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Tandem Radical Nitrile Transfer-Cyclization Reactions of 1,3-Dioxane-4-Nitriles: Synthesis of Spirocyclic Systems

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Abstract: Reduction of remote halogen substituents with *n*-Bu_3SnH leads to efficient 1,4- and 1,5-nitrile transfer from 1,3-dioxane-4-nitriles and subsequent stereoselective reduction. These radical-transfer reactions provide a mild alternative to the Li/NH_3 reductive decyanation previously used to generate *syn*-1,3-diols from 1,3-dioxane-4-nitriles. Compounds containing appropriate unsaturation undergo subsequent radical cyclization reactions to give spirocyclic products. © 1997 Elsevier Science Ltd.

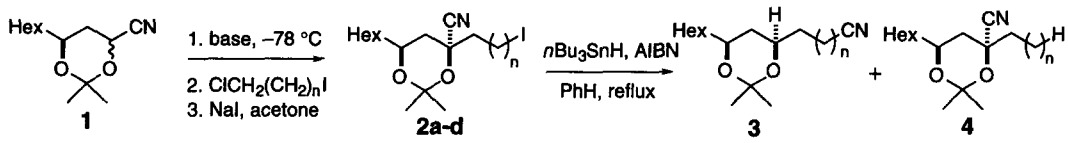
Radical group transfer reactions have been known for many years. The first well established examples were the unusual hypoiodite oxidation of steroidal cyanohydrins.[1] Kalvoda developed this reaction to introduce a cyano group at the C18 methyl position of steroids using cyanohydrins of C20-ketosteroids. He later showed that the reaction involved H-atom abstraction by alkoxy radical followed by *intramolecular* 1,4-cyano transfer, and suggested a cyclization and β-scissior. mechanism.[2] Watt developed a photolysis of α-peracetoxynitriles that lead to the analogous products by the same mechanism.[3] Kalvoda was the first to show that a radical generated by other methods underwent 1,4-cyano transfer.[4] Beckwith later demonstrated that 1,4-acyl and cyano (nitrile) transfers could be induced by *n*-Bu_3SnH reductions of the appropriate halides, although the yields of rearranged products were low.[5] More recently, a number of groups have observed 1,4-nitrile transfer reactions in radical reactions.[6] We report the radical transfer reactions and subsequent cyclizations of appropriately substituted 1,3-dioxane-4-nitriles.

Nitrile Transfer Reactions.

The nitrile transfer reaction was initially investigated using 4-iodoalkyl substrates **2**, Scheme 1. The 2,2-dimethyl-1,3-dioxane-4-nitriles (cyanohydrin acetonides) like **1** have been used extensively as 1,3-diol synthons in the convergent synthesis of alternating polyol chains.[7] Iodoalkyl substrates **2** were prepared by alkylation of the anion of **1** with α-chloro-ω-iodoalkanes, followed by Finkelstein reaction to convert the resulting chlorides to iodides.[8] Each iodoalkyl substrate **2** was treated with 2 equiv of tributyltin hydride and catalytic AIBN in refluxing benzene (0.02 M). The 1,4- and 1,5-nitrile transfer reactions (n = 2, 3) take place efficiently, but the corresponding 1,3- and 1,6-nitrile transfer reactions (n = 1, 4) were not observed and instead led to the simple dehalogenation products **4**. Where the nitrile transfer reaction did take place, *n*-Bu_3SnH reduction of the intermediate α-alkoxy radical was completely selective and gave the axial-H products **3**.[9] This alkylation and

radical reduction sequence is a nice entry into substituted *syn*-1,3-diols and avoids the relatively harsh Li/NH_3 reductive decyanations previously used for this purpose.

Scheme 1



n	% yield **3**	% yield **4**
1, **2a**	–	81
2, **2b**	95	–
3, **2c**	60	–
4, **2d**	–	98

The mechanism of the nitrile transfer is presumably the same one put forward by Kalvoda[2] and is illustrated in Figure 1. The initially formed radical **5** cyclizes onto the nitrile to form iminyl radical **6**. Iminyl radical **6** will either be reduced by *n*-Bu_3SnH to form a cyclic imine **9** or undergo a β-scission to generate the new α-alkoxy radical **7**. Subsequent reduction would lead to the nitrile transfer product **3b**. The most efficient radical transfer reactions each produce a highly stabilized α-alkoxy,[1,3,6c] α-amino,[6b] or α-cyano radical,[6a] and the reactions reported in this paper are no exception. The *n*-Bu_3SnH reduction to generate **3** (n = 3) is the first example of a 1,5-radical transfer reaction of which we are aware.

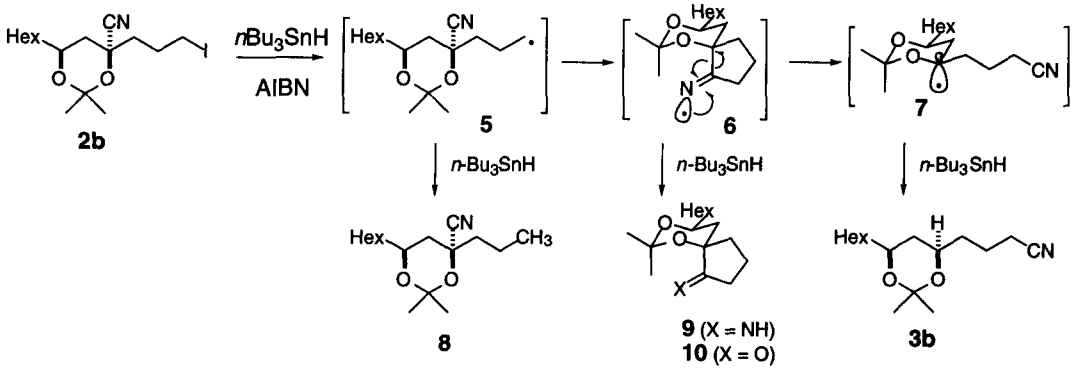
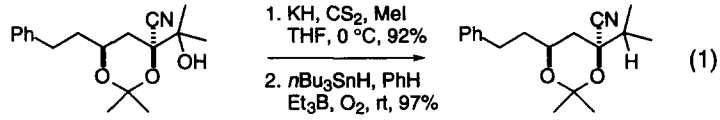


Figure 1. Possible products from the*n*-Bu_3 Sn-H reduction of iodoalkyl nitrile **2b**.

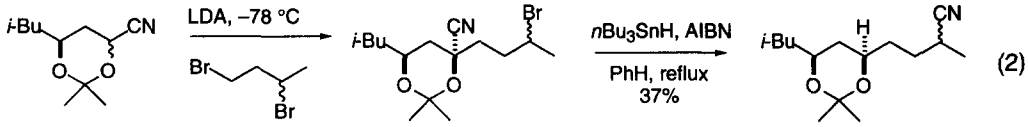
Beckwith has shown that 1,2-acyl transfer reactions proceed readily.[5] After several attempts to prepare the iodomethyl substrate **2** (n = 0) failed, the 1,2-acyl transfer was investigated in a different system, eq 1. Acetone adduct **11** could be prepared in modest yield as described elsewhere.[10] Xanthate formation proceeded uneventfully, and reaction with *n*-Bu_3SnH gave only the simple reduction product **12** with no sign of the nitrile transfer product. There are several problems with the radical transfer reaction in this system. First, the radical transfer will be less exothermic and the transfer probably will be slower beginning with a tertiary radical. The

reduction was carried out at 25 °C instead of 80 °C to avoid elimination of the xanthate, and partitioning of the radical between transfer and reduction may be less efficient at this temperature. Finally the three-membered ring intermediate for acyl transfer contains only sp^3 centers, whereas the nitrile transfer intermediate would contain an sp^2 center and be more strained. The 1,2-nitrile transfer may be observed in more favorable systems, but it was not observed with substrate **11**.



11 **12** (1)

Would nitrile transfer to a secondary center be diastereoselective? Substrate **13** was prepared to answer that question, and the results are illustrated in eq. 2. Alkylation of 1,3-dibromobutane with 1,3-dioxane-4-nitrile **1** gave the 3-bromobutyl substituent **13** as a mixture of diastereomers. Radical reduction with *n*-Bu_3SnH in refluxing benzene gave 37% of the radical transfer product **14** as a 3:2 mixture of diastereomers, as well as 56% of 2,9-dimethyl-7-hydroxy-5-oxo-decanenitrile (**15**). Ketone **15** apparently arises from air oxidation of the intermediate anomeric radical produced by nitrile transfer. Although the 1,4-radical transfer reaction to secondary centers is efficient, it is not diastereoselective in these systems.

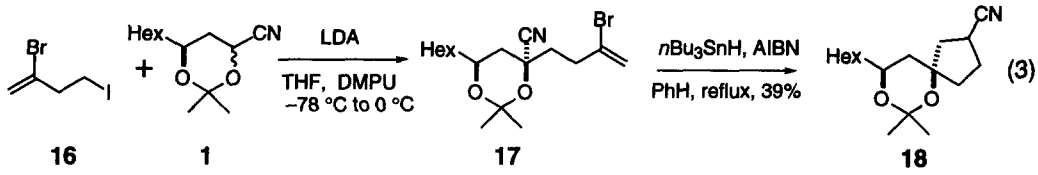


1 **13** **14** (2)

Tandem Nitrile Transfer-Cyclization Reactions.

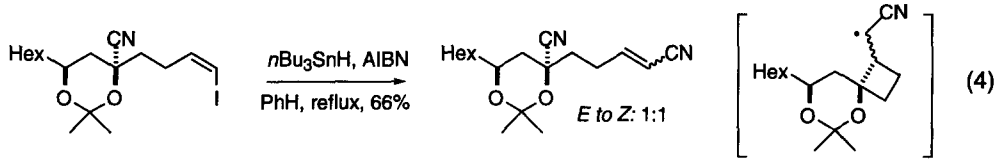
As described above, radicals resulting from nitrile transfer reactions can be reduced to provide functionalized *syn*-1,3-diols. Could they also be used to initiate a radical cyclization reaction?[11] The nitrile-transfer reaction is an equilibration between two radicals. The radical produced in a nitrile-transfer reaction must be relatively stable and would only be expected to cyclize with a good radical acceptor. Introducing appropriate unsaturated substituents in the radical nitrile-transfer substrates does indeed lead to tandem cyclization-transfer reactions as described below.

Vinyl bromide **17** was synthesized by alkylation of **1** with the iodide **16**.[7,12] A solution of *n*-Bu_3SnH and AIBN in benzene was added slowly to a solution of **17** in refluxing benzene. The spirocyclic compound **18** was obtained as a mixture of diastereomers at the nitrile center in 39% yield. A *5-endo-trig* cyclization like this one is generally disfavored according to Baldwin's rules, although the alternative "favored" *4-exo-trig* cyclization faces significant ring strain in the transition state and product.[13] The complementary electronic distributions of the α-alkoxy radical and β-cyano alkene undoubtedly favor the cyclization, and thus transfer of the nitrile group not only produces the α-alkoxy radical, but in this case serves to activate the alkene for cyclization.



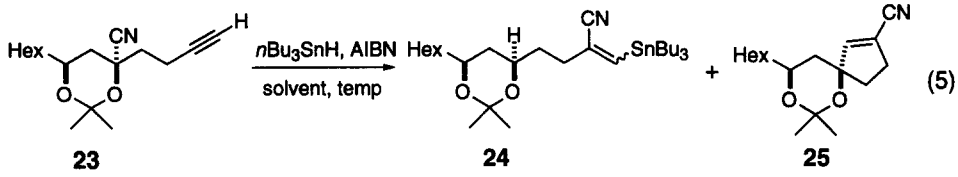
16 1 17 18

The *Z*-vinyl iodide **19** was prepared from alcohol **20**[14] by oxidation and Wittig coupling with iodomethyl triphenylphosphonium iodide.[15] Using conditions described previously for the preparation of **17**, treatment of iodide **19** with *n*-Bu_3SnH provided the transfer product **21** in 66% yield as a 1:1 mixture of *E*- and *Z*-alkenes, eq 4. The 1,5-nitrile transfer was quite efficient under these high-dilution conditions, but no cyclized product was isolated. We were surprised that **21** was isolated as a mixture of alkene isomers. The starting vinyl iodide **19** has predominantly a *Z* configuration, but this has little bearing on the cyclization as sp^2 radicals are known to invert very rapidly. In an intramolecular radical transfer process, only the *Z* vinyl radical can possibly cyclize on the nitrile, yet we observe both *E* and *Z* alkenes in the product **21**. The alkene geometry could have been scrambled by reversible addition of an external radical, or by reversible cyclization to cyclobutane **22** before *n*-Bu_3SnH reduction. Curran observed a similar mixture of *E*- and *Z*-alkene products in his single example with an unsaturated substrate.[6]



19 21 22

Stork has reported that tributyltin radicals added reversibly to alkynes to generate transient vinyl radicals that can participate in a radical cyclization reaction.[16] If a vinyl radical analogous to that generated from vinyl bromide **17** could be prepared from tributyltin radical addition to an alkyne, would it participate in nitrile transfer and cyclization reactions? Alkyne substrate **23** was prepared to test this hypothesis by alkylation of **1** using 4-iodo-1-trimethylsilyl-1-butyne and subsequent desilylation. Slow addition of *n*-Bu_3SnH and AIBN to a solution of **23** in refluxing benzene gave a mixture of the nitrile-transfer adduct **24** and the cyclized product **25** in 95% and 5% yield respectively. The tributyltin addition and nitrile transfer were very efficient, but the final cyclization worked poorly. In an effort to increase the rate of cyclization, the reaction was carried out at higher temperatures as outlined in Table 1. The cyclization was more efficient at higher temperature, generating up to 33% of the cyclized product **25** in xylenes at 140 °C. At higher temperatures the reaction was accompanied with significant decomposition, and the overall mass balance was reduced. Both the nitrile-transfer reaction generating **24** and the cyclization reaction producing **25** are interesting examples of multi-step radical transformation.



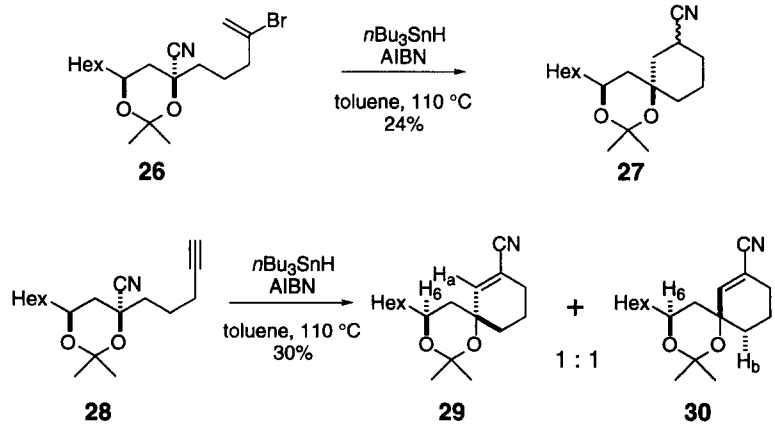
23 24 25

These cyclization reactions were successfully extended to the next higher homologs as illustrated in Scheme 2. Vinyl bromide **26** and alkyne **28** were prepared from **1** using procedures analogous to those used in the preparation of **18** and **23**. The *n*-Bu_3SnH reductive cyclization of **26** gave 24% yield of the [6.6]-spirocycle **27** as a mixture of diastereomers at the nitrile center. Slow addition of *n*-Bu_3SnH and AIBN to a refluxing solution of alkyne **28** in toluene gave 30% yield of the cyclized adduct which was isolated as a mixture of two diastereomers in a 1:1 ratio. The structure of expected diastereomer, nitrile **29**, was confirmed by NOE enhancement of H_a on irradiation of the H_6. The unexpected diastereomer was shown to be nitrile **30** by NOE enhancement between H_b and H_6. We have no explanation for the formation of the unexpected diastereomer **30**. Cyclization of both **26** and **28** involve 1,5-nitrile transfer reactions followed by 6-*endo-trig* cyclizations, and both proceed in modest yield.

Table 1. Solvent effect on nitrile transfer followed by reduction vs. cyclization.

entry	solvent, T (°C)	% yield, **24**	% yield, **25**
1	benzene, 80	95	5
2	toluene, 110	61	14
3	xylenes, 140	35	33

Scheme 2



Conclusions

The 1,4- and 1,5-nitrile transfer reactions of 4-iodoalkyl-1,3-dioxane-4-nitriles are efficient and lead to single diastereomers of the reduced products. The tandem radical transfer-cyclization reactions of vinyl bromides and alkynes produce unusual spirocyclic products in modest yields. It should be noted that radical

cyclizations often work better in more highly substituted systems. In all but one case the new spirocylic center is produced as a single diastereomer.[11] These new tandem reactions produce complex products stereoselectively from readily available precursors, and are of mechanistic and synthetic interest.

EXPERIMENTAL SECTION

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(2-iodoethyl)-1,3-dioxane (2a).** To a 100.0 mg sample of (4*R**, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(2-hydroxyethyl)-1,3-dioxane[10] (0.37 mmol, 1.0 equiv) in 1.0 mL CH_2Cl_2, was added 30 μL of pyridine (0.37 mmol, 1.0 equiv) and the solution was cooled to 0 °C. To this was added a solution of 96 mg of triphenylphosphine (0.37 mmol, 1.0 equiv) and 94 mg of iodine (0.37 mmol, 1.0 equiv) in 2.0 mL of CH_2Cl_2, also at 0 °C, by cannula. The solution was allowed to warm to room temperature over 15 hours, followed by addition of 15 mL of water. The aqueous mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with 30 mL each of 0.5 M $Na_2S_2O_3$, water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (5% ethyl acetate/hexanes, SiO_2) provided 113 mg (0.30 mmol, 80%) of the product as a colorless oil: IR (neat) 2994, 2930, 2857, 1461, 1383, 1208, 1151, 1111, 932, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.09 (m, 1 H), 3.30, (m, 2 H), 2.31 (m, 2 H), 1.80 (dd, *J* = 2.1, 13.3 Hz, 1 H), 1.66 (s, 3 H), 1.36 (s, 3 H), 1.6–1.0 (complex, 11 H), 0.87 (t, *J* = 6.3 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ *C* 121.0, 101.3, 70.8; *C*H 66.2; *C*H_2 47.2, 39.2, 35.6, 31.7, 29.1, 24.7, 22.6, -5.2; *C*H_3 30.8, 21.4, 14.1. Anal. calcd for $C_{15}H_{26}INO_2$: C, 47.50; H, 6.91. Found: C, 47.42; H, 6.89.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(3-iodopropyl)-1,3-dioxane (2b).** A solution containing 90 mg (0.4 mmol, 1.0 equiv) of **1** in 2.0 mL of THF was added via cannula to a solution of lithium diisopropylamide (0.4 mmol, 1.0 equiv) in 3.0 mL of THF at –78 °C. After 2 h at -78 °C, 86 μL (0.8 mmol, 2.0 equiv) of 3-chloro-1-iodopropane was added. The solution was stirred at -78 °C for 2 h, then transferred to a methanol/ice bath at -20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, and the mixture was extracted (3 × CH_2Cl_2), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5% ethyl acetate/hexanes, SiO_2) gave 54 mg (0.18 mmol, 44%) of (4*R**, 6*S**)-4-(3-chloropropyl)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane as a clear, colorless oil: IR (neat) 2995, 2956, 2931, 2859, 1461, 1375, 1257, 1208, 1158, 1116, 1036, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (m, 1 H), 3.58 (m, 2 H), 1.81 (dd, *J* = 1.9, 13.4 Hz, 1 H), 1.67 (s, 3 H), 1.36 (s, 3 H), 2.2–1.2 (complex, 15 H), 0.87 (t, *J* = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 121.7, 101.0, 69.6; *C*H 66.3; *C*H_2 44.4, 39.9, 39.5, 35.6, 31.7, 29.1, 26.6, 24.7, 22.6; *C*H_3 30.9, 21.4, 14.0. Anal. calcd for $C_{16}H_{28}ClNO_2$: C, 63.66; H, 9.35. Found: C, 63.58; H, 9.16.

A 276 mg sample of (4*R**, 6*S**)-4-(3-chloropropyl)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane (0.92 mmol, 1.0 equiv) was dissolved in 5.0 mL of methyl ethyl ketone and 550 mg of sodium iodide (3.67 mmol, 4.0 equiv) was added. After refluxing for 10 hours, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with 0.5 M $Na_2S_2O_3$. The layers were separated, and the aqueous was extracted (3 × CH_2Cl_2). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (5% ethyl acetate/hexanes, SiO_2) provided 170 mg (0.43 mmol, 47%) of the product as a colorless oil: IR (neat) 2995, 2929, 2859, 1460, 1382, 1260, 1208, 1154, 1114, 962, 878, 724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (m, 1 H), 3.23 (m, 2 H), 2.10 (m, 2 H), 1.85 (m, 2 H), 1.67 (s, 3 H), 1.34 (s, 3 H), 1.5–1.2 (complex, 12H),

0.89 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 121.7, 100.9, 69.2; *C*H 66.1; *C*H$_2$ 43.2, 39.4, 35.5, 31.6, 29.0, 27.3, 24.6, 22.5, 5.3; *C*H$_3$ 30.8, 21.3, 14.0

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(4-iodobutyl)-1,3-dioxane (2c).** A solution containing 226 mg (1.0 mmol, 1.0 equiv) of **1** in 2.0 mL of THF was added via cannula to a solution of lithium diisopropylamide (1.1 mmol, 1.1 equiv) in 4.0 mL of THF at –78 °C. After 1 h at -78 °C, 245 μL (2.0 mmol, 2.0 equiv) of 4-chloro-1-iodobutane was added. The solution was stirred at -78 °C for 2 h, then transferred to a methanol/ice bath at -20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, and the mixture was extracted (3 × CH_2Cl_2), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5% ethyl acetate/hexanes, SiO_2) gave 247 mg (0.79 mmol, 79%) of the product as a clear, colorless oil. A 230 mg sample was dissolved in 5.0 mL of methyl ethyl ketone and 547 mg of sodium iodide (3.65 mmol, 5.0 equiv) was added. After refluxing for 16 hours, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with 0.5 M $Na_2S_2O_3$. The layers were separated and the aqueous layer was extracted (3 × CH_2Cl_2). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (7% ethyl acetate/hexanes, SiO_2) provided 206 mg (0.51 mmol, 69%) of the product as a colorless oil: IR (neat) 2996, 2930, 2860, 2252, 1461, 1382, 1263, 1206, 1157, 911, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (m, 1 H), 3.18 (t, J = 6.9 Hz, 2 H), 1.66 (s, 3 H), 1.35 (s, 3 H), 1.9–1.2 (complex, 18 H), 0.86 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 121.8, 100.8, 69.6; *C*H 66.1; *C*H$_2$ 41.2, 39.3, 35.6, 32.9, 31.6, 29.0, 24.6, 24.2, 22.5, 5.7; *C*H$_3$ 30.8, 21.4, 14.0. Anal. calcd for $C_{17}H_{30}INO_2$: C, 50.13; H, 7.42. Found: C, 50.33; H, 7.45.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(5-iodopentyl)-1,3-dioxane (2d).** A solution containing 145 mg (0.64 mmol, 1.0 equiv) of **1** in 2.0 mL of THF was added via cannula to a solution of lithium diethylamide (0.64 mmol, 1.0 equiv) in 3.0 mL of THF at –78 °C. After 2 h at -78 °C, 166 μL (1.28 mmol, 2.0 equiv) of 5-chloro-1-iodopentane was added. The solution was stirred at -78 °C for 2 h, then transferred to a methanol/ice bath at -20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, and the mixture was extracted (3 × CH_2Cl_2), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5% ethyl acetate/hexanes, SiO_2) gave 189 mg (0.57 mmol, 89%) of the product as a clear, colorless oil. This was dissolved in 5.0 mL of methyl ethyl ketone and 429 mg of sodium iodide (2.87 mmol, 5.0 equiv) was added. After refluxing for 16 hours, the solution was cooled to room temperature and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with 0.5 M $Na_2S_2O_3$. The layers were separated and the aqueous layer was extracted (3 × CH_2Cl_2). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (10% ethyl acetate/hexanes, SiO_2) provided 121 mg (0.29 mmol, 50%) of the product as a colorless oil: IR (neat) 2995, 2930, 2861, 1461, 1378, 1259, 1206, 1160, 1116, 964, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (m, 1 H), 3.18 (t, J = 6.9 Hz, 2 H), 1.67 (s, 3 H), 1.36 (s, 3 H), 1.8–1.2 (complex, 20 H), 0.87 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 122.0, 100.9, 69.9; *C*H 66.3; *C*H$_2$ 42.3, 39.5, 35.7, 33.2, 31.6, 30.2, 29.1, 24.7, 22.6, 21.4, 6.5; *C*H$_3$ 30.9, 20.7, 14.1. Anal. calcd for $C_{18}H_{32}INO_2$: C, 51.31; H, 7.65. Found: C, 51.14; H, 7.41.

(4*R, 6*S**)-4-(3-cyanopropyl)-2,2-dimethyl-6-hexyl-1,3-dioxane (3b).** A 108 mg sample of iodide **2b** (0.27 mmol, 1.0 equiv) was dissolved in 10.0 mL of benzene and heated to reflux. To this was added a solution of 134 μL of tributyltin hydride (0.50 mmol) and 2 mg AIBN (0.01 mmol) in 5.0 mL benzene over 10 h using a syringe pump (0.51 mL/h). After refluxing an additional 8 h, the solution was cooled to room

temperature and concentrated under reduced pressure. Chromatography (7% ethyl acetate/hexanes, SiO_2) provided 62 mg (0.23 mmol, 86%) of the product as a colorless oil: IR (neat) 2992, 2932, 2859, 2246, 1459, 1379, 1262, 1201, 1115, 1012, 876 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (m, 2 H), 2.35 (dt, J =2.5, 7.2 Hz, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.7–1.1 (complex, 16 H), 0.86 (t, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 119.8, 98.4; *C*H 68.9, 68.2; *C*H_2 36.9, 36.4, 35.1, 31.7, 29.2, 24.9, 22.6, 21.4, 17.1; *C*H_3 30.2, 19.8, 14.1. HRMS (EI) $(M–CH_3)^+$ Calcd: 252.1963; found: 252.1958. Anal. calcd for $C_{16}H_{29}NO_2$: C, 71.87; H, 10.93. Found: C, 72.00; H, 11.12.

(4*R, 6*S**)-4-(4-cyanobutyl)-2,2-dimethyl-6-hexyl-1,3-dioxane (3c).** A 56 mg sample of iodide **2c** (0.14 mmol, 1.0 equiv) was dissolved in 5.0 mL of benzene and heated to reflux. To this was added a solution of 75 μL of tributyltin hydride (0.28 mmol, 2.0 equiv) and 1 mg AIBN (0.05 mmol) in 5.0 mL benzene over 10 h using a syringe pump (0.51 mL/h). After refluxing an additional 5 h, the solution was cooled to room temperature and concentrated under reduced pressure. Chromatography (7% ethyl acetate/hexanes, SiO_2) provided 26 mg (0.09 mmol, 66%) of the product as a pale yellow oil: IR (neat) 2991, 2929, 2860, 2247, 1461, 1379, 1261, 1199, 1173, 963, 873 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (m, 2 H), 2.34 (t, J = 6.9 Hz, 2 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.7–1.2 (complex, 18 H), 0.86 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 119.7, 98.4; *C*H 69.0, 68.7; *C*H_2 36.9, 36.5, 35.6, 31.8, 29.3, 25.4, 24.9, 24.3, 22.6, 17.1; *C*H_3 30.3, 19.8, 14.1. Anal. calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10. Found: C, 72.33; H, 11.25.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-4-ethyl-6-hexyl-1,3-dioxane (4a).** An 88 mg sample of iodide **2a** (0.23 mmol, 1.0 equiv), 124 μL of tributyltin hydride (0.46 mmol, 2.0 equiv) and 2 mg of AIBN (0.05 equiv) in 10.0 mL of benzene was degassed by the freeze, pump, thaw procedure (×3) and flushed with argon. The mixture was heated to 80 °C for 15 hours, cooled and concentrated under reduced pressure. Chromatography (hexanes to 20% ethyl acetate/hexanes, SiO_2) provided 47 mg (0.19 mmol, 81%) of the product as a colorless oil: IR (neat) 2938, 2868, 1460, 1376, 1255, 1195, 1146, 1046, 979, 878, 723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (m, 1 H), 1.68 (s, 3 H), 1.38 (s, 3 H), 1.8–1.2 (complex, 14 H), 1.07 (t, J = 11.1 Hz, 3 H), 0.87 (t, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 121.9, 100.8, 70.5; *C*H 66.3; *C*H_2 39.0, 35.7, 31.7, 29.1, 24.8, 22.6; *C*H_3 30.9, 21.5, 14.1, 7.5. Anal. calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74. Found: C, 70.86; H, 10.85.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-pentyl-1,3-dioxane (4d).** A 61 mg sample of iodide **2d** (0.14 mmol, 1.0 equiv), 77 μL of tributyltin hydride (0.28 mmol, 2.0 equiv) and 1 mg of AIBN (0.05 equiv) in 5.0 mL of benzene was degassed by the freeze, pump, thaw procedure (×3) and flushed with argon. The mixture was heated to 80 °C for 4 hours, cooled and concentrated under reduced pressure. Chromatography (hexanes to 10% ethyl acetate/hexanes, SiO_2) provided 41 mg (0.139 mmol, 98%) of the product as a colorless oil: IR (neat) 2995, 2929, 2862, 1462, 1378, 1259, 1205, 1165, 1058, 878 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (m, 1 H), 1.80 (dd, J = 1.8, 13.4 Hz, 1 H), 1.67 (s, 3 H), 1.36 (s, 3 H), 1.5–1.2 (complex, 19 H), 0.88 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 122.2, 100.8, 70.0; *C*H 66.3; *C*H_2 42.6, 39.5, 35.7, 31.7, 31.5, 29.1, 24.8, 22.7, 22.6, 22.4; *C*H_3 30.9, 21.5, 14.0, 13.9. Anal. calcd for $C_{18}H_{33}NO_2$: C, 73.17; H, 11.26. Found: C, 72.94; H, 11.00.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-[1-methylethyl]-1,3-dioxane (12).** A 35 mg sample of **11**[10] (0.12 mmol, 1.0 equiv) was dissolved in 1.0 mL of THF and cooled to 0 °C. To this solution was added 7 mg (0.17 mmol, 1.5 equiv) of KH. After 10 min, a premixed sample of carbon disulfide (36 μL, 0.59 mmol) and iodomethane (36 μL, 0.58 mmol) was added. After 40 min, the reaction was quenched with 3 mL of H_2O and the THF was removed under reduced pressure. Diethyl ether (25 mL) was added, and the

mixture was washed with H_2O (20 mL). The aqueous layer was extracted with ether (3×20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (15% ethyl acetate/hexanes, SiO_2) provided 42 mg (0.11 mmol, 92%) of the xanthate as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 4.09 (m, 1 H), 2.71 (m, 2 H), 2.48 (s, 3 H), 1.96 (s, 3 H), 1.84 (s, 3 H), 1.69 (s, 3 H), 1.43 (s, 3 H), 1.87 (m, 2 H), 1.24 (t, J = 7.3 Hz, 2 H). This material was dissolved in 3.0 mL of benzene. To this was added 43 μL of tributyltin hydride (0.16 mmol, 1.5 equiv) and 117 μL of triethylborane (0.12 mmol, 1.1 equiv). The flask was flushed with oxygen and stirred under an oxygen atmosphere for 13 hours. The mixture was washed with H_2O, extracted with CH_2Cl_2 (×3), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (10% ethyl acetate/hexanes, SiO_2) provided 30 mg (0.10 mmol, 97%) of a colorless oil: IR (neat) 3063, 3026, 2992, 2968, 2939, 2879, 1456, 1384, 1259, 1207, 1120, 1018, 862, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3–7.2 (m, 5 H), 4.09 (m, 1 H), 2.9–2.6 (m, 2 H), 1.9–1.8 (complex, 5 H), 1.67 (s, 3 H), 1.41 (s, 3 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H);); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 141.4, 121.1, 100.9, 73.8; *C*H 128.4 (4), 125.9, 65.3; *C*H_2 37.4, 37.0, 31.0; *C*H_3 38.9, 30.9, 21.6, 16.5, 16.0.

(4*R, 6*S**)-6-(2-methylpropyl)-4-(3-cyanobutyl)-2,2-dimethyl-1,3-dioxane (14).** A 79 mg sample of bromide **13** (0.24 mmol, 1.0 equiv) was dissolved in 4.0 mL of benzene and heated to reflux. To this was added a solution of 127 μL of tributyltin hydride (0.47 mmol, 2.0 equiv) and 2 mg AIBN (0.05 mmol) in 8.0 mL benzene over 11 h using a syringe pump (0.74 mL/h). After refluxing an additional 7 h, the solution was cooled to room temperature and concentrated under reduced pressure. Chromatography (10% ethyl acetate/hexanes, SiO_2) provided 22 mg (0.09 mmol, 37%) of product as a 3:2 mixture of isomers as determined by GCMS. The product was a colorless oil: IR (neat) 2990, 2954, 2870, 2239, 1461, 1380, 1267, 1200, 1171, 1118, 873 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (m, 2 H), 2.59 (m, 1 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.31 (d, J = 7.1 Hz, 3 H), 1.8–1.2 (complex, 9 H), 0.89 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.5, 98.4, 68.7, 66.9, 45.5, 37.4, 34.1, 31.6, 30.3, 25.8, 23.8, 22.6, 19.7, 18.1, 14.1. Several ^{13}C NMR peaks were doubled in ca. 3:2 ratio due to the presence of diastereomers.

Also isolated from the reaction mixture was 28 mg (0.13 mmol, 56%) of 2,9-dimethyl-7-hydroxy-5-oxo-decanenitrile (**15**) as a colorless oil. Doubling of several ^{13}C NMR peaks showed it to be a 3:2 mixture of diastereomers. Compound data: IR (neat) 3505, 2956, 2927, 2871, 2240, 1710, 1463, 1384, 1136, 877 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.12 (m, 1 H), 2.70 (m, 3 H), 2.54 (m, 2 H), 2.0–1.0 (complex, 6 H), 1.40 (d, J = 6.7 Hz, 3 H), 0.89 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ *C* 210, 123; *C*H 65.9, 24.9, 24.4; *C*H_2 49.9, 45.8, 40.5, 27.5; *C*H_3 23.3, 22.0, 18.1.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(4-bromo-4-pentenyl)-1,3-dioxane (17).** A solution containing 168 mg (0.75 mmol, 1.5 equiv) of **1** in 2.0 mL of THF was added via cannula to a solution of lithium diisopropylamide (0.75 mmol, 1.5 equiv) and 90 μL of DMPU (0.75 mmol, 1.5 equiv) in 3.0 mL of THF at –78 °C. After 15 min at -78 °C, 57 mg (0.5 mmol, 1.0 equiv) of 2-bromo-4-iodo-1-butene (**16**) was added dropwise. The solution was stirred at -78 °C for 2 h, then transferred to a methanol/ice bath at -20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, and the mixture was washed with 0.5 M $Na_2S_2O_3$, extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (5% ethyl acetate/hexanes, SiO_2) gave 42 mg (0.12 mmol, 24% based on iodide) of the product as a colorless oil: IR (neat) 2955, 2929, 2858, 2239, 1631, 1435, 1377, 1247, 1084, 889 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (d, J = 1.4 Hz, 1 H), 5.42 (d, J = 1.7 Hz, 1 H), 4.11 (m, 1 H), 2.66 (m, 2 H), 2.46 (t, J = 7.0 Hz, 1 H), 2.01 (t, J = 8.2 Hz, 1 H), 1.83 (dd, J = 1.8, 13.3, 1 H), 1.68 (s, 3 H), 1.38 (s,

3 H), 1.7–1.2 (complex, 11 H), 0.88 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 132.5, 120.8, 101.0, 72.7; *C*H 71.3; *C*H_2 117.5, 51.4, 44.1, 43.5, 40.6, 39.8, 38.0, 35.8, 31.6, 29.0, 26.3, 24.8, 22.5; *C*H_3 30.4, 14.0

Spirocyclic nitrile (18). A 42 mg sample (0.12 mmol, 1.0 equiv) of vinyl bromide **17** was dissolved in benzene and heated to reflux under argon. A solution of 65 μL of tributyltin hydride (0.24 mmol, 2.0 equiv) and 2 mg of AIBN (0.2 equiv) in 5.0 mL benzene was added via syringe pump (0.51 mL/h). The flask was heated at reflux for an additional 16 h, then cooled to room temperature. The solution was concentrated under reduced pressure. Column chromatography (5% ethyl acetate/hexanes, SiO_2) provided 13 mg of the spirocyclic product (0.05 mmol, 39%) as a pale yellow oil: IR (neat) 2928, 2856, 2240, 1459, 1376, 1267, 1126, 1073, 850, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (m, 1 H), 2.8–1.8 (complex, 5 H), 1.48 (s, 3 H), 1.34 (s, 3 H), 1.6–1.2 (complex, 12 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 112, 98, 80.7; *C*H 66.4, 65.9; *C*H_2 42.3, 41.7, 39.7, 36.3, 35.8, 31.7, 29.2, 24.9, 22.6; *C*H_3 27.5, 24.2, 14.0. HRMS (CI) $(M+H)^+$ Calcd: 280.2276; found: 280.2272.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(4-iodo-3-butenyl)-1,3-dioxane (19).** A 196 mg sample of alcohol **20** was dissolved in 1.0 mL of CH_2Cl_2 and cooled to 0 °C. To this was added 0.14 mL of a 0.5 M aqueous solution of KBr (0.1 equiv) and 86 μL of an 0.08 M solution of 4-methoxy-TEMPO in CH_2Cl_2 (1 mol %). With vigorous stirring, 1.22 mL of a 5% solution of NaOCl (0.83 mmol, 1.2 equiv) was added slowly over a 20 min period. After 50 min, the mixture was diluted with 20 mL each of saturated $NaHCO_3$ and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (× 2). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 189 mg of the aldehyde as a colorless oil. IR (neat) 1996, 2931, 2859, 2728, 1725, 1461, 1383, 1256, 1207, 1160, 1048, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 1 H), 4.09 (m, 1 H), 2.8–2.6 (m, 2 H), 2.09 (m, 2 H), 1.80 (dd, J = 1.8, 13.4 Hz, 2 H), 1.65 (s, 3 H), 1.35 (s, 3 H), 1.5 – 1.2 (complex, 10 H), 0.86 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ *C* 121.4, 101.2, 69.1; *C*H 200.2, 66.2; *C*H_2 39.3, 38.1, 35.5, 34.8, 31.6, 28.9, 24.6, 22.5; *C*H_3 30.7, 21.3, 13.9.

To a suspension of iodomethyltriphenylphosphonium iodide (407 mg, 0.77 mmol in 2 mL THF, 1.25 equiv) at room temperature was slowly added 770 μL of a 1 M solution of sodium hexamethyldisilazane in THF. After stirring for 1 min, the solution was cooled to –60 °C and HMPA (260 μL) was then added. The solution was cooled to –78 °C and a solution of 173 mg of the aldehyde in 1.0 mL THF was added via cannula. The cold bath was removed and the solution was stirred for 30 min. Hexanes (20 mL) were added and the mixture was washed with 0.5 M $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (5% ethyl acetate/hexanes, SiO_2) provided 107 mg of the product (0.26 mmol, 43%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25 (m, 2 H), 4.09 (m, 1 H), 2.38 (m, 2 H), 1.84 (t, J = 8.0 Hz, 2 H), 1.77 (m, 2 H), 1.68 (s, 3 H), 1.37 (s, 3 H), 1.5 – 1.2 (complex, 10 H), 0.87 (t, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ *C* 121.6, 100.9, 69.3; *C*H 139.0, 83.9, 66.1; *C*H_2 40.2, 39.2, 35.6, 31.6, 29.0, 28.8, 24.6, 22.5; *C*H_3 30.8, 21.3, 14.0.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(3-hydroxypropyl)-1,3-dioxane (20).** A solution containing 264 mg (1.17 mmol, 1.0 equiv) of **1** in 2.0 mL of THF was added via cannula to a solution of lithium diethylamide (2.34 mmol, 2.0 equiv) in 4.0 mL of THF at –78 °C. After 2 h at -78 °C, 283 μL (2.34 mmol, 2.0 equiv) of DMPU was added. After an additional 10 min, 547 mg (2.17 mmol, 1.9 equiv) of 3-bromo-1-(*t*-butyldimethylsilyloxy)propane in 1.0 mL THF was added. The solution was stirred at -78 °C for 2 h, then transferred to a methanol/ice bath at -20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl

solution, and the mixture was extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (4% ethyl acetate/hexanes, SiO_2) gave 372 mg of a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.09 (m, 1 H), 3.65 (m, 2 H), 1.80 (m, 4 H), 1.68 (s, 3 H), 1.37 (s, 3 H), 1.6–1.2 (complex, 12 H), 0.89 (s, 12 H), 0.05 (s, 6 H). This material was dissolved in 4.0 mL of THF and 1.07 mL of a 1.0 M solution of TBAF in THF (1.1 equiv) was added. The solution was stirred at room temperature for 3 h then diluted with saturated NH_4Cl solution, extracted (3×EtOAc), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 196 mg of the product (0.69 mmol, 59%, 2 steps) as a clear, colorless oil: IR (neat) 3407, 2995, 2930, 2860, 1461, 1382, 1260, 1206, 1162, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.06 (m, 1 H), 3.61 (t, J = 3.0 Hz, 2 H), 2.66 (broad s, 1 H), 2.03 (dd, J = 6.0, 12.0 Hz, 1 H), 1.63 (s, 3 H), 1.32 (s, 3 H), 1.8–1.2 (complex, 15 H), 0.86 (t, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ *C* 121.8, 101.0, 69.8; *C*H 66.3; *C*H_2 62.0, 39.5, 38.9, 35.6, 31.6, 29.0, 26.6, 24.7, 22.5; *C*H_3 30.8, 21.4, 14.0; Anal. calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31. Found: C, 67.99; H, 10.12.

(4*R, 6*S**)-4-(4-cyano-3-butenyl)-2,2-dimethyl-6-hexyl-1,3-dioxane (21).** A 107 mg sample of iodide **19** was dissolved in 10.0 mL of benzene under argon and heated to reflux. A solution of 143 μL of tri-*n*-butyltin hydride (0.53 mmol, 2.0 equiv) and 8 mg of AIBN (0.2 equiv) in 8.0 mL benzene was added via syringe pump (1.5 mL/h). The reaction flask was heated at reflux for an additional 15 h, then cooled to room temperature. The solution was concentrated under reduced pressure. Column chromatography (5% ethyl acetate/hexanes, SiO_2) provided 48 mg of a 1:1 *E*/*Z* mixture of the product (0.17 mmol, 66%) as a pale yellow oil and 13 mg (0.04 mmol, 15%) of the reduced product as a colorless oil: IR 2991, 2955, 2928, 2857, 2223, 1632, 1462, 1379, 1264, 1200, 1116, 964, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.72 (dt, J = 7.0, 16.5 Hz, 0.5 H), 6.50 (dt, J = 7.6, 10.8 Hz, 0.5 H), 5.31 (m, 1 H), 3.78 (m, 2 H), 2.51 (m, 1 H), 2.31 (m, 1 H), (t, J = 8.0 Hz, 2 H), 1.77 (m, 2 H), 1.47 (s, 3 H), 1.37 (s, 3 H), 1.5 – 1.2 (complex, 10 H), 0.87 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5, 154.7, 99.6, 99.3, 98.3, 68.7, 67.9, 67.6, 53.2, 36.6, 36.2, 34.4, 33.9, 31.5, 30.0, 29.0, 28.9, 27.7, 26.4, 24.7, 22.4, 19.6, 19.5, 16.2, 13.9, 13.3; Anal. calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46. Found: C, 73.20; H, 10.22.

(4*R, 6*S**)-4-(3-butynyl)-4-cyano-2,2-dimethyl-6-hexyl-1,3-dioxane (23).** To a solution containing 414 mg (1.84 mmol, 2.0 equiv) of **1** in 7.0 mL of THF was added 2.02 mL of a 1.0 M solution of lithium bis(trimethylsilyl)amide in hexanes (2.02 mmol, 2.2 equiv) at –78 °C. After 5 min at -78 °C, 223 μL of DMPU (1.84 mmol, 2.0 equiv) was added. After an additional 10 min at -78 °C, 232 mg (0.92 mmol, 1.0 equiv) of 4-iodo-1-trimethylsilyl-1-butyne was added dropwise. The solution was stirred at -78 °C for 2 h, then transferred to a methanol/ice bath at -20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, and the mixture was extracted (3 × CH_2Cl_2), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (3% ethyl acetate/hexanes, SiO_2) gave 221 mg (0.63 mmol, 69% based on iodide) of the product as a yellow oil. A 199 mg sample of this material was dissolved in 10 mL of MeOH and 83 mg of K_2CO_3 (0.60 mmol, 1.05 equiv) was added. The mixture was stirred at room temperature for 15 h and concentrated under reduced pressure. Chromatography (3% ethyl acetate/hexanes, SiO_2) provided 109 mg (0.39 mmol, 69%) of the product as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (m, 1 H), 2.45 (m, 2 H), 2.01 (m, 3 H), 1.83 (dd, J = 1.9, 13.4 Hz, 1 H), 1.67 (s, 3 H), 1.37 (s, 3 H), 1.4–1.2 (complex, 11 H), 0.89 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 121.3, 101.1, 82.6, 69.0; *C*H 69.0, 66.1; *C*H_2 41.2, 39.2, 35.6, 31.7, 29.0, 24.7, 22.5, 12.9; *C*H_3 30.8, 21.3, 14.0.

Spirocyclic vinyl nitrile (25) and vinyl stannane (24). A 69.1 mg sample of **23** (0.25 mmol, 1.0 equiv) was dissolved in 10.0 mL of xylenes under argon atmosphere and heated to 140 °C. A solution of 135 μL of tri-*n*-butyltin hydride (0.50 mmol, 2.0 equiv) and 4 mg of AIBN (0.025 mmol, 0.2 equiv) in 8.0 mL xylenes was added via syringe pump (1.0 mL/h). The reaction was heated at reflux for an additional 10 h, then cooled to room temperature. The solution was concentrated under reduced pressure. Column chromatography (5% ethyl acetate/hexanes, SiO_2) provided 23.1 mg of the spirocyclic product **25** (0.08 mmol, 33%) as a pale yellow oil and 50 mg (0.09 mmol, 35%) of the vinyl stannane **24** as a pale yellow oil.

Spirocyclic vinyl nitrile 25: IR (neat) 2992, 2928, 2857, 2223, 1633, 1462, 1377, 1199 cm^{-1}; 1H NMR ($CDCl_3$, 300 MHz) δ 6.93 (t, J = 2.0 Hz, 1 H); 3.84 (m, 1 H), 2.72 (dddd, J = 16.4, 8.4, 6.0, 2.2 Hz, 1 H), 2.44 (dddd, J = 16.2, 8.7, 3.8, 1.7 Hz, 1 H), 2.11 (ddd, J = 12.0, 8.1, 3.9 Hz, 1 H), 1.92 (ddd, J = 13.8, 8.4, 6 Hz, 1 H), 1.56 (s, 3 H), 1.6 – 1.0 (complex, 12 H), 0.89 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ *C* 118, 117, 99, 84; *C*H 150.2, 66.5; CH_2 40.6, 39.5, 36.2, 31.7, 31.5, 29.2, 24.9, 22.5; CH_3 31.2, 25.1, 14.1; HRMS (CI) $(M+H)^+$ Calcd: 278.2119; found: 278.2120.

Vinyl stannane 24: IR (neat) 2990, 2995, 2928, 2856, 2211, 1572, 1462, 1379, 1263, 1200, 1075, 962, 873 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.79 (s, 1 H), 3.78 (m, 2 H), 2.41 (m, 2 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.6 – 1.0 (complex, 32 H), 0.88 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz, DEPT) δ *C* 133.2, 120, 98; *C*H 152.0, 68.9, 67.4; CH_2 36.9, 36.4, 34.8, 34.4, 31.7, 29.2, 28.9, 27.1, 24.9, 22.6, 10.5, 9.9; CH_3 30.2, 19.7, 14.0, 13.6; Anal. calcd for $C_{29}H_{55}NO_2Sn$: C, 61.28; H, 9.75. Found: C, 61.39; H, 9.68.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(4-bromo-4-pentenyl)-1,3-dioxane (26).** A solution containing 235 mg (1.05 mmol, 1.6 equiv) of **1** in 2.0 mL of THF was added via cannula to a solution of lithium diisopropylamide (1.05 mmol, 1.6 equiv) in 3.0 mL of THF at –78 °C. After 5 min at -78 °C, 127 μL of DMPU (1.05 mmol, 1.6 equiv) was added. After an additional 15 min at -78 °C, 180 mg (0.65 mmol, 1.0 equiv) of 2-bromo-5-iodo-1-pentene was added dropwise. The solution was stirred at -78 °C for 2 h, then transferred to a methanol/ice bath at -20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, and the mixture was extracted (3 × CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by column chromatography (5% ethyl acetate/hexanes, SiO_2) gave 456 mg (1.26 mmol, 98% based on iodide) of the product as a colorless oil: IR (neat) 2995, 2956, 2929, 2858, 1630, 1460, 1383, 1207, 889 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.61 (s, 1 H), 5.44(s, 1 H), 4.10 (m, 1 H), 2.47 (m, 2 H), 1.69 (s, 3 H), 1.38 (s, 3 H), 1.8–1.2 (complex, 16 H), 0.89 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 133.3, 121.8, 100.9, 69.7; *C*H 66.2; CH_2 117.3, 40.9, 40.6, 39.3, 35.6, 31.7, 29.0, 24.7, 22.5, 21.4; CH_3 30.8, 21.4, 14.0. Anal. calcd for $C_{18}H_{30}BrNO_2$: C, 58.06; H, 8.12. Found: C, 58.29; H, 8.02.

Spirocyclic nitrile (27). A 21 mg sample (0.06 mmol, 1.0 equiv) of vinyl bromide **26** was dissolved in toluene and heated to reflux under argon. A solution of 31 μL of tri-*n*-butyltin hydride (0.12 mmol, 2.0 equiv) and 2 mg of AIBN (0.2 equiv) in 2.0 mL toluene was added via syringe pump (0.24 mL/h). The mixture was heated at reflux for an additional 10 h, then cooled to room temperature. The solution was concentrated under reduced pressure. Column chromatography (5% ethyl acetate/hexanes, SiO_2) provided 4 mg of the spirocyclic product (0.013 mmol, 24%) as a pale yellow oil: IR (thin film) 2991, 2929, 2858, 2239, 1459, 1379, 1248, 1199, 1170, 1144, 997 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (m, 1 H), 2.84 (m, 2 H), 2.47 (dd, J = 3.1, 13.4 Hz, 1 H), 2.06 (m, 2 H), 1.42 (s, 3 H), 1.38 (s, 3 H), 1.7–1.2 (complex, 16 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 123.0, 98.9, 83.4; *C*H 70.2, 65.2; CH_2 41.6, 40.0, 36.3, 31.8, 31.6, 29.5, 29.2, 25.0, 24.1, 22.6; CH_3 29.7, 19.9, 14.1. HRMS (CI) $(M+H)^+$ Calcd: 294.2433; found: 294.2428.

(4*R, 6*S**)-4-cyano-2,2-dimethyl-6-hexyl-4-(4-pentynyl)-1,3-dioxane (28).** To a solution containing 462 mg (2.05 mmol, 1.6 equiv) of **1** in 7.0 mL of THF was added 2.18 mL of a 1.0 M solution of lithium bis(trimethylsilyl)amide in hexanes (2.18 mmol, 1.7 equiv) at –78 °C. After 5 min, 250 μL of DMPU (2.05 mmol, 1.6 equiv) was added. After an additional 10 min, 342 mg (1.29 mmol, 1.0 equiv) of 5-iodo-1-trimethylsilyl-1-pentyne was added dropwise. The solution was stirred at -78 °C for 2 h, then transferred to a methanol/ice bath at -20 °C for 1 h. The reaction was quenched with a saturated NH_4Cl solution, and the mixture was extracted (3 x CH_2Cl_2), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (5% ethyl acetate/hexanes, SiO_2) gave 456 mg (1.26 mmol, 98% based on iodide) of the product as a yellow oil. This material was dissolved in 20 mL of MeOH and 182 mg of K_2CO_3 (1.32 mmol, 1.05 equiv) was added. The mixture was stirred at room temperature for 15 h and concentrated under reduced pressure. Chromatography (10% ethyl acetate/hexanes, SiO_2) provided 363 mg (1.25 mmol, 99%) of the product as a colorless oil: IR (neat) 3307, 2996, 2931, 2861, 2119, 1462, 1380, 1258, 1207, 1160, 1118, 1041, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (m, 1 H), 2.25 (s, 2 H), 1.96 (t, J = 2.2 Hz, 1 H), 1.66 (s, 3 H), 1.35 (s, 3 H), 2.2–1.2 (complex, 16 H), 0.87 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ *C* 121.8, 100.8, 83.2, 69.6; *CH* 69.0, 66.2; CH_2 41.4, 39.4, 35.6, 31.6, 29.0, 24.6, 22.5, 22.2, 18.1; CH_3 30.8, 21.3, 14.0. Anal. calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03. Found: C, 73.96; H, 9.97.

Spirocycles 29 and 30. A 49 mg sample (0.17 mmol, 1.0 equiv) of alkyne **28** was dissolved in 6.0 mL of toluene under argon and heated to reflux. To this was added a solution of 90 μL of tributyltin hydride (0.34 mmol, 2.0 equiv) and 6 mg AIBN (0.2 mmol) in 5.0 mL benzene over 10 h using a syringe pump (0.51 mL/h). After refluxing an additional 12 h, the solution was cooled to room temperature and concentrated under reduced pressure. Chromatography (2 to 5% ethyl acetate/hexanes, SiO_2) provided 7 mg (0.024 mmol, 14%) of **29** as a colorless oil and 8 mg (0.026 mmol, 16%) of **30** as a pale yellow oil:

Spirocycle 29: IR (thin film) 2992, 2933, 2859, 2220, 1630, 1459, 1438, 1379, 1249, 1199, 1160, 1113, 972, 873 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 1 H), 3.93 (m, 1 H), 2.2–2.1 (m, 2 H), 1.92 (m, 1 H), 1.80 (dd, J = 2.4, 9.5 Hz, 1 H), 1.46 (s, 3 H), 1.36 (s, 3 H), 1.7–1.2 (complex, 14 H), 0.88 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 119.9, 114.3, 99.0, 68.1, 64.8, 40.0, 37.7, 36.3, 31.8, 31.5, 29.2, 27.0, 25.9, 24.9, 22.6, 16.9, 14.1. HRMS (CI) $(M+H)^+$ Calcd: 292.2276; found: 292.2269.

Spirocycle 30: IR (thin film) 2991, 2932, 2859, 2220, 1645, 1460, 1379, 1247, 1227, 1198, 1163, 1144, 1006, 973, 873 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (s, 1 H), 3.87 (m, 1 H), 2.20 (m, 2 H), 1.91 (m, 4 H), 1.6–1.5 (m, 3 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.4–1.2 (complex, 9 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 123.0, 113.4, 99.2, 70.6, 65.0, 38.4, 36.3, 33.9, 31.8, 31.5, 29.1, 26.5, 25.2, 25.0, 22.6, 19.0, 14.1. HRMS (CI) $(M+H)^+$ Calcd: 292.2276; found: 292.2274.

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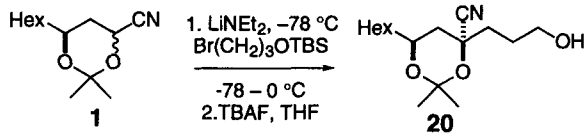

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