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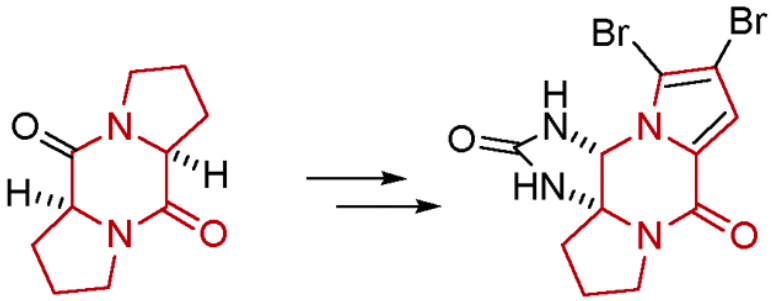
J. Am. Chem. Soc., **2003**, 125 (21), 6344-6345• DOI: 10.1021/ja034575i • Publication Date (Web): 02 May 2003



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Published on Web 05/02/2003

Enantioselective Total Synthesis of (+)-Dibromophakellstatin

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The oroidin family of marine alkaloids is a diverse and complex class of bioactive secondary metabolites, and no studies regarding their biological mechanism of action have been reported. One member of this family is (−)-dibromophakellstatin (**1a**), an antineoplastic agent, isolated by Pettit from the Indian Ocean sponge *Phakellia mauritiana*[1] along with the structurally related and previously isolated guanidine, (−)-dibromophakellin[2] (**2a**) (Figure 1). Dibromophakellstatin exhibits potent cell growth inhibitory activity against a variety of human cancer cell lines (ED_{50} 0.28−3.9 μM). The structure and absolute stereochemistry of dibromophakellstatin were determined by single-crystal X-ray analysis. This tetracyclic alkaloid poses a considerable synthetic challenge due to its compact size and corresponding dense polar functionality including two vicinal, stereogenic aminal centers. Van Soest[3] and more recently Al Mourabit and Potier[4] recognized that dibromophakellin (**2a**) could be derived biosynthetically from oroidin (**3**). Synthetic studies of these alkaloids date back to 1982 with an elegant synthesis of racemic dibromophakellin involving a biomimetic cyclization of dihydrooroidin by Büchi.[5] Other studies toward these alkaloids have been reported; however, no enantioselective syntheses have been described.[6] We targeted the enantioselective synthesis of these alkaloids and structural derivatives to enable biological investigations including mode of action studies. Furthermore, our interest in palau'amine (**4**) provided further impetus for developing routes to these substructures, as they could reveal potential strategies for phakellin annulation.[7] Herein, we describe the first enantioselective synthesis of (+)-dibromophakellstatin (**1a**), the unnatural optical isomer. The synthesis proceeds through (+)-phakellstatin (**1b**), which has not been isolated but is likely present in these organisms on the basis of the presence of nonbrominated, structurally related metabolites, for example, palau'amine (**4**).

Our strategy toward dibromophakellstatin was premised on the observation that a prolyl proline anhydride[cyclo (Pro, Pro)] was embedded within its structure and thus may be accessed via desymmetrization of a C_2-symmetric diketopiperazine (DKP), (*R*,*R*)-cyclo (Pro, Pro) ((+)-**9**) (Scheme 1). Our approach would involve a diastereoselective, desymmetrization process entailing acylation of the enolate derived from DKP (+)-**9**.[8] The ester at C10 would enable construction of the C6 aminal and then serve as a latent amine via Hofmann rearrangement. This strategy was premised on studies in our group and also those of Lindel[9] and Evans[10] demonstrating the unusual stability of pyrrole carbinolamines, for example, **6**. Following dehydrogenation and introduction of the C6 aminal, Hofmann rearrangement would give an isocyanate to be trapped by a pendant amine providing phakellstatin (**1b**) and then dibromophakellstatin (**1a**) via bromination.

The synthesis of unnatural dibromophakellstatin ((+)-**1a**) began with (*S*,*S*)-cyclo (Pro, Pro) ((−)-**9**) obtained in three steps by a modified, known procedure from less expensive L-proline.[11] A subsequent acylation with benzylchloroformate, as previously described, delivered the functionalized DKP **8** in good yield (70%)

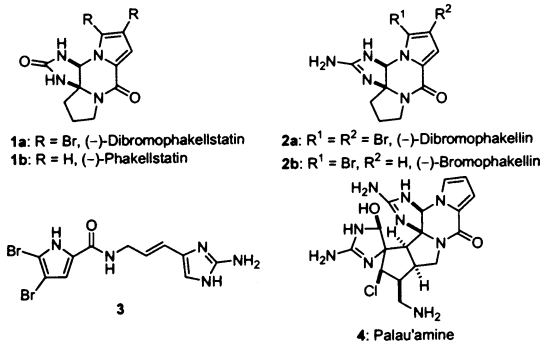
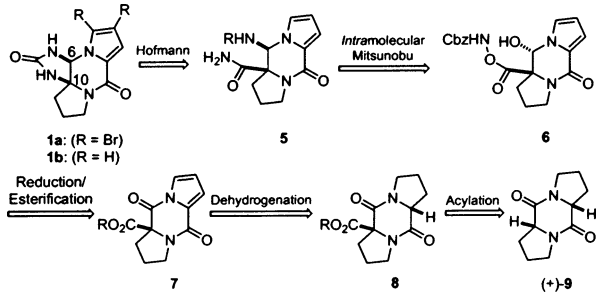


Figure 1. Structures of oroidin (**3**) and oroidin-derived alkaloids.

Scheme 1



and high diastereoselectivity (92% de).[8] Having served the purpose of controlling stereochemistry during acylation, the α-stereogenic center could be destroyed by dehydrogenation to pyrrole **10** in one step using DDQ[12] in refluxing toluene; however, yields were low (20−30%), and purification proved difficult. A more efficient, stepwise sequence was developed employing a selenation−oxidation−elimination sequence to provide an intermediate pyrroline, which was then oxidized upon exposure to SeO_2.[13] With acyl pyrrole **10** in hand, diastereoselective reduction was accomplished with $NaBH_4$ at low temperature.[14] Acetylation to give acetate **12** enabled confirmation of the expected cis relative stereochemistry of the β-acetoxy ester by single-crystal X-ray analysis (Scheme 2). Hydride addition occurs from the *concave* face of the slightly puckered tricyclic system presumably due to steric effects induced by the aromatic ring that is folded over the DKP ring in solution.[15] A trans arrangement of the β-acetoxy ester was required for the anticipated intramolecular Mitsunobu process, and so an epimerization of the carbinolamine center would be required. Fortuitously, a method for achieving this was discovered during early studies that suggested the need to introduce the C10 aminal late in the synthesis. Hydrogenolysis of benzyl ester **12** followed by treatment of the resulting acid **13** with the Shioiri[16] reagent at 85 °C produced an isocyanate, which was immediately trapped with benzylamine to deliver urea **14**. Aminolysis of the acetate **14** gave carbinolamine **15**; however, attempts to cyclize urea **15** under a variety of conditions led to decomposition due to the lability of the quaternary aminal center presumably via acyliminium chemistry. Under one

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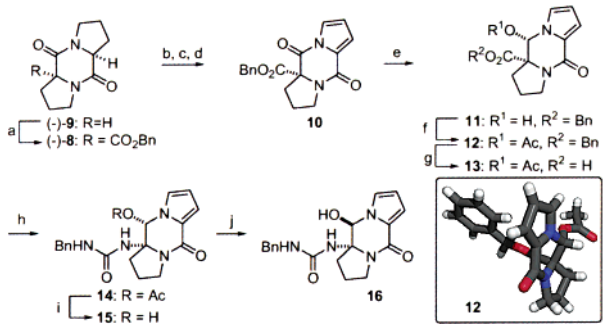
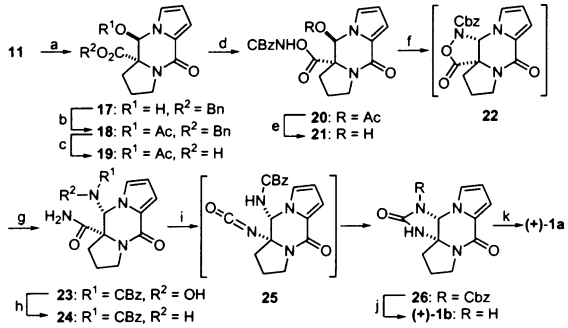
Scheme 2 [a]



[a] (a) Reference 8; (b) KHMDS, THF, −78 °C; PhSeBr (73%); (c) DMDO, CH_2Cl_2, −78 → 0 °C (93%); (d) SeO_2, dioxane, reflux (65%); (e) $NaBH_4$, MeOH, −40 °C (88%); (f) Ac_2O, py., CH_2Cl_2 (66%); (g) H_2, 10% Pd/C, EtOAc; (h) TEA, DPPA, $PhCH_3$, 4 Å MS, 85 °C; $BnNH_2$, 23 °C (50%, two steps); (i) NH_3, MeOH, (86%); (j) KO*t*-Bu, *t*-BuOH, 25 °C (99%).

Scheme 3 [a]



[a] (a) KO*t*-Bu, *t*-BuOH; (b) Ac_2O, py., CH_2Cl_2 (58%, two steps); (c) H_2, 10% Pd/C, EtOAc/EtOH (1:1); (d) (i) $(COCl)_2$, DMF_{cat}, CH_2Cl_2; (ii) CbzNHOH, DMAP (77%, two steps); (e) NH_3, MeOH, 0 °C (90%); (f) DIAD, PPh_3, THF, reflux; (g) NH_3, MeOH, 0 °C; (h) $TiCl_3$, KOAc, THF/H_2O (1:1), 23 °C (53%, three steps); (i) $PhI(O_2CCF_3)_2$, py., CH_3CN; (j) H_2, 10% Pd/C, MeOH (50%, two steps); (k) NBS (2.0 equiv), THF (69%).

set of conditions, exposure to KO*t*-Bu following attempted alcohol activation did not induce cyclization to the cyclic urea, but led instead to epimerization at C6 in quantitative yield, suggesting thermodynamic preference for *trans*-carbinolamine **16**.

With these epimerization conditions in hand and the information suggesting the instability of the aminal at C10, we explored a different strategy to complete the synthesis of phakellstatin which entailed introduction of the more stable C6 aminal followed by introduction of the more labile C10 aminal. Toward this goal, epimerization to carbinolamine **17** and subsequent acylation gave *trans*-acetoxyester **18** (Scheme 3). The benzyl group was removed, and acid **19** was subsequently coupled with benzyl *N*-hydroxycarbamate to give the hydroxamate **20**. Following aminolysis and exposure of the *N*-hydroxy ester to Mitsunobu conditions (DIAD, PPh_3),[17] tetracyclic intermediate **22** was formed but was not readily isolated due to instability. Hence, it was immediately subjected to aminolysis and then N−O bond cleavage with $TiCl_3$[18] to deliver *β*-amino amide **24**. Pleasingly, amide **24** smoothly underwent Hofmann rearrangement using $PhI(O_2CCF_3)_2$[19] and in situ cyclization giving Cbz-(+)-phakellstatin (**26**), which was hydrogenolyzed directly to deliver (+)-phakellstatin (*ent*-**1b**). Subsequent bromination with NBS delivered (+)-dibromophakellstatin (*ent*-**1a**). This material exhibited spectroscopic and physical properties identical to those of the natural product with the exception of optical rotation (syn. $[\alpha]^{25}_D$ +68.7°; nat. $[\alpha]^{25}_D$ −70.4°).

In summary, key steps in the first enantioselective synthesis of (+)-phakellstatin and (+)-dibromophakellstatin included desymmetrization of cyclo (Pro, Pro) via a diastereoselective acylation, an intramolecular Mitsunobu reaction to introduce the C6 aminal, and a tandem Hofmann rearrangement/cyclization to simultaneously introduce the C10 quaternary aminal center and deliver the cyclic urea. The synthesis also demonstrates the unusual stability of pyrrolo aminals, for example, **23**−**24**. Importantly, this strategy has the potential for producing phakellstatin derivatives, derived from (*R*, *R*)-cyclo (Pro, Pro), necessary for biological studies. The total synthesis also provides a phakellin annulation method applicable to the synthesis of palau'amine. Studies toward these goals will be reported in due course.

Acknowledgment. We thank the NIH (GM 52964-06) and Pfizer for support of these investigations. D.R. is an Alfred P. Sloan Fellow and a Camille-Henry Dreyfus Teacher-Scholar. We thank Dr. George Pettit (Arizona Cancer Res. Inst.) and Dr. David Horne (Oregon State) for samples and spectral data of dibromophakellstatin, respectively. We thank Dr. Joe Reibenspies for X-ray structure determination using instruments obtained with funds from the NSF (CHE-9807975). The NSF (CHE-0077917) provided funds for purchase of NMR instrumentation.

Supporting Information Available: Selected experimental procedures and characterization data (including ^1H and ^{13}C NMR spectra) for compounds **10**, **11**, **18**, **20**, **21**, **24**, (+)-**1b**, (+)-**1a**, and comparison spectra with natural (−)-**1a** and derived (−)-**1b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA034575I