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Synthesis of Tetrahydropyrroloiminoquinone Alkaloids Based on Electrochemically Generated Hypervalent Iodine Oxidative Cyclization

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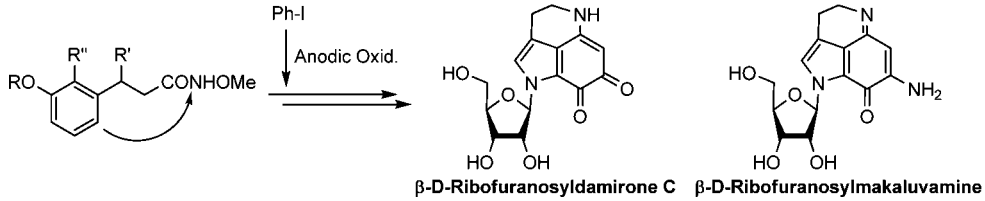
ABSTRACT



An approach to the synthesis of the tetrahydropyrroloiminoquinone alkaloids has been developed and applied to the preparation of *N*-1-β-D-ribofuranosyltetrahydropyrroloiminoquinones. The strategy utilizes oxidative cyclization of aryl-methoxyamides by hypervalent iodine to construct the quinoline framework shared by members of this alkaloid family. The hypervalent iodine oxidant is generated *in situ* by anodic oxidation of iodobenzene.

Tetrahydropyrroloiminoquinone alkaloids are of marine origin[1] and have attracted the interest of synthetic and biological groups owing to their unique structural features (Figure 1) and a wide range of biological properties. Of particular significance is the fact that these alkaloids display cytotoxic activities against KB tumor cells,[2a] L1210 (**24**: IC_{50} = 0.25 μM, **25**: IC_{50} = 2.1 μM)[2b] and doxorubicin-resistant L1210/DX murine lymphocytic leukemia cells,[2c] the human colon tumor cell line HCT-116 (**25**: IC_{50} = 17.1 μM),[2d,e] esophageal cancer cell line WHCO-1 (**20**: IC_{50} = 56 μM, **29**: IC_{50} = 38 μM, **31**: IC_{50} = 1.6 μM),[2f] and human ovarian carcinoma Ovcar 3 implanted in athymic mice,[2d,e] along with inhibition of topoisomerase II,[2d,e] and antimicrobial activity.[2g,h,3f]

Since the early reports describing the isolation and characterization of discorhabdins[3] and prianosins,[4] a number of congeners have been identified and synthetic investigations have been carried out.[1] In earlier efforts, we developed routes for the synthesis of discorhabdin C,[5] makaluvamines,[6] and isobatzellines[5b,7] that involve construction of the pyrroloquinolone intermediate **A** from the corresponding indol derivative **B** (Scheme 1), followed by introduction of an amine

(1) (a) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75. (d) Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1993**, *10*, 497. (f) Faulkner, D. J. *Nat. Prod. Rep.* **1992**, *9*, 323. (g) Faulkner, D. J. *Nat. Prod. Rep.* **1990**, *7*, 269.

(2) (a) Casapullo, A.; Cutignano, A.; Bruno, I.; Bifulco, G.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *J. Nat. Prod.* **2001**, *64*, 1354. (b) Bénéteau, V.; Pierré, A.; Pfeiffer, B.; Renard, P.; Besson, T. *Bioog. Med. Chem. Lett.* **2000**, *10*, 2231. (c) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F.; Tatò, M. *Tetrahedron* **1996**, *52*, 8899. (d) Radisky, D. C.; Radisky, E. S.; Barrows, L. R.; Copp, B. R.; Kramer, R. A.; Ireland, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 1632. (e) Barrows, L. R.; Radisky, D. C.; Copp, B. R.; Swaffar, D. S.; Kramer, R. A.; Warters, R. L.; Ireland, C. M. *Anti-Cancer Drug Des.* **1993**, *8*, 333. (f) Keyzers, R. A.; Arendse, C. E.; Hendricks, D. T.; Samaai, T.; Davies-Coleman, M. T. *J. Nat. Prod.* **2005**, *68*, 506. (g) Copp, B. R.; Fulton, K. F.; Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1994**, *59*, 8233. (h) Lill, R. E.; Major, D. A.; Blunt, J. W.; Munro, M. H. G.; Battershill, C. N.; McLean, M. G.; Baxter, R. L. *J. Nat. Prod.* **1995**, *58*, 306.

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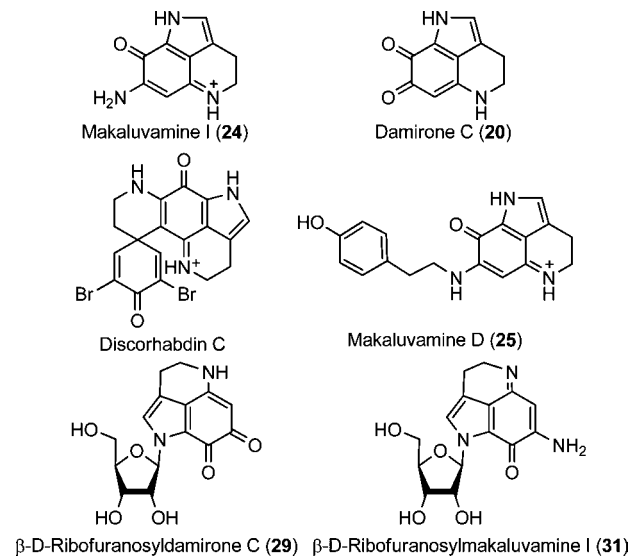
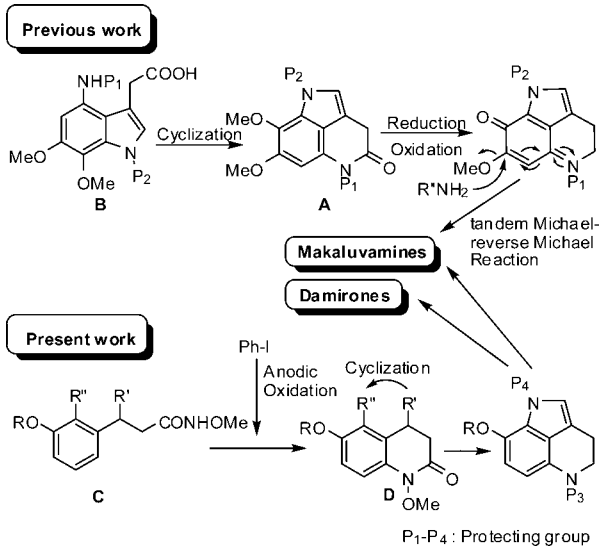


Figure 1. Tetrahydropyrroloiminoquinone alkaloids.

residue by using a tandem Michael-reverse Michael process. Assembly of the spirocyclic structure of discorhabdin C was accomplished by employing an anodic oxidation of a bromophenol precursor.[5]

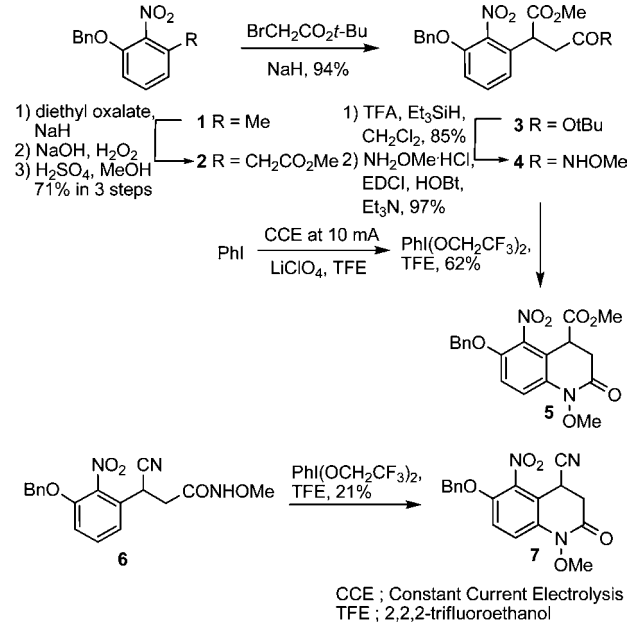
Scheme 1. Synthetic Strategies



The recent isolation of glycoside containing members of the tetrahydropyrroloiminoquinone alkaloid family from the South African latrunculid sponge *Strongylodesma aliwaliensis*[8] prompted us to reinvestigate new approaches to the synthesis of these alkaloids. In recent studies exploring synthetic applications of electrochemical methodologies, we observed that oxidative cyclization of aromatic compounds carrying a methoxyamide side chain was promoted by an electrochemically generated hypervalent iodine oxidant. These processes lead to formation of functionalized quinolinone derivatives (Scheme 1).[9] The oxidant generated in these reactions displayed a reactivity profile that is comparable to that of phenyliodine(III)bistrifluoroacetate (PIFA).

The new approach we have devised for the construction of the pyrroloiminoquinone structure involves the installation of the pyrrole ring on an appropriately substituted quinoline **D**, which is obtained by oxidation of a corresponding methoxyamide derivative **C** (Scheme 1). The crucial feature of this plan is the selection of appropriate functional groups in starting substrate **C**. To explore the new protocol, the arylpropanamide **4** was prepared by the route shown in Scheme 2. The sequence

Scheme 2. Synthesis of the Quinolinone Derivative (**5**)



was initiated by reaction of the anion generated from 3-benzyloxy-2-nitrotoluene **1**[10] with diethyl oxalate, followed by oxidative decarboxylation and esterification to give the arylac-

(3) (a) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476. (b) Blunt, J. W.; Calder, V. L.; Fenwick, G. D.; Lake, R. J.; McCombs, J. D.; Munro, M. H. G.; Perry, N. B. *J. Nat. Prod.* **1987**, *50*, 290. (c) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4127. (d) Perry, N. B.; Weavers, R. T. *Aust. J. Chem.* **1988**, *41*, 1571. (e) Munro, M. H. G.; Perry, N. B.; Blunt, J. W. U. S. *Patent* **1988**, *4*, 731–366. (f) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1988**, *44*, 1727.

(4) (a) Kobayashi, J.; Cheng, J.-F.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Lu, H.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 4939. (b) Cheng, J.-F.; Ohizumi, Y.; Walchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1988**, *53*, 4621.

(5) (a) Nishiyama, S.; Cheng, J.-F.; Tao, X. L.; Yamamura, S. *Tetrahedron Lett.* **1991**, *32*, 4151. (b) Tao, X. L.; Cheng, J.-F.; Nishiyama, S.; Yamamura, S. *Tetrahedron* **1994**, *50*, 2017.

(6) (a) Izawa, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1994**, *35*, 917. (b) Izawa, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron* **1994**, *50*, 13593.

(7) Tao, X. L.; Nishiyama, S.; Yamamura, S. *Chem. Lett.* **1991**, 1785.

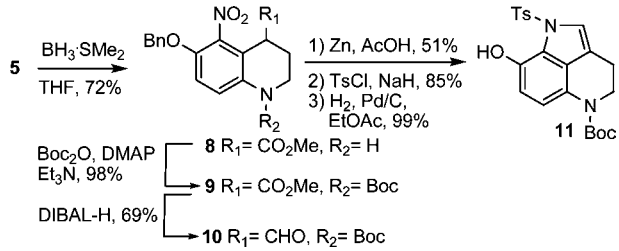
(8) Keyzers, R. A.; Samaai, T.; Davies-Coleman, M. T. *Tetrahedron Lett.* **2004**, *45*, 9415.

etate ester **2** (71%, 3 steps).[11] Exposure of **2** to $BrCH_2CO_2{}^tBu$ under basic conditions led to formation of the branched succinate diester **3**. Selective removal of the ^{t}Bu ester moiety in **3** generated the corresponding carboxylic acid, which is transformed to amide **4** by reaction with $MeONH_3Cl$.

The results of exploratory studies revealed that the yields for the oxidative cyclization process were dependent on the nature of the one carbon side-chains required for eventual installation of the pyrrole ring (Scheme 2). Importantly, compound **4**, possessing a methoxycarbonyl group underwent efficient cyclization to produce the quinolinone **5** when subjected to both electrochemically generated hypervalent iodine or PIFA. Despite having a similar structure, the corresponding nitrile **6** generated the quinolinone **7** in respective yields of only 10 and 21% when treated with PIFA or the electrochemically generated oxidant.

The route for installation of the key pyrrole unit was initiated by transformation of **5** to the corresponding dihydroquinoline **8** (72%) via borane reduction (Scheme 3). Boc

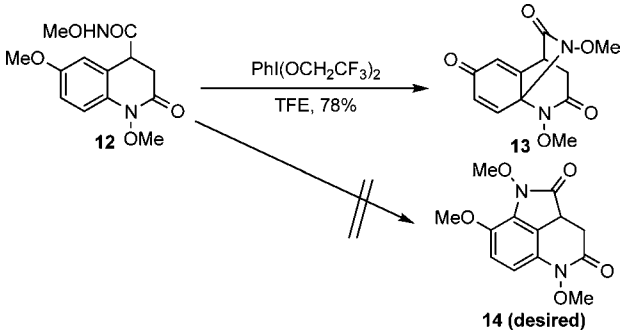
Scheme 3. Synthesis of Tetrahydropyrroloiminoquinone Derivative (**11**)



protection of **8** produced **9** (98%), which upon selective reduction with DIBAL-H, yielded aldehyde **10**. Finally reaction of **10** with Zn/AcOH, followed by treatment with TsCl-NaH and catalytic hydrogenolysis, gave **11**.[12]

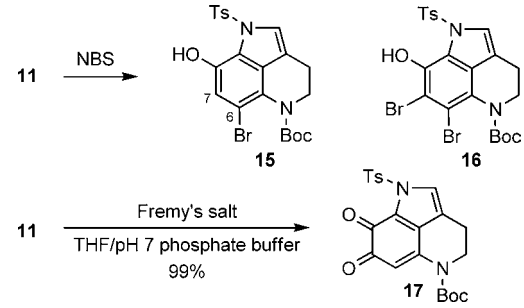
To probe an alternative route, tandem oxidative cyclization of **12** (Scheme 4), containing a methoxy amide

Scheme 4. Synthetic Approach



side chain, was attempted. When submitted to hypervalent iodine oxidation, **12** reacted by an entirely different pathway to afford the spiro tricyclic product **13** rather than the corresponding iminoquinone **14**. To introduce functionality that would enable installation of the C-7 amine side chain found in makaluvamine D (**25**, Scheme 5),

Scheme 5. Chemical Conversion of **11**



bromination of **11** was attempted. However, as a consequence of the higher reactivity of the C-6 position, treatment of **11** with NBS led to generation of the undesired monobromo and dibromo products **15** and **16**. In the course of an exploratory study, it was found that **11** was oxidized by using Fremy's salt[13] to give the α-diketone **17** (99%), which was ideally suited for introduction of C-7 functionality. Exhaustive deprotection of **17** led to formation of damirone C (**20**). Also, removal of the N-5 Boc group in **17** under acidic conditions, followed by methylation of the product **18**, gave **19**, which served as late intermediate in previous syntheses of damirones A (**22**) and B (**21**).[14] In addition, amination of **20** provided makaluvamine I (**24**).[15] Finally, removal of the N-1 tosyl group in **18** followed by coupling with tyramine hydrochloride yielded makaluvamine D (**25**).

Our attention next turned to synthesis of glycoside congeners. In addition to several varieties of antitumor activity, biological activities of nucleoside-like derivatives will be assessed. As a result of this potential, we initiated studies to prepare glycosyl iminoquinones. Among other strategies examined, coupling of **26**, produced from **17**, with the known chloro-sugar **27**[16] in the presence of NaH and 18-Crown-6 in DMF was found to yield the desired glyco-

(9) (a) Amano, Y.; Nishiyama, S. *Tetrahedron Lett.* **2006**, *47*, 6505. (b) Amano, Y.; Inoue, K.; Nishiyama, S. *Synlett* **2008**, 134. (c) Amano, Y.; Nishiyama, S. *Heterocycles* **2008**, *75*, 1997.

(10) Beer, R. J. S.; Clarke, K.; Khorana, H. G.; Robertson, A. *J. Chem. Soc.* **1948**, 1605.

(11) Reference of oxidative homologation, see: Zhang, Q.; Peng, Y.; Welsh, W. J. *Heterocycles* **2007**, *71*, 389.

(12) Similar stepwise reaction through the corresponding dimethylacetal, see: Roberts, D.; Joule, J. A. *J. Org. Chem.* **1997**, *62*, 568.

(13) Similar conversion of an aryl ether or a phenol to the corresponding α-diketone residue, see: (a) Moro-oka, Y.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **1999**, *40*, 1713. (b) Shishido, K.; Takata, T.; Omodani, T.; Shibuya, M. *Chem. Lett.* **1993**, 557.

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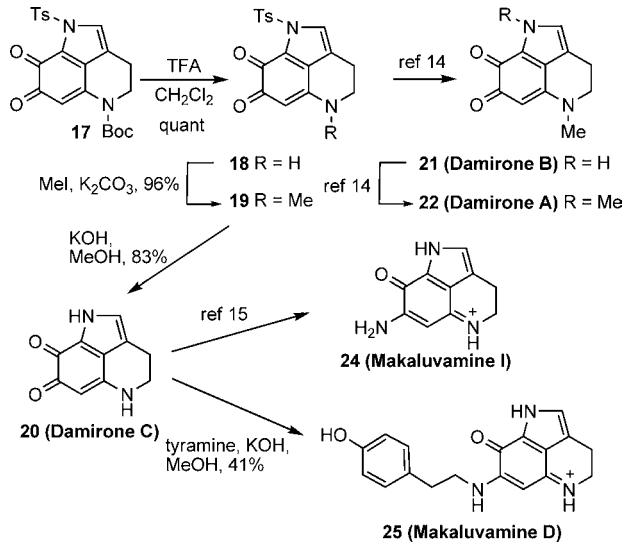
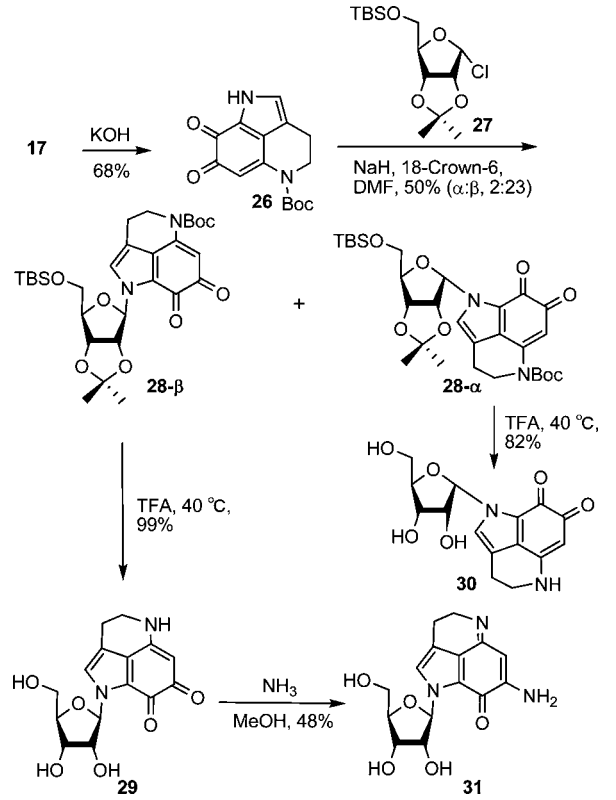
(16) Wilcox, C. S.; Otoski, R. M. *Tetrahedron Lett.* **1986**, *27*, 1011.

Scheme 6. Conversion to Natural Products



Scheme 7. Synthesis of Glycosidic Derivatives



sides **28-*β*** and **28-α** in 50% yield as a 23:2 mixture (^{1}H NMR integration) along with unreacted **26** (ca. 50% yield). The presence of a *β*-glycosidic linkage in **28-*β*** was unambiguously demonstrated by using NOE techniques. The TBS-protecting group in **28-*β*** was smoothly removed by using TFA to afford *N*-1-*β*-D-ribofuranosyldamirone C (**29**), along with its α-anomer in a 100:1 ratio determined by the same manner as described above. Another target, *N*-1-*β*-D-ribofuranosylmakaluvamine I (**31**) was obtained by ammonolysis of **29** with NH_3 in MeOH. Spectroscopic data for the synthetic iminoquinone glycosides matched those previously reported.[8]

In conclusion, a key intermediate in synthetic routes for preparation of members of the tetrahydropyrroloiminoquinone alkaloid family was generated by using a novel quinolinone synthetic methodology, involving oxidative cyclization of an aryl-methoxyamide precursor promoted by electrochemically generated hypervalent iodine species. This effort has led to the first total syntheses of *N*-1-*β*-D-ribofuranosyldamirone C (**29**) and *N*-1-*β*-D-ribofuranosylmakaluvamine I (**31**).

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

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