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A Total Synthesis of the Sesquiterpene Quinone Metachromin-A

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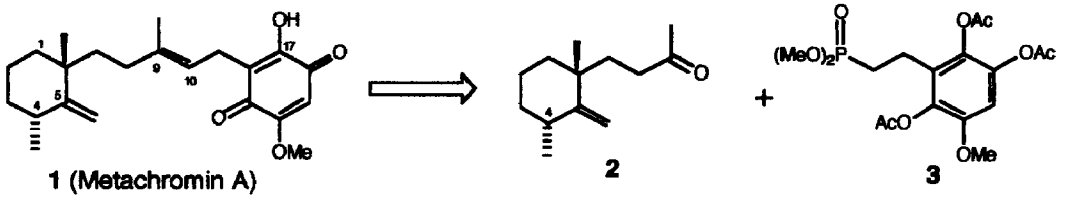
Abstracts: The first total synthesis of the marine natural product metachromin A was accomplished through a convergent synthesis amenable to the preparation of synthetic analogues. The main features of this synthesis are the introduction of the oxygenation at C_{17} employing a Thiele acetoxylation reaction and a stereoselective Horner-Wadsworth-Emmons coupling of a nonstabilized phosphonate with a methyl ketone derivative to generate the required (E)-trisubstituted double bond.

The search for biologically active natural products from marine organisms has been an intense scientific activity in the last two decades that has provided promising new leads for therapeutical investigations.[1] The recently discovered sesquiterpene quinones isolated from marine sources constitute a new and fascinating family of natural compounds possessing a diverse biological activity profile, making them valuable targets in medicinal chemistry.[2] Recently, Kobayashi and collaborators reported the isolation and structure elucidation of eight new, biologically active, sesquiterpene quinones from the purple-colored Okinawan marine sponge *Hippospongia metachromia*.[3] These were named metachromins A-H featuring an unusual carbon skeleton with few precedents in the literature. More importantly, metachromin A and B exhibited potent antineoplastic activity associated with a remarkable coronary vasodilating activity.

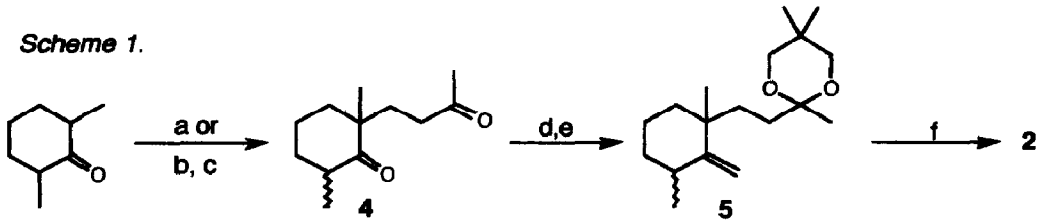
This dual biological characteristic of these new quinones makes them very attractive as synthetic targets and we herein report the first total synthesis of (+/-)metachromin A (1), the most abundant and one of the most active of the metachromins, employing a flexible and convergent synthetic strategy suitable for the preparation of synthetic analogues. The synthetic strategy was centered on a disconnection at the trisubstituted double bond between C9-C10 (figure), which generated two key fragments, the unsaturated ketone 2 and the aromatic phosphonate 3, that could be coupled by means of a Horner-Wadsworth-Emmons (HWE) reaction to construct the basic skeleton of the metachromins.

Figure: The Synthesis Plan.



We initiated the synthesis preparing the unsaturated ketone **2** (Scheme 1); Michael addition of the trimethylsilylenol ether derived from 2,6-dimethyl-cyclohexanone on methyl vinyl ketone (MVK), promoted by $BF_3.OEt_2$ in the presence of menthol, furnished diketone **4** (7:3 mixture of isomers by GC) in 70% overall yield for the two steps (silylenol ether formation and coupling to MVK). This protocol, developed by Duhamel,[4] proved to be more efficient for the preparation of diketone **4** than the one developed by Still[5] for the same compound (benzene, H_2SO_4, 53%). Protection of the less hindered keto group of **4** was accomplished using 2,2-dimethyl-1,3-propanediol (95%).[6] After blocking the aliphatic ketone the cyclic keto group was olefinated according to the conditions established by Fitjer[7] to provide the unsaturated ketal **5** in 80% yield. Attempts to hydrolyze the ketal protecting group of **5** with aqueous HCl, SiO_2 or oxalic acid resulted in isomerization of the exocyclic double bond to the thermodynamically more stable C_4-C_5 isomer. Successful removal of the protecting ketal was accomplished using PPTS in toluene to afford the unsaturated ketone **2** in 90% yield as a mixture of diastereomers at C_4 (9:1 ratio by GC). Thus, the ketone fragment bearing the appropriate stereocenters was conveniently prepared in 5 steps from 2,6-dimethycyclohexane in 48% overall yield.

Scheme 1.



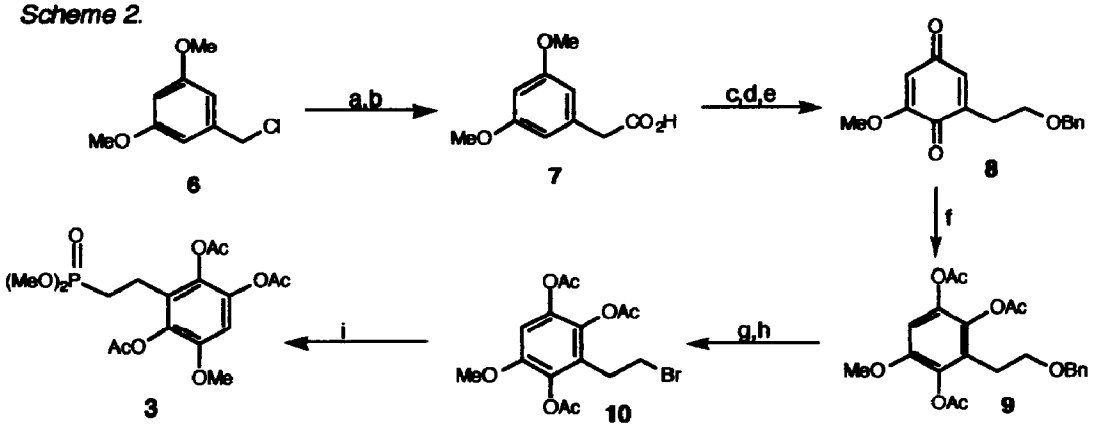
Reagents and Conditions: [a] methylvinylketone(MVK), benzene, H_2SO_4 (53%); [b] Et_3N, TMSCl, NaI-CH_3CN (82%); [c] MVK, CH_3NO_2, $BF_3.OEt_2$, menthol (85%); [d] $CH_2OHC(CH_3)_2CH_2OH$, p-TsOH, rt, C_6H_6 (95%) [e] t-BuOK, benzene, $CH_3P(C_6H_5)_3Br$ (80%); [f] PPTS, toluene, (90%)

After completion of the ketone fragment we then turned our attention to the preparation of the phosphonate **3** (Scheme 2). Reaction of the commercially available benzyl choride **6** with sodium cyanide gave the corresponding aromatic nitrile in 93% isolated yield. Basic hydrolysis of the nitrile intermediate occurred smoothly in the presence of H_2O_2 to provide the 3,5-dimethoxyphenyl acetic acid **7** in 90% isolated yield, whereas a lower yield of **7** (70%) is obtained without H_2O_2.[8] An alternative pathway to obtain the methyl ester of acid **7** employing an Arndt-Eistert synthesis[9] starting from 3,5-dimethoxybenzoic acid resulted in a very low yield of the desired compound (i: $SOCl_2$, pyr, THF (87%); ii: CH_2N_2, ET_2O; then Ag_2O (20%)) and was then abandoned. Reduction of the acid **7** by $LiAlH_4$ produced the corresponding primary alcohol (98%), which was immediately protected as the corresponding benzyl ether (84%) followed by oxidation of the 1,3-dimethoxy benzene moiety (CrO_3, $AcOH/H_2O$) to cleanly provide the known methoxy benzoquinone **8**[10] in 80% yield. The key oxygenated function at C_{17} was incorporated through a Thiele acetoxylation (Ac_2O, H_2SO_4) of the quinone **8** to give the triacetate **9** in 65% yield.[11] Next, the benzyloxy group was selectively removed by hydrogenolysis (85%) and the resulting alcohol converted into bromide **10** (80%). Finally, a Michaelis-Arbuzov reaction of bromide **10** with trimethyphosphite produced the desired phosphonate **3** in 56% yield.[12] Preparation of phosphonate **3** involved 9 steps with an overall yield of 14%.

The stage was then set for the coupling of fragments **2** and **3** (scheme 3). HWE reaction[13] of the sodium salt of phosphonate **3** (NaH, excess) with the unsaturated ketone **2** provided the known (E)-leuco-triacetate **11** in 40% isolated yield; use of t-BuOK as base gave identical results, however higher yields of **11** (~60%) were

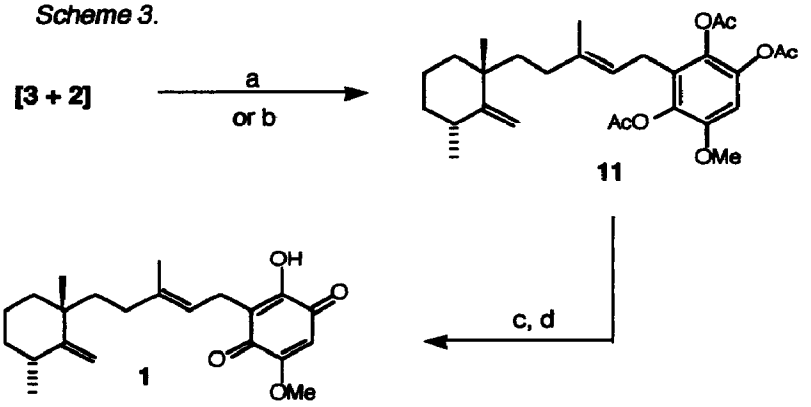
obtained when nBuLi (THF, -78 °C) was used as base to generate the lithium phosphonate salt This latter protocol produced a mixture of diastereomeric **11** (E:Z ratio 3:1) that were separated with difficulty by column chromatography (Hex-AcOEt). Removal of the acetate protecting groups with $LiAlH_4$ afforded a very polar triphenol that was not isolated, but immediately oxidized with $FeCl_3$ to produce the natural quinone metachromin A, isolated from the reaction medium as orange needles in 65% yield. The spectroscopic data obtained for the synthetic (+/-)metachromin A were in all respects identical to those reported in the literature and to the spectra (^1H NMR, ^{13}C NMR) kindly provided by Prof. Kobayashi (Hokkaido University, Japan).[3]

Scheme 2.



Reagents and Conditions: [a]: NaCN, EtOH/H_2O, reflux, 4 h (93%); [b]: NaOH (40% soltn.), EtOH, H_2O_2, reflux (90%); [c]: $LiAlH_4$, THF, reflux (98%); [d]: NaH, THF; then BnBr, reflux (84%); [e]: CrO_3, AcOH, H_2O, 0°C then rt, 2 h (80%); [f]: Ac_2O, H_2SO_4, rt, 12 h (65%); [g]: H_2, Pd-C, AcOEt, rt, 12 h (85%); [h]: CBr_4, Ph_3P, CH_2Cl_2, 0°C then rt, 6 h (80%); [i]: $(MeO)_3P$, DME, reflux, 3 h (56%)

Scheme 3.



Reagents and Conditions: [a]: **3**, THF, -78 °C then addition of n-BuLi soltn., -78 °C, 30 min., followed by slow additon of a THF soltn. of **2** (60% yield, E/Z mixture, 3:1); [b]: **3**, NaH, THF, 0 °C then rt, 30 min; followed by slow additon of a THF soltn. of **2**, reflux for 4 h (40% yield , E isomer only); [c]: $LiAlH_4$, THF, 0 °C (55%); [d]: Aqueous $FeCl_3$ 1%, benzene, rt, 20 min. (65%).

This convergent synthetic scheme has permitted us to prepare metachromin A in a straightforward manner and should be also amenable to the preparation of synthetic analogues for biological screening. Preparation of such analogues are in our future plans.

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