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DIASTEREOSPECIFIC SYNTHESIS OF 2.6-DIDEOXY- AND 2.4.6-TRIDEOXY-SUGARS VIA HETERO-DIELS-ALDER-REACTION [1)]

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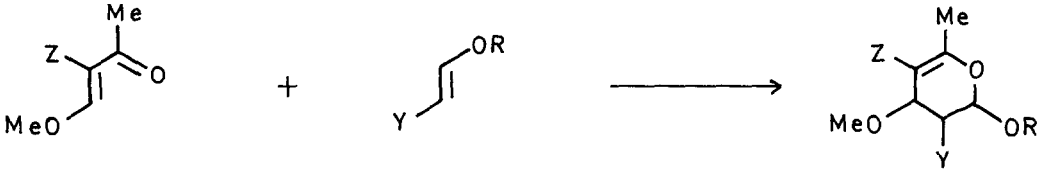
Abstract: *ß-Acyloxy-a-phenylthio a,ß-unsaturated carbonyl compounds and ethylvinylether afforded in a endo-specific hetero-Diels-Alder reaction functionalized 3.4-dihydro-2H-pyrans. These compounds were transfered diastereospecifically into deoxy sugars this way allowing a stereocontrolled generation of up to four chiral centers.*

Functionally substituted dihydro- and tetrahydropyran structures are not only present in carbohydrates and related natural products they are also useful as chiral precursors in the synthesis of various classes of naturally occurring compounds [2)]. However, the "chiron approach" [3)] to such intermediates is often lengthy and tedious because of multiple regiospecific and stereocontrolled functional group manipulations. Therefore de novo-syntheses from achiral starting materials have become competitive [4,5)].

Recently hetero-Diels-Alder reactions with inverse electron demand between α,ß-unsaturated carbonyl compounds and enol ethers [6,7)] and enediol ethers [6)] resulted in an efficient one step synthesis of highly functionalized 3,4-dihydro-2H-pyrans (hex-4-enopyranosides) Scheme 1.

Scheme 1



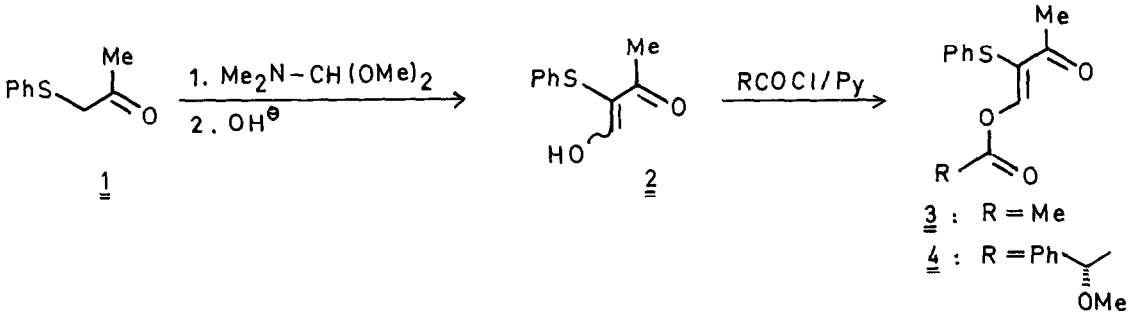
Z = COMe, COOMe; Y = H, OMe [6,7)]

Z = H; Y = H [8)]

However, with the aim of using this method for the synthesis of carbohydrates and closely related compounds, a carbon substituent in 5-position (4-position in carbohydrate numbering) is abundant. However, ß-alkoxy α,ß-unsaturated carbonyl compounds having no electron withdrawing substituent in α-position are very unreactive towards enol ethers [8] (Scheme 1). Therefore, we undertook investigations aimed at introducing a versatile functional substituent in 5-position, which (i) increases the rate and the diastereoselectivity of the cycloaddition reaction and (ii) enables a straightforward introduction of hydrogen, hydroxy and perhaps other substituents in a diastereospecific manner. Results with ß-acyloxy-α-phenylthio α,ß-unsaturated carbonyl compounds as hetero dienes demonstrate that the phenylthio group fulfills these requirements.

The starting materials were obtained in a convenient, high yielding route (Scheme 2). Reaction of α-phenylthioacetone (1) with DMF-acetal and subsequent basic hydrolysis afforded the hydroxymethylene derivative 2 in 70 % yield. Acylation with acetylchloride or with (R)-O-methyl mandelic acid chloride yielded quantitatively the ß-acyloxy-α-phenylthio substituted α,ß-unsaturated carbonyl compounds 3 and 4, respectively (3: Z/E-ratio = 9:1; 4: only Z-isomer [9]).

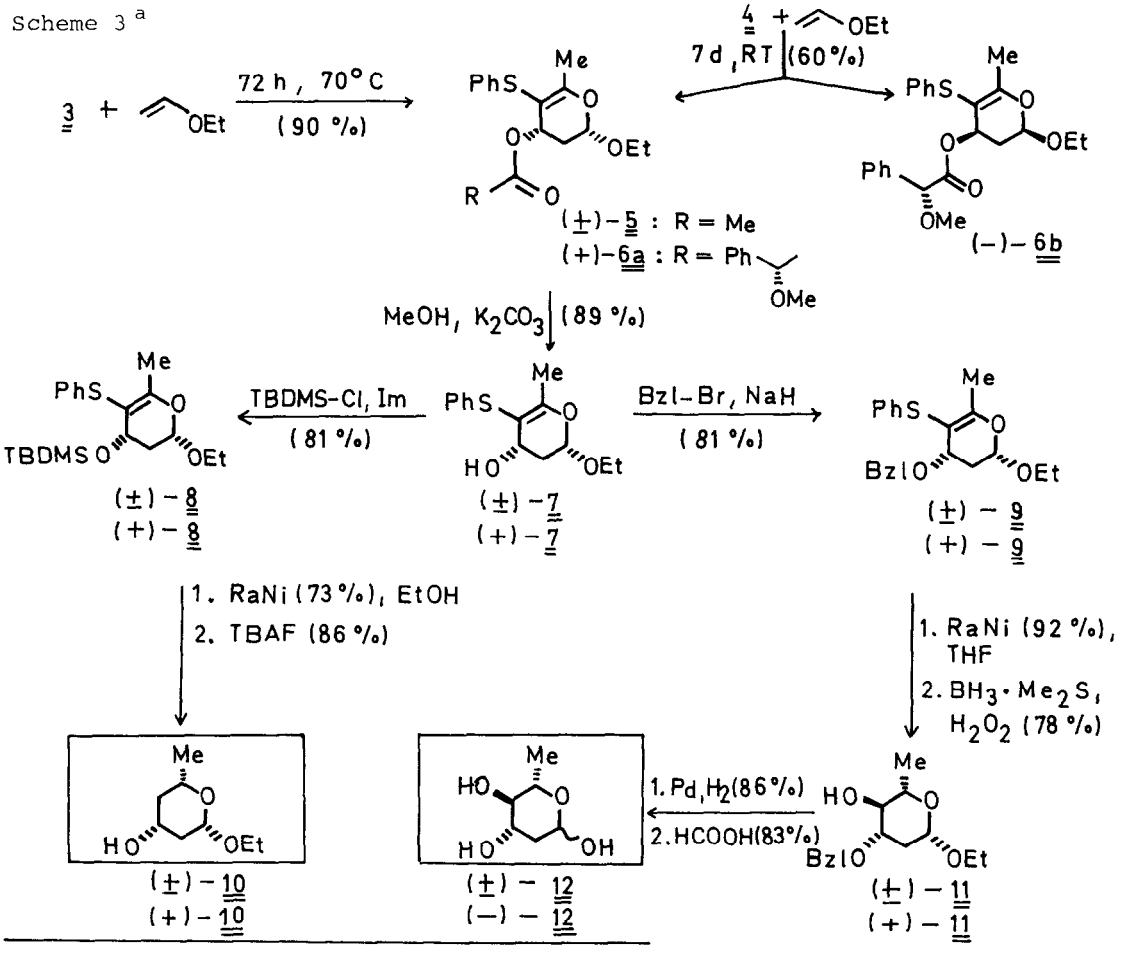
Scheme 2



Reaction of heterodiene 3 with ethyl vinyl ether gave via a highly site selective endo addition the cis-isomer (±)-5 in 90 % yield (Scheme 3; trans-isomer: < 8 %). Deacylation afforded the corresponding hydroxy compound (±)-7; O-silylation with tert.-butyldimethylsilyl chloride (TBDMS-Cl) or O-benzylation yielded the O-protected compounds (±)-8 and (±)-9, respectively. Raney nickel treatment of compound (±)-8 in ethanol led to removal of the phenylthio group and to diastereospecific hydrogenation of the double bond affording after desilylation with tetrabutylammonium fluoride (TBAF) 2,4,6-trideoxy-ß-D,L-hexopyranoside (±)-10. Raney nickel treatment of compound (±)-9 in THF led only to the removal of the phenylthio group. The intermediate was treated with the borane dimethylsulfide complex and after oxidative work up with hydrogen peroxide (30 % solution in water) the 4-O-unprotected olivose derivative (±)-11 was obtained exclusively [8,10]. Hydrogenolytic debenzylation and acidic cleavage of the glycosidic bond gave D,L-olivose (2,6-dideoxy-D,L-arabino-hexose) (±)-12.

Convenient structural proof for these compounds came from asymmetric induction experiments. The chiral heterodiene 4 afforded with ethyl vinyl ether in a endo-specific diastereoface selective addition the diastereoisomers (+)-6a and (-)-6b (ratio ~2:1) [11]. Deacylation of compound (+)-6a delivered the pure optical isomer (+)-7, which was transferred via the reaction sequences described into compounds (+)-8, (+)-10 and (+)-9, (+)-11, (-)-12, respectively [11]. Compound (-)-12 had identical rotation with (-)-L-olivose ($[\alpha]_D^{22}$ = -18.1; c = 0.57, H_2O) [12] this way proving, in addition with ^{1}H-NMR data [12,13], the structural assignments for compounds 7-11.

Scheme 3 [a]



[a] (±) denotes racemate formation

The hetero-Diels-Alder reaction based, high yielding hexopyranose synthesis allows a diastereospecific generation of up to four chiral centers [14]. The direct access to partially O-protected derivatives is an additional advantage of the method developed here. Further asymmetric induction experiments are under investigation. [15]

1) De novo-Synthesis of Carbohydrates and Related Natural Products, Part 17. - This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. - Part 16, see ref. 4g.

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9) Assigned by ^{1}H-NMR chemical shift data (80 MHz, $CDCl_3$, TMS): 3 (Z-isomer) δ = 8.60 (s, 1H, -CH=); 7.28 (s br., 5H, C_6H_5); 2.34, 2.18 (2s, 6H, 2 CH_3). - 3 (E-isomer): δ = 8.08 (s, 1H, -CH=). - 4 (Z-isomer: δ = 8.55 (s, 1H, -CH=); 7.5-7.15 (m, 10H, $2C_6H_5$); 4.83 (s, 1H, Ph-CH-OMe), 3.40 (s, 3H, OCH_3); 2.28 (s, 3H, CH_3).

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11) Optical rotations (+)-6a: $[\alpha]_{578}^{20}$ = +15.8 (c=1, $CHCl_3$); (-)-6b: $[\alpha]_{578}^{20}$ = -20.8 (c=1, $CHCl_3$); (+)-7. $[\alpha]_{578}^{21}$ = +14.3 (c=1, CH_2Cl_2; (+)-8: $[\alpha]_{578}^{22}$ = +38.4 (c=1, $CHCl_3$); (+)-9: $[\alpha]_{578}^{22}$ = 51.0 (c=2, $CHCl_3$); (+)-10: $[\alpha]_{578}^{21}$ = +57.0 (c=1, $CHCl_3$); (+)-11: $[\alpha]_{578}^{21}$ = +79.6 (c=1, $CHCl_3$).

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13) Final structural proof for compound (+)-10 came from ^{1}H-NMR data (250 MHz, $CDCl_3$,TMS): (+)-10: δ = 4.39 (dd, 1H, 1-H; $J_{1,2a}$= 9.5 Hz; $J_{1,2e}$= 2.1 Hz); 4.02-3.9 (m, 1H, OCH_2-CH_3); 3.9-3.78 (m, 1H, 3-H); 3.6-3.4 (m, 2H, OCH_2-CH_3, 5-H); 2.21-2.13, 1.96-1.88 (2m, 2H, 2e-H, 4e-H); 1.65-1.55 (m, 1H, OH); 1.38 (ddd, 1H, 2a-H; J_{gem} = 11.6 Hz, $2xJ_{trans}$= 9.5 Hz); 1.28 (d, 3H, 6-H; $J_{5,6}$= 6.1 Hz); 1.24 (t, 3H, OCH_2-CH_3); 1.24 (ddd, 1H, 4a-H; 3xJ$\approx$10 Hz).

14) Stereocontrolled introduction of a fifth chiral center at 3-position is under investigation.

15) Compound gave preferentially diastereoisomer (+)-6a. This result is not in accordance with the Trost-model: B.M. Trost, D.O'Krongly, and J.L. Belletire, J.Am.Chem.Soc. 102, 7595 (1980).

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