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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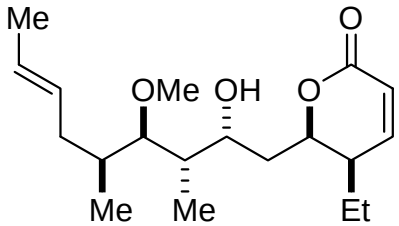
Abstract

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 pironetin[1] (**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.[2,3] 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.



Pironetin (1)

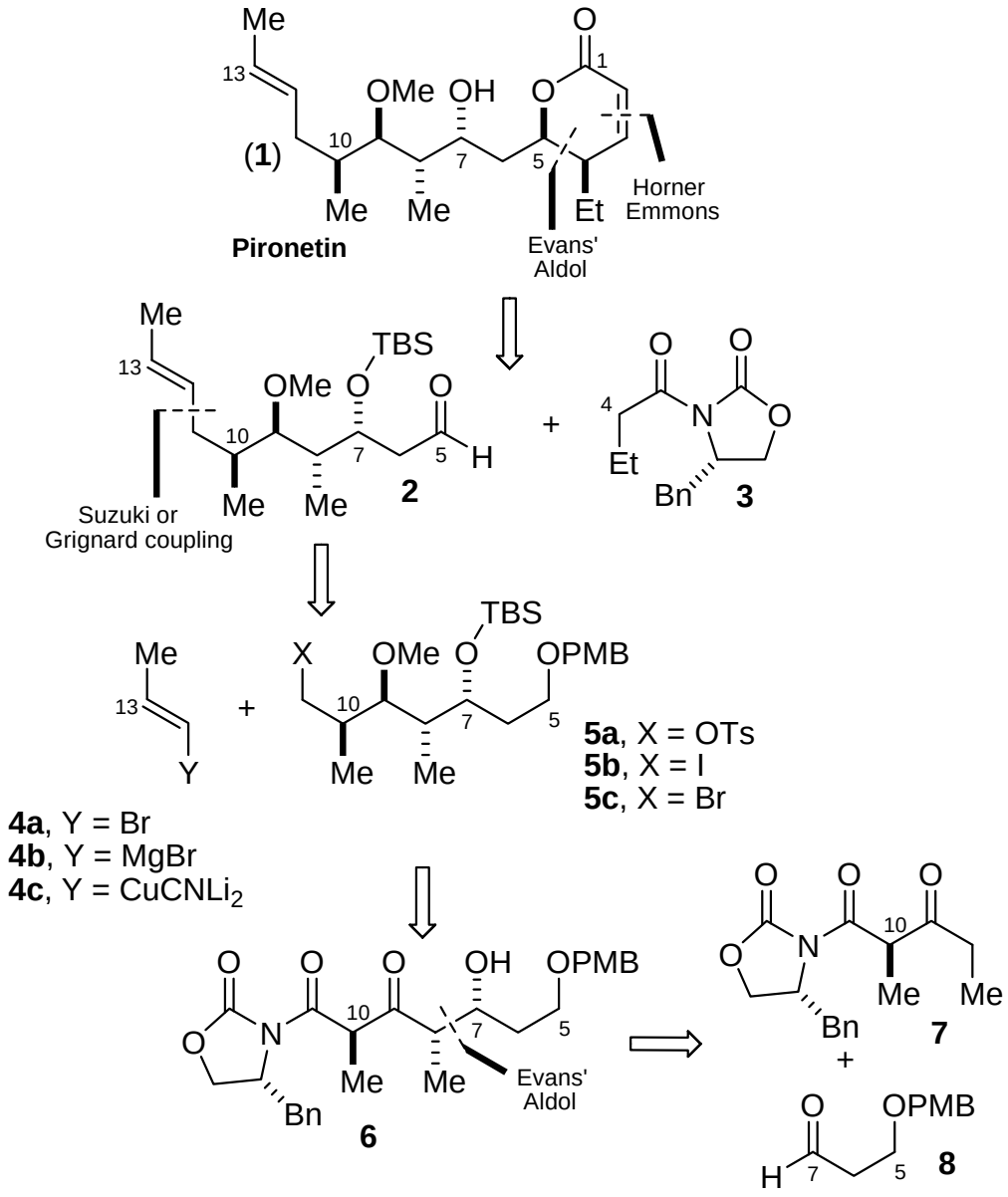
Figure 1

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.

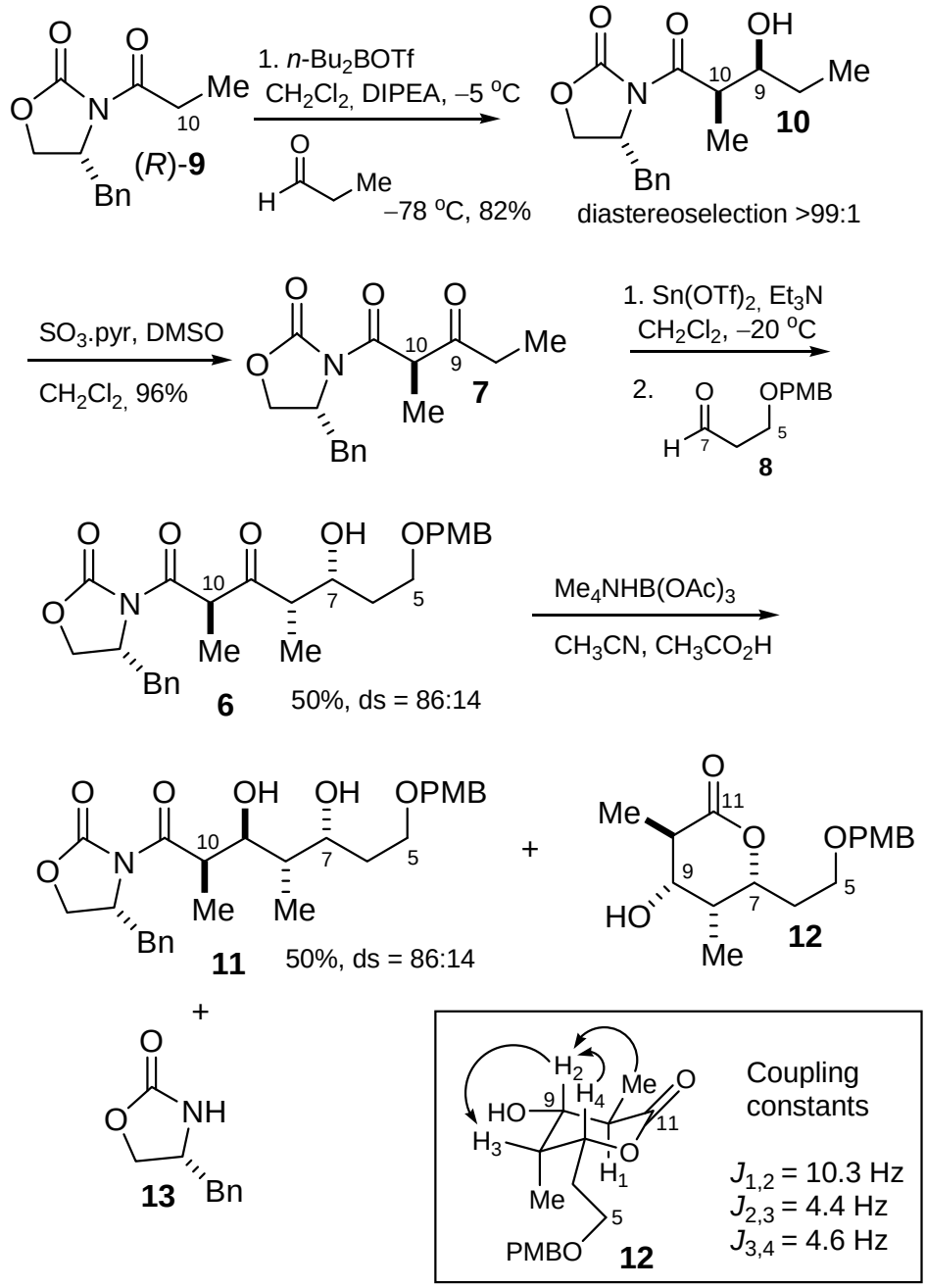
Results and Discussion

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).[9,10]

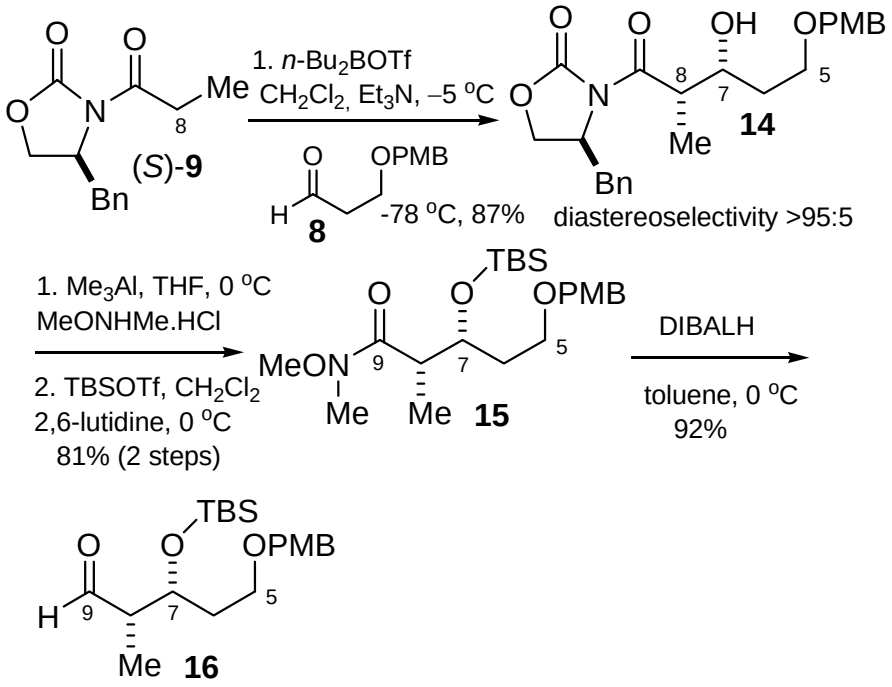


Scheme 2. First approach to fragment C5-C11.

Treatment of **10** with SO_3-pyr in a mixture of DMSO/CH_2Cl_2 gave β-ketoimide **7** in 96% yield.[11] Treatment of β-ketoimide **7** with $Sn(OTf)_2$ and Et_3N in CH_2Cl_2 followed by addition of aldehyde **8** gave aldol adduct **6** with a modest diastereoselectivity (86:14) in only 50% yield.[11,12] Attempts to improve yields and diastereoselectivities for this transformation failed. The next step involved reduction of the ketone function in **6** with $Me_4NHB(OAc)_3$ in CH_3CN/CH_3CO_2H to provide diol **11**, together with lactone **12** and chiral auxiliary **13**, a mixture which was difficult to

separate by silica gel column chromatography.[13] 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**.

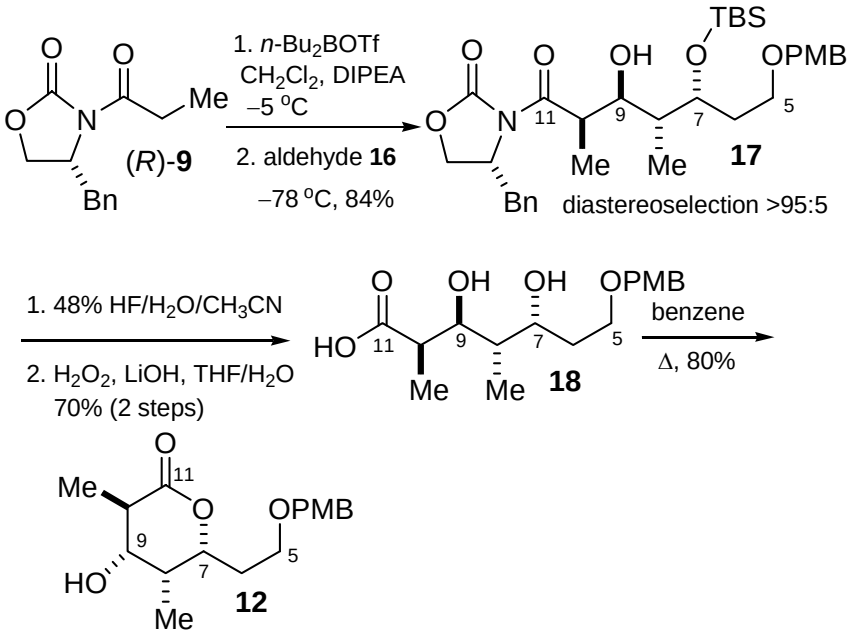
In view of these disappointing results, we decided to use another strategy for the synthesis of fragment C5-C11, which is based in the use of two consecutive asymmetric aldol reactions (Scheme 3). Synthesis of aldehyde **16** began with asymmetric aldol addition of the boron enolate derived from *N*-propionyloxazolidinone (*S*)-**9** with aldehyde **8**[12] to give aldol adduct **14** in 87% yield (ds >95:5) (Scheme 3).[9,10] Exchange of the oxazolidinone auxiliary in aldol **14** with *N,O*-dimethylhydroxylamine in the presence of Me_3Al in THF at 0 °C[14] was followed by silylation with TBSOTf and 2,6-lutidine in CH_2Cl_2 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.



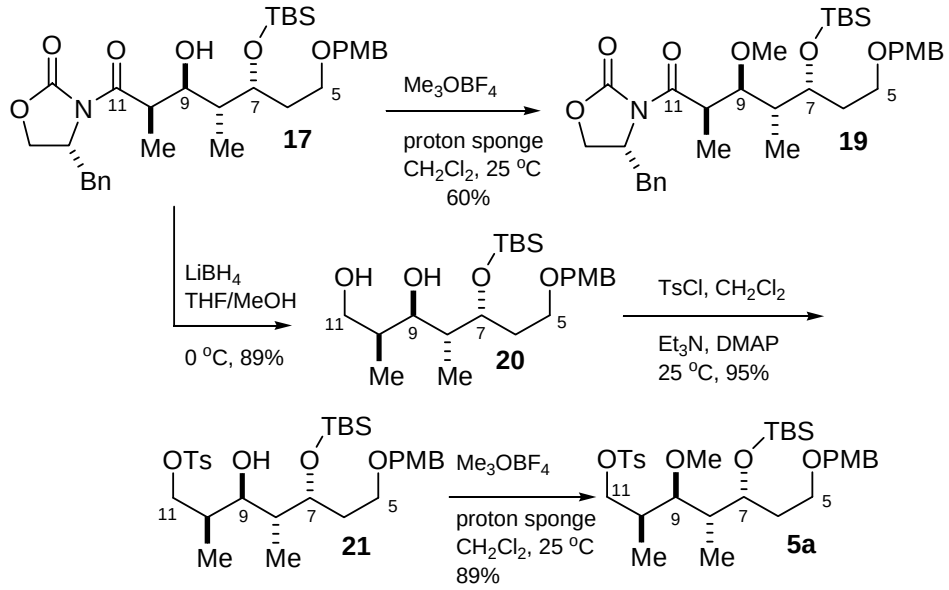
Scheme 3. Preparation of aldehyde **16**.

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).[9,15-17] At this point, the relative stereochemistry for aldol adduct **17** was determined after conversion to the the same lactone **12** prepared before (Scheme 4).[15-17] Formation of lactone **12** was accomplished after a three-step sequence (56% overall yield) that involved treatment of aldol **17** with $HF/H_2O/CH_3CN$, cleavage of the oxazolidinone auxiliary with $H_2O_2/LiOH$[14], and treatment of the carboxylic acid **18** in refluxing benzene.

Methylation of **17** with Me_3OBF_4 in the presence of a proton sponge at ambient temperature, provided **19** in 60% isolated yield (Scheme 5).[16] 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_3OBF_4 in the presence of a proton sponge at ambient temperature, providing **5a** in 89% isolated yield (Scheme 5).[16]

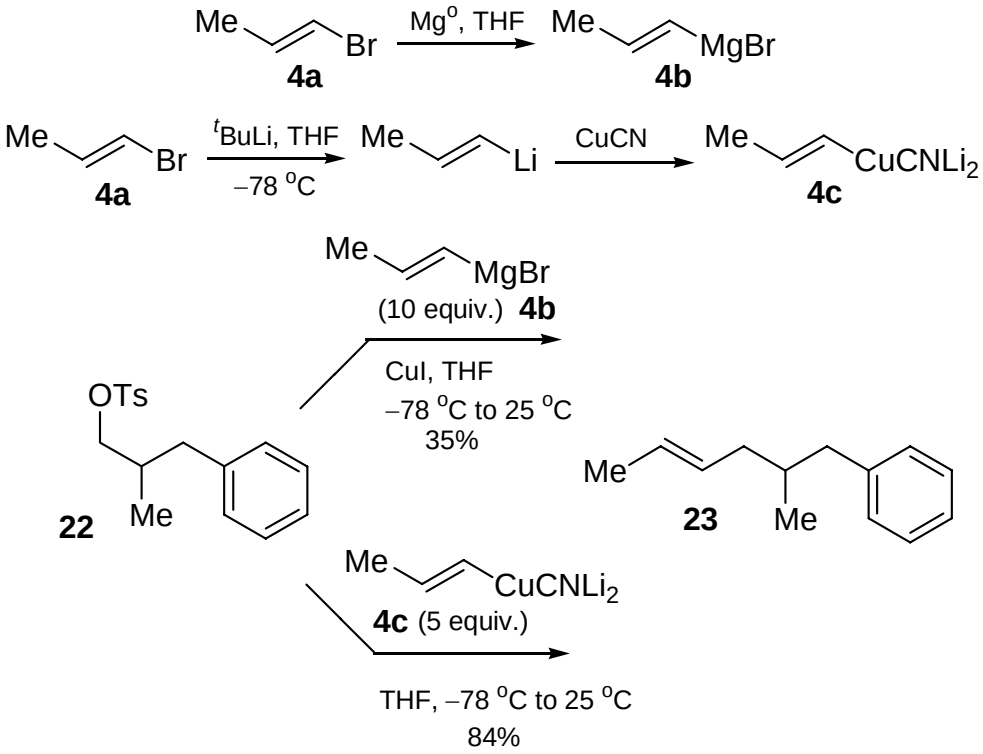


Scheme 4. Preparation of aldol adduct 17.



Scheme 5. Preparation of tosylate **5a**.

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).[18] Treatment of (*E*)-1-bromo-1-propene (**4a**) with Mg^o 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).[18] 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).

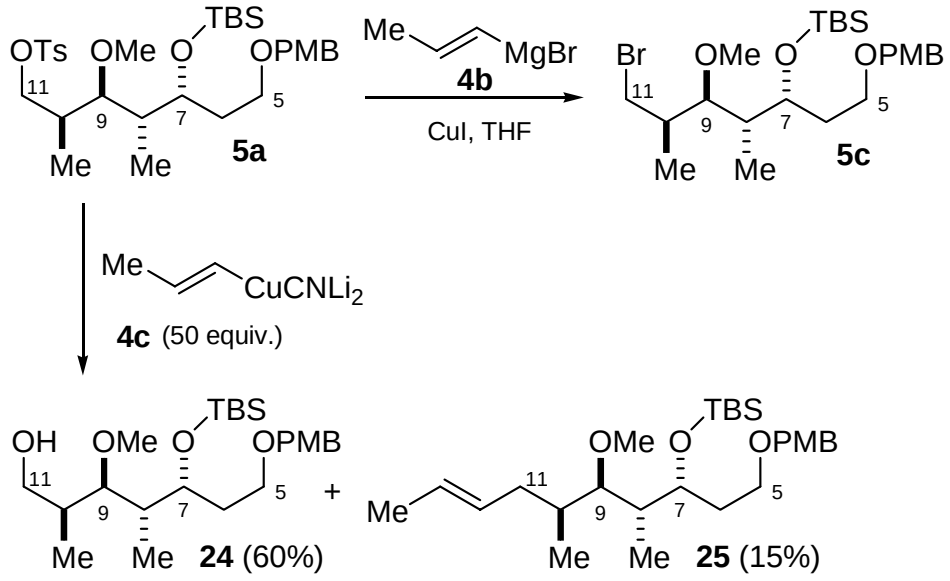


Scheme 6. Model studies with Grignard and cuprate reagents.

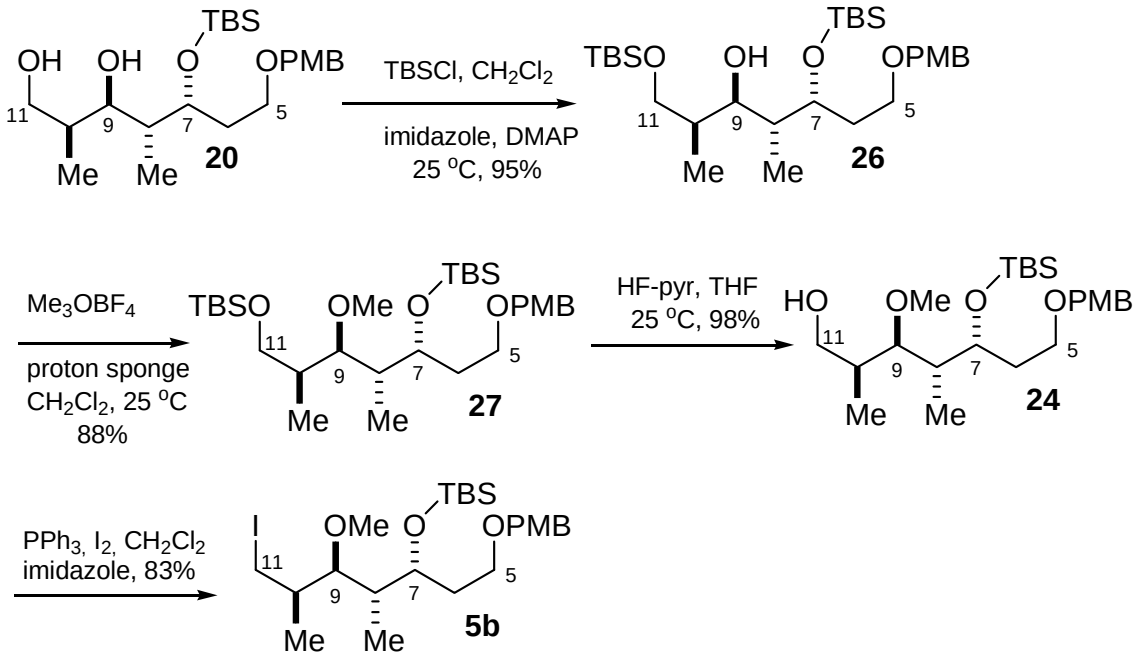
We next moved to the real system (Scheme 7). Treatment of tosylate **5a** with Grignard reagent **4b** gave bromide **5c** in good yields as the sole product, together with starting material. Treatment of tosylate **5a** with cuprate **4c** (50 equivalents) led to a mixture of primary alcohol **24** (60%) and the desired product **25** in only 15% yield.[18] 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.[19] 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 Me_3OBF_4 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 PPh_3, I_2 and imidazole gave iodide **5b** in 83% overall yield for the two-step sequence.

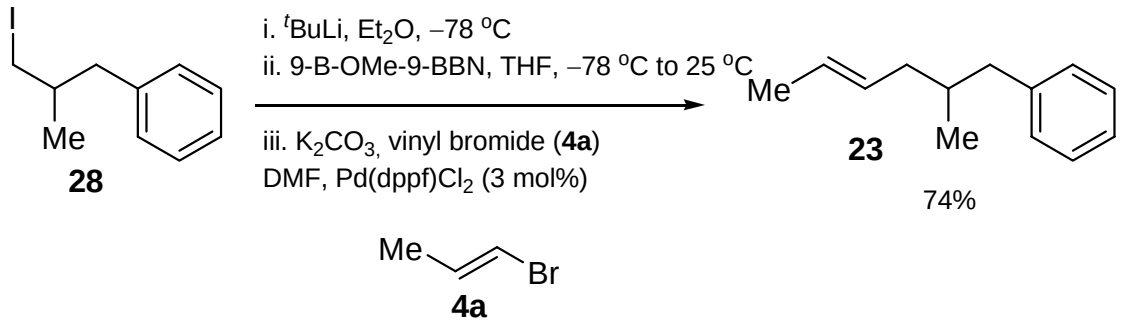


Scheme 7. Coupling studies.



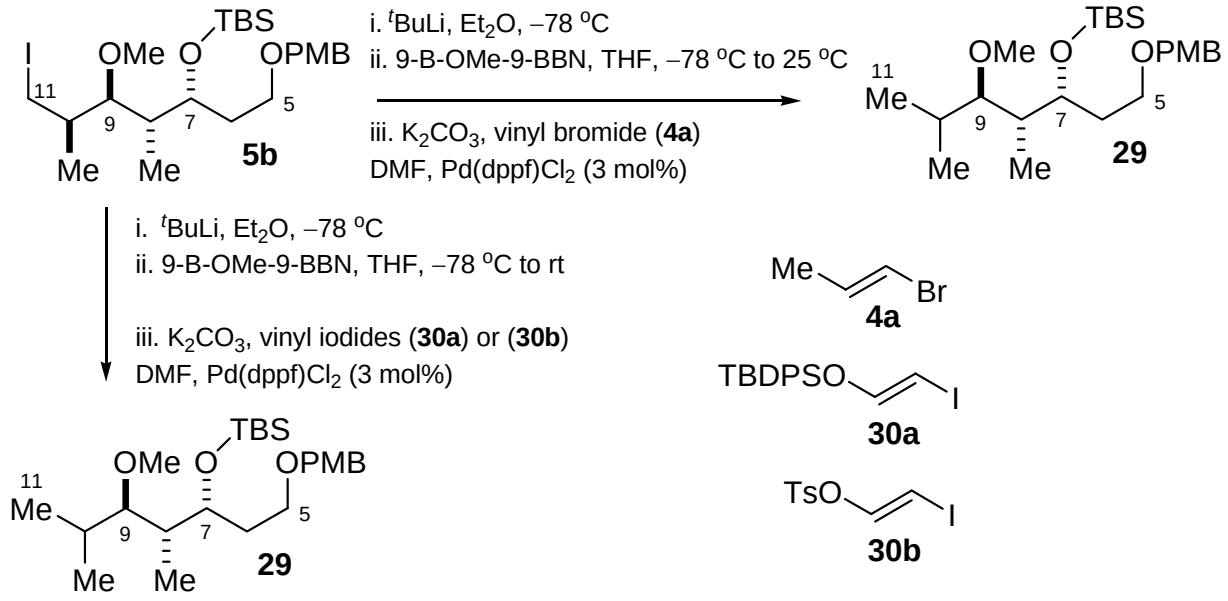
Scheme 8. Preparation of alkyl iodide **5b**.

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).[19] Treatment of alkyl iodide **28** with ^{t}BuLi in Et_2O 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)Cl_2, $AsPh_3$, K_2CO_3 and water in DMF gave coupled product **23** in 74% yield.



Scheme 9. Model studies involving Suzuki coupling.

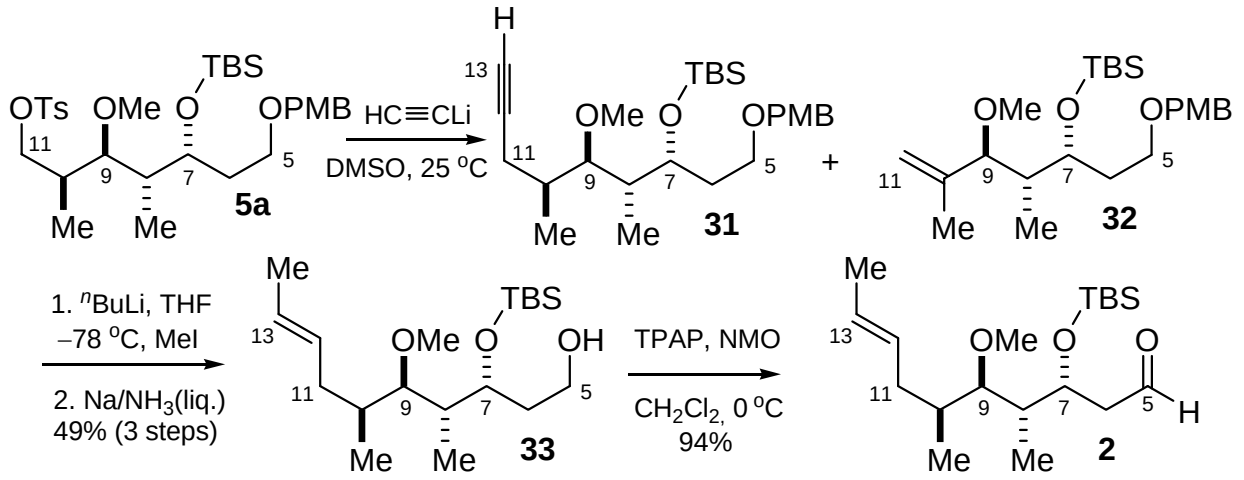
As this worked well, we tried this coupling using iodide **5b** (Scheme 10). Treatment of alkyl iodide **5b** with ^{t}BuLi in Et_2O at –78 °C followed by addition of 9-MeO-9-BBN, and vinyl bromide **4a** in the presence of Pd(dppf)Cl_2, $AsPh_3$, K_2CO_3 and water in DMF provided only product **29**, 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]

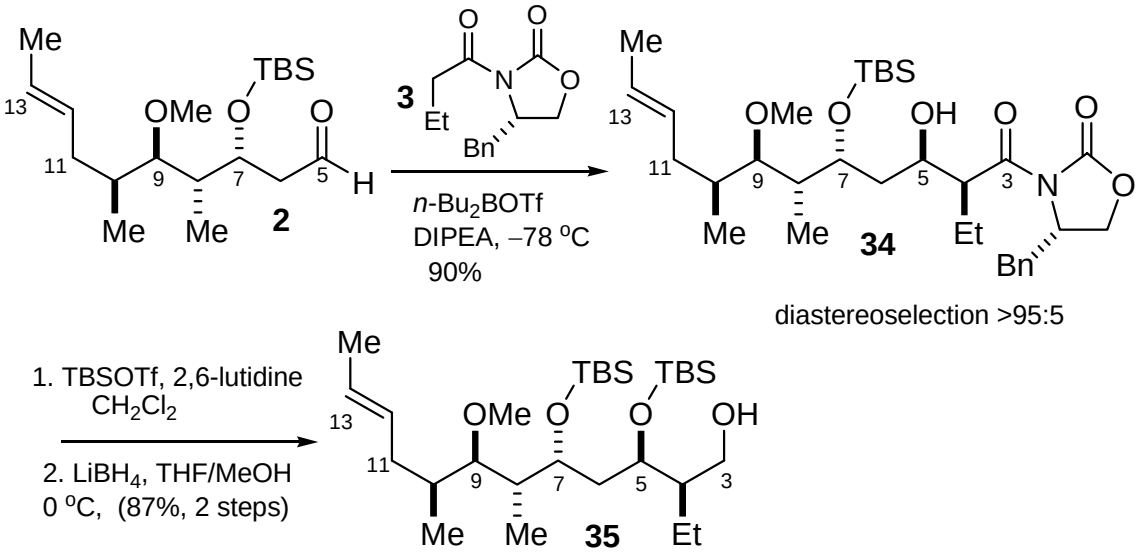
We were very pleased to find that treatment of tosylate **5a** with 5 equivalents of lithium acetylide in DMSO at room temperature produced acetylene **31** in 82% yield, together with elimination product **32** in 13% yield (Scheme 11). After treatment of **31** with ^{n}BuLi and quenching with methyl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



Scheme 11. Preparation of aldehyde **2**.

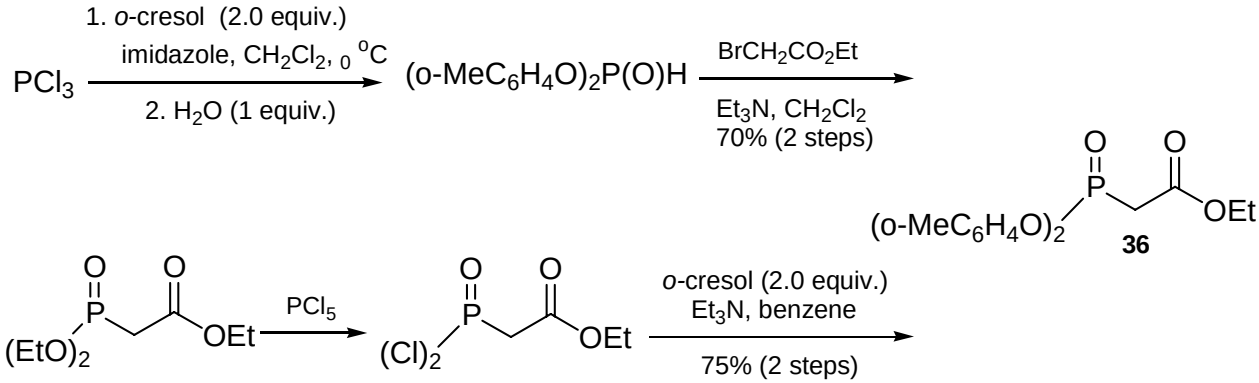
Deduction of the alkyne proceeded smoothly with Na and liquid NH_3 providing control for the (*E*)-geometry of the C12–C13 double bond with concomitant removal of the PMB group at C5, giving primary alcohol **33** in 49% yield for the three-step sequence from **5a** (Scheme 11).[23] TPAP oxidation of **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_3Al 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_2Cl_2 as solvent, followed by a sequence involving reaction with water and treatment with ethyl 2-bromoacetate in the presence of Et_3N to give **36** in 70% over two steps (Scheme 13).[25]

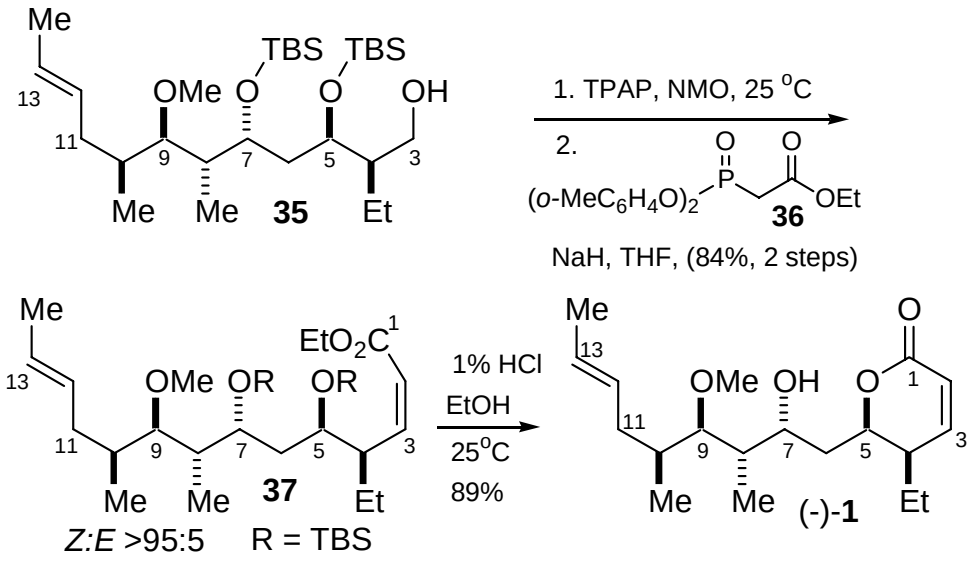


Scheme13. Preparation of phosphonate 36.

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_3N in benzene at 0 ºC, 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** [^{1}H and ^{13}C NMR, IR, $[\alpha]^{20}_D$, R_f] 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 CaH_2. 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 I_2 staining. ^{1}H-NMR spectra were taken in $CDCl_3$ at 300 MHz or at 500 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ 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 ^{13}C-NMR spectra were taken in $CDCl_3$ at 75 MHz spectrometer and are recorded in ppm.

(*S*)-3-((2*S*,3*R*)-5-(4-Methoxybenzyloxy)-3-hydroxy-2-methylpentanoyl)-4-benzyloxazolidin-2-one (14). Di-*n*-butylboryltrifluoromethanesulfonate (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 CH_2Cl_2 at such a rate to maintain the internal temperature below +3 ^{o}C (type K thermocouple thermometer). Triethylamine (0.48 mL, 3.41 mmol) was then added dropwise (internal temperature below +4 ^{o}C). The resulting yellow solution was then cooled to –78 ^{o}C and aldehyde **8** (0.56 g, 2.89 mmol) in 6 mL of CH_2Cl_2 was added slowly (internal temperature below –70 ^{o}C). After 20 min, the solution was warmed to 0 ^{o}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 ^{o}C, bath temperature = -10 ^{o}C). A solution of 12 mL of MeOH and 8 mL of 30% aqueous H_2O_2 was added carefully (internal temperature below +10 ^{o}C) and the resulting yellow solution was stirred at 0 ^{o}C for 1 h. The volatiles were removed at aspirator pressure and the residue was extracted with three 15 mL portions of Et_2O. The combined organic extracts were washed with 20 mL of saturated aqueous $NaHCO_3$ and 20 mL of brine. The organic solution was dried over anhydrous $MgSO_4$ 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). R_f 0.34 (50% EtOAc/hexanes); $[\alpha]_D$ +51.5^o (*c* 1.15, CH_2Cl_2); IR ν_{max} (film, cm^{-1}) 3489, 3031, 2938, 2866, 1774, 1691, 1609, 1511, 1454, 1243, 1207, 1104; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{29}NO_6$: C 67.43, H 6.84, N 3.28; Found: C 67.21, H 6.88, N 3.35; HRMS calcd. for $C_{24}H_{29}NO_6$: 427.1995; found: 427.1994.

(2*S*,3*R*)-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 CH_2Cl_2 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 CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, 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); $[\alpha]_D$ +4.48° (*c* 1.26, CH_2Cl_2); IR ν_{max} (film, cm-$^{-1}$) 3440, 2934, 2868, 1747, 1634, 1514, 1462, 1175, 1086; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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.

(2*S*,3*R*)-5-(4-Methoxybenzyloxy)-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 CH_2Cl_2 (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 CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 x 15 mL). All the organic layers were combined and dried with $MgSO_4$, 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); $[\alpha]_D$ +4.27° (*c* 1.17, EtOH); IR ν_{max} (film, cm^{-1}) 3488, 2954, 2936, 2862, 1658, 1616, 1503, 1461, 1379, 1299, 1249, 1175, 1100; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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), 3.01 (br s, 1H), 1.83 (m, 2H), 1.13 (d, *J* 7.1 Hz, 3H), 0.88 (s, 9H), 0.054 (s, 3H), 0.042 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 159.0, 130.6, 129.3, 113.7, 72.5, 71.3, 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 $C_{22}H_{39}NO_5Si$: C 62.08, H 9.24, N 3.29; found: C 61.93, H 9.31, N 3.38; HRMS calcd. for $C_{22}H_{39}NO_5Si$: 425.2597; found: 425.2598.

(2*S*,3*R*)-5-(4-Methoxybenzyloxy)-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 CH_2Cl_2 (10 mL). The aqueous layer was further extracted with CH_2Cl_2 and the combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give aldehyde **16** (0.465 g, 92%) as a colorless oil. R_f 0.47 (20% EtOAc/hexanes); $[\alpha]_D$ +44.7° (*c* 1.00, CH_2Cl_2); IR ν_{max} (film, cm^{-1}) 2953, 2850, 2711, 1773, 1614, 1583, 1511, 1459, 1366, 1299, 1248, 1171; ^{1}H NMR (300 MHz, C_6D_6) δ 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); ^{13}C NMR (75 MHz, C_6D_6) δ 203.9, 160.3, 131.4, 129.9, 114.6, 73.2, 69.7, 66.6, 55.1, 51.9, 35.4, 26.3, 18.5, 8.0, -4.1, -4.3; Anal. calcd. for $C_{20}H_{34}O_4Si$: C 65.53, H 9.35; found: C 65.79, H 9.3; HRMS calcd. for $C_{20}H_{34}O_4Si$ (M^+-H_2O): 348.2121; found: 348.2145.

(*R*)-3-((2*R*,3*S*,4*R*,5*R*)-7-(4-Methoxybenzyloxy)-5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-2,4-dimethylheptanoyl)-4-benzyloxazolidin-2-one(17).Di-*n*-butylboryltrifluoro-methanesulfonate (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 CH_2Cl_2 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 CH_2Cl_2 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 H_2O_2 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 Et_2O. The combined organic extracts were washed with 20 mL of saturated aqueous $NaHCO_3$ and 20 mL of brine. The organic solution was dried over anhydrous $MgSO_4$ 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). R_f 0.44 (30% EtOAc/hexanes); IR ν_{max} (film, cm^{-1}) 3463, 3036, 2928, 2856, 1784, 1701, 1608, 1511, 1454, 1387, 1294, 1243, 1212; ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

(3*R*,4*S*,5*R*,6*R*)-6-(2-(4-Methoxybenzyloxy)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 48% aqueous HF, 8.6 mL of CH_3CN, and 0.90 mL of H_20). After a total reaction time of 6 h, the solution was poured into 10 mL each of CH_2C1_2 and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2C1_2 (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, 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 5.3 mL of 30% aqueous hydrogen peroxide

and 0.043 g of LiOH (0.744 mmol, 0.2 M in H_2O). The mixture was stirred for 15 min at 0 °C and was quenched with 5 mL of aqueous 1.5 M Na_2SO_3. After 5 min, the reaction mixture was poured into 30 mL each of CH_2C1_2 and H_2O. The aqueous layer was acidified to pH 3.0 with aqueous 0.1 M HCl and was extracted with CH_2C1_2 (3 x 10 mL). The CH_2C1_2 layers were dried over anhydrous $MgSO_4$, 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). R_f 0.21 (50% EtOAc/hexanes); $[\alpha]_D$ +66.6° (*c* 1.05, CH_2Cl_2); IR ν_{max} (film, cm^{-1}) 3432, 2916, 2848, 1716, 1612, 1516, 1464, 1361, 1299, 1253, 1099; ^{1}H NMR (500 MHz, C_6D_6) δ 7.19 (d, *J* 8.5 Hz, 2H), 6.80 (d, *J* 8.5 Hz, 2H), 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); ^{13}C NMR (75 MHz, C_6D_6) 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, 4.3; MS (*m/z*) 308 (4), 203 (4), 176 (43), 137 (74), 121 (100), 109 (10), 91 (10), 69 (28), 57 (19), 41 (9); HRMS calcd. for $C_{17}H_{45}O_5$: 308.1624; found: 308.1624.

(*R*)-3-((2*R*,3*S*,4*R*,5*R*)-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 CH_2Cl_2 (5 mL) at ambient temperature under argon were added proton sponge (0.161 g, 0.75 mmol) and Me_3OBF_4 (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 CH_2Cl_2 (10 mL) and was washed with cold aqueous 1 M HCl (2 x 5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (15% EtOAc/hexanes) afforded 0.055 g (60%) of **19** as a clear oil: R_f 0.65 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 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, 9H), 0.86 (d, *J* 7.0 Hz, 3H), 0.057 (s, 3H), 0.046 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

(2*S*,3*R*,4*R*,5*R*)-7-(4-Methoxybenzyloxy)-5-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-heptane-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 $LiBH_4$ 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 CH_2Cl_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_2Cl_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 diol **20** (0.072 g, 89%) as a viscous oil. R_f 0.50 (50% EtOAc/hexanes); $[\alpha]_D$ +31.4° (*c* 1.11, CH_2Cl_2); IR ν_{max} (film, cm^{-1}) 3421, 2956, 2929, 2858, 1721, 1612, 1514, 1465, 1382, 1361, 1300, 1250, 1175, 1087; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, 1H), 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, $CDCl_3$) δ 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 $C_{23}H_{42}O_5Si$: 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 CH_2Cl_2 (1 mL) were added *p*-toluenesulfonyl chloride (0.017 g, 0.090 mmol), triethylamine (114 μL, 0.82 mmol), and 4-(dimethy1amino)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 ν_{max} (film, cm^{-1}) 3465, 2956, 2929, 2858, 1721, 1612, 1514, 1465, 1361, 1300, 1246, 1175, 1099; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 159.2, 144.5, 133.3, 130.5, 129.7, 129.3, 127.9, 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 $C_{30}H_{48}O_7SSi$: C 62.04, H 8.33; Found: C 61.89, H 8.41; HRMS calcd. for $C_{30}H_{48}O_7SSi$: 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 CH_2Cl_2 (3 mL) at ambient temperature under argon were added proton sponge (0.382 g, 1.78 mmol) and Me_3OBF_4 (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 CH_2Cl_2 (10 mL) and was washed with cold aqueous 1 M HCl (2 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, 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, $CDCl_3$) δ 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, 2H), 1.51 (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); ^{13}C 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), triethylamine (12.7 mL, 91.33 mmol), and 4-(dimethy1amino)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. R_f 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; ^{1}H 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 139.2, 133.3, 129.8, 129.1, 128.3, 127.9, 126.1, 74,1, 38.9, 34.8, 21.6, 16.2.

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; ^{1}H 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); ^{13}C 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 (1% EtOAc/hexanes) gave **23** (35%).

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 NH_4Cl-10% NH_4OH (1 mL) was added, and the mixture was warmed to 23 °C with vigorous stirring. After 20 min, water (3 mL) and Et_2O (3 mL) were added, the aqueous portion was extracted with Et_2O (2 x 5 mL), and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography on silica gel (1% EtOAc/hexanes) gave **23** (84%). R_f 0.67 (hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 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).

(2*S*,3*R*,4*R*,5*R*)-7-(4-Methoxybenzyloxy)-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 CH_2Cl_2 (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 H_2O, and then the organic layer was washed with brine, dried over anhydrous $MgSO_4$, 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, CH_2Cl_2); IR ν_{max} (film, cm^{-1}) 3494, 2959, 2928, 2859, 1734, 1615, 1516, 1463, 1385, 1363, 1250, 1173; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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* 9.7 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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, -4.5, -4.9, -5.4, -5.5; Anal. calcd. for $C_{29}H_{56}O_5Si_2$: C 64.39, H 10.43; Found: C 64.11, H 10.25; HRMS calcd. for $C_{29}H_{56}O_5Si_2$: 540.3666; found: 540.3663.

1-(((3*R*,4*R*,5*R*,6*S*)-3,7-bis(*tert*-Butyldimethylsilyloxy)-5-methoxy-4,6-dimethylheptyloxy)methyl)-4-methoxybenzene (27). To a solution of alcohol **26** (0.664 g, 1.23 mmol) in CH_2Cl_2 (6 mL) at ambient temperature under argon were added proton sponge (2.108 g, 9.84 mmol) and Me_3OBF_4 (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 CH_2Cl_2 (10 mL) and was washed with cold aqueous 1 M HCl (2 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. 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, CH_2Cl_2); IR ν_{max} (film, cm^{-1}) 2950, 2927, 2855, 1615, 1586, 1514, 1462, 1390, 1361, 1307, 1253, 1074; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{30}H_{58}O_5Si_2$: 554.3822; found: 554.3829.

(2*S*,3*R*,4*R*,5*R*)-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 μL (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_2Cl_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_2Cl_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 ^{o}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 ν_{max} (film, cm^{-1}) 3438, 2928, 2860, 2064, 1996, 1882, 1728, 1613, 1585, 1510, 1460, 1361, 1305; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

((3*R*,4*R*,5*S*,6*R*)-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_2Cl_2 (1.0 mL), at 0 ^{o}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 ^{o}C for 10 min, and then a solution of alcohol **28** (0.056 g, 0.2 mmol) in CH_2Cl_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 ν_{max} (film, cm^{-1}) 2957, 2922, 2860, 1613, 1516, 1460, 1299, 1253, 1173, 1087; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

((3*R*,4*R*,5*S*,6*R*)-1-(4-Methoxybenzyloxy)-7-bromo-5-methoxy-4,6-dimethylheptan-3-yloxy)(*tert*-butyl)dimethylsilane (5c). R_f 0.48 (10% EtOAc/hexanes); IR ν_{max} (film, cm^{-1}) 2960, 2925, 2870, 1615, 1514, 1460, 1300, 1253, 1178, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.27d, *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); ^{13}C NMR (75 MHz, $CDCl_3$) 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.

((3*R*,4*R*,5*R*)-1-(4-Methoxybenzyloxy)-5-methoxy-4,6-dimethylheptan-3-yloxy)(*tert*-butyl)dimethylsilane (29). R_f 0.52 (10% EtOAc/hexanes); IR ν_{max} (film, cm^{-1}) 2956, 2929, 2853, 1705, 1612, 1514, 1465, 1365, 1178; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* 8.4 Hz, 2H), 6.86 (d, *J* 8.4 Hz, 2H), 4.44 (d, *J* 11.7 Hz, 1H), 4.39 (d, *J* 11.4 Hz, 1H), 4.10 (td, *J* 6.8 and 1.8 Hz, 1H), 3.80 (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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{44}O_4Si$: 424.3009; found: 424.3004.

***tert*-Butyl((3*R*,4*R*,5*R*,6*S*)-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 Et_2O (10 mL), and saturated aqueous NH_4Cl (10 mL) were cautiously added to the brownish reaction mixture. The aqueous layer was extracted with Et_2O (3 x 10 mL), and the Et_2O extracts were washed with brine (2 x 50 mL) and dried over $MgSO_4$. 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%). R_f 0.56 (10% EtOAc/hexanes); $[\alpha]^{20}_D$ = + 10.5 (c 1.43, $CHCl_3$); IR ν_{max} (film, cm^{-1}) 3308, 2954, 2927, 2859, 1742, 1616, 1510, 1467, 1382, 1303, 1245; ^{1}H NMR (500 MHz, C_6D_6) 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); ^{13}C NMR (75 MHz, C_6D_6) 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 $C_{26}H_{44}O_4Si$: 448.3008; found: 448.3011.

***tert*-Butyl((3*R*,4*R*,5*R*,6*S*)-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_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL), and the Et_2O 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, $CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.74 (d, *J* 7.0 Hz, 3H), 0.83 (d, *J* 6.6 Hz, 3H), 0.90 (s, 9H), 1.09–1.37 (m, 2H), 1.77 (t, *J* 2.4 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* 6.0 Hz, 2H), 3.80 (s, 3H), 4.13 (br t, *J* 6.4 Hz, 1H) 4.39 (d, *J* 11.8 Hz, 1H), 4.45 (d, *J* 11.7 Hz, 1H), 6.86 (d, *J* 8.4 Hz, 2H), 7.26 (d, *J* 8.3 Hz, 2H).

(3*R*,4*R*,5*R*,6*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-5-methoxy-4,6-dimethyldec-8-en-1-ol (33). To a vigorously stirred –78 °C 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_4Cl 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_4Cl. The organic phase was removed and the aqueous layer extracted with Et_2O (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, $CDCl_3$) δ 5.30-5.49 (m, 2H), 4.11 (ddd, *J* 7.75, 5.64 and 2.13 Hz, 1H), 3.66-3.71 (m, 2H), 3.48 (s, 3H), 3.16 (dd, *J* 9.1 and 1.8 Hz, 1H), 2.13 (m, 1H), 2.01 (m, 1H), 1.78 (m, 2H), 1.66 (dd, *J* 5.8 and 0.5 Hz, 3H), 1.58-1.71 (m, 2H), 0.88 (s, 9H), 0.82 (d, *J* 6.71 Hz, 3H), 0.76 (d, *J* 7.02 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.4, 126.4, 84.4, 69.6, 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_2Cl_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_2Cl_2 (10 mL) and H_2O (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 °C. When the exothermic reaction was completed, the mixture was heated at 75 °C for 10 h. Distillation removed $P(O)Cl_3$ and excess PCl_5 and yielded the dichloride (4.45 g, 3 mmHg/105-110 °C), 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 Et_3N (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 NH_4Cl, and brine, dried ($MgSO_4$), 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: R_f 0.27 (25% EtOAc/hexanes); IR ν_{max} (film, cm^{-1}): 3054, 2986, 2931, 1735, 1580, 1487, 1371; ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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-((2*S*,3*R*,5*R*,6*R*,7*R*,8*S*,*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 CH_2Cl_2 (20 mL) at 0 °C, was added TPAP (0.06 g, 10 mol%) in one portion. The reaction mixture was stirred at ambiente temperature for 2 h, filtered and concentrated in vacuo to give aldehyde **2**, used in the next step without further purification (R_f 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 CH_2Cl_2 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 CH_2Cl_2 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 H_2O_2 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 Et_2O. The combined organic extracts were washed with 50 mL of saturated aqueous $NaHCO_3$ and 50 mL of brine. The organic solution was dried over anhydrous $MgSO_4$ 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). R_f 0.30 (40% EtOAc/hexanes).

(2*R*,3*R*,5*R*,6*R*,7*R*,8*S*,*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 CH_2Cl_2 (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 CH_2Cl_2 (50 mL) and 50 mL of saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 x 50 mL). All the organic layers were combined and dried with $MgSO_4$, 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 N_2 atmosphere. The solution was cooled to 0 °C and MeOH (30 μL) followed by a solution of $LIBH_4$ (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 CH_2Cl_2 (3 x 50 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give alcohol **35** (0.15 g, 87% over two steps). R_f 0.20 (20% EtOAc/hexanes).

(2*Z*,4*R*,5*R*,7*R*,8*R*,9*R*,10*S*,12*E*)-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 CH_2Cl_2 (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. R_f 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(*o*-tolyloxy))phosphoryl)acetate **36** (0.35 g, 0.10 mmol). After the mixture was stirred at 0 ^oC for 30 min the reaction mixture was cooled to –78 ^oC, 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 Et_2O and the reaction was quenched by the slow addition of 20 mL of H_2O. The layers were separated and the aqueous phase was extracted with two 20 mL portions of Et_2O. The combined organic extracts were washed with 20 mL of brine, dried over anhydrous $MgSO_4$, 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: R_f 0.70 (20% EtOAc/hexanes).

(5*R*,6*R*)-5-Ethyl-6-((2*R*,3*S*,4*R*,5*S*,*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 (**1**) (0.02 g, 89%) as a colorless solid. R_f 0.46 (15% EtOAc/hexanes); $[\alpha]^{20}_D$ = -137.5 (c 0.34, $CHCl_3$); mp 75-77 ^oC; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 150.7, 128.8, 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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