A New Efficient Route for Multigram Asymmetric Synthesis of Alkannin and Shikonin

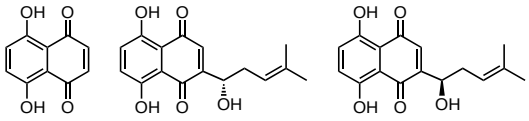
Elias A. Couladouros,*[a] Alexandros T. Strongilos,[a] Vassilios P. Papageorgiou,[b] and Zoi F. Plyta[a]

Abstract: A short and convergent approach for the synthesis of alkannin, shikonin and shikalkin is presented. A Hauser-type annulation of cyanophthalide **26** with enone **7** affords the complete aromatic system in just one step with concomitant attachment of the entire side chain. Subsequent Corey's oxazaborolidine mediated asymmetric reduction of the above advanced intermediate, leads to the required isomer in high enantiomeric excess. Finally, a selective and high yielding deprotection protocol furnishes the title compounds as pure crystalline precipitates. Thus, a multigram synthesis of shikonin, alkannin and shikalkin is achieved in high yield and enantioselectivity.

Keywords: asymmetric synthesis · Michael addition · natural products · oxidation · quinones

Introduction

The polyhydroxylated ring system of naphthazarin (**1**), is the dominant structural characteristic of a number of natural products exhibiting a wide spectrum of imposing biological activities. Dynemicin A,[1] fredericamycin A,[2] fusarubin,[3] bostrycoidin,[4] the novel antitumor antibiotics lomaiviticins A and B,[5] the structurally related pigments heliquinomycin,[6] γ-rubromycin,[7] and purpuromycin,[8] as well as the antipode pair alkannin/shikonin[9] (**2**/**3**, see below), are representative examples of this group of compounds. The latter pair and their



1 **2** **3**

closely related derivatives have recently attracted much attention attributable to their omnifarious biological profile, including antiinflammatory,[10] antibacterial,[11] antifungal,[12] anticancer,[13] analgesic and antipyretic,[14] antithrombotic,[15] immunostimulatory,[16] angiostatic[17] and wound healing properties.[18] From the chemical point of view, due to the high chemical reactivity of the naphthazarin moiety, they are difficult to handle and purify. For example, they are readily polymerized upon treatment with acids, bases, heat or light and they are susceptible to oxidation by exposure to air or light.[9c] Even a simple chromatographic separation usually results in substantial loss of material and irreversibly colored silica. Consequently, the efficient preparation of these relatively small molecules still presents a challenge. Nevertheless, to date, most of the reported syntheses[19] use naphthazarin as starting material. This approach usually results in long, non-versatile synthetic schemes, which in most cases suffer of low yielding deprotection operations and tedious purification of the final products. In one of the shortest and most elegant synthesis of shikonin and alkannin, reported by Nicolaou and Hepworth, the final deprotection step proceeds in 80% yield albeit in only 50% conversion, requiring chromatographic purification.[20]

An efficient and general synthetic scheme for naphthazarin derivatives, suitable for multigram preparations, has to overcome three main obstacles: a) To construct the fused aromatic system in a general and convergent way avoiding the use of the expensive and difficult to derivatize naphthazarin; b) to secure an orthogonal protection of the hydroxyl and keto groups of the aromatic rings inasmuch as deprotection of a tetramethoxy precursor is inefficient and complicated.[21] The ideal end-step should furnish the final product in pure form without any need of chromatographic separation; c) to introduce the side chain and establish the appropriate stereochemistry in an efficient and straightforward way, suitable for the construction of diversified analogues.

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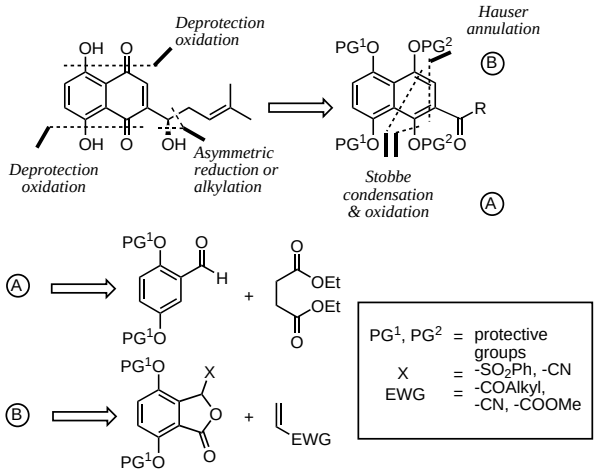
Results and Discussion

Two possible disconnections satisfying the above requirements are depicted in Scheme 1. Disconnection A appears to be more versatile, employing commercially available starting materials. From the practical point of view, it is suitable for the preparation of derivatives with modified aromatic skeleton. However, the resulting reaction sequence of this approach towards alkannin and shikonin is relatively long. A detailed investigation regarding this chemistry will be published elsewhere. On the other hand, disconnection B, which is presented herein, is shorter and more convergent.

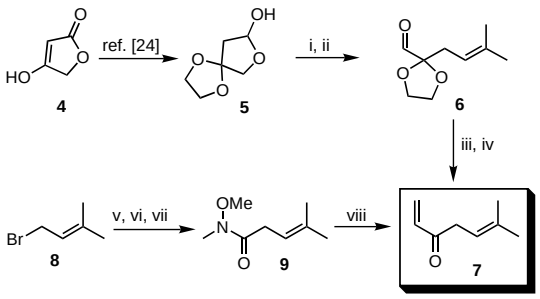


Scheme 1. Retrosynthetic analysis for the target compounds.

Following this strategy, the entire carbon skeleton was envisioned to be constructed in one step applying Hauser type annulation[22] on a suitable functionalized Michael acceptor. Thus, enone **7**,[23] the synthesis of which is depicted in Scheme 2, was targeted to be the critical building block. Tetronic acid (**4**), after protection of the carbonyl group and DIBAL reduction, was transformed to semiketal **5**[24] which was successively subjected to Wittig coupling with the ylide of

Abstract in Greek:

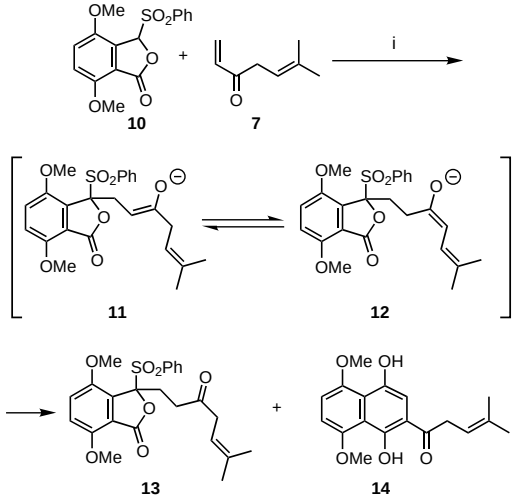
Περιγράφεται μια νέα αποτελεσματική συνθετική πορεία για την παρασκευή Σικονίνης, Αλκαννίνης και Σικαλκίνης. Ολόκληρος ο ανθρακικός σκελετός των παραπάνω μορίων σχηματίζεται σε ένα στάδιο με ταυτόχρονη προσθήκη της πλευρικής αλυσίδας, εφαρμόζοντας ανοικοδόμηση τύπου Hauser στο κυανοφθαλίδιο **26**. Το ενδιάμεσο αυτό μετά από ασύμμετρη αναγωγή με τη χρήση της οξαζοβορολιδίνης του Corey, μετατρέπεται στο επιθυμητό ισομερές σε υψηλή εναντιομερική περίσσεια. Τέλος, χρησιμοποιώντας ένα εκλεκτικό και υψηλών αποδόσεων πρωτόκολλο αποπροστασίας, παραλαμβάνονται η Σικονίνη, η Αλκαννίνη και η Σικαλκίνη ως καθαροί καθιζάνοντες κρύσταλλοι. Ούτως, επιτυγχάνεται σε υψηλή απόδοση η εναντιοεκλεκτική σύνθεση των εν λόγω ενώσεων, σε κλίμακα γραμμαρίων.



Scheme 2. Synthesis of enone **7**. i) $(CH_3)_2CHPPh_3I$, $NaN(SiMe_3)_2$, THF, $-10\rightarrow25\,^{\circ}C$, 6.5 h, 65%; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-78\rightarrow25\,^{\circ}C$; iii) CH_3PPh_3Br, $NaN(SiMe_3)_2$, THF, $-10\rightarrow25\,^{\circ}C$, 4 h, 68% (two steps); iv) Amberlyst 15, THF/H_2O, 6 h, 75%; v) KCN, DMF, 2 d, 25 °C, 86%; vi) NaOH 2N, MeOH, reflux, 8 h, 90%; vii) MeONHMe·HCl, CBr_4, pyridine, PPh_3, CH_2Cl_2, 85%; viii) CH_2=CHMgBr, THF, $-20\,^{\circ}C$, 20 min then saturated aqueous NH_4Cl solution, 61%.

2-iodo-propane and Swern oxidation, yielding intermediate **6**. The latter, upon methylenation of the aldehyde moiety and controlled deprotection of the ketal by means of an acidic resin, afforded acryloprenyl **7** in 16% total yield based on tetronic acid. Alternatively, the same enone was prepared from Weinreb amide **9**,[25] which was synthesized via a known and efficient reaction sequence[26, 27] from prenylbromide **8**. Vinylation of **9** with the appropriate Grignard reagent furnished key intermediate **7** in 40% total yield based on bromide **8**.

According to literature,[28] the anion of sulfone **10**, an 1,4-dipole equivalent, was anticipated to be cyclized spontaneously to the corresponding bicyclic product **14** upon 1,4-addition to enone **7** (Scheme 3). Unfortunately, addition of Michael acceptor **7** to a solution of sulfone **10** pretreated with



Scheme 3. Hauser annulation of sulfone **10** with enone **7**. i) *t*BuOH, *n*BuLi, $0\rightarrow-78\,^{\circ}C$ then **7**, $-78\,^{\circ}C\rightarrow$ reflux.

*t*BuOLi at $-78\,^{\circ}C$, furnished almost exclusively 1,4-adduct **13**. Presumably, between the two possible enolate intermediates **11** and **12**, the latter predominates due to its extended conjugation. Since enolate **12** cannot be cyclized intramolecularly, it is converted to ketone **13**, after workup of the reaction. Adduct **13** could not be transformed to the desired

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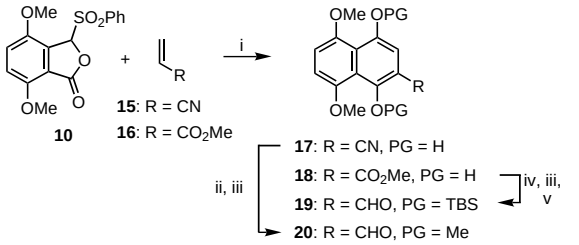
naphthazarine analogue **14**, even after treatment with mild or strong bases under a variety of conditions.[29] Interestingly, ketone **14** could be isolated in low yields (5–10%) among other by-products, when the reaction mixture was heated to reflux, right after the addition of the Michael acceptor. These observations suggested that cyclization could take place, only if the kinetically favored enolate anion **11** was trapped by the lactonic carbonylate before its conversion to the thermodynamically stable form **12**. The marginal solubility of sulfone **10** and presumably of the intermediate anion does not seem to favor this reaction sequence.

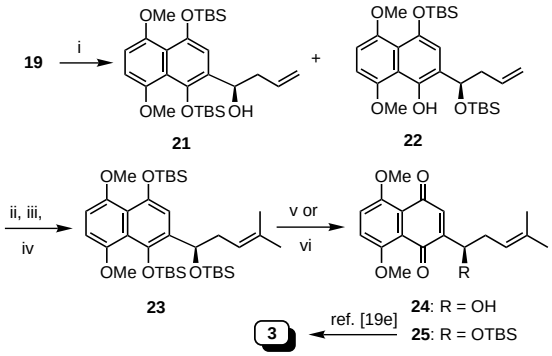
On the other hand, the use of non enolizable Michael acceptors should lead in better cyclization yields. Indeed, coupling of acrylonitrile **15** or methyl acrylate **16** with **10**, afforded the corresponding partially protected naphthazarines **17** and **18** in high yields (Scheme 4). Aldehydes **19** and **20**



Scheme 4. Hauser annulation of sulfone **10** with Michael acceptors **15** and **16**. i) LDA, THF, 0→ −78 °C then **15** or **16**, 40 min; ii) $(MeO)_2SO_2$, K_2CO_3, acetone, reflux, 6 h, 73% (based on **10**); iii) DIBAL, CH_2Cl_2, −78 °C, 1 h, 88% (**17**→**20**), 95% (**18**→**19**); iv) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 98%; v) NMO, cat. TPAP, CH_2Cl_2, 3 h, 97%. DIBAL = diisobutylaluminum hydride, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, NMO = 4-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.

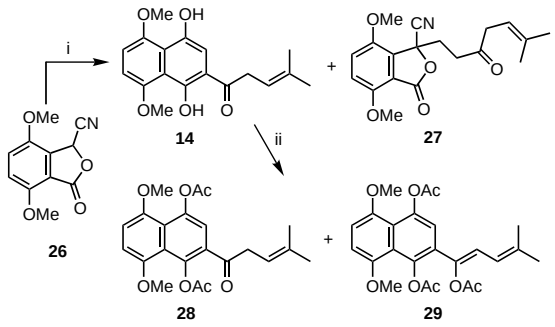
were reached applying conventional chemistry on both, nitrile **17** and carboxylate **18**. A suitable derivatization of the aldehyde **20** towards the target molecules, has been reported to be Brown's asymmetric allylboration.[30] Following this protocol, substrate **19** was successfully converted to advanced intermediate **22** in high yield and 72% *ee* (Scheme 5). During this reaction two products were monitored, the expected alcohol **21** and the isomeric compound **22**. Prolonged reaction times, however, resulted exclusively in the isolation of the migrated derivative **22**. After silylation of alcohol **22**, fully protected shikonin **23** was prepared, within a high yielding three-step sequence. Attempted deprotection of **23** with excess TBAF, afforded only traces of the expected quinone **24**. On the other hand, utilizing ammonium cerium(IV) nitrate (CAN), partially desilylated quinone **25** was obtained in almost quantitative yield. Since the deprotection of intermediate **25**, in moderate yield, has already been reported,[21] this approach is a formal synthesis of compound **3**. All attempts to deprotect effectively compound **25** as well as related model quinones were unsuccessful. Thus, in the following final approach, the demethylation was planned strategically to be carried out before unmasking the quinone moiety.

Reconsidering Hauser's annulation, cyanophthalide **26**,[31] which was more soluble than the originally used 1,4-dipole



Scheme 5. Formal synthesis of (*R*)-(+)-shikonin. i) (−)-$Ipc_2BAllyl$, Et_2O, −100 °C, then ethanolamine, 25 °C, 2–3 h, 84%; ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 20 min, 96%; iii) OsO_4, THF/H_2O, $NaIO_4$, 6 h; iv) $CH_3CH(CH_3)PPh_3I$, *n*BuLi, Et_2O, 0→ 25 °C, 3 h, 72% (two steps); v) excess TBAF, THF, 25 °C, 15 min, 5% (**23**→**24**); vi) CAN, CH_3CN/H_2O, 25 °C, 15 min, 92% (**23**→**25**). (−)-$Ipc_2BAllyl$ = (−)-*B*-allyldiisopinocampheylborane, TBAF = tetrabutylammonium fluoride, CAN = ammonium cerium(IV) nitrate.

equivalent **10**, was subjected to coupling with enone **7**, leading to the desired compound **14** in significantly higher yields (Scheme 6). Fine-tuning of the reaction conditions according to the previously described considerations, resulted in a 90% conversion of the Michael adduct **27** to the naphthazarine system **14**. This approach can be easily recognized to fulfil one

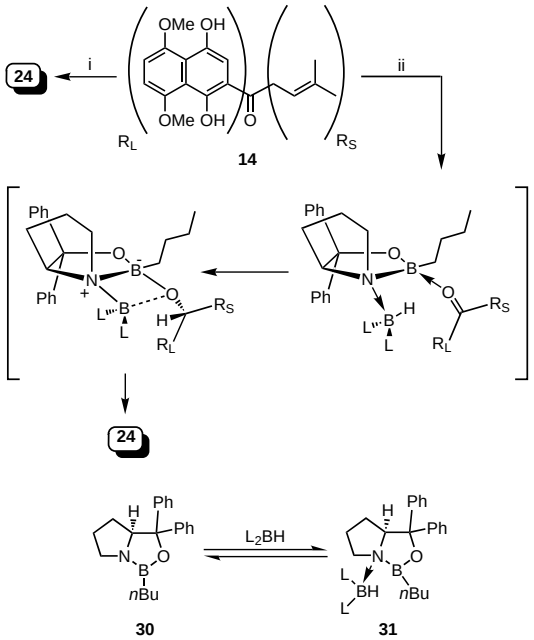


Scheme 6. Hauser annulation of nitrile **26** with enone **7**. i) LDA, THF, −78→ 0 °C then **7**, 35 min, 60%; ii) MeCOCl, pyridine, CH_2Cl_2, 0 °C, 30 min.

of our primary objectives; to construct the entire carbon skeleton of the target compound in one operation in relatively high yield and multigram scale. Based on the experience gained so far, a suitably protected precursor for both the asymmetric reduction and the final deprotection operations should be ketone **28**. This intermediate, after reduction of the carbonyl moiety, was anticipated to undergo complete and selective demethylation and oxidation to the corresponding *exo*-quinone. Subsequent saponification of the remaining acetates, under fine-tuned experimental conditions, and concomitant in situ tautomerization should provide the target compounds as pure crystalline precipitates. However, acetylation under basic conditions, strongly favored the enolisation of **14** giving rise to mixtures of **28** and **29**, whereas the unwanted isomer predominated. Furthermore, esterification under acidic conditions (AcOH/EDC) was also unsuccessful. Consequently, we were opted for a more risky but delicate

approach by introducing the required asymmetry on the unprotected precursor **14**.

Chlorodiisopinocampheylborane (DIPCl),[32] was the first reagent of choice, since it reduces acetophenones enantioselectively and does not affect double bonds. In addition there is precedent that it converts *ortho*-hydroxy-acetophenones[33] into diols with high enantioselectivity. Thus, reaction of ketone **14** with 2.1 molar equivalents of (+)-DIPCl (Scheme 7) furnished alcohol **24** in affordable enantioselectivity (78%) and moderate chemical yield (40%). In a second



Scheme 7. Asymmetric reduction of compound **14**. i) (+)-DIPCl, pyridine, THF, $-20\,^{\circ}C$, then ethanolamine, $25\,^{\circ}C$, 20 h, 48%; ii) (*S*)-Corey's catalyst, catecholborane, toluene, $-78\,^{\circ}C$, then aqueous $NaBO_3 \cdot 4H_2O$, 20 h, 80% or (*S*)-Corey's catalyst, $BH_3 \cdot THF$, toluene, $-20 \rightarrow 0\,^{\circ}C$ then aqueous $NaBO_3 \cdot 4H_2O$, 18 h, 77%. (+)-DIPCl = (+)-*B*-chlorodiisopino-campheylborane, (*S*)-Corey's catalyst = (*S*)-3,3-diphenyl-1-butyltetrahydro-3*H*-pyrrolo-[1,2-*c*][1,3,2]oxazaborole.

run, the reaction was performed in the presence of an equimolar amount of pyridine, as a scavenger for the liberated hydrogen chloride, yet, the chemical yield still did not exceed 50%. Alternatively, Corey's oxazaborolidine catalyst[34] was considered. Catecholborane and borane/tetrahydrofuran complex ($BH_3 \cdot THF$) which are the most commonly used reducing agents for the CBS (Corey–Bakshi–Shibata) reduction were employed. The relative reactivity however, of complex **31** with ketone versus phenolic hydroxyl groups, was in question. Thus, treatment of **14** with 0.1 equivalents of catalyst **30** and 2.0 equivalents of catecholborane in THF at $-78\,^{\circ}C$ for 6 h afforded, after in situ oxidation with $NaBO_3$, quinone **24** in 85% yield. The hydroquinone which was actually formed by this reaction, during the work up was partially oxidized by air to the corresponding quinone. To avoid this implication it is preferable to oxidize it in situ, right before workup. ^1H NMR analysis of the MTPA [α-methoxy-α-(trifluoromethyl)-phenylacetyl] ester revealed that the reduction proceeded with no enantioselectivity at all. The same result was obtained even when the temperature was lowered to $-100\,^{\circ}C$ and the substrate was added to a premixed solution of the catalyst and the borane. The complete lack of enantioselectivity suggested that catalyst **30** did not participate at all in the above reduction. One reasonable explanation is that the phenolic hydroxyl groups are forming strong complexes with oxaborolidine **30** or/and complex **31**. Another possibility is a preferential complexation of the borane with the substrate, followed by intramolecular delivery of the hydride. In either case, the catalyst would be excluded from the reduction complex intermediate. The use of a Lewis acid such as $B(OMe)_3$ as an in situ protective group for the free phenols did not affect the *ee* of the product. The problem was finally overcome, by adding one equivalent of the substrate to a premixed solution of three equivalents of both oxazaborolidine and catecholborane in toluene at $-78\,^{\circ}C$. In this way, the targeted chiral alcohol **24** was isolated in 80% yield and 83% *ee*, as was shown by ^1H NMR spectroscopy and HPLC analysis of corresponding MTPA ester. Similarly, when $BH_3 \cdot THF$ was employed as the reducing agent, the calculated enantioselectivities, using 0.1 or 3 equivalents of catalyst **30**, were 30 and 90%, respectively. In both cases the chemical yield was 77%. Despite the fact that Corey's oxazaborolidine is expensive, its effective recovery assures a cost efficient scale up operation. Bearing in mind that most of the biological properties of the two enantiomers are independent of their stereochemistry,[10b] reduction with $NaBH_4$ is sufficient for large-scale production of Shikalkin (trade name of their racemic mixture).

Final synthetic pathway: In summary, as it is depicted in Scheme 8, synthons **26** and **7** have been efficiently converted within two chemical steps to partially protected shikonin (**24**), alkannin (**32**) or shikalkin (**33**) employing the appropriate reduction protocol. Although these intermediates seem to be one step away from the target compounds, it has been demonstrated that any attempt to deprotect them directly will end up to a catastrophe. It is, however, well known that quinone/hydroquinone redox interconversions, as well as naphthazarine tautomerizations, are quantitative operations. As a result, a seven-step deprotection protocol which could be performed in three chemical operations, including reduction–acetylation–demethylation–oxidation–saponification–tautomerization–neutralization was envisioned. To this end, reduction and subsequent exhaustive acetylation of compounds **24**, **32** and **33** provided the corresponding triacetates in nearly quantitative yields. To our delight, CAN-mediated oxidative demethylation proceeded quantitatively, furnishing isomeric naphthazarine derivatives **34**–**36**. Based on ^1H and ^{13}C NMR data, these deprotection products were shown to be a mixture of the expected compounds **34**–**36** and their isomeric *endo*-quinones (ratio $\approx$8:2, see Experimental Section). The presence of the latter isomeric form was further confirmed after comparison with spectroscopic data of triacetylated shikonin prepared from an authentic shikonin sample of natural source. However, due to the tautomerization to the thermodynamically stable isomer, which is taking place in the following step, the formation of this mixture did not affect the total yield of the final compound. Finally,

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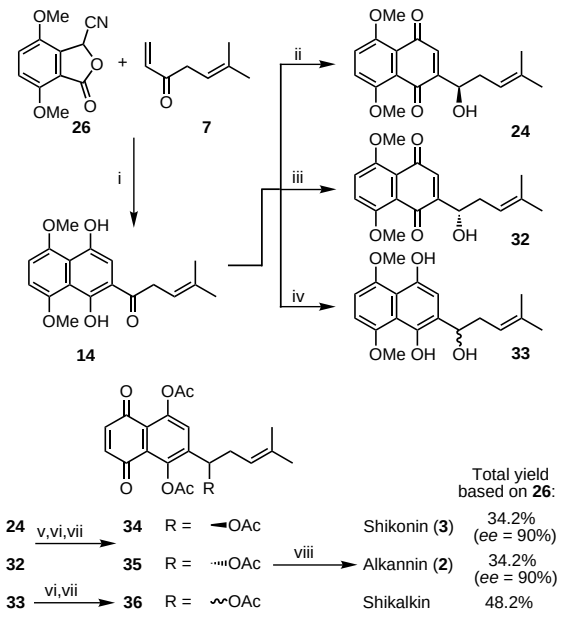

Scheme 8. Synthesis of alkannin, shikonin, and shikalkin. i) LDA, THF, $-78\rightarrow0\,^{\circ}C$ then **7**, 35 min, 60%; ii) 3 equiv (*S*)-Corey's catalyst, 3 equiv catecholborane, toluene, $-78\,^{\circ}C$ then aqueous $NaBO_3\cdot4H_2O$, 20 h, 80% or 3 equiv (*S*)-Corey's catalyst, 3 equiv $BH_3\cdot$THF, toluene, $-20\rightarrow0\,^{\circ}C$ then aqueous $NaBO_3\cdot4H_2O$, 18 h, 77%; iii) 3 equiv (*R*)-Corey's catalyst, 3 equiv catecholborane, toluene, $-78\,^{\circ}C$ then aqueous $NaBO_3\cdot4H_2O$, 20 h, 80% or 3 equiv (*R*)-Corey's catalyst, 3 equiv $BH_3\cdot$THF, toluene, $-20\rightarrow0\,^{\circ}C$ then aqueous $NaBO_3\cdot4H_2O$, 18 h, 77%; iv) $NaBH_4$, MeOH, $0\,^{\circ}C$; v) $Na_2S_2O_4$, Et_2O/H_2O; vi) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 5 h; vii) CAN, CH_3CN/H_2O, 15 min, **34**: yield = 77.9% based on **24**, **35**: yield = 77.6% based on **32**, **36**: yield = 86.5% based on **14;** viii) 1M NaOH, 1 h, then acetic acid to neutralization, 95%. DMAP = 4-dimethylaminopyridine.

saponification and tautomerization of the latter compounds utilizing an 1M aqueous NaOH solution followed by careful acidification with acetic acid in open air, provided the target molecules as golden shiny deep red crystals which were collected by simple filtration. The total chemical yield of all operations from intermediates **24**, **32**, and **33** up to the final pure crystalline products, was 75 to 80%.

Conclusion

In conclusion, a new method for the preparation of the title compounds has been found. The approach is short, very efficient and might find broad application in the synthesis of many analogues of this family of compounds. More important, this new synthetic method allows for the multigram scale preparation of chemically and enantiomerically pure shikonin or alkannin utilizing a very efficient deprotection protocol.

Experimental Section

General techniques: All reactions were carried out under anhydrous conditions and argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium/benzophenone, dichloromethane (CH_2Cl_2) from P_2O_5 and toluene from sodium. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless stated otherwise. All reagents were purchased at highest commercial quality and used without further purification, unless stated otherwise. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F_{254}) using UV light as visualizing agent and ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on Bruker AMX-500, AMX-400 or AC-250 instruments. The following abbreviations were used to explain NMR signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double of doublets. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR or Nicolet Magna system 550 FT-IR instruments. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions and matrix-assisted (MALDI-FTMS) mass spectra were recorded on a PerSeptive Biosystems Voyager IonSpect mass spectrometer. Melting points (m.p.) are uncorrected and were recorded on a Gallenkamp melting point apparatus.

2-(3-Methyl-buten-2-yl)-[1,3]-dioxalane-2-carbaldehyde (6): A solution of Me_2CHPPh_3I (6.19 g, 14.3 mmol) in anhydrous THF (24 mL) was treated with $(Me_3Si)_2NNa$ (1M solution in THF, 12.3 mL, 12.3 mmol) at $-10\,^{\circ}C$. After 2 h, a solution of **5**[24] (1.5 g, 10.3 mmol) in THF (10 mL) was added dropwise at $-10\,^{\circ}C$ and the reaction mixture was then stirred for 5 h at $25\,^{\circ}C$. Upon completion of the reaction (monitored by TLC), a saturated aqueous NH_4Cl solution (30 mL) was added and the mixture was extracted with Et_2O (2×60 mL). The organic extracts were washed with water (30 mL), brine (30 mL), dried over Na_2SO_4 and finally concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, hexanes/EtOAc 5:5), afforded [2-(3-methyl-buten-2-yl)-[1,3]-dioxalan-2-yl]-methanol as a colorless oil (1.15 g, 65%). $R_f = 0.67$ (hexanes/EtOAc 5:5); IR (neat): $\tilde{\nu} = 3470, 2970, 2910, 1630, 1435, 1050\ cm^{-1}$; ^{1}H NMR (500 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta = 5.17$ (m, 1H, =CH), 4.00 (s, 4H, OCH_2CH_2O), 3.53 (d, $J = 5.0$ Hz, 2H, CH_2OH), 2.38 (d, $J = 7.5$ Hz, 2H, $=CHCH_2$), 2.00 (brs, 1H, OH), 1.71 (s, 3H, Me), 1.62 (s, 3H, Me).

A solution of freshly distilled oxalylchloride (0.75 mL, 8.6 mmol) in anhydrous CH_2Cl_2 (12.5 mL) was cooled at $-78\,^{\circ}C$ and DMSO (1.15 mL, 16.2 mmol) was added dropwise. After 30 min a solution of [2-(3-methyl-buten-2-yl)-[1,3]-dioxalan-2-yl]-methanol (1.15 g, 6.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise and the mixture was stirred at $-78\,^{\circ}C$ for another 30 min. Finally Et_3N (5.78 mL, 41.5 mmol) was added, the cooling bath was removed and stirring was continued for 1 h. The reaction was then quenched with a saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (2×50 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated to afford crude **6**, which was used in the next step without any further purification.

6-Methyl-hepta-1,5-dien-3-one (7): A solution of $MePPh_3Br$ (6.04 g, 16.9 mmol) in anhydrous THF (30 mL) was treated with $(Me_3Si)_2NNa$ (1M solution in THF, 25.4 mL, 25.4 mmol) at $-10\,^{\circ}C$. After 2 h, a solution of the crude aldehyde **6** in THF (10 mL) was added and the mixture was stirred at $25\,^{\circ}C$ approximately 2 h (monitored by TLC). The reaction was quenched with a saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (2×50 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, pentane/Et_2O 95:5) to afford 3-(3-methyl-buten-2-yl)-2-vinyl-[1,3]-dioxalane as a colorless oil (764 mg, 68% based on [2-(3-methyl-buten-2-yl)-[1,3]-dioxalan-2-yl]-methanol). $R_f = 0.54$ (hexanes/EtOAc 95:5); IR (neat): $\tilde{\nu} = 3092, 2976, 2885, 1445, 1405, 1380, 1060, 859\ cm^{-1}$; ^{1}H NMR (250 MHz, $CDCl_3$, $25\,^{\circ}C$): $\delta = 5.78$ (dd, $J = 9.5$, 7.2 Hz, 1H, $CH_2=CH$), 5.40 (d, $J = 9.5$ Hz, 1H, $CH_2=CH$), 5.17 (m, 2H, $CH_2=CH$, $Me_2C=CH$), 3.96 (m, 4H, OCH_2CH_2O), 2.49 (d, $J = 7.2$ Hz, 2H, $=CHCH_2$), 1.76 (s, 3H, Me), 1.62 (s, 3H, Me).

Amberlyst 15 (200 mg) was added to a solution of 3-(3-methyl-buten-2-yl)-2-vinyl-[1,3]-dioxalane (250 mg, 1.48 mmol) in THF (15 mL) and water (0.5 mL). The mixture was shaken for 6 h at $25\,^{\circ}C$ and then extracted with Et_2O (2×60 mL). The combined organic extracts were washed with water (2×20 mL), brine (15 mL), dried over activated $MgSO_4$ and concentrated to 6 mL volume. The volatile crude product was used in the next step without further purification.

Alternatively, to a stirred solution of **9**[26, 27] (407 mg, 2.59 mmol) in anhydrous THF (23 mL) at $-20\,^{\circ}C$, was added dropwise a freshly prepared

solution of vinylmagnesium bromide 1M in THF (3.1 mL, 3.10 mmol). The mixture was stirred at the same temperature for 20 min and then a saturated aqueous solution NH_4Cl solution (3 mL) was added. The mixture was then extracted with pentane (2×10 mL) and the organic extracts were dried over activated $MgSO_4$ and concentrated to 10 mL volume. The resulting solution of enone **7** was used for the Michael couplings without further purification. $R_f = 0.89$ (hexanes/EtOAc 8:2); IR (neat) (crude product): $\tilde{\nu} = 2964, 2929, 1690, 1621, 1448, 1402, 1298, 1109\ cm^{-1}$; ^1H NMR NMR (250 MHz, $CDCl_3$, 25 °C) (crude product): $\delta = 6.44 - 6.13$ (m, 2H, CH=CH_2), 5.77 (d, $J = 10.0$ Hz, 1H, =CH_2), 5.28 (m, 1H, C*H*=CMe_2), 3.25 (d, $J = 7.1$ Hz, 2H, $COCH_2$), 1.72 (s, 3H, =CMe_2), 1.61 (s, 3H, =CMe_2).

Coupling of sulfone 10 with enone 7: A solution of *n*BuLi 1.6M in hexanes (0.18 mL, 0.30 mmol) was added dropwise to a stirred solution of *t*BuOH (28 μL, 0.30 mmol) in anhydrous THF (2 mL) at 0 °C. The mixture was stirred for 5 min and then the temperature was lowered to −78 °C followed by addition of a solution of **10**[22e] (40 mg, 0.12 mmol) in THF (22 mL). The resulting yellow mixture was stirred at the same temperature for 20 min followed by addition of a solution of **7** (29.6 mg, 0.24 mmol) in THF (1.5 mL). Finally, temperature was raised up to reflux for 3 h and after cooling the mixture to 25 °C, a saturated aqueous NH_4Cl solution (5 mL) was added. The mixture was extracted with EtOAc (2×20 mL), the combined organic extracts were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc 7:3) to afford **13** as a white solid (36.4 mg, 58%). $R_f = 0.31$ (hexanes/EtOAc 5:5); IR (KBr): $\tilde{\nu} = 2920, 1783, 1710, 1500, 1440, 1275\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.90 - 7.42$ (m, 5H, SO_2Ph), 7.10 (center of AB_q, $J = 9.4$ Hz, $\Delta\nu = 43.2$ Hz, 2H, CH_{ar}), 5.15 (m, 1H, =CH), 3.94 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.32 – 3.11 (m, 1H, C*H*HCH_2CO), 2.95 (d, $J = 7.3$ Hz, 2H, CH_2CH=), 2.55 – 2.00 (m, 3H, CH*H*CH_2CO), 1.68 (s, 3H, =CMe_2), 1.50 (s, 3H, =CMe_2).

A second product isolated and characterized was the hydroxyketone **14** as an orange yellow solid (6.1 mg, 8%). $R_f = 0.55$ (hexanes/EtOAc 5:5); m.p. 108 – 110 °C; IR (KBr): $\tilde{\nu} = 3368, 2925, 1632, 1581, 1392, 1256, 1194, 1095, 1048, 866, 807\ cm^{-1}$; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 13.17$ (s, 1H, OH), 9.14 (s, 1H, OH), 7.08 (s, 1H, CH_{ar}), 6.76 (center of AB_q, $J = 8.7$ Hz, $\Delta\nu = 32.9$ Hz, 2H, CH_{ar}), 5.45 (m, 1H, =CH), 3.95 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.71 (d, $J = 6.7$ Hz, 2H, CH_2), 1.75 (s, 3H, =CMe_2), 1.67 (s, 3H, =CMe_2); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 203.3, 155.3, 152.9, 149.3, 135.6, 120.4, 118.0, 116.0, 115.0, 108.8, 108.6, 106.2, 56.6, 56.5, 39.6, 25.2, 18.1$; HRMS (MALDI): calcd for $C_{18}H_{20}O_5$: 317.1383 $[M+H]^+$; found 317.1370.

Coupling of sulfone 10 with Michael acceptors 15 and 16: A suspension of **10** (250.0 mg, 0.75 mmol) in THF (90 mL) was added dropwise to a stirred solution of LDA (2.24 mmol) in anhydrous THF (15 mL) at −78 °C. The yellow suspension was stirred at the same temperature for 30 min and then Michael acceptor **15** or **16** (2.24 mmol) was added in one portion. After 10 min the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL) and temperature was raised to 25 °C under vigorous stirring. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×20 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude ester **18** was purified by small column filtration (silica gel, hexanes/Et_2O 6:4) while nitrile **17** was not subjected to any purification. Both **17** and **18** are easily oxidisable yellow oils.

Preparation of aldehyde 20 from nitrile 17: Nitrile **17** was dissolved in anhydrous acetone (5.5 mL) and transferred into an autoclave. Then, anhydrous K_2CO_3 (535.5 mg, 3.86 mmol) and $(MeO)_2SO_2$ (0.25 mL, 2.64 mmol) were added successively. The autoclave was sealed under argon and the mixture was stirred at 65 °C for 6 h. Upon completion of the reaction (monitored by TLC), water (15 mL) was added followed by extraction with EtOAc (20 mL). The organic layer was washed with brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc 7:3) to afford 1,4,5,8-tetramethoxy-naphthalene-2-carbonitrile as a pale yellow crystalline solid (204.2 mg, 73% based on **10**). $R_f =$ 0.75 (hexanes/EtOAc 5:5); m.p. 94 – 96 °C; IR (KBr): $\tilde{\nu} = 2818, 2208, 1600, 1580, 1260\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 6.98$ (center of AB_q, $J = 9.8$ Hz, $\Delta\nu = 35.5$ Hz, 2H, CH_{ar}), 6.83 (s, 1H, CH_{ar}), 3.96 (s, 6H, OMe), 3.94 (s, 3H, OMe), 3.91 (s, 3H, OMe); ^{13}C NMR (125.7 MHz, $CDCl_3$, 25 °C): $\delta = 153.5, 149.5, 144.4, 144.0, 124.1, 118.1, 115.9, 109.6, 101.5, 100.8, 91.6, 63.3, 56.0, 55.7$; HRMS (FAB): calcd for $C_{15}H_{15}ON$: 274.1079 $[M+H]^+$; found 274.1090.

A solution of DIBAL 1.0M in CH_2Cl_2 (0.20 mL, 0.20 mmol) was added dropwise to a stirred solution of 1,4,5,8-tetramethoxy-naphthalene-2-carbonitrile (50.0 mg, 0.18 mmol) in CH_2Cl_2 (12 mL) at −78 °C. The reaction mixture was stirred at the same temperature approximately 1 h (monitored by TLC) and then quenched with MeOH (1 mL) followed by addition of a saturated aqueous sodium potassium tartrate solution (8 mL) and EtOAc (5 mL). The resulting mixture was stirred vigorously for approximately 2 h whereupon the organic layer was separated and the aqueous layer extracted with EtOAc (2×8 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, concentrated under pressure and the crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc 9:1) to afford **20** as yellow crystalls (50.5 mg, 88%). All spectroscopic data were in accordance with the reported ones (see ref. [19b]).

Preparation of aldehyde 19 from ester 18: A solution of ester **18** (120.0 mg, 0.43 mmol) in anhydrous CH_2Cl_2 (7 mL) was treated with 2,6-lutidine (0.18 mL, 1.5 mmol) and TBSOTf (0.30 mL, 1.29 mmol) at 0 °C for 10 min. The reaction mixture was then quenched with MeOH (0.3 mL) and a saturated aqueous NH_4Cl solution (5 mL) was added, followed by extraction with EtOAc (2×10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/Et_2O 9:1) to afford 1,4-bis-(*tert*-butyldimethylsilyloxy)-5,8-dimethoxynaphthalene-2-carboxylic methyl ester as a white solid (213.6 mg, 98%) upon prolonged drying under high vacuo. $R_f = 0.75$ (hexanes/Et_2O 8:2); m.p. 65 – 67 °C; IR (neat): $\tilde{\nu} = 2951, 2857, 1739, 1608, 1576, 1384, 1366, 1264, 1138, 1061, 930, 809\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 7.18$ (s, 1H, CH_{ar}), 6.73 (center of AB_q, $J = 8.5$ Hz, $\Delta\nu =$ 39.0 Hz, 2H, CH_{ar}), 3.88 (s, 3H, CO_2Me), 3.84 (s, 3H, OMe), 3.82 (s, 3H, OMe), 1.07 (s, 9H, *t*BuSi), 1.03 (s, 9H, *t*BuSi), 0.20 (s, 6H, Me_2Si), 0.00 (s, 6H, Me_2Si); ^{13}C NMR (125.7 MHz, $CDCl_3$, 25 °C): $\delta = 167.7, 152.0, 150.2, 146.8, 146.0, 123.9, 123.2, 119.9, 116.8, 107.5, 105.7, 55.7, 55.3, 51.8, 26.0, 25.9, 18.0, 18.2, −4.5, −5.1$; HRMS (FAB): calcd for $C_{26}H_{42}O_6Si_2$: 507.2598 $[M+H]^+$; found 507.2614.

A solution of DIBAL 1.0M in CH_2Cl_2 (0.87 mL, 0.86 mmol) was added dropwise to a stirred solution of 1,4-bis-(*tert*-butyldimethylsilyloxy)-5,8-dimethoxynaphthalene-2-carboxylic methyl ester (200.0 mg, 0.39 mmol) in CH_2Cl_2 (20 mL) at −78 °C. The reaction mixture was stirred at the same temperature approximately 15 min (monitored by TLC) and then quenched with MeOH (1 mL) followed by addition of a saturated aqueous sodium potassium tartrate solution (10 mL) and EtOAc (10 mL). The resulting mixture was stirred vigorously approximately 2 h whereupon the organic layer was separated and the aqueous extracted with EtOAc ($2 \times$ 15 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, concentrated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, hexanes/Et_2O 7:3) to afford [1,4-bis-(*tert*-butyldimethylsilyloxy)-5,8-dimethoxy-naphthalen-2-yl]-methanol as a colorless oil (177.4 mg, 95%). $R_f = 0.35$ (hexanes/Et_2O 7:3); IR (neat): $\tilde{\nu} = 3445, 2929, 2856, 1602, 1373, 1258, 1062, 926, 839\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 6.95$ (s, 1H, CH_{ar}), 6.63 (s, 2H, CH_{ar}), 4.76 (d, $J = 3.5$ Hz, 2H, CH_2OH), 3.83 (s, 3H, OMe), 3.79 (s, 3H, OMe), 1.05 (s, 9H, *t*BuSi), 1.03 (s, 9H, *t*BuSi), 0.18 (s, 6H, Me_2Si), 0.00 (s, 6H, Me_2Si); ^{13}C NMR (125.7 MHz, $CDCl_3$, 25 °C): $\delta =$ 150.6, 150.3, 146.5, 141.9, 128.7, 122.5, 121.5, 116.8, 105.0, 104.7, 60.8, 55.5, 55.2, 25.9, 25.8, 18.5, 18.3, −4.4, −4.5; HRMS (FAB) calcd for $C_{25}H_{42}O_5Si_2$: 479.2649 $[M+H]^+$; found 479.2662.

A solution of [1,4-bis-(*tert*-butyldimethylsilyloxy)-5,8-dimethoxynaphthalen-2-yl]-methanol (160.4 mg, 0.34 mmol) in anhydrous CH_2Cl_2 (15 mL), was treated with 4-methylmorpholine *N*-oxide (98.1 mg, 0.84 mmol) and TPAP (23.5 mg, 0.07 mmol) at 25 °C for 3 h (the reaction progress was monitored by TLC). The reaction mixture was then filtered through a pad of silica gel (CH_2Cl_2) and the organic solvent was concentrated under reduced pressure to afford **19** as a yellow oil (154.9 mg, 97%), which was used in the next step without further purification. $R_f = 0.70$ (hexanes/Et_2O 7:3); IR (neat): $\tilde{\nu} = 2955, 2858, 1678, 1605, 1574, 1516, 1392, 1372, 1259, 1074, 1059, 925, 841\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 10.40$ (s, 1H, CHO), 7.15 (s, 1H, CH_{ar}), 6.78 (center of AB_q, $J = 8.7$ Hz, $\Delta\nu =$ 44.4 Hz, 2H, CH_{ar}), 3.84 (s, 3H, OMe), 3.83 (s, 3H, OMe), 1.07 (s, 9H, *t*BuSi), 1.01 (s, 9H, *t*BuSi), 0.20 (s, 6H, Me_2Si), 0.00 (s, 6H, Me_2Si);

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^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C): δ = 189.6, 152.2, 151.8, 150.8, 146.9, 130.9, 128.8, 124.6, 111.4, 109.2, 106.26, 55.9, 55.4, 25.9, 25.8, 18.5, −4.4, −4.8; HRMS (FAB) calcd for $C_{25}H_{40}O_5Si_2$: 477.2493 $[M+H]^+$; found 477.2478.

4-(*tert*-Butyldimethylsilyloxy)-2-[1-(*tert*-butyldimethylsilyloxy)-but-3-enyl]-5,8-dimethoxynaphthalen-1-ol (22): A solution of aldehyde **19** (140.1 mg, 0.29 mmol) in anhydrous ether (4 mL) was cooled to −100 °C. To this solution was added (−)-*B*-allyldiisopinocampheylborane (2.3 mL, 0.15 M in pentane, 0.35 mmol) by cannulation during 15 min. (−)-*B*-Allyldiisopinocampheylborane in pentane was typically prepared by the adaptation of the original method reported by Brown.[35] Upon completion of the addition, the mixture was stirred at the same temperature approximately 30 min and then the reaction was quenched with MeOH (0.3 mL). The mixture was then brought to 25 °C and ethanolamine (1.5 mL) was added. Stirring was continued for 2–3 h followed by addition of a saturated aqueous NH_4Cl solution (5 mL) and EtOAc (8 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 7 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc 7:3) to afford **22** as a colorless oil (127.9 mg, 84%). R_f = 0.45 (hexanes/Et_2O 7:3); $[\alpha]_D^{25}$ = +45.7 (c = 1.0 in $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3383, 2955, 2856, 1615, 1385, 1250, 1055, 902, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.66 (s, 1H, OH), 7.07 (s, 1H, CH_{ar}), 6.62 (center of AB_q, J = 8.5 Hz, $\Delta\nu$ = 41.0 Hz, 2H, CH_{ar}), 5.90–5.80 (m, 1H, =CH), 5.30 (t, J = 6.0 Hz, 1H, CH_2CHO), 5.02–4.96 (m, 2H, =CH_2), 3.99 (s, 3H, OMe), 3.84 (s, 3H, OMe), 2.47–2.44 (m, 2H, CH_2), 1.03 (s, 9H, *t*BuSi), 0.91 (s, 9H, *t*BuSi), 0.19 (s, 3H, Me_2Si), 0.17 (s, 3H, Me_2Si), 0.06 (s, 3H, Me_2Si), 0.00 (s, 3H, Me_2Si); ^{13}C NMR (125.7 MHz, $CDCl_3$, 25 °C): δ = 151.9, 150.0, 143.9, 143.5, 135.6, 130.9, 128.8, 127.0, 120.3, 116.9, 116.5, 104.1, 103.4, 67.7, 55.4, 55.5, 43.3, 26.1, 26.0, 18.6, 18.2, −4.3, −4.4, −4.7, −5.1; HRMS (FAB) calcd for $C_{28}H_{46}O_5Si_2$: 651.1938 $[M+Cs]^+$; found 651.1918. Enantiomeric excess (*ee*) of this compound was measured to be 72% by Mosher's ester analysis of final product **3** which is derived from this.

1,4-Bis-(*tert*-butyldimethylsilyloxy)-2-[1-(*tert*-butyldimethylsilyloxy)-4-methyl-pent-3-enyl]-5,8-dimethoxynaphthalene (23): A solution of **22** (107.8 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (4 mL) was treated with 2,6-lutidine (36.3 μL, 0.31 mmol) and TBSOTf (57.3 μL, 0.25 mmol) at 0 °C for 20 min. The reaction mixture was then quenched with MeOH (0.1 mL) and a saturated aqueous NH_4Cl solution (4 mL) was added followed by extraction with EtOAc (2 × 8 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/Et_2O 9:1) to afford 1,4-bis-(*tert*-butyldimethylsilyloxy)-2-[1-(*tert*-butyldimethylsilyloxy)-but-3-enyl]-5,8-dimethoxynaphthalene as a colorless oil (126.3 mg, 96%). R_f = 0.85 (hexanes/Et_2O 7:3); $[\alpha]_D^{25}$ = +7.8 (c = 1.0 in $CHCl_3$); IR (thin film): $\tilde{\nu}$ = 2953, 2857, 1601, 1472, 1375, 1256, 1063, 928, 838 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.07 (s, 1H, CH_{ar}), 6.59 (center of AB_q, J = 8.5 Hz, $\Delta\nu$ = 17.5 Hz, 2H, CH_{ar}), 5.83–5.74 (m, 1H, =CH), 5.24 (t, J = 5.5 Hz, 1H, CH_2CHOSi), 4.98–4.93 (m, 2H, =CH_2), 3.83 (s, 3H, OMe), 3.73 (s, 3H, OMe), 2.51–2.47 (m, 2H, CH_2), 1.06 (s, 9H, *t*BuSi), 1.03 (s, 9H, *t*BuSi), 0.94 (s, 9H, *t*BuSi), 0.20 (s, 3H, Me_2Si), 0.19 (s, 3H, Me_2Si), 0.14 (s, 3H, Me_2Si), −0.03 (s, 3H, Me_2Si), −0.04 (s, 3H, Me_2Si), −0.05 (s, 3H, Me_2Si); ^{13}C NMR (125.7 MHz, $CDCl_3$, 25 °C): δ = 151.0, 150.7, 146.0, 140.2, 135.3, 132.8, 122.8, 121.0, 116.7, 115.7, 106.3, 103.8, 68.7, 56.3, 55.4, 43.1, 26.1, 26.0, 18.5, 18.4, 18.2, −3.5, −4.0, −4.2, −4.3, −4.4, −4.5; HRMS (FAB): calcd for $C_{28}H_{46}O_5Si_2$: 633.3827 $[M+H]^+$; found 633.3769.

A solution of 1,4-bis-(*tert*-butyldimethylsilyloxy)-2-[1-(*tert*-butyldimethylsilyloxy)-but-3-enyl]-5,8-dimethoxynaphthalene (105.2 mg, 0.17 mmol) in a 1:1 mixture of THF/H_2O (6 mL) was treated with a solution of OsO_4 1% in H_2O (0.22 mL, 0.0085 mmol) and sodium periodate (145.4 mg, 0.68 mmol). The mixture was stirred for 6 h at 25 °C and then diluted with water (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic extracts were washed with water (15 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford crude 3-[1,4-bis-(*tert*-butyldimethylsilyloxy)-5,8-dimethoxynaphthalen-2-yl]-3-(*tert*-butyldimethylsilyloxy)-propionaldehyde. Then, a solution of Me_2CHPPh_3I (110.2 mg, 0.26 mmol) in anhydrous Et_2O (3 mL) was treated with *n*BuLi 1.6 M in hexane (0.14 mL, 0.22 mmol) at 0 °C. The ice bath was removed and the mixture was stirred at 25 °C for 45 min. To the resulting deep red solution was added dropwise at 0 °C a solution of the crude propionaldehyde in Et_2O (3 mL) and stirring was continued for 2 h at 25 °C. Upon completion of the reaction (monitored by TLC), a saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with EtOAc (2 × 10 mL). The organic extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4 and finally concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, hexanes/EtOAc 95:5), afforded **23** as a colorless oil (80.9 mg, 72% based on 1,4-bis-(*tert*-butyldimethylsilyloxy)-2-[1-(*tert*-butyldimethylsilyloxy)-but-3-enyl]-5,8-dimethoxynaphthalene). R_f = 0.85 (hexanes/EtOAc 8:2); IR (thin film): $\tilde{\nu}$ = 2954, 2859, 1600, 1472, 1378, 1254, 1063, 928, 838 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 7.07 (s, 1H, CH_{ar}), 6.56 (center of AB_q, J = 8.6 Hz, $\Delta\nu$ = 11.5 Hz, 2H, CH_{ar}), 5.22–5.07 (m, 2H, =CH, CH_2CHOSi), 3.80 (s, 3H, OMe), 3.69 (s, 3H, OMe), 2.53–2.25 (m, 2H, CH_2), 1.58 (s, 3H, =CMe_2), 1.43 (s, 3H, =CMe_2), 1.02 (s, 9H, *t*BuSi), 1.01 (s, 9H, *t*BuSi), 0.90 (s, 9H, *t*BuSi), 0.16 (s, 6H, Me_2Si), 0.10 (s, 3H, Me_2Si), 0.05 (s, 3H, Me_2Si), −0.06 (s, 3H, Me_2Si), −0.07 (s, 3H, Me_2Si); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 151.1, 150.7, 145.9, 140.2, 133.3, 132.5, 128.3, 122.8, 121.0, 115.8, 106.5, 103.7, 69.1, 56.4, 55.4, 37.4, 26.1, 26.0, 25.9, 18.6, 18.4, 18.1, 17.9, 2.9, 2.8, 2.6, 2.4, 1.9.

Preparation of quinone 25 from 23: A solution of ammonium cerium(IV) nitrate (301.5 mg, 0.55 mmol) in water (2 mL) was added dropwise to a stirred solution of **23** (70.4 mg, 0.11 mmol) in CH_3CN (5 mL) at 0 °C. The reaction mixture was brought to 25 °C, stirred for additional 15 min and then diluted with water (5 mL) and EtOAc (7 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 8 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Small column filtration of the crude product (silica gel, hexanes/EtOAc 7:3) afforded **25** as an orange-yellow oil (43.6 mg, 92%). All spectroscopic data were in accordance with the reported ones (see ref. [19e]).

Coupling of nitrile 26 with enone 7: A solution of **26**[31b] (500.0 mg, 2.28 mmol) in THF (25 mL) was added dropwise to a stirred solution of LDA (4.56 mmol) in anhydrous THF (25 mL) at −78 °C. The yellow solution was stirred at the same temperature for 30 min. The acetone/dry ice bath was then replaced by an ice bath and enone **7** (424.9 mg, 3.4 mmol) in THF (20 mL) was added in one portion. A dark red color appeared immediately and after 5 min the reaction was quenched with a saturated aqueous NH_4Cl solution (40 mL) under vigorous stirring. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and the organic solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc 7:3 to 6:4) to afford **14** as an orange yellow solid (433.0 mg, 60%, full data have been reported previously in this Experimental Section). A second product isolated and characterized was the Michael adduct **27** (94.0 mg, 12%) as a white solid. R_f = 0.50 (hexanes/EtOAc 5:5); m.p. 125–127 °C; IR (KBr): $\tilde{\nu}$ = 2927, 2843, 2248, 1788, 1713, 1512, 1443, 1283, 1021, 972, 825 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.07 (center of AB_q, J = 8.9 Hz, $\Delta\nu$ = 83.8 Hz, 2H, CH_{ar}), 5.30–5.18 (m, 1H, =CH), 3.93 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.08 (d, J = 7.0 Hz, 2H, CH_2CH=), 2.86–2.62 (m, 3H, $CHCH_2$), 2.22–2.13 (m, 1H, $CHHCH_2$), 1.72 (s, 3H, =CMe_2), 1.60 (s, 3H, =CMe_2); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 206.5, 165.0, 152.3, 147.6, 133.8, 119.0, 115.2, 114.5, 112.8, 75.6, 56.5, 56.4, 42.7, 36.2, 31.3, 25.7, 18.0; HRMS (MALDI): calcd for $C_{19}H_{21}NO_5$: 366.1312 $[M+Na]^+$; found 366.1305.

Reduction of ketone 14 with Corey's oxazaborolidine and catecholborane: A mixture of (*S*)-3,3-diphenyl-1-butyltetrahydro-3*H*-pyrrolo-[1,2-*c*]-[1,3,2]oxazaborole (Corey's oxazaborolidine, 0.2 M in toluene, 14.25 mL, 2.85 mmol) and catecholborane (1 M in THF, 2.85 mL, 2.85 mmol) was added dropwise at −78 °C to a solution of **14** (300.0 mg, 0.95 mmol) in anhydrous toluene (25 mL). The reaction mixture was stirred at −78 °C for 8 h and then quenched with methanol (2 mL) at the same temperature followed by addition of water (15 mL) and $NaBO_3 \cdot 4H_2O$ (2.2 g, 14.25 mmol). The mixture was stirred vigorously overnight and then extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed successively with an 1 N HCl solution (25 mL) for the recover of the catalyst as a salt, water (2 × 15 mL), brine (30 mL) and dried over Na_2SO_4. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, hexanes/

EtOAc 5:5) to afford **24** as an orange oil (240.0 mg, 80%). $R_f = 0.30$ (hexanes/EtOAc 5:5); $[\alpha]_D^{25} = +19.4$ ($c = 0.57$ in $CHCl_3$); IR (neat): $\tilde{\nu} =$ 3490, 2932, 1652, 1570, 1480, 1286, 1214, 1050, 829 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.30$ (s, 2H, CH_{ar}), 6.78 (s, 1H, CH_{quin}), 5.16 (m, 1H, =CH), 4.75 (m, 1H, C*H*OH), 3.94 (s, 6H, OMe), 2.60 (m, 1H, CH_2), 2.40 (m, 1H, CH_2), 1.70 (s, 3H, $=CMe_2$), 1.60 (s, 3H, $=CMe_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 184.9$, 153.8, 153.5, 150.4, 136.4, 133.7, 128.3, 120.4, 120.0, 118.9, 68.9, 56.7, 56.8, 35.4, 29.6, 25.9, 18.0; HRMS (MALDI): calcd for $C_{18}H_{20}O_5$: 317.1383 $[M+H]^+$; found 317.1380. Enantiomeric excess (*ee*) of this compound was measured to be 83% yield by Mosher's ester analysis of final product **3** which is derived from this.

Reduction of ketone 14 with Corey's oxazaborolidine and $BH_3 \cdot THF$: A mixture of (*S*)-3,3-diphenyl-1-butyltetrahydro-3*H*-pyrrolo-[1,2-*c*][1,3,2]oxazaborole (Corey's oxazaborolidine, 0.2 M in toluene, 14.25 mL, 2.85 mmol) and $BH_3 \cdot THF$ (1 M in THF, 2.85 mL, 2.85 mmol) was added dropwise to a −20 °C solution of **14** (300.0 mg, 0.95 mmol) in anhydrous toluene (25 mL). The reaction mixture was stirred at −20 °C for 1 h and then temperature was raised to 0 °C. Stirring was continued approximately 6 h (reaction progress was monitored by TLC) and then the reaction was quenched with methanol (2 mL) at the same temperature followed by addition of water (15 mL) and $NaBO_3 \cdot 4H_2O$ (2.2 g, 14.25 mmol). The mixture was stirred vigorously overnight and then extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed successively with an 1N HCl solution (25 mL) for the removal of the catalyst as a salt, water (2 × 15 mL), brine (30 mL) and dried over Na_2SO_4. The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc 5:5) to afford **24** as an orange oil (231.4 mg, 77%). $[\alpha]_D^{25} = +27.3$ ($c = 0.39$ in $CHCl_3$). Enantiomeric excess (*ee*) of this compound was measured to be 90% yield by Mosher's ester analysis of final product **3** which is derived from this.

Hydroxy-quinone **32** was prepared in a similar manner by using (*R*)-3,3-diphenyl-1-butyltetrahydro-3*H*-pyrrolo-[1,2-*c*][1,3,2]oxazaborole as a catalyst. All data were identical with these of compound **24** except from $[\alpha]_D^{25} = -27.3$ ($c = 0.39$ in $CHCl_3$).

Reduction of ketone 14 with $NaBH_4$: A solution of **14** (68.4 mg, 0.22 mmol) in MeOH (4 mL) was cooled to 0 °C and $NaBH_4$ (12.5 mg, 0.33 mmol) was added. The mixture was stirred at this temperature approximately 20 min (until no starting material was observed by TLC) and then diluted with water (10 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford crude **33** which was used in the next step without further purification.

Preparation of acetates 34–36: A saturated aqueous $Na_2S_2O_4$ solution (5 mL) was added to a stirred solution of either **24** or **32** (from oxazaborolidine/$BH_3 \cdot THF$ reduction) (200.0 mg, 0.63 mmol) in Et_2O (20 mL), and the mixture was stirred vigorously for approximately 20 min (disappearance of the orange colour of the quinone). The organic layer was then separated and the aqueous layer after being diluted with water (10 mL) was extracted with EtOAc (2 × 10 mL). The combined organic extracts (being kept under argon atmosphere to avoid partial oxidation of the trihydroxy intermediate) were washed with brine (15 mL), dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. In the case of compound **33** the above procedure was skipped. The crude mixture was then subjected to peracetylation with Ac_2O (0.3 mL, 3.16 mmol), Et_3N (0.7 mL, 5.04 mmol) and catalytic amount of DMAP in CH_2Cl_2 (3 mL) at 25 °C for 5 h. The reaction was then quenched with an aqueous saturated $NaHCO_3$ solution (6 mL) and diluted with EtOAc (10 mL). The organic layer was separated, washed with water (2 × 10 mL), brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexanes/EtOAc 7:3) to afford (*R*)-acetic acid 4-acetoxy-3-(1-acetoxy-4-methyl-pent-3-enyl)-5,8-dimethoxynaphthalen-1-yl ester (**A**), (*S*)-acetic acid 4-acetoxy-3-(1-acetoxy-4-methyl-pent-3-enyl)-5,8-dimethoxynaphthalen-1-yl ester (**B**) or (*R*,*S*)-acetic acid 4-acetoxy-3-(1-acetoxy-4-methyl-pent-3-enyl)-5,8-dimethoxynaphthalen-1-yl ester (**C**), respectively as pale yellow oils (for compounds **A** and **B**: 232.4 mg, 82% based on **24** and **32**, respectively; for compound **C**: 254.8 mg, 91% based on **14**). **A**, **B** and **C**: $R_f = 0.47$ (hexanes/EtOAc 5:5); $[\alpha]_D^{25} = +50.8$ ($c = 1$ in $CHCl_3$) for **A**, $[\alpha]_D^{25} = -50.8$ ($c = 1$ in $CHCl_3$) for **B**; IR (neat): $\tilde{\nu} = 2938$, 2853, 1771, 1735, 1611, 1462, 1368, 1214, 1048, 928, 812 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 7.17-7.05$ (m, 1H, CH_{ar}), 6.74 (s, 2H, CH_{ar}), 6.22–5.93 (m, 1H, C*H*OAc), 5.04 (t, $J = 7.4$ Hz, 1H, =CH), 3.81 (s, 6H, OMe), 2.68–2.41 (m, 2H, CH_2), 2.34 (s, 3H, OAc), 2.31 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.63 (s, 3H, $=CMe_2$), 1.53 (s, 3H, $=CMe_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 169.9$, 169.7, 149.6, 149.3, 141.2, 135.2, 128.3, 121.5, 121.0, 118.8, 118.4, 118.2, 107.7, 107.4, 70.6, 68.9, 56.7, 33.6, 25.6, 21.0, 20.8, 20.7, 17.8; HRMS (MALDI): calcd for $C_{24}H_{28}O_8$: 467.1676 $[M+Na]^+$; found 467.1678.

A solution of ammonium cerium(IV) nitrate (1.23 g, 2.25 mmol) in water (5 mL) was added dropwise to a stirred solution of either **A**, **B** or **C** (200.0 mg, 0.45 mmol) in CH_3CN (10 mL) at 0 °C. The reaction mixture was brought to 25 °C, stirred for additional 15 min and then diluted with water (15 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Small column filtration of the crude product (silica gel, hexanes/EtOAc 7:3) afforded **34**, **35**, and **36**, respectively, as yellow oils (177.2 mg, 95%). **34**, **35**, and **36**: $R_f = 0.65$ (hexanes/EtOAc 7:3); $[\alpha]_D^{25} = +54.0$ ($c = 1.05$ in $CHCl_3$) for **34**, $[\alpha]_D^{25} = -54.0$ ($c = 1.05$ in $CHCl_3$) for **35**; IR (neat): $\tilde{\nu} = 2938$, 2853, 1771, 1735, 1611, 1462, 1368, 1214, 1048, 928, 812 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ (major isomer) = 7.39 (s, 1H, CH_{ar}), 6.74 (s, 2H, CH=CH_{quin}), 6.02–5.89 (m, 1H, C*H*OAc), 5.00 (t, $J = 7.4$ Hz, 1H, =CH), 2.54–2.37 (m, 2H, CH_2), 2.43 (s, 3H, OAc), 2.40 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.64 (s, 3H, $=CMe_2$), 1.49 (s, 3H, $=CMe_2$); δ (minor isomer) = 7.33, 6.63, 5.89–5.81, 5.05, 2.56–2.27, 2.05, 1.63, 1.52; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ (both isomers) = 183.2, 183.0, 182.9, 169.7, 169.1, 148.8, 147.7, 147.3, 147.6, 147.2, 142.5, 138.6, 138.3, 136.4, 136.0, 133.3, 131.0, 130.9, 124.5, 124.1, 117.6, 117.3, 69.2, 33.3, 32.6, 29.6, 25.7, 21.0, 20.8, 17.9, 17.7; HRMS (MALDI): calcd for $C_{22}H_{22}O_8$: 437.1207 $[M+Na]^+$; found 437.1208.

Preparation of alkannin (2), shikonin (3) and shikalkin: Compounds **34**, **35**, and **36** (100.0 mg, 0.24 mmol) were treated with an 1 M NaOH solution (5 mL) for 1 h at 25 °C and then were carefully acidified with glacial acetic acid. The deep blue color disappeared and deep red crystalline solids precipitated out of the reaction mixture. Simple filtration of the solids afforded shikonin (**3**), alkannin (**2**), and shikalkin in crystalline form (66.0 mg, 95%). Shikonin (**3**), alkannin (**2**), and shikalkin: $R_f = 0.35$ (hexanes/EtOAc 7:3); m.p. 143–145 °C; IR (thin film): $\tilde{\nu} = 3456$, 2926, 1621, 1571, 1452, 1344, 1199, 1076, 776 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 25 °C): $\delta = 12.60$ (s, 1H, OH_{ar}), 12.50 (s, 1H, OH_{ar}), 7.19 (s, 2H, CH_{ar}), 7.16 (s, 1H, CH_{quin}), 5.20 (t, $J = 7.2$ Hz, 1H, =CH), 4.91 (dd, $J = 7.1$, 4.1 Hz, 1H, C*H*OH), 2.70–2.57 (m, 1H, CH_2), 2.44–2.27 (s, 1H, CH_2), 1.75 (s, 3H, $=CMe_2$), 1.65 (s, 3H, $=CMe_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta =$ 180.6, 179.8, 165.5, 164.9, 151.4, 137.4, 132.4, 132.3, 131.8, 118.4, 112.0, 111.5, 68.3, 35.7, 25.9, 18.0; HRMS (MALDI): calcd for $C_{22}H_{22}O_8$: 289.1070 $[M+H]^+$; found 289.1074.

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