entire framework. Hydrogen atom minimization was performed to alleviate any unreasonable contacts resulting from the hydrogen adding process. The resulting structures were subjected to molecular dynamics in CHARMm and the minimum energy conformation compared to the initial structures obtained from hydrogen addition to the crystal structures.

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Registry No. **1a**, 138312-87-5; **1b**, 138312-88-6; **1c**, 138333-42-3; **1d**, 138312-89-7; **1e**, 138312-90-0; **2a**, 138312-91-1; **2b**, 138312-92-2; **4a**, 87597-38-4; **4b**, 88549-97-7; **5a**, 65599-38-4; **5b**, 65540-90-1; **5c**, 138312-93-3.

Supplementary Material Available: Cartesian coordinates for the CHARMm calculated minimum structures for dimers **1a–e**, **2a**, **2b**, **4a**, **4b**, and **5b** (38 pages). Ordering information is given on any current masthead page.

An Iterative and Convergent Synthesis of Syn Polyols

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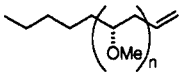
We have developed a new iterative and convergent synthesis of alternating (1,3,5...) polyol chains based on enantiomerically enriched (94% ee) chloro nitrile 1. Chloro nitrile 1 is both a potential nucleophile and a potential electrophile; orthogonal nucleophilic or electrophilic activation leads to a highly efficient synthetic strategy for alternating polyol chains. As an illustration permethylated polyol **2** (n = 10), a natural product with 10 stereogenic centers isolated from the blue green alga *Tolypothrix conglutinata* var. *chlorata*, was prepared in 10 steps from 1.

Numerous methods have been developed for the stereoselective synthesis of alternating polyol chains,[2] including several convergent approaches.[3] Our new strategy is based on the stereoselective reduction of cyanohydrin acetonides to give *syn*-1,3-diol acetonides.[4] The key synthon, cyanohydrin acetonide **1**, is the precursor for both the nucleophilic and electrophilic components of a convergent coupling (Figure 1). Orthogonal nucleophilic or electrophilic activation of chloro nitrile 1 allows polyols to be synthesized in an iterative strategy reminiscent of solution peptide synthesis.

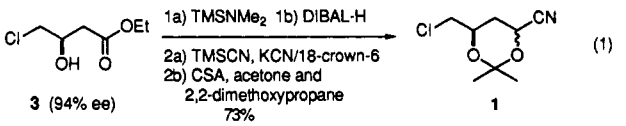
We have prepared a permethylated isotactic alternating polyol first isolated from the blue-green alga *Tolypothrix conglutinata* var. *chlorata*.[5] This alga produces numerous permethylated polyols of the general formula **2**, where n = 8–10. These permethylated polyols also have been



2 (n = 5,6,8,9 and 10)

isolated from blue-green algae belonging to the family scytonemataceae, along with homologues where n = 5 and 6.[6] Compound **2** (n = 9) has been prepared by two different groups,[3g,3e] and syntheses of permethylated polyols **2** (n = 5, 6, and 8) have been reported recently.[6] We report herein the first synthesis of permethylated polyol **2** (n = 10).

Cyanohydrin acetonide **1** was prepared from ethyl (3*R*)-4-chloro-3-hydroxybutyrate (**3**), which is available in 94% ee from ethyl 4-chloroacetoacetate by Noyori's enantioselective reduction.[7] The single stereocenter in hydroxy ester **3** controls eight of the 10 stereogenic centers in the final product. Hydroxy ester **3** was silylated with $TMSNMe_2$ and reduced with DIBAL-H in Et_2O at –78 °C. The resulting aldehyde was treated with trimethylsilyl cyanide (TMSCN) and potassium cyanide/18-crown-6 complex[8] followed by protection with acetone, 2,2-dimethoxypropane, and catalytic camphorsulphonic acid. Cyanohydrin acetonide **1** was isolated as a 1.7:1 mixture of syn- and anti-isomers which were used without separation.[9] The overall yield from hydroxy ester **3** was 73%.



(1)

Electrophilic activation of chloro nitrile **1** requires displacement of the chloride with an iodide, and that is very difficult when an α-alkoxy substituent is present.[10c] After many unsuccessful attempts,[10] we found that iodide **4** could be prepared by treatment of chloride **1** with 20 equiv of powdered potassium iodide and 1 equiv of 18-crown-6 in refluxing xylenes for 36 h. Nucleophilic activation of nitrile

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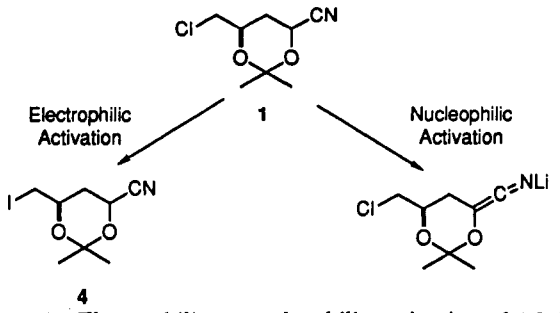


Figure 1. Electrophilic or nucleophilic activation of 1,3-diol synthon 1.

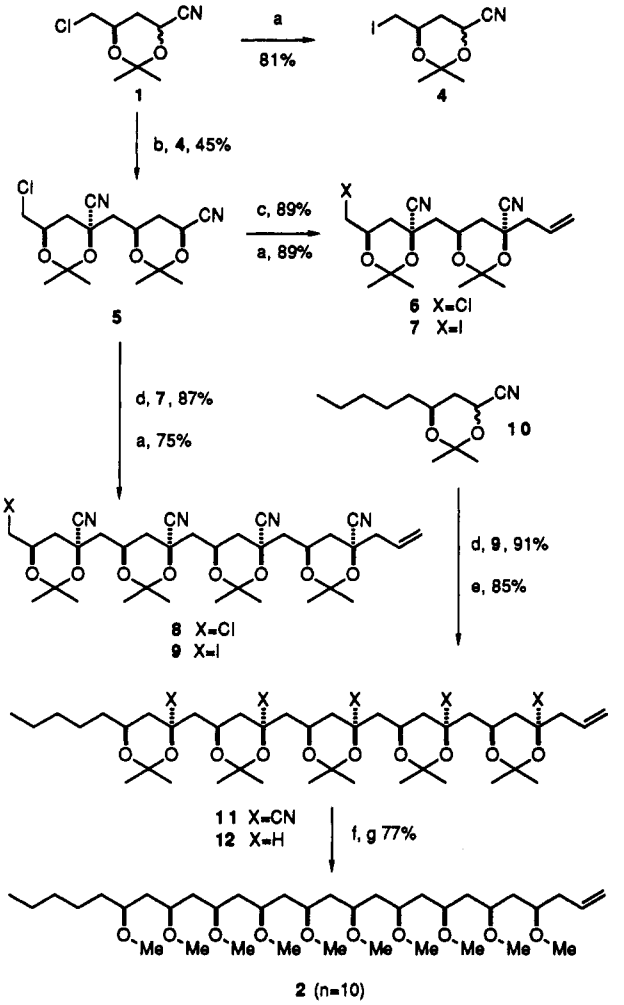
3 (1.4 equiv) by deprotonation with $LiNEt_2$ and alkylation with **4** in the presence of *N,N'*-dimethylpropyleneurea (DMPU) gave the protected tetraol **5** in 45% yield and ca. >99% ee.[11] The alkylation gave a single configuration at the newly formed carbon–carbon bond with the nitrile substituent axial.[12] Usually a single isomer was isolated with the terminal nitrile equatorial, presumably due to slow epimerization under the reaction conditions. Chloro nitrile **5** is a higher homologue of chloro nitrile **1**, and both share the same potential for orthogonal nucleophilic and electrophilic activation.

Permethylated polyol **2** (n = 10) was assembled from two molecules of chloro nitrile **5** and one molecule of cyanohydrin acetonide **10** (Scheme I). Nucleophilic activation of nitrile **5** by deprotonation with excess potassium bis(trimethylsilyl)amide followed by alkylation with allyl chloride gave **6** in 89% yield. Conversion of chloride **6** to the iodide **7** was achieved in 89% yield using potassium iodide and 18-crown-6 in refluxing xylenes. Nucleophilic activation of chloride **5** (1.4 equiv) by deprotonation with $LiNEt_2$ followed by alkylation with iodide **7** in the presence of DMPU gave the protected octol **8** in 87% yield. Electrophilic activation by iodide displacement as described above gave iodide **9** in 75% yield. The final two stereogenic centers originate with optically active (92% ee) cyanohydrin acetonide **10**.[13] Deprotonation of 2 equiv of **10** with $LiNEt_2$ followed by alkylation with **9** in the presence of DMPU gave a 91% yield of **11**, which has the complete carbon backbone of the synthetic target.

The key step in the synthesis is the reductive decyanation of pentanitrile **11** which sets five of the target's 10 stereogenic centers in a single step.[4] Treatment of pentanitrile **11** with lithium metal in ammonia gave the protected all syn polyol **12** in 85% yield. The cis relationship of the acetonide substituents was confirmed by ^{13}C NMR analysis.[12] Deprotection of **12** (Dowex 50W-X1 in MeOH) gave the polyol as an amorphous solid that was permethylated to give the desired product **2** (n = 10) in 77% overall yield.[14] The synthesis of **2** (n = 10) was accomplished in only 10 steps from synthon **1**. Furthermore, one could prepare a variety of stereoisomers of **2** (n = 10) by using the enantiomers of cyanohydrin acetonides **1** and **10**.

Cyanohydrin acetonide **1** and its enantiomer are valuable new 1,3-diol synthons. Orthogonal nucleophilic and electrophilic activation of these chloro nitriles and their homologues makes this highly convergent strategy possible.

Scheme I[a]



[a] Key: (a) KI, 18-crown-6, xylenes, reflux, 36–48 h; (b) $LiNEt_2$, THF, −78 °C; alkylating agent, DMPU; −78 °C; (c) $KN(SiMe_3)_2$, THF, −78 °C; allyl chloride; (d) $LiNEt_2$, THF, −78 °C; alkylating agent, DMPU; −78 °C to rt; (e) Li^0, NH_3, THF, −78 °C; (f) Dowex 50W-X1, MeOH, rt; (g) KH, MeI, THF.

Experimental Section[15]

Ethyl (3*R*)-4-Chloro-3-hydroxybutyrate (3).[7] Catalyst preparation: 30 mg (0.11 mmol, 1.0 equiv) of $RuCl_2$(COD), 80 mg (0.13 mmol, 1.2 equiv) of (*S*)-BINAP, 180 μL (1.29 mmol, 12 equiv) of Et_3N, and 10 mL of toluene were heated at reflux 17 h in a 100-mL Schlenk flask under Ar. The resulting orange solution was concentrated under vacuum to give the crude $[RuCl_2((S)\text{-BINAP})]_2$–$Et_3N$ catalyst as an orange solid.

Ethyl 4-chloroacetoacetate (45.0 g, 0.274 mol) was dissolved in absolute EtOH (35 mL), and the solution was degassed with a stream of N_2. This solution was transferred via cannula to the

(11) Coupling the optically enriched nitrile **1** and iodide **4** produce an amplification of optical purity in the product. A nonselective coupling of **1** (94% ee) and **4** (94% ee) will give the stereoisomers of **5** in ratio of $(0.97)^2$ *RR*:(0.97)(0.03)*RS*:(0.03)(0.97)*SR*:$(0.03)^2$*SS*. Separation of the *RS* isomers will give the major isomer of **5** in 99.8% ee. To the best of our knowledge this analysis was first reported by Saucy: Cohen, N.; Scott, C. G.; Neukom, C.; Lopresti, R. J.; Weber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, *64*, 1158–1173.

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(13) Cyanohydrin acetonide **10** was prepared from methyl 3-oxooctanoate by a procedure completely analogous to the preparation of **1**. Full experimental details are reported in the supplementary material.

(14) The ^1H and ^{13}C NMR and CI-MS spectral data for synthetic and natural **2** (n = 10) were identical. No optical rotation has been reported for natural **2** (n = 10), but it is probably 4*S* based on the synthesis of its homologues (ref 6). The optical rotation of synthetic **2** (n = 10, 4*R*) is $[\alpha]^{22}_D$ = −3.35° (c = 2.98, $CHCl_3$).

(15) Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ). Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM Reagent silica gel 60 (230–400 mesh). Tetrahydrofuran and ether were distilled from potassium/benzophenone ketyl. Dichloromethane, diisopropylamine, and toluene were distilled from calcium hydride. Air and/or moisture sensitive reactions were carried out under an atmosphere of nitrogen or argon using flame-dried glassware and standard syringe/septa techniques.

freshly prepared $[RuCl_2((S)\text{-BINAP})]_2$–$Et_3N$ catalyst under Ar. After the suspension was heated to dissolve the catalyst, the orange solution was transferred to a 125-mL pressure reaction vessel filled with Ar (Parr no. 4751) by cannula and sealed. The vessel was heated to approximately 100 °C and then pressurized to 1400 psi with H_2 gas. Additional H_2 gas was added to maintain this pressure until no more hydrogen was absorbed (5 h), and the reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by distillation to give 42.5 g (0.256 mol, 93%) of product ($[\alpha]^{25}_D$ = +20.4 (c = 0.800, $CHCl_3$), 94% ee) as a colorless liquid.

***cis*- and *trans*-(4*R*)-4-(Chloromethyl)-2,2-dimethyl-1,3-dioxane-6-carbonitrile (1).** Ethyl (3*R*)-4-chloro-3-hydroxybutyrate (3.041 g, 18.3 mmol, 1.00 equiv) and *N*,*N*-dimethyl(trimethylsilyl)amine (3.10 mL, 19.3 mmol, 1.06 equiv) were combined neat under N_2 and stirred for 16 h. The reaction was passed over a small SiO_2 plug, eluting with ether, and then concentrated under reduced pressure to give 4.31 g of the trimethylsilyl-protected product. This was dissolved in 140 mL of anhydrous Et_2O and cooled to −78 °C under N_2. DIBAL (1.0 M in cyclohexane, 22 mL, 22 mmol, 1.2 equiv) was added dropwise, and the reaction was stirred for 90 min. The reaction was quenched with 1 mL of ethyl formate followed by 25 mL of 10% aqueous AcOH solution and then warmed to 0 °C. The layers were separated and the aqueous fraction was extracted with Et_2O (3 × 50 mL). The combined organic layers were then washed with H_2O (2 × 75 mL) and saturated $NaHCO_3$ solution (2 × 75 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 3.25 g of the aldehyde as a colorless liquid. The aldehyde was cooled to 0 °C, and trimethylsilyl cyanide (2.43 mL, 18.2 mmol) was added followed by 1 mg of KCN/18-crown-6 complex. The reaction was warmed to rt, and after stirring for 1 h, 70 mg CSA and 60 mL of acetone/2,2-dimethoxypropane (4:1) were added. After the mixture was stirred for 2 d, 0.5 mL of Et_3N was added and the reaction was concentrated under reduced pressure. Chromatography (SiO_2, 5–10% ethyl acetate/hexanes) gave 2.52 g (73% overall yield) of the desired product (1.0:1.7 trans/cis isomers) as a colorless oil. A small portion was further purified in order to separate and characterize the individual isomers. Trans isomer: IR (neat) 2997, 2944, 1430, 1385, 1238, 1201, 1158, 1129, 1068, 1041, 984, 903, 880, 857, 814, 756, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.87 (t, J = 4.6 Hz, 1 H), 4.33 (m, 1 H), 3.54 (dd, J = 5.4, 11.3 Hz, 1 H), 3.47 (dd, J = 5.7, 11.3 Hz, 1 H), 2.00–1.95 (m, 2 H), 1.66 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 119.5, 101.4; *CH* 65.9, 58.5; CH_2 46.2, 31.1; CH_3 29.5, 22.0; MS(EI) 174.0324 (M − CH_3), 114, 59, 43. Anal. Calcd for $C_8H_{12}ClNO_2$: C, 50.67; H, 6.38. Found: C, 50.58; H, 6.51. Cis isomer: IR (neat 2997, 2944, 1385, 1267, 1257, 1203, 1157, 1119, 1102, 1084, 1066, 1005, 981, 910, 870, 836, 741, 704, 620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (dd, J = 2.9, 11.9 Hz, 1 H), 4.05 (m, 1 H), 3.52 (dd, J = 5.3, 11.2 Hz, 1 H), 3.41 (dd, J = 6.2, 11.2 Hz, 1 H), 2.04 (dt, J = 2.9, 12.9 Hz, 1 H), 1.84 (m, 1 H), 1.44 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 117.2, 100.3; *CH* 67.9, 58.6; CH_2 45.8, 31.9; CH_3 29.1, 19.0; MS(EI) 174.0349 (M − CH_3), 132, 115, 65, 43. Anal. Calcd for $C_8H_{12}ClNO_2$: C, 50.67; H, 6.38. Found: C, 50.44; H, 6.50.

***cis*- and *trans*-(4*R*)-4-(Iodomethyl)-2,2-dimethyl-1,3-dioxane-6-carbonitrile (4).** Chloride 1 (627 mg, 3.31 mmol, 1.0 equiv) and 18-crown-6 (874 mg, 3.31 mmol, 1.0 equiv) were dissolved in 8 mL of xylenes under N_2. Powdered potassium iodide (11 g, 20 equiv) was added, and the mixture was refluxed for 36 h with stirring. The reaction was cooled to room temperature followed by addition of 10 mL of 0.5 M $Na_2S_2O_3$. The reaction mixture was then extracted (4 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatogrphy (SiO_2, 10% ethyl acetate/hexanes) gave 758 mg (2.69 mmol, 81%) of the products as a colorless solid. A small portion was further purified in order to separate and characterize the individual isomers. The trans isomer is a colorless oil, while the cis isomer is crystalline. Trans isomer: IR (neat) 2996, 2941, 2892, 1462, 1428, 1415, 1384, 1309, 1272, 1258, 1206, 1159, 1127, 1095, 1041, 1002, 975, 953, 879, 860, 846, 786, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.84 (dd, J = 2.8, 6.4 Hz, 1 H), 4.12 (dddd, J = 2.8, 5.7, 5.8, 11.1 Hz, 1 H), 3.17 (dd, J = 5.8, 11.8 Hz, 1 H), 3.17 (dd, J = 5.7, 11.8 Hz, 1 H), 2.07 (dt, J = 2.8, 13.4 Hz, 1 H), 1.88 (ddd, J = 6.4, 11.1, 13.4 Hz, 1 H), 1.66 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 119.7, 101.9; *CH* 65.9, 58.8; CH_2 33.8, 7.7; CH_3 29.6, 22.1; MS(EI) 265.9677 (M − CH_3), 206, 43. Anal. Calcd for $C_8H_{12}INO_2$: C, 34.18; H, 4.30. Found: C, 34.20; H, 4.53. Cis isomer: mp 76–77 °C; IR (KBr) 2994, 2949, 1420, 1383, 1265, 1206, 1163, 1126, 1055, 1028, 999, 912, 877, 820, 759, 620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.75 (dd, J = 2.9, 12.0 Hz, 1 H), 3.88 (m, 1 H), 3.16 (dd, J = 5.7, 10.2 Hz, 1 H), 3.10 (dd, J = 6.4, 10.2 Hz, 1 H), 2.13 (dt, J = 2.7, 12.8 Hz, 1 H), 1.76 (br q, J = 12.1 Hz, 1 H), 1.45 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 117.2, 100.6; *CH* 67.8, 58.7; CH_2 34.1, 7.3; CH_3 29.2, 19.1; MS(EI) 265.9667 (M − CH_3), 206, 43. Anal. Calcd for $C_8H_{12}INO_2$: C, 34.18; H, 4.30. Found: C, 34.10; H, 4.39.

(1*S*,3*R*,5*R*,7*R*)-8-Chloro-1,5-di-*C*-cyano-1,3:5,7-bis-*O*-(1-methylethylidene)-1,3,5,7-octanetetrol (5). A precooled (−78 °C) solution containing 987 mg (5.21 mmol, 1.41 equiv) of 1 in 5 mL of THF was added via cannula to a solution of $LiNEt_2$ (5.46 mmol, 1.49 equiv) in 20 mL of THF at −78 °C under N_2. After the solution was stirred for 1 h, DMPU (2.5 mL, 5.7 equiv) was added followed by addition of a precooled (−78 °C) solution containing 1.031 g (3.67 mmol, 1.00 equiv) of iodide 4 in 5 mL of THF via cannula. After 3 h the reaction was quenched with 5 mL NH_4Cl solution, diluted with H_2O, and extracted with CH_2Cl_2 (4×). The combined organic layers were then washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (MPLC on SiO_2, 15% ethyl acetate/hexanes) gave 562 mg (45%) of the product as a colorless oil: IR (neat) 2996, 2942, 1463, 1432, 1385, 1309, 1261, 1204, 1166, 1124, 1060, 1002, 989, 952, 928, 881, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (m, 1 H), 4.35 (m, 1 H), 4.22 (m, 1 H), 3.56 (dd, J = 4.8, 11.5 Hz, 1 H), 3.53 (dd, J = 5.1, 11.5 Hz, 1 H), 2.13–1.96 (m, 3 H), 1.92–1.81 (m, 3 H), 1.71 (s, 3 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 121.7, 117.6, 101.8, 100.3, 67.7; *CH* 66.5, 63.5, 59.3; CH_2 46.7, 46.7, 35.4, 34.6; CH_3 30.8, 29.7, 21.7, 19.2; MS(EI) 327.1144 (M − CH_3), 140, 59, 43. Anal. Calcd for $C_{16}H_{23}ClN_2O_4$: C, 56.06; H, 6.76. Found: C, 55.99; H, 6.61.

(2*R*,4*R*,6*R*,8*R*)-1-Chloro-4,8-di-*C*-cyano-2,4:6,8-bis-*O*-(1-methylethylidene)-10-eicosene-2,4,6,8-tetrol (6). A 0.75 M solution of the $KN(TMS)_2$ (1.6 mL, 1.2 mmol, 2.4 equiv) in toluene was added to a solution of the chloride 5 (174 mg, 0.509 mmol, 1.0 equiv) in 6 mL of THF at −78 °C under N_2. After the solution was stirred for 90 min allyl chloride was added (500 mL, 6.1 mmol, 6.1 equiv) and the reaction mixture was allowed to warm slowly to rt overnight. The reaction was quenched with 3 mL of NH_4Cl solution and extracted with CH_2Cl_2 (4×). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 5% ethyl acetate/hexanes) gave the product (177 mg, 89%) as a colorless oil: IR (neat) 2996, 2974, 2942, 1735, 1643, 1432, 1409, 1385, 1331, 1258, 1232, 1204, 1185, 1170, 1084, 1056, 1012, 993, 976, 935, 894, 882, 861, 836, 774, 733, 719, 702, 684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (dddd, J = 6.9, 7.5, 10.1, 17.1 Hz, 1 H), 5.27 (br d, J = 10.1, 1 H), 5.24 (br d, J = 17.1 Hz, 1 H), 4.51 (m, 1 H), 4.36 (m, 1 H), 3.57 (dd, J = 4.9, 11.5, 1 H), 3.53 (dd, J = 5.2, 11.5 Hz, 1 H), 2.56 (dd, J = 6.9, 13.8, 1 H), 2.48 (dd, J = 7.5, 13.8, 1 H), 2.13–1.98 (m, 3 H), 1.86 (dd, J = 2.0, 13.7, 1 H), 1.80 (dd, J = 2.0, 13.5, 1 H), 1.72 (s, 6 H), 1.56 (dd, J = 11.6, 13.5, 1 H), 1.44 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 121.6, 121.3, 101.8, 101.2, 69.6, 67.6; *CH* 129.7, 66.5, 61.9; CH_2 121.2, 46.5, 46.5, 46.3, 38.6, 35.3; CH_3 30.7, 30.7, 21.5, 21.3; MS(EI) 367.1437 (M − CH_3). Anal. Calcd for $C_{19}H_{27}ClN_2O_4$: C, 59.60; H, 7.11. Found: C, 59.86; H, 6.99.

(2*R*,4*R*,6*R*,8*R*)-4,8-Di-*C*-cyano-1-iodo-2,4:6,8-bis-*O*-(1-methylethylidene)-10-eicosene-2,4,6,8-tetrol (7). Chloride 6 (340 mg, 0.890 mmol, 1.0 equiv) and 18-crown-6 (234 mg, 0.890 mmol, 1.0 equiv) were dissolved in 10 mL of xylenes under N_2. Powdered potassium iodide (3.70 g, 22.3 mmol, 25 equiv) was added, and the mixture was heated to reflux for 48 h with stirring. The reaction was cooled to rt followed by addition of 10 mL of 0.5 M $Na_2S_2O_3$. The reaction mixture was extracted with CH_2Cl_2 (4×). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 8% ethyl acetate/hexanes) gave the product (376 mg, 89% yield) as a colorless oil: IR (neat) 3080, 2995, 2941, 1642, 1460, 1431, 1385, 1292, 1278, 1259, 1206, 1172, 1082, 1039, 988, 963, 932, 882, 841, 734, 648, 613 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 5.82 (dddd, J = 6.9, 7.5, 9.2, 17.0 Hz, 1 H), 5.26 (br d, J = 9.2 Hz, 1 H), 5.23 (br d, J = 17.0 Hz, 1 H), 4.50 (m, 1 H), 4.02 (m, 1 H), 3.22 (dd, J = 5.0, 10.6 Hz, 1 H) 3.20 (dd, J = 5.3, 10.6 Hz, 1 H), 2.55 (dd, J = 6.9, 13.9 Hz, 1 H), 2.47 (dd, J = 7.5, 13.9 Hz, 1 H), 2.11–1.98 (m, 3 H), 1.89 (dd, J = 2.5, 13.5 Hz, 1 H), 1.79 (dd, J = 2.0, 13.5 Hz, 1 H) 1.73 (s, 3 H), 1.70 (s 3 H), 1.57 (dd, J = 11.8, 13.4 Hz, 1 H), 1.44 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 121.5, 121.1, 101.8, 101.0, 69.3, 67.5; *C*H 129.4, 65.7, 61.6; CH_2 120.9, 46.5, 45.9, 38.4, 37.8, 8.3; CH_3 30.5, 30.4, 21.5, 21.2; MS(EI) 459.0808 (M – CH_3). Anal. Calcd for $C_{19}H_{27}IN_2O_4$: C, 48.11; H, 5.74. Found C, 48.31; H, 5.85.

(2*R*,4*R*,6*R*,8*S*,10*R*,12*S*,14*R*,16*R*)-1-Chloro-4,8,12,16-tetra-*C*-cyano-2,4:6,8:10,12:14,16-tetrakis-*O*-(1-methylethylidene)-18-nonadecene-2,4,6,8,10,12,14,16-octol (8). A solution containing 329 mg (0.961 mmol, 1.43 equiv) of chloride **5** in 2 mL of THF was precooled to –78 °C and added via cannula to a solution of $LiNEt_2$ (0.94 mmol, 1.34 equiv) in 5 mL of THF at –78 °C under N_2. After stirring for 1 h DMPU (438 uL, 3.62 mmol, 5.5 equiv) was added followed by addition of a precooled solution (–78 °C) containing 308 mg (0.650 mmol, 1.00 equiv) of the iodide **7** in 2 mL THF via cannula. The reaction was slowly warmed to rt overnight. The reaction was quenched with 3 mL of NH_4Cl solution, diluted with H_2O, and extracted (4 × CH_2Cl_2). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 15% ethyl acetate/hexanes) gave 392 mg (0.569 mmol, 87% yield) of the product as a colorless oil: IR (neat) 2996, 2941, 1642, 1461, 1431, 1386, 1258, 1205, 1169, 1144, 1056, 993, 938, 882, 822, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (dddd, J = 6.9, 7.5, 9.1, 17.7 Hz, 1 H), 5.25 (br d, J = 9.1 Hz, 1 H), 5.23 (br d, J = 17.7 Hz, 1 Hz), 4.48 (m, 3 H), 4.36 (m, 1 H), 3.57 (dd, J = 4.8, 11.5 Hz, 1 H), 3.53 (dd, J = 5.3, 11.5 Hz, 1 H), 2.56 (dd, J = 6.9, 13.9 Hz, 1 H), 2.54 (dd, J = 7.5, 13.9 Hz, 1 H), 2.20–1.54 (m, 14 H), 1.73 (s, 6 H), 1.72 (s, 6 H), 1.43 (s, 3 H), 1.40 (s, 6 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 121.6, 121.6, 121.6, 121.2, 101.7, 101.4, 101.3, 101.1, 69.5, 67.9, 67.9, 67.5; *C*H 129.6, 66.4, 61.9, 61.9, 61.8; CH_2 121.1, 46.5, 46.4, 46.4, 46.3, 46.3, 38.6, 38.0, 38.0, 35.2; CH_3 30.8, 30.8, 30.7, 30.6, 21.5, 21.4, 21.3, 21.3; FABMS 689.3298 (M + H). Anal. Calcd for $C_{35}H_{49}ClN_4O_8$: C, 60.99; H, 7.17. Found: C, 60.74; H, 7.09.

(2*R*,4*R*,6*R*,8*S*,10*R*,12*S*,14*R*,16*R*)-4,8,12,16-Tetra-*C*-cyano-1-iodo-2,4:6,8:10,12:14,16-tetrakis-*O*-(1-methylethylidene)-18-nonadecene-2,4,6,8,10,12,14,16-octol (9). Chloride **8** (360 mg, 0.523 mmol, 1.0 equiv) and 18-crown-6 (138 mg, 0.523 mmol, 1.0 eq) were dissolved in 10 mL of xylenes under nitrogen. Powdered potassium iodide (2.17 g, 13.1 mmol, 25 equiv) was added, and the mixture was heated to reflux for 44 h with stirring. The reaction mixture was cooled to rt followed by addition of 10 mL of 0.5 M $Na_2S_2O_3$ solution and 10 mL of H_2O. The reaction mixture was extracted (4× CH_2Cl_2) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Chromatography (MPLC, SiO_2, 13% ethyl acetate/hexanes) gave the product (305 mg, 75% yield) as a colorless oil: IR (neat) 2994, 2940, 1641, 1460, 1432, 1385, 1292, 1278, 1259, 1205, 1170, 1143, 1038, 994, 933, 882, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (dddd, J = 7.0, 7.5, 10.4, 16.9 Hz, 1 H), 5.26 (br d, J = 10.4, 1 H), 5.23 (dd, J = 1.5, 16.9 Hz, 1 H), 4.48 (m, 3 H), 4.03 (m, 1 H), 3.23 (dd, J = 5.2, 12.5 Hz, 1 H), 3.22 (dd, J = 5.1, 12.5 Hz, 1 H), 2.55 (dd, J = 7.0, 13.9 Hz, 1 H), 2.46 (dd, J = 7.5, 13.9 Hz, 1 H), 2.12–1.53 (m, 14 H), 1.75 (s, 3 H), 1.72 (s, 9 H), 1.45 (s, 3 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 121.5, 121.3, 121.3, 121.0, 101.7, 101.2, 101.1, 100.9, 69.3, 67.7, 67.6, 67.4; *C*H 129.4, 65.6, 61.7, 61.6, 61.6; CH_2 120.9, 46.3, 46.2, 46.1, 46.0, 38.4, 37.9, 37.9, 37.8, 8.3; CH_3 30.6, 30.6, 30.5, 30.4, 21.5, 21.2, 21.2, 21.1; FABMS 781.2715 (M + H). Anal. Calcd for $C_{35}H_{49}IN_4O_8$: C, 53.85; H 6.33. Found: C 53.63; H 6.25.

(4*R*,6*R*,8*S*,10*R*,12*S*,14*R*,16*S*,18*R*,20*S*,22*S*)-4,8,12,16,20-Penta-*C*-cyano-4,6:8,10:12,14:16,18:20,22-pentakis-*O*-(1-methylethylidene)-1-heptacosene-4,6,8,10,12,14,16,18,20,22-decol (11). A solution containing 61.5 mg (0.291 mmol, 1.95 equiv) of **10**[13] in 1 mL of THF was precooled to –78 °C and added via cannula to a solution of $LiNEt_2$ (0.291 mmol, 1.95 equiv) in 3 mL of THF at –78 °C under N_2. After the solution was stirred for 1 h, DMPU (145 μL, 1.20 mmol, 8.0 equiv) was added followed by addition of a precooled (–78 °C) solution of the iodide **9** (116.3 mg, 0.149 mmol, 1.00 equiv) in 2 mL of THF via cannula. The reaction was allowed to warm to 0 °C over a 12-h period. The reaction mixture was then quenched with 1 mL of NH_4Cl solution and 10 mL of H_2O. The reaction was then extracted (4 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave the product (117.3 mg, 0.136 mmol, 91% yield) as a colorless oil: IR (neat) 2994, 2937, 2872, 1643, 1462, 1433, 1384, 1279, 1258, 1206, 1146, 1060, 992, 953, 923, 879, 818, 735, 672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (dddd, J = 6.9, 7.5, 9.6, 17.2 Hz, 1 H), 5.24 (br d, J = 9.6 Hz, 1 H), 5.21 (br d, J = 17.2 Hz, 1 H), 4.49 (m, 4 H), 4.11 (m, 1 H), 2.53 (dd, J = 6.9, 13.8 Hz, 1 H), 2.46 (dd, J = 7.5, 13.8 Hz, 1 H), 2.09–1.30 (m, 26 H), 1.70 (s, 12 H), 1.67 (s, 3 H), 1.39 (s, 12 H), 1.36 (s, 3 H), 0.87 (t, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 122.2, 121.7, 121.7, 121.7, 121.4, 101.5, 101.5, 101.5, 101.4, 101.2, 69.6, 68.0, 67.9, 67.9, 67.9; *C*H 129.7, 66.4, 62.1, 62.0, 62.0, 61.9; CH_2 121.2, 46.7, 46.6, 46.6, 46.5, 46.5, 38.7, 38.3, 38.3, 38.3, 38.1, 35.7, 31.7, 24.5, 22.7; CH_3 31.0, 30.9, 30.9, 30.9, 30.8, 21.6, 21.5, 21.5, 21.5, 21.4, 14.1. Anal. Calcd for $C_{47}H_{69}N_5O_{10}$: C, 65.33; H, 8.05. Found: C, 65.08; H, 7.87.

(4*R*,6*R*,8*S*,10*R*,12*S*,14*R*,16*S*,18*R*,20*S*,22*S*)-4,6:8,10:12,14:16,18:20,22-Pentakis-*O*-(1-methylethylidene)-1-heptacosene-4,6,8,10,12,14,16,18,20,22-decol (12). Lithium metal (146 mg, 21.0 mmol, 114 equiv) was dissolved in 10 mL of ammonia to give a bright blue solution which was cooled to –78 °C. Polyacetonide cyanohydrin **11** (159.6 mg, 0.185 mmol, 1 equiv) was dissolved in 4 mL of THF and added to the Li/NH_3 solution via cannula. After being stirred for 1 h, the reaction was quenched with 2 g of solid NH_4Cl and warmed to rt, and the ammonia was allowed to evaporate. The remaining residue was dissolved in 15 mL of H_2O and extracted with CH_2Cl_2 (4×). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave the product (115.4 mg, 0.156 mmol, 85%) as a colorless oil: IR (neat) 2990, 2941, 2868, 1642, 1379, 1349, 1260, 1199, 1172, 1115, 1019, 968, 945, 873 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 1 H), 5.08–5.00 (m, 2 H), 3.98 (m, 8 H), 3.85 (m, 1 H), 3.81 (m, 1 H), 2.27 (m, 1 H), 2.11 (m, 1 H), 1.77 (pentet, J = 6.9 Hz, 4 H), 1.48–1.14 (m, 22 H), 1.38 (s, 15 H), 1.33 (s, 15 H), 0.85 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 98.3, 98.2 (4); *C*H 134.1, 68.9, 68.5, 65.2, 65.1 (7); CH_2 116.9, 42.7 (3), 42.6, 40.7, 36.7, 36.5 (3), 36.4, 36.1, 31.7, 24.5, 22.5; CH_3 30.2 (5), 19.8 (5), 14.0. Anal. Calcd for $C_{42}H_{74}O_{10}$: C, 68.26; H, 10.09. Found: C, 68.25; H, 9.86.

(4*R*,6*R*,8*R*,10*R*,12*R*,14*S*,16*S*,18*S*,20*S*,22*S*)-Decamethoxy-1-heptacosene (2 (*n* = 10)). Compound **12** (69.3 mg, 0.094 mmol, 1 equiv) was dissolved in 8 mL of MeOH and treated with acid resin (Dowex W50-X1). The reaction was stirred until an equilibrium was reached by TLC. The reaction was filtered and the resin washed several times with MeOH. The MeOH washes were combined and concentrated under reduced pressure. The resulting white powder was again dissolved in 8 mL of MeOH and treated with acid resin. The reaction was stirred until a single spot was observed by TLC. Removing the resin by filtration and concentrating under reduced pressure gave 50.5 mg of the polyol as a white powder. The crude polyol was suspended in 7 mL of THF and 222 mg of KH (5.55 mmol, 60 equiv) suspended in 3 mL of THF was added via cannula followed by iodomethane (400 μL, 6.43 mmol, 70 equiv). After being stirred for 7 hr the reaction was cooled to 0 °C and quenched with NH_4Cl solution. The reaction mixture was then extracted (4 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, ethyl acetate) gave 49.2 mg (77% yield from **12**) of the product as a colorless crystalline compound: mp = 53–54 °C; $[\alpha]^{22}_D$ = –3.35 (*c* = 2.98, $CHCl_3$); IR (KBr) 2976, 2944, 2822, 1638, 1465, 1386, 1184, 1109, 974, 913, 808, 650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.1, 10.2, 7.0 Hz, 1 H), 5.07 (br d, J = 17.1 Hz, 1 H), 5.05 (br d, J = 10.2 Hz, 1 H), 3.38 (quintet, J = 6.1 Hz, 10 H), 3.31 (s, 3 H), 3.28 (s, 27 H), 2.29 (br t, J = 7.0 Hz, 2 H), 1.76 (dt, J = 6.1, 13.8 Hz, 9 H), 1.57 (dt, J = 6.1, 13.8 Hz, 9 H), 1.47 (m, 2 H), 1.28 (m, 6 H), 0.87 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C*H 134.5, 78.0, 77.3, 75.5, 75.3 (7); CH_2 117.3, 38.2 (6), 38.1, 37.9, 37.7, 37.6, 33.4, 32.1, 24.6, 22.7; CH_3 56.4, 56.2 (9), 14.1; MS(CI) (NH_3) 679 (M + 1), 647 (679 – CH_3OH), 519 (679 – 4CH_3OH), 487 (679 – 5CH_3OH), 455 (679 – 6CH_3OH), 251, 225, 199, 195, 169, 115, 101, 85, 75, 61; MS(EI) 614.4717 (M –

$C_2H_8O_2$). Anal. Calcd for $C_{37}H_{74}O_{10}$: C, 65.45; H, 10.98. Found: C, 65.21; H, 10.72.

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Supplementary Material Available: Full experimental details are reported for the preparation of compound **10** (2 pages). Ordering information is given on any current masthead page.

Rearrangement of *N*-(Alkylamino)azoles in Acid Media: A New Entry to *C*-Amino-*N*-substituted Azoles

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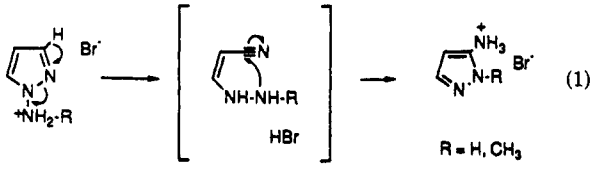
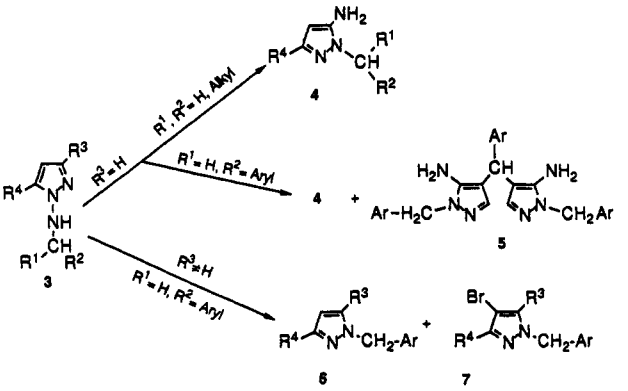
A ring-opening/ring-closure mechanism for the thermal rearrangement of 1-(alkylamino)pyrazoles into 5-amino-1-alkylpyrazoles in acid medium has been established. 1-(Benzylamino)pyrazoles show a different reactivity, affording bis(5-amino-1-benzyl-4-pyrazolyl)phenylmethanes. The reaction was extended to 1-(alkylamino)indazoles but failed in the case of 1-(alkylamino)-1,2,4-triazoles.

Among the several classes of pyrazole rearrangements,[1-3] the best known is the (1,5)-sigmatropic shift of *N*-nitropyrazoles, discovered by Habraken, by which they are transformed into *C*-nitro derivatives.[4,5] Other *N*-nitroazoles such as indazoles[6] and 1,2,4-triazoles[7] behave identically. The related case of *N*-aminoazoles had never been studied until we reported recently that 1-aminopyrazole rearranged to 3(5)-aminopyrazole by heating at 140 °C in 48% hydrobromic acid and, similarly, 1-(methylamino)-pyrazole gave 1-methyl-5-aminopyrazole.[8] This rearrangement was interpreted with the assumption that protonation on the *N*-amino group by hydrobromic acid destabilizes the pyrazole ring, allowing for a ring-opening/ring-closure sequence, which leads to the final product through a β-hydrazinoacrylonitrile intermediate (eq 1). In the present work, we study the scope of this rearrangement and provide experimental evidence for the proposed mechanism.[9]



(1)

Table I. Acid Rearrangement of 1-(Alkylamino)pyrazoles[a]



starting compound		isolated and purified products (% yield)
3a	$R^1 = R^2 = R^3 = R^4 = H$	**4a** (70)
3b	$R^1 = CH_3$, $R^2 = R^3 = R^4 = H$	**4b** (81)
3c	R^1, $R^2 = (CH_2)_5$, $R^3 = R^4 = H$	**4c** (93)
3d	$R^1 = C_6H_5$, $R^2 = R^3 = R^4 = H$	**4d** (58) + **5d** (28)
3e	$R^1 = p\text{-}FC_6H_4$, $R^2 = R^3 = R^4 = H$	**4e** (47) + **5e** (18)
3f	$R^1 = C_6H_5$, $R^2 = R^3 = H$, $R^4 = CH_3$	**4f** (35) + **5f** (39)
3g	$R^1 = C_6H_5$, $R^2 = R^4 = H$, $R^3 = CH_3$	**6g** (39) + **7g** (9)
3h	$R^1 = C_6H_5$, $R^2 = H$, $R^3 = R^4 = CH_3$	**6h** (37) + **7h** (10)

[a] All reactions were performed by heating solutions of **3** in 48% HBr acid, at reflux (external temperature of the bath, 140 °C), 1/1.3 molar equiv for **3a–c** and 1/2.3 for **3d–h** at 140 °C. Analogous results were obtained for **3a** with 99% TFA, 96% H_2SO_4, 35% HCl acids. A typical experiment uses 100 mg of starting material.

Results and Discussion

The synthesis of the starting 1-(methylamino)azoles **3a** and **3i** was performed by reduction of the corresponding *N*-formamido derivatives **1**. The remaining 1-(alkylamino)azoles, compounds **3b–h**, Table I, and **3j–m**, Table II, were prepared by reduction of the corresponding imines **2**.

Solutions of 1-(alkylamino)azole hydrobromide salts, prepared by dissolving compounds **3** in 48% hydrobromic

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