

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

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

Pterocarpanes 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

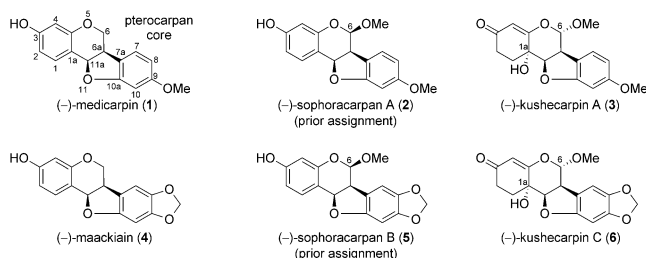


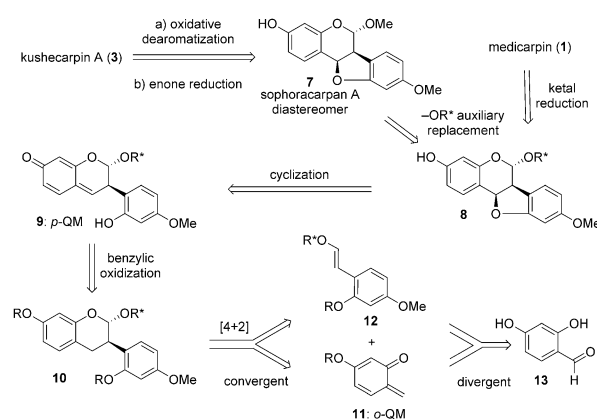
Figure 1. Some known and supposed pterocarpanes.

(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, sophoracarpin A (2)^[3] and kushecarpin A (3),^[4] remain unvetted,^[5] they have established two new subclasses of pterocarpanes; 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 pterocarpanes preparation was needed.^[1] We speculated that sophoracarpin A (2) and kushecarpin A (3) were both biosynthesized from medicarpin (1), whereas sophoracarpin 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 sophoracarpin 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.

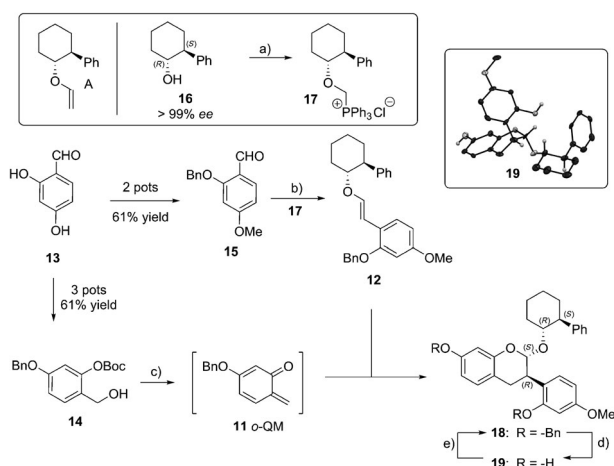
hand, could arise from reduction of the chroman ketal 8. This tetracycle would be built by an intramolecular cyclization of the free phenol with *p*-QM found in species 9. This intermediate would be formed by regioselective methylene oxidation of the chromane 10 that emerged from the *o*-QM 11 combining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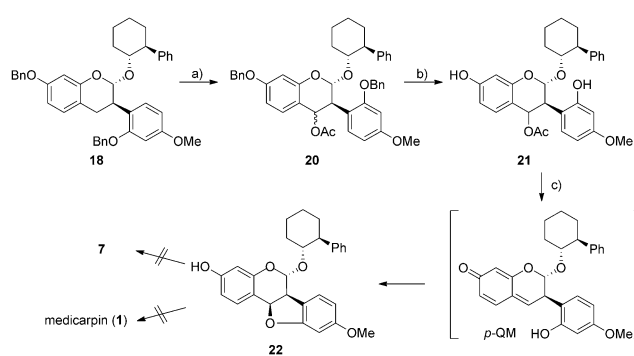


Scheme 2. Synthesis of **18**. a) **16**, CH_2O , TMSCl ; PPh_3 , benzene, reflux, 62% yield. b) **15**, NaHMDS , **17**, THF, -78°C to RT, 12 h, 59% yield from **16** (2:1, *E/Z*). c) **14**, ether, **12**, MeMgBr , -78°C to RT, 65%; d) **18**, Pd/C , H_2 , EtOH, RT, 92% yield; e) **19**, BnBr , NaH , 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.

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 ^1H 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.

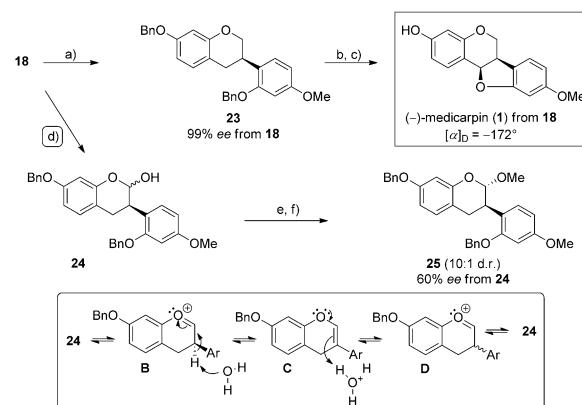
After some experimentation, we observed that red lead (Pb_3O_4) in acetic acid affected a selective benzylic oxidation of the methylene within the chromane to produce the desired benzylic acetate **20** (1:1 d.r., Scheme 3).^[14] Subsequent hydrogenolysis of the two benzyl ethers proceeded in a nearly 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



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.

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



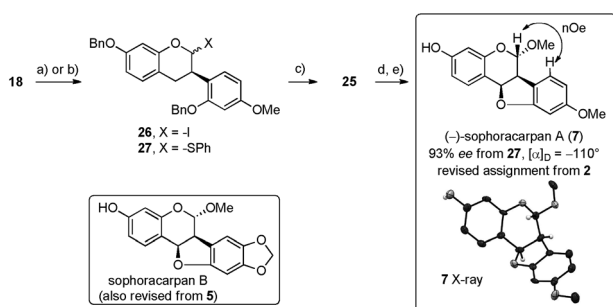
Scheme 4. Synthesis of (–)-medicarpin (**1**). a) **18**, $\text{BF}_3\cdot\text{Et}_2\text{O}$, Et_3SiH , DCM, 60% yield, 99% *ee*; b) **23**, Pb_3O_4 , AcOH , benzene, reflux; c) Pd/C , H_2 , EtOH, RT; d) K_2CO_3 , EtOAc, 51% yield from **23**; e) **18**, HCl (1 M), acetone, reflux, 18 h; f) SOCl_2 , DMF, DCM, 0°C ; g) 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 debenzylolation 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 ^1H 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]

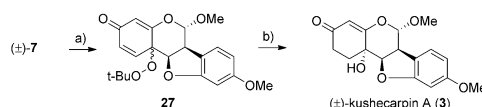
After considerable experimentation we found that with the sequential addition of boron trifluoride etherate and the appropriate nucleophile, the acetal **18** could be converted into the iodide **26** or the thioether **27**, so as to avoid the hemiketal **24** as well as enantiomeric erosion (Scheme 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**, $\text{Hg}(\text{TFA})_2$, 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, $\text{Pb}(\text{OAc})_4$, 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 ($\text{Rh}_2(\text{cap})_4$) 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) $\text{PhI}(\text{OAc})_2$, $t\text{BuOOH}$, DCE, RT, 48 % yield; b) Pd/C, $\text{H}_4\text{N}^+[\text{HCO}_2]^-$, 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 α :1 β 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 pterocarpan 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 $\text{I}^{\text{III}}/t\text{BuOOH}$ oxidative dearomatization procedure.

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- [1] A. Goel, A. Kumar, A. Raghuvanshi, *Chem. Rev.* **2013**, *113*, 1614–1640.
- [2] L. Jiménez-González, M. Álvarez-Corral, M. Muñoz-Dorado, I. Rodríguez-García, *Phytochem. Rev.* **2007**, *7*, 125–154.
- [3] a) T. Kinoshita, K. Ichinose, C. Takahashi, U. Sankawa, *Chem. Pharm. Bull.* **1986**, *34*, 3067–3070; b) T. Kinoshita, K. Ichinose, C. Takahashi, F.-C. Ho, J.-B. Wu, U. Sankawa, *Chem. Pharm. Bull.* **1990**, *38*, 2756–2759.
- [4] M. Kuroyanagi, T. Arakawa, Y. Hirayama, T. Hayashi, *J. Nat. Prod.* **1999**, *62*, 1595–1599.
- [5] a) M. Nisar, W. A. Kaleem, I. Khan, A. Adhikari, N. Khan, M. R. Shah, I. A. Khan, M. Qayum, Samiullah, M. Ismail, A. Aman, *Fitoterapia* **2011**, *82*, 1008–1011; b) I. Oh, W.-Y. Yang, S.-C. Chung, T.-Y. Kim, K.-B. Oh, J. Shin, *Arch. Pharm. Res.* **2011**, *34*, 217–222.
- [6] a) S. Soby, S. Caldera, R. Bates, H. Vanetten, *Phytochemistry* **1996**, *41*, 759–765; b) A. F. Barrero, E. Cabrera, I. R. Garcia, *Phytochemistry* **1998**, *48*, 187–190.
- [7] a) C. Selenski, T. R. R. Pettus, *J. Org. Chem.* **2004**, *69*, 9196–9203; b) Y. Huang, T. R. R. Pettus, *Synlett* **2008**, 1353–1356.
- [8] a) J. Tummatorn, P. Khorphueng, A. Petsom, N. Muangsins, N. Chaichit, S. Roengsumran, *Tetrahedron* **2007**, *63*, 11878–11885; b) W. D. Vaccaro, R. Sher, H. R. Davis, Jr., *Bioorg. Med. Chem.* **1998**, *6*, 1429–1437.
- [9] S. B. King, K. B. Sharpless, *Tetrahedron Lett.* **1994**, *35*, 5611–5612.
- [10] a) C.-V. T. Vo, T. A. Mitchell, J. W. Bode, *J. Am. Chem. Soc.* **2011**, *133*, 14082–14089; b) S. G. Pyne, M. J. Hensel, P. L. Fuchs, *J. Am. Chem. Soc.* **1982**, *104*, 5719–5728.
- [11] Y. Takashima, Y. Kaneko, Y. Kobayashi, *Tetrahedron* **2010**, *66*, 197–207.
- [12] M. Schlosser, K. F. Christmann, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 126–126; *Angew. Chem.* **1966**, *78*, 115–115.
- [13] CCDC 946677 (**19**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [14] T. Kikuchi, M. Nishimura, A. Hoshino, Y. Morita, N. Saito, T. Honda, *Heterocycles* **2003**, *60*, 1469–1475.
- [15] R. S. Khupse, P. W. Erhardt, *Org. Lett.* **2008**, *10*, 5007–5010.
- [16] W.-J. Bai, J. C. Green, T. R. R. Pettus, *J. Org. Chem.* **2012**, *77*, 379–387.
- [17] T. V. RajanBabu, T. A. Ayers, G. A. Halliday, K. K. You, J. C. Calabrese, *J. Org. Chem.* **1997**, *62*, 6012–6028.
- [18] a) R. J. Ferrier, R. W. Hay, N. Vethaviyasar, *Carbohydr. Res.* **1973**, *27*, 55–61; b) J. D. Bryant, G. E. Keyser, J. R. Barrio, *J. Org. Chem.* **1979**, *44*, 3733–3734; c) G. A. Olah, A. Husain, S. C. Narang, *Synthesis* **1983**, *1983*, 896–897; d) D. Kahne, S. Walker, Y. Cheng, D. Van Engen, *J. Am. Chem. Soc.* **1989**, *111*, 6881–6882; e) D. Crich, S. Sun, *J. Am. Chem. Soc.* **1998**, *120*, 435–436; f) X. Ding, F. Kong, *J. Carbohydr. Chem.* **1998**, *17*, 915–922; g) F. Pfengle, D. Lentz, H.-U. Reißig, *Angew. Chem. Int. Ed.* **2009**, *48*, 3165–3169; *Angew. Chem.* **2009**, *121*, 3211–3215; h) S.-R. Lu, Y.-H. Lai, J.-H. Chen, C.-Y. Liu, K.-K. T. Mong, *Angew. Chem. Int. Ed.* **2011**, *50*, 7315–7320; *Angew. Chem.* **2011**, *123*, 7453–7458.
- [19] CCDC 1022432 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [20] a) R. W. Van De Water, C. Hoarau, T. R. R. Pettus, *Tetrahedron Lett.* **2003**, *44*, 5109–5113; b) A. Pelter, R. S. Ward, *Tetrahedron* **2001**, *57*, 273–282; c) R. Tello-Aburto, A. M. Harned, *Org. Lett.* **2009**, *11*, 3998–4000; d) P. J. Krawczuk, N. Schöne, P. S. Baran, *Org. Lett.* **2009**, *11*, 4774–4776; e) J. L. Frie, C. S. Jeffrey, E. J. Sorensen, *Org. Lett.* **2009**, *11*, 5394–5397; f) A. Bérubé, I. Drutu, J. L. Wood, *Org. Lett.* **2006**, *8*, 5421–5424; g) M. C. Carreño, M. González-López, A. Urbano, *Angew. Chem. Int. Ed.* **2006**, *45*, 2737–2741; *Angew. Chem.* **2006**, *118*, 2803–2807.
- [21] M. O. Ratnikov, L. E. Farkas, E. C. McLaughlin, G. Chiou, H. Choi, S. H. El-Khalafy, M. P. Doyle, *J. Org. Chem.* **2011**, *76*, 2585–2593.
- [22] We provided this dearomatization method to Prof. Alison J. Frontier for their total synthesis of Tetrapetalone A: P. N. Carlsen, T. J. Mann, A. H. Hoveyda, A. J. Frontier, *Angew. Chem. Int. Ed.* **2014**, *53*, 9334–9338; *Angew. Chem.* **2014**, *126*, 9488–9492.
- [23] T. A. Wenderski, C. Hoarau, L. Mejorado, T. R. R. Pettus, *Tetrahedron* **2010**, *66*, 5873–5883.
- [24] C. Ovens, N. G. Martin, D. J. Procter, *Org. Lett.* **2008**, *10*, 1441–1444.