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Synthesis of the Tetracyclic Core of Tetrapetalone A Enabled by a Pyrrole Reductive Alkyation

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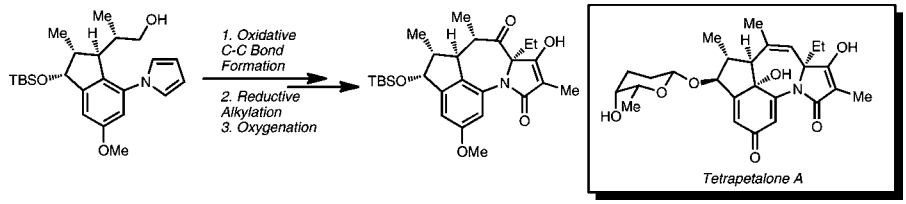
ABSTRACT



The tetracyclic framework of the tetrapetalone A aglycon has been secured through synthesis. A reductive pyrrole alkylation enables the formation of a key tetrasubstituted carbon stereocenter, and the tetramic acid portion of the molecule can be accessed through silicon or boronic ester conjugate addition to an ene-lactam.

The tetrapetalones (**1**−**4**, Figure 1) are a unique class of alkaloids first isolated by Komoda and co-workers in 2003 from a soil sample of *Streptomyces* sp. USF-4727 strain.[1,2] Following an initial structural misassignment, the molecular framework of these compounds was finally secured by comprehensive two-dimensional NMR and derivatization studies.[3] The tetrapetalones display significant soybean lipoxygenase (SBL) inhibitory activity. For example, **1** inhibits SBL with an $IC_{50} = 190\ \mu M$, which is comparable to the activity of the known SBL inhibitors nordihydroguaiareic acid (NDGA, $IC_{50} = 290\ \mu M$) and kojic acid ($IC_{50} = 110\ \mu M$). Komoda et al. have also recently reported the isolation of ansaetherone (**5**), a modest radical scavenger, which they suggest as a biogenetic precursor of the tetrapetalones.[4]

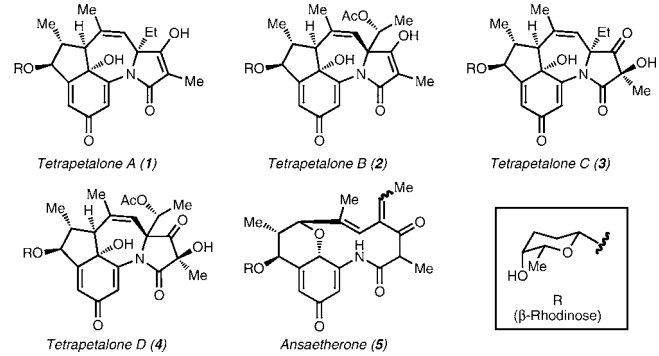


Figure 1. Tetrapetalone natural products.

The biological relevance of *ansa*-bridged compounds such as **5** to the genesis of the tetrapetalones was first proposed

(1) (a) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Hirota, A. *Tetrahedron Lett.* **2003**, *44*, 1659–1661. (b) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Tetrahedron Lett.* **2003**, *44*, 7417–7419. (c) Komoda, T.; Yoshida, K.; Abe, N.; Sugiyama, Y.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Biosci., Biotechnol., Biochem.* **2004**, *68*, 104–111.

(2) Komoda, T.; Kishi, M.; Abe, N.; Sugiyama, Y.; Hirota, A. *Biosci., Biotechnol., Biochem.* **2004**, *68*, 903–908.

(3) For a discussion, see ref 1b.

(4) Komoda, T.; Akasaka, K.; Hirota, A. *Biosci., Biotechnol., Biochem.* **2008**, *72*, 2392–2397.

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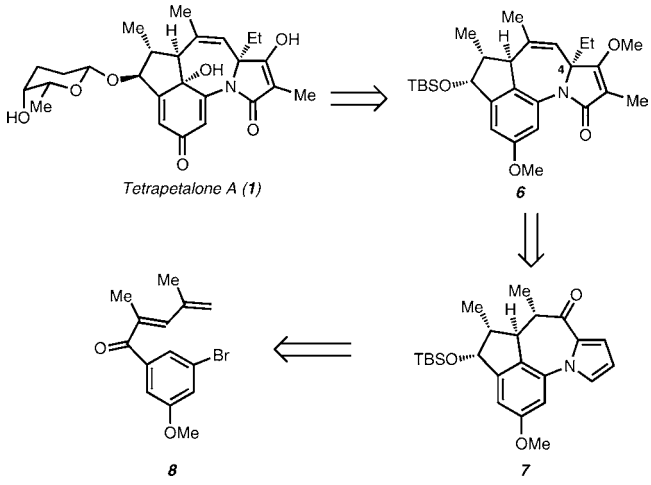
by Porco and Wang in their attempted synthesis of the tetrapetalone tetracyclic core from the ansamycins.[5]

To date, there has been no report of a total synthesis of any member of the tetrapetalone family. Recently, Hong et al. reported the use of a Speckamp cyclization to build an early stage tetracyclic core structure.[6]

Our synthetic analysis of the tetrapetalones was guided by the desire to effect sequential late-stage oxygenation chemistry, which would unveil the tetramic acid and *para*-quinol moieties from a surrogate pyrrole and phenol, respectively. In this communication, we report a partial realization of this synthetic approach, which has led to the racemic synthesis of an advanced tetracycle en route to the tetrapetalone A aglycon.

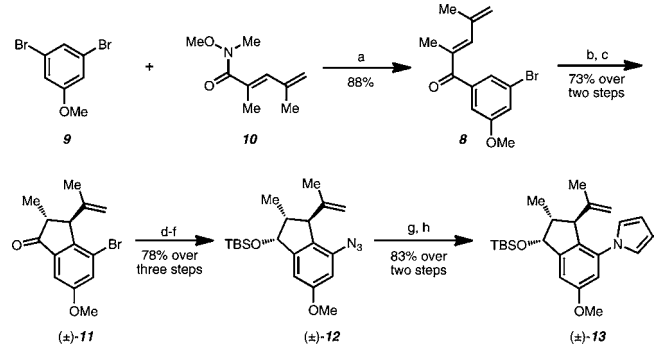
Scheme 1. Retrosynthetic Analysis of the Tetrapetalone Core



Our retrosynthetic analysis of **1** (Scheme 1) returns the natural product to tetracycle **6**, with the intention of a concluding stage introduction of the β-rhodinose fragment and an oxidative dearomatization of the A ring to install the *para*-quinol moiety. We envisioned **6** arising from acylated pyrrole **7** using a reductive alkylation of the relatively electron-deficient pyrrole to install the angular ethyl group at C4. This ambitious alkylation builds on precedent from Donohoe, who has previously demonstrated the reductive alkylation of pyrroles bearing carbamate, ester, or amide groups.[7] Although we hoped to accomplish an analogous transformation in the conversion of **7** to **6**, we recognized that Birch-type reduction of **7** could conceivably reduce either the pyrrole or arene and, as such, presented an untested extension of the Donohoe dissolving metal reduction chemistry. Tetracycle **7** could arise from aryl dienone **8**, building on pentannulation chemistry using the Nazarov cyclization, which we have previously described.[8] The advantage of using **8** as a substrate resided in the chemo-differentiation of the substituents on the benzene ring, which would positively impact subsequent functionalization chemistry.

The synthesis commenced with the preparation of aryl dienone **8** (Scheme 2), which was readily obtained in 88% yield from the coupling of the known dibromide **9** and Weinreb amide **10**.[9] It was discovered that **8** undergoes Nazarov cyclization with good regiocontrol (13:1) using stoichiometric $AlCl_3$ in toluene at room temperature. Presumably, the major regioisomer is favored because of the more significant *para* directing influence of the methoxy substituent.[10] It was necessary to effect epimerization of the methyl-bearing stereocenter to achieve the *trans* relationship of the Me and isopropenyl groups as shown in **11**. This was readily accomplished by heating with K_2CO_3 in dioxane, which produced a mixture of diastereomers (4:1 dr) with **11** as the major compound. Reduction of the carbonyl group of **11** and protection of the resulting hydroxyl group with TBSCl installed a TBS ether. At this stage, a bromide for azide exchange was accomplished via halogen−metal exchange followed by addition of tosyl azide to provide **12**.[11] Of note, a variety of palladium and copper-mediated C−N bond-forming reactions failed to accomplish the desired C−N bond

Scheme 2. Synthesis of Pyrrole **13**



[a] Reagents and conditions: (a) **9** (1.05 equiv), *n*-butyllithium (1.08 equiv, 2.5 M in hexanes), ether, −78 °C, 5 min, then **10** (1.0 equiv) in THF, −78 °C, 45 min. (b) $AlCl_3$ (1.0 equiv), toluene, rt, 2 h, 9:1 dr. (c) K_2CO_3 (0.2 equiv), dioxane, 80 °C, 10 h, 4:1 dr. (d) $NaBH_4$ (1.0 equiv), MeOH, 0 °C, 30 min. (e) TBSCl (1.1 equiv), imidazole (1.5 equiv), DMF, 80 °C, 10 h. (f) *t*-Buytllithium (2.05 equiv), THF, −78 °C, 5 min, then Ts-N_3 (1.2 equiv), −78 °C to rt, 2 h. (g) $LiAlH_4$ (0.67 equiv), THF, 0 °C, 1 h. (h) 2,5-Dimethoxytetrahydrofuran (1.2 equiv), acetic acid (0.1 equiv), 1,2-dichloroethane/H_2O (4:1), 80 °C, 4 h.

(5) Porco's earlier report of an advanced tetracyclic intermediate has been retracted, see: (a) Wang, X.; Porco, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6607. (b) Wang, X.; Porco, J. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3067–3071.

(6) Li, C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036–4039.

(7) For selected examples, see: (a) Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 667–676. (b) Donohoe, T. J.; Ace, K. W.; Guyo, P. M.; Helliwell, M.; McKenna, J. *Tetrahedron Lett.* **2000**, *41*, 989–993. (c) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1331–1334. (d) Turner, P. G.; Donohoe, T. J.; Cousins, R. P. C. *Chem. Commun.* **2004**, 1422–1423. (e) Donohoe, T. J.; Thomas, R. E. *Nat. Protoc.* **2007**, *2*, 1888–1895.

(8) Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6379–6383.

(9) Tisserand, S.; Baati, R.; Nicolas, M.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 8982–8983, For details see, Supporting Information.

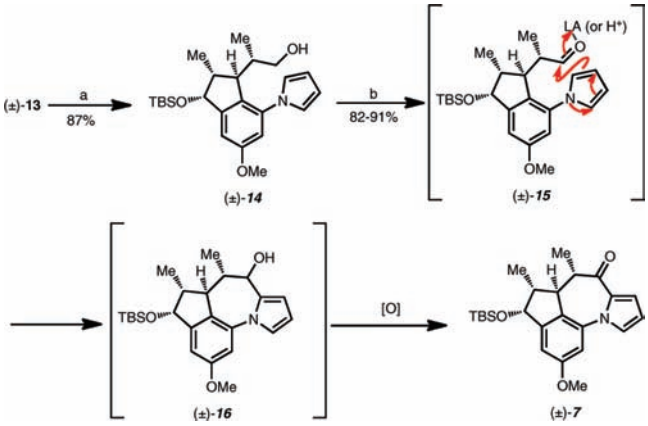
(10) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

(11) Matsumoto, T.; Ishida, T.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1992**, *114*, 9952–9959.

formation.[12] The azide **12** was cleanly reduced with LAH to afford an aniline, which upon exposure to modified Paal–Knorr conditions[13,14] yielded the pyrrole **13** in 97% yield.

The synthetic sequence up to this point is easily amenable to scale-up, which has provided **13** on a multigram scale. The next major challenge of the synthesis became the installation of the functionalized azepine ring. To set the stage for this task, hydroboration of **13** (Scheme 3) provided

Scheme 3. Oxidative C–C Bond-Forming Construction of **7**



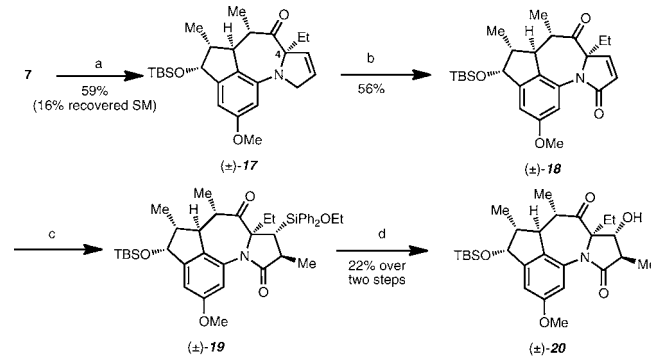
[a] Reagents and conditions: (a) borane–THF complex (10 equiv), rt, 12 h, then EtOH, 30% aq H_2O_2, 10% aq NaOH, 0 °C to rt, 24 h. (b) Dess–Martin periodinane (2.5 equiv), H_2O (2.5 equiv), CH_2Cl_2, 50 °C, 16 h.

primary alcohol **14** following oxidative workup in 87% yield. We had anticipated that oxidation of **14** to the corresponding carboxylic acid (via an aldehyde intermediate using the Pinnick conditions) would be necessary. At that juncture, we expected that subjection of the acid to intramolecular Friedel–Crafts acylation conditions would effect closure to the seven-membered ring. Although an initial survey of oxidation conditions (e.g., Swern, Parikh–Doering, PCC, or PDC) failed to produce an intermediate aldehyde (see **15**) from **14**, we were gratified to find that treatment of **14** with 2.5 equiv of Dess–Martin periodinane[15] resulted in the formation of tetracycle **7** in excellent yield. Presumably, this transformation proceeds via the intermediate aldehyde (**15**) followed by activation of the carbonyl group (by the hypervalent iodine species or residual acetic acid),[16] which leads to attack by the proximal pyrrole. The resulting pseudobenzylic secondary hydroxyl group (see **16**) can then undergo further oxidation to produce tetracyclic ketone **7**. This mechanistic scenario is corroborated by the observation of mixtures of **15**, **16**, and **7** when less than 2 equiv of Dess–Martin reagent was used for this transformation.

With a route to the tetracyclic core of the tetrapetalones secured, we next turned our attention to the installation of the angular ethyl group at C4. Donohoe and co-workers have shown previously that pyrroles bearing amide or ester groups at the 2-position can be reduced under dissolving metal conditions and quenched with a variety of alkylating and acylating reagents.[7] In the context of the existing precedent, pyrrole tetracycle **7** represents an ambitious extension from several vantage points: (1) the participation of pyrroles bearing *ketone* groups is not known (only esters and amides were used previously) and (2) substrates bearing an aryl group on the pyrrole nitrogen have not been demonstrated as viable reaction partners; generally, the pyrrole nitrogen bears a highly electron-withdrawing group such as a BOC group. Importantly, an arene moiety is also susceptible to single-electron reduction, which inherently introduces a kinetic competition.

In the event, exposure of **7** to sodium in ammonia/THF in the presence of bis(methoxyethyl)amine[7c] for 45 min followed by quenching with ethyl iodide resulted in the formation of pyrrolidine **17** (Scheme 4). Notably, the arene

Scheme 4. Elaboration of Tetracycle **7**



[a] Reagents and conditions: (a) sodium (5 equiv), bis(methoxyethyl)amine (20 equiv), NH_3/THF (3:1), −78 °C, 45 min, then EtI (5 equiv), −78 °C, 1 h. (b) $Mn(OAc)_3 \cdot 2H_2O$ (0.1 equiv), TBHP (5.0 equiv), EtOAc, rt, 48 h. (c) $Ph_2(Et_2N)SiLi$ (6.0 equiv), CuCN (2.5 equiv), THF, −78 °C, 30 min, then MeI (10.0 equiv), −78 °C, 1 h, then sat. NH_4Cl in EtOH, rt, 16 h. (d) 30% aq H_2O_2 (3.0 equiv), KHF_2 (3.0 equiv), DMF, rt, 12 h.

moiety remained intact, and the ethyl group was introduced on the α-face of the tetracycle with excellent diastereocontrol.

We next focused on the construction of the tetramic acid, which began with oxidation of the pyrrolidine moiety (see **17**) to α,β-unsaturated lactam **18**. Our initial attempts at this oxygenation sequence employed chromium trioxide and 3,5-dimethylpyrazole, following the precedent of Donohoe.[7a] However, this led to variable yields of the desired product. Additionally, this reaction was not easily amenable to scale up. We found that the desired transformation could be accomplished in improved yield using catalytic manga-

(12) Several conditions including those popularized by Buchwald and Hartwig were attempted, see: (a) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104. (b) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467. (c) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934–936. (d) Andersen, J.; Madsen, U.; Björkling, F.; Liang, X. *Synlett* **2005**, *14*, 2209–2213. (e) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888–889.

(13) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095–3110.

(14) For details, see the Supporting Information.

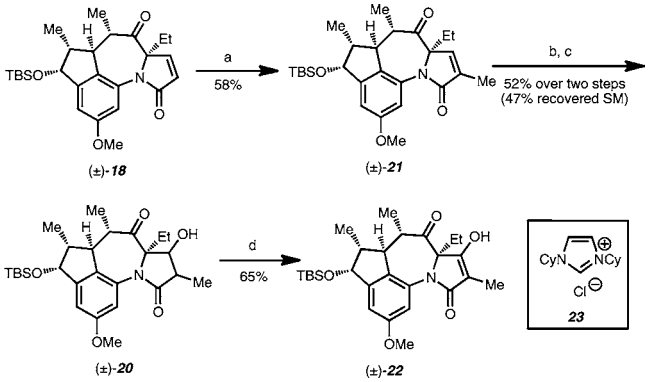
(15) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552.

(16) The addition of $NaHCO_3$ inhibits this oxidation reaction, suggesting the importance of acid for the transformation.

nese(III) acetate along with TBHP as a stoichiometric oxidant to afford **18**.[17] Silyl conjugate addition (see **18** to **19**) was effected with diethylaminodiphenylsilyllithium[18] in the presence of CuCN, which afforded **19** following quenching with MeI. To complete the tetramic acid fragment, a modified Tamao−Fleming oxidation was planned.[19] Treatment of **19** with either *m*-CPBA or H_2O_2 and potassium hydrogenfluoride produced alcohol **20**.

Given the modest yield for the oxidation of the dihydropyrrolidone (see **18**→**20**), we have developed an alternative approach to the tetramic acid as outlined in Scheme 5.

Scheme 5. Alternative Installation of the Tetramic Acid



[a] Reagents and conditions: (a) LDA (5 equiv), then MeI. (b) $B_2(pin)_2$ (1.1 equiv), CuCl (0.08 equiv), NaO*t*Bu (0.16 equiv), **23** (0.08 equiv), THF, rt, 18 h. (c) $NaBO_3$ (5.0 equiv), 1:1 THF/H_2O, rt, 2 h. (d) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C.

Sequential treatment of tetracycle **18** with LDA and MeI resulted in methylation of the ene-lactam moiety to provide **21** without competing methylation alpha to the ketone functional group in the seven-membered ring.[20] Conjugate addition of boron pinacolato ester to ene-lactam **21** was accomplished in 52% yield (along with 47% recovered starting material) using a modification of a procedure recently reported by Hoveyda.[21,22] Immediate oxidation of the boronic ester adduct yielded **20** in quantitative yield. Swern oxidation[23] at this stage completed the installation of the tetramic acid moiety to give **22** in 65% yield.[24]

In summary, we report the synthesis of a tetracycle bearing a tetramic acid en route to tetrapetalone A. This late-stage intermediate contains all the carbons of the aglycon of the natural product. Our synthetic sequence proceeds in 15 steps from dibromide **9** and provides tetracycle **7** on a multigram scale. Key developments include the use of oxidative conditions for the construction of the tetracyclic core of tetrapetalone A and a reductive alkylation reaction for the installation of the angular ethyl group.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L. *Org. Lett.* **2006**, *8*, 3149–3151.

(18) Kawachi, A.; Tamao, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 945–955.

(19) (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694–1696. (b) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120–2122. (c) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37–C39.

(20) Deprotonation alpha to the ketone group is presumably not favorable because of poor orbital overlap of the C−H bond and the π^* of the C═O bond.

(21) Lee, K.-s.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255.

(22) Modification of the original conditions included addition of a CuCl.

(23) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.

(24) Prolonged exposure of **20** to Dess−Martin periodinane resulted in the formation of **24**, which is closely related to the tetracyclic core of tetrapetalones C and D.