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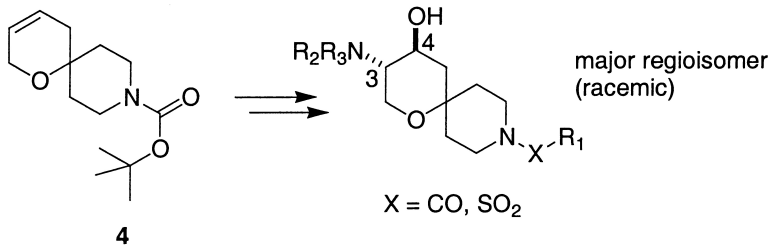

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Templates for Exploratory Library Preparation. Derivatization of a Functionalized Spirocyclic 3,6-Dihydro-2*H*-Pyran Formed by Ring-Closing Metathesis Reaction

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The preparation of a novel spirocyclic template from *tert*-butoxycarbonyl-4-piperidone is reported. The synthesis of *N*-(*tert*-butoxycarbonyl)-1-oxa-9-aza-spiro[5.5]undec-3-ene (**4**) for exploratory library generation involves ketone allylation, etherification, and ring-closing metathesis (RCM) reactions. Epoxidation of the alkene formed in the RCM followed by addition of volatile amines to the epoxides led rapidly to an exploratory library of structurally novel spirocyclic amino alcohols. The addition of amines to epoxides derived from **4** was determined to occur primarily at C3.

Introduction

The chemical processes that are hallmarks of combinatorial chemistry are generally applied in the preparation of lead-optimization or lead-generation libraries.[2] This latter exercise, also known as exploratory library synthesis, usually involves the preparation of novel templates to which are appended diversity elements.[3] Among many strategies, two criteria that have been applied to the design of useful templates are the incorporation in the molecular core of easily transformable functional groups (diversity-enabling moieties, DEMs)[4] and the novel spatial arrangement of these functional groups within the template.[5] We report herein the application of ring-closing metathesis (RCM) to the preparation of a novel, spirocyclic template **5**, which fits these two criteria, and its use as the core of an amino alcohol library.[6]

Ring-closing metathesis is a powerful C═C bond-forming reaction that occurs under very mild conditions and is generally undiminished in its efficiency by the presence of ancillary functional groups.[7] A ring-forming, spiroannulation[8] process based on this methodology that would convert readily available ketones into novel DEMs[9] would lead to a wide variety of useful core molecules, particularly if applied to ketones already possessing a site of potential diversity.

Results and Discussion

With the potential of such compounds in mind, the novel hydrochloride salt **5** was prepared from commercially available *tert*-butoxycarbonyl-4-piperidone (**1**) via the four-step procedure outlined in Scheme 1.[10] Addition of allylmagnesium bromide to **1** in ether at room temperature furnished **2**. Etherification of **2** was accomplished using excess NaH (DMF) followed by treatment of the incipient alkoxide with excess allyl bromide to give **3**. The key ring-closing metathesis reaction was cleanly effected by treatment of a degassed CH_2Cl_2 solution of **3** at room temperature with 5−10% of Grubbs' catalyst for ∼15 h. This gave **4** in approximately 40−60% yield after Kugelrohr distillation. Deprotection of **4** using concentrated ethereal HCl gave compound **5** as a white powder in ∼ 30% overall yield from **1**. Compound **5** was transformed into epoxides **8** in a two-step parallel process involving acylation or sulfonylation (Et_3N, **6**{*1*−*3*} in Chart 1) and epoxidation with MCPBA in CH_2Cl_2.

A small exploratory library of β-amino alcohols was prepared to highlight the utility of these new spirocyclic templates. Aminolysis of the unpurified epoxides **8**{*1*−*3*} was effected by heating them in ethanol at 80 °C with an excess (15−20 equiv) of low molecular weight primary and secondary amines **9**{*1*−*4*} (Chart 2) for 15−24 h.[11] Concentration of the reactions in vacuo gave good to quantitative conversion to the β-amino alcohols **10**{*6*(*1*−*3*),*9*(*1*−*4*)} (Table 1; major isomer shown (vide infra) in Scheme 2).[12]

The formation of both regioisomeric amino alcohols **10** was observed in these reactions. Surprisingly, while the regiochemical control in the reaction of nucleophiles with 3,4-epoxytetrahydropyran, **13**,[13] and the cis and trans diastereomers of 2-(benzyloxy)-3,6-dihydro-2*H*-pyran, **14**, has been studied extensively,[14] apparently no comparable investigations have been carried out on 6,6-dialkyltetrahydropyran-3,4-epoxides such as **15** (Figure 1). To more rigorously establish the probable structures of the amino alcohols **10**{*6*(*1*−*3*),*9*(*1*−*4*)}, epoxide **8**{*2*} was treated with 40% CH_3NH_2/H_2O or pyrrolidine/EtOH at 80 °C. The major regioisomer formed in each reaction was that resulting from attack of the nucleophile at C-3 of the epoxide (**16a** and **16b**).[15]

This assignment is consistent with the regiochemistry observed in the reaction of the structurally related epoxide **17** under the same conditions (Figure 2). Nucleophilic attack was again favored at C-3, a 3:1 ratio of isomers being

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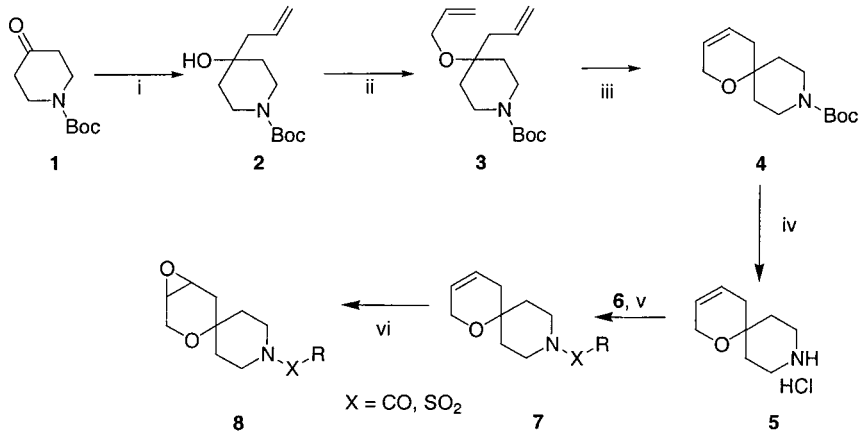
Scheme 1. Synthesis of Spirocyclic Epoxides[a]



[a] Key: (i) CH_2=$CHCH_2MgBr$ (1.1 equiv, Et_2O, room temp); (ii) CH_2=$CHCH_2Br$ (3 equiv, 4 equiv NaH, 1 M DMF, room temp); (iii) $Cl_2(Cy_3P)_2Ru$=CHPh (CH_2Cl_2, room temp); (iv) HCl (g), Et_2O; (v) **6**{*1*−*3*}, Et_3N, CH_2Cl_2; (vi) MCPBA, CH_2Cl_2.

Chart 1. Acyl and Sulfonyl Building Blocks **6**{1−3}

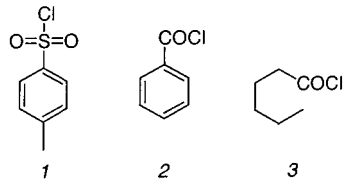


Chart 2. Amine Building Blocks **9**{1−4}

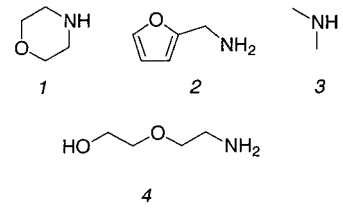
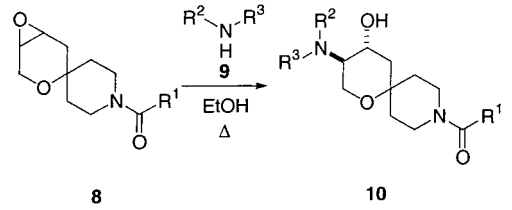


Table 1. Yield and HPLC Purity of Amino Alcohols

	10{*6*(*1*−*3*),*9*(*1*−4)} amino alcohols yield[a] (%), purity[b] (%)		
	6{*1*} acyl or sulfonyl chloride	**6**{*2*}	**6**{*3*}
9{*1*} amine	78, 100	73, 98	74, 100
9{*2*}	78, ND	80, 74	82, 78
9{*3*}	73, 99	74, 97	88, 91
9{*4*}	78, 81	74, 100	81, 100

[a] By weight (mixture of regioisomers). [b] HPLC purity. ND = not determined.

Scheme 2. Reaction of Template with Primary and Secondary Amines



obtained with methylamine (**18a**), while a 7:1 ratio of regioisomers was produced with pyrrolidine (**18b**).[15]

While we have not yet assigned the structure of the predominant isomer in all reactions of **8**, the major isomer being related to **16** and **18** is consistent with the observations that **13** reacts with nitrogen nucleophiles primarily at C-3

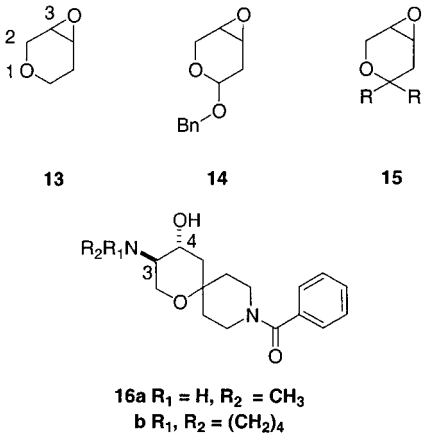


Figure 1. Related epoxides and the major regioisomer formed in the reaction of **8**{*2*} with amines.

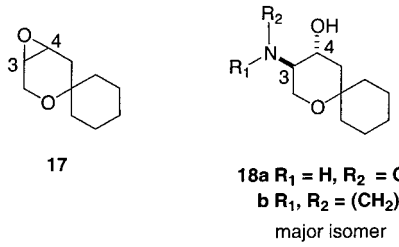
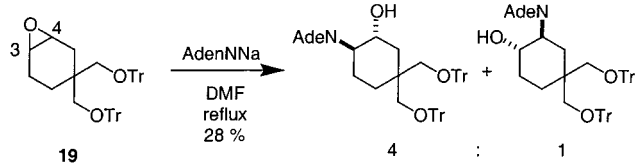


Figure 2. Regiochemistry of amine addition to **17**.

Scheme 3. Addition of an Amine Nucleophile to a 1,1-Disubstituted Cyclohexane-3,4-epoxide



(∼6:1 ratio[13] with diethylamine under conditions analogous to those employed herein) and that the 1,1-disubstituted cyclohexane epoxide **19** (Scheme 3) gives predominantly the C-3 regioisomer when treated with the sodium salt of adenine.[16]

The regiochemistry of the reaction of epoxides **8** and **17** with simple amines under nonchelating conditions is consistent with a consideration of both the Fürst−Plattner rule[17] and the steric environment experienced by a nucleophile

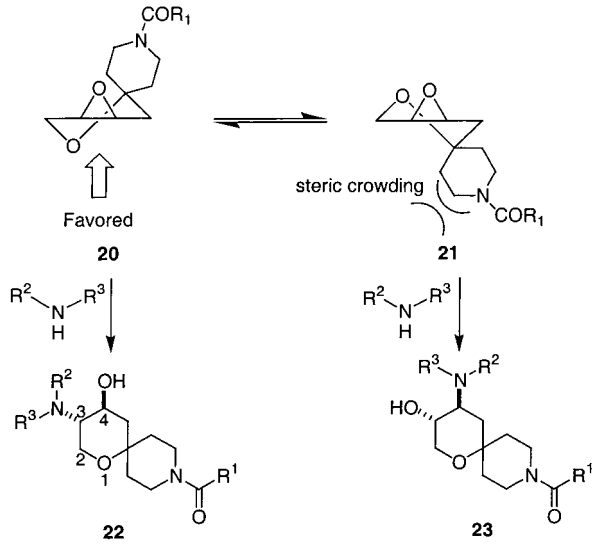


Figure 3. Rationalization of the regiochemistry of amine addition to spirocyclic epoxides **16**.

approaching the epoxide conformers **20** and **21** with an S_N2 trajectory (Figure 3). The Fürst−Plattner rule suggests that nucleophilic attack on **20** should give rise to predominantly C-3 addition of the nucleophile, while amine addition to **21** should preferentially form the C-4 amine. Consideration of the steric interactions experienced by an incoming nucleophile in each case suggests that the S_N2 ring opening of epoxide **20** should be kinetically favored over attack on epoxide **21**, leading to preferential formation of regioisomer **22** (as observed) over preference to **23**.

Conclusion

In summary, we have employed RCM to create a readily functionalized, spirocyclic template and demonstrated its use in the preparation of libraries of novel compounds using combinatorial techniques. The reaction sequence by which **4** was generated appears to be mild enough to apply to a wide variety of other ketones. Future investigations in our laboratory are aimed at exploring the reactivity of other 6,6-disubstituted spirotetrahydropyran 3,4-epoxides with nucleophiles with an aim of gaining a further understanding of the regioselectivity of these reactions.

Experimental Section

General. Unless otherwise indicated, all reactions were run in capped 2 dram glass vials, which were agitated on an orbital shaker. Heated reactions were run in a stationary heat block. Commercially available reagents and solvents were used without further purification. Anhydrous solvents were purchased and employed without further drying. ^{1}H NMR spectra were recorded at the indicated field strength as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts are expressed in parts per million (ppm, δ) downfield from TMS and are referenced to $CDCl_3$ (7.24 ppm) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex (or overlapping) multiplet; br, broad. Coupling constants are given in hertz (Hz). ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDC1_3$ unless otherwise indicated. Coupling constants (J) are reported in hertz. IR spectra were taken as KBr pellets or neat films, and absorptions are reported in cm^{-1}. The HPLC purity of array **10** was determined using an Altima C18, 5 μm, 150 mm Alltech column. The mobile phase was CH_3CN in H_2O (+0.1% TFA) from 5% to 100% over 10 min, and the flow rate was 1 mL/min at 214 nM.

Synthetic Details. *N*-(*tert*-butoxycarbonyl)-1-oxa-9-aza-spiro[5.5]undec-3-ene (**4**) was prepared from commercially available *N*-(*tert*-butoxycarbonyl)-4-piperidone (**1**) without purification of the intermediates.

***N*-(*tert*-butoxycarbonyl)-4-allyl-4-hydroxypiperidine (2).** A 250 mL round-bottomed flask was charged with 85 mL of anhydrous Et_2O and 5.0 g of **1** (0.025 mol) and cooled on an ice bath. To this cooled solution was added a total of 29 mL of allylmagnesium bromide (1.0 M in Et_2O, 0.029 mol), and the reaction mixture was allowed to slowly warm to room temperature overnight. The reaction became heavy with a white ppt. It was quenched by the dropwise addition of 5 mL of NH_4Cl(aq) and worked up with Et_2O. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo to give a quantitative yield of **2** as a yellow-orange liquid. This material was used in the next reaction without further purification.

***N*-(*tert*-Butoxycarbonyl)-4-allyl-4-allyloxypiperidine (3).** A 250 mL round-bottomed flask was charged with 1.5 g of NaH (0.038 mol) as a 60% dispersion in mineral oil. The NaH was washed (2 × 6 mL) with anhydrous petroleum ether and then slurried in 50 mL of anhydrous DMF with the reaction flask in an ice bath. To this cooled slurry was added 5.73 g (0.024 mol) of a solution of **2** in anhydrous DMF. This reaction mixture was allowed to warm to room temperature over the course of 1 h and then recooled to ice-bath temperature and treated with 6.5 mL of freshly purified (filtered through a basic alumina column) allyl bromide (0.075 mol). The heterogeneous reaction mixture was removed from the ice bath and stirred overnight. After approximately 10−15 h at room temperature the reaction was cooled on an ice bath and quenched by the slow and cautious addition of 100 mL of H_2O (*warning: hydrogen gas evolution!*). The resulting mixture was extracted with 3 × 100 mL of Et_2O, the combined Et_2O extracts were washed with 3 × 100 mL of H_2O and 1 × 100 mL brine, and the organic extracts were dried over $MgSO_4$. Filtration followed by concentration in vacuo gave 5.35 g (~80% yield) of a light-orange liquid, which was used for the next reaction without further purification.

***N*-(*t*-Butoxycarbonyl)-1-oxa-9-aza-spiro[5.5]undec-3-ene (4).** A 500 mL round-bottomed flask was charged with 100 mL of anhydrous CH_2Cl_2 and 5.35 g of **3** (0.019 mol) and degassed using three evacuation/argon-fill cycles. In a separate flask a degassed solution of 0.62 g of $Cl_2Ru(PCy_3)_2$-CHPh (0.75 mmol, 0.04 equiv) and 7.0 mL of anhydrous CH_2Cl_2 was prepared. The solution of **3** was cooled on an ice bath and then treated dropwise with the purple catalyst solution over the course of 20 min (*caution: gas evolution!*). Upon completion of this addition, the reaction mixture was removed from the ice bath and allowed to warm to room

temperature and stirred overnight. After the reaction was deemed complete by ^{1}H NMR of an aliquot, the solvent was removed and the dark-brown liquid residue was taken up in 50 mL of 25% EtOAc/hexanes. Compressed air was bubbled through this heterogeneous mixture for 3 h, and it was then passed through a small plug of silica gel to remove the insoluble material. This solution was concentrated and Kugelrohr distilled (~1 mm, oven temp of ~100 °C) to give 2.28 g (47% yield) of the desired alkene **4** as a clear, colorless liquid. ^{1}H NMR (400 MHz): δ 5.72−5.62 (comp, 2 H), 4.06−4.04 (comp, 2 H), 3.73−3.70 (comp, 2H), 3.2−3.1 (comp, 2H), 1.92 (comp, 2H), 1.75−1.72 (comp, 2H), 1.41−1.34 (comp, 11H). ^{13}C NMR (100 MHz): δ 155.1, 125.3, 122.7, 79.46, 68.81, 60.53, 41−39 (br), 35.51, 35−33 (br), 28.65. IR (neat): 2920, 1696 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.69; H, 9.20; N, 5.48.

1-Oxa-9-aza-spiro[5.5]undec-3-ene hydrochloride (5). HCl(g) was bubbled through 100 mL of Et_2O in an ice bath cooled in a 500 mL round-bottomed flask. When enough HCl(g) had dissolved to make the solution about 5 M, 10.5 g (0.041 mol) of **4** were added in 50 mL of CH_2Cl_2. The solution rapidly became deep-orange and thick with a whitish precipitate. After 2 h at room temperature, the reaction was filtered and the white solid washed with 2 × 100 mL of Et_2O. The solid was dried in vacuo to give 6.89 g (88% yield) of a white powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.2−9.0 (br comp, 2H), 5.69 (s, 2H), 3.99 (br s, 2H), 3.0−2.9 (comp, 2H), 2.90−2.87 (comp, 2H), 2.0−1.6 (comp, 6H). ^{13}C (100 MHz, DMSO-d_6): δ 125.8, 122.4, 67.16, 60.34, 35.09, 30.76. Anal. Calcd for $C_9H_{16}ClNO$: C, 56.99; H, 8.50; N, 7.38. Found: C, 56.98; H, 8.68; N, 7.27.

Representative Preparation of 7{X}. Preparation of *N*-Benzoyl-1-oxa-9-aza-spiro[5.5]undec-3-ene (7{*2*}, X = CO, R= Ph). A 100 mL round-bottomed flask was charged with the amine hydrochloride salt **5** (4.51 g, 23.8 mmol), methylene chloride (35 mL), benzoyl chloride (3.0 mL, 3.76 g, 26.8 mmol), and a magnetic stir bar. The flask was cooled in an ice−water bath, and triethylamine (7.3 mL, 5.3 g, 52.4 mmol) was added by syringe over 10 min with stirring. The cooling bath was removed, and the reaction was allowed to stir at ambient temperature for 16 h. The reaction mixture was filtered, and the solvent was removed from the filtrate. The residue was taken up in hot hexanes (100 mL), and the resulting slurry was filtered. The solids were washed with additional hot hexanes (100 mL), and the combined filtrates were dried over magnesium sulfate, filtered, and concentrated to give a yellow oil (6.60 g). This oil was chromatographed on a 6.5 cm × 35 cm silica gel column eluting with 50:50 ethyl acetate/hexanes. The product fractions were concentrated to give an 88% yield (5.40 g) of the desired product as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.4 (s, 5H), 5.8−5.7 (m, 2H), 4.5−4.2 (br s, 1H), 4.2−4.0 (br s, 2H), 3.6−3.2 (comp, 4H), 2.1−1.4 (comp, 5H). ^{13}C ($CDCl_3$, 100 MHz): δ 170.5, 136.5, 133.5, 129.7, 128.6, 127.0, 125.2, 125.1, 122.5, 70.64, 68.93, 60.69, 59.09, 43.80, 38.25, 35.57, 35.40, 33.67, 25.46. MS *m*/*z*: $(M + H)^+$, 258.0. **7**{*1,3*} were prepared in an analogous fashion and taken on without purification to **8**{*1,3*}.

Representative Preparation of 8{X}. Preparation of *N*-Benzoyl-1-oxa-9-aza-spiro[5.5]undec-3,4-epoxide (8{*2*}, X = CO, R= Ph). A flask was charged with 4.11 g of **7** (R = Ph) and 80 mL of CH_2Cl_2 and, by portionwise addition, 5.5 g of MCPBA (60−80% purity; 2 equiv). After the mixture was stirred at room temperature for 24 h, the reaction was quenched with 25 mL of 1 M Na_2SO_3 and diluted with 100 mL of EtOAc. The layers were separated, and the aqueous layer was back-extracted with 100 mL of EtOAc. The combined organic layers were washed with 3 × 50 mL of saturated $NaHCO_3$ and with 50 mL of brine and then dried over $MgSO_4$. Filtration and concentration in vacuo gave 3.31 g (76%) of a sticky foam. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38−7.34 (m, 5H), 4.4−4.3 (m, 1H), 4.1−3.0 (comp, 8H), 2.2−1.2 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 136.2, 129.6, 128.5, 126.8, 68.76, 56.49, 55.63, 50.87, 43.23, 37.63, 34.31, 30.60, 25.16. MS *m*/*z*: $(M + H)^+$, 274.0. **8**{*1,3*} were prepared in an analogous fashion and used for **10** without further purification.

General Method for the Preparation of Amino Alcohols 10{X,X}. To an ethanolic solution of **8**{*1−3*} (~30 mg, 0.1 mmol, 1 mL of EtOH) was added 10−25 equiv of volatile amine **9**{*1−4*}. The reaction mixture was heated to 80 °C for 15−20 h. The solutions were cooled to room temperature and were concentrated in parallel using a centrifugal evaporator to provide ~20−30 mg of the desired amino alcohols (>73% yield, purity (LC) > 74%).

Preparation of 1-Oxa-spiro[5.5]undec-3,4-epoxide. A flask was charged with 3.12 g (0.02 mol) of 1-oxa-spiro-[5.5]undec-3-ene,[10c] 8.46 g (0.049 mol) of MCPBA, and 200 mL (~0.1 M) of CH_2Cl_2. After the mixture was stirred overnight at room temperature, the reaction mixture was worked up with ether and 1 M Na_2SO_3 and then dried over $MgSO_4$. Filtration and concentration of the organic extracts gave 2.9 g (86%) of a volatile, colorless liquid. Purification by column chromatography using 10% ethyl acetate/hexanes as eluant gave 1.35 g of the desired epoxide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.00−3.87 (m, 2H), 3.28−3.25 (m, 1H), 3.10−3.08 (m, 1H), 1.84−1.17 (m, 14H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 69.14, 58.40, 49.34, 48.96, 37.95, 34.56, 33.04, 25.81, 21.85, 21.63.

Preparation of Amino Alcohols 16a and 16b. Approximately 0.09 g of epoxide **8**{*2*} was dissolved in 3 mL of 40% CH_3NH_2 (aqueous solution), and another 0.09 g was dissolved in 3 mL of EtOH and treated with 300 μL of pyrrolidine (~10 equiv, 0.1 M). Both reactions were heated to 80 °C for ~20 h and concentrated in vacuo. No further purification was performed. The crude yield of amino alcohols **16a** and **16b** was 71% and 91%, respectively. For **16a**. ^{1}H NMR (CH_3OD, 400 MHz), mixture of isomers, integration relative to δ 7.4−7.3 (m), which was set to 5H: δ 7.4−7.3 (m, 5H), 4.30−4.27 (br m, 1H), 3.93−3.90 (m, 0.8H), 3.8−1.2 (comp, 18H). ^{13}C NMR (CH_3OD, 100 MHz), mixture of isomers: δ 171.2, 135.9, 129.8, 128.5, 126.6, 72.08, 71.44, 67.06, 62.88, 61.53, 43.36, 37.70, 32.94. MS *m*/*z*: $(M + H)^+$, 305.1. For **16b**. ^{1}H NMR (CH_3OD, 400 MHz), mixture of isomers, integration relative to δ 7.32−7.23 (m), which was set to 5H: δ 7.32−7.23 (m, 5H), 4.27−4.24 (br m, 1H), 3.8−1.3 (comp, 22H). ^{13}C NMR (CH_3OD,

100 MHz), mixture of isomers: δ 171.2, 135.9, 129.8, 128.5, 126.6, 71.55, 71.34, 66.36, 65.76, 60.49, 51.61, 43.74, 43.47, 43.31, 38.05, 37.78, 22.82. MS *m*/*z*: $(M + H)^+$, 345.2.

Amino alcohols **18a** and **18b** were prepared in quantitative yield and, in an analogous fashion, from epoxide **17**. For **18a**, mixture of isomers. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.88−3.84 (m, 1H), 3.68−3.53 (m, 2.3H), 3.36−3.27 (m, 1H), 3.17 (tr, 1H, $J = 11$ Hz), 2.61−2.58 (m, 0.33H), 2.38−2.31 (m, 5.66H), 1.94−1.82 (m, 3H), 1.60−1.22 (m, 16H), 1.07 (tr, 0.33H, $J = 12$ Hz). Integration relative to integral of 3.88−3.84 multiplet, which is arbitrarily set to 1H. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 76.97, 74.29, 73.61, 70.09, 67.99, 64.37, 63.71, 62.31, 62.31, 62.31, 58.64, 43.75, 39.86, 39.80, 39.12, 34.08, 32.55, 30.77, 30.31, 26.16, 22.05, 22.00, 21.64, 21.61. MS *m*/*z*: $(M + H)^+$, 200.1; $(M + H + CH_3CN)^+$, 241.1. For **18b**, mixture of isomers. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.8−3.7 (m, 1H), 3.50−3.44 (m, 0.44H), 3.31−3.28 (m, 0.11H), 2.7−2.5 (m, 1.88H), 1.99−1.2 (m, 6.66H). Integration relative to integral of δ 3.8−3.7 multiplet, which is arbitrarily set to 1H. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 73.96, 73.87, 68.59, 66.01, 64.54, 64.08, 59.25, 57.50, 48.83, 47.82, 43.50, 40.00, 39.97, 32.14, 30.89, 30.39, 26.26, 26.19, 23.90, 23.72, 22.10, 22.05. MS *m*/*z*: $(M + H)^+$, 240.1.

Structural assignments were made on the basis of extensive ^{13}C distortionless enhancement by polarization transfer (DEPT), ^{1}H−^{3}C heteronuclear single quantum coherence (HSQC) or heteronuclear multiple-quantum coherenc (HMQC), and ^{1}H−^{1}H correlation spectroscopy (COSY) data, which were consistent with the structures as depicted.

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Supporting Information Available. Characterization data on all new compounds (including copies of NMR spectra), data supporting the structural assignments of **16 a,b** and **18 a,b**, and ^{1}H NMR, HPLC, and MS data on **10**{**X,X**}. This material is available free of charge via the Internet at http://pubs.acs.org.

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