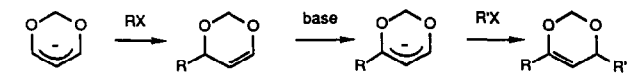
Tetrahedron Letters,Vol.29,No.10,pp 1111-1114,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF 4,6-DIALKYL-1,3-DIOXINS. VERSATILE INTERMEDIATES FOR THE PREPARATION OF (E)-ALKENONES, *anti,anti*-1,2,3-TRIOLS AND *syn*-1,3-DIOLS

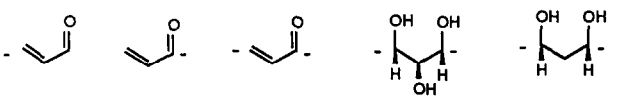
Raymond L. Funk[1,*] and Gary L. Bolton
Department of Chemistry
University of Nebraska
Lincoln, Nebraska 68588

Summary: The title compounds 4 are prepared from 4-alkyldioxins 2 via a metalation, alkylation sequence. The dialkyl dioxins 4 are thermally labile (providing enones) and undergo highly stereoselective hydroboration or hydrogenation reactions to provide *anti,anti*-1,2,3-triols and *syn*-1,3-diols, respectively. This methodology has been exploited in the synthesis of (±)-endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane.

We recently reported that the allyl anion 1 represents an improvement in β-acyl vinyl anion (5) methodology.[2] Thus, anion 1 is obtained by exclusive allylic deprotonation of readily available 4*H*-1,3-dioxin[3] with *sec*-butyllithium and can be alkylated with a variety of electrophiles to provide monosubstituted dioxins 2. The dioxins 2 can then be *thermally* converted to formaldehyde and the desired α,β-unsaturated aldehydes (5 + R⁺) via a novel retro Diels-Alder reaction. We now disclose our studies concerning a second metalation alkylation sequence (cf. 2→3→4) and subsequent transformations of the resulting disubstituted dioxins 4. Overall, these synthetic operations constitute new methods which correspond to the umpoled synthons 6-9.

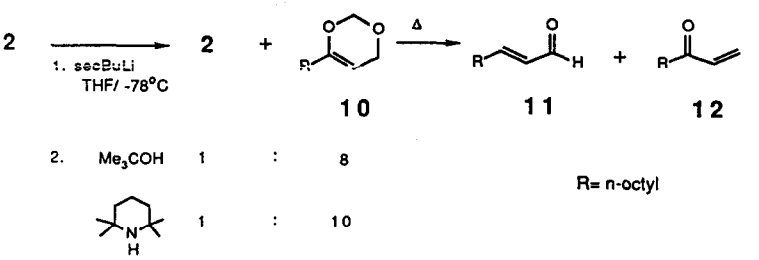


1 2 3 4



5 6 7 8 9

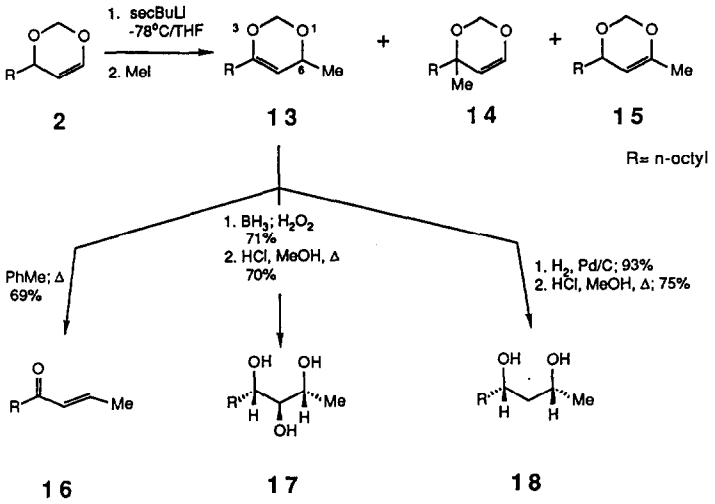
Deprotonation of n-octyl dioxin 2 with *sec*-butyllithium proceeded smoothly (-78°C) to provide an anion which was quenched with excess *t*-butanol. The crude reaction product consisted



10 11 12

solely of a new isomeric dioxin 10 and recovered dioxin 2 (8:1). The regiocontrol during the protonation step could be modestly improved (10:1) by using the less acidic and sterically more encumbered tetramethylpiperidine as the proton source. Thermolysis of the 10:1 mixture of dioxins 10 and 2 (refluxing toluene, 10 h) afforded a chromatographically separable mixture of enone 12 and enal 11. The enone 12 was isolated in 80% yield starting from dioxin 2 and completes the sequence which demonstrates the equivalency to synthon 6.[5]

These experiments establish that the most kinetically acidic proton in 4*H*-alkyl-1,3-dioxins is the tertiary allylic proton rather than the α-vinyl proton as was similarly observed for the simple unsubstituted 4*H*-1,3-dioxin. However, allylic deprotonation of 2 is not exclusive. Thus, alkylation of the anion generated from octyl dioxin 2 with MeI afforded a mixture of three disubstituted dioxins 13,14,15 (20:1:1, 70%). The dioxin 15 is most likely obtained from the corresponding α-vinyl anion [6] whereas dioxins 13 and 14 are regioisomeric alkylation products derived from allyl anion 3 (R=octyl).



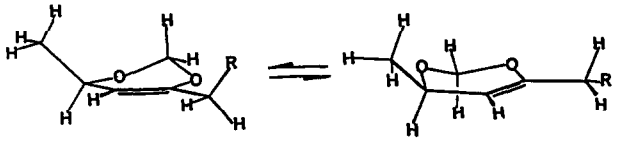
2 13 14 15

16 17 18

The major disubstituted dioxin 13 could be purified by silica gel chromatography and was subjected to three separate reactions (thermolysis, anti-Markovnikov hydration, and hydrogenation) which consummate the correlations with synthons 7[7], 8, and 9, respectively. Thus, a toluene solution of 13 was refluxed and produced the retro-Diels Alder product, enone 16, in 69% yield. Hydroboration (BH_3, THF, 0°C) of 13 proceeded with complete stereoselectivity from the face opposite the 6-methyl substituent (>98:2 by ^{13}C NMR) to provide after oxidative workup (H_2O_2) a single 5-hydroxy-substituted dioxin (71%) which was then hydrolysed (1M HCl, MeOH, reflux) to the desired *anti,anti*-triol 17.[8] Excellent diastereofacial discrimination was similarly observed in the hydrogenation reaction of 13 (5% Pd/C, MeOH, 91%) to provide only the *syn*-1,3-diol 18 (>98:2 by ^{13}C NMR) after hydrolysis (1M HCl, MeOH, reflux, 75%).

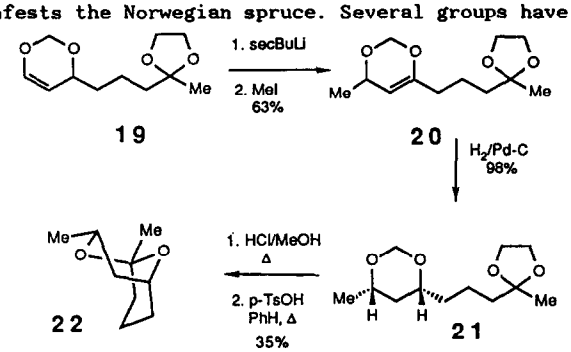
It is instructive to compare the stereoselectivities observed in the hydroboration and hydrogenation reactions of 13 with those reported for 1,3-dimethylcyclohexene. The hydroboration reaction was reported by Brown[9] to give only the *trans,trans* isomer, albeit the more selective 9-BBN reagent was employed. However, the hydrogenation reaction reported by Augustine[10] using 5%

Pd/C in ethanol is much less stereoselective and gives a 4:1 mixture of cis- and trans-1,3-dimethylcyclohexane. The diminished stereoselectivity in Augustine's work may reflect the conformational differences between 1,3-dimethylcyclohexene and dioxin 13. The main conformation of cyclohexene is the half-chair,[11] whereas recent NMR evidence suggests that 4*H*-1,3-dioxin prefers the 1,2 diplanar(sofa)C_2 conformation (A or B).[3] Moreover, catalyst adsorption may be assisted by the O(3) axial lone pair[12] in dioxin 13 which is clearly more accessible in conformer A (sofa with pseudo-axial methyl) leading to the observed product rather than conformer B (sofa with pseudo equatorial methyl).[13]



A B

Finally, we have exploited this methodology in a concise, stereospecific total synthesis of (±)-endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (22), a host specific substance for the ambrosia beetle which infests the Norwegian spruce. Several groups have reported syntheses of



22[14] in the context of testing new synthetic methods for the preparation of *syn*-1,3-diols.[15] To that end, compound 19 was prepared by alkylation of 1 with 2-(3-iodopropyl)-2-methyldioxolane (82%). Metalation of dioxin 19 with *sec*-butyllithium followed by methylation gave the disubstituted dioxin 20 (63%) which, upon hydrogenation (H_2, Pd/C), furnished *only* the *syn*-1,3-dioxane 21 (98%). Simultaneous hydrolysis of the acetal and ketal functionalities of 21 gave rise to *syn*-6,8-dihydroxy-2-nonanone as well as some bicyclic ketal 22. Brief treatment of this mixture with p-TsOH in benzene completed the internal ketalization reaction to provide the extremely volatile bicycle 22 (35%) whose ^{1}H NMR spectrum was indistinguishable from that reported in the literature.

In summation, we have shown that 4-alkyl-1,3-dioxins can be converted to the corresponding allyl anions and then protonated or alkylated with high regioselectivity. The resulting products are subject to facile thermal retrocycloaddition to provide conjugated enones. Moreover, these substituted dioxins undergo hydroboration and hydrogenation reactions ultimately to afford *anti,anti*-1,2,3 triols and *syn*-1,3 diols with complete stereoselectivity. The diastereofacial bias of the substituted dioxins 2 and 4 might also be expressed in other types of reactions (e.g cycloadditions) and these investigations will be reported in due course.

Acknowledgment. We thank the National Science Foundation (CHE-8205144), National Institutes of Health (GM-28663), and Eli Lilly and Company for financial support. High-field (360 MHz) ^{1}H and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (CHE80-24328); mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (CHE-82-11164).

References

1. Fellow of the Alfred P. Sloan Foundation, 1985-1989. Address correspondence to Department of Chemistry, 152 Davey Laboratory, The Pennsylvania State University, University Park, PA 16802.
2. Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.*, in press.
3. Anteunis, M.; Camerlynck, R. *Tetrahedron* **1975**, *31*, 1837.
4. For definition and compilations of umpoled synthons, see (a) Seebach, D. *Angew. Chem. Intl. Ed. Engl.* **1979**, *18*, 239. (b) Hase, T. A. "Umpoled Synthons. A Survey of Sources and Uses in Synthesis" **1987**, Wiley, New York.
5. For other synthetic equivalents of the acyl anion **6**, see: (a) Corbel, B.; Paugam, J. P.; Drevy, M.; Savignac, P. *Tetrahedron Lett.* **1976**, 835. (b) Gould, S. J.; Remillard, B. D. *ibid.* **1978**, 4353.
6. For the alkylation of the α-vinyl anion derived from metalation of 1,3-dibutoxypropene, see reference 5b.
7. For other synthetic equivalents of the dianion **7**, see: (a) Reich, H. J.; Shah, S. K. *J. Am. Chem. Soc.* **1977**, *99*, 263. (b) Reich, H. J.; Shah, S. K.; Gold, P. M.; Olson, R. E. *Ibid.* **1981**, *103*, 3112. (c) Reich, H. J.; Clark, M. C.; Willis, W. W., Jr. *J. Org. Chem.* **1982**, *47*, 1618. (d) Clinet, J. C.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 1137. (e) *Ibid.* **1976**, 835.
8. The stereochemical assignment for **17** was based on 8.8 Hz coupling constants for both H_4,H_5 and H_5,H_6 in the corresponding hydroxy-substituted dioxin.
9. Brown, H. C.; Brener, L. *J. Org. Chem.* **1977**, *42*, 2702. For the hydroboration of more highly substituted 1,3-dialkylcyclohexenes, see: Robinson, M. J. T.; Gordon, M. H. *Tetrahedron Lett.* **1975**, 3867.
10. Augustine, R. L.; Yaghmaie, F. *J. Org. Chem.* **1987**, *52*, 1863.
11. See reference 3 for leading references.
12. For previous examples of heterogeneous catalytic hydrogenation reactions which benefit from heteroatom-assisted adsorption to the catalyst surface, see: (a) Thompson, H. W.; Wong, J. K. *J. Org. Chem.* **1985**, *50*, 4270. (b) Mundy, B. P.; Wilkening, D. *Ibid.* **1985**, *50*, 5727.
13. MNDO calculations identify the sofa conformations of dioxin **13** as true minima and place the axial conformer **A** slightly higher in energy than the equatorial conformer **B** (R=H, $\Delta\Delta H_f$ = 0.3 kcal/mol). Sofa conformations have also been implicated in the alkylation reactions of *cis*-2-*t*-butyl-6-methyl-1,3-dioxin-4-one enolates wherein a similar diastereofacial selectivity is observed, see: Seebach, D.; Zimmerman, J. *Helv. Chim. Acta.* **1986**, *69*, 1147.
14. (a) Adams, J.; Frenett, R. *Tetrahedron Lett.* **1987**, *28*, 4773. (b) Gerlach, H.; Kunzler, P. *Helv. Chem. Acta* **1977**, *60*, 638. (c) Redlich, H.; Schneider, B.; Francke, W. *Tetrahedron Lett.* **1980**, *21*, 3013. (d) Sato, T.; Itoh, T.; Hattori, C.; Fujisawa, T. *Chem. Lett.* **1983**, 1391. (e) Kongkathip, B.; Kongkathip, N. *Tetrahedron Lett.* **1984**, *25*, 2175. (f) Nakata, T.; Nagao, S.; Takao, S.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 73. (g) Guidon, Y.; St-Denis, Y.; Daigneault, S.; Morton, H. E. *Ibid.* **1986**, *27*, 1237. (h) Mohr, P.; Tamm, C. *Ibid.* **1987**, *28*, 395. (i) Ghiringhelli, D.; Bernardi, R. *J. Org. Chem.* **1987**, *52*, 5021.
15. For other methodology, in addition to that cited in reference 14, for the preparation of *syn*-1,3-diols, see: (a) Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* **1987**, *109*, 6556 and reference 4 therein. (b) Mohr, P.; Tamm, C. *Tetrahedron Lett.* **1987**, *25*, 391 and reference 1 therein. (c) Kiyooka, S.-Y.; Duroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3004. (d) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Ibid.* **1987**, *28*, 155. (e) Solladie, G.; Hutt, J. *Ibid.* **1987**, *28*, 797. (f) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 1043. (g) Feldman, K. S.; Simpson, R. E.; Parvez, M. *J. Am. Chem. Soc.* **1986**, *108*, 1328. (h) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *Ibid.* **1986**, *108*, 6090.

(Received in USA 14 December 1987)