ethenes (**4a,b**) and 1,1-dicyano-1-alkenes (**6a,b**) underwent the three component coupling reactions with allylic stannanes and methyl iodide, giving the corresponding products **5a,b** and **7a,b**[14,15] (see Scheme III).

An important feature of the above reactions is that the coupling reactions occur efficiently under neutral, mild conditions in a highly regioselective manner. The functional group compatibility in these reactions is also wide. For example, this reaction tolerates the presence of some functional groups and can be applied to the compounds with carbonyl and lactone functionalities (Table I).

The detailed mechanism and synthetic applications of the above three component coupling reaction are now under investigation.

**Acknowledgment.** This work was partially supported by a Grant-in-Aid for Special Project Research from the Ministry of Education, Science, and Culture of Japan (no. 61225024 and 62215032).

**Supplementary Material Available:** NMR data given for **3a-u**, **5a,b**, and **7a,b** (9 pages). Ordering information is given on any current masthead page.

(13) The nucleophilic alkyl radical first attacks 1,1-dicyanoethenes rather than allylic stannanes; however, the new radical so produced has an electrophilic nature and attacks allylic stannanes in a manner shown in Scheme II: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: London, 1976; Chapter 5.

(14) The reactivity of the electron-deficient alkenes decreased in the order: **1a > 6a > 4a**.

(15) (*E*)-1-Nitro-2-phenylethene, (*E*)-1-cyano-2-phenylethene, 1,1-dicyano-2-phenyl-1-propene, and cyclohexylidenepropanedinitrile were unreactive under similar conditions.

## Metalation and Alkylation of 4*H*-1,3-Dioxin: A New β-Acyl Vinyl Anion Equivalent

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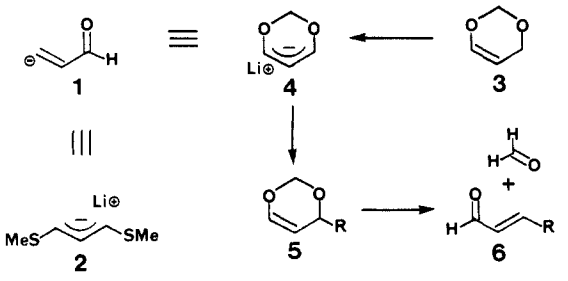
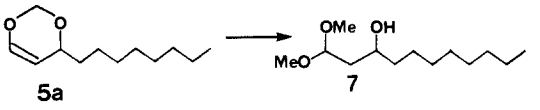
Synthetic equivalents of the β-acyl vinyl anion **1** have been extensively pursued[2] since the first report by Corey[3] that 1,3-bis(methylthio)allyllithium (**2**) functions in this capacity. All of



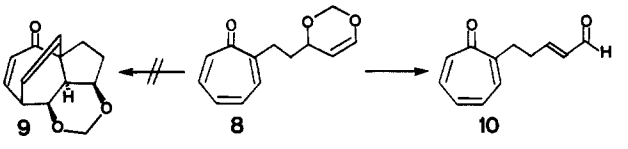

these methods require at least one reagent-mediated step to unravel the α,β-unsaturated aldehyde **6** from the alkylated synthetic equivalent. For example, the Corey method requires a hydrolytic step with use of mercuric chloride in warm, aqueous acetonitrile.[3] In some situations, it may become necessary to generate the α,β-unsaturated aldehyde by using even milder conditions. We describe herein a possible solution to this problem. In particular, we show that a new β-acyl vinyl anion equivalent, allyl anion **4**, affords alkylation products which then are simply heated in order to promote a facile bis-hetero retro-Diels-Alder reaction (**5** → **6**) and unmask the α,β-unsaturated aldehyde.

We have found that 4*H*-1,3-dioxin (**3**)[4] undergoes rapid metalation upon treatment with *sec*-butyllithium in THF at −78 °C to provide only the allylic anion **4**.[5] The various electrophiles employed in alkylation reactions with allyl anion **4** are shown in Table I. Typically, the alkylating agent was added to a solution of anion **4** (1.5 equiv, THF, −78 °C) and allowed to warm to room temperature before quenching the reaction mixture with aqueous $NaHCO_3$. The resulting 4-substituted 4*H*-1,3-dioxins **5** were then




isolated in good yields by using silica gel chromatography. It is worthwhile to note that none of the compounds **5** showed any tendency to decompose on silica gel. In fact, octyldioxin (**5a**) is stable to pyridinium tosylate (0.1 equiv) in refluxing MeOH (12 h). However, treatment of **5a** under more acidic conditions (HCl, MeOH, 0 °C; 1 h) did provide the β-hydroxy acetal **7** (90%).

Although liberation of the desired α,β-unsaturated aldehydes **6** could be accomplished by using aqueous acid, a much more convenient and milder procedure was discovered serendipitously. Thus, an attempted intramolecular Diels-Alder cycloaddition reaction of 2-[2-(dioxinyl)ethyl]tropone[8] (**8**) in refluxing toluene




gave none of the desired cycloadduct **9** but, instead, furnished aldehyde **10** and "white material" that collected on the condenser. Evidently, a bis-hetero retrocycloaddition[9] reaction had intervened. It might be argued that this result should have been anticipated based on a report that benzylidenemalonaldehyde[10] equilibrates with the Diels-Alder cycloadduct dimer at room temperature and that acrolein and hexafluoroacetone produce a [4 + 2] cycloadduct.[11] Nonetheless, the susceptibility of substituted 4*H*-1,3-dioxins to [4 + 2] retrocycloaddition has not been previously documented,[12] despite numerous preparations of these com-

(1) Fellow of the Alfred P. Sloan Foundation, 1985-1987. Address correspondence to Department of Chemistry, 152 Davey Laboratory, The Pennsylvania State University, University Park, PA 16802.

(2) (a) Reich, H. J.; Clark, M. C.; Willis, W. W., Jr. *J. Org. Chem.* **1982**, *47*, 1618. (b) Oshima, K.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1567. (c) Wada, M.; Nakamura, H.; Taguchi, T.; Takei, H. *Chem. Lett.* **1977**, 345. (d) Cohen, T.; Bennett, D. A.; Mura, A. J., Jr. *J. Org. Chem.* **1976**, *41*, 2506. (e) Otera, J.; Mandai, T.; Moriyama, T.; Nakayama, Y.; Sugino, K.; Kawada, M. *Tetrahedron Lett.* **1984**, *25*, 5913. (f) Ogura, K.; Iihama, T.; Takahashi, K.; Iida, H. *Tetrahedron Lett.* **1984**, *25*, 2671. (g) Clinet, J.-C.; Linstrumelle, G. *Ibid.* **1980**, *21*, 3987. (h) Bakuzis, P.; Bakuzis, M. L. F.; Weingarten, T. F. *Ibid.* **1978**, 2371. (i) Lansbury, P. T.; Britt, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 4577. (j) Corbel, B.; Paugam, J.-P.; Dreux, M.; Savignac, P. *Tetrahedron Lett.* **1976**, 835. (k) Carlson, R. M.; Jones, R. W.; Hatcher, A. S. *Ibid.* **1975**, 1741. (l) Kondo, K.; Tunemoto, D. *Ibid.* **1975**, 1007. (m) Nakai, T.; Shiono, H.; Okawara, M. *Ibid.* **1974**, 3625. (n) Leroux, Y.; Roman, C. *Ibid.* **1973**, 2585. (o) Leroux, Y.; Mantione, R. *Ibid.* **1971**, 591, 593. (p) Leroux, Y.; Mantione, R. *J. Organomet. Chem.* **1971**, *30*, 295.

(3) Corey, E. J.; Erickson, B. W.; Noyori, R. *J. Am. Chem. Soc.* **1971**, *93*, 1724.

(4) Anteunis, M.; Camerlynck, R. *Tetrahedron* **1975**, *31*, 1837.

(5) This result is contrasted with the work of Gould[6] who reported that deprotonation of *cis*-1,3-dibutoxypropene under similar conditions afforded only the α-vinyl anion. To rationalize this regioselectivity, Gould and Rossi[7] employed ab initio calculations which suggested that the α-vinyl C-H bond of *cis*-1,3-dibutoxypropene is weakened and attributed this effect to a hyperconjugative interaction between the $sp^2$ lone pair on the vinyl oxygen and the adjacent C-H σ* orbital. Overlap of this type (antiperiplanar) is geometrically precluded for dioxin **3**, and, therefore, the kinetic acidity of the α-vinyl C-H bond in **3** may be diminished.

(6) Gould, S. J.; Remillard, B. D. *Tetrahedron Lett.* **1978**, 4353.

(7) Rossi, A. R.; Gould, S. J.; Remillard, B. D. *Tetrahedron Lett.* **1978**, 4357.

(8) (a) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655. (b) Funk, R. L.; Bolton, G. L. *J. Org. Chem.* **1987**, *52*, 3173.

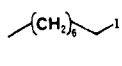
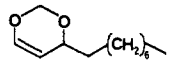
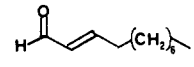
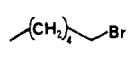
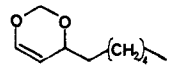
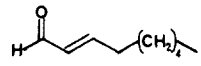
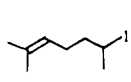
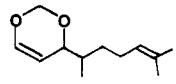
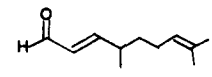
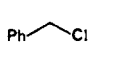
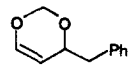
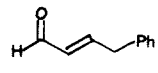
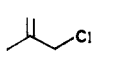
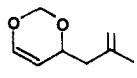
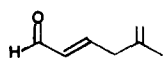
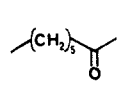
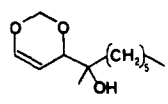
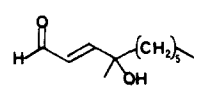
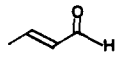
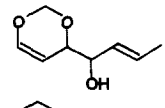
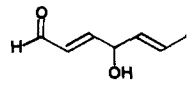
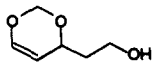
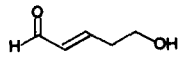
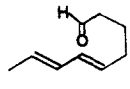
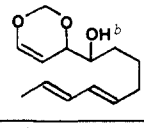
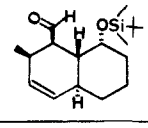
(9) (a) Ripoll, J.-L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19. (b) Lasne, M.-C.; Ripoll, J. L. *Nouv. J. Chim.* **1982**, 6.

(10) (a) Reichardt, C.; Yun, K. Y. *Tetrahedron Lett.* **1982**, *23*, 3163. (b) Reichardt, C.; Yun, K.-Y.; Massa, W.; Schmidt, R. E. *Liebigs Ann. Chem.* **1985**, 1987.

(11) Fokin, A. V.; Kolomiets, A. F.; Krolevets, A. A. *Izv. Akad Nauk SSSR* **1978**, 849.

0002-7863/88/1510-1290$01.50/0 

**Table I.** β-Acyl Vinyl Anion (**1**) Equivalency

| entry | electrophile | alkyltn prod. **5**[a] | % yield | thermolysis prod. **6**[a] | % yield |
|---|---|---|---|---|---|
| a |  |  | 95 |  | 74 |
| b |  |  | 79 |  | 80 |
| c |  |  | 51 |  | 73 |
| d |  |  | 71 |  | 83 |
| e |  |  | 66 |  | 45 |
| f |  |  | 82 |  | 80 |
| g |  |  | 65 |  | 70 |
| h |  |  | 57 |  | 60 |
| i |  |  | 72 |  | 61 |

[a] All new compounds reported herein exhibited satisfactory spectral (IR, NMR), analytical, and/or high-resolution mass spectral characteristics. [b] The alcohol **5i** was silylated (*t*-BuMe$_2$SiCl, imidazole, DMF, 92%) before thermolysis.

pounds,[13] and in some cases may be advantageous.[13b]

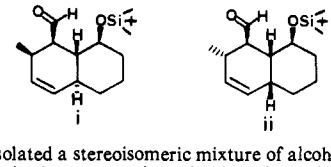
Thus, the dioxins **5** were dissolved in dry toluene and refluxed under nitrogen until their complete disappearance (4–12 h) was noted (TLC) to afford the (*E*)-α,β-unsaturated aldehydes after column chromatography. The stereoselectivity of these reactions can be rationalized by retrocycloaddition through a boatlike transition state with the alkyl substituent in a pseudoequatorial position, rather than the flagpole position which would give rise to the *Z* isomer. Thermodynamic $Z \rightleftharpoons E$ equilibration is unlikely since the aldehydes **6e** and **6g** were not contaminated by tautomeric isomers and is indicative of the neutral conditions used to release the α,β-unsaturated aldehydes.

Thermolysis (150 °C, 72 h) of the *tert*-butyldimethylsilyl ether of dioxin **5i** demonstrates that these dioxins can be employed in a one-pot retrocycloaddition, cycloaddition sequence to deliver, in this case, the major cycloadduct **6i**.[14] Furthermore, this transformation could be accomplished at low temperatures (−20 °C) in the presence of $Et_2AlCl$ (1.1 equiv, $CH_2Cl_2$, 1 h) to provide **6i** as the sole cycloadduct (50% yield).[15] We are unable to distinguish between two possible pathways for this transformation, namely, catalyzed retrocycloaddition[16] to provide the α,β-unsaturated aldehyde and complexed formaldehyde which undergo Lewis acid exchange to facilitate the subsequent catalyzed in-

(12) However, the retrocycloaddition reactions of 1,3-dioxin-4-ones and 1,3-dioxin-2-ones is well known, see: (a) Hyatt, J. A.; Clemens, R. J. *J. Org. Chem.* **1985**, *50*, 2431 and references cited therein. (b) Buynak, J. D.; Chandrasakaran, R.; Barrett, A. G. M.; Attrill, R. P. *J. Org. Chem.* **1985**, *50*, 5362.

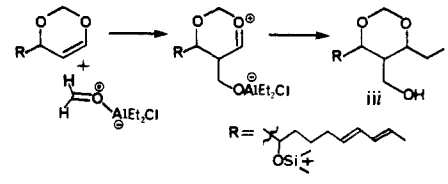
(13) For example, see: (a) Kawai, W. *J. Poly. Sci., A-1* **1968**, *6*, 137. (b) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 3775. (c) Ireland, R. E.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 198. (d) Safarov, M. G.; Ibatullin, U. G.; Murza, M. M. *Otkrytiya, Izobret., Prom. Obraztay, Tovarnye Znaki* **1980**, *45*, 94; *Chem. Abstr.* **1981**, 94:174284b. (e) Thiem, J.; Wessel, H.-P. *Liebigs Ann. Chem.* **1982**, 595. (f) Fernandez, M. V.; Herrera, F. J. L.; Cobos, T. L.; Escribano, G. P. *Carbohydr. Res.* **1983**, *118*, 286. (g) Troyanskii, E. I.; Ioffe, U. A.; Mizintsey, U. U.; Nikishin, G. I. *Akad Nauk SSR Bull., Div. Chem. Sci.* **1984**, 1661. (h) Seebach, D.; Zimmerman, J. *Helv. Chim. Acta* **1986**, *69*, 1147.

(14) The diastereomeric endo adduct i and an exo adduct ii were also isolated in 10% and 8% yields, respectively. Structural assignments are based on analysis of the high field (360 MHz) $^1$H NMR spectra and comparison with the spectra of the analogous ester cycloadducts, see: Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180.



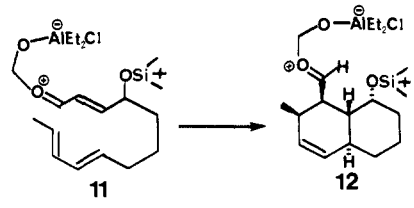
i ii

(15) We also isolated a stereoisomeric mixture of alcohols **iii** (20%) which most likely arises via the suggested mechanism shown below.



(16) For a recent report of acid-catalyzed heterocycloreversion, see: Grieco, P. A.; Parker, D. T.; Forbare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859.

tramolecular [4 + 2] cycloaddition[17] or Lewis acid-mediated ring opening of the dioxin to produce oxonium ion **11** which cyclizes to **12** and then ejects complexed formaldehyde to afford cycloadduct **6i**.



**11** **12**

In summation, we have shown that the anion **4** represents an improvement in β-acyl vinyl anion (**1**) methodology since the desired α,β-unsaturated aldehydes can be generated under exceptionally mild conditions. This methodology can be extended by using dioxins **6** as metalation substrates. Moreover, the carbon–carbon double bond of substituted dioxins participate in stereoselective hydrogenation, oxidation, cycloaddition reactions, etc. These investigations will be reported in due course.

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## A General Strategy for the Chemical Sequencing of Polysaccharides

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The sequencing of polysaccharides is more difficult than for proteins or nucleic acids because one must not only establish the identities and sequence of the monomers but also their ring forms, position(s) of linkage, and anomeric configurations as well. We recently described[1-10] a new method for the simultaneous determination of ring forms and positions of linkage which we refer to as the reductive cleavage method. The salient feature of this method, reductive cleavage of the glycosidic carbon–oxygen bonds in a fully methylated polysaccharide, gives rise to partially methylated *anhydroalditols* which are subsequently analyzed as their acetyl derivatives by gas–liquid chromatography–mass spectrometry (GC/MS). Depending upon the catalyst employed, either *total* or *selective* reductive cleavage[3,5,7-9] can be accomplished. The former serves to identify the monomeric species of the polymer, whereas the latter, which gives rise to small oligomers, can potentially be used to establish the sequence of the polymer and the configurations of selected glycosidic linkages.[5,7,9]

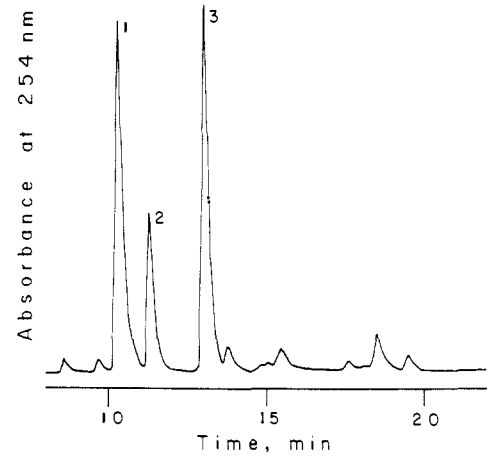


**Figure 1.** HPLC on a column (9.2 mm × 25 cm) of DuPont Zorbax ODS of the product obtained by $Me_3SiOSO_2CF_3$-catalyzed reductive cleavage and in situ benzoylation of the permethylated and reduced ($LiAlH_4$) K2 polysaccharide. The column was eluted with a 20-min gradient (curve 3, Waters Associates Model 660 solvent programmer) from 40% MeCN in $H_2O$ to 80% MeCN at a flow rate of 3 mL/min.

The identification of monomeric cleavage products, however, requires comparison of their mass spectra and GC retention times to those of synthetic standards. During the course of our synthetic studies it became apparent that products of this type were readily identified from their $^1H$ NMR spectra, due to the fact that a different pattern of couplings between ring protons is observed for the various configurational isomers. Oligomeric cleavage products, if isolated from the reaction mixtures,[5] could also be characterized by $^1H$ NMR spectroscopy in order to establish the configurations of intact glycosidic linkages and, in some cases, sequence.[5,9]

The foregoing studies therefore suggested an integrated approach to the structural characterization of polysaccharides involving both total- and selective-reductive cleavage, separation of the products by high performance liquid chromatography (HPLC), and characterization of the latter by chemical ionization mass spectrometry (CIMS), $^1H$ NMR spectroscopy, and, where necessary, further chemical sequencing. The polysaccharide chosen to demonstrate the feasibility of this approach, the *Klebsiella* K2 capsular polysaccharide, is well characterized[11,12] and serves as a good model for the structural complexities that can be encountered.

Shown in Figure 1 is the HPLC profile of the product obtained when the methylated and reduced ($LiAlH_4$)[13] polysaccharide was subjected to $Me_3SiOSO_2CF_3$-catalyzed reductive cleavage and in situ benzoylation (benzoic anhydride).[14] The numbered peaks were identified as methylated/benzoylated anhydroalditols by CIMS ($NH_3$, positive) and were characterized by 300 MHz $^1H$–$^1H$ COSY NMR spectroscopy as solutions in deuteriochloroform.

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(13) GC/MS analysis of the anhydroalditol acetates derived by reductive cleavage of the permethylated polysaccharide had demonstrated that a uronic acid was present (ref 9).
(14) After workup in the usual way (ref 5), the product was applied to a column of silica gel in chloroform. Elution with chloroform to remove benzoic acid followed by 5% methanol in chloroform afforded the mixed benzoyl esters.

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