Stereoselective Total Synthesis and Enantioselective Formal Synthesis of the Antineoplastic Sesquiterpene Quinone Metachromin A

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The first total synthesis of the antineoplastic marine natural product metachromin-A (1) was accomplished through a convergent synthetic approach amenable to the preparation of analogues for biological studies. The synthesis involved twelve steps in its longest sequence and sixteen steps overall. The total synthesis of the racemic metachromin-A features: (1) an efficient synthesis of the quinone intermediate 11; (2) efficient protocols for the preparation of the key fragments 5 and 6; (3) a highly regioselective Thiele-Winter acetoxylation step; and (4) a stereoselective Horner-Wadsworth-Emmons coupling reaction employing fragment 6 as a non-stabilized phosphonate as an effective partner. The metachromin-A synthesis was made formally enantioselective by the asymmetric synthesis of fragment 5 employing the methodologies developed by Simpkins (asymmetric deprotonation with a chiral nitrogenated base) and d’Angelo (enantioselective deracemization). This latter protocol furnished fragment 5 with an enantiomeric excess of ~85%, as determined by \textsuperscript{1}H-NMR spectroscopy.

Keywords: metachromin A, sesquiterpene quinones, total synthesis, enantioselective synthesis

Introduction

The search for biologically active natural products from marine sources continues to be an important scientific endeavor\textsuperscript{1}. In the last twenty five years the number of compounds isolated from marine organisms has increased dramatically and has furnished a number of promising therapeutic leads. The recently discovered sesquiterpene hydroxyquinones and hydroquinones isolated from sponges constitute a fascinating family of natural products possessing a diverse biological profile, which has made them valuable targets in medicinal chemistry and synthesis. For instance, the metachromins A (1), B (2), and C (3), (Fig. 1) isolated from the purple-colored Okinawan marine sponge \textit{Hippospongia metachromia} displayed potent antineoplastic activity against L 1210 Leukemia cells \textit{in vitro}, as well as coronary vasodilating activity with IC\textsubscript{50} of 3 x 10\textsuperscript{-6} M\textsuperscript{2}. The recently discovered boliaquinone, 4, also
displayed cytotoxic activity with IC50 of 1.9 µg/mL against human colon tumor cell line HCT116, as well as mild inhibition of Bacillus subtilis at 80 µg/disk<sup>2</sup>. The pharmacological profile of bolinaquinone also suggested that the cytotoxicity displayed by these sesquiterpene hydroquinones results from interference with DNA or damage caused by them to DNA.

In view of the growing medicinal importance of compounds that interact directly with DNA we became interested in the total synthesis of members of this family of natural products. In 1994 we reported the first total synthesis of racemic metachromin A, the most abundant and most active of the metachromins, employing a convergent methodology amenable to the synthesis of derivatives and analogues<sup>3</sup>. Herein we report these findings in full and the incorporation of some synthetic advancements that permitted a formal total synthesis of metachromin A in enantioenriched form.

**Results and Discussion**

**The synthesis plan**

The synthetic strategy was centered around a convergent plan that involved a key disconnection at the (E)-trisubstituted double bond between C9-C10 (Fig. 2). This disconnection generates two fragments, an unsaturated ketone 5 and the rather complex phosphonate 6, which in principle could be coupled by means of a Horner-Wadsworth-Emmons (HWE) protocol<sup>4</sup>. The use of a phosphonate instead of the more basic Wittig triphenylphosphonium derivative was conceived due to the E geometry of the trisubstituted double bond. The choice of a phosphonate posed some challenges to the synthetic strategy in view of the very few precedents in the literature for olefinations involving non-stabilized phosphonates<sup>5</sup>. Despite the unfavorable number of precedents we thought it would be worth going ahead with this planning since, if successful, it could extend the use of non-stabilized phosphonates as reasonable olefinating agents in organic synthesis. Another point of concern was related to the stereochemistry of the substituents on the unsaturated cyclohexane moiety on fragment 5. However, in this regard some initial calculations permitted to anticipate a preferential orientation of the methyl group at C4 and the 3-oxobutyl group at C6 as cis-diequatorial, as required by our synthetic planning<sup>6</sup>.

As the ensuing discussion demonstrates, preparation of the unsaturated ketone fragment 5 was rather straightforward, whereas preparation of phosphonate fragment 6 was more involving requiring more experimentation for its construction in good overall yields.

**Synthesis of ketone fragment 5**

We initiated our synthetic route to ketone 5 by performing a Michael addition of the trimethylsilylenol ether derived from 2,6-dimethylcyclohexanone on methyl vinyl ketone (MVK) as described in Scheme 1. This reaction, which requires BF₃·OEt₂ as promoter in presence of racemic menthol (a hindered alcohol), furnished diketone 7 in 70% overall yield as a mixture of stereoisomers (7:3 by GC). This protocol developed by Duhamel<sup>7</sup>, which most probably involves the participation of the ionic intermediate depicted in Scheme 1, proved more efficient than that developed by Still for the construction of the same compound. Still’s procedure<sup>8</sup> involves coupling of 2,6-dimethylcyclohexanone to MVK promoted by H₂SO₄ in benzene, and furnished a maximum yield of 53% for diketone 7. A regioselective protection of the acyclic carbonyl group was necessary at this stage in order to accomplish the planned olefination reaction on the cyclic keto group. Protection of the less hindered and acyclic keto group was more troublesome than initially anticipated. Several attempts employing ethylene glycol/H₂SO₄ and azeotropic removal of water led to mixtures of mono and diketal products. Since propanediols are usually more efficient for monoprotection of keto groups we decided to replace 1,2-ethylene glycol by 2,2-dimethyl-1,3-propanediol, and to our satisfaction the desired monoprotected ketone 8 was obtained in 95% yield<sup>9</sup>.

![Figure 2. Retrosynthetic analysis for the construction of Metachromin A.](image-url)
After blocking the acyclic ketone group, the cyclic keto group of 8 was olefinated according to the conditions established by Fitjer to provide the unsaturated ketal 9 in 80% yield (Scheme 2)\(^{10}\). Unexpectedly, attempts to hydrolyze the ketal protecting group of 9 with aqueous HCl, silica gel or oxalic acid resulted in isomerization of the exocyclic double bond to the thermodynamically more stable endocyclic C4-C5 isomer. Successful removal of the ketal protecting group was accomplished using PPTS in toluene to afford the desired unsaturated ketone 5 in 90% yield as a mixture of diastereomers at C4 (9:1 ratio by GC). Thus, the sequences depicted in schemes 1 and 2 afforded the ketone fragment 5 bearing the appropriate stereocenters (major stereoisomer) in 5 steps from 2,6-dimethylcyclohexanone in 48% overall yield.

The 9:1 diastereomeric ratio observed for ketone 5 was interesting and somewhat intriguing because we started with a 7:3 diastereomeric mixture of diketone 7. It is conceivable that the rather strong basic conditions required for the olefination step (t-BuOK in benzene) led to equilibration of the two epimers at C-4, thereby favoring the thermodynamic more stable epimer, as depicted in Fig. 2. It is also worth mentioning that compound 5 prepared in this work is structurally very similar to the natural sesquiterpene ketone shown in Fig. 3\(^{11}\).

**Synthesis of the phosphonate fragment 6**

After completion of the ketone fragment 5 we then focused our attention to the preparation of the protected hydroquinone phosphonate 6. The strategy set forward for the construction of this fragment was based on the acetoxylation of benzoquinone 11\(^{12}\) by means of a Thiele acetoxylation\(^{13}\) to provide the protected tetraphenol 12 (Eq. 1). Despite the good precedent available for the synthesis of benzoquinone 11, the route reported by Corey and coworkers is somewhat lengthy involving seven steps, although the reported overall yield of 42% should be considered quite good. Aiming at developing a shorter route to benzoquinone 11, we then decided to investigate a new synthetic scheme to benzoquinone 11, which hopefully would provide compound 11 in an overall yield higher than that reported by Corey.

As illustrated in Scheme 3 (route A) we initiated our synthetic route by reacting the commercially available benzyl chloride 13 with sodium cyanide to obtain the aromatic

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\begin{align*}
\text{MeO} & \quad \text{OAc} \\
\text{O} & \quad \text{OAc} \\
\text{OBnMeO} & \quad \text{OBnMeO} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

**Figure 3.** Structural analogy of the unsaturated ketone 5 with natural products.

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**Scheme 1.** Reagents and conditions: (a) MVK, H₂SO₄, benzene, 0 °C (53%). (b) i: Et₃N, TMSCl, NaI-CH₃CN (82%); ii: MVK, CH₃NO₂, BF₃·OEt₂, menthol (85%). (c) CH₂OHC(CH₃)₂CH₂OH, p-TsOH, rt benzene (95%).

**Scheme 2.** Reagents and conditions: (a) t-BuOK, benzene, CH₃P(C₆H₅)₃Br, 85 °C. (b) PPTS, toluene (90%).
nitrile 14 in 93% isolated yield. Basic hydrolysis of nitrile 14 occurred smoothly in presence of H2O2 to provide the 3,5-dimethoxyphenyl acetic acid 15 in 90% isolated yield, whereas acidic hydrolysis of 14 gave only an intractable mixture of products. The use of H2O2 during basic hydrolysis seems crucial to obtain high yields of the corresponding carboxylic acid; lower yields of 15 (~70%) were obtained when hydrolysis was performed in the absence of H2O2. An alternative pathway leading to methyl ester 17 was also examined by performing an Arndt-Eistert sequence starting with the readily available 3,5-dimethoxybenzoic acid 16 (route B, Scheme 3). Unfortunately, the Arndt-Eistert sequence resulted in very low yields of the desired methyl ester 17, and this alternative pathway was then abandoned.

Reduction of the carboxylic acid 15 by LiAlH4 occurred uneventfully to produce the corresponding primary alcohol 18 in 98% yield, which was protected as the benzyl ether 19 in 84% yield (Scheme 4). At this point oxidation of the 1,3-dimethoxybenzene moiety was another critical step in the synthesis of metachromin A. Quinones are usually obtained from the oxidation of phenols and a number of reagents are available to effect such transformation. In our case, however, a selective deprotection of 19 to a monophenol was discarded in view of its low probability of success - single cleavage of an aromatic methyl ether vs. a benzyl ether. Alternative procedures would make the route rather lengthy.

Oxidation of aromatic ether 19 with chromium trioxide, although risky due to the presence of benzylic methylenes, was sought as a possible solution. After some experimentation we were pleased to find out that CrO3 in acetic acid for a maximum of 2 h at 0 °C cleanly provides the known methoxy quinone 11 in 80% yield. Extended oxidation periods led to several side products and lower yields of the desired quinone. This new sequence for the preparation of Corey’s quinone 11 involved only five steps in an overall yield of 55%, thus making it superior to the procedure reported in the literature (seven steps, overall yield of 42%).

By analogy to literature precedents, the oxygenated functionality at C17 of metachromin A was incorporated through the use of a Thiele-Winter acetoxylation. There-, as anticipated, reaction of quinone 11 with Ac2O promoted by H2SO4 led to the triacetate 12 regioselectively in 65% isolated yield (Scheme 5a). The regioselectivity observed can be explained as indicated in the rationale presented in Scheme 5b. Supposedly, the electron-donating methoxy group decreases the partial positive charge at the β-position of the protonated enone that is next to it (it forms

Scheme 4. Reagents and conditions: (a) LAH, THF, reflux. (b) NaH, THF then BnBr, reflux; (c) CrO3, AcOH, 0 °C, 30 min, then rt, 2 h.

Scheme 5a.

Scheme 5b. Rationale for the Thiele-Winter acetoxylation.
a methyl enol ether), thus favoring acetic acid attack on the opposite enone cross-conjugated system.

En route to phosphonate 6, the benzyloxy group of 12 was removed by hydrogenolysis (H₂, Pd/C)¹⁷ to give the primary alcohol 20 in 85% yield (Scheme 5), which was converted into bromide 21 (CBr₄, Ph₃P)¹⁸ in 80% yield. Finally, a Michaelis-Arbuzov¹⁹ reaction of bromide 21 with trimethylphosphite produced the phosphonate fragment 6 in 56% yield. Preparation of phosphonate 6 by the route described here involved 9 steps with an overall yield of 14%.

With the synthesis of the ketone moiety 5 and the phosphonate moiety 6 completed the stage was then set for the planned coupling aiming at constructing the core framework of metachromin A. The coupling process involving a Horner-Wadsworth-Emmons (HWE)²⁰ reaction was then studied in some extent due to the fact that there are very few examples of this type of reaction involving a nonstabilized phosphonate and a ketone. In all the experiments carried out we first generated the phosphonate anion followed by addition of a solution of the ketone. Reaction of the sodium salt of phosphonate 6 (NaH, excess) with ketone 5 afforded the known leucotriacetate 22 in 40% isolated yield as an apparent mixture of E/Z isomers in a 9:1 ratio. Changes in solvent, from THF to DME or DMF, did not improve yields, neither the 9:1 diastereoselectivity (Scheme 7).

In spite of the low yield obtained for the above HWE coupling this initial result can be considered a relative success when one considers the scarcity of precedents for this type of reaction. All attempts to separate the diastereomer E-22 from the Z-22 by chromatographic means were fruitless, thus stereochemical assignments were made on the diastereomeric mixtures. As expected the major product had the E configuration, which was assigned based on the NMR chemical shifts for hydrogens 10, 11 and 15, and for carbons 8, 11 and 15. Relevant chemical shifts are displayed in Fig. 4.

The main features on the ¹³C-NMR spectrum of 22 were the occurrence of a significant, and diagnostic, steric compression involving C-15 and C-11 for the E-stereoisomer, as well as a significant steric compression involving C-8 and C-11 on the minor Z-stereoisomer²¹. This steric compression effect caused pronounced shielding of C-15 in 22-E and of C-8 of 22-Z. Further corroboration for these assignments came by comparing the ¹³C NMR data for the leucotriacetate 22 with those reported for metachromins A, F and G (Table 1)²⁰.

After securing the structure of leucotriacetate 22, we concentrated our attention on the performance of the HWE coupling. Thereby, changes on the base employed for the HWE coupling were examined. Use of n-BuLi in ether increased yields of the leucotriacetates 22 to 60%. However, a significant decrease in stereoselectivity was also observed and a 6:4 mixture of E:Z leucotriacetates was observed by GC/MS. Potassium tert-butoxide in ether provided similar results and so a 6:4 mixture leucotriacetates 22-E and 22-Z was obtained in 55% yield.

To conclude this brief study related to the construction of the trisubstituted double bond of metachromin A we performed a Wittig reaction⁴ of the ketone fragment 5 with phosphorane 23, as described in Scheme 8. The precursor triphenylphosphonium bromide was generated from the
primary bromide 21 by reaction with triphenylphosphine in acetonitrile. Unfortunately this Wittig coupling gave a complex mixture of products that could not be identified properly.

Completion of the synthesis of the metachromin A

The leucotriacetates 22 obtained by reaction of phosphonate 6 with NaH (E:Z; 9:1) were reacted with LiAlH₄ to remove the acetate protecting groups, affording the putative and very polar triphenol 24 that was not purified, but immediately oxidized with FeCl₃ to produce the quinone metachromin A (1), isolated from the reaction medium as orange needles in 65% yield (Scheme 9). Spectroscopic data obtained for the synthetic (±)-metachromin A (mp, UV, IR, ¹H NMR, ¹³C-NMR and MS) were almost identical to those reported in the literature²b and its ¹H and ¹³C-NMR spectra correlated very well with those kindly provided by Prof. Kobayashi from Hokkaido University, Tokyo.

The total synthesis of (±)-metachromin A was therefore completed by a convergent and flexible approach amenable to the synthesis of metachromin analogues. A final evaluation of the synthetic route indicates that the total synthesis encompassed twelve steps in its longest sequence and sixteen steps overall, thereby providing pure (±)-metachromin A in approximately 4% overall yield.

Synthesis of the enantiomerically enriched ketone 5

In order to make a formal total synthesis of a chiral, nonracemic, metachromin A we decided to prepare the
ketone moiety 5 employing an asymmetric method (Scheme 10). A direct route to enantioenriched 5 would be the application of the procedure described by Simpkins\textsuperscript{22} that makes use of a chiral, nonracemic, strong amine base to asymmetrically deprotonate a prochiral ketone. Thus, enantioenriched silylenol ether 25 was obtained by asymmetric deprotonation of the \textit{cis}-2,6-dimethylcyclohexanone with the lithium amide prepared from aromatic amine 26, which was obtained from (\textit{R})(+)-camphor and aniline following literature procedure\textsuperscript{22}. Enantiomeric excess of silylenol ether 25 was not accessed at this stage. Instead, we moved forward to react the silylenol ether 25 with MVK and BF\textsubscript{3}.OEt\textsubscript{2} in the presence of menthol, as described previously (Scheme 1), to obtain the optically active diketone 7 in 73\% yield (two steps) as a 7:3 mixture of C-4 epimers as determined by GC. The levorotatory nature of diketone 7 ([\alpha]_{20} D -35) suggested the 4R,6R configuration for the major diastereoisomer. This stereochemical assignment was based on the specific rotation of diketone 7 ([\alpha]_{18} D -39) obtained from ozonolysis of the metachromin A\textsuperscript{2b}.

As demonstrated previously the fact that diketone 7 constitutes a C-4 mixture of epimers is not deleterious since it is subsequently converted into the desired epimer under basic conditions. Nevertheless, a new protocol for the preparation of an enantioenriched diketone 7 was pursued. We envisioned that d’Angelo’s deracemization methodology\textsuperscript{23} could be a better alternative to Simpkins’ protocol in our case, and so the asymmetric imine 27 was prepared by reaction of \textit{cis}-2,6-dimethylcyclohexanone with (S)-(−)-\textit{α}-methylbenzylamine in 68\% yield.\textsuperscript{24} Reaction of imine 27 with methyl vinyl ketone as described in Scheme 10 followed by treatment with aqueous acetic acid provided a mixture of diketone 7 and octalone 28. The octalone formation can be suppressed by adding sodium acetate to the aqueous acetic acid during workup which permitted the preparation of the optically active diketone 7 ([\alpha]_{20} D -31) in moderate yield (60\%). Diketone 7 was then submitted to the same synthetic route outlined on Scheme 2 leading to the fragment 5 (unsaturated ketone) in enantiomerically enriched form. The enantiomeric excess of fragment 5 was judged from \textit{1}H-NMR experiments using the chiral shift reagent \textit{[Eu(hfc)\textsubscript{3}] to be ca. 85\%.

**Experimental**

**General experimental**

Tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, toluene and benzene were distilled from sodium benzophenone ketyl. Triethylamine, nitromethane and CH\textsubscript{2}Cl\textsubscript{2} were distilled from CaH\textsubscript{2}. Ag\textsubscript{2}O was freshly prepared by adding a 10\% aqueous solution of NaOH to 9.2 mL of a 10\% aqueous solution of AgNO\textsubscript{3} (918 mg) until precipitation stopped. The slurry of Ag\textsubscript{2}O formed was then filtered and
the excess of water removed in vacuo. All the procedure was performed under low light. Melting points (uncor rected) were determined on a Büchi 510 apparatus. 1H NMR (CDCl 3 /TMS) and 13 C-NMR were recorded on a Bruker AM500 or 250 spectrometers. 13 C-NMR spectra were assisted by the DEPT technique. Infrared spectra were obtained on a Nicolet FT-IR 510. GC-MS were recorded on a HP5970. UV spectra were recorded on a Beckman HP5901A. Optical rotation was measured using a Polamat A or a Optical Activity A 1000 Polarimeter. Elemental analyses were performed at the Chemistry Institute of the Queen Mary College, London.

Preparation of the silylenol ether derived from 2,6-dimethylcyclohexanone

To a stirred solution of triethylamine (0.1 mol) and 2,6-dimethylcyclohexanone (10.08 g, 0.08 mol) in 100 mL of CH3 CN, at room temperature, was added 12.7 mL of chlorotrimethylsilane (0.1 mol) followed by dropwise addition of 15.04 g of NaI (0.1 mol). The reaction was monitored by TLC (pentane/ether 1:1). Upon completion the reaction mixture was diluted with pentane (60 mL), filtered, and the filtrate extracted with pentane (4 x 60 mL). The combined organic layer was concentrated, washed with brine, and dried over MgSO4. After filtration the solvent was rotaevaporated in vacuo to furnish a colorless oil. Next, the silylenol ether was purified by filtration on Florisil yielding the silylenol ether as an homogeneous material by TLC (14.03 g, 82% yield).

IR (neat, cm -1 ), ν 2923, 2860, 1675; 1 H-NMR: δ 2.2-1.3 (m, 10H); 1.1 (d, J = 7 Hz, 3H); 0.2 (s, 9H).

Preparation of Chiral Amine 26

A mixture of aniline (10 g, 0.11 mol), (R)-(+) Camphor (4.09 g, 0.023 mol), and camphorsulfonic acid (0.074 g, 0.32 mmol) was heated with 3 Å molecular sieves at 110 °C for 3 days. The mixture was cooled, diluted with diethyl ether (10 mL) and filtered through a pad of Celite. The organic solution was washed with saturated NaHCO3 and 10% aq. NaHSO3, dried over MgSO4 and the solvent removed in vacuo. The crude product was dissolved in MeOH (15 mL) and the pH of the resulting solution adjusted to 6-7 by the addition of 6 N methanolic HCl. Then, NaBH4CN (2.21 g, 0.035 mol) was added and the mixture stirred at room temperature for 48 h. After this period the solvent was removed under reduced pressure and 25 mL of water added to the mixture followed by addition of solid KOH until pH ~10 was attained. The mixture was then saturated with solid NaCl and extracted with EtOAc (3 x 25 mL). The combined organic extract was washed with 20% aq. FeSO4 and brine. After drying over MgSO4, filtration and solvent removal in vacuo afforded a crude oil that was distilled (142 °C, 0.2 Torr) to furnish the pure chiral amine 26 as a colorless oil in 42% yield.

IR (film, cm -1 ), ν 3420, 2940, 2868, 1600, 1509, 1315, 680; 1 H-NMR: δ 7.19-7.05 (m, 2H); 6.62-6.50 (m, 3H); 3.72 (br s, 1H); 3.25 (dd, J = 1.2 and 9.1 Hz, 1H); 1.90 (dd, J = 12.8 and 8.9 Hz, 1H); 1.33-1.07 (m, 3H); 1.02 (s, 3H); 0.93 (s, 3H); 0.87 (s, 3H).

[(α) 20 D] = -105.2 (c 1.5, CHCl3).

(R)-Silylenol ether 25

To a solution of chiral amine 26 (710 mg, 3.1 mmol) in dry THF (5.0 mL) at -10 °C, under N2, was added n-BuLi (3.7 mL, 1.3 M solution in hexanes, 2.85 mmol). After 30 min the cooling bath was removed and the mixture stirred at room temperature for 2 h before cooling to -78 °C. Then, cis-2,6-dimethylcyclohexanone (300.5 mg, 2.5 mmol) in 1.5 mL of THF was added dropwisely and the mixture allowed to warm very slowly to -40 °C overnight (cold-plate). The resulting enolate solution was recooled to -78 °C and chlorotrimethylsilane (0.4 mL, 325 mg, 2.5 mmol) and dry triethylamine (10 mL) were added to the reaction mixture. After a further 1 h at -78 °C the solution was poured into saturated NH4Cl (30 mL) and the product extracted with pentane (2 x 15 mL). The combined organic extracts were washed with saturated NH4Cl (3 x 25 mL),
brine (3 x 25 mL), dried over MgSO₄, filtered, and the solvent removed in vacuo. Column chromatography of the residue on Florisil gave the chiral silylenol ether 25 in 65% yield as a colorless oil. ¹H-NMR: δ 2.15 (m, 1H); 1.94 (m, 2H); 1.75 (m, 1H); 1.71-1.55 (m, 1H); 1.53 (s, 3H); 1.51-1.23 (m, 2H); 1.06 (d, J = 7 Hz, 3H); 0.19 (s, 3H). [α]²⁵ D = -25 (c 1.0, CH₂Cl₂)

Diketone 7. (2,6-dimethyl-2(3-oxobutyl)-cyclohexanone) (method A)

To a stirred solution of the silylenol ether prepared as described above (297 mg, 1.5 mmol) in nitromethane (3 mL), under N₂, at -20 °C, was added dropwise a solution of 210 mg of methyl vinyl ketone (3.0 mmol) dissolved in 3 mL of nitromethane, followed by addition of 0.1 mL (106.4 mg, 0.75 mmol) of BF₃·OEt₂ and a solution of menthol (468.8 mg, 3.0 mmol) in 1.5 mL of CH₂Cl₂. The resulting mixture was kept at -20 °C for 1 h, warmed up to -10 °C, when 10 mL of aq.10% NaHCO₃ was added, and stirring continued for 10 min. Extraction with CH₂Cl₂ (6 x 20 mL), drying over Na₂SO₄, filtration and solvent removal under reduced pressure gave an oil that was purified by flash chromatography (ether-pentane 15%). Ketone 7 was obtained in 89% yield. IR (neat, cm⁻¹): ν 2963, 2924, 1712; ¹H-NMR: δ 2.6 (m, 1H); 2.1-1.3 (m, 13H); 1.0 (s, 3H); 1.05 (d, J = 6.5Hz, 3H); 1.0 (s, 3H). ¹³C-NMR: δ 213.8, s; 208.5, s; 47.9, s; 41.4, d; 41.1, t; 38.3, t; 36.6, t; 32.4, t; 29.9, q; 23.4, q; 21.1, t; 14.9, q. MS: m/z (%): M⁺ 196 (10); 126 (35); 69 (38); 69 (20); 41 (100).

Silylenol ether 25 was submitted to the same conditions described in method A. The diketone 7 was obtained in 86% yield from silylenol ether 25. [α]²⁵ D = -35 (c 1.0, CHCl₃).

Ketal 8. 2,6-dimethyl-2-(3-[2,2-dimethyl-1,3-dioxolan]butyl)-cyclohexanone (method B)

A solution of 9.5 g of 2,6-dimethylcyclohexanone (75 mmol), 5.25 g of freshly distilled methyl vinyl ketone (75 mmol) in 50 mL of benzene or toluene, was cooled to 0 °C in a 100 mL flask equipped with a drying tube (CaCl₂). The mixture was manually stirred while 1.5 mL of concentrated sulfuric acid was added. After addition was completed the reaction mixture was left standing at 0 °C for 2 h. The mixture was then magnetically stirred and a second portion of MVK (2.6 g, ~37.5 mmol) and sulfuric acid (0.5 mL) were mixed with the dark reaction mixture. After standing for 12 h at 0 °C, the orange reaction mixture was decanted from the dark polymer and poured into 100 mL of diethyl ether. The polymer was rinsed with ether and the combined ethereal solution was carefully washed with 1N sodium hydroxide and brine. The resulting aqueous washing was back-extracted with ether and the combined ethereal solution dried over MgSO₄ and the solvents removed under reduced pressure to give an orange oil, that was fractionally distilled. The fraction collected at 86-98 °C (0.5 Torr) exhibit spectroscopic data identical to the product obtained from method A.(53% yield)

Diketone 7.

A mixture of diketone 7 (294 mg, 1.5 mmol), 2,2-dimethyl-1,3-propanediol (94 mg, 0.9 mmol) and 20 mg of p-toluenesulfonic acid dissolved in 25 mL of benzene or toluene, in a flask equipped with a Dean-Stark apparatus, was refluxed for 3 h. The reaction was then washed with 10% aq. NaHCO₃ (3 x 20 mL), and water (5 x 20 mL). The organic layer was removed and dried over Na₂SO₄. Filtration and removal of the solvent under reduced pressure gave an oil that was purified in a Kulgelrohor apparatus (90 °C, 25 Torr), to furnish the ketal (241 mg) in 95% yield. IR (neat, cm⁻¹): ν 2965, 2940, 2868, 1716; ¹H-NMR: δ 3.5 (br, 1H); 2.6 (m, 1H); 2.1-1.3 (m, 13H); 1.1 (s, 3H); 1.05 (d, J = 6.5 Hz, 3H); 0.85 (s, 6H). MS: m/z (%): M⁺ 282 (85); 267 (100); 126 (18); 69 (40). Anal. calcd. for C₁₇H₃₂O₃: C, 72.29; H, 10.71. Found: C, 72.16; H, 10.68.

Chiral Ketal 8.

Enantiomerically enriched diketone 7 was submitted to the same conditions described above. The chiral, non-racemic keto-dioxolane was obtained in 92% yield. [α]²⁵ D = -33 (c 1.0, CHCl₃).

Unsaturated Ketal 9

To a stirred suspension of potassium tert-butoxide (1.23 g, 11 mmol) in 20 mL of dry benzene under N₂, was added an equimolar amount of methyltriphenylphosphonium bromide and the mixture heated to reflux. After 45 min most of the benzene was distilled off under nitrogen until the temperature of the remaining slurry reached 85 °C. Then, ketone 8 (10 mmol) dissolved in 20 mL of diethyl ether was added via syringe causing a vigorous exothermic reaction. Stirring was continued for 2.5 h and the reaction mixture cooled to room temperature. Pentane (20 mL) and water (5 mL) were added with vigorous stirring and the aqueous layer extracted with pentane (5 x 15 mL). The combined organic layer was washed with water (5 x 30 mL), dried over MgSO₄ and then concentrated. Distillation of the residual oil at reduced pressure (112 - 114 °C, 16 Torr), yielded the pure unsaturated ketal 9 (2.2 g, 80% yield). IR
(neat, cm$^{-1}$), ν: 2940, 1632, 1370; 1210, 1090. NMR$^1$H: δ 4.7 (s, 1H); 4.65 (s, 1H); 3.5 (br, 4H); 2.3 (m, 1H); 2.2-1.3 (m, 13H); 1.0 (s, 3H); 1.0 (d, J = 6.5 Hz, 3H); 0.85 (s, 6H). MS: m/z (%): M$^+$ 280 (10); 265 (75); 250 (20); 123 (100); 107 (55). Anal. calcd. for C$_{13}$H$_{22}$O: C, 80.35; H, 11.42. Found: C, 80.12; H, 11.39.

**Chiral Unsaturated Ketone 5**

To a solution of ketone 9 (560 mg, 2 mmol) in toluene (20 mL), was added a solution of pyridinium p-toluenesulfonate (PPTS, ca 25 mg) in 5 mL of acetic acid. The mixture was kept under stirring at room temperature for 4 h, and then 20 mL of water were added. After 1 h of additional stirring the organic layer was removed, washed with water (4 x 10 mL), and concentrated. The residual oil was dried over Na$_2$SO$_4$. The ketone 5 was obtained in 90% yield (349 mg) after filtration through a silica gel column. IR (neat, cm$^{-1}$), ν: 2938, 2930, 1715; 1635, 1370. $^1$H-NMR: δ 6.47 (s, 1H); 4.65 (s, 1H); 2.3 (m, 1H); 2.2-1.3 (m, 13H); 1.0 (s, 3H); 1.0 (d, J = 6.5Hz, 3H); $^{13}$C-NMR: δ 213.3, s; 158.1, s; 104.9, t; 41.4, t; 39.5, s; 37.3, t; 35.4, t; 33.4, d; 30.7, t; 29.9; q; 26.3; q; 21.8, t; 19.2, q. MS: m/z (%): M$^+$194 (3); 123(100); 43 (86). Anal. calcd. for C$_{10}$H$_{12}$O$_4$: C, 61.22; H, 6.16. Found: C, 61.07; H, 6.18.

**Chiral Imine 27**

A mixture of 1.68 g (13 mmol) of 2,6-dimethylcyclo-hexanone and 5.0 g (40 mmol) of (S)-(−)-α-methylbenzyl-amine in 35 mL of dry toluene was cooled to -78 °C. After this, a solution of TiCl$_4$ (1.33 g, 7 mmol) in 15 mL of toluene was cooled to -78 °C. After this period the solution was poured onto 85 g of ice and the solid formed collected on a filter and purified by recrystallization from heptane to provide 429 mg of 14 as colorless fine needles (93% yield). $\text{mp}$: 53 °C; IR (KBr, cm$^{-1}$), ν: 2928, 2846; 2362; 2335; 1603; 1465; 1431; 1156. $^1$H-NMR: δ 6.45 (br, 3H); 3.8 (s, 6H); 3.7 (s, 2H). MS: m/z (%): M$^+$177 (8); 176 (53); 159 (69); 151 (100).
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to a 20 mL of a 0.1 M solution of CH₂N₂ in ether, at 0 °C and stirred for 30 min. When the gas evolution stopped, the ice-bath was removed and stirring continued at room temperature for 12 h. After this period the solvent was removed under reduced pressure, the residue diluted with 10 mL of MeOH and a slurry of Ag₂O added in small portions. The resulting mixture was stirred for 30 min at room temperature and then heated to reflux for 2 h. After cooling, filtration and solvent removal in vacuo, the residue was diluted with CH₂Cl₂ and dried over Na₂SO₄. Filtration followed by solvent removal in vacuo gave 126.2 mg of an pale yellow oil corresponding to ester (Arndt-Eistert Reaction).

**Ester 17** (Arndt-Eister Reaction)

A solution of 3,5-dimethoxybenzyl chloride (611.5 mg, 3.05 mmol) in 5 mL of diethyl ether, was slowly added to a 20 mL of a 0.1 M solution of CH₂N₂ in ether, at 0 °C and stirred for 30 min. When the gas evolution stopped, the ice-bath was removed and stirring continued at room temperature for 12 h. After this period the solvent was removed under reduced pressure, the residue diluted with 10 mL of MeOH and a slurry of Ag₂O added in small portions. The resulting mixture was stirred for 30 min at room temperature and then heated to reflux for 2 h. After cooling, filtration and solvent removal in vacuo, the residue was diluted with CH₂Cl₂ and dried over Na₂SO₄. Filtration followed by solvent removal in vacuo gave 126.2 mg of an pale yellow oil corresponding to ester (Arndt-Eistert Reaction).

**Alcohol 18**

To a stirred suspension of lithium aluminum hydride (969 mg, 25.5 mmol) in dry THF (10 mL) at 0 °C was added a solution of acid 15 (500 mg, 2.55 mmol) in 10 mL of THF. The mixture was then refluxed for 12 h after which the reaction mixture was cooled in an ice bath while 1.0 mL of 10% aq. NaOH. The mixture was then poured into a mixture water-ice. The crude product was washed with brine and water. The organic phase was dried over MgSO₄, filtered and concentrated in vacuo, the residue was diluted with 10 mL of MeOH and a slurry of Ag₂O added in small portions. The resulting mixture was stirred at 0 °C for 30 min., at room temperature for 2 h, and then poured into a mixture water-ice. The crude product was extracted with EtOAc (6 x 10 mL) and after concentration, washed with brine and water. The organic phase was dried over Na₂SO₄, filtered and the solvent evaporated in vacuo to provide an orange solid that was purified by preparative TLC (EtOAc-Hex. 10%) to yield benzoiquinone 11 as orange crystals. Yield: 80% (85 mg). mp: 70-71 °C. UV: λ (acetone, nm): 362, 286, 210; IR (KBr, cm⁻¹): v: 3105; 2822; 1650; 1450. ¹H-NMR: δ 6.45 (m, 3H); 3.82 (s, 6H); 3.71 (t, J = 8 Hz, 2H). 13 C-NMR: δ 186.2, s; 178.2, s; 152.0, s; 145.0, d; 134.2, s; 128.5, d; 127.8, d; 107.3, d; 72.9, t, 67.4, t; 56.2, q; 29.3, t. MS: m/z (%): M⁺ 272 (21); 244 (8); 166 (51); 91 (100).

**Triacetate 12**

To a solution of quinone 11 (100 mg, 0.36 mmol) in acetic anhydride (2 mL) was added concentrated sulfuric acid (2 drops) and the mixture stirred at room temperature for 12 h. At the end of this period the solution was poured into ice and the crude product isolated by extraction with diethyl ether (5 x 50 mL). The combined organic layer was concentrated and then washed with 5% aq. NaHCO₃ and water. The resulting organic solution was dried over MgSO₄, filtered and concentrated in vacuo to give an oil that was purified by flash chromatography (EtOAc-Hex. 20%). The pure triacetoxibenzen 12 was obtained in 65% (97 mg). IR (neat, cm⁻¹): v: 3070; 2920; 1760; 1605; 1452; 1238; 1H-NMR: δ 7.41-7.29 (m, 5H); 6.72 (s, 1H); 4.51 (s, 3H); 2.25 (s, 3H); 2.22 (s, 6H). Anal. calcd. for C₁₂H₁₀O₃: C, 63.45; H, 5.81. Found: C, 63.41; H, 5.76.

**Alcohol 20**

A suspension of the benzyl ether 12 (180 mg, 0.43 mmol) and 112 mg of 10% Pd/C in 30 mL of ethyl acetate was stirred under an atmosphere of hydrogen for 12 h. After this period, the reaction mixture was filtered and the solvent removed in vacuo to furnish 138 mg of alcohol 12 as an oil (yield: 98%). IR (neat, cm⁻¹): v: 3422, 3086, 2924, 1762, 1604, 1238. ¹H-NMR: δ 6.70 (s, 1H); 4.51 (s, 2H); 3.8 (s, 6H); 3.71 (t, J=8Hz, 2H); 2.9 (d, J = 8 Hz, 2H). MS: m/z (%): M⁺ 272 (12); 166 (25); 152 (32); 91 (100). Anal. calcd. for C₁₂H₂₀O₃: C, 74.97; H, 7.40. Found: C, 74.69; H, 7.34.
was diluted with diethyl ether and dried over MgSO₄. The solvent was removed, and the resulting solution filtered through a short column of silica gel. The solvent was then removed in vacuo to give 527 mg (80% yield) of the pure bromide 21. IR (neat, cm⁻¹), ν: 3005, 2938, 1764, 1606, 699; NMR: δ 6.75 (s, 1H); 3.85-3.70 (m, 5H); 2.90 (t, J = 8 Hz, 2H); 2.25 (s, 3H); 2.20 (s, 6H); MS: m/z (%): M⁺388 (4); 390 (M+2); 346 (3); 304 (5); 295 (28); 262 (100).

Bromide 21

To a solution of 556 mg (1.7 mmol) of alcohol 20, and 699 mg (2.1 mmol) of tetrabromomethane in 10 mL of dry CH₂Cl₂, cooled at 0 °C, was added 558 mg (2.1 mmol) of triphenylphosphine in small portions. The reaction mixture was warmed to room temperature and stirred for 6 h. Then, 50 mL of pentane were added and the resulting solution filtered with brine (4 x 10 mL), dried over Na₂SO₄ and filtered. The solvent was evaporated to provide 139.7 mg of leucotriacetate as a 60:40 diastereomeric mixture (60% yield). ¹H-NMR: δ 6.7 (s, 1H); 5.15 (m, 1H); 4.70 (s, 1H); 4.65 (s, 1H); 3.80 (s, 3H); 3.2 (m, 2H); 2.25 (s, 3H); 2.20 (s, 6H); 1.9 (m, 1H); 1.75 (br s, 3H); 1.7 - 1.1 (m, 12H); 1.05 (s, 3H); 1.0 (d, J = 6.5 Hz, 3H). ¹³C-NMR: δ 183.4, s; 168.4, s; 168.3, s; 168.2, s; 159.5, s; 149.1, s; 138.3, s; 135.5, s; 133.9, s; 130.6, s; 118.6, d; 104.7, d; 103.6, t; 56.4, q; 39.7, t; 39.4, s; 39.2, q; 38.7, t; 37.6, t; 37.1, t; 34.0, t; 33.9, d; 24.7, q; 21.8, t; 20.6, q; 20.3, q; 20.2, q; 19.6, q; 16.4, q. MS: m/z (%): M⁺486 (3); 443 (64); 349 (65); 295 (28); 123 (100); 109 (46).

Phosphonate 6

To a solution of trimethylphosphite (0.09 mL, 0.74 mmol) in 3 mL of dry 1,2-dimethoxyethane, under N₂, at room temperature was added a solution of bromide 21 (262 mg, 0.68 mmol) in 10 mL of DME. After addition was completed the resulting mixture was refluxed for 3 h. Next, the solvent was removed in vacuo and the residue diluted with CH₂Cl₂. The dichloromethane solution was washed with brine (4 x 10 mL), dried over Na₂SO₄ and filtered. The solvent was evaporated in vacuo to provide 157 mg of the desired phosphonate (56%) as an homogeneous material as assayed by TLC. IR (neat, cm⁻¹), ν: 3001, 2930, 1760, 1605, 1253, 1190, 1048, 820. ¹H-NMR: δ 6.8 (s, 1H); 3.95 - 3.45 (m, 11H); 3.1 (t, J = 8 Hz, 2H); 2.3-2.1 (m, 9H).

Leucotriacetate 22

(method A)

To a stirred suspension of 2.0 mmol of NaH (96 mg of a 50% NaH dispersion in mineral oil, previously washed with hexane) in dry THF (10 mL), at 0 °C, under nitrogen, was added dropwise a solution of 209 mg (0.5 mmol) of phosphonate 6 in 10 mL of dry THF. The reaction mixture was then warmed to room temperature and stirred for 30 min, when a solution of ketone 5 (108 mg, 0.56 mmol) in 20 mL of dry THF was added to the reaction mixture forming a brown suspension. The mixture was then refluxed for 4 h, cooled to room temperature and then to 0 °C, when a 5% aq. NH₄Cl solution was added dropwise and the reaction let stir for 10 min at 30 °C. After cooling to room temperature the reaction mixture was filtered and the solvent partially evaporated in vacuo to provide a residue that was diluted with diethyl ether and dried over MgSO₄. The usual work-up procedure gave an oil that was purified by silica-gel chromatography to provide 96.8 mg of leucotriacetate 22 (diastereomeric mixture, 9:1) in 40% yield.
Trihydroxybenzene 24

A solution of leucotriacetate 22 (60 mg, 0.12 mmol) in 8 mL of dry THF was added dropwise to a stirred suspension of lithium aluminum hydride (20 mg, 0.53 mmol) in THF (8 mL), at 0 °C, under nitrogen, and the resulting mixture stirred at room temperature for 15 min. After recooling to 0 °C, 5 mL of a 10% aq. HCl were added carefully, and the mixture was immediately filtered through MgSO₄. After evaporation of the solvent in vacuo, a dark residue corresponding to the trihydroxy benzene 24 was obtained (24 mg). This sample was analyzed by IR spectroscopy and used in the next step without further purification. IR (neat, cm⁻¹, v): 3569-3253; 2963; 2852; 1602; 1459; 1304.

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A solution of trihydroxy benzene 24 (70 mg, 0.21 mmol in 50 mL of benzene) was shaken vigorously with 1% aqueous iron (III) chloride solution (150 mL) for 20 min. To the resulting yellow mixture was then added 30 mL of 1% aqueous iron (III) chloride solution (150 mL) for 20 min. After filtration, the filtrate was washed with saturated brine, dried over Na₂SO₄ and evaporated to give an amorphous orange solid that was recrystallized from pentane to provide 54 mg (65% yield) of metachromin-A as orange needles. mp: 79-81 °C. UV: λ (MeOH, nm): 510, 286, 220. IR: λ (KBr, cm⁻¹, v): 3338; 2930; 1632; 1590; 1370; 1298. 1 H-NMR: δ: 79-81 °C.

Conclusions

The first racemic total synthesis of sesquiterpene quinone metachromin A was accomplished by a convergent synthetic route that is amenable to the preparation of synthetic analogues of metachromin A for biological studies. The two critical fragments for the synthesis were prepared in an efficient way involving five steps for fragment 5 (48% overall yield) and nine steps for fragment 6 (14% overall yield). The synthetic scheme also features: (1) a very efficient synthesis of quinone 11 in five steps with an overall yield of 55%, against the seven steps and 42% yield reported by Corey and coworkers, (2) the use of nonstabilized phosphonates as effective partners in Horner-Emmons-Wadsworth reactions, which have rarely been used in organic synthesis.

In complement, a formal synthesis of enantioenriched metachromin A was also accomplished with the preparation of the key intermediates diketone (−)-7 and of the advanced intermediate unsaturated ketone (−)-5 employing two distinct methodologies: an asymmetric deprotonation with the chiral base 26 (Simpkin’s protocol) to generate the enantioenriched silylenol ether 25, and the enantioenriched imine (d’Angelo’s protocol) 27, which were both reacted with methyl vinyl ketone. The enantiomeric excess of the unsaturated ketone 5 was evaluated by 1H-NMR spectroscopy employing the chiral shift reagent [Eu(hfc)₃], and estimate to be ~85%.

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