chemistry was obtained at a later stage of the synthesis. The major amino ester (**15**) was converted to β-keto phosphonate **17** [$(MeO)_2P(O)CH_2Li$, 99%][15] and a Horner–Wadsworth–Emmons reaction (NaH, DME) with *m*-iodoanisaldehyde gave unsaturated ketone **18** (mp 201–202 °C, 81%).[16] Treatment of **18** with lithium triethylborohydride gave an easily separable mixture of allylic alcohols **19** (mp 100–102 °C, 71%) and **20** (25%). The major alcohol (**19**) was reduced with diimide ($TsNHNH_2$, NaOAc, H_2O–DME) to afford **21** (mp 163.5–165.5 °C, 95%), whose structure was established by X-ray crystalography.[18]

With the C(6) side chain in place, we were set for the critical biaryl construction using methodology developed by Semmelhack and co-workers.[19] Thus, alcohol **21** was converted to acetate **22** (mp 61–64 °C, 85%; Et_3N, Ac_2O, 4-DMAP).[20] Treatment of **22** with 1.5 equiv of freshly prepared tetrakis(triphenylphosphine)nickel(0) in *N,N*-dimethylformamide at 55 °C for 48 h gave biaryl **23** (mp 169–169.5 °C, 20%). Cleavage of the benzyl ether (BBr_3, CH_2Cl_2, 1 min, 0 °C)[21,22] gave (±)-lythrancepine II (mp 139–142 °C, 60%), which was identical (500-MHz ^1H NMR, IR, MS, TLC) with an authentic sample of natural 1.[23]

In summary, we have completed the first total synthesis of a member of the largest structural family of Lythraceae alkaloids. The synthesis requires 17 steps from *m*-iodoanisaldehyde and proceeds in approximately 1% overall yield. Furthermore, the basic strategy should allow the synthesis of all other members of this family of Lythraceae alkaloids.

Acknowledgment. We thank the National Institutes of Health for their support of this research (GM-27647). We thank Richard Weisenberger and Dr. Chuck Cottrell for recording mass and 500-MHz ^1H NMR spectra, respectively, at The Ohio State University Chemical Instrumental Center.

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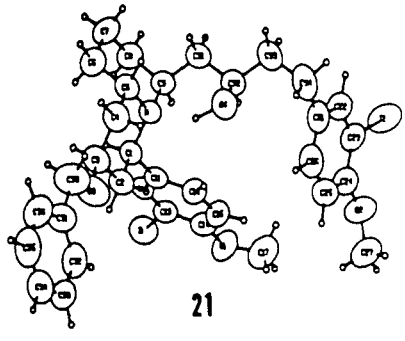
(17) Footnote deleted in proof.
(18) We thank Dr. Ruth Hsu for performing this analysis at the Ohio State University Department of Chemistry X-Ray Crystallographic Facility. Questions regarding the structure determination should be directed to Dr. Hsu.



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(22) Hydrogenolysis of **23** under a variety of conditions gave benzylic C–N bond cleavage in addition to benzyl ether cleavage.
(23) We thank Professor Eiichi Fujita for graciously supplying a sample of authentic (+)-lythrancepine II. Further proof of structure has obtained by acetylation of (±)-1 to give (±)-lythrancepine III (mp 82–84 °C).[2] This material was also identical with a sample of (+)-lythrancepine III supplied by Professor Fujita.

(24) Fellow of the Alfred P. Sloan Foundation, 1983–1987.

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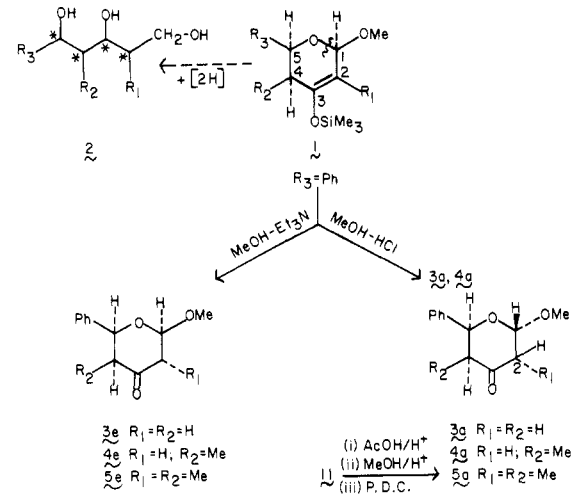
On the Steric Course of the Reduction of 2-Alkoxy-4-pyranones: A Remarkable Demonstration of Anomeric Control

Summary: The stereochemistry about the anomeric alkoxy center governs the facial selectivity of reduction of the title compounds with metal hydrides.

Sir: Recently developed chemistry provides access to compounds of the type implied in formula **1**.[1] In addition to their pertinence to the synthesis of complex saccharides, such systems, upon suitable disconnection of the pyran ring at the acetal carbon, could well serve as useful intermediates in the synthesis of polypropionates (viz., **1** → **2**).[2,3]



Of course, the efficacy of such a strategy would depend, to no small extent, on the stereochemical control that can be exercised during the rehybridization of unsaturated carbons 2 and 3. Treatment of such systems with triethylamine in methanol leads to axial protonation. Thus, in the case of cycloadduct **1** (R_1 = R_2 = Me; R_3 = Ph) compound **5e** is obtained stereospecifically. As a consequence of de facto endo addition[4] in the cycloaddition step, a cis stereochemical relationship is established between the "glycosidic" center and C_5. Examination of the ^1H NMR spectra of these "cis–cis" compounds establishes the methoxy, phenyl, and R^1 centers (see compound **5e**) to be equatorial, while the R_2 methyl group (see compounds **4e** and **5e**) is axial.[5]

(1) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.
(2) For an important demonstration of polypropionate synthesis, see: Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(3) For a recent description of a new strategy in this area, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
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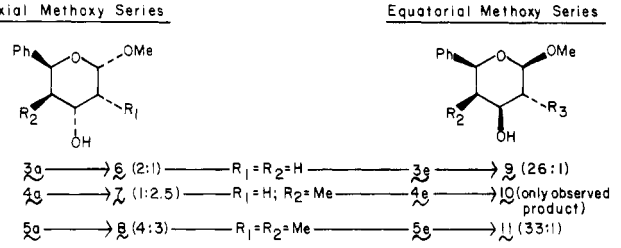
Access to the axial methoxy anomers (see compounds **3a–5a**) is less direct. Compounds **3a** and **4a** arise from treatment of **1** (R = Ph) with methanolic HCl.[6] Unfortunately, this technology is totally ineffective for the synthesis of the more substituted system **5a** bearing a methyl group at C_2. The compound was prepared in only low yield (ca. 16%) starting with compound **11** (vide infra). The sequence began with cleavage of the methyl glycoside linkage with aqueous acetic acid. This step was followed by reaction of the resultant hemiacetal with methanolic HCl, providing a mixture of methoxy anomers. Oxidation of the axial methoxy product, afforded the required pyranone substrate **5a**, in which the 1-methoxy and 4-methyl groups are axial while the C_2-methyl and C_5-phenyl functions are equatorial.[7] Attempts to achieve simpler access to **5a** by direct anomerization of **5e** were unsuccessful. In this paper, we relate some results encountered during the reduction of the pyranones.

Treatment of the axial methoxy anomers **3a**, **4a**, and **5a**[8] with sodium borohydride in methanol afforded, in each case, a serious mixture of C_3 alcohols. In addition to the axial compounds (i.e., α-OH in the arbitrary configuration), which are shown, there was obtained the equatorial alcohols.[9] The sum of the yields of homogeneous alcohols, after chromatographic separation, was uniformly in the range of 65–80%. The ratios of the axial to the equatorial alcohols (structures not shown here) are indicated.

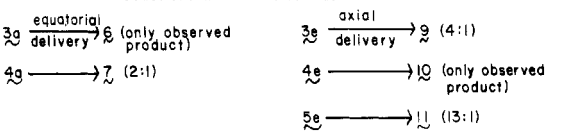
Reductions of Pyranones 3a–5e With NaBH4



The results of reduction of the equatorial anomers ***3e***, ***4e***, *and* ***5e***[6] *with sodium borohydride are in sharp contrast with those of the axial analogues. In these cases, highly selective reactions were observed, leading, in each case, to a substantially single product in which the hydroxyl group is equatorial (i.e., β in the arbitrary configuration shown).* In the case of substrates **3e** and **5e**, trace amounts of axial alcohols (structures not shown) were produced in the indicated ratios. Upon reduction of anomer **4e**, compound **10** was the only product observed. Thus, the configuration at the anomeric center strongly influences the course of reduction.

It was of interest to test the extent of anomeric control[10] when L-Selectride[11] (Aldrich) is the reducing agent. The results are shown below. In the unsubstituted substrate **3a**, bearing the axial methoxy groups, a very strong pref-

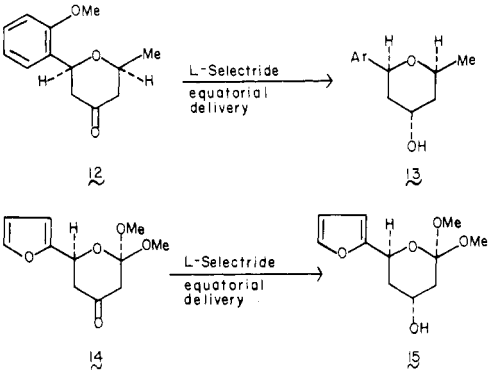
Reductions with L-Selectride



erence for the usual equatorial hydride delivery is manifested. In the case of **4a**, this specificity is, not unexpectedly,[11] eroded by the presence of the vicinal axial methyl group.[12]

*The clearest demonstration of the influence of the stereochemistry at the anomeric center is seen in the equatorial series (****3e****, ****4e****, and* ***5e****) wherein, in each case, the major product has arisen via axial hydride delivery.* Although with **3e** and **5e** the preference for axial delivery by L-Selectride is less than that exhibited by sodium borohydride, the extraordinary reversal from the normal tendency of Selectrides to react via steric approach control is most striking.[13]

The limits of this apparent anomaly were probed more closely. In this connection, the reduction of compound **12**[14] with L-Selectride was examined. Compound **13** was produced stereospecifically. Thus, as the anomeric equatorial



methoxy group is replaced by an equatorial "*C*-glycosidic" methyl group, normal Selectride behavior reemerges. Another striking result is provided in the reduction of the orthocarbonate derivative **14**,[15] which contains "anomeric"

(5) The following NMR data for compound **3e** are illustrative of those encountered in the series: ^{1}H NMR ($CDCl_3$) δ 2.56–2.72 (m, 4 H), 3.56 (s, 3 H), 4.59–4.82 (m, 2 H), 7.37 (s, 5 H).

(6) Treatment of cycloadduct **1** (R_1 = R_2 = H; R_3 = Ph) with 90% CH_3OH/H_2O–catalytic HCl gave in 56% yield (from benzaldehyde) a 7:1 mixture of **3a**/**3e** which could not be separated and was used in all reduction experiments. The 10% H_2O was needed to discourage ketal formation. Compound **4a** was obtained by treating cycloadduct **1** (R_1 = H; R_2 = Me; R_3 = Ph) with methanolic HCl in 43% yield (from benzaldehyde). Ketal formation was not observed, even in the absence of added water. That methoxypyranones **3a–4b** probably arose from addition to the corresponding dihydropyrones was suggested by TLC analysis during the course of the reaction.

(7) The following NMR data for compound **3a** are illustrative of those encountered in the series: ^{1}H NMR ($CDCl_3$) δ 2.56–2.76 (m, 4 H), 3.40 (s, 3 H), 5.05 (dd, J = 9, 6 Hz, 1 (benzylic) H), 5.25 (dd, J = 5, 2 Hz, 1 (anomeric) H), 7.40 (s, 5 H).

(8) It is assumed that in each case, reduction is indeed occurring through the ground-state[5,7] conformation. While the strong conformational definition of the systems would tend to support this formulation, it is not proven.

(9) The following NMR data for the respective compounds are illustrative of those encountered in the series. **6** (equatorial alcohol): ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 3 H), 2.26 (m, 2 H), 3.56 (s, 3 H), 4.08 (dd, J = 11, 7 Hz, 1 (C_3H) H), 4.42 (dd, J = 9, 2 Hz, 1 H), 4.54 (dd, J = 9, 2 Hz, 1 H), 7.40 (s, 5 H). **6** (axial alcohol): ^{1}H NMR ($CDCl_3$) δ 1.40–2.17 (m, 5 H), 3.56 (s, 3 H), 4.46 (m, 1 (C_3H), H), 4.88–5.08 (m, 2 H), 7.41 (s, 5 H). **9** (equatorial alcohol): ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 3 H), 2.20 (m, 2 H), 3.37 (s, 3 H), 4.23 (m, 1 (C_3H) H), 4.73 (dd, J = 12, 3 Hz, 1 (benzylic) H), 4.95 (d, J = 3 Hz, 1 (anomeric) H), 7.36 (s, 5 H). **9** (axial alcohol): ^{1}H NMR ($CDCl_3$) δ 1.67–2.19 (m, 4 H), 3.43 (s, 3 H), 3.70 (d, J = 9 Hz, 1 (OH) H), 4.13 (m, 1 (C_3H) H), 4.97 (d, J = 3 Hz, 1 (anomeric) H), 5.05 (dd, J = 11, 3 Hz, 1 (benzylic) H), 7.33 (s, 5 H).

(10) For an in depth treatment of the anomeric effect, see: Szarek, W. A., Horton, D., Eds. "Anomeric Effect: Origin and Consequences"; American Chemical Society: Washington, 1979; Vol. 87.

(11) Lithium tri-*sec*-butylborohydride, commercially available, is known to have a high proclivity toward steric-approach (e.g., equatorial) control. See: Brown, H. C.; Krishnamurthy, S. *Aldrichimica Acta* **1979**, *12*, 3.

(12) L-Selectride reduction of **5a** led to a very complex mixture of products including those in which NMR analysis indicated methanol to have been lost.

(13) A tendency toward axial delivery, via LAH reduction of equatorial alkoxypyranone anomers, is seen in a recent publication by the Oishi group, which appeared during the preparation of this manuscript. However, the Japanese workers did not report on the use of Selectrides for this purpose. See: Nakata, T.; Nagao, S.; Oishi, T. *Tetrahedron Lett.* **1985**, 75.

(14) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285.

axial and equatorial methoxy groups in the same molecule. Here again, normal Selectride behavior reemerges in the product, **15**, arising from apparent equatorial delivery of hydride.

These findings can be accommodated within the theoretical construct recently proposed by Cieplak.[16] The following arguments would be advanced. The combination of the conformationally defined equatorial methoxy groups (cf., **3e**, **4e**, and **5e**), in conjunction with the ring oxygen, erodes the capacity of the adjacent C–C bond to stabilize the $\sigma_{\ddagger}^*$ orbital which begins to emerge from equatorial attack on the ketone. Therefore, axial delivery is favored even with L-Selectride. In the case of compound **12**, where the additional methoxy group is absent, normal equatorial delivery pertains.[17,18] In the compounds bearing axial methoxy groups (**3a**, **4a**, and **14**), the steric constraints against axial attack may override the stabilization factor and equatorial delivery preference is observed with L-Selectride.[9]

While the precise reasons for this effect will continue to be appropriate matters for conjecture and experiment, it is already clear that the capacity to control the facial sense of reduction of the 4-pyranone ketone by stereochemical fine tuning of the anomeric center has many implications. The results of investigations which build upon the findings recorded above will be provided in due course.

Acknowledgment. This work was supported by PHS Grant HL 25848. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. We are grateful for the contribution of Mark Bednarski via the preparation of compound **14** and in the study of its reduction with L-Selectride.

(15) Compound **14** (78%) was prepared from 1,1-dimethoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene and furfural ($Eu(fod)_3$ catalysis) by M. Bednarski of these laboratories. Alcohol **15** was characterized as its acetate. The reduction is apparently stereospecific.

(16) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. A careful reading of the Cieplak paper is necessary to understand the arguments presented herein.

(17) The highly selective reduction of compound **12** stands in contrast to the result obtained by Monti[18] and co-workers and repeated in our laboratory with 2-methyltetrahydropyran-2-one. The weak selectivity for equatorial delivery (3:1) manifested in the monosubstituted case could well reflect its much greater conformational mobility relative to the cis-2,6-disubstituted compound **12**. Thus, in the Monti case, the nature of the reacting conformer is open to considerable question.

(18) Catelani, G.; Monti, L.; Ugazio, M. *J. Org. Chem.* **1980**, *45*, 919.

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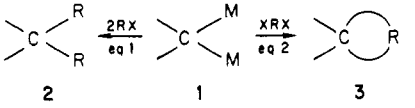
[(Phenylsulfonyl)methylene]dilithium as a Novel Cyclizing and Homologizing Reagent for Bifunctional Organic Substrates[1]

Summary: [(Phenylsulfonyl)methylene]dilithium, generated from methyl phenyl sulfone and 2 equiv of *n*-butyllithium in THF, reacts readily with a series of bifunctional organic substrates, such as dihalides, halo epoxides, halo carbonyls, halo nitriles, dicarbonyls, and α,β-unsaturated carbonyls, to give carbocyclic and homologous derivatives in good to excellent yields.

Sir: The formation of carbon–carbon bonds by the cross-coupling reaction between organometallic reagents and organic halides or sulfonates is a versatile, indispensable mainstay of the synthetic organic chemist.[2,3] Accordingly, an appealing extension of this method has been the generation of reagents bearing geminal carbon–metal bonds (**1**, where, e.g., M = Na,[4] Li,[5] Al,[6] Ti[7-9]), so that



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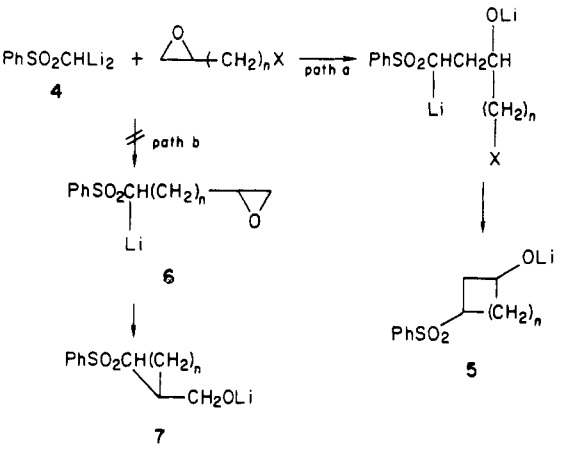
subsequent treatment with carbon electrophiles ($R_2C{=}O$ or 2RX) would lead to the formation of two new carbon–carbon bonds (**2**, eq 1). Alternatively, were a carbon electrophile bearing two reactive centers to be employed, reaction with **1** should lead to carbocyclic products (**3**, eq 2). Indeed, the classic Perkin synthesis of cycloalkanes can be viewed as representing this course of reaction.[10]

Because of the ease of generating geminal dilithio derivatives from alkyl sulfones,[11] we have been encouraged to investigate the little-studied[12] reaction of such geminal dilithioalkyl sulfones with electrophilic bifunctional organic substrates. We now wish to report our finding of a wide variety of high-yielding carbocyclizations and several most

Scheme I



(1) Part 7 of the series Sulfone Reagents in Organic Synthesis; for Part 6, see: *J. Organomet. Chem.* **1985**, *285*, 121.

(2) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 492–595.

(3) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669.

(4) Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 4237.

(5) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019.

(6) Lehmkuhl, H.; Schäfer, R. *Tetrahedron Lett.* **1966**, 2315.

(7) Tebbe, F. N. Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1980**, *102*, 6149.

(8) Howard, T. R.; Lee, J. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876.

(9) Eisch, J. J.; Piotrowski, A. *Tetrahedron Lett.* **1983**, *24*, 2043.

(10) Fuson, R. C. In "Organic Chemistry, An Advanced Treatise"; Gilman, H., Ed.; New York, 1943; Vol. I, pp 82–86.

(11) (a) Truce, W. E.; Christensen, L. W. *J. Chem. Soc., Chem. Commun.* **1971**, 558. (b) Pascali, V.; Tangari, N.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1166. (c) Bosworth, N.; Magnus P. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2319. (d) Kondo, K.; Tunemoto, T. *Tetrahedron Lett.* **1975**, 1397. (e) Bongini, A.; Savoia, D.; Umani-Ronchi, A. *J. Organomet. Chem.* **1976**, *112*, 1. (f) Bartlett,. P. A.; Green, F. R., III; Rose, E. A. *J. Am. Chem. Soc.* **1978**, *100*, 4852.

(12) The reaction between 1,1-dilithioalkyl phenyl sulfones and ω-bromo esters, which leads principally to cyclic vinyl ethers, has been investigated: Mussatto, M. C.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1*, **1980**, 260.

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