a pale yellow residue. Column chromatography on silica gel (5% EtOAc/hexanes) provided 36 (5.82 g, yield 75% over two steps) as a colorless oil: Rf 0.27 (25% EtOAc/hexanes); IR νmax (film, cm⁻¹): 3054, 2986, 2931, 1735, 1580, 1487, 1371; ¹H NMR (300 MHz, CDCl3) δ 7.20-7.31 (m, 2H); 7.05-7.18 (m, 6H), 4.23 (q, 2H, J 7.1 Hz), 3.34 (d, 2H, J H-P 22.0 Hz), 2.26 (s, 6H), 1.27 (t, 3H, J 7.1 Hz); 13C NMR (75 MHz, CDCl3) δ 164.5, 148.6, 148.5, 131.3, 129.0, 126.9, 125.2, 120.1, 85.6, 61.9, 34.7 (d, J C-P 136.7 Hz), 16.3, 14.1. 

(S)-4-Benzyl-3-((2S,3R,5R,6R,7R,8S,E)-5-(tert-Butyldimethylsilyloxy)-2-ethyl-3-hydroxy-7-methoxy-6,8-dimethyldodec-10-enoyl)oxazolidin-2-one (34). To a solution alcohol 33 (0.58 g, 1.7 mmol), NMO (0.32 g, 2.5 mmol) and molecular sieves 4Å (0.9 g, powder) in CH2Cl2 (20 mL) at 0 °C, was added TPAP (0.06 g, 10 mol%) in one portion. The reaction mixture was stirred at ambient temperature for 2 h, filtered and concentrated in vacuo to give aldehyde 2, used in the next step without further purification (Rf 0.52 (20% EtOAc/hexanes)). Di-n-butylboryltrifluoromethanesulfonate (0.64 mL, 2.6 mmol) was added to a solution of N-butanoyloxazolidin-2-one 3 (5.5g, 2.2 mmol) in 50 mL of CH2Cl2 at such a rate to maintain the internal temperature below +3 °C (type K thermocouple thermometer). Diisopropylethylamine (0.5 mL, 2.8 mmol) was then added dropwise (internal temperature below +4 °C). The resulting yellow solution was then cooled to −78 °C and aldehyde (0.57 g, 1.7 mmol) in 20 mL of CH2Cl2 was added slowly (internal temperature below −70 °C). After 20 min, the solution was warmed to 0 °C and stirred at that temperature for 1 h. The reaction was quenched by the addition of 10 mL of pH 7.0 aqueous phosphate buffer solution and 15 mL of MeOH (internal temperature below +10 °C, bath temperature = -10 °C). A solution of 20 mL of MeOH and 10 mL of 30% aqueous H2O2 was added carefully (internal temperature below +10 °C) and the resulting yellow solution was stirred at 0 °C for 1 h. The volatiles were removed at aspirator pressure and the residue was extracted with three 50 mL portions of Et2O. The combined extracts were washed with 50 mL of saturated aqueous NaHCO3 and 50 mL of brine. The organic solution was dried over anhydrous MgSO4 and concentrated to give 0.84 g of the syn aldol adduct 34 as a colorless oil (84% yield over two steps, >95:5 diastereoselectivity). Rf 0.30 (40% EtOAc/hexanes). 

(2R,3R,5R,6R,7R,8S,E)-3,5-bis(tert-Butyldimethylsilyloxy)-2-ethyl-7-methoxy-6,8-dimethyldodec-10-en-1-ol (35). To a solution of 34 (0.20 g, 0.36 mmol) and 2,6-lutidine (220 µL, 1.9 mmol) in CH2Cl2 (20 mL) at ambient temperature, tert-butyldimethylsilyl trifluoromethanesulphonate (TBSOTf) (450 µL, 1.8 mmol) was added dropwise. The reaction mixture was stirred for 30 min at ambient temperature before it was diluted with CH2Cl2 (50 mL) and 50 mL of saturated aqueous NaHCO3 solution. The organic layer was separated, and the aqueous layer was further extracted with CH2Cl2 (2 x 50 mL). All the organic layers were combined and dried with MgSO4, filtered, and concentrated in vacuo. The aldol prepared before (0.25 g, 3.6 mmol) was dissolved in freshly distilled THF (3 mL) under an N2 atmosphere. The solution was cooled to 0 °C and MeOH (30 µL) followed by a solution of LIBH4 (1.0 M in THF,
350 µL, 0.72 mmol) were added. The solution was stirred 2 h at 0 °C and allowed to warm to ambient temperature before an aqueous solution of Rochelle’s salt was added (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 50 mL), and the combined organic extracts were dried (MgSO₄), filtered, and concentrated to give alcohol 35 (0.15 g, 87% over two steps). Rf 0.20 (20% EtOAc/hexanes).

(2Z,4R,5R,7R,8R,9R,10S,12E)-Ethyl 5,7-bis(tert-Butyldimethylsilyloxy)-4-ethyl-9-methoxy-8,10-dimethyltetradeca-2,12-dienoate (37). To a solution alcohol 35 (0.06 g, 0.11 mmol), NMO (0.05 g, 0.38 mmol) and molecular sieves 4Å (0.10 g, powder) in CH₂Cl₂ (20 mL) at 0 oC, was added TPAP (0.01 g, 10 mol%) in one portion. The reaction mixture was stirred at ambiente temperature for 2 h, filtered and concentrated in vacuo to give an intermediate aldehyde. Rf 0.55 (20% EtOAc/hexanes). ¹H NMR spectroscopy of the unpurified aldehyde was very clean. To a stirred suspension of NaH (0.32 g, 0.8 mmol) in THF (20 mL) at 0 oC under argon was added ethyl 2-((bis(ortho-tolyloxy))phosphoryl)acetate 36 (0.35 g, 0.10 mmol). After the mixture was stirred at 0 °C for 30 min the reaction mixture was cooled to –78 °C, and then a solution of the previously prepared aldehyde (0.06, 0.11 mmol) in THF (1 mL) was added dropwise. After the mixture was stirred for 1 h, the reaction was diluted with 20 mL of Et₂O and the reaction was quenched by the slow addition of 20 mL of H₂O. The layers were separated and the aqueous phase was extracted with two 20 mL portions of Et₂O. The combined organic extracts were washed with 20 mL of brine, dried over anhydrous MgSO₄, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (20% EtOAc/hexanes) to give unsaturated ester 37 (0.05 g, 84% over two steps, ratio Z:E = 94:06) as a colorless oil: Rf 0.70 (20% EtOAc/hexanes).

(5R,6R)-5-Ethyl-6-((2R,3S,4R,5S,E)-2-hydroxy-4-methoxy-3,5-dimethylnon-7-enyl)-5,6-dihydropyran-2-one (pironetin). To a solution of unsaturated ester 37 (0.05 g, 0.08 mmol) in anhydrous ethanol (10 mL) at ambient temperature was added a solution of 2% HCl in ethanol (15 mL). The reaction mixture was stirred at ambient temperature for 15 h before it was concentrated in vacuo. The remaining organic residue was purified by flash chromatography on silica gel using (15% acetone/hexanes) to provide pironetin (I) (0.02 g, 89%) as a colorless solid. Rf 0.46 (15% EtOAc/hexanes); [α]²⁰°D = -137.5 (c 0.34, CHCl₃); mp 75-77 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.02 (dd, J 9.8, 5.8 Hz, 1H), 6.03 (d, J 10.0 Hz, 1H), 5.43-5.47 (m, 1H), 5.35-5.42 (m, 1H), 4.74 (dt, J 8.8, 3.7 Hz, 1H), 4.20 (m, 1H), 3.47 (s, 3H), 3.43 (d, J 2.5 Hz, 1H), 2.98 (dd, J 6.2, 4.6 Hz, 1H), 2.30 (m, 1H), 2.09 (m, 1H), 1.83 (m, 1H), 1.77 (m, 1H), 1.72 (m, 1H), 1.71 (m, 2H), 1.67 (d, J 5.8 Hz, 3H), 1.51 (m 1H), 1.01 (d, J 7.0 Hz, 3H), 0.97 (t, J 7.6 Hz, 3H), 0.96 (d, J 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 164.7, 150.7, 128.8, 126.8, 126.9, 120.8, 99.1, 77.7, 67.4, 61.6, 39.1, 38.9, 37.2, 36.7, 36.1, 20.7, 18.2, 15.2, 12.2, 10.9.
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References


8. The numbering of 1 follows that suggested in ref 1b.


12. Aldehyde 8 was prepared in 3 steps and 77% overall yield from 1,3-propanediol following protection with anisaldehyde in the presence of amberlyst resin, acetal opening with DIBAL-H followed by Swern oxidation.


26. New compounds and the additional isolated intermediates gave satisfactory $^1$H and $^{13}$C NMR, IR, HRMS, and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.