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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 mauritiana1 along with the structurally related and previously isolated guanidine, (-)-dibromophakellin² (2a) (Figure 1). Dibromophakellstatin exhibits potent cell growth inhibitory activity against a variety of human cancer cell lines (ED₅₀ 0.28-3.9 μ M). 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 Soest³ and more recently Al Mourabit and Potier⁴ 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 Lindel⁹ and Evans¹⁰ 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.



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 DDQ¹² 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 SeO2.13 With acyl pyrrole 10 in hand, diastereoselective reduction was accomplished with NaBH₄ 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 Shioiri¹⁶ 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



^a (a) Reference 8; (b) KHMDS, THF, -78 °C; PhSeBr (73%); (c) DMDO, CH_2Cl_2 , $-78 \rightarrow 0 \ ^{\circ}C \ (93\%)$; (d) SeO₂, dioxane, reflux (65%); (e) NaBH₄, MeOH, -40 °C (88%); (f) Ac₂O, py., CH₂Cl₂ (66%); (g) H₂, 10% Pd/C, EtOAc; (h) TEA, DPPA, PhCH₃, 4 Å MS, 85 °C; BnNH₂, 23 °C (50%, two steps); (i) NH₃, MeOH, (86%); (j) KOt-Bu, t-BuOH, 25 °C (99%).

Scheme 3^a



^a (a) KOt-Bu, t-BuOH; (b) Ac₂O, py., CH₂Cl₂ (58%, two steps); (c) H₂, 10% Pd/C, EtOAc/EtOH (1:1); (d) (i) (COCl)2, DMFcat, CH2Cl2; (ii) CbzNHOH, DMAP (77%, two steps); (e) NH₃, MeOH, 0 °C (90%); (f) DIAD, PPh3, THF, reflux; (g) NH3, MeOH, 0 °C; (h) TiCl3, KOAc, THF/ H₂O (1:1), 23 °C (53%, three steps); (i) PhI(O₂CCF₃)₂, py., CH₃CN; (j) H₂, 10% Pd/C, MeOH (50%, two steps); (k) NBS (2.0 equiv), THF (69%).

set of conditions, exposure to KOt-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, PPh₃),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 TiCl318 to deliver β -amino amide 24. Pleasingly, amide 24 smoothly underwent Hofmann rearrangement using PhI(O₂CCF₃)₂¹⁹ 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.

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Supporting Information Available: Selected experimental procedures and characterization data (including ¹H and ¹³C 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.

References

- Pettit, G. R.; McNulty, J.; Herald, D. L.; Doubek, D. L.; Chapuis, J.-C.; (1)
- Brakman, J.-C.; Daloze, D.; Stoller, C.; Van Soest, R. W. M. Biochem.
 Syst. Ecol. 1992, 20, 417. (3)

- Syst. Ecol. 1992, 20, 417.
 Al Mourabit, A.; Potier, P. Eur. J. Org. Chem. 2001, 237.
 Foley, L. H.; Büchi, G. J. Am. Chem. Soc. 1982, 104, 1776.
 (a) Wiese, K. J.; Yakushijin, K.; Horne, D. A. Tetrahedron Lett. 2002, 43, 5135. (b) Jacquot, D. E. N.; Hoffmann, H.; Polborn, K.; Lindel, T. Tetrahedron Lett. 2002, 43, 3699. (6)
- Dilley, A. S.; Romo, D. Org. Lett. 2001, *3*, 1535.
 Poullennec, K. G.; Kelly, A. T.; Romo, D. Org. Lett. 2002, *4*, 2645.
 Jacquot, D. E. N.; Hoffmann, H.; Polborn, K.; Lindel, T. Tetrahedron
- Lett. 2002, 43, 3699.
- (10) Evans, D. A.; Borg, G.; Scheidt, K. A. Angew. Chem., Int. Ed. 2002, 41, 3188. (11) Ishibashi, N.; Kouge, K.; Shinoda, I.; Kanehisa, H.; Okai, H. Agric. Biol.
- Chem. 1988, 52, 819. (12) (a) Walker, D.; Hiebert, J. D. Chem. Rev. 1967, 67, 153-195. (b) Kodato,
- S.-I.; Nakagawa, M.; Hongu, M.; Kawate, T.; Hino, T. Tetrahedron 1988, 44 359
- (13) Bernstein, S.; Littell, R. J. Am. Chem. Soc. 1960, 82, 1235-1240.
- (14) Lee, S. D.; Brook, M. A.; Chan, T. H. Tetrahedron Lett. 1983, 24, 1569. Chemical shift analysis indicated shielding effects due to anisotropy of the phenyl ring of DKP 9. For related studies, see: Rajappa, S.; Natekar, M. V. Adv. Heterocycl. Chem. 1993, 57, 187.
- (16) Shioiri, T.; Ninomiya, K.; Yamada, S.-I. J. Am. Chem. Soc. 1972, 94, 6203.
- Hughes, D. L. Org. Prep. Proced. Int. 1996, 28, 127. (17)
- Matingly, P. G.; Miller, M. J. J. Org, Chem. 1980, 45, 410.
 Pallai, P.; Goodman, M. J. Chem. Soc., Chem. Commun. 1982, 5, 280.