Acyclic Stereoselection for 1,2-Diol Systems via Vinyl Acetal Rearrangement: Control of Relative Stereochemistry in the Rearrangement of 2,2,4-Trimethyl-1,3-dioxolan-4-yl Prop-1-enyl Ethers to 2,3-Dimethyl-3,4-(isopropylidenedioxy)butanals†

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A straightforward diastereoselective synthesis of 2,3-dimethyl-3,4-(isopropylidenedioxy)butanals **12** and **13** from easily accessible 2,2-dimethyl-4-methylene-1,3-dioxolane (**8**) in three steps is described. Acid-catalyzed addition of allyl alcohol to **8** affords 2,2,4-trimethyl-1,3-dioxolan-4-yl allyl ether (**9**), which is isomerized to (*E*)- or (*Z*)-2,2,4-trimethyl-1,3-dioxolan-4-yl prop-1-enyl ether (**10**, **11**) by use of bases or transition-metal complexes, respectively. The rearrangement of these mixed vinyl acetals **10** and **11** in the presence of Lewis acids leads to 2,3-dimethyl-3,4-(isopropylidenedioxy)butanals (**12**, syn, and **13**, anti) with high diastereoselectivity. The stereochemical course of this rearrangement depends on the configuration of the double bond of **10** and **11**. Compounds **12** and **13** may have advantages for the synthesis of natural compounds which contain the 1,2-diol system as structural subunit.

The rearrangement of cyclic vinyl acetals like 4,5-dihydro-1,3-dioxepins **2** has proved to be a useful method for the stereoselective synthesis of substituted tetrahydrofuran rings (Scheme I).[1] The stereoselective course of the rearrangement of these 4,5-dihydro-1,3-dioxepins **2** is possibly due to their conformational rigidity.[2]

We have been interested in generalizing this type of rearrangement, particularly to study the stereochemical course of such vinyl acetal rearrangements for acyclic systems (Scheme II). In these cases aldol ethers **7** are obtained with high diastereoselectivity.

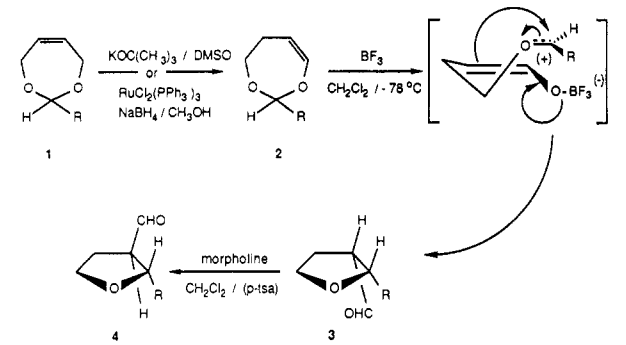
Mixed acetals of type **5** are readily prepared by acid-catalyzed alcohol addition to enol ethers. Especially 4-methylene-1,3-dioxolanes (e.g. **8**)—prepared in two steps from epichlorohydrin and aldehydes or ketones[3]—rapidly add alcohols in the presence of catalytic amounts of trifluoroacetic acid,[4] e.g., the addition of allyl alcohol to 2,2-dimethyl-4-methylene-1,3-dioxolane (**8**) gives 2,2,4-trimethyl-1,3-dioxolan-4-yl allyl ether (**9**) in 79% yield (Scheme III).

The synthesis of the dioxolanyl vinyl ethers **10** and **11** from the dioxolanyl allyl ether **9** is achieved by double-bond isomerization. This isomerization is effected by bases[1,5] as well as transition-metal complexes (Scheme IV).[6] Whereas the isomerization of **9** with $KOC(CH_3)_3$ gives the dioxolanyl vinyl ether **10** with *Z* configuration at the double bond (98% ds), the isomerization of **9** with Ru complexes affords the compounds of *E* configuration **11** predominantly (see also Experimental Section).

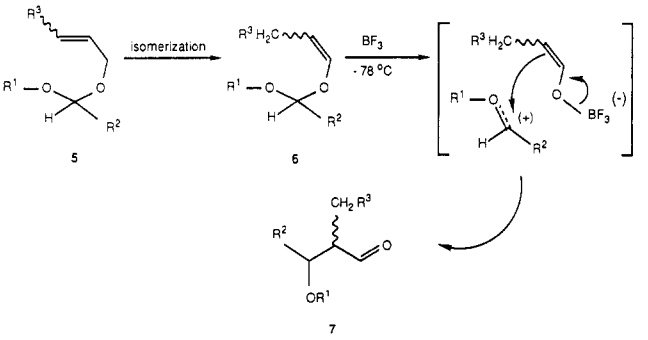
The dioxolanyl vinyl ether **10** with *Z* configuration at the double bond is rearranged in the presence of a Lewis acid (e.g. BF_3) in high yield (88%) and with high diastereoselectivity (79% ds) to **12**, showing a syn relationship with respect to the methyl group of the side chain and the oxygen of the dioxolane ring (Scheme V).

On the other hand, the rearrangement of **11** with *E* configuration gives aldehyde **13** (anti) in 87% yield (73% ds). Epimerization of *syn*-**12** and *anti*-**13**, respectively, with morpholine[1] affords a nearly 1:1 mixture of **12** and **13**.

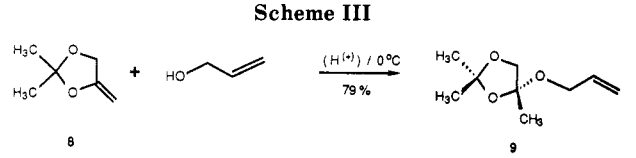
Scheme I



Scheme II



Scheme III



The Zimmerman–Traxler model, normally applied to stereoselective aldol reactions,[7] may also serve as a model

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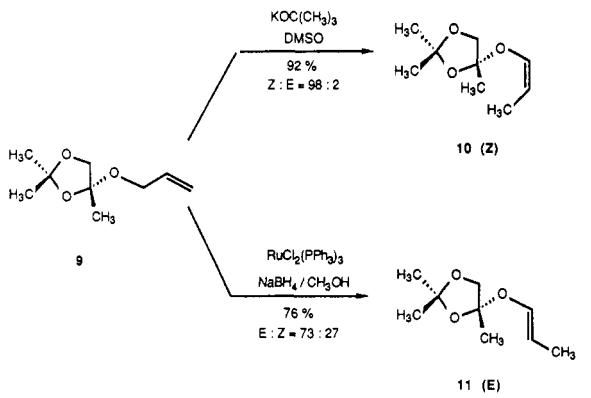
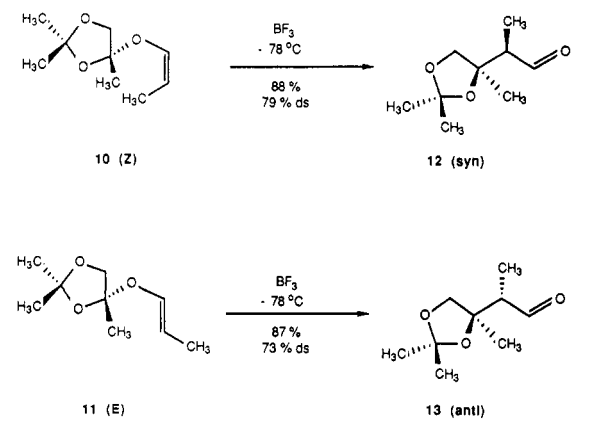
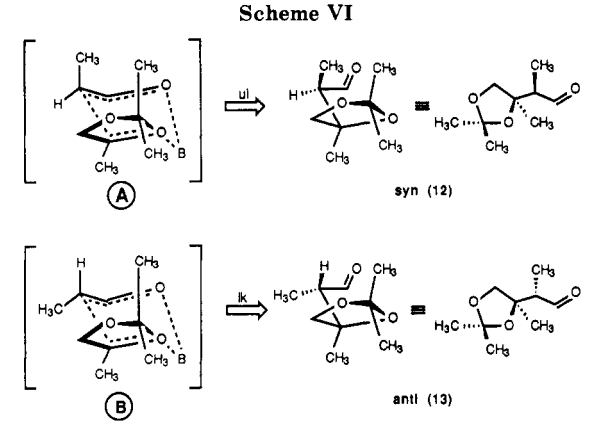
Scheme IV



Scheme V



Scheme VI



to rationalize the stereochemical course of this type of rearrangement (Scheme VI). The attack of the Lewis acid to **10** and **11** should lead to a six-membered transition state with a chair conformation (figures A and B, Scheme VI). Then *ul* addition[8] in the transition state of the *Z* boron enolate to the carboxonium ion (figure A, Scheme VI) preferentially should give **12** with a syn relationship, whereas compound **13** with the anti relationship is formed predominantly by *lk* addition[8] of the E boron enolate to the carboxonium ion (figure B, Scheme VI).

Compounds of type **12** and **13** may be useful for the synthesis of natural products possessing the 1,2-diol system as a structural subunit, e.g. macrolides. This procedure is not limited only to 4-methylene-1,3-dioxolane (**8**) but may also be applied to other substituted 4-methylene-1,3-dioxolanes.[4]

Experimental Section

General Procedures. IR spectra were recorded on a Perkin-Elmer 377 instrument, 90-MHz ^{1}H NMR spectra on a Varian EM 390 instrument, 300-MHz ^{1}H NMR spectra on a Varian XR 300 instrument, and ^{13}C NMR spectra on a Varian XR 300 instrument. Melting points (not corrected) were measured on a Büchi apparatus (Dr. Tottoli). HPLC was performed with a Abimed-Gilson apparatus: pump 303, module 803, RI detector (Bischoff LCD 202), column 7 μm Li-Chrosorb Si 60 (2.2 × 26 cm preparative). All solvents were purified by usual methods prior to use.

2,2,4-Trimethyl-1,3-dioxolan-4-yl Allyl Ether (9). 2,2-Dimethyl-4-methylene-1,3-dioxolane (**8**, 57.1 g, 0.5 mol) is added dropwise with cooling to a solution of 100 mL of allyl alcohol and 2 mL of trifluoroacetic acid in such a rate that the temperature of the reaction mixture is maintained between 0 °C and 10 °C. After stirring for another 1 h at 30 °C, 10 mL of triethylamine is added with stirring. Then the reaction mixture is diluted with 100 mL of ether. The ethereal solution is washed twice with 50 mL of water. The aqueous layers are extracted two times with 50 mL of ether, and the ethereal layers are dried (K_2CO_3). After filtration and evaporation of the solvent the crude product is distilled in vacuo: colorless liquid (68.1 g, 79%); bp 103–105 °C/100 Torr; IR (film) 3180, 2995, 2940, 2875, 1645, 1455, 1425, 1405, 1380, 1375, 1275, 1245, 1225, 1180, 1165, 1110, 1070, 1055 1030, 995, 925, 890, 865, 830, 800 cm^{-1}; 90-MHz ^{1}H NMR ($CDCl_3$) δ 5.93 (ddt, *J* = 17, 10, 5 Hz, 1 H, C*H*=CH_2), 5.26 (dq, *J* = 17, 1 Hz, 1 H, C=C*H*$_2$), 5.12 (dq, *J* = 10, 1 Hz, 1 H, C=C*H*$_2$), 4.08 (m, 3 H, OC*H*$_2$C=C, OC*H*C), 3.80 (d, *J* = 9 Hz, 1 H, OCHC), 1.50 (s, 6 H, 2 CH_3), 1.36 (s, 3 H, CH_3). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.99; H, 9.49.

(*Z*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl Prop-1-enyl Ether (10). 2,2,4-Trimethyl-1,3-dioxolan-4-yl allyl ether (**9**, 17.2 g, 0.1 mol) is dissolved in 100 mL of DMSO, and 13.4 g of $KOC(CH_3)_3$ is added in several portions. The mixture is heated with stirring to 80 °C for 4 h, then cooled to room temperature, and poured into 100 mL of saturated aqueous K_2CO_3 solution. The aqueous layer is extracted three times with 100 mL of ether, and the combined ethereal layers are washed two times with 100 mL of brine and dried (K_2CO_3). After filtration the ether is distilled off, and the crude product is distilled in vacuo: colorless liquid (15.8 g, 92%, 98% ds); bp 65 °C/10 Torr; IR (film) 3050, 2990, 2960, 2940, 2880, 1675, 1455, 1380, 1375, 1270, 1245, 1220, 1185, 1155, 1105, 1070, 995, 985, 930, 895, 865, 835, 795 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.30 (1, dq, *J* = 6.3, 1.5 Hz, OCH=C), 4.58 (1, dq, *J* = 6.8, 6.3 Hz, OC=CH), 4.17 (1, *d*, *J* = 9 Hz, OCHC), 3.84 (1, d, *J* = 9 Hz, OCHC), 1.57 (3, dd, *J* = 6.8, 1.5 Hz, C=CCH_3), 1.51, 1.47, 1.38 (9, 3 each, 3 s, CH_3CCH_3, $OCCH_3$); ^{13}C NMR δ 138.09 (O*C*=C), 110.42 (O*C*(CH_2)O), 105.05 (OCO), 103.98 (OC=*C*), 75.21 (OCH_2), 26.70, 26.67 (H_3CCCH_3), 26.24 ($OCCH_3$), 22.19 (C=CCH_3). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.69; H, 9.44.

(*E*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl Prop-1-enyl Ether (11). 2,2,4-Trimethyl-1,3-dioxolan-4-yl allyl ether (**9**, 3.44 g, 0.02 mol) is dissolved in 20 mL of CH_3OH under nitrogen. Then 192 mg of $RuCl_2(PPh_3)_3$ (0.2 mmol, 1 mol %) and 50 mg of $NaBH_4$ are added, and the reaction mixture is heated to 60 °C for 2 h. After cooling to room temperature, the mixture is filtered, and the solvent is distilled off. The crude product is distilled in vacuo. An analytically pure sample was provided by HPLC: colorless liquid (2.61 g, 76%, 73% ds); bp 130 °C/8 Torr (Kugelrohr); IR (film) 3050, 2990, 2940, 2880, 1740, 1725, 1620, 1455, 1400, 1380, 1375, 1275, 1245, 1220, 1185, 1155, 1105, 1065, 1050, 995, 980, 930, 895, 865, 835, 795 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.34 (1, dq, *J* = 12.3, 1.5 Hz, OCH=C), 5.06 (1, dq, *J* = 12.3 6.8 Hz, OC=CH), 4.11 (1, d, *J* = 9 Hz, OCHC), 3.80 (1, d, *J* = 9 Hz, =CHC), 1.57 (3, dd, *J* = 6.8, 1.5 Hz, C=CCH_3), 1.50, 1.48, 1.38 (9, 3 each, 3 s, H_3CCCH_3 and $OCCH_3$); ^{13}C NMR ($CDCl_3$) δ 138.19 (O*C*=C), 111.47 (O*C*(CH_2)O), 105.52 (OCO), 105.37 (OC=*C*), 74.99 (OCH_2), 26.70, 26.67 (H_3CCCH_3), 26.20 ($OCCH_3$), 22.24 (C=CCH_3). Anal.

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Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.56; H, 9.53.

General Procedure for the Lewis Acid Catalyzed Rearrangement of 10 and 11. **10** or **11** (8.6 g, (0.05 mol) is dissolved in 100 mL of CH_2Cl_2 and cooled to -78 °C. $BF_3{\cdot}Et_2O$ (1 mL) is added, and the reaction mixture is stirred for 3 h at -78 °C. Then the reaction mixture is poured into 100 mL of aqueous K_2CO_3 solution. The organic layer is washed twice with K_2CO_3 solution, and the aqueous layer is extracted with 20 mL of CH_2Cl_2. The combined organic layers are dried (K_2CO_3). After filtration and evaporation of the solvent the crude products are distilled in vacuo. Analytically pure samples are obtained by spinning band distillation. **(2*R**,3*R**)-2,3-Dimethyl-3,4-(isopropylidenedioxy)butanal (12)**: colorless liquid (7.6 g, 88%, 79% ds); bp 70 °C/10 Torr; IR (film) 2995, 2940, 2880, 2730, 1725, 1455, 1380, 1370, 1250, 1215, 1120, 1110, 985, 950, 925, 905, 870, 845, 800 cm^{-1}; ^1H NMR (CCl_4) δ 9.62 (1, d, J = 1.6 Hz, CHO), 3.85, 3.72 (2, 1 each, d, J = 9 Hz, CH_2), 2.51 (1, qd, J = 7.2, 1.6 Hz, O=CC*H*CH_3), 1.35, 1.30 (6, 3 each, q, J = 0.6 Hz, CH_3CCH_3), 1.24 (3, br s, CH_2CCH_3) 1.16 (3, d, J = 7.2 Hz, O=CCCH_3); ^{13}C NMR (C_6D_6) δ 202.12 (CO), 109.04 (CH_3CCH_3), 81.18 (*C*HOC), 72.91 (CH_2OC), 54.16 (O=*C*C), 27.21, 26.69 (CH_3CCH_3), 22.81 ($OCCH_3$), 9.23 (O=CCCH_3). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.55; H, 9.44. **(2*S**,3*R**)-2,3-Dimethyl-3,4-(isopropylidenedioxy)butanal (13)**: colorless liquid (7.5 g, 87%, 73% ds); bp 75-76 °C/16 Torr, IR (film) 3080, 2990, 2940, 2875, 1650, 1460, 1425, 1410, 1380, 1375, 1275, 1240, 1225, 1180, 1160, 1110, 1070, 1055, 995, 920, 890, 865, 830, 795 cm^{-1}; ^1H NMR (CCl_4) δ 9.70 (1, d, J = 1.6 Hz, CHO), 3.85, 3.66 (2, 1 each, d, J = 9 Hz, CH_2), 2.50 (1, qd, J = 7.2, 1.6 Hz, O=CC*H*CH_3), 1.37, 1.37 (6, 3 each, q, J = 0.6 Hz, CH_3CCH_3) 1.22 (3, br s, CH_2CCH_3), 1.01 (3, d, J = 7.2 Hz, O=CCCH_3); ^{13}C NMR (C_6D_6) δ 202.12 (CO), 109.78 (CH_3CCH_3), 81.89 (*C*HOC), 72.16 (CH_2OC), 54.08 (O=*C*C), 27.21, 26.97 (CH_3CCH_3), 22.20 ($OCCH_3$), 9.63 (O=CCCH_3). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.50; H, 9.36.

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Registry No. **8**, 19358-05-5; **9**, 113273-97-5; **10**, 113273-98-6; **11**, 113273-99-7; **12**, 113274-00-3; **13**, 113274-01-4; allyl alcohol, 107-18-6.

Intra- and Intermolecular Diels-Alder Reactions of Glutaconaldehyde Derivatives

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The intramolecular Diels-Alder reaction of the alcohols **10a-d** and maleic anhydride gave the cis-fused cycloadducts **12a-d**, whereas the esters **13a** and **13c** prepared from **10a** and fumaric acid ethyl or methyl ester monochloride produced trans-fused adducts **14a** and **14c**, respectively. The trienes **16-22** did not undergo intramolecular Diels-Alder reaction even at 240 °C, whereas the acetylene system **24** (corresponding to the olefin system **16**) underwent Diels-Alder reaction to **26** at 60 °C. The acid group in **12a** or **12b** could be esterified to **27-30** and the cyclohexene unit in **14a** or **27a** was brominated. The alcohol **10a** with protection of the hydroxy group was able to participate in the intermolecular Diels-Alder reaction with a range of dienophiles.

Introduction

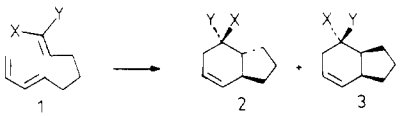
Compared to the intramolecular version, the IMDA (intramolecular Diels-Alder) reaction is more effective due to entropy, reactivity, and regio-, stereo-, and diastereoselectivity. As a result there has been an explosive growth in the study and application of the IMDA reaction.[1]

Normally trans dienes give the fused products[2] exclusively, in the majority of intramolecular Diels-Alder reactions.

Trans dienes containing chains of three or four atoms constitute the majority of substrates known to undergo the IMDA reaction. These may cyclize via either the syn transition state to give the cis-fused product or the anti transition state to give the trans-fused product. Chain length, substitutents on the chain, type of diene, type of dienophile, and catalysts are factors that influence the stereochemistry.

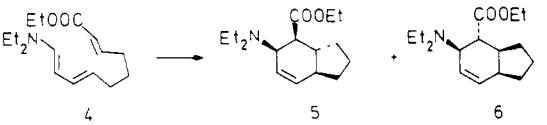
Trans dienes with three carbon atoms in the chain connecting the diene and the dienophile and an electron-withdrawing substituent on the terminal carbon atom of the dienophile (an activated dienophile) cyclize preferentially via the anti transition state to give mainly the trans-fused cycloadducts. Roush[3] found that **1a** (Scheme I) underwent cycloaddition to give a mixture of trans-fused hydroindane **2a** and the cis-fused isomer **3a** in the ratio 60:40, indicating that the anti transition state prevailed

Scheme I

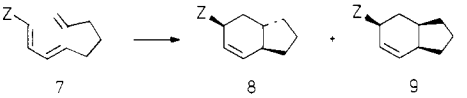


a: X = COOMe, Y = H
b: X = H, Y = COOMe

Scheme II



Scheme III



a: Z = H
b: Z = COOEt

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