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SYNTHESIS OF SPECIFICALLY O-ALKYLATED ANTHRAQUINONES BY CYCLOADDITION

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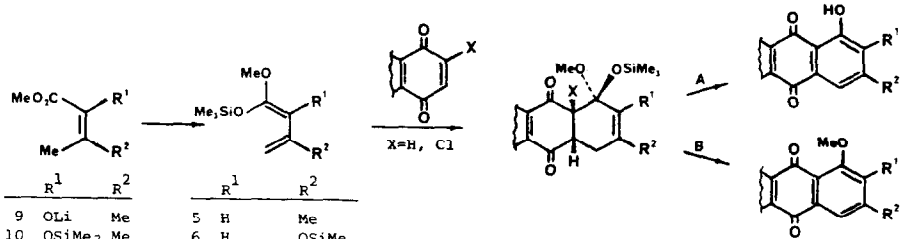
Abstract. Cycloadducts from naphthoquinonoid dienophiles and 1-methoxy-1-trimethylsilyloxy butadienes undergo controlled aromatisation to form chiefly α-hydroxy- or α-methoxy-anthraquinones; this has led to synthesis of several natural O-methyl polyoxyanthraquinones.

In recently characterising cycloadducts of certain 1-methoxy-1-trimethylsilyloxy butadienes with quinonoid dienophiles[1] we noted their potential, through the mixed acetal function at C1, for alternative aromatisation to either α-hydroxy (A) or α-methoxy (B) products (Scheme). Other workers have observed examples of both products from related cyloadducts.[2,3]

This paper systematises these processes, so that either can be made to predominate, for a range of cycloadducts (1a,b - 4a,b), all involving dienes derived by O-silylation of ester enolates[2]. It then applies the resulting selectivities to synthesising for the first time several partially O-methylated polyoxy anthraquinones of natural origin.

The cycloadducts (1a,b - 4a,b) comprise two types (X=H, Cl), the former one oxidation level lower than the latter and than the corresponding aromatisation products. They were derived from the standard dienophiles 5-hydroxy-1,4-naphthoquinone and its 3-chloro derivative according to established regioselectivity.[1,2] The diene components included the known 1,1-dioxy-[2], 1,1,3-trioxy-[1] and 1,1,2,3-tetraoxy-[4] systems (5-7) and the new 1,1,2-trioxy diene (8). Compound (8) [δ_{CDCl_3} 0.17, 0.22 (2 x $SiMe_3$); 1.93, 3.59 (C-, O-Me); 4.76, 5.04 ($=CH_AH_B$)], required for synthesis of the natural quinones discussed later, was obtained by adapting a known preparation of α-keto esters.[5] Thus the enolate (9), derived from dilithiated 2-methylpropanoic acid with dimethyl oxalate and subsequent decarboxylation, was quenched with Me_3SiCl to give the silyloxy ester (10) [δ 0.07 ($SiMe_3$); 1.87, 2.04 (2 x CMe); 3.86 (OMe)] (73%); subsequent silylation of its dienolate (LDA) then gave (8) (79%).

Cycloadducts (1a,b - 4a,b) in CH_2Cl_2 were subjected at room temperature to several aromatisation procedures, some of which proved consistently useful. Thus the strongest preference for formation of hydroxy products (11-14) (71-96%) over their methoxy analogs (15-18) (0-13%) resulted from deliberate hydrolysis (HCl/MeOH or Bu_4NF/THF), aerial oxidation



	R^1	R^2
9	OLi	Me
10	$OSiMe_3$	Me

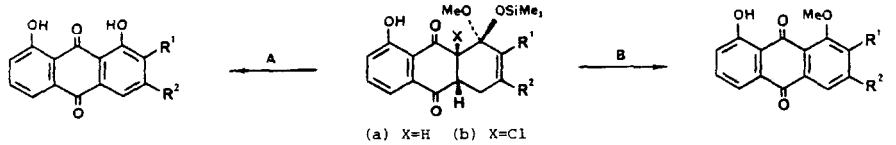
	R^1	R^2
5	H	Me
6	H	$OSiMe_3$
7	OMe	$OSiMe_3$
8	$OSiMe_3$	Me

Scheme

accompanying the process where X=H. A similar preference for methoxy (59-90%) over hydroxy (5-15%) resulted from direct oxidation (DDQ) of the four adducts (1a-4a). For the chloro adducts (1b-4b) no conditions were found which consistently gave as sharp a preference for methoxy. The most effective yields of methoxy products (31-63%) resulted from base-catalysed elimination (NaOAc/MeOH). The hydroxy analogs (18-62%) were also invariably formed; however, in only one case [adduct (4b)] did the latter product (14) (62%) predominate over the former (18) (31%). Alternative catalysis by the stronger base DBU proved unpredictably substrate-dependent; thus with adducts (1b) and (4b) it gave almost exclusively the methoxy- (15) (96%) and hydroxy- (14) (95%) products respectively while with the two remaining chloro adducts (2b, 3b) it gave comparable proportions of both types of product.

Similar trends were observed also for aromatisation of bicyclic adducts of the dienes (5, 8) with 2,6-dichloro-1,4-benzoquinone. These observed selectivities are likely to involve conformational as well as electronic factors but, given the complexity of the overall process, they have not been accounted for in detail nor is it clear to what extent they can be generalised. However the examples as a whole serve as ideal models for controlled synthesis of partially O-methylated polyoxy quinones not amenable to conventional techniques for selective methylation or demethylation. Target systems, all of plant origin, are well exemplified by structures (19, 23, 27). Apart from O-alkylation they incorporate a common A-ring. All have now been synthesised by cycloaddition of diene (8) to appropriately substituted naphthoquinones with subsequent aromatisation under the relevant conditions. As the simplest possible example, treatment of the adduct from (8) and 1,4-naphthoquinone with DDQ gave digitolutein (19)[6], m.p. 220-222.5° (81%); acidic treatment of the analogous adduct from 2-chloro-1,4-naphthoquinone gave 3-methylalizarin (20)[6], m.p. 240-241° (91%).

More highly substituted systems have been synthesised analogously, the necessary regiochemical control being achieved conventionally by a 2(3)-chloro group in the naphthoquinonoid dienophile or, in its absence, equivalently by an 8(5)-hydroxy group.[1,2] Thus adduct (4a) with DDQ gave obtusifolin (18),[7,8] m.p. 242-243° (59%) and nor-obtusifolin (14),[7,8] m.p. 244-245° (13%), the former synthesised for the first time. A high yield of the latter (96%) resulted from acidic hydrolysis of the chloro adduct (4b). The regioisomeric series, compounds (21), m.p. 249-251° (52%) and (22), m.p. 271-272° (36%) were obtained by treatment of the cycloadduct from (8) and 2-chloro-5-hydroxy-1,4-naphthoquinone with NaOAc/MeOH. Structure (21) has been reported from teak tissue cultures.[9] As expected, the spectra of regioisomers (18), (21) were qualitatively similar but the former structure was established originally by unambiguous degradation.[7] Furthermore the two isomers had $\delta_{\alpha\text{-OH}}$ 12.83, 12.70 respectively, the small deshielding of the former being orientationally significant[10] [cf. also the model compounds 1-hydroxy-5(8)-methoxy-9,10-anthraquinone, δ_{OH} 12.46 (12.95)[11] and

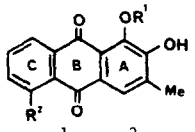


(a) X=H (b) X=Cl

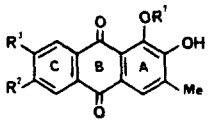
	R^1	R^2
11	H	Me
12	H	OH
13	OMe	OH
14	OH	Me

	R^1	R^2
1	H	Me
2	H	$OSiMe_3$
3	OMe	$OSiMe_3$
4	$OSiMe_3$	Me

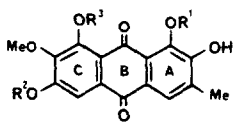
	R^1	R^2
15	H	Me
16	H	OH
17	OMe	OH
18	OH	Me



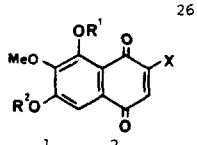
	R^1	R^2
19	Me	H
20	H	H
21	Me	OH
22	H	OH



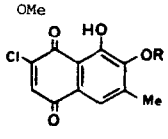
	R^1	R^2	R^3
23	Me	OMe	H
24	Me	H	OMe
25	H	OMe	H
26	H	H	OMe



	R^1	R^2	R^3
27	Me	H	H
29	Me	Me	H
31	Me	Me	Me
33	H	Me	Me
34	H	H	H
35	H	Me	H
38	H	H	Me



	R^1	R^2	X
28	H	Ac	H
30	H	Me	H
32	Me	Me	Cl
36	H	Ac	Cl
37	H	Me	Cl



39 R=H
40 R=Ac

2,5(8)-dihydroxy-9,10-anthraquinone, $\delta_{\alpha\text{-OH}}$ 12.72 (12.38)[12].

In an analogous regiochemical problem the structure of a β-methoxy anthraquinone, from a Digitalis sp., formulated[13] as either the 6- or the 7-methoxy compound (23), (24) respectively, is now confirmed as (23)[8] by unambiguous synthesis of both. As expected these isomers were very similar but they were resolved by hplc. Compound (23), m.p. 233-234.5° (61%) was formed by treatment of the adduct from (8) and 2-chloro-6-methoxy-1,4- naphthoquinone[14] with NaOAc/MeOH; compound (24), m.p. 224-225° (54%) resulted similarly from 2-chloro-7-methoxy-1,4-naphthoquinone.[14] Regiochemistry was independently confirmed by consideration of the α-hydroxy compounds (25), m.p. 226-227°, $\delta_{\alpha\text{-OH}}$ 12.92 (23%) and (26), m.p. 258-259°, $\delta_{\alpha\text{-OH}}$ 12.67 (44%), obtained as by-products from the respective aromatisations; the greater deshielding of the α-OH resonance in the former compound is consistent with expectation.[10]

Attention was then directed towards the several derivatives of 1,2,3,7,8-pentaoxy-6-methyl-9,10-anthraquinone from Cassia spp. Synthesis of aurantioobtusin (27)[15], as example, requires not only regiochemical control but selectivity in assembling two α- and three β-oxy substituents with only one out of each group specifically methylated. It was synthesised from the dienophile (28), m.p. 143-144° [δ 2.36 (OAc), 4.04 (OMe), 12.28 (OH)] (76%), itself obtained by successive treatment of 1,4-benzoquinone with diene (7), acidic aromatisation (HCl/MeOH) and selective β-acetylation (Ac_2O/C_5H_5N). The cycloadduct from (28) and diene (8) was aromatised with retention of α-methoxy (DDQ); deprotection of the resulting acetate (87%) with NaOH then gave aurantioobtusin (27)[8,15], m.p. 268-269°. This procedure was readily adapted also to give obtusin (29)[8]. Selective β-methylation (MeI/Ag_2O) rather than β-acetylation gave the dienophile (30), m.p. 163-164° [δ 4.00, 4.01 (2 x OMe), 12.05 (OH)] (63%), treatment of which with diene (8) then DDQ gave (29)[8], m.p. 244.5-246° (71%).

Another co-metabolite, chrysoobtusin (31),[15] was derived from the chloro dienophile (32)[16], the chloro group assisting correct regioselection in the presence of the α-methoxy. Its adduct with diene (8) was aromatised (NaOAc/MeOH) to give (31)[8,15], m.p. 215-216° (58%) together with its α-hydroxy analog (33), m.p. 208-209° (23%), itself a natural product.[17] Compound (33) was obtained more efficiently (77%) by acidic aromatisation of the cycloadduct (HCl/MeOH). Because cycloaddition of the dienophile (32) to a less reactive diene has been observed to proceed with unconventional regiochemistry[18] a further, independent synthesis of chrysoobtusin (31) was

devised. Thus successive β-acetylation (Ac_2O/C_5H_5N) of obtusin (29) (93%), methylation (MeI/Ag_2O) (82%) and deprotection (NaOH) gave the same (31) (95%).

By simple extrapolation structures recently assigned[17] to two further natural products (34), m.p. 297-300° (78%) and (35), m.p. 259-260° (84%) have also been synthesised from the respective dienophiles (36) and (37) by reaction with (8) and hydrolytic aromatisation of the cycloadducts (HCl/MeOH), with deprotection where needed. The two dienophiles were derived unexceptionally by reaction of diene (7) with 2,6-dichloro-1,4-benzoquinone, aromatisation (HCl/MeOH) and either selective β-acetylation (Ac_2O/C_5H_5N) or selective β-methylation (MeI/Ag_2O) as required. Finally synthesis of structure (38), also assigned to a natural compound,[19] has been carried out by variation of procedure so as to form the A-ring before the C-. Thus aromatisation (HCl/MeOH) of the cycloadduct from (8) and 2,6-dichloro-1,4-benzoquinone gave the α-hydroxy product (39) (93%), selective protection of which gave the β-acetate (40), m.p. 175-176°, [δ 2.32 (6-CH_3), 2.41 (OAc), 7.17 (H3), 7.53 (H5), 11.75 (OH)]. Addition of diene (7), aromatisation (NaOAc/MeOH) and deprotection (NaOH) gave (38)[19], m.p. 258-260° [50% from (40)]. A synthesis by Friedel-Crafts chemistry has also been reported.[20]

Satisfactory spectra and analytical data or exact masses have been obtained for all new compounds herein. We are grateful to Professor M. Takido for authentic samples of (14), (18), (27), (29), (31), to Professor S. Imre for a sample of (23) and to Dr C. L. Gibson for discussion. We acknowledge financial support from the Australian Research Grants Scheme and an Australian Postgraduate Research Award (to J.S.)

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