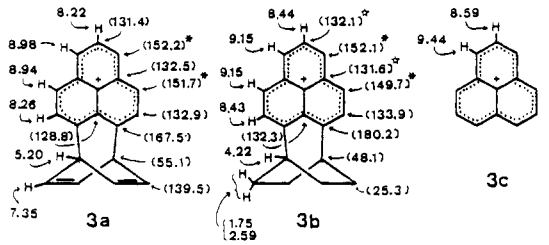
Table I. Reduction Potentials of 3a-c

cation salt	$E_1^{red.}$ ($R^+/R\cdot$)	$E_2^{red.}$ ($R\cdot/R^-$)	ΔE
3a[a]	0.21	−1.11[b]	−1.32
3b[a]	0.11	−1.18[b]	−1.29
3c[c]	0.7	−0.9	−1.6

[a] Potentials are determined in CH_3CN with 0.1 M n-Bu_4NBF_4 as supporting electrolyte at −78 °C and are given in volts vs. SCE. [b] Irreversible. [c] Data taken from ref 14.

shown alongside the following structures where the values in parentheses denote carbon shift (starred values may be interchanged). All the protons attached to the phenalenyl



skeleton of both **3a** and **3b** appear at rather high field compared to the parent cation **3c**. The upfield shifts are more pronounced in **3a** than **3b**.[12] Furthermore, all aromatic protons of **3a** are about equally shielded from those of **3b** ($\Delta\delta$ for H-1, -2, -4, and -5 are 0.17, 0.22, 0.21, and 0.17 ppm, respectively). Since the chemical shifts of the most remote protons, H-2, from the bridges are at least not considered to be influenced by the anisotropy difference between etheno and ethano bridges, the observed upfield shift in **3a** implies an additional electron supply (besides inductive effect of the alkyl bridge) from the etheno bridge in **3a**. Of the phenalenyl carbons in **3a** and **3b**, the marked upfield shifts of C-5a, C-9a, and C-11c are observed in **3a**. However, this strong shielding cannot be accounted for in terms of electron delocalization from the etheno bridge in **3a** since same shielding is observed in the etheno-bridged acenaphthylene **4a** (δ 130.5) compared to the ethano-bridged one (δ 143.8). Although the chemical shifts of remaining phenalenyl carbons in **3a** and **3b** show no significant difference,[13] those of the etheno and ethano carbons (C-7, -8, -12, and -13) need comment. Within the comparison between **4**, **5**, and **3**, the signals of ethano-bridge carbons are shifted to higher field in the order of **4b** (δ 29.0), **5b** (δ 27.2), and **3b** (δ 25.3), whereas the appearance of the etheno-bridge carbon signal in **3a** (δ 139.5) approximately 5 and 7 ppm to lower field than those in **5a** (δ 134.0, 134.3) and **4a** (δ 132.2), respectively, is seemed to be the deshielding arising from charge delocalization in **3a**.

Measurements of the reduction potentials of **3a** and **3b** by cyclic voltammetry showed first reversible and second irreversible reductions. The results are summarized in Table I together with those for **3c**.[14] The second reduction potentials ($R\cdot/R^-$) of **3a** and **3b** are found to be approximately −1.1 V, which are valid for the reduction potentials of the neutral species having either nonbonding LUMO or SOMO.[15] Taking into account the first reduction potentials as a measure of the thermodynamic stability of a series of cations, **3a**, not to mention **3b**, is substantially more stable than **3c**.[16] Although the pK_{R^+} of **3a** and **3b** could not be determined due to the irreversible disproportionation of the corresponding carbinols that occured under the conditions employed, the observed pK_{BH^+} data for a series of phenalenones, **5a** (−0.8),[8] **5b** (+0.2), and the parent ketone (−1.4),[8] which reflect mainly the stability of the corresponding hydroxyphenalenyl cations, are compatible with the electrochemical data.

In conclusion, the available experimental data suggest that the cations **3a** and **3b** are more stable than **3c** and the ^1H and ^{13}C NMR spectra of **3a** are indicative of charge delocalization into the etheno bridge to some extent.[17]

Registry No. **3a**$^+\cdot BF_4^-$, 88887-56-3; **3a**·, 88980-87-4; **3a**$^-$, 88887-57-4; **3b**$^+\cdot BF4^-$, 88887-59-6; **3b**·, 88980-88-5; **3b**$^-$, 88887-60-9; **3c**$^+\cdot BF_4^-$, 88887-61-0; **4a**, 82655-70-7; **4b**, 88887-62-1; **5a**, 82655-78-5; **5b**, 88887-63-2.

(11) Prinzbach, H.; Freudenberger, V.; Scheidegger, U. *Helv. Chim. Acta* **1967**, *50*, 1087.

(12) Although a referee has suggested that small differences in ^1H NMR absorption values in **3c**, **3b**, and **3a** could also be rationalized as resulting from reduced delocalization as a result of deviation from planarity caused by increased strain in going from **3c** to the ethano to the etheno structures, it should be stressed that differences in chemical shifts of aromatic protons between ethano- (**4b**, **6b**) and etheno-bridged intermediates (**4a**, **6a**) are less than 0.1 ppm.

(13) A referee has pointed out that ^{13}C values for ring carbons of **3a** offer no evidence of charge delocalization. However, it has been claimed that correlations between ^{13}C NMR shifts and atomic populations of aromatic compounds should not be interpreted in terms of π-electrons only. See: Fliszár, S.; Cardinal, G.; Beraldin, M.-T. *J. Am. Chem. Soc.* **1982**, *104*, 5287.

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(15) Dietz, R.; Peover, M. E. *Trans. Faraday Soc.* **1966**, *62*, 3535.

(16) Inductively, the stabilizing effect of the etheno bridge in **3a** is weaker than that of the ethano bridge in **3b** (Nakazawa, T.; Niimoto, Y.; Kubo, K.; Murata, I. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 545. Nakazawa, T.; Kubo, K.; Murata, I. *Ibid.* **1981**, *20*, 189). Nevertheless, the comparable stability observed for **3a** and **3b** suggests that the unfavorable stabilizing effect in **3a** is offset by the electron delocalization in **3a**.

(17) Spectral data of new compounds. **4a**: colorless needles, mp 116–117 °C; UV (CH_3CN) λ_{max} nm (log ϵ) 229 (4.57), 299 (3.89), 311 (4.03), 325 (3.89); ^1H NMR ($CDCl_3$) δ 3.21 (s, 4 H), 4.01 (m, 2 H), 6.43 (m, 4 H), 6.97 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 30.2, 45.3, 118.6, 124.5, 126.0, 130.5, 132.2, 141.3, 145.2. **4b**: colorless crystals, mp 171–172 °C; UV (CH_3CN) λ_{max} nm (log ϵ) 236 (4.90), 291 (3.96), 303 (4.04), 314 (3.91), 320 (3.89), 334 (3.74); ^1H NMR ($CDCl_3$) δ 1.88–2.17 (m, 8 H), 3.07 (m, 2 H), 3.33 (s, 4 H), 7.08 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 29.0, 30.3, 39.7, 119.2, 124.8, 130.8, 141.0, 143.4, 143.8. **5a**: for mp, IR, UV, and ^1H NMR, see ref 8; ^{13}C NMR ($CDCl_3$) δ 47.6, 48.0, 124.9, 125.7, 126.9, 127.2, 127.4, 128.9, 129.7, 130.0, 130.7, 134.0, 134.3, 139.6, 141.9, 143.0, 185.1; ^{13}C NMR (CF_3COOD) δ 52.0, 52.3, 119.3, 123.1, 127.5, 128.2, 129.3, 129.9, 137.6, 140.5, 145.4, 153.6, 156.6, 159.8, 178.4. **5b**: yellow crystals, mp 155–156 °C; IR (KBr) 1631 cm^{-1}; UV (CH_3CN) λ_{max} nm (log ϵ) 267 (4.34), 324 (3.47), 366 (3.82), 411 (4.13); UV (60% H_2SO_4) 210 (4.47), 223 (4.49), 263 (3.97), 365 (4.13), 415 (4.10), 459 (4.17), 477 (4.21); ^1H NMR ($CDCl_3$) δ 1.70–2.28 (m, 8 H), 3.35 (m, 2 H), 6.69 (d, J = 9.8 Hz, 1 H), 7.32 (d, J = 7.2 Hz, 1 H), 7.52 (d, J = 7.6 Hz, 1 H), 7.62 (d, J = 7.2 Hz, 1 H), 7.71 (d, J = 9.8 Hz, 1 H), 8.57 (d, J = 7.6 Hz, 1 H); ^1H NMR (CF_3COOD) δ 1.87 (m, 4 H), 2.52 (m, 4 H), 4.00 (m, 2 H), 7.74 (d, J = 8.9 Hz, 1 H), 8.09 (d, J = 7.8 Hz, 1 H), 8.20 (d, J = 8.1 Hz, 1 H), 8.72 (d, J = 7.8 Hz, 1 H), 8.82 (d, J = 8.9 Hz, 1 H), 9.45 (d, J = 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.2, 41.9, 42.2, 125.4, 126.3, 126.7, 128.1, 128.5, 129.4, 131.1, 131.7, 131.9, 141.9, 153.4, 156.5, 185.6; ^{13}C NMR (CF_3COOD) δ 25.9, 26.0, 45.8, 46.2, 119.4, 122.6, 127.2, 127.3, 130.6, 131.4, 132.1, 141.7, 146.9, 152.6, 172.2, 174.8, 176.6.

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A Reiterative Route to Chiral *all-syn*-1,3-Polyols

Summary: An efficient, enantioselective procedure for obtaining *syn*-1,3-polyols is described. The method relies on a reiterative two-step protocol involving stereoselective homoallylic alcohol epoxidation followed by ring opening via a higher order, mixed organocuprate.

Sir: Among the myriad advances in synthetic methodology reported over the past 2 decades, those concerned with

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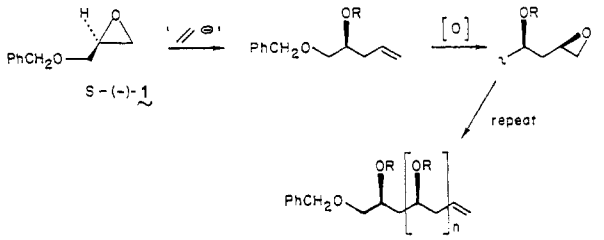
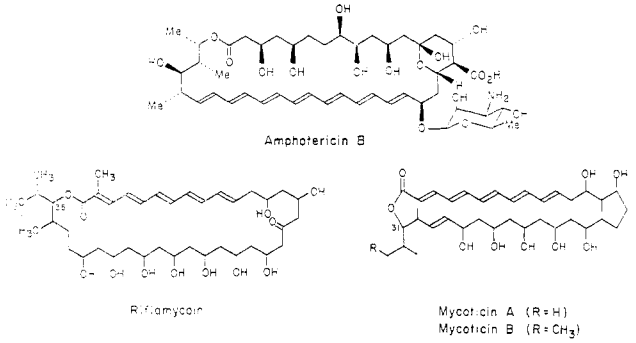
Scheme I



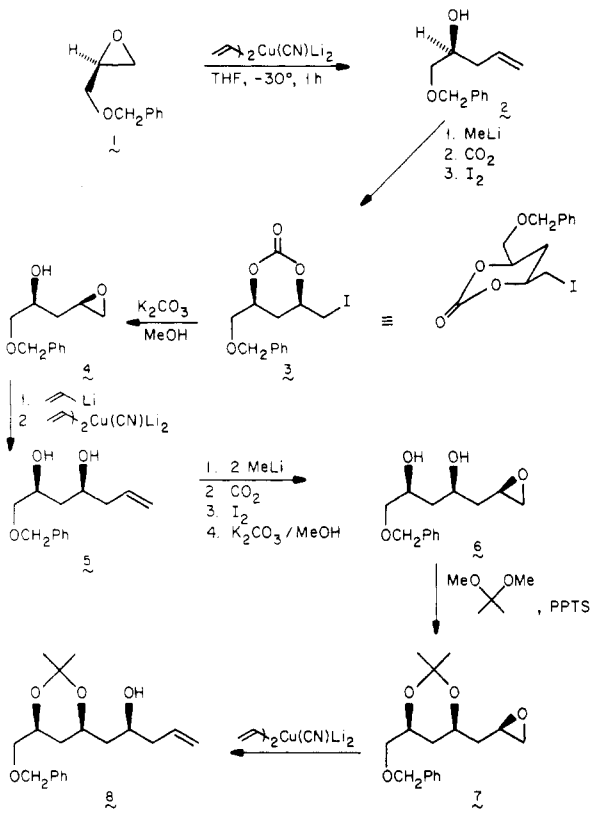
control of acyclic stereochemistry are among the most recently and intensively investigated.[1] The presence of one or more 1,3-polyol segments, the hydroxyl groups of which oftentimes bear an all-syn relationship to each other, in complex natural products has encouraged a number of research groups to devise ways of generating this key structural unit[2] or its equivalent.[3] Our interest in the polyene macrolides,[4] typified by amphotericin B,[5] roflamycoin,[6] and the mycoticins,[7] which as a class display



powerful antifungal activity,[4] coupled with our contributions in organocopper chemistry,[8] suggested that a straightforward, reiterative two-step sequence might permit construction of the polyol network. Herein we describe such a protocol, which enables realization of *all-syn*-1,3-polyols, in principle of unlimited chain length, in optically pure form.

Toward this goal we invoked the concept of "stereochemical linearity"[9] and hence chose optically active epoxide **1**,[10,11] fortunately obtainable in either antipodal form,[11] as our point of departure. The chirality of **1**, therefore, determines that induced at each carbon to which a hydroxyl group is to be delivered. The availability of both enantiomeric forms of this oxirane is, indeed, of

Scheme II



paramount concern, as the majority of chiral centers in most polyene macrolides are of unknown configurations.[4] The overall strategy is illustrated in Scheme I.

In practice, treatment of **1** with the higher order cuprate[12] derived from vinyllithium and cuprous cyanide (i.e., $(vinyl)_2Cu(CN)Li_2$) in THF at −30 °C for 1 h afforded homoallylic alcohol **2** in 86% yield (Scheme II). In contrast, the same substrate under the influence of the Gilman reagent,[13] $(vinyl)_2CuLi$, gave **2** to the extent of 73%. Stereoselective epoxidation relied on a modification of the Cardillo procedure[14] and proceeded in 83% overall yield. Thus, initial treatment of **2** with MeLi followed by exposure of the alkoxide to dry, gaseous CO_2 for 30 min and then azeotropically dried ($PhCH_3$) I_2 in THF, all at −78 °C, led to a mixture of iodo carbonates (**3** + isomers) as determined by TLC (Et_2O, R_f(major) = 0.34). These adducts proved to be quite sensitive to chromatography and hence were immediately converted to epoxy alcohol **4**, via an acyclic mixed carbonate, with K_2CO_3 in MeOH (−78 → 0 °C, 1 h). This two-carbon extension, two-pot operation directly provides material suitable for repetition of the sequence. Alkoxide formation (vinyllithium,[15] −78 °C) followed by oxirane cleavage as before results in 1,3-diols (**5** + isomers) in a combined yield of 96%.[16] At this point, the isomer ratio of desired syn to anti diols[17] was repro-

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(2) (a) Finan, J. M., Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719. (b) Hirama, M.; Uei, M. *Ibid.* **1982**, *23*, 5307. (c) Brooks, D. W., Kellogg, R. P. *Ibid.* **1982**, *23*, 4991. (d) Floyd, D. M., Fritz, A. W. *Ibid.* **1981**, *22*, 2847. (e) Bartlett, P. A., Jerstedt, K. K. *Ibid.* **1980**, *21* 1607. (f) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378.
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(12) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.
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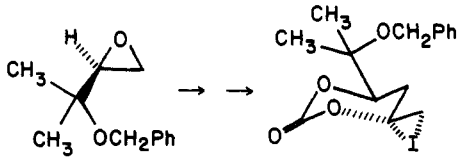
(14) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626.
(15) Vinyllithium was used as base rather than MeLi to insure that traces of unreacted MeLi did not enter into cuprate formation and lead to products of methyl rather than vinyl transfer. Furthermore, any unconsumed vinyllithium would react with the (vinyl)Cu(CN)Li produced following transfer of a vinyl ligand from the higher order cuprate, reforming $(vinyl)_2Cu(CN)Li_2$.
(16) By way of comparison, $(vinyl)_2CuLi$ afforded an 82% yield from this oxirane opening.
(17) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

ducibly determined to be between 10–14.5:1, based on VPC analyses of the derived acetonides. Chromatographic separation, however, was best carried out at the diol olefin stage to afford pure **5** ($[\alpha]^{22}_D = -1.2°$ (*c* 10, $CHCl_3$)).

In the next iodocyclization, diol **5** required 2 equiv of base (MeLi) to form the bis alkoxide, only the homoallylic oxyanion of which reacted productively with CO_2[18] and thence I_2 at −78 °C to give a new mixture of epoxy diols (**6** + isomers) in ca. 75% yield.[19] Ketalization (dimethoxypropane, CH_2Cl_2, PPTS; 98%) led to a single new spot by TLC, the capillary VPC trace, however, indicating an 18–20:1 ratio of syn:anti products **7**.[20] Separation was best effected on homoallylic alcohol **8**, arrived at via subsequent cuprate-induced opening of **7**, thereby culminating in a stereochemically homogeneous, derivatized polyol [**7** → **8**,[21] 90%, $[\alpha]^{22}_D = +16.7°$ (*c* 3.6, $CHCl_3$)].

Interestingly, improved stereoselectivity is obtained from the second epoxidation sequence. This raises the attractive possibility that additional steric bulk on the side chain, in this case relative to that of the benzyloxymethyl moiety in the cyclization of **2**, as in the dimethyl analogue **9**, should better encourage its equatorial-like positioning in a cyclic transition state, thereby further improving the syn:anti ratio.



9

Finally, there are two other aspects of this work that are worthy of note. Upon completion of the polyol portion of interest using this route, each 1,3-diol unit is already in protected (potentially differentiated) form, most likely an essential feature for eventual macrocyclization. Moreover, each terminus exists as a latent aldehyde, which may be individually unleashed under unique chemical circumstances (i.e., ozonolysis or, e.g., $Pb(OAc)_4$).

In summary, epoxide **1** has been parlayed into a chiral, *syn*-1,3-polyol by means of a cuprate-mediated cleavage, re-epoxidation. This series can be repeated until the fragment corresponding to that of a target molecule has been attained. In each step the efficiency is high, as is the stereoselectivity, which thus far varies from 10–20:1. Improvements in this ratio may be forthcoming with refinements in the substitution pattern of the initial educt. The specific applications of these concepts to polyene macrolide synthesis will be reported in due course.

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Registry No. **1**, 14618-80-5; **2**, 88981-35-5; **3**, 88981-36-6; **4**, 88981-37-7; **5**, 88981-38-8; **6**, 88981-39-9; **7**, 88981-40-2; **8**, 88981-41-3; $(vinyl)_2Cu(CN)Li_2$, 87136-18-3.

Supplementary Material Available: Full experimental and spectral details for compounds **2** and **4**–**8** (5 pages). Ordering information is given on any current masthead page.

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(18) Treatment of the bis alkoxide with dry CO_2 leads to a fairly viscous mixture at −78 °C. The addition of 10% HMPA to a THF solution of **5** prior to its conversion to **6** solubilized a good deal of the dianion; however, the product to starting material ratio did not improve.

(19) Presumably due to occlusion at −78 °C,[18] ca. 10% starting material was also usually isolated (thus, the yield based on recovered educt was ca. 86%).

(20) Not surprisingly, if the reaction mixture is warmed to 0 °C in an attempt to further solubilize the dioxyanion, the ratio of syn:anti products drops to ca. 11:1.

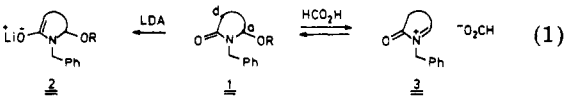
(21) All compounds derived from epoxide **1** gave satisfactory IR, NMR, and mass spectral data, as well as acceptable combustion or high-resolution MS analyses.

(22) A. P. Sloan Foundation Fellow, 1984–1986.

ω-Alkoxy Lactams as Dipolar Synthons. Silicon-Assisted Synthesis of Azabicycles and a γ-Amino Acid

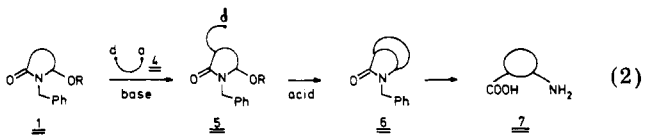
Summary: Alkylation of the lithium enolates derived from ω-alkoxy lactams **1a–c** with unsaturated iodides **4** affords **5** in high yields (Table I). Those alkylation products **5**, which contain an allyl- or propargylsilane moiety, undergo cyclization on acid treatment to furnish a variety of bicyclic nitrogen compounds, one of which has been further transformed into a γ-amino acid.

Sir: Simple and stable reagents possessing a nucleophilic (donor, d) and an electrophilic (acceptor, a) site,[1] which can be deployed selectively and sequentially, are of great potential use in synthesis.[2] It occurred to us that ω-alkoxy lactams (**1**, eq 1) might show such dipolar behavior. De-



(1)

protonation using LDA was expected to afford the nucleophilic amide enolate anion **2**[3] whereas acid treatment should result in formation of the electrophilic *N*-acyliminium ion **3**.[4] We were particularly interested in performing the second of the two C–C bond-forming reactions in an intramolecular fashion by using another dipolar reagent of type **4** in order to arrive at bicyclic systems **6** via alkylation products **5** (eq 2). Both the azabicycles **6**



(2)

and the amino acids **7**, which result from hydrolysis of the amide bond in **6**, are interesting molecules for which a general synthetic approach did not yet exist. We now disclose our results, which provide a facile entry to these molecules.

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(4) For a review, see: Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345.

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