Reductive Lithiation Mediated Anionic Cyclizations and [2,3]-Sigmatropic Rearrangements

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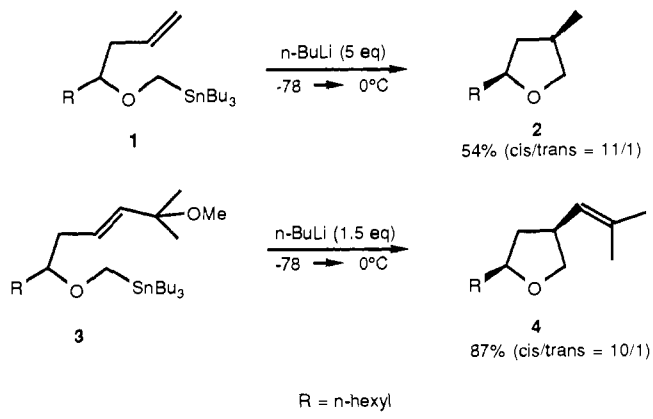
Abstract: The anionic cyclization of several α-alkoxylithiums derived by transmetalation from their corresponding (tributylstannyl)methyl ethers is described. The resulting 2,4-disubstituted tetrahydrofurans are primarily the cis stereoisomers. It is also shown that *O,S*-acetals derived from homoallylic alcohols and α-chloro sulfides, as well as *N,S*-acetals derived from homoallylic secondary amines, paraformaldehyde, and thiophenol, undergo anionic cyclization upon treatment with lithium naphthalenide in THF. The reactions presumably involve exchange of the phenylthio unit for lithium followed by cyclization of the resulting α-heteroatom-stabilized carbanions. The 2,3-disubstituted tetrahydrofurans and pyrrolidines prepared in this manner are mainly the trans stereoisomers (stereoselectivity between 6 and 10:1). Reductive lithiation of *O,S*-acetals derived from allylic alcohols leads to α-alkoxylithiums which undergo [2,3]-sigmatropic rearrangements to afford homoallylic alcohols. A similar rearrangement has been shown to occur in the case of an *N,S*-acetal yielding a homoallylic amine. In this case, however, the rearrangement is complicated by formation of the *N*-methyl system which results from protonation of the intermediate anion.

Recently, a number of synthetic methods have been introduced which employ anionic cyclizations for the construction of 5-membered rings. In most cases[1] the rings formed have been carbocyclic although some work has appeared dealing with the preparation of tetrahydofurans.[2] This report outlines several routes to tetrahydrofurans and pyrrolidines which involve anionic cyclizations of α-heteroatom-stabilized carbanions. These anions are, in turn, generated from readily available precursors by using established transmetalation and reductive lithiation chemistry. Moreover, it is shown that reductive lithiation provides an expeditious route to α-alkoxy- and α-aminolithium species capable of undergoing [2,3]-sigmatropic rearrangement to homoallylic alcohols and amines.

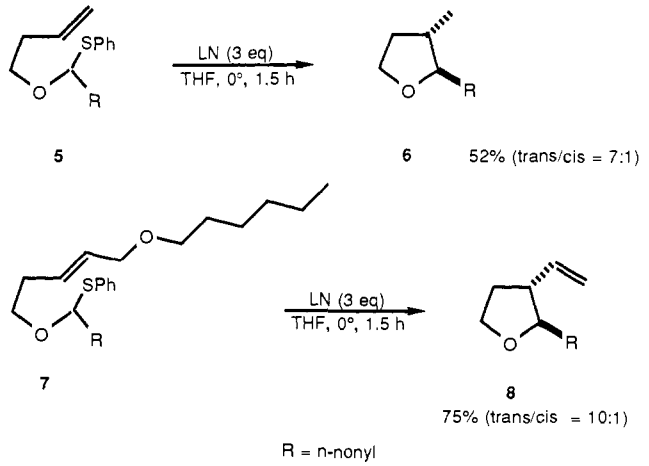
Transmetalation-Initiated Cyclizations. A previous paper from these laboratories described a stereoselective route to 2,4-disubstituted tetrahydrofurans which involves the anionic cyclization of α-alkoxylithiums.[2] As indicated (Scheme I) these organolithiums were generated by treatment of the corresponding (tributylstannyl)methyl ethers with *n*-BuLi. In the second example a double bond is produced by the expulsion of methoxide from the initially formed anion.

The cis stereoselectivity exhibited by these reactions is consistent with the intermediacy of a chairlike transition state similar to that assumed to operate in analogous 5-hexenyl radical cyclizations although the degree of stereoselectivity is superior to that generally encountered in radical-mediated processes. One limitation of this cyclization protocol, not shared by most radical reactions, is its seeming inability to generate rings of more than 5 members. Another is the fact that alkyl substituents on the double bond inhibit or markedly retard cyclization, presumably due to destabilization of the cyclized anion by the electron-donating alkyl group. (The successful formation of **4** is compatible with this idea since here the incipient negative change can be displaced onto the departing methoxy unit.) Analogous observations relating to substituent effects, as well as to the formation of 6-membered and higher membered rings, have been made by Bailey[1c] and Chamberlin[1e] in work dealing with the preparation of carbocyclic systems. We also attempted, unsuccessfully, to generate 3-methylenetetrahydrofurans by means of transmetalation-induced

Scheme I



Scheme II



cyclizations involving alkyne terminators.

Reductive Lithiation Mediated Cyclizations. In an effort to increase the versatility of this method, we were led to examine alternative strategies for the generation of α-heteroatom-substituted organolithiums. An exceedingly useful route to α-alkoxylithiums, developed by Cohen, involves treatment of α-(phenylthio) ethers with either lithium naphthalenide (LN) or lithium (dimethylamino)naphthalenide (LDMAN) in THF.[3] In the presence

(1) (a) Utimoto, K.; Imi, K.; Shiragami, H.; Fujikura, S.; Nozaki, H. *Tetrahedron Lett.* **1985**, 2101. (b) Chamberlin, A. R.; Bloom, S. H. *Tetrahedron Lett.* **1986**, 551. (c) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442. (d) Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1986**, *51*, 4880. (e) Chamberlin, A. R.; Bloom, S. H.; Cervini, L. A.; Fotsch, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 4788.

(2) (a) Lansbury, P. T.; Caridi, F. J. *J. Chem. Soc., Chem. Commun.* **1970**, 714. (b) Klumpp, G. W.; Schmitz, R. F. *Tetrahedron Lett.* **1974**, 2911. (c) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336.

(3) (a) Cohen, T.; Daniewski, W. M.; Weisenfeld, R. B. *Tetrahedron Lett.* **1978**, 4665. (b) Cohen, T.; Matz, J. R. *Synth. Commun.* **1980**, *10*, 311. (c) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6902. (d) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130.

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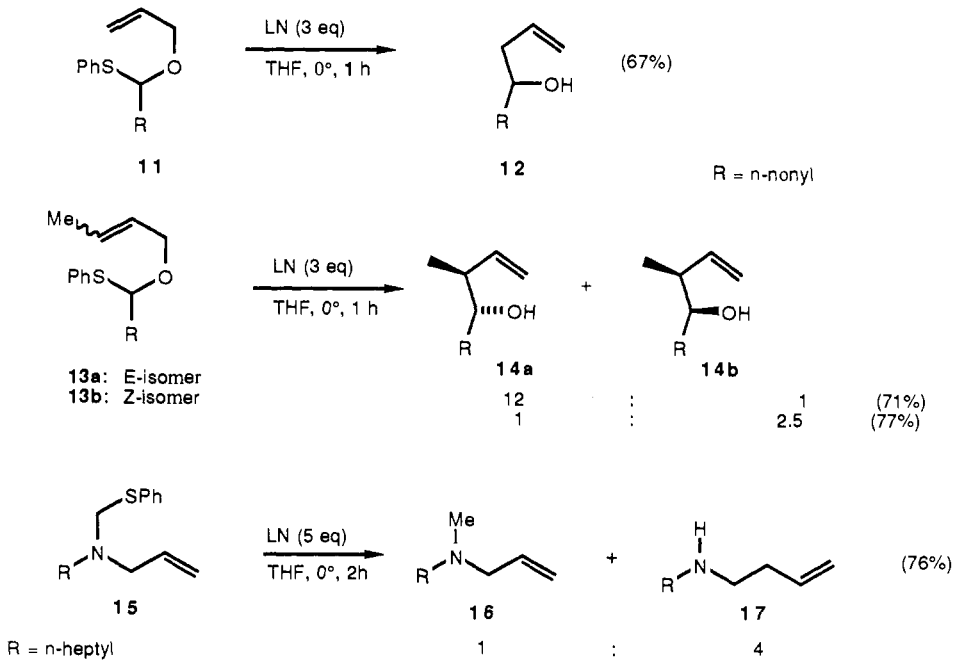
Scheme III

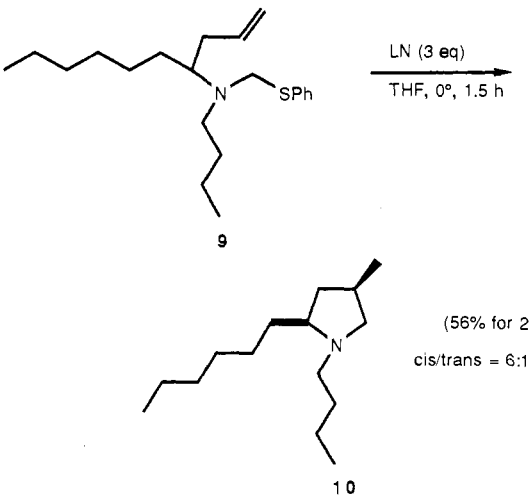


of 2 equiv of LN or LDMAN, the phenylthio group is cleanly exchanged for lithium and the resulting organometallic species may be trapped with a range of electrophiles, generally in quite good yield. This method is rendered especially attractive by the fact that a wide variety of α-(phenylthio) ethers may be prepared readily. Hence, it makes available an equally wide variety of α-alkoxylithiums.

The α-(phenylthio) ether **5** was prepared from 3-butenol and the corresponding α-chloro sulfide by using established procedures.[3c,4] Upon treatment of **5** with LN (3 equiv) at 0 °C, anionic cyclization took place smoothly to yield the 2,3-disubstituted tetrahydrofuran **6** (Scheme II).[5-7] Although the stereoselectivity was good, the yield was only fair. Anionic cyclization of the allylic ether **7** and concomitant expulsion of alkoxide proceeded with good stereoselectivity and in considerably improved chemical yield, giving **8**. This improvement in yield, observed in going from **5** to **7**, was to be expected on the basis of our earlier experience with the 2,4-disubstituted systems.[2c]

Since reductive lithiation is believed to proceed through the α-alkoxy radical, which is reduced to the anion by a further equivalent of LN or LDMAN, it is conceivable that these cyclizations are, in reality, radical rather than anionic processes.[8] The pronounced trans stereoselectivity of the reaction, however, seems to argue against this possibility. In similar situations, radical cyclizations generally exhibit the opposite stereochemical preference.[9,10] A similar trans stereoselectivity has been observed by Bailey in the cyclization of 2-lithio-6-heptene.[1c] It may be that anionic cyclizations, in contrast to their radical counterparts,[11] proceed through rather productlike transition states. If this is the case, the transition state leading to *cis*-**6** may be destabilized by nonbonded interactions between the nonyl group and the incipient lithiomethylene unit. The steric bulk of the latter would presumably be increased by solvation of the lithium cation thus contributing to the overall trans stereoselectivity of the anionic process.

A related method can be used to prepare pyrrolidines (eq 1). The phenylthiomethyl amine **9** was prepared from the corresponding secondary amine by treatment with paraformaldehyde



(1)

and PhSH in the presence of a trace of 4,4′-methylenebis(2,6-di-*tert*-butylphenol) (toluene, 100 °C, 20 h).[12] Upon treatment

(4) For an alternative procedure using DMF as the solvent, see: Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965.

(5) These cyclizations can also be effected with LDMAN; however, the limited stability of this reagent renders its use somewhat inconvenient.

(6) The stereochemistry of **6** was verified by its synthesis from the anti homoallylic alcohol **14a** by hydroboration–oxidation followed by treatment with TsCl in pyridine. An authentic sample of **14a** was prepared from decanal with crotyl bromide and $CrCl_2$ (Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179).

(7) Beckwith has investigated the generation of α-alkoxy radicals from sulfides analogous to **5** (Beckwith, A. L. J. and Pigou, P. E. *Aust. J. Chem.* **1986**, *39*, 77). For a radical-mediated approach to ring-fused γ-butyrolactones, see: Marino, J. P.; Laborde, E.; Paley, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 996.

(8) The formation of olefin **8** via a radical-mediated process would have to involve cyclization to the tetrahydrofurylcarbinyl radical followed by further reduction of this species to the anion by LN and subsequent elimination of alkoxide. Although we consider this scenario unlikely, experiments aimed at providing definitive proof of the anionic nature of our cyclizations have so far yielded ambiguous results. In particular, Garst has demonstrated that anionic cyclizations are suppressed in the presence of *t*-$BuNH_2$ whereas radical cyclization proceed normally under these conditions (Garst, J. F.; Hines, J. B., Jr.; Bruhnke, J. D. *Tetrahedron Lett.* **1986**, *27*, 1963). Unfortunately, attempts to apply this test in the case of **5** were complicated by the rapid reaction of LN with *t*-$BuNH_2$.

(9) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(10) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(11) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N. G.; Nagase, S. *J. Org. Chem.* **1986**, *51*, 2874.

with LN in the manner described for **5**, **9** afforded pyrrolidine **10** in acceptable yield.[13] Unfortunately, our attempts to extend this method to the synthesis of piperidines have so far met with little success.

Sigmatropic Rearrangements. The [2,3]-sigmatropic rearrangements of α-alkoxylithiums provide useful routes to a variety of homoallylic alcohols.[14] The stereoselectivity of these rearrangements, particularly those of allyl propargyl ethers, has been carefully studied by Nakai,[15] Midland,[16] and Marshall.[17] Although representing a valuable tool for achieving acyclic stereocontrol, these reactions suffer from a drawback in that the substrate ethers, whose deprotonation yields the α-alkoxylithiums, are restricted to those types possessing relatively acidic α-hydrogens. Reductive lithiation provides a means of overcoming this limitation (Scheme III).

The rearrangement substrates were prepared, as before, from the allylic alcohols and α-chlorodecyl phenyl sulfide with Na_2CO_3 as the base. Treatment of these ethers with LN brought about their rearrangement in good yield. The anti selective rearrangement of **13a** is in accord with literature precedent. However, the mediocre stereoselectivity observed in the rearrangement of **13b** is surprising, especially inasmuch as (*Z*)-crotyl systems often rearrange with greater stereoselectivity than their (*E*)-crotyl counterparts.[15,16]

In order to determine whether a similar rearrangement could be made to occur with allyl-substituted (aminomethyl)lithiums, the substrate **15** was treated with LN (both at −78 °C at 0 °C). While no rearrangement was observed at −78 °C, reactions conducted at 0 °C did afford primarily the butenylamine **17**. Although the formation of **16**, perhaps involving competitive protonation of the (aminomethyl)lithium by THF, limits the synthetic utility of this reaction, it is nevertheless interesting that it occurs at all. The rearrangements of the α-alkoxylithiums are expected to be highly exothermic since they convert carbanions into alkoxides. The rearrangement leading to **17** produces a relatively less stable amide anion but proceeds in spite of this disadvantage.

Experimental Section

Lithium Naphthalenide. Lithium naphthalenide in THF was prepared by allowing equimolar amounts of lithium metal and naphthalene to stir overnight in a volume of THF sufficient to afford a final concentration of 0.5 M.

***cis*-2-Hexyl-4-methyltetrahydrofuran (2).** To a solution of 1-decen-4-ol (1.38 g, 8.85 mmol) in THF (25 mL) was added potassium hydride (497 mg, 12.39 mmol). The mixture was allowed to stir at room temperature for 1 h before the dropwise addition of (iodomethyl)tributyltin (4.40 mL, 7.3 mmol). After 40 min the reaction was quenched with water and extracted with ether, and it furnished 6.26 g of an oily residue, which was purified on silica gel (elution with hexane) to afford 4-[(tri-*n*-butylstannyl)methyl)oxy]-1-decene (**1**) (2.41 g, 59%): IR (neat) 3076, 2995.3, 2924.4, 2856.9, 1485.4, 1053.3, 910.5 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.75–5.84 (m, 1 H), 4.98–5.06 (m, 2 H), 3.59–3.75 (m, 2 H), 3.30–3.07 (m, 1 H), 2.20–2.26 (m, 2 H), 1.26–1.50 (m, 28 H), 0.85–0.91 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 135.54, 116.15, 83.17, 58.81, 37.60, 30.30, 31.97, 29.58, 29.34, 27.37, 25.33, 22.69, 14.08, 13.72, 8.95.

To a solution of the stannylmethyl ether (459.1 mg, 0.782 mmol) in THF (7 mL) cooled to −78 °C was added 5 equiv of *n*-BuLi (2.5 mL, 4.0 mmol, 1.6 M in hexane) dropwise. It was stirred at −78 °C for 5 min and then at 0 °C for 20 min. Following ether–water workup, drying ($MgSO_4$), and solvent removal, a colorless, fragrant liquid was obtained. Flash chromatographic purification on silica gel (2% ether–hexane) afforded **2** (71.8 mg, 54%): IR (neat) 2957.2, 2926.4, 2858.9, 1458, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.77–3.87 (m, 2 H), 3.30–3.35 (t, 1 H, *J* = 7 Hz), 2.23–2.33 (m, 1 H), 2.30–2.15 (m, 1 H), 1.20–1.60 (m, 10 H), 1.00–1.03 (d, 3 H, *J* = 6 Hz), 0.84–0.88 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 80.2, 74.3, 40.9, 36.1, 34.2, 31.8, 29.4, 26.3, 22.5, 17.9, 14.0, HRMS calcd for $C_{11}H_{22}O$ 170.1670, found 170.1667. (For the ^{13}C NMR of *trans*-**2**, see ref 2c.)

2-Hexyl-4-ethenyltetrahydrofuran. Stannane **3** was prepared from the corresponding alcohol by the same procedure outlined above. IR (neat) 2957.2, 2924.4, 2872.4, 2855.0, 11464.2, 1377.3, 116.9, 1053.3, 972.2 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.57–5.69 (m, 2 H), 3.85–3.87 (d, 2 H, *J* = 6 Hz), 3.70–3.73 (m, 1 H), 3.57–3.61 (m, 1 H), 3.30–3.32 (s, 3 H), 3.03–3.07 (t, 2 H, *J* = 6 Hz), 2.21–2.25 (t, 2 H, *J* = 6 Hz), 1.23–1.69 (m, 19 H), 0.76–0.96 (m, 20 H).

To a solution of **3** (160 mg, 0.32 mmol) in THF (2 mL) was added *n*-BuLi (1.6 mL, 2.56 mmol, 1.6 M in hexane) dropwise. The mixture was stirred for 5 min at −78 °C and for 20 min at 0 °c. Ether–H_2O workup, drying over $MgSO_4$, concentration of solvent in vacuo, and purification on silica gel (elution with 0–10% ethyl acetate in petroleum ether) gave **4** (51 mg; 87%): IR (neat) 3030.7, 2959.2, 2926.4, 2856.9, 1642.6, 1458.4, 1379.3, 1100.5, 1070.6, 1040.7, 992.5 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.67–5.79 (m, 1 H), 5.02–5.07 (m, 2 H), 3.81–3.98 (m, 1 H), 3.49–3.55 (t, 2 H, *J* = 9 Hz), 2.84–2.92 (m, 1 H), 2.10–2.18 (m, 2 H), 1.13–1.61 (m, 10 H), 0.84–0.88 (t, 3 H, *J* = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 139.32, 114.81, 80.20, 72.11, 44.42, 39.25, 35.83, 31.81, 29.38, 26.28, 22.58, 14.06; HRMS calcd for $C_{12}H_{22}O$ − H 181.1592, found 181.1592.

Preparation of *O,S*-Acetals 5, 7, 11, 13a,b (Illustrated for 11). A solution of decyl phenyl sulfide (500 g, 1.9 mmol) in 1 mL of CCl_4 was cooled to 0 °C and treated with NCS (257 mg, 1.9 mmol). After stirring overnight at 0 °C, the solution was filtered through a plug of glass wool inserted in a pipet and the residual succinamide was washed with a little CCl_4. The solvent was removed leaving the unstable α-chloro sulfide, which was immediately dissolved in allyl alcohol (0.5 mL). After the addition of 200 mg of anhydrous Na_2CO_3, the mixture was stirred for 3 h. The resulting product was diluted with Et_2O, and the solution was extracted with 2 N NaOH and brine and then evaporated to dryness. The crude *O,S*-acetal was purified on silica gel (0–10% EtOAc–hexane) to afford **11** (386 mg, 65%): IR (neat) 2924, 2855, 1466, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 2 H), 7.28 (m, 3 H), 4.89 (m, 1 H), 5.21 (m, 2 H), 4.73 (t, *J* = 6.2 Hz, 1 H), 4.40 (m, 1 H), 4.08 (m, 1 H), 1.77–1.24 (m, 16 H), 0.88 (t, *J* = 6 Hz, 3 H); HRMS calcd for $C_{19}H_{30}SO$ 306.2017, found 306.2018.

Also prepared in this manner were the following.

5: IR (neat) 2928, 2855, 1466 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 2 H), 7.27 (m, 3 H), 5.85 (m, 1 H), 5.06 (m, 2 H), 4.71 (t, *J* = 6 Hz, 1 H), 3.94 (q, *J* = 9 Hz, 1 H), 3.48 (q, *J* = 9 Hz, 1 H), 2.36 (q, *J* = 9 Hz, 2 H), 1.75 (m, 2 H), 1.44–1.25 (m, 16 H), 0.88 (t, *J* = 9 Hz, 3 H); HRMS calcd for $C_{20}H_{32}OS$ 320.2174, found 320.2181.

7: IR (neat) 2926, 2855, 1477, 1466 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 2 H), 7.28 (m, 3 H), 5.67 (m, 2 H), 4.69 (t, *J* = 6 Hz, 1 H), 3.90 (m, 1 H), 3.89 (d, *J* = 6 Hz, 2 H), 3.46 (m, 1 H), 3.38 (t, *J* = 6 Hz, 2 H, 2.34 (m, 2 H), 1.75–1.23 (m, 24 H), 0.87 (m, 6 H); HRMS calcd for $C_{27}H_{46}O_2S$ − SPh 325.3107, found 325.3109.

13a: IR (neat 2995, 2882, 1091, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 2 H), 7.28 (m, 3 H), 5.68 (m, 1 H), 5.58 (m, 1 H), 4.71 (t, *J* = 6 H, 1 H), 4.29 (m, 1 H), 3.99 (m, 1 H), 1.70 (d, *J* = 6 Hz, 3 H), 1.24 (m, 16 H), 0.88 (t, *J* = 6 Hz, 3 H).

13b: IR (neat) 2924, 2855, 1377, 997 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.26 (m, 3 H), 5.69 (m, 1 H), 45.57 (m, 1 H), 4.71 (t, *J* = 6 Hz, 1 H), 4.40 (dd, *J* = 12, 6 Hz, 1 H), 4.18 (dd, *J* = 12, 6 Hz, 1 H), 1.70 (m, 2 H), 1.66 (d, *J* = 6 Hz, 3 H), 1.23 (m, 14 H), 0.87 (t, *J* = 6 Hz, 3 H); HRMS calcd for $C_{20}H_{32}OS$ − SPh 211.2062, found 211.2057.

Reductive Lithiation Mediated Cyclizations (Illustrated for 6). *O,S*-Acetal **5** (152 mg, 0.47 mmol) in 3 mL of THF was cooled to 0 °C and 3 mL of an 0.5 M solution of LN in THF was introduced. After 20 min another 1-mL portion of LN was added. After 1 h the mixture was poured into water and extracted with Et_2O. Flash chromatography on silica gel furnished **6** (51 mg, 52%): IR (neat) 2855, 1456, 1377 cm^{-1};

(12) This procedure is a modification of one introduced by Grillot (Grillot, G. F.; Felton, H. R.; Garrett, B. R.; Greenberg, H.; Green, R.; Clementi, R.; Moskowitz, M. *J. Am. Chem. Soc.* **1954**, *76*, 3969). ^{1}H NMR indicated the somewhat labile product to be >90% pure. *N,S*-acetal **9** was not purified prior to cyclization and the yield is based upon the amount of parent secondary amine employed. Reductive lithiation of *N,S*-acetals with LN or LDMAN is, to our knowledge, unprecedented and would seem to provide a direct and simple route to the corresponding organometallics. However, our attempts to trap aminomethyllithiums, prepared in this manner, with PhCHO (see: Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027) have failed for reasons that are, at present, unclear.

(13) Padwa has shown that treatment of *N,S*-acetals similar to **9** with Bu_3SnH leads mainly to reduction, indicating that radical cyclization is, in such cases, relatively slow (Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620). This fact provides a measure of support for our belief that **10** arises via an anionic process. Assignment of cis stereochemistry to the major product of this reaction and trans to the minor isomer follows from a comparison of the ^{13}C NMR spectra of these materials with those of the 2,4-disubstituted tetrahydrofurans, whose preparation was described in ref 2c. Although the analogy would appear to be a reasonable one, these assignments should still be viewed as tentative.

(14) For transmetalation-mediated rearrangements, see: Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1987**, *109*, 1927.

(15) Mikami, K.; Azuma, K.-I.; Nakai, T. *Tetrahedron* **1984**, *40*, 2303.

(16) (a) Tsai, D. J.-S.; Midland, M. M. *J. Org. Chem.* **1984**, *49*, 1843. (b) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, 5013, 5017, 5021.

(17) Marshall, J. A.; Jenson, T. M. *J. Org. Chem.* **1984**, *49*, 1707.

^{1}H NMR ($CDCl_3$) δ 3.80 (m, 2 H), 3.26 (m, 1 H), 2.05 (m, 1 H), 1.77 (m, H), 1.53-1.25 (m, 17 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.86 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 86.0, 66.6, 39.0, 34.8, 34.4, 31.9, 29.9, 29.7, 29.6, 29.5, 26.6, 22.7, 17.3, 14.1; HRMS calcd for $C_{14}H_{28}O - H^+$ 211.2062, found 211.2053.

The major (trans) stereoisomer could not be effectively separated from the minor product, *cis*-**6**. The ratio between them was therefore estimated from the relative sizes of the ^{13}C signals at 66.6 and 86.0 ppm and the much smaller signals at 66.7 and 81.8 ppm. The latter signals corresponded to carbon resonances present in the spectrum of **6** prepared from **14b**.

Also prepared in this manner was **8**: IR (neat) 2922, 2853, 1464, 912 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.64 (m, 1 H), 5.04 (m, 2 H), 3.84 (m, 2 H), 3.43 (m, 1 H), 2.35 (m, 1 H), 2.10 (m, 1 H), 1.77-1.25 (m, 17 H), 0.87 (t, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 139.1, 115.5, 83.7, 67.0, 49.8, 33.9, 33.2, 31.9, 29.7, 29.5, 29.3, 26.47, 22.7, 14.1 (one peak, probably 29.7, 29.5, or 29.3, corresponds to two carbon resonances); HRMS calcd for $C_{15}H_{28}O$ 224.2140, found 224.2140. (Note: Occasionally the green color of LN faded partway through the reaction, perhaps due to reaction of the excess LN with the Teflon-covered stirring bar. In these cases an additional portion of LN was added, after which the reactions proceeded normally.)

2-n-Hexyl-4-methyl-N-butylpyrrolidine (10). 4-(*n*-Butylamino)-1-decane was prepared, at 0 °C in Et_2O, by the reaction of the appropriate imine with allylmagnesium bromide and purified by Kugelrohr distillation (75 °C, 5 mm): IR (neat) 2957, 2924, 2856, 1466 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.76 (m, 1 H), 5.05 (m, 2 H), 2.54 (m, 2 H), 2.19 (m, 4 H), 1.25 (m, 12 H), 0.87 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 135.8, 116.8, 56.9, 46.7, 38.3, 33.9, 32.4, 31.7, 29.4, 25.6, 22.5, 20.4, 13.9, 13.8. Anal. Calcd for $C_{14}H_{29}N$: C, 79.55; H, 13.83; N, 6.63. Found: C, 79.20; H, 13.69; N, 6.53.

A solution of the above-prepared amine (402 mg, 1.9 mmol) in 5 mL of toluene was treated with PhSH (212 μL, 2.1 mmol), paraformaldehyde (74 mg, 2.4 mmol), and a few crystals of 4,4′-methylenebis(2,6-di-*tert*-butylphenol). The mixture was stirred overnight at 100 °C. The volatiles were removed under reduced pressure, leaving the crude *N,S*-acetal **9**: ^{1}H NMR ($CDCl_3$) δ 7.48-7.17 (m, 5 H), 5.77 (m, 1 H), 4.97 (m, 2 H), 4.58 (s, 2 H), 2.69-2.53 (m, 4 H), 2.11 (m, 2 H), 1.27 (m, 12 H), 0.85 (m, 6 H).

The *N,S*-acetal **9** was taken up in 10 mL of THF and added to 11 mL of 0.5 M LN in THF at 0 °C. After 1.5 *h* at 0 °C, the mixture was poured into dilute HCl and the nonbasic material was removed by Et_2O extraction. The solution was basified with NaOH and then extracted with CH_2Cl_2. The organic extracts were dried (K_2CO_3) and concentrated, and the product was purified on silica gel with a 0-3% gradient of methanolic ammonia in CH_2Cl_2 to give **10** (143 mg, 56% for two steps): IR (neat) 2957, 2928, 2859, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.73 (m, 1 H), 2.32-1.98 (m, 4 H), 1.45-1.24 (m, 17 H), 1.00 (d, J = 6 Hz, 3 H), 0.85 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 6.66, 61.0, 54.3, 40.2, 33.5, 31.8, 30.2, 29.9, 29.5, 26.7, 22.5, 20.8, 20.7, 14.0, 13.9; HRMS calcd for $C_{15}H_{31}N$ 225.2456, found 225.2451.

Sigmatropic Rearrangements of 11, 13a,b. These reactions were carried out by using the same reductive-lithiation protocol employed for **5** and **7**. The rearrangements were allowed to proceed for 1.5 h at 0 °C. Workup and product isolation was performed as in the case of **6** and **8**. The resulting alcohols were identified by comparison with authentic samples prepared by using established methods (see ref 6).

Amines 16 and 17. *N,S*-Acetal **15** was prepared in the same manner as was **9** from allyl heptylamine (bp 170 °C/5 mm): IR (neat) 2955, 2928, 2855, 742, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 2 H), 7.25 (m, 3 H), 5.73 (m, 1 H), 5.05 (m, 2 H), 4.55 (s, 2 H), 3.16 (d, J = 6 Hz, 2 H), 2.54 (t, J = 6 Hz, 2 H), 1.21 (m, 10 H), 0.87 (t, J = 6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.5, 135.2, 132.3, 128.6, 126.2, 117.7, 63.9, 55.9, 52.0, 31.7, 29.0, 27.2, 27.1, 22.5, 14.0. Anal. Calcd for $C_{17}H_{27}NS$: C, 73.58; H, 9.81; N, 5.05; S, 11.55. Found: C, 73.48; H, 9.90; N, 5.14; S, 11.68.

A solution of 0.5 M LN in THF (10 mL) was cooled to 0 °C and a solution of **15** (280 g, 1.0 mmol) in 5 mL of THF was added slowly. After stirring for 2 h, the reaction was worked up in the manner described for the cyclization leading to **10**. Purification of the products on silica gel (eluting with 3% methanolic ammonia in CH_2Cl_2) gave **17** and **16** (130 mg, 76%). Their ratio was determined to be 4:1 by NMR. (The minor product **16** was identified by comparison with a nearly pure sample prepared by quenching a reaction similar to the above but conducted at -78 °C immediately after reductive lithiation). **17**: IR (neat) ^{1}H NMR ($CDCl_3$) δ 5.76 (m, 1 H), 5.04 (m, 2 H), 2.60 (t, J = 6 Hz, 2 H), 2.52 (t, J = 6 Hz, 2 H), 2.19 (m, 2 H), 1.20 (m, 11 H), 0.79 (t, J = 6 Hz, 3 H). **16**: IR (neat) 2955, 2928, 916, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1 H), 5.15 (m, 2 H), 2.95 (d, J = 6 Hz, 2 H), 2.28 (t, J = 7 Hz, 2 H), 2.17 (s, 3 H), 1.48-1.25 (m, 10 H), 0.85 (t, J = 6 Hz, 3 H).

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Registry No. 1, 113352-43-5; *cis*-**2**, 113352-45-7; *trans*-**2**, 113352-46-8; **3**, 113352-55-9; *cis*-**4**, 113352-60-6; *trans*-**4**, 113352-61-7; **5**, 119010-67-2; *trans*-**6**, 119010-68-3; *cis*-**6**, 119010-80-9; **7**, 119010-69-4; *trans*-**8**, 119010-70-7; *cis*-**8**, 119010-81-0; **9**, 119010-71-8; *cis*-**10**, 119010-72-9; *trans*-**10**, 119010-83-2; **11**, 119010-73-0; **12**, 117951-87-8; **13a**, 119010-74-1; **13b**, 119010-84-3; **14a**, 94453-48-2; **14b**, 94453-47-1; **15**, 119010-75-2; **16**, 119010-76-3; **17**, 119010-77-4; $CH_3(CH_2)_5CH(OH)CH_2CH{=}CHC(CH_3)_2OCH_3$, 119010-78-5; (*E*)-$CH_3CH{=}CHCH_2OH$, 504-61-0; (*Z*)-$CH_3CH{=}CHCH_2OH$, 4088-60-2; $CH_2{=}CHCH_2CH_2OH$, 627-27-0; $CH_3(CH_2)_5OCH_2CH{=}CHCH_2CH_2OH$, 119010-79-6; PhSH, 108-98-5; 1-decen-4-ol, 36971-14-9; (iodomethyl)-tributyltin, 66222-29-5; decyl phenyl sulfide, 13910-18-4; allyl alcohol, 107-18-6; 4-(*n*-butylamino)-1-decene, 119010-82-1; 1-(butylimino)heptane, 6898-76-6; allyl heptylamine, 91342-40-4.

A Highly Stereoselective Synthesis of (+)-Olivin, the Aglycon of Olivomycin A

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Abstract: The first total synthesis of (+)-olivin (**1**), the naturally occurring enantiomer of the aglycon of olivomycin A, is described. The synthesis is highly stereoselective, featuring the reaction of (γ-methoxyallyl)boronate **21** with chiral aldehyde **17** and the addition of lithiodivinylcuprate to unsaturated aldehyde **40** as the key diastereoselective transformations. The anthracenone nucleus of **1** was constructed beginning with the coupling of unsaturated ester **42** and phthalide **46**. The vinyl unit of naphthoate **48** was oxidized to the acetic ester appendage in **53**, and then the final C–C bond of anthracenone **54** was established by a Dieckmann cyclization. The C(2′) hydroxyl group of **57** was oxidized to the necessary side-chain carbonyl function, and then the C(2) hydroxyl group was introduced stereoselectively by the *m*CPBA epoxidation of the mono TBDMS enol ether prepared from **58**. All five acid-labile protecting groups were removed in a single operation to complete the synthesis.

Olivin (**1**) is the aglycon of olivomycin A (**2**), a member of the aureolic acid family of antitumor antibiotics,[2] Also included in this group are the chromomycins and the mithramycins [e.g., aureolic acid (**4**)]. Several of these antibiotics have undergone

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