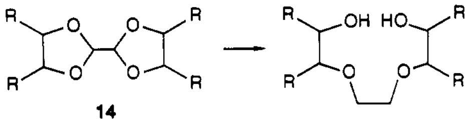
not broken in the reduction process.

It was anticipated that reduction of a 2,2′-bi-1,3-dioxolane of type **14** would produce substituted triethylene glycols **15**, which we required as precursors to substituted 18-crown-6 derivatives.



14 **15**

However the reaction of glyoxal with 1,2-diols gave a mixture of the desired 2,2′-bi-1,3-dioxolane **14** and the tetraoxadecalin isomers **16** (Scheme II).[4,9] The reaction of ethylene glycol and glyoxal produced a 70:30 mixture of **14a** (R = H) to **16a** (R = H).[10] Reduction of this mixture with either BH_3 or BH_2Cl was complicated by the presence of **16**: the bidioxolane **14a** reduced cleanly to triethylene glycol (confirmed by the reduction of a pure sample of **14a** obtained by fractional recrystallization). However the tetraoxadecalin **16** can yield triethylene glycol if bonds labeled a and b are cleaved but also dioxane and ethylene glycol if bonds a and c are reduced. The latter appears to be the more favored mode. The reaction of (*S*,*S*)-2,3-butanediol with glyoxal gave a 1:1 mixture of **14b** (R = CH_3) and **16b** (R = CH_3).[10] We were unable to separate this mixture, and reduction of the mixture with monochloroborane gave only a 30% yield of (*S*,*S*,*S*,*S*)-3,8-dimethyl-2,9-decanediol after chromatography on silica gel.[11] We are currently developing alternative procedures for the preparation of substituted triethylene glycols of type **15**.

We also found that bis(hemithioacetals) **17** and **18**, prepared from **3** and the appropriate mercapto alcohol, were reduced to the dithioether diols **19** (OH stretch at 3336 cm^{-1})[8] and **20**[12] in good yields (Scheme III). Under no circumstances did we see the cleavage of a C–S bond in these reductions.[13] This procedure is complementary to other work in our laboratories wherein the C–S bond in these systems is reduced by tributyltin hydride (TBTH) to the isomeric diether dimercaptan **21** (SH stretch at 2550 cm^{-1}).[14] The hemithioacetal carbons in **17** and **18** are chiral, so these compounds are produced as mixtures of diastereomers. Destruction of the chiral centers by reduction produced the products **19** and **20**, each as a single compound.

In conclusion, the selective reduction of bis(cyclic acetals) by borane (or monochloroborane) is a viable way to produce diether diols bearing several substituents. Reduction of bis(hemithioacetals) produces dithioether diols. The procedure is conceptually and experimentally simple and provides the essentially pure products in high yield. We are presently elaborating these diether diols, and dithioether diols, into substituted crown ether compounds and/or to crowns bearing both oxygen and sulfur donor atoms.

Acknowledgment. We thank the National Institutes of Health [NIGMS-MARC (GM 08228) and MBRS-DRR (S06 RR-08101)] for support of this work.

Registry No. **3**, 102-52-3; **4**, 4405-17-8; **5**, 67439-82-1; **6**, 116261-28-0; **7**, 30963-84-9; **8**, 30859-70-2; **9**, 116185-04-7; **10**, 116185-05-8; **11**, 4161-32-4; **12**, 116185-06-9; **13**, 116210-21-0; **14a**, 6705-89-1; **14b**, 116261-29-1; **15a**, 112-27-6; **16a**, 4362-05-4; **16b**, 38737-48-3; **17** (isomer 1), 116185-08-1; **17** (isomer 2), 116210-22-1; **18** (isomer 1), 116185-09-2; **18** (isomer 2), 116185-10-5; **19**, 76124-47-5; **20**, 16260-48-3; **21**, 88458-55-3; $HO(CH_2)_2OH$, 463-57-0; OHCCHO, 107-22-2; (2*S*,3*S*)-2,3-butanediol, 19132-06-0; (*S*,*S*,*S*,*S*)-3,8-dimethyl-2,8-decanediol, 116185-07-0; 1,3-propanediol, 504-63-2; 2,2-dimethyl-1,3-propanediol, 126-30-7; (*S*,*S*)-2,4-pentanediol, 72345-23-4; *o*-mercaptobenzyl alcohol, 4521-31-7; 2-mercaptoethanol, 60-24-2.

Supplementary Material Available: Experimental procedures for compounds **6** and **10**; combustion analyses, complete ^1H NMR spectra, and selected IR data for compounds **6**, **8–10**, **12**, **13**, **17**, and **19** and for the mixture **14b** and **16b** (2 pages). Ordering information is given on any current masthead page.

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[9] Sprung, M. M.; Guenther, F. O. *J. Am. Chem. Soc.* **1951**, *73*, 1884.

[10] The composition of the bidioxolane and tetraoxadecalin mixture was determined by ^1H NMR. E. Caspi, Th. A. Wittstruck, and D. M. Piatak (*J. Am. Chem. Soc.* **1962**, *27*, 3183) have found that the chemical shift of the methine protons in **14a** and **16a** depends on the ring size of the heterocycle. In bidioxolane **14a** they absorb at ∂ = 4.85 ppm; those on the tetraoxadecalin **16a** at ∂ = 4.65 ppm. We found that this trend toward lower field for the dioxolane acetal methine protons relative to the dioxane acetal methine protons was consistent with the shifts (in $CDCl_3$) observed in unambiguous compounds: **4** (4.95 ppm) and **7** (4.45 ppm); **6** (5.15 ppm) and **9** (4.85 ppm). Extending this, we assigned the absorbance at 4.85 ppm to the acetal methine protons in tetramethylbidioxolane **14b** and the resonance at 4.65 to those on tetramethyltetraoxadecalin **16b**.

[11] There is evidence that perchlorate salts selectively complex bis(dioxolanes) in preference to the isomeric tetraoxadecalins. We are currently pursuing this as a means of purifying **14b**: Chastrette, F.; Hassambay, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* **1976**, *607*, 613.

[12] Rosen, W.; Busch, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 4694.

[13] A TLC comparison (with authentic samples of **20** and **21**) showed that the crude reaction product exhibited only the one spot by TLC, which corresponded to the dithioether diol **20**. Also, no S–H stretch was observed in the infrared.

[14] Alexis, C. P.; Uribe, J.; Gutierrez, C. G., unpublished results.

Facile Synthesis of 2,6-Dialkylphenols by Cross-Aromatization of Cyclohexanones with Aldehydes Catalyzed by Zirconocene Complexes

Summary: 2,6-Dialkylphenols, which are difficult to prepare by conventional methods, have been conveniently synthesized in one step via zirconocene-catalyzed cross-aromatization of cyclohexanones with aldehydes.

Sir: Although phenol derivatives are versatile compounds from the pharmaceutical and industrial points of view, there is no practical method available to prepare 2,6-dialkylphenols except for 2,6-dimethyl- or 2,6-di-*tert*-butylphenol derivatives.[1] Direct alkylation of phenols with olefins,[2] alcohols,[3] or alkyl halides[4] generally results in mixtures of mono- and polysubstituted phenols alkylated preferentially at the para position. 2,6-Dibenzylphenol has been synthesized by $IrCl(CO)(PPh_3)_2$-catalyzed isoaromatization of 2,6-dibenzylidenecyclohexanone,[5] derived

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[1] (a) Fullerton, T. J.; Ahern, S. P. *Tetrahedron Lett.* **1976**, 139. (b) Nishinaga, A.; Tominaga, H.; Matsuura, T. *Tetrahedron Lett.* **1980**, *21*, 1261. (c) Nishinaga, A.; Tominaga, H.; Tarumi, Y.; Matsuura, T. *Tetrahedron Lett.* **1980**, *21*, 2833.

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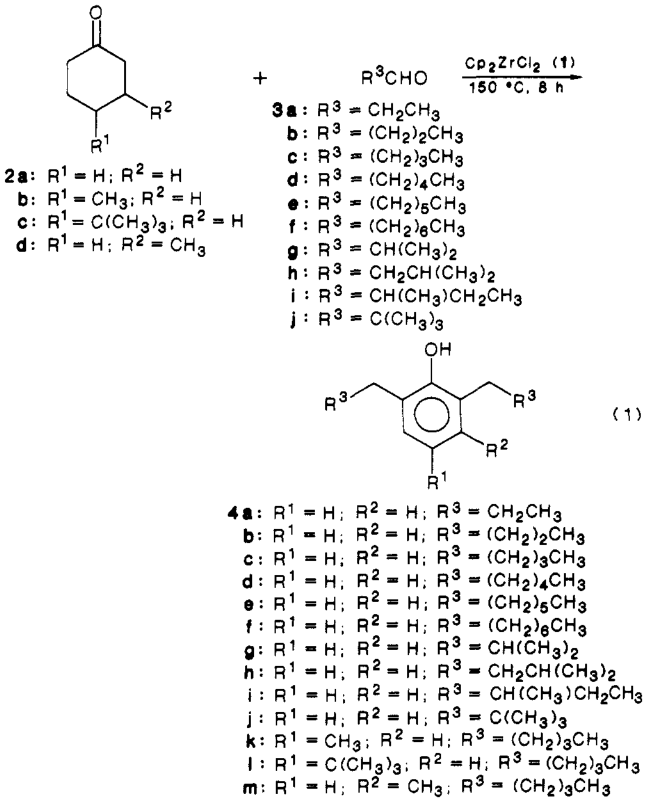
readily from aldol condensation of cyclohexanone with benzaldehyde in basic media.[6] However, this strategy cannot be extended to the general preparation of 2,6-disubstituted alkylphenols because of the difficulty in preparing the precursors, 2,6-dialkylidenecyclohexanones.[7]

Recently we reported that bis(η^5-cyclopentadienyl)zirconium dihydride, Cp_2ZrH_2, catalyzes the hydrogen-transfer reaction of alcohols to carbonyl compounds, i.e., Meerwein–Ponndorf–Verley type reduction and Oppenauer type oxidation.[8] In addition, Cp_2ZrH_2 also catalyzes selective cross-condensations between alicyclic ketones and aldehydes or primary alcohols, which give 2-alkylidenecycloalkanones or 2-alkylcycloalkenones, respectively.[9] In the course of studies to extend the scope of zirconocene-catalyzed reactions, we found that bis(η^5-cyclopentadienyl)zirconium dichloride, Cp_2ZrCl_2 (**1**), is a highly efficient catalyst for the cross-aromatization of cyclohexanones (**2**) with aldehydes (**3**) and affords 2,6-dialkylphenols (**4**) with high selectivity (eq 1).



The use of 2 equiv of **3d** to 1 equiv of **2a** under the influence of a catalytic amount (0.1 equiv) of **1** at 150 °C for 8 h without solvent was found to be optimal to give 2,6-dihexylphenol (**4d**) in 96% yield. The cross-aromatization of **2a** with a variety of aldehydes (**3a–j**) was carried out under these conditions. These results are shown in Table I.

The reaction by homologues of **1**, Cp_2TiCl_2 and Cp_2HfCl_2, gave **4d** in 77% and 69% yields, respectively.

Table I. Group IV$_A$ Metallocene Complex Catalyzed Cross-Aromatization of Cyclohexanones (2a–d) with Aldehydes (3a–j)[a]

run	ketone	aldehyde	catalyst	product	yield,[b] %
1	**2a**	**3a**	Cp_2ZrCl_2 (**1**)	**4a**	75 (69)
2	**2a**	**3b**	**1**	**4b**	83 (79)
3	**2a**	**3c**	**1**	**4c**	83 (78)
4	**2a**	**3d**	**1**	**4d**	96 (81)
5	**2a**	**3d**	**1**	**4d**	81[c]
6	**2a**	**3d**	Cp_2TiCl_2	**4d**	77
7	**2a**	**3d**	Cp_2HfCl_2	**4d**	69
8	**2a**	**3d**	Cp_2ZrH_2	**4d**	74[d]
9	**2a**	**3d**	$Cp_2Zr(O\text{-}^iPr)_2$	**4d**	71[d]
10	**2a**	**3d**	$Cp_2Zr(H)Cl$	**4d**	90
11	**2a**	**3e**	**1**	**4e**	84 (79)
12	**2a**	**3f**	**1**	**4f**	– (64)
13	**2a**	**3g**	**1**	**4g**	22 (16)
14	**2a**	**3h**	**1**	**4h**	87 (75)
15	**2a**	**3i**	**1**	**4i**	31 (22)
16	**2a**	**3j**	**1**	**4j**	43 (37)
17	**2b**	**3c**	**1**	**4k**	71 (63)
18	**2c**	**3c**	**1**	**4l**	60 (48)
19	**2d**	**3c**	**1**	**4m**	47 (40)
20	**2a**	**3k**	**1**	**5**	88 (81)
21	**2a**	**3l**	**1**	**6**	84 (78)

[a] A mixture of catalyst (1 mmol), **2** (10 mmol), and **3** (20 mmol) was allowed to react at 150 °C for 8 h. [b] Determined by VPC. The number of parentheses showed the isolated yields. [c] **1** (0.2 mmol) was used. [d] The yield of 2-hexylidenecyclohexanone.

In the case of Cp_2ZrH_2 and $Cp_2Zr(O\text{-}^iPr)_2$, as reported previously,[9] the reaction stopped at the stage of monocondensation to form 2-hexylidenecyclohexanone. Although $Cp_2Zr(H)Cl$ afforded **4d** in relatively high yield (90%), there is little advantage in its use as the catalyst since $Cp_2Zr(H)Cl$ is prepared by the reduction of **1** with $LiAlH_4$.

Surprisingly, 2,6-dialkylphenols (**4a–f**), which are very difficult to prepare by the conventional method,[10-12] are synthesized by the one-step reaction of **2a** with linear aldehydes (**3a–f**) in satisfactory yields (75–96%). The reaction with branched aldehdyes (**3g–j**), especially **3g**, took place with difficulty to bring about 2,6-diisobutylphenol (**4g**) in low yield (22%). Contrary to our expectation, sterically crowded pivalaldehyde **3j** reacted with **2a**, giving 2,6-bis(2,2-dimethylpropyl)phenol (**4j**) in fair yield (43%).

The cross-aromatization of substituted cyclohexanones with aldehydes proceeded in a similar manner as **2a**. For example, 4-methyl- or 4-*tert*-butylcyclohexanones, **2b** and **2c**, reacted with **3c** to afford the corresponding phenols, 4-methyl-2,6-dipentylphenol (**4k**) and 4-*tert*-butyl-2,6-dipentylphenol (**4l**), in 71% and 60% yields, respectively.

From the synthetic point of view, it is interesting and important that 3-methyl-2,6-dipentylphenol (**4m**) was obtained from the reaction of 3-methylcyclohexanone (**2d**) with **3c**, since meta-substituted phenol derivatives are difficult to synthesize by known methods.[5]

With α,β-unsaturated aldehydes such as cinnamaldehyde (**3k**) or furfural (**3l**), **2a** gave biscondensation products, 2(*E*),6(*E*)-dicinnamylidenecyclohexanone (**5**) and 2(*E*),6(*E*)-difurfurylidenecyclocyclohexanone (**6**), respectively, in good yield,[13] but the reaction terminated at this

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[5] Pickholtz, Y.; Sasson, Y.; Blum, Y. *Tetrahedron Lett.* **1974**, 1263.

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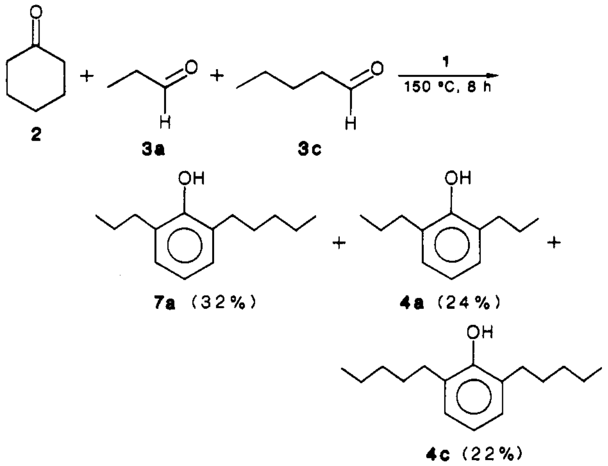
[12] Andrieux, J.; Barton, D. H. r.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.

[13] Dialklylidenecyclohexanones, **5** and **6**, are isoaromatized by some group VIII metal catalysts (e.g., $RuCl_2(PPh_3)_3$ or $RhCl(PPh_3)_3$) under reratively severe conditions.[5,14]

[14] (a) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2561. (b) Sasson, Y.; Blum, J. *Synthesis* **1973**, 359.

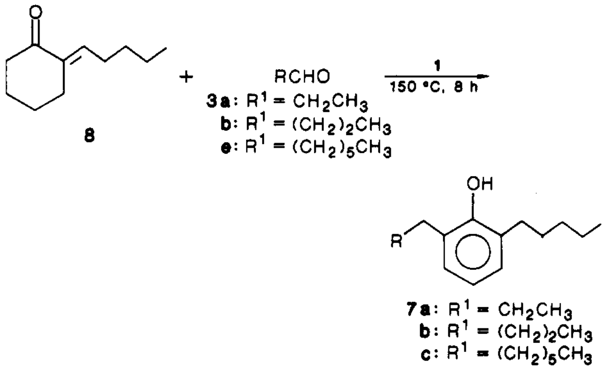
stage probably because of the stability of the resulting conjugated alkylidene compounds.

The preparation of unsymmetrical 2,6-dialkylphenols substituted by different alkyl substituents may further enhance the utility of the present method. Thus, **2a** was allowed to react with a equimolar mixture of different kinds of aldehydes, **3a** and **3c**. As expected, 2-pentyl-6-propylphenol (**7a**) was formed in 32% yield together with symmetrical phenols, **4a** (24%) and **4c** (22%) (eq 2).



(2)

This problem was solved by employing a two-step sequence involving the reaction between 2-alkylidenecycloalkanones and aldehydes. The reaction of 2-pentylidenecyclohexanone (**8**), prepared in advance by Cp_2ZrH_2-catalyzed cross-condensation of **2a** with **3c**,[9] with aldehydes **3** in the presence of **1** afforded unsymmetrical phenols (**7**) in good yields. 2-Pentyl-6-propylphenol (**7a**), 2-butyl-6-pentylphenol (**7b**), and 2-heptyl-6-pentylphenol (**7c**) were synthesized from the reaction with **3a**, **3b**, and **3e**, respectively, in high yields (eq 3).



(3)

Although the detailed mechanism remains unclear, it is probable that the present cross-aromatization proceeds via continuous three steps: (i) double aldol condensation of **2** with **3** to give 2,6-dialkylidenecyclohexanone, (ii) isomerization of an exo-cyclic double bond to an endo-cyclic one, and (iii) aromatization to **4**. These processes fully conform to the driving force of the formation of thermodynamically favored products.

In conclusion, this efficient synthesis of a wide variety of substituted phenols offers great synthetic versatility.

Registry No. **1**, 1291-32-3; **2a**, 108-94-1; **2b**, 589-92-4; **2c**, 98-53-3; **2d**, 591-24-2; **3a**, 123-38-6; **3b**, 123-72-8; **3c**, 110-62-3; **3d**, 66-25-1; **3e**, 111-71-7; **3f**, 124-13-0; **3g**, 78-84-2; **3h**, 590-86-3; **3i**, 96-17-3; **3j**, 630-19-3; **3k**, 104-55-2; **3l**, 98-01-1; **4a**, 6626-32-0; **4b**, 62083-20-9; **4c**, 116374-97-1; **4d**, 91069-45-3; **4e**, 116374-98-2; **4f**, 3307-31-1; **4g**, 52348-51-3; **4h**, 116374-99-3; **4i**, 54116-67-5; **4j**, 81216-68-4; **4k**, 116375-00-9; **4l**, 116375-01-0; **4m**, 116405-66-4; **5**, 116375-02-1; **6**, 62085-75-0; **7a**, 116375-03-2; **7b**, 116375-04-3; **7c**, 116375-05-4; **8**, 25677-40-1; Cp_2TiCl_2, 1271-19-8; Cp_2HfCl_2, 12116-66-4; Cp_2ZrH_2, 37342-98-6; $Cp_2Zr(O\text{-}{}^{i}Pr)_2$, 78091-18-6; $Cp_2Zr(H)Cl$, 37342-97-5.

Supplementary Material Available: General experimental procedures and spectral data for metallocene complexes, **4a–m**, **5–8** (8 pages). Ordering information is given on any current masthead page.

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Comparative Analysis via Secondary Deuterium Isotope Effects of Transition State Structural Features Associated with Cycloadditions to Norbornadiene[$2_\pi + 2_\pi + 2_\pi$] and Quadricyclane-[$2_\sigma + 2_\sigma + 2_\pi$]

Summary: Quadricyclane-*1-d* and norbornadiene-*2-d* undergo cycloaddition to 2π addends of differing reactivity to give products wherein the distribution of deuterium is commensurate with the operation of concerted processes but with asynchronous capture of the attacking reagent.

Sir: Whereas the valence isomeric ring systems described by norbornadiene (N) and quadricyclane (Q)[2] present a similar steric profile to attacking reagents, they differ appreciably in having sets of frontier orbitals of inverse symmetry.[3] Adherence by N and Q to orbital symmetry restrictions consequently allows for operation of contrasting types of cycloaddition chemistry. While experimental documentation of the orbital-correlated processes abound,[4,5] the homo-Diels–Alder reactivity exhibited by N is not commonly found in other bridged dienes[6] because

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(1) Postdoctoral fellowship awardee of the Deutsche Forschungsgemeinschaft, 1985–1986.

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