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ORIGINAL ARTICLE

Large-scale preparation of key building blocks for the manufacture of fully synthetic macrolide antibiotics

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Key building blocks for the production of fully synthetic macrolides have been scaled-up in first time pilot plant and kilo-lab campaigns. These building blocks have supported the discovery of new macrolide antibiotics as well as ongoing preclinical studies.

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INTRODUCTION

All members of the macrolide antibiotic class that are approved for human use are manufactured by semisynthetic modification of the natural product erythromycin (**1**).[1,2] It is evident that the pace of discovery of novel macrolide antibiotics by semisynthesis has slowed as routes have lengthened,[3,4] while at the same time once important agents such as clarithromycin[5] (**2**) and azithromycin[6] (**3**, Figure 1, both approved in 1991)[7] currently face widespread resistance within modern clinical isolates, diminishing their efficacy. Seiple *et al.*[8] have recently described a broad and general platform for the synthesis of macrolide scaffolds of various ring sizes and substitution patterns, which to date has provided >1400 individual fully synthetic antibiotic candidates for evaluation. To facilitate both the discovery and eventual manufacture of any given fully synthetic macrolide candidate, we have investigated and here report our successful campaigns to provide on scale the essential building blocks **4–7** that we use to assemble, among other macrolides, the 15-membered aza-ketolide scaffold **10**, depicted in Figure 2. Details of these early, fit-for-purpose manufacturing campaigns, providing building blocks **4–7** in multi-hundred-gram to multi-kilogram quantities, are provided below.

RESULTS AND DISCUSSION

Pseudoephenamine glycinamide 4

To prepare (*R,R*)-pseudoephenamine glycinamide (building block **4**), it was necessary first to establish a preferred route to the versatile chiral auxiliary (*R,R*)-pseudoephenamine (**18**). Although a large-scale route to this substance has been previously described,[9] we explored the alternative sequence depicted in Scheme 1 in light of two features of the plan: its use of the highly practical starting material benzoin (**11**), and the existence of a prior report defining conditions to execute a dynamic kinetic asymmetric reduction of the racemic sulfamylimine **14** to furnish product **15** with high enantioselectivity and diastereoselectivity.[10] We evaluated two different methods to prepare the sulfamylimine **14**. Initially, we made use of the product of the reaction of *N*-chlorosulfonyl isocyanate and formic acid with benzoin in *N,N*-dimethylacetamide (DMA) as solvent. A general preparation of the latter reagent in the literature describes the addition of formic acid to neat *N*-chlorosulfonyl isocyanate, with subsequent additions of DMA and **11** to the sequence.[10] After extractive workup, a mixture of **14** and the non-cyclized intermediate **12** is obtained. Further conversion of the remaining **12–14** is accomplished by action of *p*-toluenesulfonic acid in refluxing toluene with azeotropic removal of water. In our hands, yields as high as 85% could be achieved after isolation of **14** from a re-slurry in *t*-butyl methyl ether (MTBE). Upon preliminary evaluation of the process, we observed that a significant exotherm occurred during addition of formic acid to neat *N*-chlorosulfonyl isocyanate. Furthermore, the mixture became heterogeneous in the process, leading to incomplete mixing. On one occasion during the subsequent addition of DMA, a violent exotherm took place, resulting in partial ejection of the reactor contents. We surmise that the heterogeneous reaction conditions led to incomplete mixing, and therefore incomplete reaction, during the first stage and that the subsequent addition of DMA facilitated the mixing and reaction of the unreacted starting materials. We were encouraged to explore an alternative preparation of **14** pursuing the report of Mclaughlin *et al.*[11] describing an alternative means to prepare sulfamylimines. Accordingly, to a solution of *t*-butanol (*t*-BuOH, 1.35 equiv.) in tetrahydrofuran (THF) was charged *N*-chlorosulfonyl isocyanate (1.25 equiv.) maintaining an internal temperature below 0 °C. Benzoin (**11**, 1 equiv.) was then added as a solid, followed by triethylamine (Et_3N, 1.45 equiv.). The resultant *N*-*tert*-butoxycarbonyl-protected sulfamate **13** was isolated by addition of water directly to the reaction mixture followed by collection of the product, which had precipitated, by filtration. After vacuum drying, **13** was transformed into **14** by refluxing a suspension of **13** in toluene in the presence of catalytic *p*-toluenesulfonic acid (0.03 equiv.) with azeotropic removal of water using a Dean–Stark apparatus. The material obtained after workup and re-slurry with MTBE was comparable in quality to that

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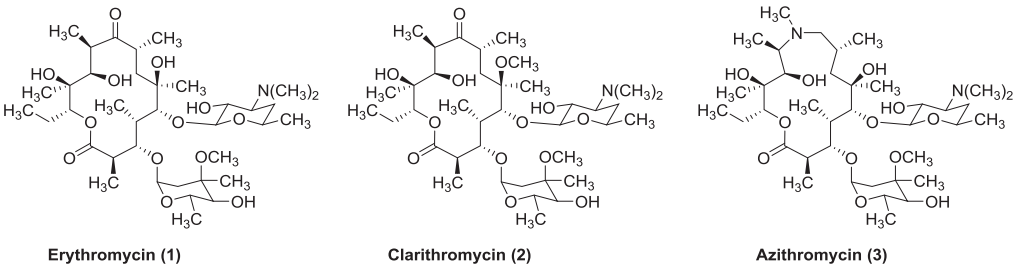


Figure 1 Representative macrolide antibiotics.

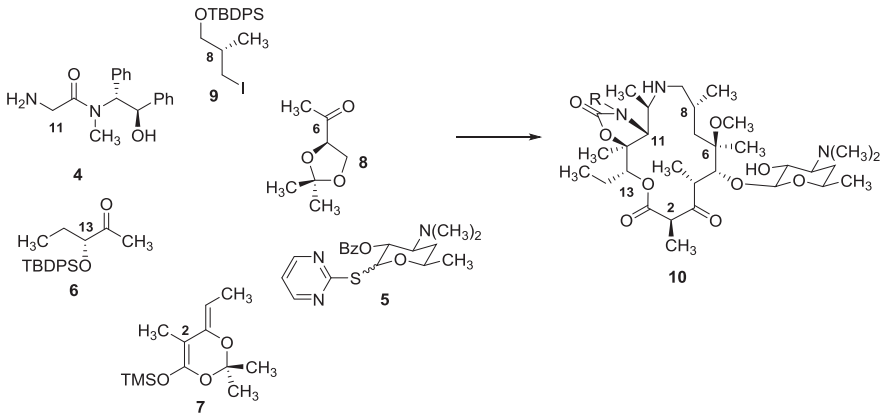
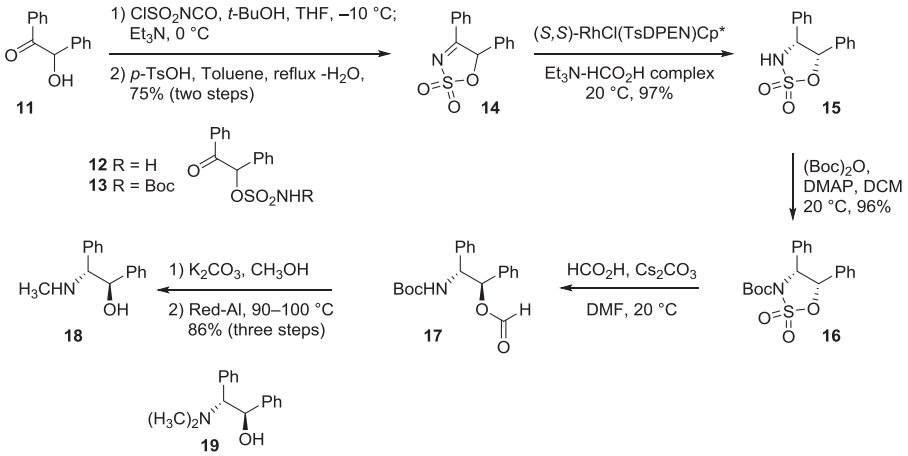
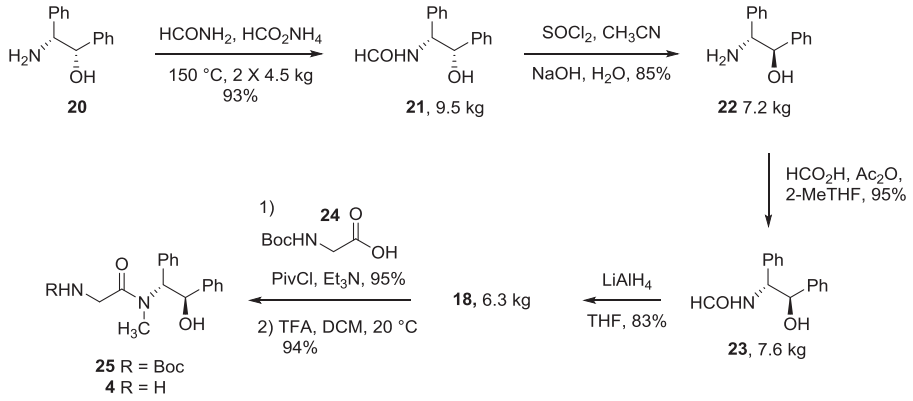


Figure 2 Building blocks and their assembly product, a 15-membered aza-ketolide antibiotic.



Scheme 1 Preparation of pseudoephenamine (**18**) by catalytic asymmetric transfer hydrogenation.

obtained by the other method, albeit with a slightly diminished yield (~75%), but offered the welcome advantage of being easily controlled and therefore safer. The kinetic dynamic asymmetric transfer hydrogenation of **14** to provide **15** was then investigated. We quickly learned that, in our hands, to permit low catalyst loadings (0.0005 equiv.), it was necessary to first distill the triethylamine–formic acid complex. A multi-hundred-gram run provided **15** in 97% yield after workup and silica gel filtration. The sulfamate **15** was treated with di-*tert*-butyl dicarbonate ($(Boc)_2O$, 1.05 equiv.) and 4-(dimethylamino)pyridine, 0.045 equiv. (DMAP) in dichloromethane to provide the *N*-Boc derivative **16** in 96% yield.[8] Invertive displacement of the C-O bond within **16** was most conveniently accomplished using a mixture of cesium carbonate and formic acid followed by decomposition of the intermediate sulfamate salt with citric acid; other, larger and more basic carboxylate nucleophiles led to mixtures containing as impurities side products arising from beta-elimination of the C-O bond within **16**. Treatment of the crude formate ester **17** with Red-Al in toluene with heating at 90–100 °C led to a mixture of products containing the undesired dimethylamino product **19** as a major component. We attributed the formation of **19** to the presence of the formate ester within **17**. When the formate ester within **17** was first cleaved in basic methanol, subsequent reduction of the resultant Boc-protected amino alcohol with Red-Al at 90–100 °C provided (*R,R*)-pseudoephenamine (**18**) in high purity after a heptane re-slurry of the material obtained from aqueous workup (86%, three steps from **16**). Although this route provided our discovery team with hundreds of grams of the desired auxiliary, we felt that as a manufacturing protocol the route was lengthy and somewhat tedious, and several intermediates were poorly soluble, necessitating the use of large amounts of solvent.



Scheme 2 Manufacture of pseudoephenamine (**18**) and glycinamide 4 using previously reported procedure.

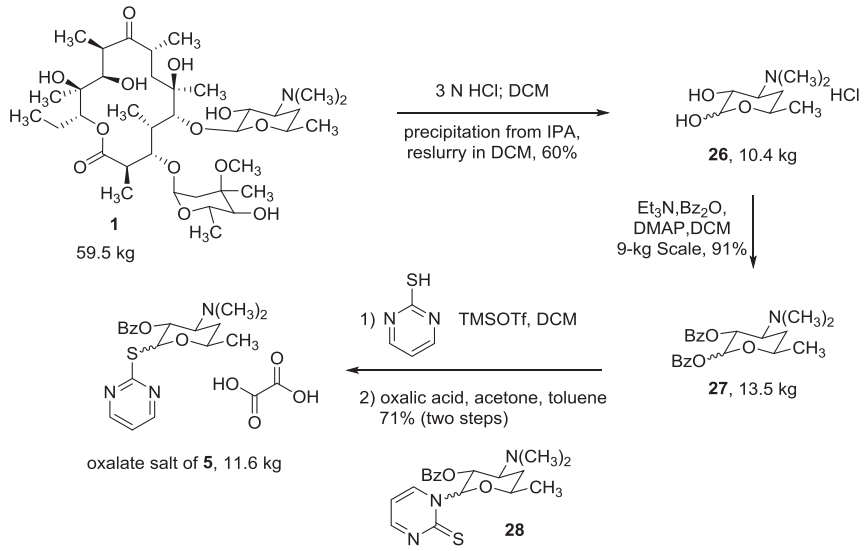
We returned to the earlier described preparation of **18**, which was attractive from the standpoint that it used cheap and readily available reagents of high optical purity, obviating the need for the use of an expensive chiral catalyst.[9] This route, depicted in Scheme 2, has been used for manufacturing of multi-kilogram amounts of **18**. The route begins with the commercially available amino alcohol **20**. The formamide derivative (**21**) was conveniently prepared by treatment of **20** with catalytic ammonium formate in formamide with heating at 150 °C. Inversion of the hydroxyl group within **21** to provide **22** was achieved essentially by the method of Tishler and colleagues, with slight modifications.[12] In our hands, treatment of **21** with neat thionyl chloride led to modest yields of **22**, and the quench of almost neat thionyl chloride produced large volumes of gas as well as a significant exotherm. Alternatively, we found that use of acetonitrile as solvent provided **22** in good yield after hydrolysis, and the quench was a well-controlled process. Formylation of the amino group within **22** with formic acid and acetic anhydride proceeded uneventfully to afford **23** in 95% yield provided that a slight excess of formic acid relative to acetic anhydride was used. Otherwise, small amounts of the corresponding acetamide were observed as a contaminant. Reduction of the formamide **23** provided (*R,R*)-pseudoephenamine (**18**) in 83% yield and 100% ee after crystallization from heptane. An improved procedure to make the glycinamide derivative **4** was also developed. Treatment of **18** with the reagent derived from addition of pivaloyl chloride (PivCl) to *N*-Boc glycine (**24**) and triethylamine provided the amide **25**, conveniently recrystallized from 2:1 toluene–heptane in 95% yield. Cleavage of the Boc group within **25** provided **4**, obtained in pure form from a toluene re-slurry.[13]

Desosamine donor

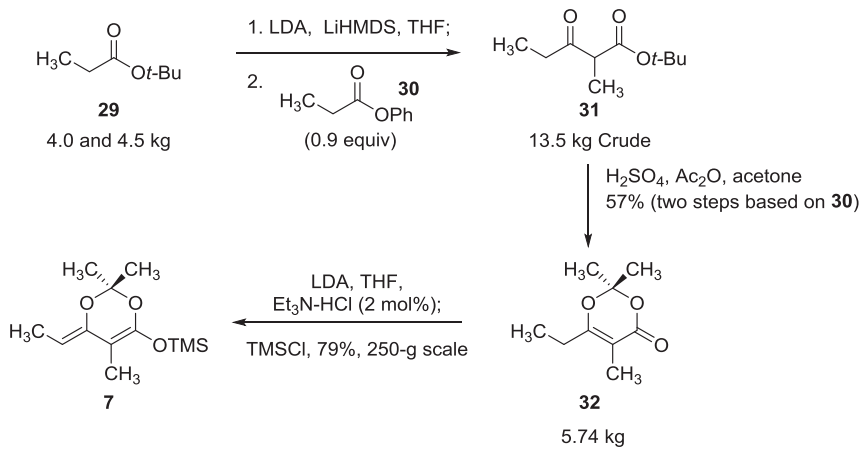
We have developed a suitable manufacturing route to the desosamine donor **5** by modification of literature protocols (Scheme 3).[14] In the optimized sequence, erythromycin (**1**, 59 kg) was treated with 3 N hydrochloric acid (HCl, 125 kg), at a temperature of 85 °C for 6 h. Toluene (45 kg) was added to the hot (85 °C) mixture and then the biphasic solution was allowed to cool to 25 °C whereupon dichloromethane (250 kg) was added. Failure to follow this protocol of solvent additions led to thick unstirrable mixtures. This first step differs from the original protocol reported using ethanol as a co-solvent. Omission of ethanol from this procedure avoided the formation of the corresponding ethyl glycoside of desosamine, a deleterious side product. Additionally, the original procedure used extensive extractions with chloroform, a solvent whose use is generally not considered acceptable for scale-up, to separate organic soluble by-products from the aqueous solution containing desosamine. After extraction of organic-soluble materials, the aqueous layer was concentrated and remaining water was removed azeotropically with 2-propanol, leading directly to the precipitation of desosamine hydrochloride **26**, conveniently isolated by filtration after a re-slurry in dichloromethane. This provided a smoother and more scalable isolation of **26** than the previously reported trituration of crude **26** with ethyl ether. After collection of the solids and drying, 10.4 kg of **26** was obtained in high purity. The anomeric benzoate esters **27** were prepared by treatment of **26** with benzoic anhydride and triethylamine in dichloromethane as solvent. The activated glycosidic donor **5** was best obtained by treatment of the anomeric benzoate esters **27** with thiopyrimidine and trimethylsilyl trifluoromethanesulfonate in dichloromethane.[15] In our hands, the use of boron trifluoride ethyl etherate provided lower yields. A small amount of a side product, tentatively assigned as **28**, was removed by filtration through a silica gel plug. As the free base of **5** is generally obtained as a foam after concentration, the donor **5** was most conveniently isolated on scale by precipitation from acetone/toluene as the corresponding oxalate salt (the free base form is typically obtained as a foam upon concentration) in 99.8 % HPLC purity (sum of anomers).

Silyl enol ether 7

The keto-ester **31** was manufactured using the practical and scalable cross-Claisen methodology reported by Zhang *et al.*[16] (Scheme 4). Thus the propionate ester **29** was added to a solution of lithium diisopropylamide (1.03 equiv.) in THF maintaining an internal temperature of < -65 °C. A solution lithium bis(trimethylsilylamide) (1.02 equiv.) in THF was then added, maintaining an internal temperature of < -65 °C, followed by a solution of phenyl propionate (**30**) in THF. A quenching solution of saturated ammonium chloride was then added. After phase separation, the organics were washed with 2 N sodium hydroxide followed by a water wash. This procedure was performed at the 4–4.5 kg scale of **29** twice, and the batches were combined without purification for the preparation of **32**. To a mixture of the combined batches of crude **31** (13.5 kg, uncorrected), acetone (8.5 kg) and acetic anhydride (22.5 kg) cooled to 0 °C was added sulfuric acid (7.4 kg) maintaining a temperature of < 15 °C. The mixture was then stirred for 4 h at 20 °C. After neutralization and workup, the product was distilled to provide 5.74 kg of **32** in 57% yield (two steps) in 99% purity (HPLC analysis). The silyl enol ether **7** has been prepared on ~300 g laboratory scale. This was achieved by adding the dioxinone **32** neat to a solution of lithium diisopropylamide (1.2 equiv.) containing a small amount of triethylamine hydrochloride (Et_3N•HCl, 0.02 equiv.) as recommended by Collum and colleagues for reactions promoted by lithium diisopropylamide.[17] Chlorotrimethylsilane (1.2 equiv.), distilled from



Scheme 3 Preparation of the oxalate salt of **5**.



Scheme 4 Manufacture of the silyl enol ether **7**.

calcium hydride, was added neat at −65 °C and the resultant mixture was allowed to stir for 2 h at this temperature. The mixture was allowed to warm to 0 °C and distillation *in vacuo* of the solvent led to the precipitation of inorganic salts. The mixture was further concentrated from heptanes and the suspended solids removed by filtration through a thin pad of Celite. Omission of the Celite as a filter aid led to slow filtrations not suitable for scale-up. After concentration of the filtrate, the residue was purified by high vacuum distillation to provide **7**. We typically observe the product to be contaminated with ~10% **32** (79% yield corrected), presumably due to some hydrolysis of **7** by adventitious moisture during processing.

(*R*)-3-((*tert*-butyldiphenylsilyl)oxy)pentan-2-one (6)

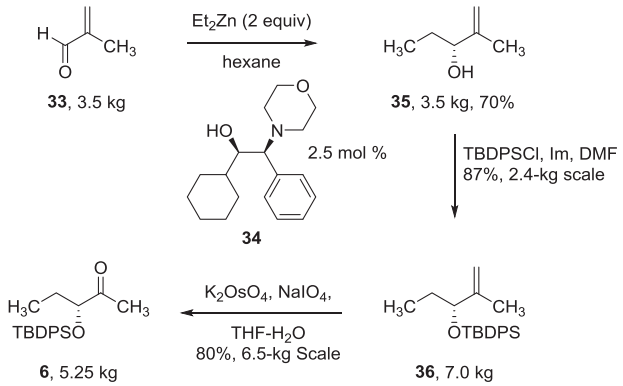
The fit-for-purpose manufacturing route to the ketone **6** was essentially performed without modification of the reported sequence (Scheme 5).[18] Thus a mixture of the ligand **34** (2.5 mol%) and diethylzinc in hexanes (1.0 M, 2 equiv.) was prepared at a temperature of <15 °C, and then the mixture was heated to a temperature of 35 °C for 1 h to generate, in our experience, the most active catalyst; incubation of diethylzinc and **34** at lower temperatures led to sluggish reactions with methacrolein (**33**) or reactions that did not proceed appreciably. After cooling, a solution of **33** in hexane (1 equiv.) was added maintaining a temperature of <15 °C. The alcohol **35** was isolated by vacuum distillation. Protection of the hydroxyl group within **35** was accomplished using *tert*-butyl(chloro)diphenylsilane (TBDPSCI) and imidazole (Im) to provide **36** in 87% yield. Oxidative cleavage of the alkene within **36** was then achieved using catalytic potassium osmate (1.5 mol%) and sodium periodate as the stoichiometric oxidant on a 6.5-kg scale. The final compound was purified by a fit-for-purpose silica gel filtration to obtain 5.25 kg of **6** in 80% yield and 98% ee (chiral HPLC).

In conclusion, we have preliminarily verified and demonstrated the scalability of building blocks that have been used to discover and manufacture on preclinical scales fully synthetic macrolide antibiotics. We anticipate improving both the cost of goods and efficiency of the processes described above as our program advances.

EXPERIMENTAL PROCEDURES

4,5-Diphenyl-5*H*-1,2,3-oxathiazole 2,2-dioxide (14)

To a solution of *tert*-butanol (420 ml, 4.44 mol, 1.35 equiv.) in anhydrous THF (3.5 litres) was added *N*-chlorosulfonyl isocyanate (357 ml, 4.11 mol, 1.25 equiv.) keeping the temperature between −10 and 0 °C. After 15 min, **11** (700 g, 3.3 mol, 1 equiv.) was added as a solid and then triethylamine (663 ml, 4.77 mol, 1.45 equiv.) was added via addition funnel keeping the temperature



Scheme 5 Manufacturing of ketone **6**.

between −10 and 0 °C. A suspension formed during the addition and after 30 min only a trace of benzoin remained by LC analysis. Water (11 litres) was added and the resulting suspension was cooled to 5 °C. The solids containing **13** were collected by filtration and washed with water (2 litres). The solids were suction dried for 48 h and then suspended in toluene (7 litres). *p*-Toluenesulfonic acid (20 g, 105 mmol, 0.03 equiv.) was added and the mixture was refluxed under Dean–Stark conditions with water removal until the reaction was complete by LC. The reaction was allowed to cool to 40 °C and ethyl acetate (6 litres) was added followed by saturated aqueous sodium bicarbonate (2 litres). The organics were separated and dried over sodium sulfate (250 g). The sodium sulfate was removed by filtration and the organics were concentrated *in vacuo* to dryness. The obtained solids were suspended in *tert*-butyl methyl ether (2.8 litres) and heated to 55 °C while stirring for 1.5 h. The resulting slurry was cooled to 2 °C for 2 h, and the solids were collected by filtration and washed with *tert*-butyl methyl ether (1.5 litres). The solids were dried *in vacuo* to provide **14** (672 g, 75% yield) whose spectral properties were found to be in accordance with those previously reported.[10]

(4*R*,5*S*)-4,5-Diphenyl-1,2,3-oxathiazolidine 2,2-dioxide (15)

To a mixture of **14** (669 g, 2.44 mol) and ethyl acetate (6 litres) was added freshly distilled formic acid-triethylamine complex (1.83 kg). The catalyst RhCl[(S,S)-TsDPEN)Cp* (780 mg, 0.05 mol %) was added in a single portion and the resulting mixture was allowed to stir at 20 °C for 18 h at which time LC/MS analysis indicated consumption of **14**. The mixture was added to 20% w/w citric acid in water (5 litres) and stirred for 15 min. The phases were separated and the organics were washed with water (3 litres). The organics were passed through a silica gel pad (500 g) which was preequilibrated with ethyl acetate. The silica gel pad was further eluted with ethyl acetate (2.5 litres) and the combined filtrates were concentrated *in vacuo* to provide **15** (655 g, 97% yield) whose spectral properties were found to be in accordance with those previously reported.[10]

tert-Butyl (4R,5S)-4,5-diphenyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (16)

To a solution of **15** (254 g, 922 mmol, 1 equiv.) in dichloromethane (1.2 litres) was added di-*tert*-butyl dicarbonate (211 g, 968 mmol, 1.05 equiv.) and DMAP (4.5 g, 37 mmol, 0.04 equiv.). The resulting mixture was allowed to stir for 1 h at 20 °C, and then saturated aqueous sodium bicarbonate (600 ml) was added. The mixture was stirred vigorously for 0.5 h, and the resultant phases were allowed to separate. The organics were separated and passed through a pad of silica gel (250 g) preequilibrated with dichloromethane. The silica gel pad was further eluted with ethyl acetate (1.25 litres), and the combined filtrates were concentrated *in vacuo* to provide **16** (334 g, 96% yield) whose spectral properties were found to be in accordance with those previously reported.[10]

(1*R*,2*R*)-Pseudoephenamine (18) from *tert*-butyl (4R,5S)-4,5-diphenyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (16)

To a cooled mixture of cesium carbonate (289 g, 889 mmol, 1 equiv.) in dimethylformamide (DMF; 600 ml) was added formic acid (67 ml, 1.77 mol, 2 equiv.) while stirring and maintaining a temperature of <25 °C. A solution of **16** (60 g, 160 mmol) was charged in DMF (300 ml) and a separate portion of **16** (273 g, 728 mmol) was charged as a solid. DMF (450 ml) was used as a rinse to quantitate transfers. After stirring 19 h at 20 °C, the mixture was added to 20% w/w citric acid in water (4.75 litres) and ethyl acetate (2.75 litres). The organics were separated and the aqueous layer was washed with MTBE (500 ml). The combined organics were washed with saturated sodium bicarbonate (1 litres), followed by consecutive washes of water (2 litres) and saturated aqueous sodium chloride (1 litre). The organics were then concentrated *in vacuo* to give **17** as a solid. To the crude **17** suspended in methanol (1.5 litres) was added potassium carbonate (50 g). The resultant mixture was vigorously agitated at 20 °C for 1 h. The suspension was filtered through a thin pad of Celite and the resultant Celite bed was washed with methanol (2 litres). The combined filtrates were concentrated *in vacuo*. To the obtained solids were added ethyl acetate (2.5 litres) and water (1 litre). The resultant organic phase was separated, dried over sodium sulfate and concentrated *in vacuo*. To the residue was added toluene (2.5 litres) and 500 ml was removed by distillation on a rotary evaporator at reduced pressure. To this solution was added Red-Al (290 ml, ~ 60% wt in toluene, 891 mmol) while keeping the temperature between −20 and 0 °C. The reaction was allowed to warm to 20 °C and Red-Al (655 ml, 2.01 mol) was added while warming the reaction with a heating mantle (set to 80 °C). After the addition, the temperature exceeded 80 °C and went as high as 105 °C. The mantle was then removed, and cooled with a water bath until the temperature fell below 80 °C. The mixture was maintained at 80 °C for 3 h and then cooled in a dry ice/acetone bath. Methanol (280 ml) was added keeping the temperature <30 °C. The reaction contents were added to mixture of toluene (1 litre), Na/K tartrate tetrahydrate (850 g) and water (2 litres). The mixture was stirred overnight. The organics were separated and the aqueous phase was extracted with MTBE (1 litre). The combined organics were washed with 1 N hydrochloric acid (1×1 litre, 1×0.5 litres). To the combined acidic washes was added a mixture of 1:1 MTBE–toluene (1.5 litres) and sodium hydroxide (80 g) while stirring. The organics were separated when all the solids dissolved and the aqueous was re-extracted with 1:1 toluene–MTBE (0.5 litres). The combined organics were dried over sodium sulfate and concentrated *in vacuo*. The resultant solids were slurried in heptane (1 litre) at 60 °C and then cooled to 0 °C . After 1 h, the solids were collected by filtration and dried to give **18** (175 g, 86% yield over three steps) whose spectral properties were found to be in accordance with those previously reported.[9]

Analytical data for 17

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (s, 1H), 7.31–7.22 (m, 8H), 7.18–7.16 (m, 2H), 6.15 (d, *J*=6.0 Hz, 1H), 5.19 (s, 1H), 5.15 (s, 1H), 1.38 (bs, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.96, 155.11, 138.56, 136.53, 128.47, 128.40, 128.34, 127.74, 127.1, 126.99, 79.97, 77.61, 58.82, 28.27.

N-((1*R*,2*S*)-2-Hydroxy-1,2-diphenylethyl)formamide (21)

To a 30-litre glass reactor was added formamide (18.0 kg, 400 mol, 18.9 equiv.), (1*S*,2*R*)-2-amino-1,2-diphenylethan-1-ol (**20**, 4.50 kg, 21.1 mol, 1 equiv.) and ammonium formate (270 g, 428 mmol, 0.02 equiv.). The resulting mixture was heated to 150 °C for 2 h with agitation. The mixture was cooled to 50 °C and the reaction was repeated at the same scale. The combined reactions were treated with H_2O (36.0 litres) and stirred at 25 °C for 2 h. The resultant solid was isolated by filtration and the wet cake was washed with H_2O (18.0 litres). The solid was dried *in vacuo* at 50 °C to provide **21** (9.48 kg, 93% yield) whose spectral properties were found to be in accordance with those previously reported.[9]

(1*R*,2*R*)-2-Amino-1,2-diphenylethan-1-ol (22)

To a 50-litre reactor was added CH_3CN (14.0 kg) and alcohol **21** (9.35 kg, 38.8 mol 1 equiv.). The resulted mixture was cooled to 0 °C and the first portion of $SOCl_2$ (11.2 kg, 94.1 mol, 2.42 equiv.) was added slowly while maintaining the temperature at <15 °C. The reaction was then stirred at 0 °C for 30 min. The second portion of $SOCl_2$ (21.1 kg, 177.4 mol, 4.57 equiv.) was added slowly while maintaining the temperature at <15 °C. The reaction was then stirred at 0 °C for 2 h. To a 500-litre reactor was added H_2O (140 litres) and then cooled to 5 °C. The $SOCl_2$ solution was then added slowly into the

reactor while maintaining the temperature at <30 °C. The suspension was heated to 90 °C. After 12 h, the mixture was cooled to 5 °C and then aqueous sodium hydroxide (25%, 112 kg) was added slowly to adjust to pH >11. The suspension was stirred at 15 °C for 2 h and the solid was isolated by filtration. The wet cake was washed with H_2O (19 litres) and dried at 50 °C for 18 h. The solid was slurried in *n*-heptane (15.9 kg) and anhydrous ethanol (3.65 kg) at 15 °C for 18 h. The solid was isolated by filtration and the wet cake was washed with *n*-heptane (13.0 kg). The solid was dried *in vacuo* at 50 °C to provide **22** (7.2 kg, 85% yield, 100% ee) whose spectral properties were found to be in accordance with those previously reported.[9]

N3-((1*R*,2*R*)-2-Hydroxy-1,2-diphenylethyl)formamide (23)

To a 50-litre reactor was added acetic anhydride (Ac_2O, 6.7 kg, 65.5 mol, 2.00 equiv.) and formic acid (3.63 kg, 78.6 mol, 2.4 equiv.). The mixture was warmed to 60 °C, stirred for 1 h and then cooled to 10 °C. To a 300-litre reactor was added 2-methyltetrahydrofuran (2-MeTHF, 91 kg) and amino alcohol **22** (6.98 kg, 32.7 mol, 1 equiv.). The suspension was cooled to -40 °C. The solution of anhydride was added slowly into the suspension of **22** while maintaining the temperature at <-30 °C. The resultant solution was stirred at -40 °C for 1 h and then warmed to 25 °C. After 2 h, the mixture was cooled to 0 °C and aqueous sodium hydroxide (20%, 84.0 kg) was added slowly into the mixture while maintaining the temperature at <15 °C. The mixture was then stirred at 25 °C for 2 h. Stirring was discontinued and the layers were allowed to separate. After 1 h, the aqueous was removed and the organic phase was washed with 10% aqueous sodium chloride (63.0 kg). The organic phase was concentrated *in vacuo* to a total volume of 21 litres. 2-MeTHF (18.2 kg) was added into the reactor and the mixture was concentrated *in vacuo* to about 21 litres, and this process was repeated once more. *n*-Heptane (28.7 kg) was added slowly with stirring and the resultant suspension was stirred at 10 °C for 2 h. The solid was isolated by filtration and the wet cake was washed with *n*-heptane (9.8 kg). The solid was dried *in vacuo* at 50 °C to provide **23** (7.6 kg, 95% yield) whose spectral properties were found to be in accordance with those previously reported.[9]

(1*R*,2*R*)-2-(Methylamino)-1,2-diphenylethan-1-ol (18)

To a 200-litre reactor was added toluene (31.0 kg), THF (13.0 kg) and **23** (7.28 kg, 30.2 mol, 1 equiv.). The mixture was cooled to 0 °C and lithium aluminum hydride (1.0 M in THF, 48.0 kg, 53.5 mol, 1.77 equiv.) was added slowly into the mixture while maintaining the temperature at <15 °C. The mixture was stirred at 0 °C for 0.5 h and then warmed at 50 °C for 12 h. The mixture was cooled to 0 °C and H_2O (2.2 kg) was added slowly while maintaining the temperature <20 °C. Aqueous sodium hydroxide (8%, 4.6 kg) was added followed by H_2O (6.6 litres). The resultant suspension was stirred at 20 °C for 1 h and then filtered. The wet cake was washed with THF (13.0 kg). The combined filtrate was concentrated *in vacuo* to a volume 22 litres. THF (20 kg) was added and the mixture was concentrated *in vacuo* to about 22 litres. *n*-Heptane (30.0 kg) was added slowly and the suspension was stirred at 15 °C for 2 h. The resultant solid was isolated by filtration and the wet cake was washed with *n*-heptane (10.0 kg). The solid was dried *in vacuo* at 50 °C to provide **18** (6.28 kg, 83% yield, 99% HPLC purity) whose spectral properties were found to be in accordance with those previously reported.[9]

tert-Butyl (2-(((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)(methyl) amino)-2-oxoethyl)carbamate (25)

N-Boc-glycine (**24**, 114 g, 0.651 mol, 1.28 equiv.) was dissolved in dichloromethane (920 ml) and cooled to 0 °C. Triethylamine (91.4 ml, 0.655 mol, 1.3 equiv.) was then added dropwise while maintaining the temperature at <3 °C (5 min addition time). The mixture was stirred for 0.5 h. Pivaloyl chloride (74.4 ml, 0.605 mol, 1.20 equiv.) was then added dropwise while maintaining the temperature at <3 °C. The resultant white suspension was stirred for 40 min and then a second portion of triethylamine (91.4 ml, 0.655 mol, 1.3 equiv.) was added dropwise while maintaining the temperature at <5 °C. Finely powdered (1*R*,2*R*)-pseudoephenamine (**18**, 115 g, 0.506 mol, 1 equiv.) was added in portions over 20 min while maintaining the temperature at <5 °C. The reaction mixture was allowed to stir at 0 °C for 1 h. The mixture was then washed with H_2O (920 ml) and saturated aqueous sodium bicarbonate (920 ml). The organics were concentrated *in vacuo* while azeotropically drying with toluene (2×575 ml). The residue was slurried in a mixture of toluene (581 ml) and hexanes (290 ml) at 20 °C for 1 h. The suspension was filtered and the wet cake was washed with toluene (290 ml) and hexanes (145 ml). The solid was dried under a stream of nitrogen to provide **25** (178 g, 95% yield) whose spectral properties were found to be in accordance with those previously reported.[13]

2-Amino-*N*-((1*R*,2*R*)-2-hydroxy-1,2-diphenylethyl)-*N*-methylacetamide (4)

To a solution of **25** (178 g, 0.478 mol) in dichloromethane (558 ml) cooled to 10 °C, trifluoroacetic acid (291 ml, 3.82 mol, 8 equiv.) was added slowly while maintaining the temperature at <15 °C. After 1 h, the reaction was warmed to 20 °C and stirred for 16 h. Upon reaction completion, the reaction mixture was concentrated *in vacuo* with toluene (3×581 ml) to yield a yellow oily residue (385 g). The residue was dissolved in dichloromethane (2.61 litres) and cooled to 10 °C. The solution was stirred vigorously while 3 M aq. NaOH was added slowly at a temperature of $\leqslant15$ °C until the solution reached a pH of ~13–14. Stirring was discontinued and the layers were separated. The aqueous layer was back extracted with dichloromethane (2×372 ml). The combined organic layers were washed with H_2O (2×558 ml) and then concentrated *in vacuo* to a total volume of ~1 litre. Potassium carbonate (160 g) was added and the suspension was stirred for 0.5 h. The solids were removed by filtration through Celite and the filtrate was concentrated *in vacuo* with toluene (3×581 ml). The formed solids were re-slurried in toluene (744 ml) at 23 °C for 6 h and then 0 °C for 2 h. The product was isolated by filtration, washed with toluene (127 ml) and dried *in vacuo* to provide **4** (130 g, 94% yield) in 98% HPLC purity whose spectral properties were found to be in accordance with those previously reported.[13]

(3*R*,4*S*,6*R*)-4-(Dimethylamino)-6-methyltetrahydro-2*H*-pyran-2,3-diol, hydrochloric acid salt (26)

Erythromycin (**1**, 59.5 kg, 81.1 mol) and 3 N hydrochloric acid (125 kg) were added to a 500-litre reactor. The mixture was heated to 85 °C and stirred for 6 h. Toluene (41 kg) was added to the mixture at 85 °C. The mixture was cooled to 25 °C and dichloromethane (250 kg) was added. The mixture was stirred for 1 h and the layers were then allowed to settle for 1 h. The organic layer was removed and the aqueous layer was washed with dichloromethane (3×44 kg). The aqueous solution was concentrated *in vacuo* at <70 °C. 2-Propanol (141 kg) was added to the residue and the mixture was concentrated *in vacuo* at <55 °C (repeated $2\times$) to yield an off-white solid. Dichloromethane (154 kg) was added to the residue and the mixture was concentrated *in vacuo* at <40 °C. The resultant solid was slurried in dichloromethane (78 kg) at 15 °C for 12 h. The suspension was filtered and the wet cake was washed with dichloromethane (24 kg) and dried *in vacuo* at 40 °C to provide **26** (11.26 kg solid, 10.4 kg corrected, 60% yield) whose spectral properties were found to be in accordance with those previously reported.[15]

(3*R*,4*S*,6*R*)-4-(Dimethylamino)-6-methyltetrahydro-2*H*-pyran-2,3-diyl dibenzoate (27)

In a 500-litre reactor, diol **26** (9.00 kg, 42.5 mol, 1 equiv.) was suspended in dichloromethane (96 kg). The mixture was cooled to 0 °C and triethylamine (17.1 kg, 169 mol, 4 equiv.) was added slowly while maintaining the temperature at <5 °C. DMAP (0.60 kg, 4.91 mol, 0.12 equiv.) was added. A solution of benzoic anhydride (23.4 kg, 103 mol, 2.42 equiv.) in dichloromethane (24 kg) was then added slowly over 20 h while maintaining the temperature at <5 °C. After 0.5 h, the mixture was warmed to 25 °C and stirred for 16 h. Upon reaction completion, the mixture was cooled to 15 °C and quenched with saturated aqueous $NaHCO_3$ (98 kg) while maintaining the temperature at <30 °C. The layers were separated and the organic was washed with saturated aqueous sodium bicarbonate (48 kg) and H_2O (46 kg). The organics were concentrated *in vacuo* at <40 °C. Toluene (78 kg) was added to the residue and the mixture was concentrated *in vacuo* at <60 °C. The mixture was cooled to 15 °C and 0.5 N hydrochloric acid (109 kg) was added to the residue. The aqueous mixture was washed with MTBE (40 kg) and then adjusted to a pH of 9 with solid potassium carbonate (5.5 kg). The aqueous mixture was extracted

with MTBE (67 kg) and the organic layer was concentrated *in vacuo* at <45 °C. Ethyl acetate (18 litres), heptane (9 litres) and silica gel (5.1 kg) were added and the resultant mixture was stirred at 25 °C for 2 h. The mixture was filtered through a silica gel pad (9 kg) and the pad was further eluted with a mixture of ethyl acetate (68 litres) and heptane (23 litres). The combined filtrates were concentrated *in vacuo* to about ~30 litres at <50 °C to provide **27** as a solution (25.4 kg solution, Assay: 53.3%, 90.5% yield) whose spectral properties were found to be in accordance with those previously reported.[15]

(3*R*,4*S*,6*R*)-4-(Dimethylamino)-6-methyl-2-(pyrimidin-2-ylthio) tetrahydro-2*H*-pyran-3-yl benzoate, oxalate salt (oxalate salt of 5)

A solution of **27** (25.2 kg, 53.3% assay, 35.0 mol, 1 equiv.) was charged into a 200-litre reactor. The mixture was concentrated *in vacuo* at <50 °C. Toluene (47 kg) was added and the mixture was concentrated *in vacuo* at <55 °C. The mixture was cooled to 20 °C and dichloromethane (74 kg) was charged to the residue. Pyrimidine-2-thiol (4.6 kg, 41.0 mol, 1.17 equiv.) was added and the mixture was cooled to −5 °C. Trimethylsilyl trifluoromethanesulfonate (23.2 kg, 104 mol, 3 equiv.) was added slowly while maintaining the temperature at <0 °C. The mixture was stirred for 0.5 h and then allowed to slowly warm to 25 °C. The mixture was stirred for 16 h. Upon reaction completion, the mixture was cooled to 0 °C and added slowly to saturated aqueous sodium bicarbonate (146 kg) while maintaining the temperature at <5 °C. Dichloromethane (74 kg) was added followed by saturated aqueous potassium carbonate (35 kg). The mixture was heated to 25 °C and stirred for 0.5 h (aqueous pH = 9). The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate (58 kg). The organic layer was concentrated *in vacuo* at <40 °C. The mixture was cooled to 15 °C and dissolved in aqueous citric acid (136 kg, 4.63% w/w). The aqueous mixture was washed with MTBE (2 × 26 kg) and the aqueous layer was made basic with potassium carbonate (9.7 kg) to a pH of 8.4. The product was extracted with MTBE (81 kg) and the organic layer was washed with H_2O (41 kg). The organics were concentrated *in vacuo* at <45 °C. Toluene (47 kg) was added to the residue and the mixture was concentrated *in vacuo* at <60 °C. Toluene (11 kg) was added to the residue and the mixture was heated to 25 °C and stirred for 0.5 h. The toluene solution was filtered through a silica pad (25.9 kg, preequilibrated with hexanes). The silica pad was washed with a mixture of 20% acetone in hexanes containing 1% triethylamine (323 kg). Sufficiently pure fractions were combined and concentrated *in vacuo* at <45 °C. Toluene (47 kg) was added to the residue and the mixture was concentrated at <60 °C. The mixture was cooled to 25 °C and acetone (16 kg) was added followed by anhydrous oxalic acid (2.70 kg, 30.0 mol). The suspension was stirred at 25 °C for 2 h. Toluene (24 kg) was added slowly to the mixture and then cooled to 10 °C. After 2 h, the suspension was filtered and the wet cake was washed with toluene (12 kg). The yellow solid was dried *in vacuo* at ⩽45 °C to provide the oxalate salt of 5 (11.6 kg, 71.4% yield) in 99.8 % HPLC purity (sum of anomers).

Analytical data for the oxalate salt of 5

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 5.2 Hz, 2H), 7.88–7.86 (m, 2H), 7.65–7.60 (m, 1H), 7.46 (dd, J = 7.6 Hz, 2H), 7.25 (dd, J = 4.8 Hz, 1H), 5.88 (d, J = 9.6 Hz, 1H), 5.31 (t, J = 10.0 Hz, 1H), 3.88 (dtt, J = 13.3, 7.1, 3.5 Hz, 1H), 3.77–3.71 (m, 1H), 2.55 (s, 6H), 2.11 (bd, J = 12.0 Hz, 1H), 1.67 (q, J = 12.1 Hz, 1H), 1.23 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 170.17, 167.40, 165.88, 159.10, 159.03, 134.93, 131.08, 130.18, 129.63, 119.24, 84.14, 74.25, 69.14, 66.11, 40.56, 31.28, 21.28, 21.24.

tert-Butyl 2-methyl-3-oxopentanoate (31)

Hexamethyldisilazane (5.08 kg, 31.5 mol, 1.02 equiv.) was dissolved in THF (11 kg) and cooled to −20 °C. A solution of *n*-BuLi (2.5 M, hexanes, 12.6 litres, 31.6 mol, 1.03 equiv.) was added slowly while maintaining the temperature at <−5 °C. In another vessel, diisopropylamine (3.20 kg, 31.6 mol, 1.03 equiv.) was dissolved in THF (22 kg) and then cooled to −65 °C. *n*-BuLi (2.5 M, hexanes, 12.6 litres, 31.6 mol, 1.03 equiv.) was added slowly followed by slow addition of *tert*-butyl propionate (**29**, 4.00 kg, 30.7 mol, 1 equiv.) at ⩽−65 °C. The solution of LiHMDS in THF was then added slowly at ⩽−65 °C followed by a solution of phenyl propionate (**30**, 4.16 kg, 27.7 mol, 0.90 equiv.) in THF (6 kg) at ⩽−65 °C. The reaction was stirred at ⩽−65 °C for 1 h. Upon reaction completion, 20% aqueous ammonium chloride (24 kg) was added slowly. The mixture was allowed to warm to 23 °C and the phases were separated. A solution of 2 N sodium hydroxide (28 kg) was added to the organic phase and the mixture was stirred for 6 h. The phases were then separated and the organic phase was washed with water (3 × 20 litres). The organic layer was concentrated *in vacuo* to provide crude **31** (6.7 kg). This procedure was repeated on a second batch at a similar scale (*tert*-butyl propionate (4.5 kg, 34.6 mol)) using the same procedure to yield crude product (7.0 kg) whose spectral properties were found to be in accordance with those previously reported.[16] This material was used directly in the next step.

6-Ethyl-2,2,5-trimethyl-4*H*-1,3-dioxin-4-one (32)

A mixture of the combined lots of crude **31** (13.5 kg, 73.5 mol, 1 equiv.), acetone (8.50 kg, 146 mol) and acetic anhydride (22.5 k g, 220 mol, 3 equiv.) was cooled to 0 °C. A solution of concentrated sulfuric acid (7.40 kg, 74.0 mol, 1.01 equiv.) was added slowly while maintaining the temperature at ⩽15 °C. The reaction was then stirred at 23 °C for 4 h. Upon reaction completion, the reaction mixture was added into cooled water (15.1 litres) at ⩽10 °C. A solution of 4 N sodium hydroxide was added while maintaining the temperature at ⩽10 °C until pH 7–8. The mixture was stirred for 0.5 h at 10 °C. The mixture was then extracted with MTBE (2 × 67 kg) and the combined organic layers were washed with H_2O (25 litres). The organic phase was concentrated *in vacuo*. The residue was then purified by vacuum distillation (100 °C, −0.09 MPa) to provide **32** (5.74 kg, 57% 2-step yield, 99% HPLC purity) whose spectral properties were found to be in accordance with those previously reported.[16]

(*Z*)-((4-Ethylidene-2,2,5-trimethyl-4*H*-1,3-dioxin-6-yl)oxy) trimethylsilane (7)

To a cooled suspension of triethylamine hydrochloride (0.02 eq, 4.41 g) in THF (1620 ml) was added diiisopropylamine (270 ml) and *n*-BuLi (2.5M, 784 ml) keeping the temperature between −10 and −20 °C. The mixture was cooled in a dry ice acetone bath and **32** (d = 1.04, 264 ml) was added maintaining a temperature between −65 and −70 °C, The resultant orange mixture was stirred for 1 h at −73 °C and chlorotrimethylsilane (244 ml) was added keeping the temperature at <−68 °C. After 2 h, the reaction was allowed to warm freely to 20 °C over 1 h and then concentrated at 35 °C (bath temperature) at a pressure of 30 mbar. Heptane (1 litre) was added and the mixture was concentrated *in vacuo*. To the resulting suspension was added heptane (2 litres) and the solids were removed by filtration through a small pad of Celite while under a blanket of nitrogen. The pad was further eluted with heptane (1 litre). Concentration of this solution and distillation of the residue as previously reported provided the silyl enol ether 7 (330 g) containing ~10 mol% **32** (79% yield corrected) by 1H NMR analysis and whose spectral properties were found to be in accordance with those previously reported. 15

(*R*)-2-Methylpent-1-en-3-ol (35)

To a 200-litre vessel was added (1*R*,2*S*)-1-cyclohexyl-2-morpholino-2-phenylethan-1-ol (**34**, 360 g, 1.25 mol%) and *n*-hexane (9.5 kg) under an atmosphere of nitrogen. A solution of diethylzinc (1.0 M in hexanes, 100 litres, 100 mol, 2 equiv.) was added to the mixture while maintaining the temperature at ⩽15 °C. The mixture was heated to 35 °C and stirred for 1 h. The mixture was cooled to 15 °C and a solution of methacrolein (**33**, 3.50 kg, 50.0 mol, 1 equiv., freshly distilled) in hexane (21.0 kg) was added slowly over 2 h while maintaining the temperature at ⩽15 °C. The mixture was stirred for 16 h at 15 °C. Upon reaction completion, the reaction mixture was quenched slowly into a solution of 20% aqueous ammonium chloride (120 kg). The mixture was filtered and the solid was washed with hexane (24.0 kg). The combined filtrates were separated and the organic layer was washed with aqueous sodium chloride (15%, 2 × 60.0 kg). The organics were concentrated *in vacuo* at <10 °C. The residue was purified by vacuum distillation (65–68 °C at ~40 Torr) to provide **35** as a colorless liquid (3.5 kg, 70% yield) whose spectral properties were found to be in accordance with those previously reported.[18]

(*R*)-*tert*-Butyl((2-methylpent-1-en-3-yl)oxy)diphenylsilane (36)

To a 50-litre vessel was charged **35** (2.40 kg, 24.0 mol, 1 equiv.) and imidazole (3.30 kg, 48.0 mol, 2 equiv.) in DMF (24 litres). TBDPSCl (7.90 kg, 28.8 mol, 1.2 equiv.) was added to the mixture over 0.5 h while maintaining the

temperature at ⩽15 °C. The reaction was stirred for 20 h at 23 °C. The reaction was added to a mixture of H_2O (72 litres) and heptane (66 litres). The aqueous layer was removed and the organic phase was washed with H_2O (72 litres). The organics were concentrated *in vacuo* at ⩽40 °C. The crude product was filtered through a pad of silica gel (12.0 kg) eluting with heptane to provide **36** as a colorless oil (7.0 kg, 86.4% yield) whose spectral properties were found to be in accordance with those previously reported.[18]

(*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)pentan-2-one (6)

To a 300-litre vessel was charged **36** (6.5 kg, 19.2 mol, 1 equiv.), 2,6-lutidine (4.1 Kg, 38.4 mol, 2 equiv.), THF (3.5 litres), and water (1.5 liters) and the resultant mixture was cooled to 15 °C. Potassium osmate dihydrate (0.11 kg, 0.29 mol) and $NaIO_4$ (16.4 kg, 76.8 mol, 4 equiv.) were added and the mixture was heated to 25 °C and stirred for 20 h. Upon reaction completion, the mixture was cooled 5 °C. An aqueous solution of sodium thiosulfate (18%, 142 kg) was added to the mixture over 2 h. Upon complete addition, the mixture was stirred at 5 °C for 1 h. Heptane (93.0 kg) was added and the resultant suspension was filtered. The solid was washed with hexane (10.0 kg). The organic layer was separated from the filtrate and washed with a solution sodium thiosulfate (4%, 2×73 kg) and aqueous copper (II) sulfate (5%, 2×73 kg). The organics were concentrated *in vacuo* at ⩽40 °C. The crude product was purified by filtration through a pad of silica gel (35.0 kg) eluting with 10% ethyl acetate in heptane to provide **6** as a pale yellow oil (5.25 kg, 80.4% yield) in 98% HPLC purity and 99% chiral HPLC purity whose spectral properties were found to be in accordance with those previously reported.[18]

DEDICATION

This manuscript is dedicated with respect and admiration to Professor KC Nicolaou in recognition of his manifold contributions to chemistry.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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