increased solvent viscosity and correspondingly reduced limiting diffusion rates in solution. The third regime is that where $E_{1/2}(Q)$ is ca. −1.6 V (i.e., where $\Delta G_{el}°$ is slightly positive according to the reported $Cu(dpp)_2^{2+}/^3[Cu(dpp)_2^{+}]^*$ reduction potential[10]). In this regime, electron transfer quenching is competitive with energy transfer and the other deactivation mechanisms, and the pressure effect is expressed as a negative $\Delta V^{\ddagger}_q$. The dominant pressure-dependent factor in this regime is concluded to be the outer-sphere rearrangement energy λ_{os},[33] the negative contribution to $\Delta V^{\ddagger}_q$ reflecting solvent electrostriction coupled to the charge separation accompanying electron transfer in this case.

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(33) McMillin et al. (ref 10) have proposed (based on calculated self-exchange rates) that Cr(II) product formed in the electron transfer may be a low-spin d^4 species, either the ground or a low-lying excited state of the unknown tris(β-dionato) Cr(II) intermediate. One might speculate that, if a high-spin d^4 Cr(II) were formed, the expected tetragonal distortion would make a strongly positive contribution to the $\Delta V^{\ddagger}_{el}$. However, under conditions where $\Delta V^{\ddagger}_{el}$ appears to be the predominate contributor to $\Delta V^{\ddagger}_q$, the latter is strongly negative. This observation is consistent with but certainly does not substantiate the proposed low-spin Cr(II) intermediate.

Communications to the Editor

Reductive Aromatization of Quinol Ketals: A New Synthesis of *C*-Aryl Glycosides†

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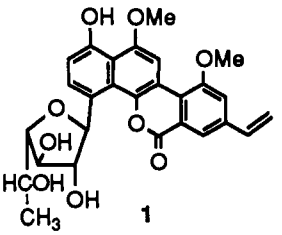
The polyketide-derived *C*-aryl glycosides[1] are a rapidly growing class of natural products with a variety of interesting biological activities. For example, gilvocarcin V (**1**)[2] exhibits significant antitumor activity.



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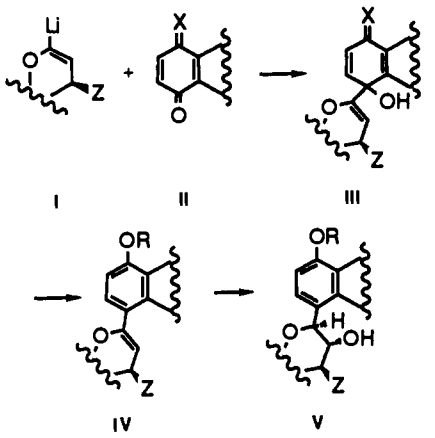
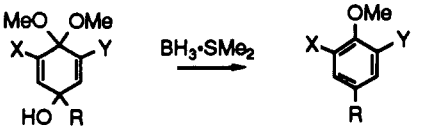
While several of the aromatic "aglycons" of the polyketide *C*-aryl glycosides have been prepared,[3] the problem of regiospecifically attaching sugar moieties to complex substrates has generally been avoided.[4] Most known methods for direct formation of *C*-aryl glycosides[5] rely on the reaction of an electron-rich aromatic with a carbohydrate-derived electrophile;[5b] some recent methods utilize palladium-mediated coupling.[5c-e]

Scheme I



Scheme II. Reductive Aromatization of Simple Quinol Ketals[a]



2 **3**

[a] (**a**) X = H, Y = H, R = CH_3, 96%; (**b**) X = H, Y = H, R = *n*-Bu, 88%; (**c**) X = H, Y = H, R = Ph, 83%; (**d**) X = H, Y = Br, R = CH_3, 85%; (**e**) X = OCH_3, Y = OCH_3, R = CH_3, 82%.

We now report an efficient *C*-aryl glycoside synthesis which is based on a novel "reverse polarity" strategy (Scheme I) and which requires no unusually hazardous or esoteric reagents. The key step is the reductive aromatization of quinol ketals, **III**, the

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† Portions of this work were described at the 199th National Meeting of the American Chemical Society, Boston, MA, April 1990; paper ORGN 165.

(1) For an excellent review, see: Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1-65.

(2) Misra, R.; Tritch, H. R.; Pandey, R. C. *J. Antibiot.* **1985**, *38*, 1280.

(3) For synthetic work on the gilvocarcin "aglycons", see: (a) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1991**, *56*, 1666. (b) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1988**, *29*, 2517. (c) McGee, L. R.; Confalone, P. N. *J. Org. Chem.* **1988**, *53*, 3695. (d) Patten, A. D.; Nguyen, N. H.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 1003. (e) Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427. (f) McKenzie, T. C.; Hassen, W.; Macdonald, S. J. F. *Tetrahedron Lett.* **1987**, *28*, 5435. McKenzie, T. C.; Hassen, W. *Tetrahedron Lett.* **1987**, *28*, 2563. (g) Hua, D. H.; Saha, S.; Maeng, J. C.; Bensoussan, D. *Synlett* **1990**, 233. (h) For previous work on glycosylation of model gilvocarcin aglycones, see ref 5e.

(4) For total syntheses of *C*-aryl glycoside natural products, see: (a) Tius, M. A.; Gu, X.-q.; Gomez-Galeno, J. *J. Am. Chem. Soc.* **1990**, *112*, 8188. (b) Nomura, K.; Okazaki, K.; Hori, K.; Yoshii, E. *J. Am. Chem. Soc.* **1987**, *109*, 3402. (c) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285.

(5) For methods which result in the direct coupling of a glycosyl moiety and an arene, see ref 4a and the following: (a) Hanessian, S.; Pernet, A. G. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 111. (b) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752 and references therein. See also the summary of methods presented in ref 5c. (c) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 2572. See also references therein. (d) Dubois, E.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1990**, 1191. (e) Kwok, D.-I.; Outten, R. A.; Huhn, R.; Daves, G. D., Jr. *J. Org. Chem.* **1988**, *53*, 5359. See also: Outten, R. A.; Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 5064; **1989**, *54*, 29. Kwok, D.-I.; Farr, R. N.; Daves, G. D., Jr. *J. Org. Chem.* **1991**, *56*, 3711. (f) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293. (g) Kraus, G. A.; Shi, J. *J. Org. Chem.* **1990**, *55*, 4922 and references therein. (h) Bellosta, V.; Czernecki, S. *Carbohydr. Res.* **1987**, *171*, 279.

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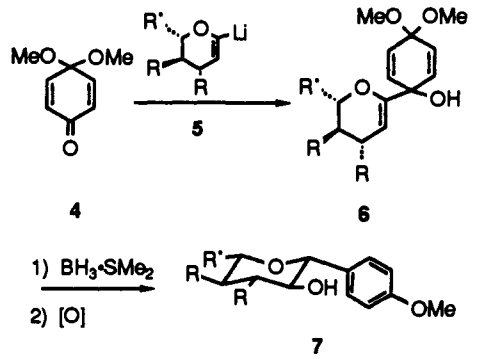
Scheme III. Model Reactions



5, 6, 7a R = R' = H
5, 6, 7b R = OTBS; R' = CH_3

adducts of C-1 lithiated glycals **I**[6a] and quinone derivatives **II**. The resulting C-1 aryl glycals **IV** can then be converted to glycosides **V** in which the substitution pattern in the sugar moiety is trans,trans at C-1′,2′,3′. Among the natural products with this substitution pattern are the gilvocarcin antitumor antibiotics.

The feasibility of the strategy shown in Scheme I was tested in model systems. However, standard conditions for the reductive aromatization of quinols[7] were not applicable to the quinol adduct of 2-lithiodihydropyran and *p*-benzoquinone.[8]

A reductive aromatization of a system synthetically equivalent to a quinol was therefore sought. The reductive aromatization of the readily available quinol ketals[9] was suggested by the known conversion of ketals to ethers by various aluminum and boron hydride reagents.[10]

Examination of the reaction of several borane reagents with the model quinol ketal **2a** revealed that reductive aromatization proceeded as projected to give *p*-methylanisole (**3a**); the optimum conditions involved treatment with borane–methyl sulfide in CH_2Cl_2 at room temperature. Likewise, substituted quinol ketals **2b–e** afforded the corresponding substituted benzenes **3b–e**. Yields were generally high (Scheme II).

In principle, treatment of a quinol ketal of type **III** (Scheme I, X = $(OMe)_2$) with excess borane–methyl sulfide could result in reductive aromatization accompanied by the desired hydroboration of the glycal double bond. This premise was tested with the model substrate **6a** (Scheme III). Treatment of quinol ketal **6a** with 1.3 molar equiv of borane–methyl sulfide followed by basic peroxide afforded a mixture, from which the *C*-aryl glycoside model **7a** was isolated in 50–60% yield.

Aromatization of the quinol moiety proceeds more rapidly than hydroboration of the electron-rich enol ether double bond.[11] Therefore, it is unlikely that aromatization involves hydroboration of one of the electron-poor quinol carbon–carbon double bonds. Furthermore, deuterioboration of ketal **6a** afforded the C-1′ deuterio **7a**; if the mechanism of the reaction had involved the deuterioboration of a quinol double bond, deuterium could have been incorporated in the aromatic ring of **7a**.

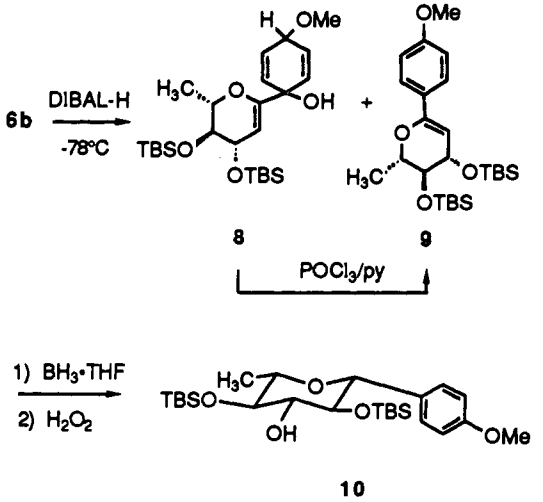
We believe, therefore, that the quinol ketal **6a** is reduced by diborane to a species in which a ketal methoxyl group is replaced by hydride to form an intermediate which eliminates water to afford an aromatized species. Subsequently hydroboration affords **7a**.

When the C-1-lithiated rhamnal derivative **5b** was added to quinone ketal **4**, quinol ketal **6b** was isolated; however, the reaction of ketal **6b** with BH_3•SMe_2 followed by alkaline hydrogen peroxide was capricious, generally affording only traces of *C*-aryl glycoside **7b**.[12]

For the relatively complex substrate **6b**, in which both reductive aromatization and hydroboration of the enol ether double bond are desired, a stepwise approach proved to be a reliable and efficient alternative. Thus, addition of ketal **6b** to DIBAL-H in CH_2Cl_2 gave a mixture of methyl ether **8** and aromatized product **9** (2:1); treatment of this mixture with $POCl_3$ in pyridine afforded **9** in 94% yield (for the two steps). Subsequent hydration of the glycal double bond (BH_3•THF/H_2O_2) gave the desired *C*-aryl glycoside **10** (in which silyl migration had occurred)[13] in 51% yield (Scheme IV).

The reductive aromatization approach to *C*-aryl glycosides creates an alternative to classical C-glycosylation methods. The position of attachment of the carbohydrate to the aromatic ring is determined by the substitution pattern of the quinol ketal starting material. We are examining applications of this methodology in

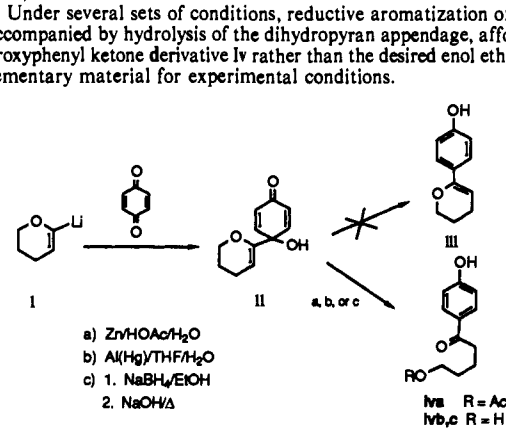
Scheme IV. Preparation of a *C*-Aryl Glycoside



(6) (a) Lesimple, P.; Beau, J.-M.; Jaurand, G.; Sinaÿ, P. *Tetrahedron Lett.* **1986**, *27*, 6201. (b) Schmidt, R. R.; Preuss, R.; Betz, R. *Tetrahedron Lett.* **1987**, *28*, 6591. (c) Lesimple, P.; Beau, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1985**, 894. (d) Beau, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1985**, *26*, 6185, 6189, 6193. (e) Lancelin, J.-M.; Morin-Allory, L.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1984**, 355. (f) Meuwly, R.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 751. (g) Valverde, S.; Garcia-Ochoa, S.; Martin-Lomas, M. *J. Chem. Soc., Chem. Commun.* **1987**, 383. (h) Lesimple, P.; Beau, J.-M.; Sinaÿ, P. *Carbohydr. Res.* **1987**, *171*, 289.

(7) (a) Manning, M. J.; Henton, D. R.; Swenton, J. S. *Tetrahedron Lett.* **1977**, 1679. (b) Evans, D. A.; Hart, D. J.; Koelsch, P. M.; Cain, P. A. *Pure Appl. Chem.* **1979**, *51*, 1285. (c) Stahly, G. P.; Bell, D. R. *J. Org. Chem.* **1989**, *54*, 2873.

(8) Under several sets of conditions, reductive aromatization of quinol ii was accompanied by hydrolysis of the dihydropyran appendage, affording the *p*-hydroxyphenyl ketone derivative Iv rather than the desired enol ether iii. See supplementary material for experimental conditions.



(9) For reviews and leading references, see: (a) Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74. (b) Swenton, J. S. *The Chemistry of the Quinoid Compounds*; Rappoport, Z., Patai, S., Eds.; John Wiley: New York, 1988; Vol. 2, Part 2, p 899.

(10) (a) Fleming, B.; Bolker, H. I. *Can. J. Chem.* **1975**, *52*, 888. (b) Bolker, H. I.; Fleming, B. I. *Can. J. Chem.* **1974**, *53*, 2818. (c) Eliel, E. L.; Badding, V. G.; Rerick, M. N. *J. Am. Chem. Soc.* **1962**, *84*, 2371. (d) Bonner, T. G.; Lewis, D.; Rutter, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1807. (e) For selective ketal reduction in the presence of a double bond, see: Borders, R. J.; Bryson, T. A. *Chem. Lett.* **1984**, 9.

(11) Evidence for this was acquired by following the progress of the reaction by ^1H NMR.

(12) In these reactions, silyl migration from the 3′-oxygen to the 2′-oxygen was not observed; see ref 13.

(13) Friesen, R. W.; Daljeet, A. K. *Tetrahedron Lett.* **1990**, *31*, 6133.

the context of gilvocarcin synthesis.

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Supplementary Material Available: Experimental procedures and spectroscopic data for ii, iva,b, **2a–e**, **6a,b**, **7a**, and **8–10** (6 pages). Ordering information is given on any current masthead page.

C_2-Symmetric Bis(phospholanes) and Their Use in Highly Enantioselective Hydrogenation Reactions†

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Asymmetric catalysis is one of the most powerful, economically feasible methods for the generation of enantiomerically enriched compounds. C_2-Symmetric chiral diphosphines have emerged as a valuable class of ligands in transition-metal-based asymmetric catalysis, and in certain cases, spectacular enantioselectivity has been observed.[1] We recently reported the preparation and use of a variety of new electron-rich chiral phospholane ligands.[2] We now describe a versatile synthetic route which allows ready access to a series of ethane-bridged bis(phospholanes) **1**, as well as the 1,2-bis(phospholano)benzene analogues **2**. High catalytic efficiencies and enantiomeric excesses (ee's) have been realized in the rhodium-catalyzed asymmetric hydrogenation of various olefinic substrates, including enol acetates where only limited success previously had been achieved.

The key intermediates in our current synthetic strategy are the 1,4-diol cyclic sulfates[3] (**4**), which were prepared from the readily available[2a,c] homochiral 1,4-diols **3** (R = Me, Et, *i*-Pr) by adaptation of a method described by Sharpless and co-workers[4] for the synthesis of 1,2-diol cyclic sulfates (Scheme I). Deprotonation of 1,2-bis(phosphino)ethane with *n*-BuLi (2 equiv) gave dilithium bis(phosphido)ethane,[5] which then was reacted with 1,4-diol cyclic sulfate **4** (2 equiv), followed, after 1 h, by a second addition of *n*-BuLi (Scheme I). Standard workup procedures directly afforded the pure 1,2-bis(phospholano)ethanes **1** in good yield (70–90%). In a similar fashion, the use of 1,2-bis(phosphino)benzene provided the 1,2-bis(phospholano)benzenes **2** (abbreviated Me-DuPHOS (R = Me); Et-DuPHOS (R = Et); *i*-Pr-DuPHOS (R = *i*-Pr)). Our interest in the DuPHOS ligands **2** derived from the expected greater rigidity of the 1,2-phenylene backbone relative to the ethano bridge of **1**. By this simple one-pot procedure, either antipode of **1** and **2** can be routinely prepared.

Scheme I

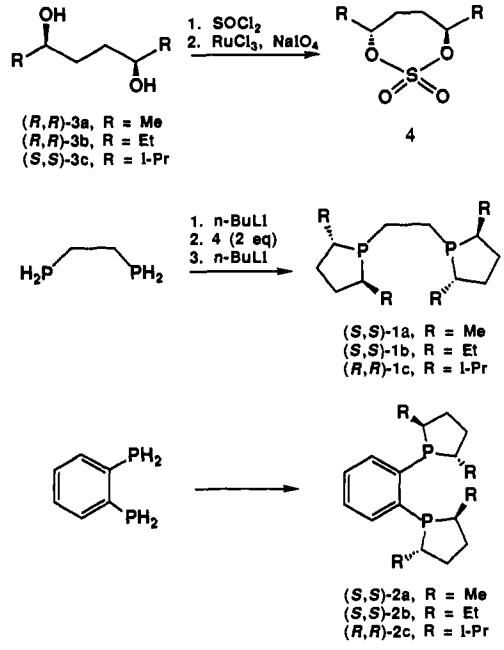

Table I. Asymmetric Hydrogenation of Acetamidoacrylates[a]

	(%ee)[b] Substrate		
Ligand	Ph, CO_2Me, N(H)Ac	i-Pr, CO_2Me, N(H)Ac	CO_2Me, N(H)Ac
1a	85	64.4	91.4
1b	93	81.2	98.1
1c	93	98.8	96.4
2a	98	95.2	99.0
2b	99	99.0	99.4
2c	87	96.9	95.4

[a] Reactions were carried out at 20–25 °C and an initial H_2 pressure of 30 psi (2 atm) with 0.25–0.35 M methanol solutions of substrate and the catalyst precursors $[(COD)Rh(P_2)]^+OTf^-$ (0.1 mol %). Reaction time for complete (100%) conversion was 1–2 h. Product absolute configurations established by sign of optical rotations; for phosphines **1a**, **1b**, **2a**, and **2b**, *R,R* and *S,S* ligands afforded *R* and *S* products, respectively; *R,R*-**1c** and *R,R*-**2c** gave *S* products. Essentially identical results were obtained at 1 atm of H_2. [b] Enantiomeric excesses were determined by chiral HPLC (Daicel Chiralcel OJ, methyl acetamidophenylalanine) or capillary GC (Chrompack XE-60-*S*-Val, methyl acetamidoleucine and methyl acetamidoalanine) as described in the supplementary material.

For the purpose of comparison, we have examined the enantioselectivity associated with the series of ligands **1** and **2** in rhodium-catalyzed hydrogenations involving the much-studied acetamidoacrylate substrates **6** (Table I). With the homochiral series of ligands **1** and **2**, we are uniquely situated to *easily and systematically vary the steric environment imposed by the phosphines without significantly varying the electronic nature of the metal centers in a corresponding series of complexes.* Using this approach, it has been possible to optimize the enantioselectivity in hydrogenations by matching the steric demand of the ligands to the substrate of interest. We find that Et-DuPHOS (**2b**) is the ligand of choice for substrates **6**, and in general, enantioselectivities consistently approaching 100% were observed; the ee's listed are as high as or higher than any previously reported[1,6] for

† Dedicated to Professor K. Barry Sharpless on the occasion of his 50th birthday.

(1) (a) Bosnich, B., Ed. *Asymmetric Catalysis*; Martinus Nijhoff Publishers: Dordrecht, 1986. (b) Kagan, H. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 1. (c) Koenig, K. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 3. (d) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. (e) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(2) (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653. (b) Burk, M. J.; Harlow, R. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1462. (c) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569.

(3) For a recent application of 1,4-diol cyclic sulfates in pyrrolidine syntheses, see: Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1990**, *35*, 3637.

(4) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 655.

(5) (a) Issleib, K.; Thorausch, P. *Phosphorus Sulfur* **1977**, *3*, 203. (b) Hey, E. *J. Organomet. Chem.* **1989**, *378*, 375.

(6) (a) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326. (b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

0002-7863/91/1513-8518$02.50/0