Total Synthesis

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Unified Total Syntheses of (−)-Medicarpin, (−)-Sophoracarpan A, and (±)-Kushecarpin A with Some Structural Revisions**

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Abstract: *The total syntheses of medicarpin, sophoracarpan A, and kushecarpin A from a common intermediate are achieved by using ortho- and para-quinone methide chemistry. Additionally, the relative stereochemistry of sophoracarpan A and B have been reassigned.*

Pterocarpans constitute the second largest family of plant-derived isoflavonoids (Figure 1).[1,2] They all share a fifteen carbon tetracyclic core comprised of a dihydrobenzopyran or chromane conjoined in *cis* fashion with a dihydrobenzofuran

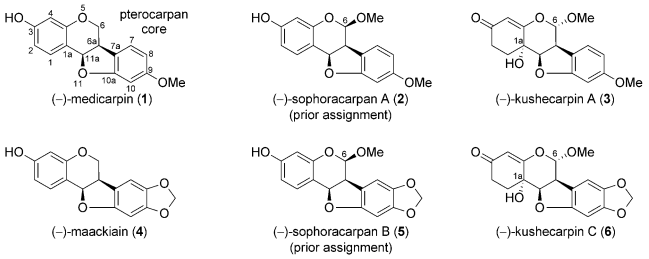
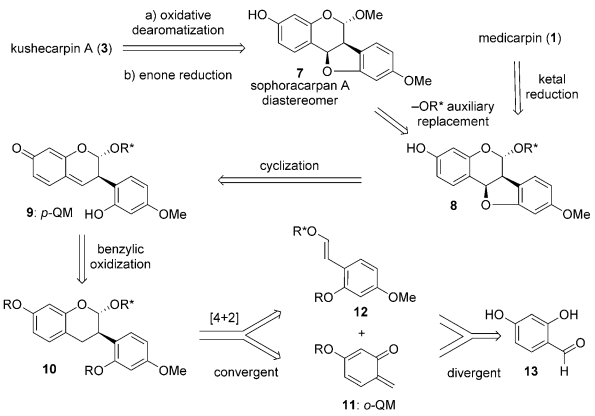


Figure 1. Some known and supposed pterocarpans.

(Figure 1). Various oxygen and carbon substituents decorate the periphery resulting in a broad range of biological activities.[2] Derivatives exhibiting strong potency toward both *Mycobacterium tuberculosis* and *Staphylococcus aureus* display unprotected phenols at their C3 and C9 carbon atoms.[2] Moderate antibacterial activity has been reported for (−)-medicarpin A (**1**),[2] in which one of these phenolic residues is methylated. Whereas the biological activities of the most recent family additions, sophoracarpan A (**2**)[3] and kushecarpin A (**3**),[4] remain unvetted,[5] they have established two new subclasses of pterocarpans; one in which the C6 carbon atom is part of an acetal, and another in which the benzopyran aryl ring is reformulated as an enone that bears a hydroxy substituent at C1a.[6]

Our interest in the natural products **2** and **3** originates from an appreciation of their tunable biological activities, a desire to advance quinone methide (QM) methods, and the recognition that a general enantioselective strategy for pterocarpans preparation was needed.[1] We speculated that sophoracarpan A (**2**) and kushecarpin A (**3**) were both biosynthesized from medicarpin (**1**), whereas sophoracarpan B (**5**) and kushecarpin C (**6**) arose from maackiain (**4**). However, the differing acetal stereochemistry of compounds **2** and **3** compared with compounds **5** and **6** was puzzling.

For our planned chemical synthesis, we imagined producing kushecarpin A (**3**) by an oxidative dearomatization of the supposed diastereomer of sophoracarpan A (**2**), the phenolic ketal **7**. Compound **7** would arise from diastereoselective replacement of the chiral auxiliary (OR*) in compound **8** with a methoxy residue (Scheme 1). Medicarpin (**1**), on the other



Scheme 1. Strategy for kushecarpin A via **7**, a supposed diastereomer of **2**.

hand, could arise from reduction of the chroman ketal **8**. This tetracycle would be built by an intramolecular cyclization of the free phenol with *p*-QM found in species **9**. This intermediate would be formed by regioselective methylene oxidation of the chromane **10** that emerged from the *o*-QM **11** combining with the enol ether **12**. These two starting components would both arise from benzaldehyde **13**.

Sometime ago we had found satisfactory diastereoselectivities in the cycloaddition reaction of enol ether **A** with various *o*-QMs (inset, Scheme 2).[7] We thought that its *E*-phenylated analogue **12** would perform similarly. We began its construction starting from benzaldehyde **15**, which was available from compound **13** in two pots and 61% yield.[8] Next, the phosphonium chloride salt **17** was constructed in 62% yield from the nonracemic alcohol **16** (99% *ee*).[9,10] This salt was then combined with benzaldehyde **15** and sodium

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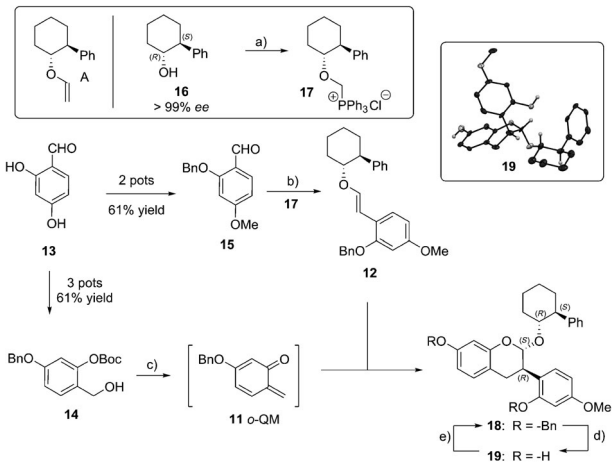
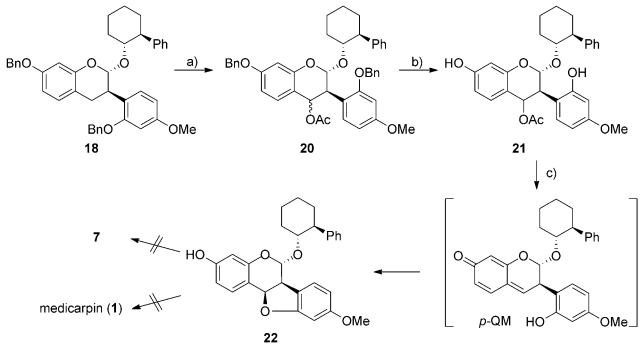


Scheme 2. Synthesis of **18**. a) **16**, CH_2O, TMSCl; PPh_3, benzene, reflux, 62% yield. b) **15**, NaHMDS, **17**, THF, −78°C to RT, 12 h, 59% yield from **16** (2:1, *E*/*Z*). c) **14**, ether, **12**, MeMgBr, −78°C to RT, 65%; d) **18**, Pd/C, H_2, EtOH, RT, 92% yield; e) **19**, BnBr, NaH, DMF, −78°C to RT, 88% yield. TMSCl = trimethylsilyl chloride, Boc = *tert*-butoxycarbonyl, NaHMDS = sodium hexamethyldisilazide. 24% overall yield from **13** to **18** via **19** in six steps.



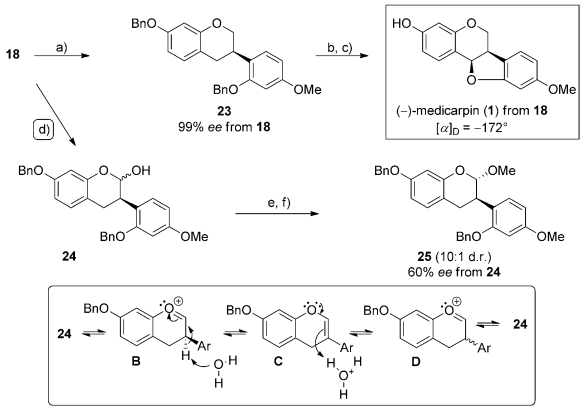
Scheme 3. Initial strategy. a) **18**, Pb_3O_4, AcOH, benzene, reflux; b) **20**, Pd/C, H_2, EtOH, RT; c) K_2CO_3, EtOAc. 46% yield from **18** to **22** over three steps.

hexamethyldisilazide to afford the enol ether **12** in 59% yield as a 2:1 mixture of *E* and *Z* isomers.[11] Although our many attempts to improve this ratio were futile,[12] chromatography gave the pure *E* isomer in a 37% overall yield from the starting alcohol **16**. On the other hand, compound **14**, which served as the precursor to *o*-QM **11**, was synthesized in three steps from the identical compound **13**.[7b]

Pure compounds **12** and **14** were then combined with the assistance of methylmagnesium bromide (−78 to 0°C) so as to release the *o*-QM **11** in a slow controlled manner. The ensuing cycloaddition produced the chromane ketal **18** in 65% yield with a 10:1 diastereomeric ratio (d.r.) as determined by ^{1}H NMR spectroscopy. Whereas the two diastereomers proved inseparable, hydrogenolysis of the mixture afforded the bis-phenol **19** that crystallized as a single diastereomer (75% yield). Its X-ray analysis confirmed the relative and absolute stereochemistry.[13] Compound **19** was then rebenzylated to return the pure benzyl ether derivative **18** as a single diastereomer.

After some experimentation, we observed that red lead (Pb_3O_4) in acetic acid affected a selective benzylic oxidation of the methylene within the chromane to produce the desired benzylic acetate **20** (1:1 d.r., Scheme 3).[14] Subsequent hydrogenolysis of the two benzyl ethers proceeded in a nearly quantitative yield over Pd/C in ethanol to give the crude bis-phenolic acetate **21**. Deprotonation with potassium carbonate in ethyl acetate continued to the presumed *p*-QM intermediate that underwent further cyclization to yield the *cis*-fused tetracycle **22** as a single diastereomer in 46% yield from the starting chromane **18**.[15] However, we were unable to convert the acetal **22** into its corresponding methyl acetal **7**. In addition, we were unable to reduce the acetal **22** to afford medicarpin (**1**). All acidic/reductive conditions that we tested led to decomposition of the starting ketal **22**. We attributed these problems to the pseudo-equatorial positioning of the C–O acetal bond that had consequently thwarted oxonium formation, so we changed the order of events.

The acetal **18**, which lacked the additional dihydrofuran ring, was found to undergo smooth reduction with boron trifluoride etherate in triethyl silane to produce the corresponding chromane **23** in 60% yield (Scheme 4).[16] HPLC



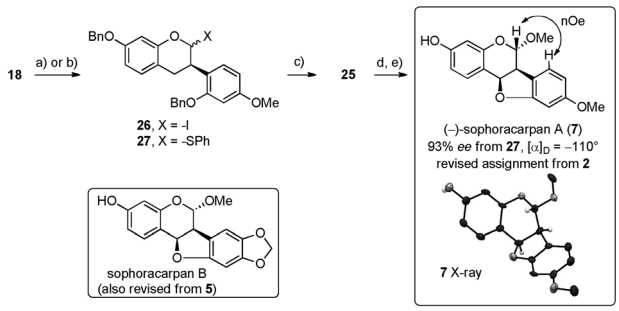
Scheme 4. Synthesis of (−)-medicarpin (**1**). a) **18**, $BF_3{\cdot}Et_2O$, Et_3SiH, DCM, 60% yield, 99% *ee*; b) **23**, Pb_3O_4, AcOH, benzene, reflux; c) Pd/C, H_2, EtOH, RT; K_2CO_3, EtOAc, 51% yield from **23**; d) **18**, HCl (1 M), acetone, reflux, 18 h; e) $SOCl_2$, DMF, DCM, 0°C; f) Ag_2CO_3, 4 Å MS, MeOH, DCM, RT, 12 h; 64% yield three steps from **18** to **25**.

comparison with a racemic standard, previously prepared from the corresponding vinyl methyl ether analogue of **12** in early investigations, showed that compound **23** possessed 99% enantiomeric excess *(ee)*. Further debenzylation and oxidative cyclization, as previously described, afforded (−)-medicarpin (**1**) as a single diastereomer in a 51% yield. Bolstered by evidence of formation of the desired oxonium intermediate **B**, the acetal **18** was next submitted to various *trans*-acetalization reactions involving methanol and acid in the hope that the simplified methyl acetal **25** might arise.

Under the thermodynamic conditions, the methyl acetal **25** arose albeit as a 1:1 mixture of diastereomers. We thus explored stepwise procedures amenable to acetal formation in a second kinetically controlled step. Treatment of the acetal **18** with 1 M aqueous hydrochloric acid resulted in the epimeric

hemiketal **24** along with the recoverable chiral alcohol **16**. The epimeric hemiketal **24** was then converted into its corresponding epimeric chloro derivative by treatment with thionyl chloride. Its subsequent exposure to Ag^I in the presence of methanol resulted in the desired acetal **25** in 84% yield; an *anti*/*syn* ratio of >10:1 was obtained, as shown by ^{1}H NMR spectroscopy.[17] We speculate that the addition of the methanol proceeds unimpeded, opposite the axially disposed aryl substituent, as there are no 1,3-diaxial interactions to dissuade addition. However, the *ee* of the diastereomerically pure compound **25** in large batches was found to have eroded to just 60%; 88% *ee* for smaller batches. We thought that this unfortunate circumstance was due to partial formation of the glycal-**C** from the oxonium-**B**, whereupon protonation afforded scalemic **D**, resulting in compound **26** with reduced optical purity. To circumvent this problem, we investigated controlled methods that might avoid the hemiketal **24**.[18]

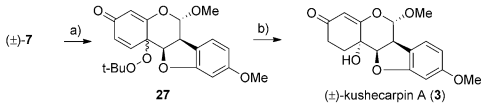
After considerable experimentation we found that with the sequential addition of boron trifluoride etherate and the appropriate nucleophile, the acetal **18** could be converted into the iodide **26** or the thioether **27**, so as to avoid the hemiketal **24** as well as enantiomeric erosion (Scheme 5). However, the



Scheme 5. Synthesis of (−)-sophoracarpan A (**7**). a) **18**, TBAI, BF_3 Et_2O, DCM, 35% yield of **26**. b) **18**, PhSH, BF_3 Et_2O, DCM, 85% yield of **27**. c) **27**, $Hg(TFA)_2$, DTBMP, 4 Å MS, MeOH, DCM, RT, 84% yield. d) **25**, Pb_3O_4, AcOH, benzene, reflux; e) Pd/C, H_2, EtOH, RT; K_2CO_3, EtOAc, 50% yield from **25**. TBAI = tetrabutyl ammonium iodide, TFA = trifluoroacetic acid, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, MS = molecular sieve.

iodide proved quite fragile and ineffective in providing the acetal **25** using Ag^I. In contrast, the phenyl thioether **27** was smoothly converted to the methyl acetal **25** in 85% yield (9:1 d.r.) upon exposure to mercuric trifluoride acetate and methanol. Yields from reactions employing mercuric acetate were substantially lower (30%). Debenzylation and oxidative cyclization of compound **25** afforded the tetracycle **7** in 50% overall yield and 93% *ee*. Comparison of the proton and carbon NMR spectra of synthetic **7** to its supposed diastereomer **2**, claimed as natural sophoracarpan A (**2**), showed them to be identical. The crystal structure of compound **7**[19] and comparative nOe study further confirmed that sophoracarpan A (**7**) had been misassigned upon its isolation as compound **2**.[3] As similarly unsound nOe arguments were used for the original assignment of sophoracarpan B (**5**), we speculate that its stereochemical assignment is incorrect and it should be revised to be that shown (inset, Scheme 5).

Running low on material, we investigated the conversion of the sophoracarpan A (**7**), used as the racemic standard, to kushecarpin A (**1**). All of the typical oxidants for resorcinol dearomatization including various hypervalent iodine reagents, $Pb(OAc)_4$, and even an oxone procedure failed in our hands to afford any of the desired cyclohexadienone.[20] Broadening our scope, we examined Doyle's dirhodium caprolactamate ($Rh_2(cap)_4$) catalyzed phenol dearomatization procedure.[21] Our expectations were lifted upon finding that the cyclohexadienone adduct (**27**, Scheme 6) had indeed



Scheme 6. Synthesis of kushecarpin A (**3**). a) $PhI(OAc)_2$, *t*BuOOH, DCE, RT, 48% yield; b) Pd/C, $H_4N^+[HCO_2]^-$, EtOH, MW, 120°C, 10 min,18% yield. DCE = 1,2-dichloroethane, MW = microwave.

formed in 25% yield. After considering its mechanism, we revisited the hypervalent iodine procedure using *tert*-butyl hydroperoxide as the nucleophile and found that the adduct **27** had formed in a 48% yield in a 3α:1β mixture of diastereomers about the C1a hydroxy residue.[22] Selective reduction of the enone within the dienone **27** and cleavage of the peroxy bond remained. Reductions of similar resorcinol-derived dienones are known to be problematic leading to reductive rearomatization so as to return the pre-dearomatized material.[23] We were therefore surprised to discover that microwave irradiation of enone **22**, together with ammonium formate and palladium on carbon offered (±)-kushecarpin A (**3**) in 18% isolated yield.[24] Spectroscopic comparison of coupling constants and resonances between synthetic and natural kushecarpin A (**3**) showed them to be identical.

In summary, we have developed a reliable and unified strategy that is able to assemble nearly all of the pterocarpans in an enantioselective manner. We completed the first enantioselective total syntheses of (−)-medicarpin (**1**) and (−)-sophoracarpan A (**7**) in nine steps (4% overall yield) and ten steps (5% overall yield), respectively, from the chiral alcohol **16**, as well as (±)-kushecarpin A (**3**) in 11 steps and 1.1% overall yield from the benzaldehyde **13**. All compounds were synthesized in a divergent/convergent manner with their two halves arising from the same commercial benzaldehyde **13**. In addition, the relative stereochemistries for sophoracarpan A (**2**) and B (**5**) have both been reassigned. Our effort touts the utility of *ortho*-quinone methide Diels–Alder reactions to form benzopyran rings in a diastereoselective manner, an oxidative cyclization likely involving a *para*-quinone as well as a new I^{III}/*t*BuOOH oxidative dearomatization procedure.

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