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

Zhen-Gao Feng, Wen-Ju Bai, and Thomas R. R. Pettus\*

**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.

**P**terocarpans constitute the second largest family of plantderived isoflavonoids (Figure 1).<sup>[1,2]</sup> 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.<sup>[2]</sup> Derivatives exhibiting strong potency toward both *Mycobacterium tuberculosis* and *Staphylococcus aureus* display unprotected phenols at their C3 and C9 carbon atoms.<sup>[2]</sup> Moderate antibacterial activity has been reported for (–)-medicarpin A (1),<sup>[2]</sup> in which one of these phenolic residues is methylated. Whereas the biological activities of the most recent family additions, sophoracarpan A (2)<sup>[3]</sup> and kushecarpin A (3),<sup>[4]</sup> remain unvetted,<sup>[5]</sup> 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.<sup>[6]</sup>

Our interest in the natural products **2** and **3** originates from an appreciation of their tunable biological activities,

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a desire to advance quinone methide (QM) methods, and the recognition that a general enantioselective strategy for pterocarpans preparation was needed.<sup>[1]</sup> 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).<sup>[7]</sup> 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.<sup>[8]</sup> Next, the phosphonium chloride salt **17** was constructed in 62 % yield from the nonracemic alcohol **16** (99 % *ee*).<sup>[9,10]</sup> This salt was then combined with benzaldehyde **15** and sodium

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Scheme 2. Synthesis of 18. a) 16,  $CH_2O$ , TMSCI;  $PPh_3$ , 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. TMSCI = trimethylsilyl chloride, Boc = *tert*-butoxycarbonyl, NaHMDS = sodium hexamethyldisilazide. 24% overall yield from 13 to 18 via 19 in six steps.

hexamethyldisilazide to afford the enol ether **12** in 59% yield as a 2:1 mixture of *E* and *Z* isomers.<sup>[11]</sup> Although our many attempts to improve this ratio were futile,<sup>[12]</sup> 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**.<sup>[7b]</sup>

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 <sup>1</sup>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.<sup>[13]</sup> 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<sub>3</sub>O<sub>4</sub>) 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).<sup>[14]</sup> Subsequent hydrogenolysis of the two benzyl ethers proceeded in a nearly quantitative yield over Pd/C in ethanol to give the crude bisphenolic 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.<sup>[15]</sup> 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



Scheme 3. Initial strategy. a) 18,  $Pb_3O_4$ , AcOH, benzene, reflux; b) 20, Pd/C, H<sub>2</sub>, EtOH, RT; c) K<sub>2</sub>CO<sub>3</sub>, EtOAc. 46% yield from 18 to 22 over three steps.

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).<sup>[16]</sup> HPLC



Scheme 4. Synthesis of (-)-medicarpin (1). a) 18, BF<sub>3</sub>·Et<sub>2</sub>O, Et<sub>3</sub>SiH, DCM, 60% yield, 99% *ee*; b) 23, Pb<sub>3</sub>O<sub>4</sub>, AcOH, benzene, reflux; c) Pd/C, H<sub>2</sub>, EtOH, RT; K<sub>2</sub>CO<sub>3</sub>, EtOAc, 51% yield from 23; d) 18, HCl (1 M), acetone, reflux, 18 h; e) SOCl<sub>2</sub>, DMF, DCM, 0°C; f) Ag<sub>2</sub>CO<sub>3</sub>, 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 1M aqueous hydrochloric acid resulted in the epimeric

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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<sup>I</sup> 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 <sup>1</sup>H NMR spectroscopy.<sup>[17]</sup> 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.<sup>[18]</sup>

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<sub>3</sub> Et<sub>2</sub>O, DCM, 35% yield of **26**. b) **18**, PhSH, BF<sub>3</sub> Et<sub>2</sub>O, DCM, 85% yield of **27**. c) **27**, Hg(TFA)<sub>2</sub>, DTBMP, 4 Å MS, MeOH, DCM, RT, 84% yield. d) **25**, Pb<sub>3</sub>O<sub>4</sub>, AcOH, benzene, reflux; e) Pd/C, H<sub>2</sub>, EtOH, RT; K<sub>2</sub>CO<sub>3</sub>, 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<sup>I</sup>. 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.<sup>[3]</sup> 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)<sub>4</sub>, and even an oxone procedure failed in our hands to afford any of the desired cyclohexadienone.<sup>[20]</sup> Broadening our scope, we examined Doyle's dirhodium caprolactamate (Rh<sub>2</sub>(cap)<sub>4</sub>) catalyzed phenol dearomatization procedure.<sup>[21]</sup> 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)<sub>2</sub>, tBuOOH, 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  $3\alpha$ :1 $\beta$  mixture of diastereomers about the C1a hydroxy residue.<sup>[22]</sup> 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.<sup>[23]</sup> 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.<sup>[24]</sup> 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  $(\pm)$ -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 paraquinone as well as a new III/tBuOOH oxidative dearomatization procedure.

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### Communications

#### Total Synthesis

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Unified Total Syntheses of (–)-Medicarpin, (–)-Sophoracarpan A, and ( $\pm$ )-Kushecarpin A with Some Structural Revisions



#### Ortho- and para-quinone methide

chemistry is used to accomplish the total syntheses of medicarpin, sophoracarpan A, and kushecarpin A from a common intermediate. Additionally, the relative stereochemistry of sophoracarpan A and B have been reassigned. QM = quinone methide.