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UNEXPECTEDLY HIGH DIASTEREOMERIC INDUCTION IN THE DIELS-ALDER REACTION OF QUINONES WITH CHIRAL ARYL CONTAINING 1-ALKOXY-3-TRIMETHYLSILYLOXY-BUTA-1,3-DIENES.

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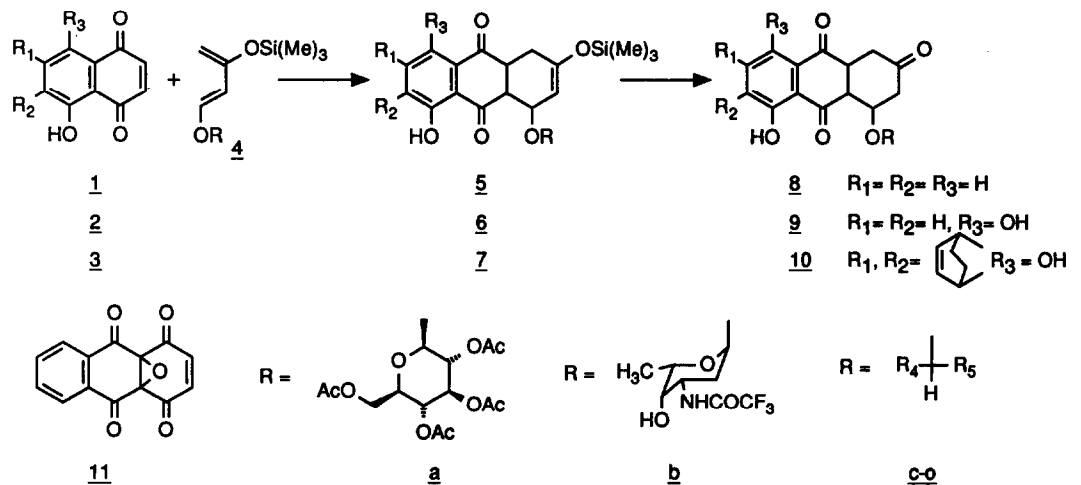
Abstract: Chiral 1-alkoxy-3-trimethylsilyloxybuta-1,3-dienes induce a high diastereomeric excess in the cycloaddition with quinones when the chiral alkoxy group is of the type $OCH(CH_3)R$ with R = aryl. Also for R = vinyl, CH_2OCH_3 the found induction is higher than that observed for R = *tert.* butyl. The highest diastereomeric excess (>95%) was achieved in the cycloaddition of 1-[1-(*p*-methoxyphenyl)-ethoxy]-3-trimethyl-silyloxybuta-1,3-diene with benzoquinone. An explanation is given based on the assumption that the R substituent is strongly enlarged in size by complexation with the used quinones.

The high therapeutic index of the antitumor drugs adriamycin and daunomycin[1,2] has stimulated an intensive research into the synthesis of these compounds and their analogs[3]. In several syntheses of daunomycinon and ring D-substituted analogs the Diels Alder reaction of a quinone precursor with 1-alkoxy-3-trimethylsilyloxy-buta-1,3-diene is a key step[4] (Scheme 1).

Scheme 1.



Stoodley[5] and Penco[6] respectively studied 2,3,4,6-tetra-O-Acetyl-β-D-glucopyranoside (4a) and 3-protected-α-D-daunosamine (4b) as chiral alkoxy group in the cycloaddition with the very reactive dienophile quinizarine quinone epoxide (11). In our hands these dienes are not reactive enough to give satisfactory conversions with

less reactive quinones such as naphthazarin (2)[4a,7] and 1,4,9,10-tetrahydro-5,8,-dihydroxy-9,10-dioxo-1,4-ethanoanthracene (3)[4b] used in our and other approaches. Therefore we have studied in a systematic way the diastereomeric induction of a series of more electron-rich 1-alkoxy-3-trimethylsilyloxybuta-1,3-dienes in the cycloaddition with quinones.[8]

First we investigated dienes having secondary alkoxy groups in the cycloaddition with naphthazarin (2) and juglone (1) (Scheme 1). The dienes were synthesized according to the method of Danishefsky[9] from the racemic alcohols. The formed cycloadducts (5-7) were hydrolysed to the corresponding ketones (8-10). The diastereomeric excess (d.e.)[10] could be determined by ^{1}H-NMR spectroscopy[11] and HPLC analysis. The highest d.e. (30%) was measured for substance 9e (Table 1). There is an obvious but low steric effect of the size of the R_5 group on the diastereomeric induction.

Table 1. Diels-Alder reactions of dienes 4c-m with dienophiles 1 and 2*.

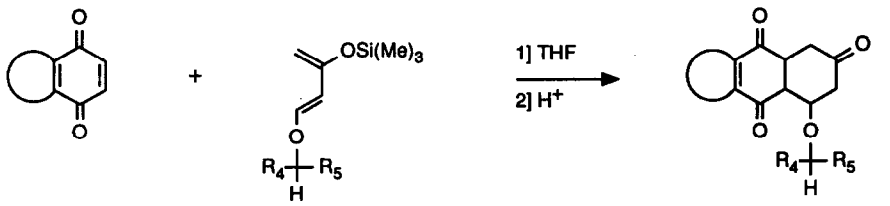
Entry	Diene	R_4	R_5	8		9	
				d.e.**	yield	d.e.**	yield
1	4c	Me	Et	3	72	5	71
2	4d	Me	i-Pr	6	74	15	75
3	4e	Me	t-Bu	15	78	30	69
4	4f	Me	cyclohexyl	26	45	26	63
5	4g	Me	Ph	66	79	70	68
6	4h	Et	Ph	60	76	50	67
7	4i	i-Pr	Ph	50	86	30	48
8	4j	Me	CH_2OMe	30	77	35	80
9	4k	Me	$CH{=}CH_2$	45	76	50	62
10	4l	Me	CH_2CH_2OMe	0	63	0	69
11	4m	H	PhCH(Me)-	5	88	8	55

* reactions were carried out using racemic dienes 4 in THF (0.1 molar solutions with the dienes in 50% excess). The cycloaddition has completed after 16-20 hr at room temperature . The yields are isolated yields after precipitation in THF/n-hexane.
** diastereomeric excess (d.e.) in % determinated by ^{1}H-NMR spectroscopy. The d.e. of the reaction mixture determined with HPLC for the cycloadditions of 2 showed the same ratios as found with ^{1}H-NMR.

However the chiral dienes 4 with R_4 = alkyl and R_5 = phenyl (4 g-i) cause an unexpectedly high d.e. (Table 1). The highest induction (70%) was found in the cycloaddition of naphthazarin (2) with 1-[1-phenylethoxy]-3-trimethylsilyloxybuta-1,3-diene (4g). This is clearly higher than can be expected for steric differences between R_4 and R_5. This effect was also observed for other alkoxy groups with R_5 having π-electrons or non bonded electronpairs close to the chiral centre such as 2-methoxyisopropoxy (4j) and 1-vinylethoxy (4k). Variation of the R_4 group for R_5 = phenyl (4 g-i) lowers the d.e. Increasing the distance of the methoxy or phenyl-substituent in R_5 leads to a strong lowering of the d.e. (e.g. 4l and 4m).

The effect of the electron density of the phenyl group in R_5 on the d.e. is presented in Table 2. Besides naphthazarin (2), juglone (1) and benzoquinone (12) were used. For all the quinones presented in Table 2 we found that the d.e. decreases with decreasing electron-density of the phenyl-ring in the chiral group. The largest d.e. was found in the reaction of benzoquinone (12) with 1-[1-(*p*-methoxyphenyl)-ethoxy]-3-trimethylsilyloxy-buta-1,3- diene (4o).

Table 2. Diels-Alder reaction of dienes 4 with dienophiles 1, 2 and 12*.



1, 2 and 12 4 8, 9 and 13

			9		8		13	
Diene	R_4	R_5	d.e.**	yield	d.e.**	yield	d.e.**	yield
4n	Me	p-CF_3-Ph	57	51	46	53	63	49
4g	Me	Ph	70	62	66	79	90	53
4o	Me	p-MeO-Ph	92	54	68	40	99	55

* reactions were carried out using racemic dienes 4 in THF (0.1 molar solutions with the diene in 50% excess). The cycloaddition has completed after 16-20 hr at room temperature. The yields are isolated yields after precipitation in THF/n-hexane.

** diastereomeric excess (d.e.) in % determinated by ^{1}H-NMR spectroscopy. The d.e. of the reaction mixture determined with HPLC for the cycloadditions of 4n-o with 2 showed the same ratios as found with ^{1}H-NMR.

Only one isomer can be detected by ^{1}H-NMR spectroscopy. Because the optically active 1-(*p*-methoxyphenyl)-ethanol was not available we used S-(-)- and R-(+)-1-phenylethanol to determine the absolute configuration of the Diels-Alder adduct with benzoquinone (12). The d.e. found for this reaction was 90% and we were able to isolate the pure diastereoisomer after several crystallizations.

The X-ray analysis (Figure 1) of the cycloadduct of benzoquinone (12) and S-(-)-diene (4g) shows that the formed chiral centre also has the S-configuration at the position where the chiral alkoxy group is attached.

Figure 1

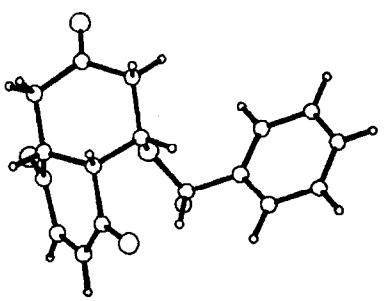
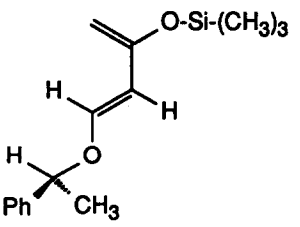


Figure 2



The results presented above are in agreement with a mechanism in which the diene adopts in the transition state the conformation presented in Figure 2 and in which the diene is approached from the side of the methyl-substituent.

This conformation is the most stable one as appears from CPK models and Computer Assisted Molecular

Modelling. First this model explains the decreasing d.e. found for the dienes 4g, 4h and 4i. As the aryl group is smaller in size than the *tert.* butyl group the observed high induction for the dienes 4g, 4n and 4o can however only be understood when the aryl-substituent is strongly enlarged by complexation with an electron-poor molecule. As this can not be the solvent (THF) it must be the quinone part of the used dienophile. In agreement with this supposition the d.e. decreases with decreasing electron-density of the aryl-substituent (Table 2). The relatively high induction caused by the dienes 4j and 4k can be explained in the same way. Also in agreement with this model the d.e. decreases when the complexing substituent is too far removed from the chiral centre (dienes 4l and 4m).

In a cycloaddition of acrylic esters with dienes having the same chiral 1-alkoxy groups Charlton et al[12] observed also a higher induction for phenyl (compare 4g) substituent than for the *tert.* butyl (compare 4e) substituent. The stronger effect of the phenyl substituent was ascribed to enlargement of the effective size of the phenyl group due to specific and stronger solvatation (solvent toluene). We found practically the same induction for the cycloaddition of diene (4g) with the dienophiles naphthazarin, juglone and benzoquinone in the solvents cyclohexane, benzene and THF which makes such a solvent effect unlikely.

In agreement with the conclusions of Charlton et al[12] we conclude from CPK models that π-stacking according to the Trost[13]-model is not possible in our case.

We are currently applying the chiral dienes in the synthesis of chiral daunomycinone analogs.

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8 As appears from literature and our investigations substituted quinizarine quinone epoxides are not/or very difficult available. Therefore these chiral synthesis seem to be restricted to the synthesis of 4-demethoxydaunomycinone.

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10 The ^{1}H-NMR of the cycloadducts 5-7 shows only the *endo* isomer for R = *tert.* butyl (see also reference 7). Therefore the assumption has been made that only the *endo* adducts are formed (see also references 4a and 4b). The d.e. of the cycloadducts (8, 9 and 13) can be determined by ^{1}H-NMR using the racemic dienes. In three cycloadditions (dienophiles 1, 2 and 12) we have also used the optically active diene 4g made from the (R)-(+)- and (S)-(-)-1-phenylethanol.

11 400 Mhz ^{1}H-NMR was used out in most examples. The d.e. was determined by integration of the aromatic OH protons at 12-14 ppm that have different shifts for both diastereoisomers. Also the alkyl substituent (R_4) at ~1 ppm show sufficient shift differences to determine the d.e.

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