Organometallic Additions to Protected Quinone Bis-epoxides and Quinone Monoacetals: Synthesis of the Aranorosin Nucleus

Alexander McKillop,*[a] Richard J. K. Taylor,*[a] Robert J. Watson[a] and Norman Lewis[b]

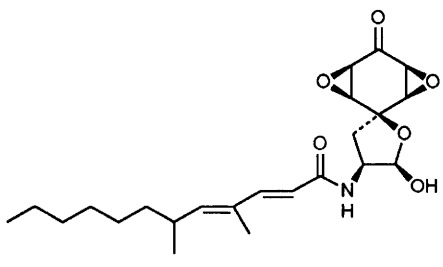
[a] *School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK*
[b] *SmithKline Beecham Pharmaceuticals, Leigh, Tonbridge, Kent TN11 9AN, UK*

The addition reactions of organometallic reagents to monoprotected quinone bis-epoxides **7** and quinone monoacetals **5** provide a route to the highly oxygenated cyclohexanols **2** and **3**; the application of this methodology to the preparation of the aranorosin analogue **4** is described.

Aranorosin **1** has been isolated from a fungal strain, *Pseudoarachniotus roseus*, and shown to possess antibiotic, antifungal and antitumour properties.[1,2] Potential biomimetic routes to aranorosin have recently been described.[3,4] In this communication, we report a general method for the synthesis of protected 4-substituted-4-hydroxycyclohexanone bis-epoxides **2** and the parent ketones **3**, together with a short synthesis of desamido-aranorosin **4**. To our knowledge this is the first synthesis of the tetracyclic aranorosin nucleus.

Two approaches were investigated for the preparation of requisite cyclohexanones **3** in a stereocontrolled manner (Scheme 1). We first examined organometallic addition to the monoprotected quinone bis-epoxides **7a,b**, which were prepared from protected quinones **5a, b**[5] *via* adducts **6a**† using a modification of the procedure described by Keller in the patent literature.[6]

Organolithium reagents underwent clean addition to ketone **7a** at −78 °C in tetrahydrofuran (THF) as solvent giving diastereoisomeric alcohols **2a** and **8a** (Table 1).‡ The isomeric



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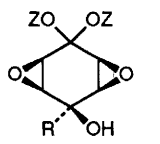
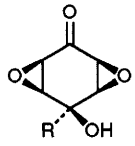


2a; Z, Z = $-CH_2CH_2-$
b; Z = Me



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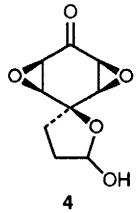

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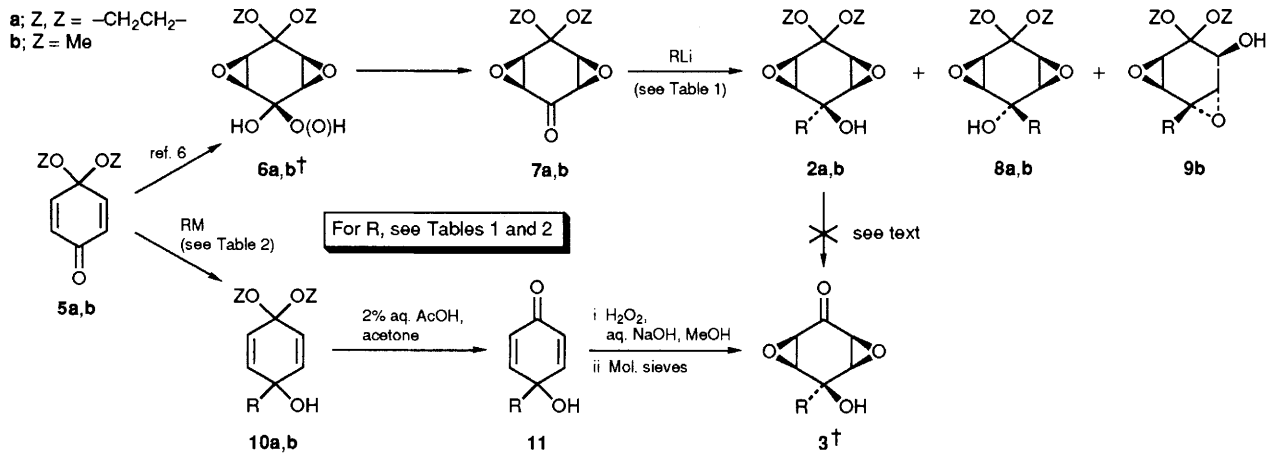
† **CAUTION:** Although compounds **6a,b** are described as hydrates in the patent literature,[6] it seems likely that they are, in fact, monoperoxyhydrates. Certainly, compound **6a** gave a positive peroxide test and an elemental analysis consistent with monoperoxyhydrate structure. The bis-epoxidation of dienones **11** appeared to proceed by way of related intermediates. Great care should therefore be taken when repeating any of these bis-epoxidation reactions.

‡ All new compounds gave consistent spectral and analytical/mass spectrometric data.



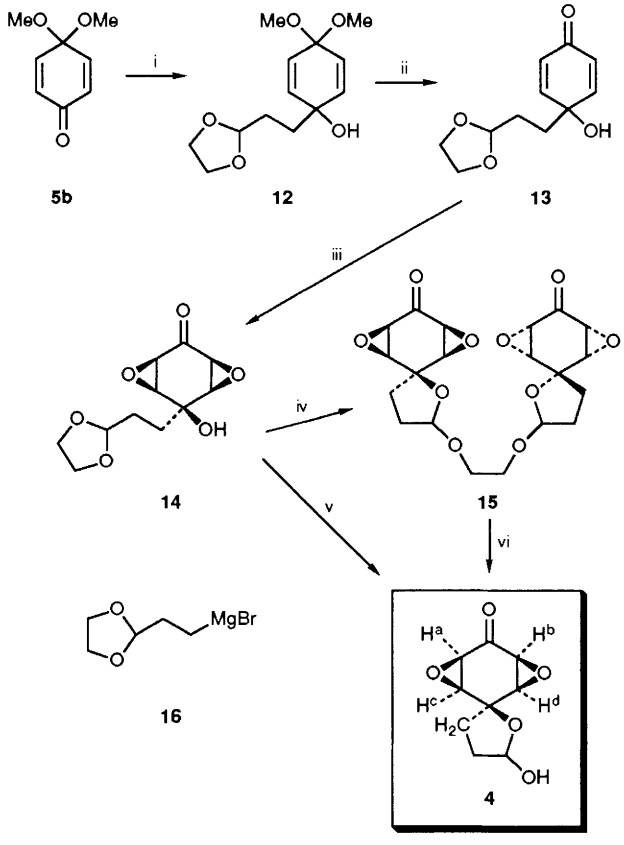
Scheme 1

Table 1 Organometallic addition to ketones (**7a,b**)

		Isolated product yield (%)		
Ketone	Reaction conditions, (*T*/°C)	**2**	**8**	**9**
7a	MeLi/THF (−78)	49	16	—
7a	MeLi·LiI/THF (−78)	39	39	—
7a	PhLi/THF (−78)	49	16	—
7a	$PhSO_2CH(Li)Me$/THF (−78)	53	26	—
7b	PhLi/THF (−78)	35	20	6
7b	PhLi/THF (−95)	45	20	10
7b	PhLi/Et_2O (−78)	20	15	35
7b	PhLi/Et_2O (−95)	10	12	47

Table 2 Organometallic addition to ketones **5a,b**; isolated yields of **11** and **3**

		Product yields (%)	
Ketone	Organometallic reagent	**11**	**3**
5a	PhLi/THF	75	80
5b	MeLi/THF	86	45
5b	BuLi/THF	77	55
5b	$ClMg(CH_2)_3OMgCl$/THF	50	60
5b	PhLi/THF	80	80



Scheme 2 *Reagents and conditions*: i, **16**, THF, −78 °C; ii, SiO_2, $(COOH)_2$, CH_2Cl_2 (72% from **5b**); iii, H_2O_2, aq. NaOH, MeOH then 4A molecular sieves, EtOAc (80%); iv, $PdCl_2·(MeCN)_2$, acetone, 3 h (93%); v, $PdCl_2·(MeCN)_2$, aq. acetone, 3 d (60%); vi, SiO_2, aq. H_2SO_4, CH_2Cl_2 (ca. 25%)

alcohols could be separated by chromatography on silica gel. The structures were confirmed by ^1H NMR spectroscopy, nuclear Overhauser experiments being particularly informative [*e.g.* an NOE enhancement was observed between the hydroxy proton and the adjacent epoxy methine for (**8a**, R = Me) but not for **2a** and an NOE of 15% was observed between the *ortho*-phenyl proton and the adjacent epoxy methine proton of (**2a**, R = Ph)]. With dimethyl acetal **7b**, epoxide migration[7] took place, (**9b**, R = Ph) being formed in low yield from the PhLi/THF reaction and as the major product when diethyl ether was employed as solvent. It is also noteworthy that the stereoselectivity of the organometallic addition reaction is higher (in the desired sense) with the dioxolane acetal **7a** than with the dimethyl acetal **7b**. In order to complete the preparation of the desired cyclohexanones **3** all that remained was to remove the acetal protecting group. Unfortunately, despite trying a wide range of deprotection procedures[8] on both **2a** and **2b** the transformation to ketones **3** could not be accomplished: no reaction occurred under mild conditions and the use of more forcing conditions resulted in decomposition.

We therefore reversed the order of events and first carried out the addition reactions on the monoprotected quinones **5a,b** to give adducts **10a,b** using Swenton's methodology.[5,9] Removal of the acetals was now straightforward and epoxidation gave the desired bis-epoxides **3**† in reasonable overall yields (Table 2). The two main advantages of this second sequence are that it gives the target system in unprotected form and the epoxidation reaction appears to proceed with total stereoselectivity in the required manner.

This methodology was then applied to the preparation of the aranorosin analogue **4** as shown in Scheme 2. The Grignard reagent derived from 3-bromopropanal ethylene acetal[10] underwent efficient addition to **5b** to give adduct **13** in

72% yield after selective acetal hydrolysis. Dienone **13** was epoxidised under standard conditions† and again only the *cis*-stereoisomeric product **14** was observed. Attempted acetal hydrolysis under acidic conditions gave only low yields of the desired lactol **4**. The use of $PdCl_2{\cdot}(MeCN)_2$[11] in anhydrous acetone gave the dimeric product **15** in high yield but the use of aqueous acetone and longer reaction times proved more successful. The structure of **4** was confirmed by 400 MHz NMR spectroscopy, large W-coupling being observed between H^a/H^b (2.7 Hz) and H^c/H^d (4 Hz). In addition, a strong NOE was observed between H^c and H^d and the nearby tetrahydrofuranyl methylene protons. Aranorosin analogue **4** displays a low level of antibiotic activity (100 μg ml^{-1}) against a range of Gram-negative bacilli and against *Staphylococcus aureus*.

We are currently exploring the synthetic utility of epoxides **2** and **3** as well as applying the above methodology to the synthesis of aranorosin itself.

We are grateful to the SERC and SmithKline Beecham for the award of a CASE studentship to R. J. W. We also thank Dr O. W. Howarth and the SERC WH-400 NMR Service, University of Warwick, for assistance with the NMR studies.

Received, 20th July 1992; Com. 2/03866H

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