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CHELATION CONTROLLED REGIOSELECTIVE ALKYLATION AND 1,4 CHIRALITY TRANSFER IN OPTICALLY ACTIVE 1-ALKOXY-1,4-CYCLOHEXADIENES

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SUMMARY : Chelation controlled alkylation of optically active 1-alkoxy-1,4-cyclohexadienes leads to a mixture of 1,4-cyclohexadienes 4a-c and 1,3-cyclohexadienes 5a-c. The regio- and diastereoselectivities depend upon the nature of the chiral auxiliary and the reaction conditions.

It is now well established that Birch reduction products of various aromatic compounds are very useful intermediates in carbocyclic synthesis[3]. Recently, Schultz et al. have described the first enantioselective Birch reduction-alkylations of chiral amides derived from salicylic[4] or anthranilic acid[5] and L-prolinol. High diastereoselectivities were observed, while the carbonyl group is the regiocontrolling element for the alkylation step. This approach is especially designed for the synthesis of highly functionalized chiral cyclohexylcarboxylic acids and derivatives.

In connection with our continuous efforts in the area of polycarbocyclic molecules, we were attracted by the synthetic potential offered by alkylation of Birch reduction products of suitable phenol ethers. We therefore decided to investigate an enantioselective variant of Sutherland's method[6]; here the regioselectivity of the metallation is governed by the chelating properties of the amino function in 1a.

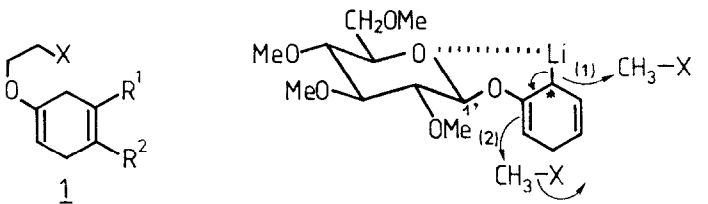
For our introductory study we selected a per-O-methylated β-D-glucopyranosyl group as the chiral auxiliary. Phenyl β-D-glucopyranoside, the precursor of 2a, is commercially available, while the methyl derivatives 2b and 2c are readily accessible via substitution by the appropriate cresol at the anomeric position of acetobromo-α-D-glucopyranose[7]. The 1,4-cyclohexadienes 3a-c, obtained after Birch reduction[3] and isolation under Ar, were deprotonated (1.3 equiv sec-BuLi, THF, -78°C, 0.5 h) and subsequently methylated (4 equiv MeI), whereby profit was taken from the chelation of the lithium cation with oxygen. A mixture of the 1,4-cyclohexadienes 4a-c and the isomeric 1,3-cyclohexadienes 5a-c was formed. Acid hydrolysis led to two easily differentiated 2-cyclohexenones 6a-c and 7a-c, respectively. As can be seen from table 1 the ratio is dependent on the reaction conditions.

The low regioselectivity is somewhat surprising, as it has not been observed previously when starting from 1a[6] or 1b[8]. The phenomenon could be specific for substrates 3a-c, due to steric hindrance of the monosaccharide substituent. The formation of 5a-c must arise from a chelation controlled SE'_2-reaction ((2) in the scheme)[9]. Unambiguous proof was provided by the formation of a gem dimethyl group (in 5b) upon alkylation of 3b.

Under our standard reaction conditions substrates 1c and 1d (entries 13 and 14) also displayed poor regioselectivity. In Sutherland's study the metallation of 1a occurred with n-BuLi-HMPA, while the alkylating reagents were all primary homoallylic halides[6]. The

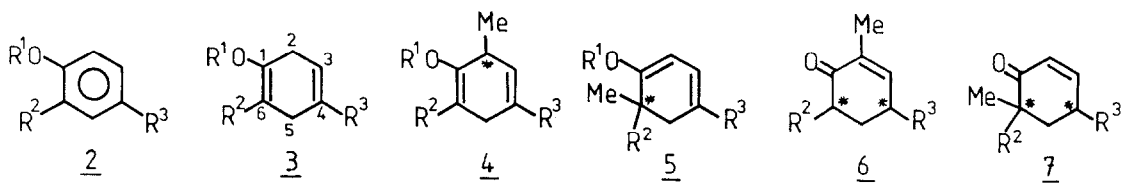
conditions were also used in the alkylation of 1c, as reported by Wolf[8]. In both cases the formation of conjugated dienes (such as 5) has not been mentioned. As can be deduced from table 1 a steric effect is of importance (compare entries 1,12 and 18,19, respectively). When additionally a stereoelectronic effect operates, the regioselectivity is highly enhanced (entries 12 and 19). Somewhat surprisingly substantial SE'_2 reaction occurred as well when a 6-methyl substituent (3b) is present (entries 16 and 17). A solvent effect is apparent also.

On the other hand, the diastereoselectivity is markedly influenced by the solvent. The d.e. values are largely increased when replacing THF by diethyl ether or toluene, but the total yield is much lower; as expected, HMPA has a negative effect (entries 1,3,4 and 6). The use of alkylating agents other than iodides (entries 9-11) decreases the % d.e..



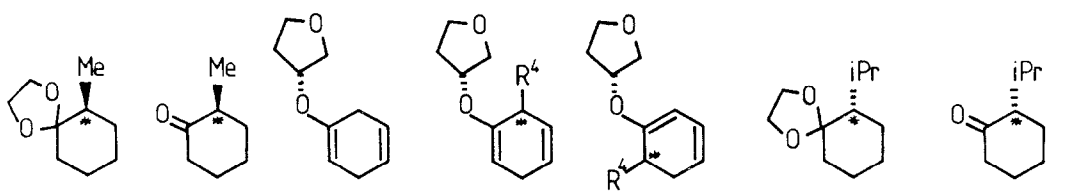
1

a: X = NEt_2; R^1 = Me; R^2 = H
b: X = NEt_2; R^1 = H; R^2 = i-Pr
c: X = NEt_2; R^1 = H; R^2 = Me
d: X = OMe; R^1 = H; R^2 = Me



2 3 4 5 6 7

a : R^1 = per-O-methyl-β-D-glucopyranosyl; R^2 = R^3 = H
b : R^1 = per-O-methyl-β-D-glucopyranosyl; R^2 = Me; R^3 = H
c : R^1 = per-O-methyl-β-D-glucopyranosyl; R^2 = H; R^3 = Me



8 9 10 11 12 13 14

a : R^4 = Me
b : R^4 = i-Pr

The low chemical yields observed in diethyl ether or toluene solutions were attributed to insufficient solubility or to partial degradation of the monosaccharide part. These problems could be overcome by the introduction of the readily available and optically pure (+)-3(S)-hydroxytetrahydrofuran as chiral auxiliary[9]. SN_2 reaction with phenol (PPh_3; diethyl azodicarboxylate)[10] and subsequent Birch reduction-alkylation of 10 provided compounds 11a-b and 12a-b (table 1; entries 20 to 22). The reaction of 10 with i-PrI in diethyl ether (entry 22) proceeded with complete regioselectivity, good diastereoselectivity

and excellent chemical yield. This last result encourages us to continue this study with other chiral auxiliaries and functionalized alkyl iodides.

TABLE 1 : Influence of varying reaction conditions[a] on the regio- and diastereoselectivity for the alkylation of various chiral 1-alkoxy-1,4-cyclohexadienes

Entry	Substrate	Regioselectivity (ratio 4:5 for 3 and 1; ratio 11:12 for 10)	Diastereoselectivity (% d.e. of 4 for 3 and 1; % d.e. of 11 for 10)	Total yield (%)	Solvent	Reaction conditions
1	3a	4.6	46	74	THF	src
2	3a	2.3	40	58	THF	deprotonation during 4h30min
3	3a	3.8	78	34	Et_2O	src
4	3a	3.8	79	34	C_6H_5Me	src
5	3a	3.8	50	57	DME	src
6	3a	3.8	28	70	THF	cosolvent HMPA
7	3a	4.6	48	72	THF	-100°C
8	3a	3.3	20	50	THF	-20°C
9	3a	7.3	10	68	THF	MeBr
10	3a	5.7	8	68	THF	MeOTs
11	3a	4.9	40	60	THF	BnBr
12	3a	10.1	40	67	THF	i-PrI
13	1c	4.6	-	90	THF	src
14	1d	4.6	-	92	THF	src
15	1d	8.1	-	90	Et_2O	src
16	3b	4.6	4	68	THF	src
17	3b	6.1	6	66	THF	i-PrI
18	3c	5.7	42	72	THF	src
19	3c	> 100	44	65	THF	i-PrI
20	10	5.7	26	90	THF	src
21	10	19	30	90	THF	i-PrI
22	10	> 100	60	90	Et_2O	i-PrI

[a] Standard reaction conditions (src) : 1.3 equiv sec-BuLi, THF, -78°C, 0.5 h, 4 equiv MeI, unless otherwise noted.

The relevant ^1H NMR parameters of compounds 4a-c and 5a-c are given in table 2; d.e. determination was possible for 4a-c based on the distinct signals of the vinylic protons (4a and 4c) or the vinylic methyl protons (4b) in the respective diastereomers. The corresponding ^1H NMR signals of compounds 5a-c are not well separated. The d.e. of 4a and 11b was substantiated by determination of the enantiomeric excess of the respective acetals 8 and 13, accessible via consecutive acetalisation ($HO(CH_2)_2OH$, THF, $BF_3.Et_2O$)[11] and hydrogenation (H_2, Pt, MeOH)[12]. The absolute configuration was established by hydrolysis (HCl 0.1 N, acetone) of 8 and 13 to the known (+)-2(S)-methylcyclohexanone (9)[13] and (-)-2(S)-isopropylcyclohexanone (14)[14], respectively. Thus the predominant enantiomers of 4a and 11b have opposite chirality[15]. At present it is not known whether the electrophilic substitution at C-2 (or C-6) in the 1-alkoxy-1,4-cyclohexadienes studied occurs with retention or inversion.

TABLE 2 : ^{1}H NMR parameters[a] of relevant protons in compounds 4a-c and 5a-c

4a	1.18 (Me, d, J = 7.0 Hz); 4.61 (H-1',d, J = 7.5 Hz); 4.67 (H-1', d, J = 7.5 Hz); 4.93 (0.73 H-2, t, J = 3.2 Hz); 5.00 (0.27 H-2, t, J = 3.2 Hz); 5.54-5.63 (H-4 + H-5, m).
5a	1.05 (0.79 Me[b], d, J = 7.0 Hz); 1.09 (0.21 Me, d, J = 7.0 Hz); 4.63 (H-1', d, J = 7.5 Hz); 4.67 (H-1', d, J = 7.5 Hz); 5.15 (H-2, d, J = 6.0 Hz); 5.17 (H-2, d, J = 6.0 Hz); 5.40 (H-3, m); 5.81 (H-4, m).
4b	1.16 (Me, d, J = 6.8 Hz); 1.69 (0.52 Me, d, J = 1.2 Hz); 1.71 (0.48 Me, d, J = 1.2 Hz); 4.34 (H-1', d, J = 7.5 Hz); 4.41 (H-1', d, J = 7.5 Hz); 5.50-5.62 (H-4 + H-5, m).
5b	1.04 (Me, s); 1.09 (Me, s); 4.34 (H-1', d, J = 7.5 Hz); 4.44 (H-1', d, J = 7.5 Hz); 4.57 (H-2, d, J = 7.8 Hz); 5.40-5.46 (H-4, m); 5.76-5.82 (H-3, m).
4c	1.15 (Me, d, J = 7.0 Hz); 1.67 (Me, s); 4.60 (H-1', d, J = 7.5 Hz); 4.66 (H-1', d, J = 7.5 Hz); 4.91 (0.71 H-2, t, J = 3.6 Hz); 4.98 (0.29 H-2, t, J = 3.6 Hz); 5.26 (H-5, m).
5c	1.15 (Me, d, J = 7.0 Hz); 1.67 (Me, s); 4.61 (H-1', d, J = 7.5 Hz); 4.67 (H-1', d, J = 7.5 Hz); 5.10-5.12 (H-2, m); 5.33 (H-3, m).

[a] The ^{1}H NMR data were extracted from first order analysis of the spectra taken at 360 MHz(Bruker WH-360) in $CDCl_3$ soln (1 % wt/vol) with Me_4Si as internal standard. The chemical shift values are expressed in ppm. Assignments were confirmed by mass spectral analysis of the corresponding 2-cyclohexenones 6 and 7.

[b] The fractional values for peak areas allow direct determination of % d.e..

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References and Notes

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15. Note the change in CIP priorities.

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