Enantiospecific total synthesis of (+)- and (−)-avarone and -avarol

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Enantiopure avarol and its oxidized congener avarone are synthesized in both podal series from an optically pure Wieland–Miescher enone; preliminary results from biochemical studies are summarized.

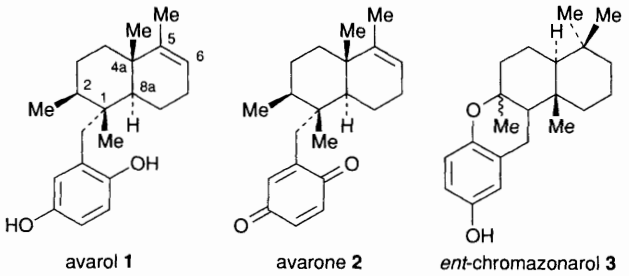
The sesquiterpene hydroquinones and quinones represent a class of natural products of mixed biogenesis having both a cyclized isoprenoid skeleton derived from a farnesyl precursor and a common 1,4-dioxygenated aromatic substituent. Although well characterized structurally, many of these compounds are associated with a wide array of relatively unexplored biological activities.[1] Dissection of the nature of these activities at a mechanistic level has been hampered by the absence of any reported synthesis of optically pure material. Herein we report the first enantioselective syntheses of avarol **1**[2] and avarone **2**[2] and the results of initial biochemical studies intended to define the basis for the behaviour of these compounds in biological systems. To facilitate an analysis of biochemical properties that derive from spatially selective interactions, we also report the first syntheses of the antipodes of avarol and avarone.

Avarol **1** was originally isolated[2] from the marine sponge *Disidea avara* in 1974 along with minor amounts of its oxidized congener avarone **2**. Its structure, which was determined through degradative and spectroscopic studies,[2,3] and later by chemical synthesis,[4] represents the first example of a naturally occurring sesquiterpene possessing a 9,4-friedodrimane skeleton. Avarol possesses the same absolute configuration[2,3] as *ent*-chromazonarol **3**,[5] polygodial[6] and other related bioactive sesquiterpenes and may be related to these drimane terpenoids biogenetically through an interesting 'friedo'-rearrangement.[2,7]†

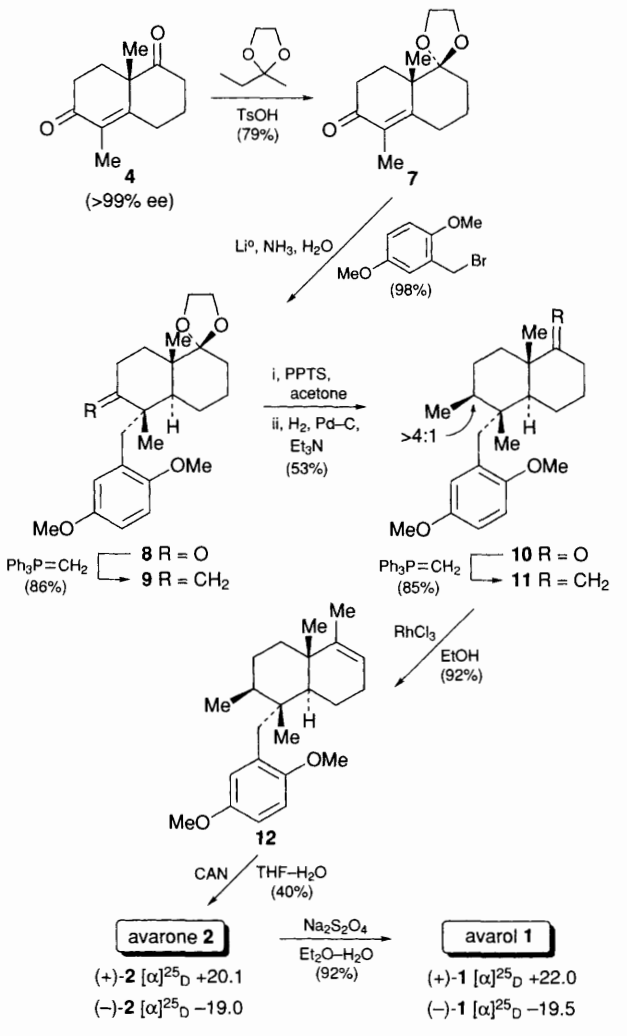
Both avarol and avarone are reported to possess antimiotic[8] and antimutagenic activity,[9] and are highly potent antileukemic agents *in vitro*, as well as in L5178Y lymphoma-bearing mice.[10] Additionally, these compounds inhibit the replication of HTLV-III/LAV,[11] the etiologic agent of AIDS. Although the molecular events responsible for these phenomena remain obscure, it may be noted that avarone and avarol have been shown to inhibit the reverse transcriptase from HIV.[12]

Our synthetic approach began from optically pure‡ enone **4** which was readily available in either podal series through an asymmetric Robinson annulation and recrystallization (60–65% yield, >99% ee).[15] Chemoselective protection of **4** *via* transketalization[16] provided **7** cleanly in 79% yield (Scheme 1). Reductive alkylation§ of dioxolane **7** (Li, liquid NH_3, H_2O) employing 2,5-dimethoxybenzyl bromide¶ as the alkylating agent gave ketone **8** diastereoselectively and in excellent yield (92–98%).

Elaboration of the stereocentre at C-2 was accomplished by Wittig olefination[17] of the ketone and subsequent palladium-catalysed hydrogenation of the resulting exocyclic double bond. The extent of diastereoselectivity in the reduction was affected significantly by the nature of the substituent at C-5. When catalytic hydrogenation was carried out on ketal **9**, a 3:2 mixture‖ of chromatographically separable stereoisomers at C-2 was obtained, favouring the desired β-isomer. However, if the ketone was unmasked prior to the reduction step, the selectivity was increased to >4:1 (β:α) at C-2. In spite of the small energetic difference reflected in this change in selectivity, we reasoned that removal of the axial ketal functionality at C-5 might relieve steric interactions with the catalyst surface, allowing for improved facial selectivity.[18] In fact, reversing the order of the reduction–deprotection sequence improved the diastereoselective induction at C-2 significantly, and provided



avarol **1** avarone **2** *ent*-chromazonarol **3**



Scheme 1

the desired ketone **10** in 46% overall yield from **8**. A single crystal X-ray structure analysis of **10** established its structure and relative stereochemistry unambiguously.[19]

With all of the stereocentres present in avarol established in ketone **10**, the remaining transformations required for completion of the synthesis involved introduction of a vinyl methyl group at C-5 and deprotection of the aryl moiety. In Sarma's report,[4] the vinyl methyl group was introduced in 68% yield by 1,2-addition of MeLi, subsequent dehydration of the tertiary alcohol to afford a mixture of alkene regioisomers, and finally complete isomerization to the *endo*-alkene employing rhodium trichloride as catalyst. We have found that Wittig olefination of **10** cleanly provides *exo*-alkene **11** which can be isomerized completely to avarol dimethyl ether **12** in an overall yield of 78% using 20 mol% of the rhodium trichloride catalyst.

Initial attempts to convert ether **12** directly to avarol proved problematic. Treatment of **12** with BuSLi in hot HMPA[4] or *N,N'*-dimethylpropyleneurea gave complex mixtures, unsatisfactory yields (< 20%) and poor reproducibility. The use of BBr_3 resulted in deprotection with concomitant loss of the $\Delta^{5,6}$-alkene. Subsequently, we found that oxidative removal of the ether protecting groups with ceric ammonium nitrate[20] at 0 °C cleanly afforded avarone **2**, which was then reduced in the presence of sodium hydrosulfite[21] to the target compound **1**. This last sequence of transformations proceeded under relatively mild conditions and provided avarol **1** and avarone **2** in 37 and 40% yields, respectively, from dimethyl ether **12**. Synthetic avarol was identical with a naturally derived sample.

The foregoing route requires nine synthetic steps and proceeds in 10% overall yield from the readily available Wieland–Miescher type enone **4**. Both the natural and unnatural isomers of avarol and avarone are obtained by this approach with equal facility. With significant quantities of avarol and avarone in hand, we have initiated studies to define the biochemical properties of avarol and avarone responsible for the observed antitumour and antiviral activities of these compounds.[22]

Initial evaluation of the effects of the enantiomers of avarol on critical biochemical loci in HIV-1 has indicated that both inhibited HIV-1 reverse transcriptase when employed at high concentrations, and inhibited the transcription/translation of a DNA construct identical in sequence with the *gag-pol* junction. However, neither isomer of avarol specifically inhibited ribosomal frameshifting nor the function of the derived HIV-1 protease. Both enantiomers of avarol and avarone exhibited moderately strong inhibition of HIV-1 integrase, with the natural isomers being slightly more potent. The binding of both isomers of avarol and avarone to DNA was reflected in their ability to modulate DNA cleavage by Fe^{II}-bleomycin.

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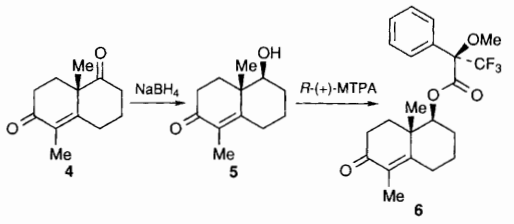
Footnotes

† The feasibility of this type of rearrangement involving a series of 1,2-shifts was used to show the relationship between β-amyrin and the cork constituent friedelin. Minale *et al.*[2] proposed that a similar relationship exists between avarol and drimane sequiterpenes such as *ent*-chromazonarol, hence the classification 'friedodrimane.' Thus, rearrangement of a putative intermediate derived from cyclization of a farnesyl precursor plausibly links the biogenesis of the drimane and friedodrimane sesquiterpenes.

‡ The enantiomeric purity of recrystallized **4** was determined by a procedure similar to that described in ref. 13. Stereoselective reduction of **4** ($NaBH_4$, EtOH, 0 °C) furnished alcohol **5**, the latter of which was treated with *R*-(+)-Mosher's acid[14] (DCC, DMAP, CH_2Cl_2) to give Mosher's ester **6**. Analysis of the δ 3.40–3.60 region of the ^1H NMR spectrum of optically active **6** revealed a single diagnostic methoxy resonance at δ 3.56. Racemic **6** prepared in the same manner showed two singlet resonances (48 : 52 ratio) at δ 3.50 and 3.56 for the diastereotopic methoxy substituents. These findings, along with the optical rotation obtained for **4** {$[\alpha]_D$ + 150.8 (*c* 1.49, CH_2Cl_2); lit.[15] $[\alpha]_D$ + 140 (*c* 0.20, CH_3OH)}, indicate >99% ee.



§ Reductive alkylation was carried out on dioxolane **7** using the method described in ref. 4, but using H_2O as a proton source.

¶ Synthesized from commercially available 2,5-dimethoxybenzyl alcohol and Ph_3PBr_2: mp 74–75 °C (lit.[4] mp 74–75 °C).

‖ The ratio of diastereoisomers was determined as previously described (ref. 4).

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