JOC The Journal of Organic Chemistry

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Asymmetric Syntheses of APTO and AETD: the β-Amino Acid Fragments within Microsclerodermins C, D, and E

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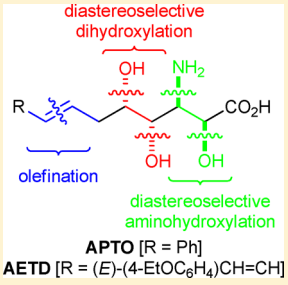
Supporting Information

ABSTRACT: Efficient asymmetric syntheses of APTO and AETD, the highly functionalized β-amino acid fragments within microsclerodermins C, D, and E, are reported. The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl (*E*,*E*)-7-(triisopropylsilyloxy)hepta-2,4-dienoate and in situ enolate oxidation with (−)-camphorsulfonyloxaziridine, diastereoselective dihydroxylation of a 2,3-*syn*-γ,δ-unsaturated-α-hydroxy-β-amino ester derivative under Donohoe conditions, and a Julia−Kocieński olefination were used as the key steps.



INTRODUCTION

Microsclerodermins A−I are a family of nine cyclic hexapeptide natural products, isolated from marine sponges of the *Microscleroderma* and *Theonella* genera native to the waters off New Caledonia and the Philippines.[1] All nine of these compounds exhibit antifungal activity against *Candida albicans* in a paper disk diffusion assay,[1] and microsclerodermins F−I have also been shown to display moderate cytotoxicity against the HCT-116 cell line.[1b] The structures of microsclerodermins A−I were elucidated by a combination of spectroscopic methods and chemical degradation studies. All the members of this family contain a 23-membered ring constructed of six amino acid residues; three amino acid residues are common to all members of the microsclerodermin family viz. glycine, sarcosine (*N*-methylglycine) and (*R*)-4-amino-3-hydroxybutyric acid (GABOB). In each case the three remaining amino acids comprise a substituted tryptophan residue, a 4-aminopyrrolidin-2-one-5-acetic acid residue, and a 2,4,5-trihydroxy substituted β-amino acid residue, with considerable variation in their substitution across the microsclerodermin family. In each case the identity of the 2,4,5-trihydroxy substituted β-amino acid residue was identified by a combination of evidence, including ^{1}H NMR NOE data, derivatization of the 4,5-dihydroxy unit to the corresponding *trans*-configured acetonide, and degradation to give (*S*,*S*)-3-hydroxyaspartic acid via oxidative cleavage of the 4,5-dihydroxy unit followed by hydrolysis of the resultant peptide. Microsclerodermin C **1** and microsclerodermin D **2**, for example, both contain the common β-amino acid residue (2*S*,3*R*,4*S*,5*S*,*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid (APTO), and microsclerodermin E **3** contains a (2*S*,3*R*,4*S*,5*S*,*E*,*E*)-3-amino-10-(4′-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid (AETD) residue (Figure 1).

The potent biological activity of the microsclerodermins has made them attractive targets for total syntheses. However, to date, only one member of the microsclerodermin family has been synthesized: in 2003 Zhu and Ma reported a total synthesis of microsclerodermin E **3**,[2] employing an enantiospecific synthesis of a protected AETD−GABOB dipeptide

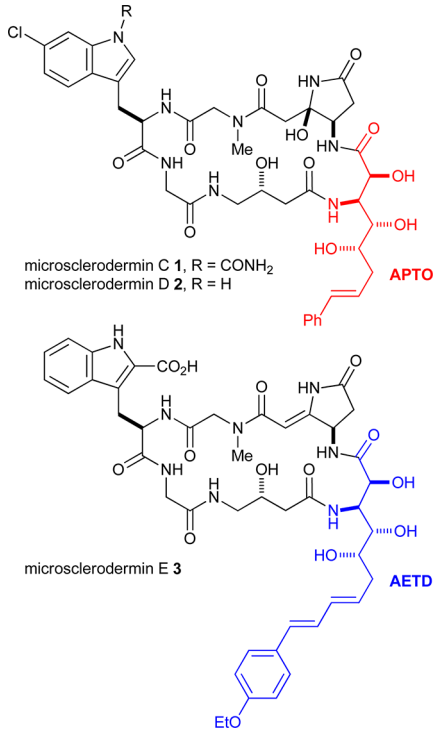


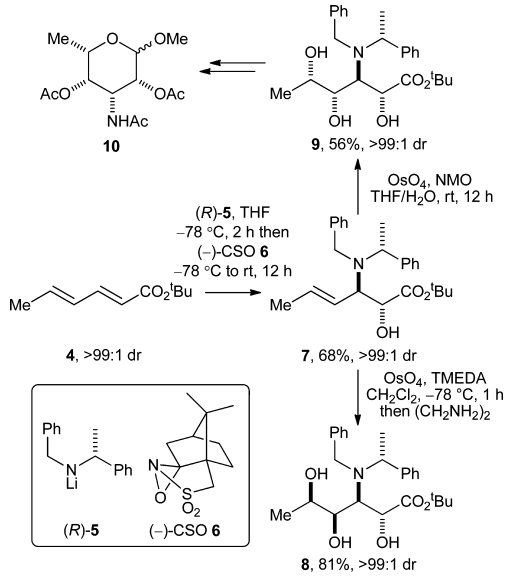
Figure 1. The structures of microsclerodermins C, D, and E **1**−**3**.

Received: December 17, 2012
Published: February 4, 2013

fragment from δ-gluconolactone. Since then, several other reports have described syntheses of the 2,4,5-trihydroxy substituted β-amino acid fragments within microsclerodermins A−I in protected form.[3] Shioiri et al. reported an enantiospecific synthesis of (2*S*,3*R*,4*S*,5*S*,6*S*,*E*)-3-amino-12-(4′-methoxyphenyl)-6-methyl-2,4,5-trihydroxydodec-11-enoic acid (AMMTD), the β-amino acid component within both microsclerodermins A and B, from methyl (*R*)-3-*O*-*tert*-butyldiphenylsiloxy-2-methylpropionate,[4] Chandrasekhar and Sultana have also reported an enantiospecific synthesis of AMMTD from (*S*)-citronellol,[5] and Burnett and Williams have reported studies toward (2*S*,3*R*,4*S*,5*S*,6*S*,*E*,*E*,*E*)-3-amino-6-methyl-12-phenyl-2,4,5-trihydroxydodeca-7,9,11-trienoic acid (AMPTD), the core β-amino acid component within microsclerodermins F and G.[6] However, of all the β-amino acid components within microsclerodermins A−I, (2*S*,3*R*,4*S*,5*S*,*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid (APTO), the β-amino acid component within both microsclerodermins C **1** and D **2**, has received the most interest from synthetic chemists. In 2007 McLeod et al. reported an asymmetric synthesis of APTO in protected form,[7] and as a Wittig olefination was used in the final step, their route was also applied to the synthesis of (2*S*,3*R*,4*S*,5*S*,*E*,*E*)-3-amino-10-(4′-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid (AETD), the β-amino acid component within microsclerodermin E **3**, also in protected form. More recently, Aitken et al.[8] have reported syntheses of protected forms of APTO and AETD from a 2-deoxy-D-ribose derivative,[9] and this was followed by a report by Dodd et al. in which APTO was produced from L-gulose.[10]

Previous investigations from our laboratory have demonstrated that the conjugate addition of enantiopure secondary lithium amides (derived from α-methylbenzylamines) to α,β-unsaturated esters represents a general and efficient synthetic protocol for the synthesis of β-amino esters and their derivatives.[11] This methodology has found numerous applications, including the total syntheses of natural products,[12] molecular recognition phenomena[13] and resolution protocols,[14] and has been reviewed.[15] We have recently extended the utility of this methodology to encompass the synthesis of amino sugars.[16] For example, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **5** to *tert*-butyl sorbate **4** followed by in situ oxidation of the resultant enolate with (−)-camphorsulfonyloxaziridine [(−)-CSO] **6** gave α-hydroxy-β-amino ester **7** in 68% yield as a single diastereoisomer (>99:1 dr). Subsequent *syn*-dihydroxylation of the C−C double bond within **7** upon treatment with the OsO_4/TMEDA complex (Donohoe conditions)[17] gave amino triol **8** in 81% yield and >99:1 dr. Alternatively, oxidation of **7** with OsO_4/NMO (Upjohn conditions)[18] produced antipodal diastereoselectivity, giving amino triol **9** as a single diastereoisomer (>99:1 dr). Subsequent elaboration of **9** gave the target 3,6-dideoxy-3-amino sugar **10** as a mixture of protected pyranose and furanose anomers (Scheme 1). As part of our ongoing research program in this area we became interested in the application of this methodology for the preparation of the 2,4,5-trihydroxy substituted β-amino acid fragments within the microsclerodermins, and we report herein our full investigations concerning the total asymmetric syntheses of APTO and AETD.

Scheme 1



RESULTS AND DISCUSSION

We envisaged that 2,3-*syn*-γ,δ-unsaturated-α-hydroxy-β-amino ester **13** would be a useful substrate for the synthesis of APTO (in the first instance) as it could be accessed from 2,3-*anti*-α-hydroxy-β-amino ester **12** via epimerization at the C(2)-position; in turn, **12** can be produced from **11** using our diastereoselective aminohydroxylation protocol.[15,19,20] Two alternative strategies for the elaboration of 2,3-*syn*-γ,δ-unsaturated-α-hydroxy-β-amino ester **13** were investigated. In the first of these two approaches, diastereoselective dihydroxylation of **13** would be followed by subsequent introduction of the styryl unit using the (protected) ζ-hydroxyl group within **14** as a synthetic handle (Route A, Figure 2). The second approach would involve olefination of **13** followed by regioselective dihydroxylation of γ,δ,ζ,η-diunsaturated-α-hydroxy-β-amino ester **16** (Route B, Figure 2). As we have already established that remarkable diastereoselectivity can be achieved upon dihydroxylation of acyclic γ,δ-unsaturated-α-hydroxy-β-amino

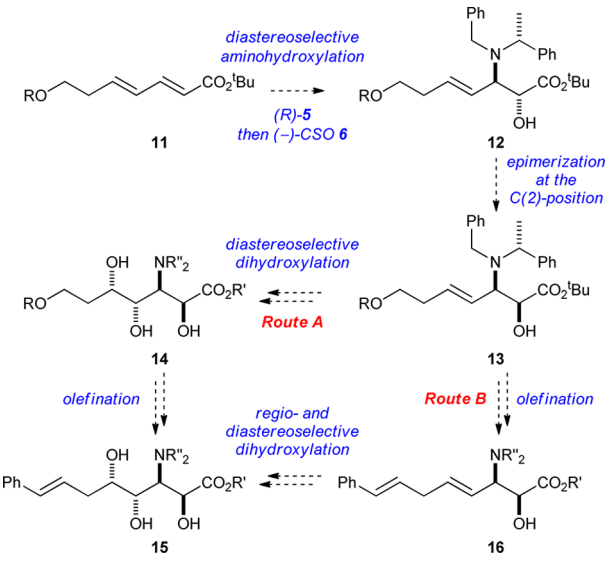


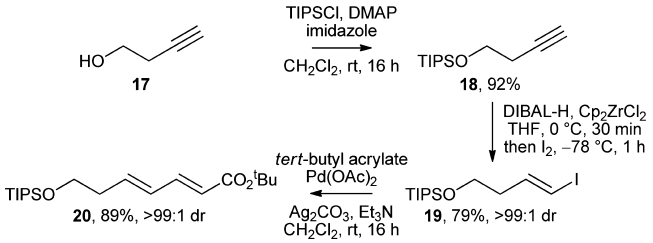
Figure 2. Proposed strategies to access APTO.

dx.doi.org/10.1021/jo302731m | *J. Org. Chem.* 2013, 78, 2500−2510

esters,[16] we sought to develop a reliable olefination procedure to install the required styryl moiety and therefore investigated "Route B" first.

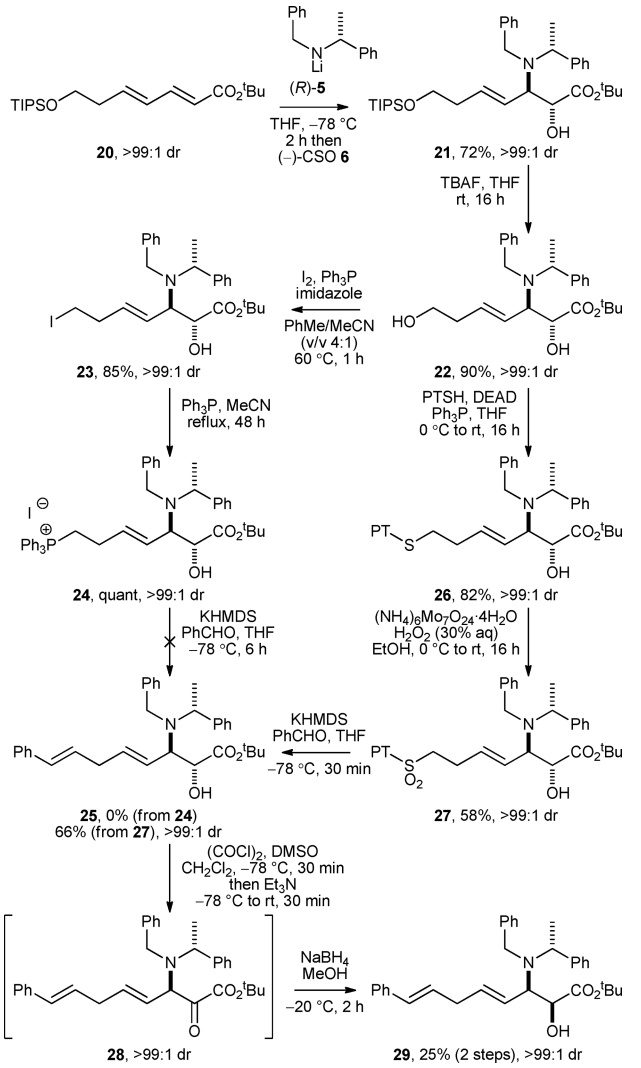
We have previously employed *O*-TIPS protection of *ω*-hydroxyl groups to good effect in the lithium amide conjugate addition reaction,[12a,b] so this protecting group was selected for our proposed syntheses of APTO and AETD. The requisite *α,β*-unsaturated ester **20** was prepared via a three step procedure from 3-butyn-1-ol **17**: initially, protection of the hydroxyl group within **17** was achieved upon treatment with TIPSCl in the presence of DMAP and imidazole, which gave **18** in 92% isolated yield. Subsequent reduction of **18** with DIBAL-H and Cp_2ZrCl_2,[21] followed by treatment with I_2 gave vinyl iodide **19** ($^3J_{1,2}$ = 14.4 Hz) in 79% yield as a single diastereoisomer (>99:1 dr). Heck coupling[22] of **19** with *tert*-butyl acrylate then gave *α,β*-unsaturated ester **20** in 89% yield and >99:1 dr (Scheme 2). The (*E,E*)-configuration within **20** was confirmed by ^{1}H NMR ^3J coupling constant analysis ($^3J_{2,3}$ = 15.4 Hz; $^3J_{4,5}$ = 15.4 Hz).

Scheme 2



Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(*α*-methylbenzyl)amide **5** to *α,β*-unsaturated ester **20** followed by oxidation of the intermediate lithium (*Z*)-*β*-amino enolate[23] with (−)-CSO **6** produced *β*-amino ester **21** as a single diastereoisomer (>99:1 dr), which was isolated in 72% yield and >99:1 dr after chromatographic purification. The stereochemical outcome of this transformation was initially assigned by reference to the well-established transition state mnemonic developed by us to rationalize the diastereoselectivity observed upon conjugate addition of lithium amides derived from *α*-methylbenzylamines,[24] and by analogy to the outcome of our aminohydroxylation protocol.[15,19,20] Subsequent treatment of **21** with TBAF gave **22** in 90% yield and >99:1 dr. The relative configuration within **22** was unambiguously assigned via single crystal X-ray diffraction analysis,[25] with the absolute (*R,R,R,E*)-configuration within **22** following from the known (*R*)-configuration of the *N*-*α*-methylbenzyl stereocenter; this analysis therefore also allowed the absolute configuration within **21** to be assigned unambiguously. Two potential routes to install the desired styryl moiety were then investigated. In the first instance, Appel reaction of **22** produced the corresponding iodide **23** in 85% yield, which was then converted to phosphonium iodide salt **24** in quantitative yield. Unfortunately all attempts at Wittig reaction of the ylid derived from **24** with benzaldehyde were unsuccessful. Attention then turned to our alternative strategy via a Julia–Kocieński olefination with benzaldehyde. Thus, Mitsunobu reaction of **22** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) gave **26** in 82% yield. Oxidation of **26** to the corresponding sulfone **27** was achieved upon treatment with ammonium molybdate tetrahydrate and H_2O_2, which gave **27** in 58% yield. Julia–Kocieński olefination, upon deprotonation of **27** with KHMDS followed by the addition of benzaldehyde, gave **25** in 66% yield and >99:1 dr. An oxidation/diastereoselective reduction sequence was then used to invert the configuration of the C(2)-stereogenic center within **25**: oxidation of **25** under Swern conditions, followed by immediate reduction of the intermediate ketone **28** with $NaBH_4$ gave 2,3-*syn*-*α*-hydroxy-*β*-amino ester **29** as a single diastereoisomer (>99:1 dr), which was isolated in 25% yield after purification (Scheme 3).

Scheme 3



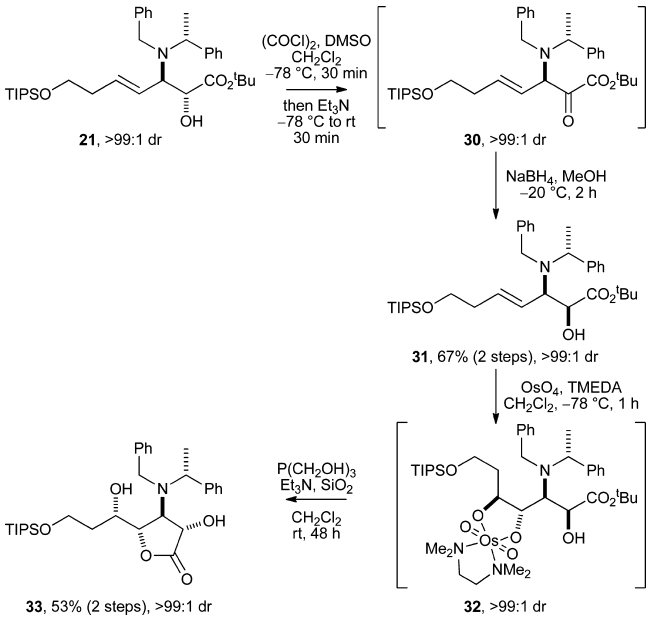
Unfortunately, attempted regioselective dihydroxylation of the C(4)–C(5) double bonds within both **25** and **29** under Donohoe conditions produced complex mixtures of products consistent with preferential oxidation of the styryl units, although it was not possible to isolate any of the products from these reactions.

With a reliable procedure for the installation of the styryl unit established, our attention turned toward our alternative synthetic strategy in which the chemo- and diastereoselective oxidation of the C–C double bond within 2,3-*syn*-*α*-hydroxy-*β*-amino ester **31** would be followed by olefination. Oxidation of the C(2)-hydroxyl functionality within 2,3-*anti*-*α*-hydroxy-*β*-amino ester **21** under Swern conditions followed by immediate reduction of the intermediate ketone **30** upon treatment with $NaBH_4$ gave 2,3-*syn*-*α*-hydroxy-*β*-amino ester **31** as a single

dx.doi.org/10.1021/jo302731m | J. Org. Chem. 2013, 78, 2500–2510

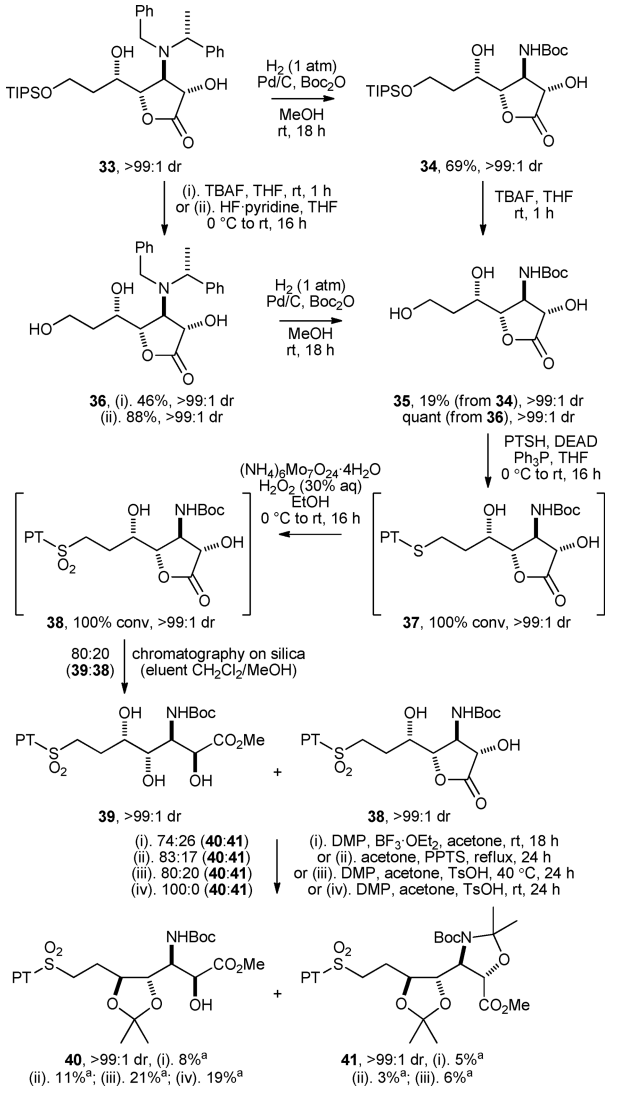
diastereoisomer (>99:1 dr). After purification of the crude reaction mixture, **31** was isolated in 67% yield (from **21**) and >99:1 dr. On the basis of our previous observations concerning the chemo- and diastereoselective oxidation of the corresponding *tert*-butyl 2-hydroxy-3-aminohex-4-enoates,[16,26] we anticipated that *syn*-dihydroxylation of **31** under Donohoe conditions (using the OsO_4/TMEDA complex)[17] would install the correct stereochemistry for syntheses of both APTO and AETD. Indeed, dihydroxylation of *α*-hydroxy-*β*-amino ester **31** under Donohoe conditions[17] gave a single osmate ester-TMEDA complex **32**, which after treatment with trishydroxymethylphosphine,[27] gave lactone **33** in 53% yield (from **31**) and >99:1 dr (Scheme 4). The relative configuration within **33** was initially established by ^{1}H NMR NOE analysis and was later confirmed by single crystal X-ray diffraction analysis of a derivative.

Scheme 4



Hydrogenolytic deprotection of **33** in the presence of Boc_2O gave **34** in 69% yield, and subsequent *O*-silyl deprotection of **34** upon treatment with TBAF produced **35** in only 19% isolated yield. An improved yield of **35** was obtained upon *O*-silyl deprotection of **33** followed by hydrogenolysis: desilylation of **33** with either TBAF or HF·pyridine gave **36** in 46 or 88% yield, respectively, and then hydrogenolysis of **36** in the presence of Pd/C and Boc_2O gave **35** in quantitative yield.[28] Mitsunobu reaction of **35** with PTSH gave the corresponding sulfide **37** in 100% conversion, although attempted reaction of **36** under identical conditions was not successful. Sulfide **37** could not be separated from the resultant $Ph_3P{=}O$ residues, so the mixture of **37** and $Ph_3P{=}O$ was therefore treated with ammonium molybdate tetrahydrate to give sulfone **38** in 100% conversion. Upon attempted chromatographic purification of the crude reaction mixture on silica (using a mixture of CH_2Cl_2/MeOH as the eluent), an 80:20 mixture of ester **39** and lactone **38** was isolated. Treatment of this mixture with 2,2-dimethoxypropane (DMP) and $BF_3{\cdot}OEt_2$ in acetone produced a 74:26 mixture of **40** and **41**, respectively. Upon purification of this mixture, **40** was isolated in 8% yield (from **35**), and **41** was isolated in 5% yield (from **35**), as single diastereoisomers (>99:1 dr) in each case. Further optimization of the reaction conditions revealed that treatment of the 80:20 mixture of **39** and **38** with DMP and TsOH in acetone at rt for 24 h produced **40** exclusively, which was isolated in 19% yield (from **35**) and >99:1 dr (Scheme 5). The relative configuration within **40** was

Scheme 5



[a]Isolated yields from **35**

unambiguously assigned via single crystal X-ray diffraction analysis,[25] and the determination of a Flack *x* parameter[29] of 0.17(5) for the crystal structure of **40** allowed the absolute (*S*,*S*,*S*,*S*)-configuration within **40** (and therefore the absolute configurations within **21**–**39** and **41**) to be determined, thereby confirming the sense of diastereofacial selectivity observed upon oxidation of **31** under Donohoe conditions.[17]

Repetition of this process, followed by treatment of sulfone **38** with DMP and TsOH in acetone (i.e., omitting the attempted purification of **38**), gave **40** as the sole reaction product. Upon chromatographic purification of the crude reaction mixture, **40** was isolated as a single diastereoisomer (>99:1 dr) in 30% overall yield for the three step procedure from **35** (Scheme 6).

Olefination of **40** produced **42** as a single diastereoisomer (>99:1 dr), which was isolated in 79% yield and >99:1 dr after

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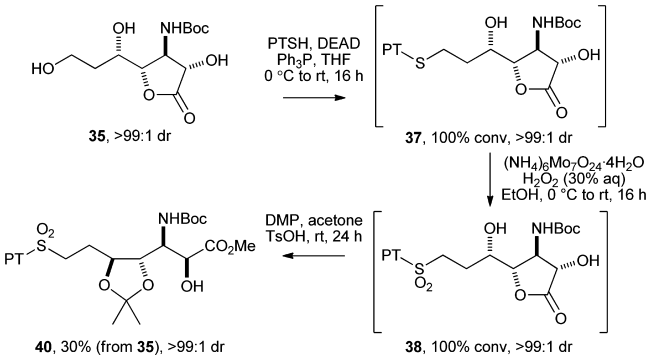
Scheme 6



purification (Scheme 7), concluding the synthesis of a protected derivative of APTO in 14 steps and 3.4% overall yield from commercially available starting materials. Furthermore, the relative configuration within **42** was unambiguously assigned via single crystal X-ray diffraction analysis,[25] and the determination of a Flack *x* parameter[29] of −0.08(9) for the crystal structure of **42** allowed the assigned absolute (*S*,*S*,*S*,*S*,*E*)-configuration within **42** to be confirmed. In order to correlate our synthesis with that of McLeod et al.,[7] treatment of **42** with $BF_3{\cdot}OEt_2$ and DMP gave 66% conversion to **43** (i.e., the final product in McLeod's synthesis of the APTO fragment). After purification, **43** was isolated in 37% yield and >99:1 dr; the spectroscopic data for this sample of **43** were found to be consistent with those reported previously.[7] This route produced **43** in superior yield when compared with the Julia−Kocieński olefination of **41**, which proceeded in only 28% conversion, giving **43** in 16% yield in addition to returning starting material **41**, which was isolated in 31% yield. While a shorter enantiospecific route to an alternative protected form of APTO has previously been reported,[8] the yield of **42** obtained via this strategy is comparable with that of **43** obtained by McLeod et al.[7] in their asymmetric synthesis.

Analogous reaction of **40** with (*E*)-3-(4′-ethoxyphenyl)-acrylaldehyde **44** (which was prepared in 82% yield and >99:1 dr via Heck coupling of 4-iodophenetole with acrolein diethyl acetal, followed by hydrolysis of the resultant acetal),[30] produced **45** in >99:1 dr. After chromatographic purification of the crude reaction mixture, **45** was isolated in 23% yield and >99:1 dr (Scheme 7). Again, single crystal X-ray diffraction analysis of **45**[25] and the determination of a Flack *x* parameter[29] of 0.11(6) for the crystal structure of **45** allowed the assigned absolute (*S*,*S*,*S*,*S*,*E*,*E*)-configuration within **45** to be confirmed. This route therefore constitutes a synthesis of a protected form of AETD in 14 steps and 1.0% overall yield from commercially available starting materials.

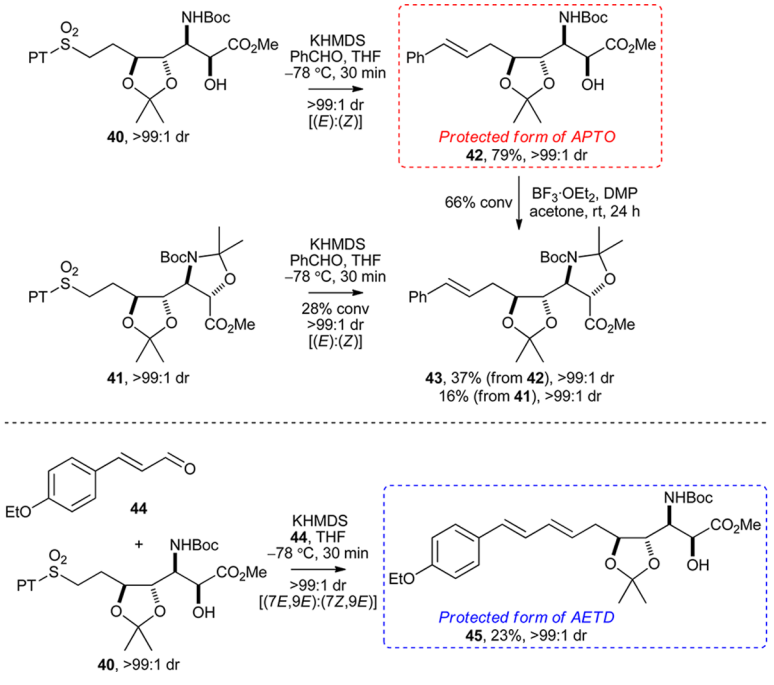
CONCLUSION

In conclusion, the asymmetric syntheses of APTO and AETD, the *β*-amino acid fragments within microsclerodermins C, D, and E, were achieved using the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(*α*-methylbenzyl)amide to *tert*-butyl (*E*,*E*)-7-(triisopropylsilyloxy)hepta-2,4-dienoate and in situ enolate oxidation with (−)-camphorsulfonyloxaziridine, diastereoselective dihydroxylation of a 2,3-*syn*-*γ*,*δ*-unsaturated-*α*-hydroxy-*β*-amino ester derivative under Donohoe conditions, and a Julia−Kocieński olefination as the key steps. Overall, APTO and AETD (in protected form) were produced in 3.4 and 1.0% yield, respectively, in 14 steps from commercially available starting materials in each case.

EXPERIMENTAL SECTION

General Experimental Details. All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[31] BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. All other reagents were used as supplied without prior purification. Organic layers were dried

Scheme 7



dx.doi.org/10.1021/jo302731m | J. Org. Chem. 2013, 78, 2500−2510

over $MgSO_4$. Thin layer chromatography was performed on aluminum plates coated with 60 F_{254} silica. Plates were visualized using UV light (254 nm), 1% aq $KMnO_4$ or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. When the diastereotopic methyl groups of acetonide functionalities could not be unambiguously assigned, the descriptor *Me*CMe was employed. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

4-Triisopropylsilyloxy-but-1-yne 18. Imidazole (14.6 g, 214 mmol), DMAP (350 mg, 2.85 mmol) and TIPSCl (15.3 mL, 71.3 mmol) were sequentially added to a solution of **17** (5.00 g, 71.3 mmol) in CH_2Cl_2 (500 mL) at rt, and the resultant solution was stirred at rt for 16 h. The reaction mixture was then concentrated in vacuo. The residue was dissolved in Et_2O (500 mL), and the resultant solution was washed with 1.0 M aq HCl (250 mL) and then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol) gave **18** as a colorless oil (14.8 g, 92%):[32] δ_H (400 MHz, $CDCl_3$) 1.01–1.14 (21H, m, Si(C*H*Me_2)$_3$), 1.97 (1H, t, *J* 2.6, C(1)*H*), 2.45 (2H, td, *J* 7.3, 2.6, C(3)H_2), 3.83 (2H, t, *J* 7.3, C(4)H_2).

(*E*)-1-Iodo-4-(triisopropylsilyloxy)but-1-ene 19. DIBAL-H (1.0 M in THF, 9.72 mL, 9.72 mmol) was added to a solution of Cp_2ZrCl_2 (2.84 g, 9.72 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and then a solution of **18** (2.00 g, 8.83 mmol) in THF (12 mL) was added via cannula. The reaction mixture was allowed to warm to rt, and stirring was continued until a homogeneous solution resulted (ca. 30 min). The reaction mixture was then cooled to −78 °C, and a solution of I_2 (2.91 g, 11.4 mmol) in THF (38 mL) was added via cannula. The reaction mixture was stirred at −78 °C for 1 h, and then 1.0 M aq HCl (40 mL) was added, and the resultant mixture was extracted with Et_2O (2 × 40 mL). The combined organic extracts were washed sequentially with satd aq $Na_2S_2O_3$ (40 mL) and satd aq $NaHCO_3$ (40 mL) and then dried and concentrated in vacuo. The residue was passed through a short plug of silica gel (eluent 40–60 °C petrol/Et_2O, 200:1) and then concentrated in vacuo to give **19** as a pale yellow oil (2.46 g, 79%, >99:1 dr):[33] δ_H (400 MHz, $CDCl_3$) 1.02–1.14 (21H, m, Si(C*H*Me_2)$_3$), 2.30 (2H, m, C(3)H_2), 3.73 (2H, t, *J* 6.5, C(4)H_2), 6.09 (1H, d, *J* 14.4, C(1)*H*), 6.58 (1H, dt, *J* 14.4, 7.2, C(2)*H*).

***tert*-Butyl (*E*,*E*)-7-(triisopropylsilyloxy)hepta-2,4-dienoate 20.** $Pd(OAc)_2$ (68 mg, 0.30 mmol) was added to a solution of **19** (2.13 g, 6.01 mmol, >99:1 dr), *tert*-butyl acrylate (1.74 mL, 11.9 mmol), Ag_2CO_3 (1.82 g, 6.61 mmol) and Et_3N (1.72 mL, 12.3 mmol) in CH_2Cl_2 (30 mL) at rt, and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (15 mL) was then added, and the resultant mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **20** as a pale yellow oil (1.90 g, 89%, >99:1 dr): ν_{max} (ATR) 2943, 2867 (C–H), 1710 (C=O), 1645, 1618 (C=C); δ_H (400 MHz, $CDCl_3$) 1.02–1.09 (21H, m, Si(C*H*Me_2)$_3$), 1.49 (9H, s, CMe_3), 2.40 (2H, app q, *J* 6.5, C(6)H_2), 3.76 (2H, t, *J* 6.5, C(7)H_2), 5.73 (1H, d, *J* 15.4, C(2)*H*), 6.13 (1H, dt, *J* 15.4, 6.5, C(5)*H*), 6.22 (1H, dd, *J* 15.4, 10.3, C(4)*H*), 7.16 (1H, dd, *J* 15.4, 10.3, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 10.2 (Si(CHMe$_2$)$_3$), 16.2 (Si(CH*Me*$_2$)$_3$), 26.4 (CMe_3), 34.9 (*C*(6)), 60.7 (*C*(7)), 78.3 (*C*Me$_3$), 119.8 (*C*(2)), 128.2 (*C*(4)), 138.4 (*C*(5)), 142.0 (*C*(3)), 164.9 (*C*(1)); *m*/*z* (ESI$^+$) 377 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{38}NaO_3Si^+$ ([M + Na]$^+$) requires 377.2482; found 377.2470.

***tert*-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)hept-4-enoate 21.** BuLi (2.45 M in THF, 16.3 mL, 39.9 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (8.70 g, 41.2 mmol) in THF (180 mL) at −78 °C, and stirring was continued at −78 °C for 30 min. A solution of **20** (7.30 g, 20.6 mmol, >99:1 dr) in THF (180 mL) was then added via cannula, and the reaction mixture was stirred at −78 °C for 2 h. (−)-CSO **6** (9.44 g, 41.2 mmol) was then added, the reaction mixture was allowed to warm to rt over 12 h, and then satd aq NH_4Cl (20 mL) was added, and the resultant mixture was concentrated in vacuo. The residue was partitioned between Et_2O (150 mL) and H_2O (150 mL), and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed sequentially with 10% aq citric acid (300 mL), satd aq $NaHCO_3$ (300 mL) and brine (300 mL) and then dried and concentrated in vacuo to give **21** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **21** as a pale yellow oil (10.3 g, 72%, >99:1 dr): $[\alpha]_D^{25}$ −41.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3505 (O–H), 2941, 2866 (C–H), 1724 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 1.05–1.10 (21H, m, Si(C*HMe*$_2$)$_3$), 1.33 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 2.29 (2H, app q, *J* 6.7, C(6)H_2), 2.93 (1H, d, *J* 5.6, O*H*), 3.55 (1H, dd, *J* 9.1, 2.7, C(3)*H*), 3.71 (2H, t, *J* 6.7, C(7)H_2), 3.77 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 3.97 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.08 (1H, dd, *J* 5.6, 2.7, C(2)*H*), 4.23 (1H, q, *J* 6.8, C(α)*H*), 5.60 (1H, dt, *J* 15.6, 6.7, C(5)*H*), 5.75 (1H, dd, *J* 15.6, 9.1, C(4)*H*), 7.18–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(CHMe$_2$)$_3$), 14.8 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 27.9 (C*Me*$_3$), 36.5 (*C*(6)), 51.4 (NCH$_2$Ph), 56.8 (*C*(α)), 63.0 (*C*(3)), 63.1 (*C*(7)), 74.5 (*C*(2)), 81.9 (*C*Me$_3$), 126.6, 126.7 (*p*-*Ph*), 127.0 (*C*(4)), 128.0, 128.0, 128.2, 128.5 (*o*,*m*-*Ph*), 131.7 (*C*(5)), 141.6, 144.2 (*i*-*Ph*), 172.7 (*C*(1)); *m*/*z* (ESI$^+$) 582 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{56}NO_4Si^+$ ([M + H]$^+$) requires 582.3973; found 582.3972.

***tert*-Butyl (*R*,*R*,*R*,*E*)-2,7-dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-4-enoate 22.** TBAF (1.0 M in THF, 15.0 mL, 15.0 mmol) was added dropwise to a stirred solution of **21** (1.74 g, 2.99 mmol, >99:1 dr) in THF (50 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (50 mL) and washed with H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **22** as a white crystalline solid (1.15 g, 90%, >99:1 dr): mp 61–65 °C; $[\alpha]_D^{25}$ −53.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3474, 3318 (O–H), 3064, 3027, 2983, 2968, 2931, 2882 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 2.05 (1H, br s, C(7)O*H*), 2.24–2.39 (2H, m, C(6)H_2), 3.01 (1H, br s, C(2)O*H*), 3.52–3.60 (2H, m, C(3)*H*, C(7)H_A), 3.61–3.69 (1H, m, C(7)H_B), 3.85 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 4.04 (1H, d, *J* 14.4, NCH$_A$*H*$_B$Ph), 4.17 (1H, app s, C(2)*H*), 4.24 (1H, q, *J* 6.8, C(α)*H*), 5.47 (1H, dt, *J* 15.4, 7.4, C(5)*H*), 5.85 (1H, dd, *J* 15.4, 9.4, C(4)*H*), 7.20–7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.9 (C*Me*$_3$), 36.1 (C(6)), 51.4 (NCH$_2$Ph), 56.9 (*C*(α)), 61.4 (*C*(7)), 63.0 (*C*(3)), 74.8 (*C*(2)), 82.2 (*C*Me$_3$), 126.7, 126.8 (*p*-*Ph*), 127.0, 128.1, 128.2, 128.4 (*o*,*m*-*Ph*), 129.2 (*C*(4)), 130.6 (*C*(5)), 141.4, 144.0 (*i*-*Ph*), 173.3 (*C*(1)); *m*/*z* (ESI$^+$) 426 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_4^+$ ([M + H]$^+$) requires 426.2639; found 426.2640.

***tert*-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-iodohept-4-enoate 23.** PPh_3 (89 mg, 0.34 mmol) and imidazole (29 mg, 0.42 mmol) were added to a solution of **22** (120 mg, 0.28 mmol, >99:1 dr) in PhMe and MeCN (v/v 4:1, 3.42 mL). I_2 (86 mg, 0.34 mmol) was then added, and the resultant mixture was heated to 60 °C for 1 h. The reaction mixture was allowed to cool to rt and diluted with Et_2O (5 mL), and then the resultant solution was washed sequentially with satd aq $Na_2S_2O_3$ (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **23** as a colorless oil (129 mg, 85%, >99:1 dr): $[\alpha]_D^{25}$ −55.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3499 (O–H), 3061, 3027, 2976, 2933 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 2.56–2.71 (2H, m, C(6)H_2), 2.94 (1H, br s, O*H*), 3.16 (1H, dt, *J* 14.8, 7.2, C(7)H_A), 3.18 (1H, dt, *J* 14.8, 7.2, C(7)H_B), 3.61 (1H, dd, *J* 9.1, 2.3, C(3)*H*), 3.85 (1H, d, *J* 14.5, NC$H_A$$H_B$Ph), 4.02 (1H, d, *J* 14.5,

dx.doi.org/10.1021/jo302731m | *J. Org. Chem.* 2013, 78, 2500–2510

NCH_AH_BPh), 4.14 (1H, d, *J* 2.3, C(2)*H*), 4.28 (1H, q, *J* 6.8, C(*α*)*H*), 5.49 (1H, dt, *J* 15.4, 6.8, C(5)*H*), 5.83 (1H, dd, *J* 15.4, 9.1, C(4)*H*), 7.20−7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.0 (C(7)), 15.3 (C(*α*)*Me*), 28.0 (CMe_3), 36.5 (C(6)), 51.4 (NCH_2Ph), 56.9 (C(*α*)), 62.7 (C(3)), 74.4 (C(2)), 82.1 (CMe_3), 126.7, 126.7 (*p-Ph*), 128.0, 128.1, 128.2, 128.4 (*o,m-Ph*), 128.5 (C(4)), 132.7 (C(5)), 141.4, 144.2 (*i-Ph*), 172.7 (C(1)); *m/z* (ESI$^+$) 536 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{35}INO_3^+$ ([M + H]$^+$) requires 536.1656; found 536.1667.

{*tert*-Butyl (*R,R,R,E*)-2-hydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]hept-4-en-7-yl}triphenylphosphonium iodide 24. PPh_3 (43 mg, 0.16 mmol) was added to a solution of **23** (88 mg, 0.16 mmol, >99:1 dr) in MeCN (4 mL) at rt, and the resultant mixture was heated at reflux for 48 h. The reaction mixture was then concentrated in vacuo to give **24** as a pale yellow solid (131 mg, quant, >99:1 dr): mp 73−77 °C; $[\alpha]_D^{25}$ −47.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3324 (O−H), 3057, 3027, 2976, 2932, 2872 (C−H), 1730 (C═O); δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, CMe_3), 1.33 (3H, d, *J* 6.8, C(*α*)*Me*), 2.32−2.44 (2H, m, C(6)H_2), 2.96 (1H, br s, O*H*), 3.50−3.68 (3H, m, C(3)*H*, C(7)H_2), 3.82 (1H, d, *J* 14.9, NCH_AH_BPh), 3.88 (1H, d, *J* 14.9, NCH_AH_BPh), 4.05 (1H, app s, C(2)*H*), 4.10 (1H, q, *J* 6.8, C(*α*)*H*), 5.69 (1H, dd, *J* 15.4, 8.8, C(4)*H*), 5.86 (1H, dt, *J* 15.4, 6.6, C(5)*H*), 7.09−7.82 (25H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 16.2 (C(*α*)*Me*), 22.6 (C(7)), 25.7 (C(6)), 28.0 (CMe_3), 51.4 (NCH_2Ph), 57.5 (C(*α*)), 62.3 (C(3)), 73.4 (C(2)), 82.3 (CMe_3), 172.6 (C(1)); *m/z* (ESI$^+$) 670 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{44}H_{49}NO_3P^+$ ([M]$^+$) requires 670.3445; found 670.3453.

***tert*-Butyl (*R,R,R,E,E*)-2-hydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-8-phenylocta-4,7-dienoate 25.** KHMDS (0.5 M in PhMe, 0.47 mL, 0.24 mmol) was added dropwise to a solution of **27** (66 mg, 0.11 mmol, >99:1 dr) and PhCHO (13 *μ*L, 0.13 mmol) in THF (2.5 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. H_2O (2 mL) was then added, and the reaction mixture was allowed to warm to rt. The aqueous layer was then extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed sequentially with satd aq NH_4Cl (20 mL) and brine (20 mL) and then dried and concentrated in vacuo to give **25** in >99:1 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 10:1) gave **25** as a pale yellow oil (35 mg, 66%, >99:1 dr): $[\alpha]_D^{25}$ −49.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3499 (O−H), 3083, 3066, 3026, 2977, 2933, 2824 (C−H), 1722 (C═O), 1600 (C═C); δ_H (500 MHz, $CDCl_3$) 1.33 (9H, s, CMe_3), 1.40 (3H, d, *J* 6.8, C(*α*)*Me*), 2.96 (2H, app t, *J* 6.6, C(6)H_2), 3.61 (1H, dd, *J* 9.1, 2.5, C(3)*H*), 3.83 (1H, d, *J* 14.5, NCH_AH_BPh), 3.99 (1H, d, *J* 14.5, NCH_AH_BPh), 4.14 (1H, d, *J* 2.5, C(2)*H*), 4.26 (1H, q, *J* 6.8, C(*α*)*H*), 5.58 (1H, dt, *J* 15.5, 6.6, C(5)*H*), 5.79 (1H, dd, *J* 15.5, 9.1, C(4)*H*), 6.17 (1H, dt, *J* 15.9, 6.6, C(7)*H*), 6.41 (1H, d, *J* 15.9, C(8)*H*), 7.18−7.45 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.1 (C(*α*)*Me*), 27.9 (CMe_3), 36.0 (C(6)), 51.4 (NCH_2Ph), 56.9 (C(*α*)), 62.9 (C(3)), 74.5 (C(2)), 82.0 (CMe_3), 126.6, 126.7, 127.0 (*p-Ph*), 127.0 (C(4)), 126.0, 127.9, 128.0, 128.2, 128.4, 128.5 (*o,m-Ph*), 128.1 (C(7)), 130.9 (C(8)), 132.4 (C(5)), 137.5, 141.5, 144.1 (*i-Ph*), 172.7 (C(1)); *m/z* (ESI$^+$) 498 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{40}NO_3^+$ ([M + H]$^+$) requires 498.3003; found 498.3011.

***tert*-Butyl (*R,R,R,E*)-2-hydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-7-(1′-phenyl-1*H*-tetrazol-5′-ylthio)hept-4-enoate 26.** DEAD (48 *μ*L, 0.31 mmol) was added dropwise to a solution of **22** (100 mg, 0.23 mmol, >99:1 dr), PTSH (50 mg, 0.28 mmol) and PPh_3 (74 mg, 0.28 mmol) in THF (2 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 16 h. EtOAc (10 mL) was then added, and the reaction mixture was washed sequentially with brine (10 mL) and H_2O (10 mL) and then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 2:1) gave **26** as a colorless oil (113 mg, 82%, >99:1 dr): $[\alpha]_D^{25}$ −53.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3493 (O−H), 3061, 3027, 2976, 2933 (C−H), 1722 (C═O); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, CMe_3), 1.32 (3H, d, *J* 6.9, C(*α*)*Me*), 2.59 (2H, app q, *J* 7.1, C(6)H_2), 2.87 (1H, d, *J* 4.4, O*H*), 3.45 (2H, t, *J* 7.1, C(7)H_2), 3.57 (1H, dd, *J* 9.0, 2.2, C(3)*H*), 3.77 (1H, d, *J* 14.5, NCH_AH_BPh), 3.96 (1H, d, *J* 14.5, NCH_AH_BPh), 4.10 (1H, app br s, C(2)*H*), 4.21 (1H, q, *J* 6.9, C(*α*)*H*), 5.54 (1H, dt, *J* 15.5, 7.1, C(5)*H*), 5.82 (1H, dd, *J* 15.5, 9.0, C(4)*H*), 7.17−7.59 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.1 (C(*α*)*Me*), 27.9 (CMe_3), 32.0 (C(6)), 32.8 (C(7)), 51.3 (NCH_2Ph), 56.8 (C(*α*)), 62.6 (C(3)), 74.4 (C(2)), 82.1 (CMe_3), 123.8, 127.9, 128.1, 128.2, 128.3, 129.8 (*o,m-Ph*), 126.7, 126.7, 130.1 (*p-Ph*), 129.1 (C(4)), 130.9 (C(5)), 133.6, 141.3, 144.0 (*i-Ph*), 154.2 (C(5′)), 172.6 (C(1)); *m/z* (ESI$^+$) 608 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{39}N_5NaO_3S^+$ ([M + Na]$^+$) requires 608.2666; found 608.2664.

***tert*-Butyl (*R,R,R,E*)-2-hydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-7-(1′-phenyl-1*H*-tetrazol-5′-ylsulfonyl)hept-4-enoate 27.** $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (48 mg, 0.04 mmol) was dissolved in 30% aq H_2O_2 (0.33 mL, 2.89 mmol) at 0 °C, and the resultant solution was added dropwise to a solution of **26** (113 mg, 0.19 mmol, >99:1 dr) in EtOH (3 mL) at 0 °C. The resultant suspension was allowed to warm to rt, stirred at rt for 16 h, and then added to brine (10 mL). The reaction mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 2:1) gave **27** as a pale yellow oil (69 mg, 58%, >99:1 dr): $[\alpha]_D^{25}$ −46.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3507 (O−H), 3062, 3028, 2977, 2934 (C−H), 1722 (C═O), 1345, 1150 (S═O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, CMe_3), 1.37 (3H, d, *J* 6.8, C(*α*)*Me*), 2.65−2.80 (2H, m, C(6)H_2), 2.93 (1H, br s, O*H*), 3.61 (1H, dd, *J* 9.1, 2.3, C(3)*H*), 3.72−3.78 (2H, m, C(7)H_2), 3.86 (1H, d, *J* 14.7, NCH_AH_BPh), 3.98 (1H, d, *J* 14.7, NCH_AH_BPh), 4.15 (1H, app s, C(2)*H*), 4.23 (1H, q, *J* 6.8, C(*α*)*H*), 5.56 (1H, dt, *J* 15.4, 6.8, C(5)*H*), 5.89 (1H, dd, *J* 15.4, 9.1, C(4)*H*), 7.20−7.73 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(*α*)*Me*), 25.3 (C(6)), 28.0 (CMe_3), 51.3 (NCH_2Ph), 55.4 (C(7)), 57.0 (C(*α*)), 62.3 (C(3)), 74.2 (C(2)), 82.3 (CMe_3), 125.0, 127.9, 128.1, 128.3, 128.3, 129.8 (*o,m-Ph*), 126.7, 126.8, 131.5 (*p-Ph*), 127.9 (C(5)), 130.1 (C(4)), 133.0, 141.4, 143.8 (*i-Ph*), 153.4 (C(5′)), 172.6 (C(1)); *m/z* (ESI$^+$) 640 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{39}N_5NaO_5S^+$ ([M + Na]$^+$) requires 640.2564; found 640.2546.

***tert*-Butyl (2*S*,3*R*,*αR*,*E*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]-8-phenylocta-4,7-dienoate 29.** *Step 1.* DMSO (0.43 mL, 6.82 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (51 *μ*L, 0.60 mmol) in CH_2Cl_2 (2 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 5 min. A solution of **25** (150 mg, 0.30 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) was then added via cannula, and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (0.17 mL, 1.20 mmol) was then added, and stirring was continued at −78 °C for a further 10 min. The reaction mixture was allowed to warm to rt over 20 min. H_2O (20 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried and concentrated in vacuo to give **28** as a yellow oil (175 mg, >99:1 dr): *m/z* (ESI$^+$) 496 ([M + H]$^+$, 100%).

Step 2. The residue of **28** (175 mg, >99:1 dr) was dissolved in MeOH (6 mL), and the resultant solution was cooled to −20 °C. $NaBH_4$ (11 mg, 0.30 mmol) was then added, and the reaction mixture was stirred at −20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated in vacuo. The residue was partitioned between H_2O (30 mL) and Et_2O (30 mL), and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were then dried and concentrated in vacuo to give **29** in >99:1 dr. Purification via flash column chromatography (gradient elution, 20:1 → 10:1 30−40 °C petrol/Et_2O) gave **29** as a pale yellow oil (37 mg, 25% from **25**, >99:1 dr): $[\alpha]_D^{25}$ −37.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3387 (O−H), 3027, 2977, 2932 (C−H), 1736 (C═O), 1585 (C═C); δ_H (500 MHz, $CDCl_3$) 1.36 (9H, s, CMe_3), 1.48 (3H, d, *J* 6.9, C(*α*)*Me*), 2.98−3.03 (2H, m, C(6)H_2), 3.37−3.44 (1H, m, C(3)*H*), 3.68 (1H, d, *J* 13.6, NCH_AH_BPh), 3.88 (1H, d, *J* 13.6, NCH_AH_BPh), 3.90 (1H, d, *J* 9.1, C(2)*H*), 4.12 (1H, q, *J* 6.9, C(*α*)*H*), 5.65−5.75 (2H, m, C(4)*H*, C(5)*H*), 6.22 (1H, dt, *J* 15.8, 6.8, C(7)*H*), 6.46 (1H, d, *J* 15.8, C(8)*H*), 7.21−7.39 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.8 (C(*α*)*Me*), 27.9 (CMe_3), 36.0 (C(6)), 50.2 (NCH_2Ph), 56.5 (C(*α*)), 62.6 (C(3)), 71.8 (C(2)), 81.3 (CMe_3), 126.8 (C(4)), 127.2, 127.2, 127.3 (*p-Ph*), 127.5 (C(7)), 126.0, 127.8, 128.4, 128.5, 128.5, 129.0 (*o,m-Ph*), 131.3 (C(8)), 133.9 (C(5)), 137.4, 139.4, 143.2 (*i-*

dx.doi.org/10.1021/jo302731m | *J. Org. Chem.* 2013, 78, 2500−2510

Ph), 171.4 (*C*(1)); *m*/*z* (ESI$^+$) 498 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{40}NO_3^+$ ([M + H]$^+$) requires 498.3003; found 498.3007.

***tert*-Butyl (2*S*,3*R*,α*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)hept-4-enoate 31.** *Step 1.* DMSO (1.22 mL, 17.2 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.15 mL, 1.72 mmol) in CH_2Cl_2 (6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 5 min. A solution of **21** (500 mg, 0.86 mmol, >99:1 dr) in CH_2Cl_2 (6 mL) was then added via cannula, and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (0.45 mL, 3.43 mmol) was then added, and stirring was continued at −78 °C for a further 10 min. The reaction mixture was allowed to warm to rt over 20 min. H_2O (20 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried and concentrated in vacuo to give **30** as a yellow oil (570 mg, >99:1 dr): δ_H (400 MHz, $CDCl_3$) 1.04−1.09 (21H, m, Si(C*H*Me$_2$)$_3$), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.46 (9H, s, C*Me*$_3$), 2.32 (2H, app q, *J* 6.6, C(6)H_2), 3.70 (2H, t, *J* 6.6, C(7)H_2), 3.81 (1H, d, *J* 14.6, NCH_AH$_B$Ph), 3.88 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.60 (1H, d, *J* 8.1, C(3)*H*), 5.66 (1H, dt, *J* 15.9, 6.6, C(5)*H*), 5.75 (1H, dd, *J* 15.9, 8.1, C(4)*H*), 7.20−7.37 (10H, m, *Ph*); *m*/*z* (ESI$^+$) 580 ([M + H]$^+$, 100%).

Step 2. The residue of **30** (570 mg, >99:1 dr) was dissolved in MeOH (6 mL), and the resultant solution was cooled to −20 °C. $NaBH_4$ (33 mg, 0.86 mmol) was added portionwise, and the reaction mixture was then stirred at −20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated in vacuo. The residue was partitioned between H_2O (30 mL) and Et_2O (30 mL), and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were then dried and concentrated in vacuo to give **31** in >99:1 dr. Purification via flash column chromatography (gradient elution, 20:1 → 10:1 30−40 °C petrol/Et_2O) gave **31** as a pale yellow oil (333 mg, 67% from **21**, >99:1 dr): $[\alpha]_D^{25}$ −49.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3439 (O−H), 3087, 3062, 3028, 2942, 2892, 2866 (C−H), 1733 (C═O), 1630 (C═C); δ_H (400 MHz, $CDCl_3$) 1.08−1.15 (21H, m, Si(C*H*Me$_2$)$_3$), 1.36 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 6.8, C(α)*Me*), 2.30−2.40 (2H, m, C(6)H_2), 3.33−3.40 (1H, m, C(3)*H*), 3.66 (1H, d, *J* 13.3, NCH_AH$_B$Ph), 3.75−3.81 (3H, m, C(7)H_2, O*H*), 3.86 (1H, d, *J* 13.3, NCH$_A$$H_B$Ph), 3.88 (1H, d, *J* 6.6, C(2)*H*), 4.11 (1H, q, *J* 6.8, C(α)*H*), 5.63−5.75 (2H, m, C(4)*H*, C(5)*H*), 7.20−7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 14.7 (C(α)*Me*), 18.0 (Si(CH*Me*$_2$)$_3$), 27.9 (C*Me*$_3$), 36.6 (*C*(6)), 50.1 (NCH_2Ph), 56.5 (*C*(α)), 62.6 (*C*(3)), 62.9 (*C*(7)), 71.8 (*C*(2)), 81.1 (*C*Me$_3$), 127.2 (*C*(4)), 127.2, 127.2 (*p-Ph*), 127.8, 128.4, 128.5, 129.1 (*o,m-Ph*), 133.3 (*C*(5)), 139.5, 143.3 (*i-Ph*), 171.5 (*C*(1)); *m*/*z* (ESI$^+$) 582 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{56}NO_4Si^+$ ([M + H]$^+$) requires 582.3973; found 582.3969.

(2*S*,3*S*,4*S*,5*S*,α*R*)-2,5-Dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)-4-heptylolactone 33. *Step 1.* OsO_4 (265 mg, 1.04 mmol) was added to a stirred solution of **31** (552 mg, 0.95 mmol, >99:1 dr) and TMEDA (0.21 mL, 1.34 mmol) in CH_2Cl_2 (40 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to rt over 15 min and was then concentrated in vacuo. The residue was then passed through a short plug of silica gel (eluent CH_2Cl_2/MeOH, 20:1) and concentrated in vacuo.

Step 2. The residue was dissolved in CH_2Cl_2 (150 mL), and then P(CH_2OH)$_3$ (5.89 g, 47.5 mmol)[34] and Et_3N (2.64 mL, 19.0 mmol) were added sequentially. The reaction mixture was stirred at rt for 5 min, and then SiO_2 (∼2.0 g) was added. The resultant mixture was stirred at rt for 48 h and then concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 3:1) gave **33** as a colorless oil (272 mg, 53%, >99:1 dr): $[\alpha]_D^{25}$ +36.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3454 (O−H), 3086, 3062, 3030, 2942, 2891, 2866 (C−H), 1770 (C═O); δ_H (500 MHz, $CDCl_3$) 1.07−1.14 (21H, m, (Si(C*H*Me$_2$)$_3$), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 1.56−1.63 (1H, m, C(6)H_A), 1.91−2.00 (1H, m, C(6)H_B), 2.92 (1H, d, *J* 6.3, C(2)O*H*), 3.45 (1H, d, *J* 3.8, C(5)O*H*), 3.79 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 3.83 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.89−3.95 (3H, m, C(3)*H*, C(4)*H*, C(7)H_A), 3.99−4.04 (1H, m, C(7)H_B), 4.09 (1H, q, *J* 6.9, C(α)*H*), 4.13−4.18 (1H, m, C(5)*H*), 4.28−4.33 (1H, m, C(2)*H*), 7.21−7.46 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.7 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 18.1 (C(α)*Me*), 35.2 (*C*(6)), 50.0 (NCH_2Ph), 60.1 (*C*(α)), 62.3 (*C*(7)), 64.1 (*C*(3)), 68.8 (*C*(2)), 69.1 (*C*(5)), 82.7 (*C*(4)), 127.2, 127.5 (*p-Ph*), 127.9, 128.0, 128.4, 128.6 (*o,m-Ph*), 140.2, 142.8 (*i-Ph*), 175.7 (*C*(1)); *m*/*z* (ESI$^+$) 564 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{47}NNaO_5Si^+$ ([M + Na]$^+$) requires 564.3116; found 564.3115.

(*S*,*S*,*S*,*S*)-2,5-Dihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-7-(triisopropylsilyloxy)-4-heptylolactone 34. Pd/C (50% w/w of substrate, 204 mg) was added to a stirred solution of **33** (408 mg, 0.753 mmol, >99:1 dr) and Boc_2O (181 mg, 0.829 mmol) in MeOH (10 mL) at rt. The resultant mixture was degassed and saturated with H_2 and then left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 3:1 → 2:1 30−40 °C petrol/EtOAc) gave **34** as a colorless oil (232 mg, 69%, >99:1 dr): $[\alpha]_D^{25}$ +10.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3366 (O−H), 2943, 2867 (C−H), 1782, 1689 (C═O); δ_H (500 MHz, $CDCl_3$) 1.01−1.15 (21H, m, (Si(C*H*Me$_2$)$_3$), 1.45 (9H, s, C*Me*$_3$), 1.70−1.80 (1H, m, C(6)H_A), 1.90−2.01 (1H, m, C(6)H_B), 3.91−4.04 (2H, m, C(7)H_2), 4.05−4.18 (2H, m, C(3)*H*, C(5)*H*), 4.23−4.29 (1H, m, C(4)*H*), 4.51 (1H, d, *J* 7.6, C(2)*H*), 4.69 (1H, br s, O*H*), 5.47 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 11.7 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 28.2 (C*Me*$_3$), 33.5 (*C*(6)), 56.4 (*C*(3)), 61.8 (*C*(7)), 69.6 (*C*(5)), 72.7 (*C*(2)), 81.1 (*C*Me$_3$), 81.3 (*C*(4)), 156.4 (NCO), 173.6 (*C*(1)); *m*/*z* (ESI$^+$) 470 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{41}NNaO_7Si^+$ ([M + Na]$^+$) requires 470.2545; found 470.2531.

(*S*,*S*,*S*,*S*)-2,5,7-Trihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-4-heptylolactone 35. *Method A (from **34**).* TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol) was added dropwise to a stirred solution of **34** (121 mg, 0.27 mmol, >99:1 dr) in THF (4 mL) at rt, and the resultant mixture was stirred at rt for 1 h. The reaction mixture was then diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc) gave **35** as a colorless oil (15 mg, 19%, >99:1 dr):[28] $[\alpha]_D^{25}$ +21.8 (*c* 1.0 in MeOH); ν_{max} (ATR) 3347 (O−H), 2977, 2934 (C−H), 1778, 1689 (C═O); δ_H (500 MHz, MeOH-d_4) 1.48 (9H, s, C*Me*$_3$), 1.72−1.92 (2H, m, C(6)H_2), 3.70−3.77 (2H, m, C(7)H_2), 3.86−3.92 (1H, m, C(5)*H*), 4.10 (1H, dd, *J* 9.6, 2.2, C(4)*H*), 4.27 (1H, app t, *J* 9.6, C(3)*H*), 4.49 (1H, d, *J* 9.6, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 28.7 (C*Me*$_3$), 37.0 (*C*(6)), 56.6 (*C*(3)), 59.6 (*C*(7)), 66.8 (*C*(5)), 72.9 (*C*(2)), 80.9 (*C*Me$_3$), 82.9 (*C*(4)), 158.0 (NCO), 176.1 (*C*(1)); *m*/*z* (ESI$^+$) 314 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{21}NNaO_7^+$ ([M + Na]$^+$) requires 314.1210; found 314.1213.

*Method B (from **36**).* Pd/C (50% w/w of substrate, 258 mg) was added to a stirred solution of **36** (516 mg, 1.34 mmol, >99:1 dr), and Boc_2O (321 mg, 1.47 mmol) in MeOH (10 mL) at rt. The resultant mixture was degassed, saturated with H_2, and then left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite (eluent MeOH), and the filtrate was concentrated in vacuo to give **35** as a yellow oil (390 mg, quant, >99:1 dr).

(2*S*,3*S*,4*S*,5*S*,α*R*)-2,5,7-Trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-heptylolactone 36. *Method A.* TBAF (1.0 M in THF, 0.20 mL, 0.20 mmol) was added dropwise to a stirred solution of **33** (92 mg, 0.17 mmol, >99:1 dr) in THF (4 mL) at rt, and the resultant mixture was stirred at rt for 1 h. The reaction mixture was then diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 1:2) gave **36** as a pale yellow oil (30 mg, 46%, >99:1 dr): $[\alpha]_D^{25}$ +22.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3362 (O−H), 2933 (C−H), 1769 (C═O); δ_H (500 MHz, C_6D_6) 1.29−1.34 (1H, m, C(6)H_A), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.63−1.71 (2H, m, C(6)H_B, C(7)O*H*), 2.55 (1H, d, *J* 6.3, C(5)O*H*), 2.78 (1H, d, *J* 4.9, C(2)O*H*), 3.32−3.39 (1H, m, C(7)H_A), 3.41−3.48 (1H, m, C(7)H_B), 3.57 (1H,

dx.doi.org/10.1021/jo302731m | *J. Org. Chem.* 2013, 78, 2500−2510

d, *J* 15.1, NC*H*$_A$H$_B$Ph), 3.61 (1H, d, *J* 15.1, NCH$_A$*H*$_B$Ph), 3.70 (1H, dd, *J* 8.1, 1.4, C(4)*H*), 3.98−4.03 (1H, m, C(5)*H*), 4.04 (1H, app t, *J* 8.1, C(3)*H*), 4.09 (1H, q, *J* 6.9, C(*α*)*H*), 4.32 (1H, dd, *J* 8.1, 4.9, C(2)*H*), 7.10−7.49 (10H, m, *Ph*); δ_C (125 MHz, C_6D_6) [selected peaks] 19.0 (C(*α*)*Me*), 35.5 (*C*(6)), 50.1 (NCH$_2$Ph), 60.7 (*C*(7)), 61.4 (*C*(*α*)), 64.9 (*C*(3)), 68.5 (*C*(5)), 68.8 (*C*(2)), 81.3 (*C*(4)), 141.4, 143.8 (*i-Ph*), 175.2 (*C*(1)); *m*/*z* (ESI$^+$) 408 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{27}NNaO_5^+$ ([M + Na]$^+$) requires 408.1781; found 408.1769.

Method B. HF·pyridine solution (70%, 1.27 mL, 49.3 mmol) was added dropwise to a stirred solution of **33** (922 mg, 1.70 mmol, >99:1 dr) in THF (6 mL) at 0 °C. The resultant solution was allowed to warm to rt, stirred at rt for 16 h, and then neutralized by the dropwise addition of satd aq $NaHCO_3$ (∼50 mL). The reaction mixture was extracted with EtOAc (3 × 100 mL), and the combined organic extracts were then dried and concentrated in vacuo. The residue was passed through a short plug of silica gel (eluent 30−40 °C petrol/EtOAc, 1:2) and concentrated in vacuo to give **36** as a pale yellow oil (579 mg, 88%, >99:1 dr).

(*S*,*S*,*S*,*S*)-2,5-Dihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-7-(1′-phenyl-1*H*-tetrazol-5′-ylthio)-4-heptylolactone 37. DEAD (98 *μ*L, 0.62 mmol) was added dropwise to a solution of **35** (140 mg, 0.48 mmol, >99:1 dr), PTSH (103 mg, 0.58 mmol) and PPh_3 (151 mg, 0.58 mmol) in THF (6 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 16 h. EtOAc (10 mL) was then added, and the reaction mixture was washed sequentially with brine (10 mL) and H_2O (10 mL) and then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 10:1 → 2:1 30−40 °C petrol/acetone) gave a sample of **37** contaminated with Ph_3P═O (258 mg): δ_H (400 MHz, MeOH-d_4) [selected peaks] 1.41 (9H, s, C*Me*$_3$), 2.03−2.18 (2H, m, C(6)*H*$_2$), 3.40−3.51 (1H, m, C(7)*H*$_A$), 3.55−3.65 (1H, m, C(7)*H*$_B$), 3.86−3.94 (1H, m, C(5)*H*), 4.10−4.16 (1H, m, C(4)*H*), 4.33 (1H, app t, *J* 9.8, C(3)*H*), 4.55 (1H, d, *J* 9.8, C(2)*H*); δ_C (100 MHz, MeOH-d_4) [selected peaks] 27.8 (C*Me*$_3$), 30.0 (*C*(6)), 33.0 (*C*(7)), 55.7 (*C*(3)), 67.5 (*C*(5)), 71.9 (*C*(2)), 79.9 (*C*Me$_3$), 81.7 (*C*(4)), 155.0 (*C*(5′)), 156.9 (NCO), 174.9 (*C*(1)); *m*/*z* (ESI$^+$) 474 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{25}N_5NaO_6S^+$ ([M + Na]$^+$) requires 474.1418; found 474.1405.

(*S*,*S*,*S*,*S*)-2,5-Dihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-7-[*N*(1′)-phenyl-1*H*-tetrazol-5′-ylsulfonyl]-4-heptylolactone 38 and Methyl (2*S*,3*R*,4*S*,5*S*)-2,4,5-trihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-7-[*N*(1′)-phenyl-1*H*-tetrazol-5′-ylsulfonyl]heptanoate 39. $(NH_4)_6Mo_7O_{24}·4H_2O$ (60 mg, 0.05 mmol) was dissolved in 30% aq H_2O_2 (0.42 mL, 3.65 mmol) at 0 °C, and the resultant solution was added dropwise to a solution of **37** (258 mg, contaminated with Ph_3P═O) in EtOH (4.5 mL) at 0 °C. The resultant suspension was allowed to warm to rt, stirred at rt for 16 h, and then added to brine (10 mL). The resultant mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo to give **38**. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 50:1) gave an 80:20 mixture of **39** and **38** as a white solid (67 mg). Data for **39**: δ_H (500 MHz, DMSO-d_6) 1.35 (9H, s, C*Me*$_3$), 1.76−1.84 (1H, m, C(6)*H*$_A$), 1.93−2.03 (1H, m, C(6)*H*$_B$), 3.26−3.32 (1H, m, C(2)*H*), 3.50−3.56 (1H, m, C(5)*H*), 3.58 (3H, s, O*Me*), 3.75−3.82 (2H, m, C(7)*H*$_2$), 3.91 (1H, app td, *J* 10.0, 1.6, C(3)*H*), 4.40 (1H, d, *J* 7.3, C(5)O*H*), 4.43 (1H, dd, *J* 7.6, 1.6, C(4)*H*), 4.91 (1H, d, *J* 8.2, C(2)O*H*), 5.11 (1H, d, *J* 7.6, C(4)O*H*), 6.29 (1H, d, *J* 10.0, N*H*), 7.63−7.79 (5H, m, *Ph*); δ_C (125 MHz, DMSO-d_6) 26.3 (*C*(6)), 28.1 (C*Me*$_3$), 51.4 (O*Me*), 53.5 (*C*(7)), 54.3 (*C*(3)), 67.2 (*C*(5)), 68.9 (*C*(4)), 70.1 (*C*(2)), 78.1 (*C*Me$_3$), 126.4, 129.4 (*o*,*m-Ph*), 131.5 (*p-Ph*), 133.0 (*C*(5′)), 153.3 (*i-Ph*), 155.3 (NCO), 174.0 (*C*(1)). Data for **38**: δ_H (500 MHz, DMSO-d_6) [selected peaks] 1.39 (9H, s, C*Me*$_3$), 1.89−2.04 (2H, m, C(6)*H*$_2$), 3.18 (1H, d, *J* 5.0, C(2)O*H*), 3.60−3.67 (1H, m, C(5)*H*), 3.75−3.82 (1H, m, C(7)*H*$_A$), 3.84−3.92 (1H, m, C(7)*H*$_B$), 3.99 (1H, dd, *J* 8.8, 2.2, C(4)*H*), 4.10−4.18 (1H, m, C(2)*H*), 4.36 (1H, dd, *J* 9.6, 7.2, C(3)*H*), 5.39 (1H, d, *J* 7.3, C(5)O*H*), 6.18 (1H, d, *J* 7.2, N*H*); δ_C (125 MHz, DMSO-d_6) [selected peaks] 25.8 (*C*(6)), 28.2 (C*Me*$_3$), 53.0 (*C*(7)), 54.6 (*C*(2)), 65.9 (*C*(5)), 71.0 (*C*(3)), 78.4 (*C*Me$_3$), 80.8 (*C*(4)), 153.3 (*C*(5′)), 155.1 (NCO), 174.2 (*C*(1)). Data for mixture: mp 177−181 °C; ν_{max} (ATR) 3514, 3415, 3385 (N−H, O−H), 2985, 2953, 2913 (C−H), 1740, 1668 (C═O), 1332, 1151 (S═O); *m*/*z* (ESI$^+$) 538 ([M(**39**) + Na]$^+$, 100%), 506 ([M(**38**) + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{28}N_5Na_2O_9S^+$ ([M(**39**) − H + 2Na]$^+$) requires 560.1398; found 560.1383; HRMS (ESI$^+$) $C_{19}H_{25}N_5NaO_8S^+$ ([M(**38**) + Na]$^+$) requires 506.1316; found 506.1308.

Methyl (*S*,*S*,*S*,*S*)-2,4,5-trihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-4,5-*O*-isopropylidine-7-[*N*(1′)-phenyl-1*H*-tetrazol-5′-ylsulfonyl]heptanoate 40 and (5*S*,4*R*,1′*S*,2′*S*)-2,2-Dimethyl-*N*(3)-(*tert*-butoxycarbonyl)-4-(1′,2′-dihydroxy-1′,2′-*O*-isopropylidene-4′-{[*N*(1″)-phenyl-1*H*-tetrazol-5″-yl]sulfonyl}but-1′-yl)-5-methoxycarbonyloxazolidine 41. *Method A.* PPTS (5 mg, cat.) was added to a solution of an 80:20 mixture of **39** and **38** (50 mg) in acetone (2.5 mL) at rt. The resultant mixture was then heated at reflux for 24 h. The reaction mixture was allowed to cool to rt, $NaHCO_3$ was then added until pH 7 was achieved, and the reaction mixture was filtered and concentrated in vacuo to give an 83:17 mixture of **40** and **41**. Purification via flash column chromatography (gradient elution, 5:1 → 2:1 30−40 °C petrol/EtOAc) gave **41** as a colorless oil (7 mg, 3% from **35**, >99:1 dr):[35] $[\alpha]_D^{25}$ −5.7 (*c* 0.6 in $CHCl_3$); ν_{max} (ATR) 2984, 2938 (C−H), 1740, 1691 (C═O), 1369, 1153 (S═O); δ_H (500 MHz, $CDCl_3$) 1.40 (6H, app s, 2 × *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 1.56 (3H, s, *Me*CMe), 1.60 (3H, s, *Me*CMe), 2.11−2.21 (1H, m, C(3′)*H*$_A$), 2.23−2.34 (1H, m, C(3′)*H*$_B$), 3.78−3.92 (2H, m, C(1′)*H*, C(4′)*H*$_A$), 3.80 (3H, s, O*Me*), 3.96−4.06 (1H, m, C(4′)*H*$_B$), 4.23−4.32 (1H, m, C(2′)*H*), 4.49 (1H, app br s, C(4)*H*), 4.72 (1H, app br s, C(5)*H*), 7.57−7.75 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 26.0 (*C*(3′)), 26.9, 27.2, 27.2, 27.3 (4 × *Me*CMe), 28.3 (C*Me*$_3$), 52.6 (O*Me*), 53.3 (*C*(4′)), 61.4 (*C*(4)), 75.0 (*C*(5)), 76.4 (*C*(2′)), 80.3 (*C*(1′)), 81.4 (*C*Me$_3$), 96.5 (*C*(2)), 109.4 (MeC*M*e), 125.1, 129.7 (*o*,*m-Ph*), 131.5 (*p-Ph*), 133.0 (*i-Ph*), 152.3 (NCO), 154.4 (*C*(5″)), 171.8 (*C*O$_2$Me); *m*/*z* (ESI$^+$) 618 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{37}N_5NaO_9S^+$ ([M + Na]$^+$) requires 618.2204; found 618.2181. Further elution gave **40** as a white solid (20 mg, 11% from **35**, >99:1 dr): mp 143−146 °C; $[\alpha]_D^{25}$ −3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3388 (O−H, N−H), 2984, 2936 (C−H), 1741, 1712 (C═O), 1341, 1156 (S═O); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.42 (6H, app s, 2 × *Me*CMe), 2.11−2.21 (1H, m, C(6)*H*$_A$), 2.27−2.36 (1H, m, C(6)*H*$_B$), 3.11 (1H, br s, O*H*), 3.77 (1H, dd, *J* 9.6, 7.0, C(4)*H*), 3.78−3.84 (1H, m, C(7)*H*$_A$), 3.81 (3H, s, O*Me*), 3.98 (1H, app ddd, *J* 15.3, 11.5, 4.4, C(7)*H*$_B$), 4.16−4.22 (2H, m, C(3)*H*, C(5)*H*), 4.57 (1H, app br s, C(2)*H*), 4.91 (1H, d, *J* 10.1, N*H*), 7.58−7.72 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 26.9 (*C*(6)), 27.0, 27.3 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 53.0 (*C*(7)), 53.0 (O*Me*), 55.2 (*C*(5)), 69.8 (*C*(2)), 77.4 (*C*(3)), 78.7 (*C*(4)), 80.5 (*C*Me$_3$), 109.8 (MeC*M*e), 125.0, 129.7 (*o*,*m-Ph*), 131.5 (*p-Ph*), 133.0 (*i-Ph*), 153.3 (*C*(5′)), 155.2 (NCO), 173.8 (*C*(1)); *m*/*z* (ESI$^+$) 578 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{33}N_5NaO_9S^+$ ([M + Na]$^+$) requires 578.1891; found 578.1894.

Method B. BF_3 (1.0 M in Et_2O, ∼2 drops) was added dropwise to a solution of an 80:20 mixture of **39** and **38** (30 mg) and DMP (0.4 mL) in acetone (2.0 mL) at rt until a permanent color change from colorless to dark orange was observed. The resultant mixture was stirred at rt for 18 h. Et_3N (∼0.1 mL) was added until pH 7 was achieved, and the reaction mixture was then concentrated in vacuo gave a 74:26 mixture of **40** and **41**. Purification via flash column chromatography (gradient elution, 5:1 → 2:1 30−40 °C petrol/EtOAc) gave **41** as a colorless oil (6 mg, 5% from **35**, >99:1 dr) and **40** as a white solid (9 mg, 8% from **35**, >99:1 dr).

Method C. TsOH·H_2O (6 mg, cat.) was added to a solution of an 80:20 mixture of **39** and **38** (32 mg) in acetone (2.8 mL) and DMP (0.2 mL) at rt, and the resultant solution was then heated at 40 °C for 24 h. The reaction mixture was allowed to cool to rt, and solid Na_2CO_3 was then added until pH 7 was achieved. The resultant mixture was then filtered and concentrated in vacuo to give an 80:20 mixture of **40** and **41**. Purification via flash column chromatography (gradient elution, 5:1 → 2:1 30−40 °C petrol/EtOAc) gave **41** as a colorless oil (7 mg, 6% from **35**, >99:1 dr). Further elution gave **40** as a white solid (24 mg, 21% from **35**, >99:1 dr).

dx.doi.org/10.1021/jo302731m | *J. Org. Chem.* 2013, 78, 2500−2510

Method D. $TsOH{\cdot}H_2O$ (7 mg, cat.) was added to a solution of an 80:20 mixture of **39** and **38** (36 mg) in acetone (2.8 mL) and DMP (0.2 mL) at rt. The resultant solution was then stirred at rt for 24 h, and then solid Na_2CO_3 was added until pH 7 was achieved. The resultant mixture was then filtered and concentrated in vacuo to give **40** in >99:1 dr. Purification via flash column chromatography (gradient elution, 5:1 → 2:1 30−40 °C petrol/EtOAc) gave **40** as a white solid (24 mg, 19% from **35**, >99:1 dr).

Method E. $TsOH{\cdot}H_2O$ (7 mg, cat.) was added to a solution of **38** (34 mg, >99:1 dr) in acetone (2.8 mL) and DMP (0.2 mL) at rt. The resultant solution was then stirred at rt for 24 h, and then solid Na_2CO_3 was added until pH 7 was achieved. The resultant mixture was then filtered and concentrated in vacuo to give **40** in >99:1 dr. Purification via flash column chromatography (gradient elution, 5:1 → 2:1 30−40 °C petrol/EtOAc) gave **40** as a white solid (20 mg, 30% from **35**, >99:1 dr).

Methyl (*S,S,S,S,E*)-2,4,5-trihydroxy-3-(*N-tert*-butoxycarbonylamino)-4,5-*O*-isopropylidine-8-phenylocta-7-enoate 42. KHMDS (0.5 M in PhMe, 0.70 mL, 0.35 mmol) was added dropwise to a solution of **40** (61 mg, 0.11 mmol, >99:1 dr) and PhCHO (36 μL, 0.13 mmol) in THF (2.2 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. H_2O (1 mL) was added, and the reaction mixture was allowed to warm to rt. The aqueous layer was then extracted with EtOAc (3 × 5 mL), and the combined organic extracts were dried and concentrated in vacuo to give **42** in >99:1 dr. Purification via flash column chromatography (gradient elution 10:1 → 3:1 30−40 °C petrol/EtOAc) gave **42** as a white solid (38 mg, 79%, >99:1 dr): mp 131−135 °C; $[\alpha]_D^{25}$ −7.9 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 3437, 3360 (N−H, O−H), 3027, 2983, 2935 (C−H), 1741, 1716 (C═O); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, CMe_3), 1.45 (6H, app s, 2 × *Me*CMe), 2.44−2.53 (1H, m, C(6)H_A), 2.53−2.61 (1H, m, C(6)H_B), 3.18 (1H, d, *J* 3.5, O*H*), 3.77−3.84 (1H, m, C(4)*H*), 3.79 (3H, s, O*Me*), 4.16−4.25 (2H, m, C(3)*H*, C(5)*H*), 4.59 (1H, app s, C(2)*H*), 4.88 (1H, d, *J* 10.1, N*H*), 6.24 (1H, dt, *J* 15.8, 7.3, C(7)*H*), 6.46 (1H, d, *J* 15.8, C(8)*H*), 7.18−7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.2, 27.5 (2 × *Me*CMe), 28.2 (CMe_3), 37.7 (*C*(6)), 52.9 (O*Me*), 55.3 (*C*(5)), 69.9 (*C*(2)), 78.4 (*C*(4)), 79.5 (*C*(3)), 80.1 (CMe_3), 109.4 (MeCMe), 125.6 (*C*(7)), 126.2, 128.5 (*o,m-Ph*), 127.2 (*p-Ph*), 132.6 (*C*(8)), 137.3 (*i-Ph*), 155.0 (NCO), 174.0 (*C*(1)); *m/z* (ESI$^+$) 458 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{33}NNaO_7^+$ ([M + Na]$^+$) requires 458.2149; found 458.2135.

(5*S*,4*R*,1′*S*,2′*S*,*E*)-2,2-Dimethyl-*N*(3)-(*tert*-butoxycarbonyl)-4-(1′,2′-dihydroxy-1′,2′-*O*-isopropylidene-5′-phenylpent-4′-en-1′-yl)-5-methoxycarbonyloxazolidine 43. *Method A (from 42).* A solution of **42** (37 mg, 0.08 mmol, >99:1 dr) in acetone (2.9 mL) and DMP (0.58 mL) was stirred at rt, and BF_3 (1.0 M in Et_2O, ∼3 drops) was added dropwise until a permanent color change from colorless to dark orange was observed. The resultant mixture was then stirred at rt for 24 h. Et_3N (∼5 drops) was then added until pH 7 was achieved, and the reaction mixture was concentrated in vacuo to give a 66:34 mixture of **43** and **42**. Purification via flash column chromatography (gradient elution 20:1 → 10:1 30−40 °C petrol/EtOAc) gave **43** as a pale yellow oil (15 mg, 37%, >99:1 dr):[35] $[\alpha]_D^{25}$ −0.4 (*c* 1.0 in CH_2Cl_2); {lit.[7] $[\alpha]_D^{21}$ −3.1 (*c* 3.8 in CH_2Cl_2)}; $[\alpha]_D^{25}$ −2.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2983, 2936 (C−H), 1740, 1697 (C═O); δ_H (250 MHz, $CDCl_3$, 327 K) 1.43 (6H, s, 2 × *Me*CMe), 1.52 (9H, s, CMe_3), 1.58 (3H, s, *Me*CMe), 1.63 (3H, s, *Me*CMe), 2.40−2.66 (2H, m, C(3′)H_2), 3.76 (3H, s, O*Me*), 4.02 (1H, dd, *J* 7.9, 5.5, C(1′)*H*), 4.12−4.23 (1H, m, C(2′)*H*), 4.45−4.53 (1H, m, C(4)*H*), 4.73 (1H, d, *J* 2.1, C(5)*H*), 6.29 (1H, dt, *J* 15.8, 7.0, C(4′)*H*), 6.51 (1H, d, *J* 15.8, C(5′)*H*), 7.16−7.39 (5H, m, *Ph*); δ_C (62.5 MHz, $CDCl_3$, 327 K) 27.2, 27.2, 27.4, 27.7 (4 × *Me*CMe), 28.5 (CMe_3), 36.5 (*C*(3′)), 52.3 (O*Me*), 61.3 (*C*(4)), 75.2, 78.3, 80.0 (*C*(5), *C*(1′), *C*(2′)), 80.9 (CMe_3), 96.7 (*C*(2)), 109.0 (MeCMe), 125.5 (*C*(4′)), 126.2, 128.5 (*o,m-Ph*), 127.2 (*p-Ph*), 132.9 (*C*(5′)), 137.6 (*i-Ph*), 151.8 (NCO), 172.1 (CO_2Me); *m/z* (ESI$^+$) 498 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{37}NNaO_7^+$ ([M + Na]$^+$) requires 498.2462; found 498.2464.

Method B (from 41). KHMDS (0.5 M in PhMe, 64 μL, 32.2 μmol) was added dropwise to a solution of **41** (16 mg, 26.9 μmol, >99:1 dr) and PhCHO (3.5 μL, 32.2 μmol) in THF (0.6 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. H_2O (1 mL) was then added, and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were dried and concentrated in vacuo to give a 28:72 mixture of **43** and **41**. Purification via flash column chromatography (gradient elution 20:1 → 5:1 30−40 °C petrol/EtOAc) gave **43** as a yellow oil (2 mg, 16%, >99:1 dr).[7] Further elution gave **41** as a colorless oil (5 mg, 31%, >99:1 dr).

(*E*)-3-(4′-Ethoxyphenyl)acrylaldehyde 44. 4-Iodophenetole (120 mg, 0.48 mmol) was dissolved in DMF (2 mL) at rt, and then acrolein diethyl acetal (0.22 mL, 1.45 mmol), Bu_4NOAc (292 mg, 0.97 mmol), K_2CO_3 (100 mg, 0.73 mmol), KCl (36 mg, 0.48 mmol) and $Pd(OAc)_2$ (3.3 mg, 0.01 mmol) were sequentially added. The reaction vessel was evacuated, placed under an atmosphere of N_2, and then heated at 90 °C for 18 h. The reaction mixture was allowed to cool to rt, and then 2.0 M aq HCl (7 mL) was added dropwise, and the resultant mixture was stirred at rt for 10 min. The reaction mixture was diluted with Et_2O (50 mL) and washed with H_2O (3 × 50 mL), and then the organic layer was dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution 40:1 → 10:1 30−40 °C petrol/EtOAc) gave **44** as a yellow solid (70 mg, 82%, >99:1 dr): mp 50−52 °C; ν_{max} (ATR) 1673 (C═O), 1600 (C═C); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, t, *J* 7.0, CH_2CH_3), 4.10 (2H, q, *J* 7.0, CH_2CH_3), 6.62 (1H, dd, *J* 15.9, 7.9, C(2)*H*), 6.94 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.43 (1H, d, *J* 15.9, C(3)*H*), 7.52 (2H, d, *J* 8.7, C(2′)*H*, C(6′)*H*), 9.66 (1H, d, *J* 7.9, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 14.7 (CH_2CH_3), 63.7 (CH_2CH_3), 115.0 (*C*(3′), *C*(5′)), 126.4 (*C*(2)), 126.6 (*C*(1′)), 130.4 (*C*(2′), *C*(6′)), 152.9 (*C*(3)), 161.6 (*C*(4′)), 193.8 (*C*(1)); *m/z* (FI$^+$) 176 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{11}H_{12}O_2^+$ ([M]$^+$) requires 176.0832; found 176.0841.

Methyl (*S,S,S,S,E,E*)-2,4,5-trihydroxy-3-(*N-tert*-butoxycarbonylamino)-4,5-*O*-isopropylidine-10-(4′-ethoxyphenyl)deca-7,9-dienoate 45. KHMDS (0.5 M in PhMe, 1.89 mL, 0.94 mmol) was added dropwise to a solution of **40** (164 mg, 0.30 mmol, >99:1 dr) and **44** (166 mg, 0.94 mmol, >99:1 dr) in THF (30 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. H_2O (5 mL) was added, and the reaction mixture was allowed to warm to rt. The aqueous layer was then extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried and concentrated in vacuo to give **45** in >99:1 dr. Purification via flash column chromatography (gradient elution 7:1 → 5:1 30−40 °C petrol/EtOAc) gave **45** as a yellow solid (35 mg, 23%, >99:1 dr): mp 116−120 °C; $[\alpha]_D^{25}$ −11.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3364 (N−H, O−H), 2982, 2934 (C−H), 1741, 1716 (C═O), 1604, 1510 (C═C); δ_H (400 MHz, $CDCl_3$) 1.37−1.50 (18H, m, CMe_3, 2 × *Me*CMe, CH_2CH_3), 2.35−2.45 (1H, m, C(6)H_A), 2.45−2.54 (1H, m, C(6)H_B), 3.17 (1H, br s, O*H*), 3.76 (1H, dd, *J* 9.5, 6.5, C(4)*H*), 3.80 (3H, s, O*Me*), 4.03 (2H, q, *J* 7.1, CH_2CH_3), 4.13−4.21 (2H, m, C(3)*H*, C(5)*H*), 4.58 (1H, app s, C(2)*H*), 4.85 (1H, d, *J* 10.4, N*H*), 5.76 (1H, dt, *J* 15.0, 7.5, C(7)*H*), 6.24 (1H, dd, *J* 15.0, 10.5, C(8)*H*), 6.41 (1H, d, *J* 15.5, C(10)*H*), 6.63 (1H, dd, *J* 15.5, 10.5, C(9)*H*), 6.83 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.30 (2H, d, *J* 8.7, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 14.8 (CH_2CH_3), 27.1, 27.5 (2 × *Me*CMe), 28.2 (CMe_3), 37.5 (*C*(6)), 52.9 (O*Me*), 55.3 (*C*(3)), 63.4 (CH_2CH_3), 70.0 (*C*(2)), 78.4 (*C*(4)), 79.5 (*C*(5)), 80.0 (CMe_3), 109.3 (MeCMe), 114.6 (*C*(3′), *C*(5′)), 126.8 (*C*(9)), 127.4 (*C*(2′), *C*(6′)), 128.6 (*C*(7)), 130.0 (*C*(1′)), 130.8 (*C*(10)), 133.4 (*C*(8)), 155.0 (NCO), 158.4 (*C*(4′)), 174.0 (*C*(1)); *m/z* (ESI$^+$) 528 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{39}NNaO_8^+$ ([M + Na]$^+$) requires 528.2568; found 528.2564.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra, and crystallographic information files (for structures CCDC 907676−907679). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 907676 (**22**), 907677 (**40**), 907678 (**42**) and 907679 (**45**).

(26) Analogous reaction of the 2,3-*syn*-configured substrates produced antipodal diastereoselectivity.

(27) In comparable systems, treatment of osmate ester-TMEDA complexes with trishydroxymethylphosphine gives superior yields to those obtained upon treatment with ethylenediamine.

(28) As lactone **35** was found to be susceptible to decomposition it was necessary to prepare fresh samples to be used immediately in subsequent reactions.

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(35) The peaks in the ^{1}H and ^{13}C NMR spectra of both **41** and **43** in $CDCl_3$ at rt were found to be broad because of the rotameric nature of these compounds.