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Article

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

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A primeira síntese total da substância antitumoral de origem marinha metacromina-A (**1**) foi alcançada através de uma abordagem sintética convergente e aplicável a preparação de análogos para estudos biológicos. A síntese envolveu doze etapas na sua sequência mais longa e dezesseis no total, apresentando como destaques (1) a eficácia na síntese da quinona intermediária **11**; (2) a preparação eficiente dos fragmentos chaves **5** e **6**; (3) uma reação de acetoxilação do tipo Thiele-Winter altamente regiosseletiva e (4) uma reação de acoplamento do tipo Horner-Wadsworth-Emmons empregando o fragmento **6** como fosfonato não estabilizado capaz de atuar como um agente produtivo no acoplamento. Uma síntese formal e enantiosseletiva da metacromina-A também é descrita a partir da síntese assimétrica do fragmento **5**, utilizando as metodologias desenvolvidas por Simpkins (desprotonação assimétrica com bases nitrogenadas quirais) e d'Angelo (alquilações desracemizantes). Este último processo forneceu o fragmento **5** com um excesso enantiomérico de ~85%, determinado por espectroscopia de RMN ^{1}H.

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 ^{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[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 *Hippospongia metachromia* displayed potent antineoplastic activity against L 1210 Leukemia cells *in vitro*, as well as coronary vasodilating activity with IC_{50} of 3 x 10^{-6} M[2]. The recently discovered boliaquinone, **4**, also

displayed citotoxy activity with IC_{50} of 1.9 μg/mL against human colon tumor cell line HCT116, as well as mild inhibition of *Bacillus subtilis* at 80 μg/disk[2a]. The pharmacological profile of boliaquinone also suggested that the cytotoxicity displayed by these sesquiterpene hydroquinones results from interference with DNA or damage caused by them to DNA.

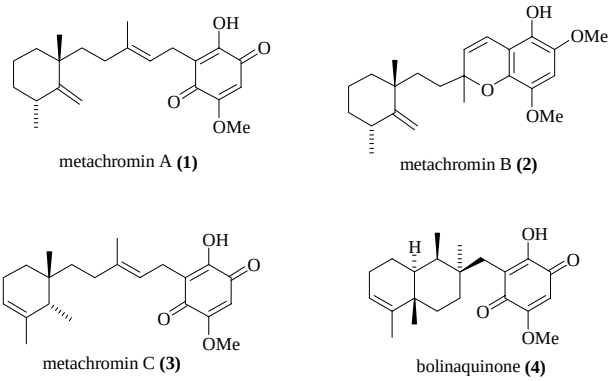
In view of the growing medicinal importance of compounds that interact directly with DNA we became interested in the total synthesis of members of this family of natural products. In 1994 we reported the first total synthesis of racemic metachromin A, the most abundant and most active of the metachromins, employing a convergent methodology amenable to the synthesis of derivatives and analogues[3]. 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[4].

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[5]. 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[6].



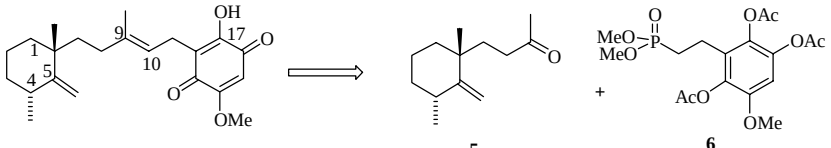
metachromin A **(1)** metachromin B **(2)** metachromin C **(3)** bolinaquinone **(4)**

Figure 1. Examples of natural sesquiterpene hydroxyquinones.

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.

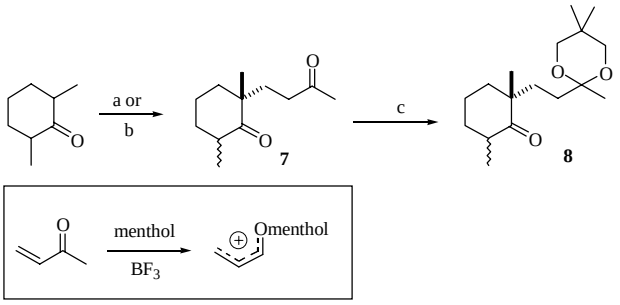
Synthesis of ketone fragment **5**

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 $BF_3.OEt_2$ 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[7], 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[8] involves coupling of 2,6-dimethylcyclohexanone to MVK promoted by H_2SO_4 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/H_2SO_4 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[9].



metachromin A **(1)** **5** **6**

Figure 2. Retrosynthetic analysis for the construction of Metachronim A.



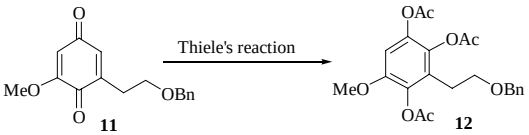
Scheme 1. Reagents and conditions: (a) MVK, H_2SO_4, benzene, 0 °C (53%). (b) i: Et_3N, TMSCl, NaI-CH_3CN (82%); ii: MVK, CH_3NO_2, $BF_3.OEt_2$, menthol (85%). (c) $CH_2OHC(CH_3)_2CH_2OH$, *p*-TsOH, rt benzene (95%).

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-dimethycyclohexanone 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**

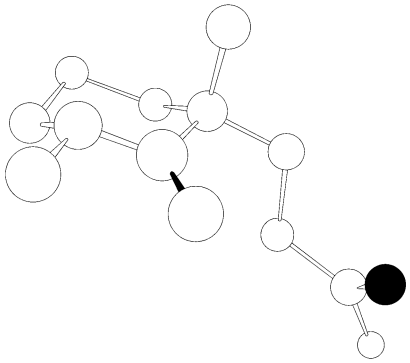
After completion of the ketone fragment **5** we then focused our attention to the preparation of the protected hydroquinone phosphonate **6**. The strategy set forward for the construction of this fragment was based on the acetoxylation of benzoquinone **11**[12] by means of a Thiele acetoxylation[13] 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.



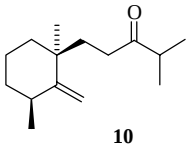
(1)

Corey's benzoquinone

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



The unsaturated ketone **5** as minimized using MOPAC (Chem 3D Pro).



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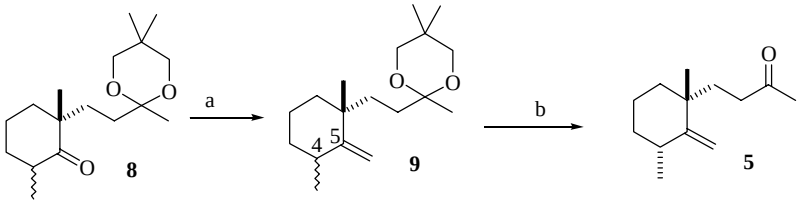
Natural sesquiterpenic ketone related to ketone fragment **5**.

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



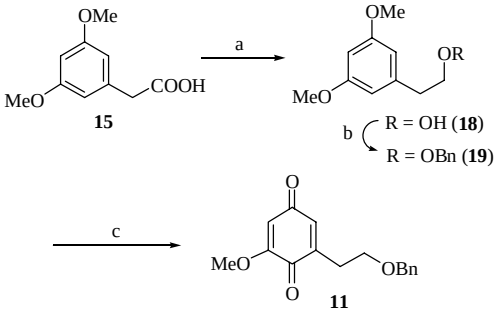
Scheme 2. Reagents and conditions: (a) t-BuOK, benzene, $CH_3P(C_6H_5)_3Br$, 85 °C. (b) PPTS, toluene (90%).

nitrile **14** in 93% isolated yield. Basic hydrolysis of nitrile **14** occurred smoothly in presence of H_2O_2 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 H_2O_2 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 H_2O_2 [14]. An alternative pathway leading to methyl ester **17** was also examined by performing an Arndt-Eistert sequence[15] 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.

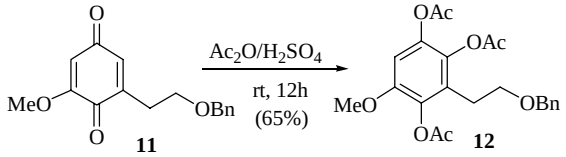
Reduction of the carboxylic acid **15** by $LiAlH_4$ occurred uneventfully to produce the corresponding primary alcohol **18** in 98% yield, which was protected as the benzyl ether **19** in 84% yield (Scheme 4). At this point oxidation of the 1,3-dimethoxy benzene moiety was another critical step in 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 CrO_3 in acetic acid for a maximum of 2 h at 0 °C cleanly provides the known methoxy quinone **11** in 80% yield[16]. 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%).

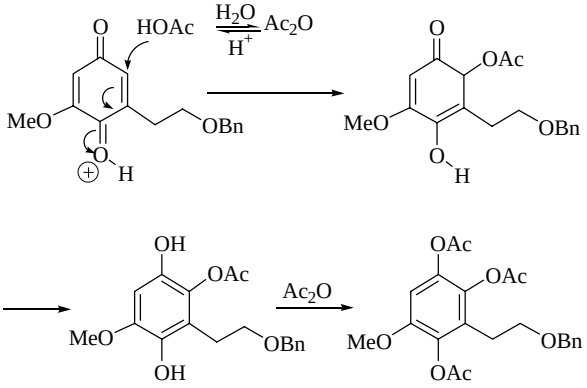
By analogy to literature precedents, the oxygenated functionality at C17 of metachromin A was incorporated through the use of a Thiele-Winter acetoxylation.[13] Therefore, as anticipated, reaction of quinone **11** with Ac_2O promoted by H_2SO_4 led to the triacetate **12** regioselectively in 65% isolated 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



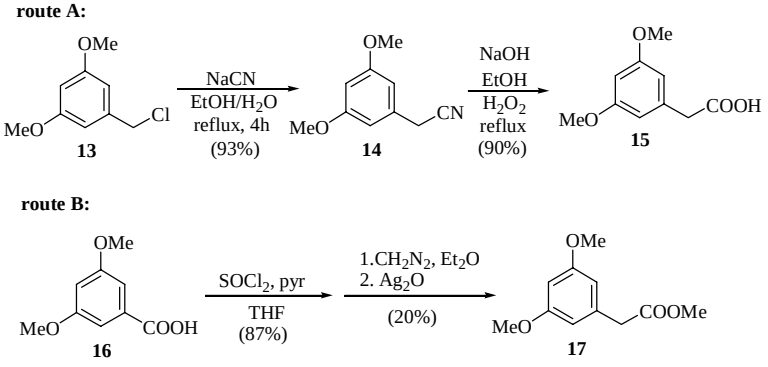
Scheme 4. Reagents and conditions: (a) LAH, THF, reflux. (b) NaH, THF then BnBr, reflux; (c) CrO_3, AcOH, 0 °C, 30 min, then rt, 2 h.



Scheme 5a.



Scheme 5b. Rationale for the Thiele-Winter acetoxylation.

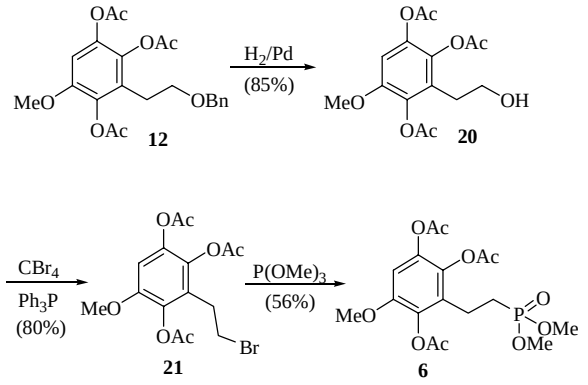


Scheme 3.

a methyl enolether), 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 (H_2, Pd/C)[17] to give the primary alcohol **20** in 85% yield (Scheme 5), which was converted into bromide **21** (CBr_4, Ph_3P)[18] in 80% yield. Finally, a Michaelis-Arbuzov[19] 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).



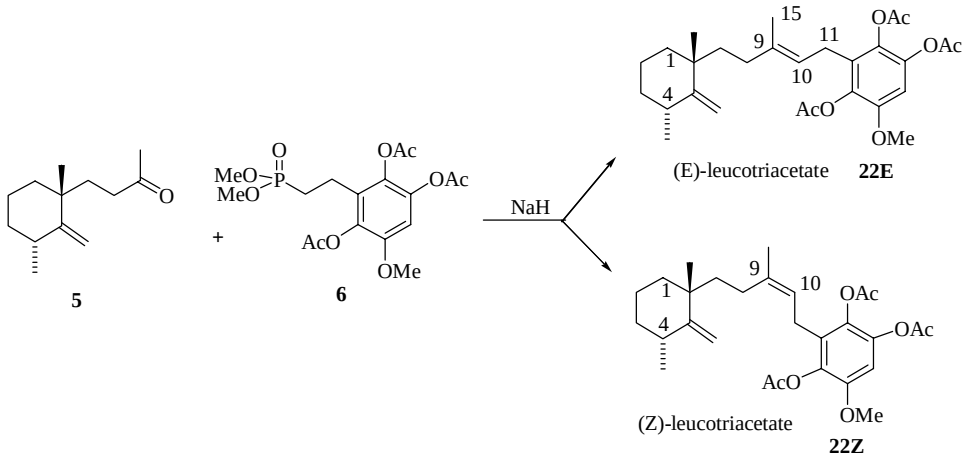
Scheme 6.

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.

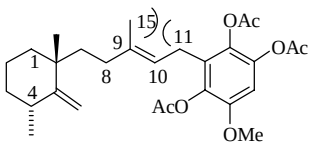
The main features on the ^{13}C-NMR spectrum of **22** were the occurrence of a significant, and diagnostic, steric compression involving C-15 and C-11 for the E-stereoisomer, as well as a significant steric compression involving C-8 and C-11 on the minor Z-stereoisomer[21]. This steric compression effect 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 ^{13}C NMR data for the leucotriacetate 22 with those reported for metachromins A, F and G (Table 1)[2b].

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.

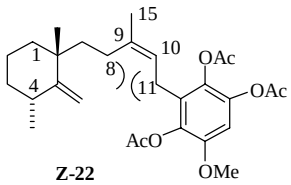
To conclude this brief study related to the construction of the trisubstituted double bond of methacromin A we performed a Wittig reaction[4] of the ketone fragment **5** with phosphorane **23**, as described in Scheme 8. The precursor triphenylphosphonium bromide was generated from the



Scheme 7.



E-22



Z-22

NMR	^{13}C	^{1}H	NMR	^{13}C	^{1}H
8	**34.1**	--	**8**	**28.0***	--
9	138.3	--	9	--	--
10	118.8	5.5 (t, J = 6.5 Hz)	10	--	--
11	37.8	3.2 (d, J = 6.5 Hz)	11	37.8	3.15*
15	**16.4**	1.75 (bs, 3H)	**15**	**23.4***	1.75 (bs, 3H)

*Minor signals in the NMR spectrum.

Figure 4. Relevant NMR data for stereochemical assignments of C9-C10 double bond.

Table 1. ^{13}C chemical shifts for metachromins A, F and G and leucotriacetate 22.

Carbons	Metachromin-A	Metachromin-F	Metachromin-G	Triacetate 22
1	38.70 (t)	38.70 (t)	38.67 (t)	38.69 (t)
2	21.88 (t)	21.90 (t)	21.90 (t)	21.83 (t)
3	37.24 (t)	37.26 (t)	37.24 (t)	37.23 (t)
4	33.94 (d)	33.97(d)	33.94(d)	33.90(d)
5	159.70 (s)	159.75 (s)	159.76 (s)	159.54 (s)
6	39.22 (s)	39.25(s)	39.23 (s)	39.17(s)
7	39.98 (t)	39.99 (t)	40.03 (t)	39.97 (s)
8	34.02 (t)	34.04 (t)	34.01 (t)	34.08 (t)
9	138.47 (s)	138.37 (s)	137.37 (s)	138.30 (s)
10	118.72 (s)	118.92 (d)	119.41 (d)	118.81 (d)
11	21.87 (t)	21.90(t)	21.87(t)	37.80 (t)
15	16.40 (q)	16.40(q)	16.33(q)	16.38 (q)

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.

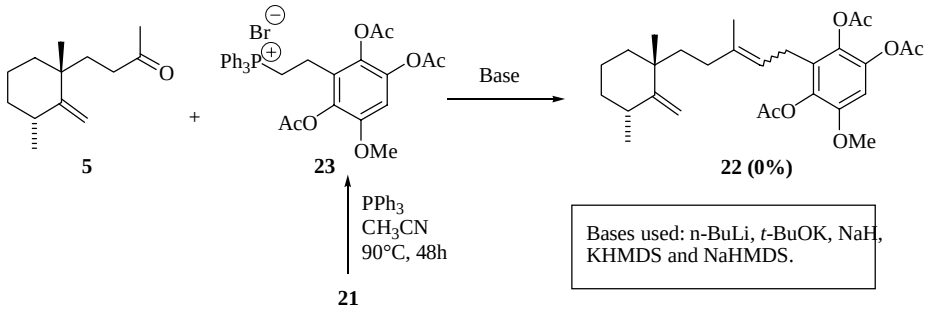
Completion of the synthesis of the metachromin A

The leucotriacetates **22** obtained by reaction of phosphonate **6** with NaH (E:Z; 9:1) were reacted with $LiAlH_4$ to remove the acetate protecting groups, affording the putative and very polar triphenol **24** that was not purified, but immediately oxidized with $FeCl_3$ 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, ^{1}H NMR ,^{13}C-NMR and MS) were almost identical to those reported in the literature[2b] and its ^{1}H and ^{13}C-NMR spectra correlated very well with those kindly provided by Prof. Kobayashi from Hokkaido University, Tokyo.

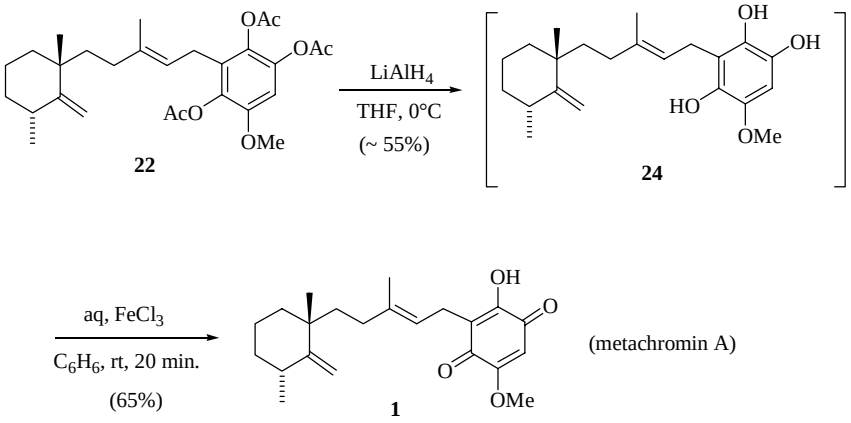
The total synthesis of (±)-metachromin A was therefore completed by a convergent and flexible approach amenable to the synthesis of metachromin analogues. A final evaluation of the synthetic route indicates that the total synthesis encompassed twelve steps in its longest sequence and sixteen steps overall,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



Scheme 8.



Scheme 9.

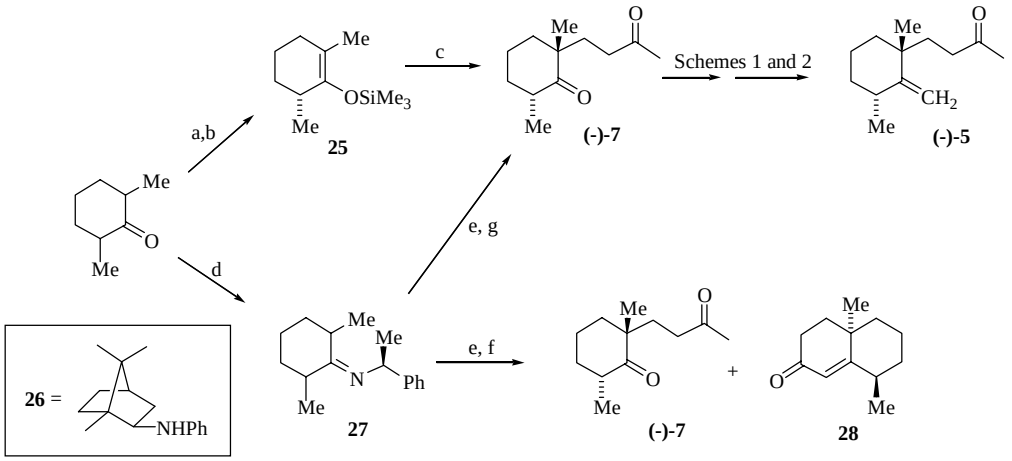
ketone moiety **5** employing an asymmetric method (Scheme 10). A direct route to enantioenriched **5** would be the application of the procedure described by Simpkins[22] that makes use of a chiral, nonracemic, strong amine base to asymmetrically deprotonate a prochiral ketone. Thus, enantioenriched silylenol ether **25** was obtained by asymmetric deprotonation of the *cis*-2,6-dimethylcyclohexanone with the lithium amide prepared from aromatic amine **26**, which was obtained from (*R*)-(+)-camphor and aniline following literature procedure[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 $BF_3.OEt_2$ 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[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[23] could be a better alternative to Simpkins' protocol in our case, and so the asymmetric imine **27** was prepared by reaction of *cis*-2,6-dimethylcyclohexanone with (S)-(-)-α-methylbenzylamine in 68% yield.[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 ^{1}H-NMR experiments using the chiral shift reagent [Eu(hfc)$_3$] 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_2Cl_2 were distilled from CaH_2. Ag_2O was freshly prepared by adding a 10% aqueous solution of NaOH to 9.2 mL of a 10% aqueous solution of $AgNO_3$ (918 mg) until precipitation stopped. The slurry of Ag_2O formed was then filtered and



Scheme 10.

the excess of water removed *in vacuo*. All the procedure was performed under low light. Melting points (uncorrected) were determined on a Büchi 510 apparatus. ^{1}H-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 CH_3CN, 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 $MgSO_4$. After filtration the solvent was rotaevaporated *in vacuo* to furnish a colorless oil that 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 $NaHCO_3$ and 10% aq. $NaHSO_3$, dried over $MgSO_4$ 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, $NaBH_3CN$ (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. $FeSO_4$ and brine. After drying over $MgSO_4$, 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); 1.76-1.55 (m, 4H); 1.33-1.07 (m, 3H); 1.02 (s, 3H); 0.93 (s, 3H); 0.87 (s, 3H). $[\alpha]^{20}_{D}$ = -105.2 (*c* 1.5, $CHCl_3$).

(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 N_2, 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, 3 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 NH_4Cl (30 mL) and the product extracted with pentane (2 x 15 mL). The combined organic extracts were washed with saturated NH_4Cl (3 x 25 mL),

brine (3 x 25 mL), dried over $MgSO_4$, 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. ^{1}H-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). $[\alpha]^{25}_D$ = -25 (c 1.0, CH_2Cl_2)

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 N_2, 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 $BF_3.OEt_2$ and a solution of menthol (468.8 mg, 3.0 mmol) in 1.5 mL of CH_2Cl_2. The resulting mixture was kept at -20 °C for 1 h, warmed up to -10 °C, when 10 mL of aq.10% $NaHCO_3$ was added, and stirring continued for 10 min. Extraction with CH_2Cl_2 (6 x 20 mL), drying over Na_2SO_4, 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; ^{1}H-NMR: δ 2.6 (m, 1H); 2.1-1.3 (m, 13H); 1.0 (d, J = 6.5Hz, 3H); 1.0 (s, 3H). ^{13}C-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); 168 (30); 126 (35); 69 (38); 43 (100).

Diketone **7**. *2,6-dimethyl-2(3-oxobutyl)-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 ($CaCl_2$). 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 0.5 mL of sulfuric acid was added. After additional 2 h, a final 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 $MgSO_4$ 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**. *(2R,6R-dimethyl-2-(3-oxobutyl)-cyclohexanone)*

(*R*)-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**. $[\alpha]^{20}_D$ = -35 (*c* 1.0, $CHCl_3$).

Ketal **8**. *2,6-dimethyl-2-(3-[2,2-dimethyl-1,3-dioxolan]butyryl)-cyclohexanone*

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. $NaHCO_3$ (3 x 20 mL), and water (5 x 20 mL). The organic layer was removed and dried over Na_2SO_4. 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; ^{1}H-NMR: δ 3.5 (br, 4H); 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 $C_{17}H_{30}O_3$: C, 72.29; H, 10.71. Found: C, 72.16; H, 10.68.

Chiral Ketal **8**. *2,6-dimethyl-2-(3-[2,2-dimethyl-1,3-dioxolan]butyryl)-cyclohexanone*

Enantiomerically enriched diketone **7** was submitted to the same conditions described above. The chiral, non-racemic keto-dioxolane was obtained in 92% yield. $[\alpha]^{20}_D$ = -33 (*c* 1.0, $CHCl_3$).

Unsaturated Ketal **9**

To a stirred suspension of potassium tert-butoxide (1.23 g, 11 mmol) in 20 mL of dry benzene under N_2, 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 $MgSO_4$ 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 $C_{18}H_{32}O_2$: C, 77.08; H, 11.50. Found: C, 77.23; H, 11.41.

Chiral unsaturated Ketal **9**

Enantiomerically enriched ketal **8** was submitted to the same conditions described above to afford the optically active unsaturated ketal **9** in 78% yield. $[\alpha]^{20}_D$ = -29 (*c* 1.5, $CHCl_3$).

Ketone **5**

To a solution of ketal **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 acetone. 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_2SO_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 4.7 (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 $C_{13}H_{22}O$: C, 80.35; H, 11.42. Found: C, 80.12; H, 11.39.

Chiral Unsaturated Ketone **5**

Enantiomerically enriched ketal **9** was submitted to the same conditions described above. The optically active unsaturated ketone **5** was obtained in 78% yield. $[\alpha]^{20}_D$ = -22 (c1.0, $CHCl_3$).

Chiral Imine **27**

A mixture of 1.68 g (13 mmol) of 2,6-dimethylcyclohexanone and 5.0 g (40 mmol) of (S)-(-)-α-methylbenzylamine 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 pentane was slowly added over a period of 20 min. Next, the reaction mixture was allowed to warm to room temperature and then heated to reflux for 24 h. After cooling to room temperature, the solid was filtered and washed twice with toluene. The filtrate and washings were combined, the solvent removed *in vacuo*, and the brown viscous oil diluted with ether. The resulting solution was washed with aq. 10% Na_2CO_3 and water, dried over $MgSO_4$, and filtered. After solvent removal in *vacuo* the crude product was purified in a Kugelrohr apparatus (126 °C, 0.1 Torr) to give 2.02 g of the chiral imine **27** (68% yield). IR (neat, cm^{-1}), ν: 3015, 2905, 1652, 1598, 1010, 990, 832. ^{1}H-NMR: δ 7.42-7.18 (m, 5H); 4.38 (q, J = 6.7Hz, 1H); 2.38 (m, 2H); 2.12-1.38 (m, 6H); 1.42 (d, J = 6.9 Hz, 3H); 1.12 (d, J = 7.1 Hz, 3H); 1.09 (d, J = 6.9 Hz, 3H).

Preparation of chiral diketone **7** *from chiral imine* **27**

Methyl vinyl ketone (675 mg, 9.75 mmol) in 15 mL of dry THF was added dropwise to a solution of chiral **27** (745 mg, 3.25 mmol) in 15 mL of THF. The resulting mixture was magnetically stirred at room temperature for 3 days. After this period, the reaction mixture was cooled to 0 °C and 30 mL of 20% aq. acetic acid were added, followed by 31 mg (0.375 mmol) of sodium acetate. The mixture was stirred overnight at room temperature and then extracted with ether (3 x 25 mL), washed with brine, 10% aq. $NaHCO_3$, and brine once again. The organic layer was concentrated *in vacuo*, dried over $MgSO_4$ and filtered. After solvent removal, the residual oil was purified by flash chromatography (ether-pentane 15%) furnishing the optically active diketone **7** in 60% yield. $[\alpha]^{20}_D$ = -31 (*c* 1.0, $CHCl_3$).

Nitrile **14**

A mixture of 0.46 g of 3,5-dimethoxybenzylchloride (2.61 mmol), 60 mL of ethanol, 6.4 g of sodium cyanide (13.06 mmol) in 15 mL of water was refluxed for 4 h. 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). **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).

Acid **15**

To a suspension of nitrile **14** (2 g, 11.3 mmol) in 50 mL of 30% aq. NaOH, were carefully added 10 mL of THF and 5 mL of H_2O_2. When the evolution of gas stopped, the reaction mixture was refluxed for 18 h. After cooling to room temperature, the mixture was washed with diethyl ether (3 x 20 mL), and the aqueous layer acidified until pH = 1, and extracted with EtOAc (8 x 50 mL). The combined organic layer was washed with brine and concentrated *in vacuo* to a fraction of the original volume. Next, the concentrated organic layer was dried (Na_2SO_4) followed by solvent removal *in vacuo* to furnish a white solid corresponding to the acid **15**, that was purified by recrystallization (EtOAc-Hex. 5%) to give 1.98 g of the pure compound (90% yield). **mp**: 97-99 °C. **IR** (KBr, cm^{-1}), ν: 3539-2608; 1711; 1598; 1153, 835. ^{1}H-NMR: δ 9.0 (br, 1H); 6.45 (m, 3H); 3.8 (s, 6H); 3.55 (s, 2H). **MS**: m/z (%): M^+196 (10); 168 (55); 151 (100); 139 (71). Anal. calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.07; H, 6.18.

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

A solution of 3,5-dimethoxybenzoyl 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 CH_2N_2 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 Ag_2O 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 CH_2Cl_2 and dried over Na_2SO_4. Filtration followed by solvent removal in *vacuo* gave 126.2 mg of an pale yellow oil corresponding to ester **17** (20% yield). **IR** (neat, cm^{-1}): ν 3001; 2942, 2837, 1735, 1601, 1460, 1202, 831; ^{1}H-NMR: δ 6.45 (m, 3H); 3.82 (s, 6H); 3.75 (s, 3H); 3.7 (s, 2H).

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 water was added (*the first drops with extreme caution*), followed by 1.5 mL of 10% aq. NaOH. The mixture was warmed to room temperature, stirred for 1 h, filtered and dried over $MgSO_4$. After filtration the solvent was removed *in vacuo* and the residual oil purified by flash chromatography (EtOAc-Hex. 20%). Alcohol **18** was obtained as a colorless oil (462 mg, 98% yield). **IR** (neat, cm^{-1}), ν: 3415, 2934,1600; 1153, 835. ^{1}H-NMR: δ 6.35 (m, 3H); 3.8-3.7 (m, 8H); 2.9(d, J = 8 Hz, 2H). **MS**: m/z (%): M^+ 182 (100); 168 (55); 151 (76); 139 (64). Anal. calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.89; H, 7.68.

Benzyl ether **19**

To a stirred suspension of 2.87 mmol of NaH (138 mg of a 50% NaH dispersion in mineral oil, previously washed with hexane) in dry THF (5 mL), under nitrogen, was added dropwise a solution of 174 mg (0.96 mmol) of alcohol **18** in 10 mL of THF and the resulting mixture stirred for 15 min. A solution of benzyl bromide (326.4 mg, 1.92 mmol) was added and the reaction mixture refluxed for 18 h. The solvent was removed at reduced pressure and the residue diluted with CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (4 x 25 mL), and the organic layers combined, concentrated *in vacuo*, and dried over Na_2SO_4. Filtration gave an oil that was purified by flash chromatography (EtOAc-Hex. 10%) to afford benzyl ether **19**. Yield: 219 mg (84%). **IR** (neat, cm^{-1}), ν: 3026, 2920,1598; 1450; 1202; 1150, 832. ^{1}H-NMR: δ 7.41-7.30 (m, 5H); 6.42 (m, 2H); 6.37 (m, 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 $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.69; H, 7.34.

Benzoquinone **11**

A solution of chromium trioxide (156 mg, ~1.56 mmol) in water (0.5 mL) and acetic acid (2.0 mL) was added dropwise to a stirred solution of the benzyl ether **19** (107 mg, 0.39 mmol) in acetic acid (2.5 mL).The solution 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 Na_2SO_4, filtered and the solvent evaporated *in vacuo* to provide an orange solid that was purified by preparative TLC (EtOAc-Hex. 10%) to yield benzoquinone **11** as orange crystals. Yield: 80% (85 mg). **mp**: 70-71 °C. **UV:** λ (acetone, nm): 362, 286, 210; **IR** (KBr, cm^{-1}), ν: 3105; 2822; 1650; 1601; 1450. ^{1}H-NMR: δ 7.4-7.2 (m, 5H); 6.58 (m, 1H); 5.83 (d, J = 2 Hz, 1H); 4.50 (s, 2H); 3.82 (s, 3H); 3.62 (d, J=8Hz, 2H); 2.72 (m, 2H). ^{13}C-NMR: δ 186.2, s; 178.2, s; 158.9, s; 144.9, s; 134.5, 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. $NaHCO_3$ and water. The resulting organic solution was dried over $MgSO_4$, filtered and concentrated in *vacuo* to give an oil that was purified by flash chromatography (EtOAc-Hex. 20%). The pure triacetoxybenzene **12** was obtained in 65% (97 mg). **IR** (neat, cm^{-1}), ν: 3070; 2920; 1760; 1605; 1452; 1238. ^{1}H-NMR: δ 7.41-7.29 (m, 5H); 6.72 (s, 1H); 4.51 (s, 2H); 3.82 (s, 3H); 3.72 (t, J = 8 Hz, 2H); 2.91 (t, J = 8 Hz, 2H); 2.25 (s, 3H); 2.22 (s, 6H). Anal. calcd. for $C_{22}H_{24}O_8$: 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}), ν:3422, 3086, 2924, 1762, 1604, 1238. ^{1}H-NMR: δ6.70 (s, 1H); 3.85-3.70 (m, 5H);

2.90 (t, J=8Hz, 2H); 2.25 (s, 3H); 2.20 (s, 6H). **MS**: m/z (%): M^+326 (10); 301 (18); 295 (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 CH_2Cl_2, 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 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** ^{1}H: δ6.75 (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).

Phosphonate **6**

To a solution of trimethylphosphite (0.09 mL, 0.74 mmol) in 3 mL of dry 1,2-dimethoxyethane, under N_2, 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 CH_2Cl_2. The dichloromethane solution was washed with brine (4 x 10 mL), dried over Na_2SO_4 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. ^{1}H-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. NH_4Cl 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 $MgSO_4$. 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. **IR** (neat, cm^{-1}), ν: 2987; 2928; 1762; 1604; 1585; 1368; 1287. ^{1}H-NMR: δ 6.7 (s, 1H); 5.15 (t, J = 6.5 Hz, 1H); 4.70 (s, 1H); 4.65 (s, 1H); 3.82 (s, 3H); 3. 2 (d, J = 6.5 Hz, 2H); 2.25 (s, 3H); 2.20 (s, 6H); 1.75 (br, 3H); 1.02 (s, 3H); 1.0 (d, J = 6.5 Hz, 3H). ^{13}C-NMR: δ 168.4, s; 168.30, s; 168.2, s; 159.5, s; 149.1, s; 138.3, s; 135.8, s; 133.7, s; 130.8, s; 118.8, d; 104.7, d; 103.5, t; 56.5, q; 39.9, t; 39.2, s; 38.7, t; 37.8, t; 37.2, t; 34.1, t; 33.9, d; 24.7, q; 21.8, t; 20.7, 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).

(method B)

To a solution of 125 mg (0.3 mmol) of phosphonate **6** in dry THF (3 mL) at -78 °C, under nitrogen, was added dropwise a 0.25 mL (0.3 mmol) of a 1.2 M solution of *n*-BuLi in hexane. The resulting red mixture, was warmed to 0 °C followed by addition of a solution of ketone **5** (58.2 mg, 0.3 mmol) in 1.0 mL of dry THF. The mixture was then stirred at 0 °C for 1.5 h. After an additional stirring at room temperature for 1 h, 20 mL of a saturated solution of NH_4Cl were added and the mixture extracted with EtOAc (6 x 15 mL). The combined organic layer was rotaevaporated to reduce its volume, dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo* to furnish 86.5 mg of leucotriacetate **22** as a 60:40 diastereomeric mixture (60% yield). ^{1}H-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). ^{13}C-NMR: δ 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, s; 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.

(method C)

To a stirred suspension of potassium *tert*-butoxide (168 mg, 1.5 mmol) in dry diethyl ether (10 mL), at 0 °C, under nitrogen, was added a solution of phosphonate **6** (0.5 mmol) in diethyl ether (10 mL). The mixture was warmed to room temperature (~30 °C) and stirred for 40 min. Next, a solution of ketone **5** (126 mg, 0.65 mmol) in diethyl ether (15 mL) was added dropwise, and the mixture refluxed for 6 h. After cooling to 0 °C, 15 mL of a 5% aq. NH_4Cl were added. The product was isolated from extraction with ether and the combined organic layer concentrated *in vacuo*, dried over $MgSO_4$, and filtered. Rotaevaporation of the solvent *in vacuo* provided 139.7 mg of the leucotriacetate **22** as a 60:40 diastereomeric mixture (58% 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 $MgSO_4$. 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}), ν: 3569-3253; 2963; 2852; 1602; 1459; 1304.

Metachromin-A **1**

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 brine and the organic layer separated. The remaining aqueous layer was extracted again with diethyl ether (6 x 20 mL) and the combined organic layer rotaevaporated to afford a residue that was dissolved in ether (20 mL). The ethereal solution was washed with saturated brine, dried over Na_2SO_4 and evaporated *in vacuo* 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): 426, 282, 205; **UV**: λ (MeOH+KOH, nm): 510, 286, 220. **IR** (KBr, cm^{-1}), ν: 3338; 2930; 1632; 1590; 1370; 1298. ^{1}H-NMR: δ 7.35 (br, 1H); 5.83 (s, 1H); 5.15 (t, J = 7.5 Hz, 1H); 4.70 (s, 1H); 4.65 (s, 1H); 3.85 (s, 3H); 3.15 (d, J = 7.5 Hz, 2H); 2.3 (m, 1H); 1.75 (br, 3H); 1.0 (s, 3H); 1.02 (d, J = 6.5Hz, 3H). ^{13}C-NMR: δ 182.8; s; 181.3, s; 161.1, s; 159.6, s; 151.1, s; 138.3, s; 118.7, d; 118.2, s; 103.4, t; 102.1, d; 56.5, q; 39.9, t; 39.2, s; 38.6, t; 37.1, t; 34.1, t; 33.9, d; 24.6, q; 21. 8, t; 21.7, t; 19.5, q; 16.2, q. **MS**: m/z (%): M^+ 358 (89); 207 (85); 168 (75); 123(100); 95 (81); 69 (37).

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 ^{1}H-NMR spectroscopy employing the chiral shift reagent [Eu(hfc)$_3$], and estimate to be ~85%.

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