Alkaloid Synthesis

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Enantioselective Synthesis of (+)-Monobromophakellin and (+)-Phakellin: A Concise Phakellin Annulation Strategy Applicable to Palau'amine**

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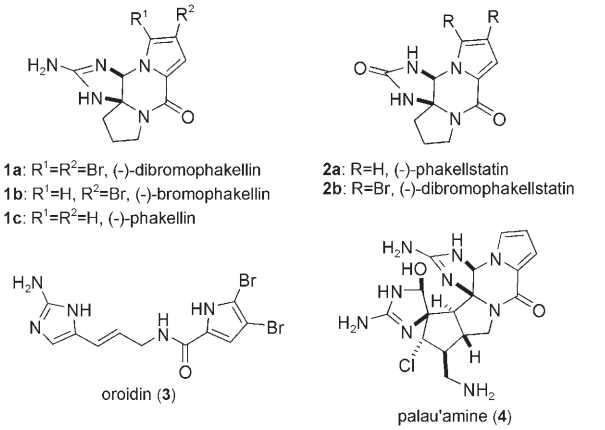
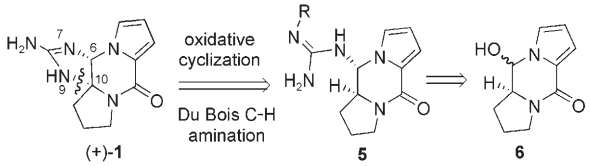
The phakellin group of natural products (**1a–c**) belong to the pyrrole–imidazole family of marine sponge derived alkaloids and are proposed to be biosynthetically derived from oroidin (**3**) and related congeners (Scheme 1).[1] This family of marine alkaloids has attracted great interest from both synthetic and biological perspectives because of their intriguing structural features and, in some cases, potent biological activities. The monomeric pyrrole–imidazole members (−)-dibromophakellin (**1a**) and (−)-monobromophakellin (**1b**) were isolated in 1969 by Burkholder and Sharma from the marine sponge *Phakellia flabellata*.[2] Subsequently, enantiomeric (+)-dibromophakellin (*ent*-**1a**) was isolated from *Pseudoaxinyssa cantharella* in 1985.[3] Phakellins (**1c** and *ent*-**1c**) have not been isolated but were obtained by hydrogenolysis of (−)- and (+)-dibromophakellin, respectively.[2b,3] The phakellstatin (**2**) group of natural products[4] are related members of this alkaloid family and bear a cyclic urea rather than a cyclic guanidine group. The dimeric pyrrole–imidazole alkaloids palau'amine (**4**)[5] and related congeners[1] contain a phakellin subunit within their structure, and a stereochemical revision of this molecule was recently proposed.[6]



Scheme 1. Structures of tetracyclic marine alkaloids from the phakellin (**1**) and phakellstatin (**2**) families, oroidin (**3**), and a more complex member, palau'amine (**4**).

The concise biomimetic synthesis of *rac*-dibromophakellin reported by Foley and Büchi stands as a benchmark for syntheses of these alkaloids.[7a] In fact, most subsequent syntheses of racemic phakellins and phakellstatin alkaloids have used related oxidative cyclization strategies.[7] We have previously reported an enantioselective synthesis of (+)-dibromophakellstatin that employed a Hoffman rearrangement to simultaneously introduce the second aminal center (C10; Scheme 2) and cyclize the incipient isocyanate to deliver the cyclic urea.[8] In connection with our synthetic efforts toward palau'amine (**4**),[9] we have sought expedient strategies to annulate the phakellin substructure onto a cyclopentane core. In our previous studies,[9b] we recognized the stability of C6 aminals in these tricyclic systems and this enabled us to consider an enantioselective strategy involving a key C–H amination disconnection at N9–C10. This strategy was based on recent studies by Du Bois and co-workers,[10] and employed guanidine **5** (Scheme 2) as a substrate, which is accessible from the known carbinolamines **6** derived from L-proline. This procedure would enable installation of the cyclic guanidine in a stereospecific fashion, thus giving synthetic entry to the phakellin alkaloids. Herein we describe a simple oxidative process that generates the N9–C10 bond of guanidine **5** and leads to the first enantioselective synthesis of members of the phakellin family of marine alkaloids, namely (+)-monobromophakellin and (+)-phakellin. This annulation strategy is potentially applicable to the preparation of the complex spiro alkaloid palau'amine (**4**).

Initially, we set out to synthesize a guanidine substrate, for example **5**, with a prerequisite of obtaining the required *syn* arrangement between the guanidine group and the adjacent C–H bond for subsequent intramolecular amination. Accordingly, L-proline was converted into the known compound **6** in three steps as an inconsequential (see below) mixture of diastereomers (d.r. ≈ 3:1; Scheme 3).[11a] Carbinol-



Scheme 2. Retrosynthetic analysis of (+)-phakellin involving a N9–C10 disconnection.

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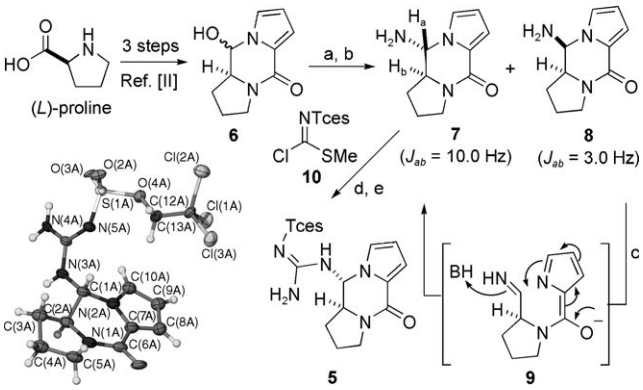
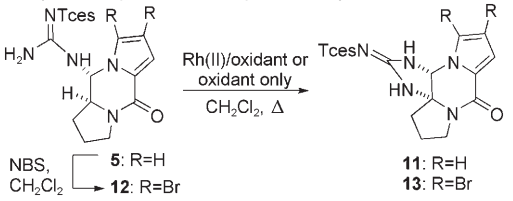


Scheme 3. Reagents and conditions: a) DPPA, DBU, THF, 20 °C, 63 %; b) H_2, Pd/C, CH_3OH, 20 °C, (31 % of **7**; 39 % of **8**); c) K_2CO_3, CH_3OH, 60 °C, 94 %; d) **10**, Et_3N, CH_2Cl_2, 93 %; e) $HgCl_2$, HMDS, CH_3CN, 20 °C, 77 %. DPPA = diphenylphosphoryl azide, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, Tces = 2,2,2-trichloroethoxysulfonyl.

amines **6** were converted into the aminals **7** and **8** by azidation with diphenylphosphoryl azide and subsequent reduction by hydrogenolysis. The diastereomeric aminals **7** and **8** (d.r. ≈3:4) could be separated by flash chromatography and each compound showed distinctive coupling constants (J_{ab} = 10.0 and 3.0 Hz) that enabled assignment of the relative stereochemistry as shown (Scheme 3). Aminal **8** was readily converted into the thermodynamically favored aminal **7** by warming in methanol with K_2CO_3. This provided the epimerized product **7** in 94 % yield, presumably via the ring-opened imine intermediate **9**. Thus, we had an efficient route for the synthesis of the required *anti*-substituted pyrazinone **7** needed for the projected C–H amination. The trichloroethoxysulfonyl (Tces) protected guanidine **5** was then prepared in two steps by the procedure developed by Du Bois and co-workers.[10] The relative stereochemistry of the Tces-protected guanidine was confirmed by single-crystal X-ray analysis (Scheme 3).

We next examined the C–H insertion process by employing conditions reported by Du Bois.[10] After some experimentation, we found that *N*-Tces-phakellin (**11**) could indeed be obtained in low yield when $[Rh_2(tfa)_4]$ was used (Table 1, entry 1). However, a control experiment revealed that the Rhodium(II) catalyst was not required, thus implying that rather than a C–H amination, a simple oxidative cyclization mechanism might be in operation. Several other oxidants, which were previously reported for amide oxidations to acyliminium species, including 2-iodoxybenzoic acid, cerium(IV) ammonium nitrate, and copper(II) salts were investigated, however these gave inferior yields or primarily decomposition.[12] Among the various oxidants and bases studied, the initially employed iodonium benzenediacetate ($PhI(OAc)_2$) in combination with MgO gave the highest yields of **11** (30–38 %; Table 1, entry 3). Considering that the pyrrole is known to be susceptible to oxidation, we also tested the dibrominated guanidine **12** with various oxidant/base combinations, however this led to only traces of cyclized product **13** (Table 1, entry 6). Attempts to further optimize this process by changing the solvents and reaction temperature did not lead to further improvement of the yield. While complete conversion of the starting materials was typically observed, very polar decomposition products always accompanied the cyclized product. The corresponding *N*-tosyl-protected guanidine was also examined, however under identical reaction conditions this did not yield *N*-tosyl-phakellin. One possible mechanistic scenario involves cyclization of the pendant guanidine to an acyliminium intermediate **16**, generated by oxidation of the vinylogous urea **14** with $PhI(OAc)_2$ (Scheme 4). Interestingly, under the same reaction conditions, the diastereomeric guanidine derived from amine **8** did not afford (−)-phakellin, which may point to the necessity of an intramolecular deprotonation by the pendant guanidine as shown in Scheme 4.[13] This mode of cyclization proceeds through an acyliminium species and is reminiscent of intermediates proposed by Al-Mourabit and co-workers in the interconversion of ugibohlin and dibromoisophakellin (Scheme 4).[14]

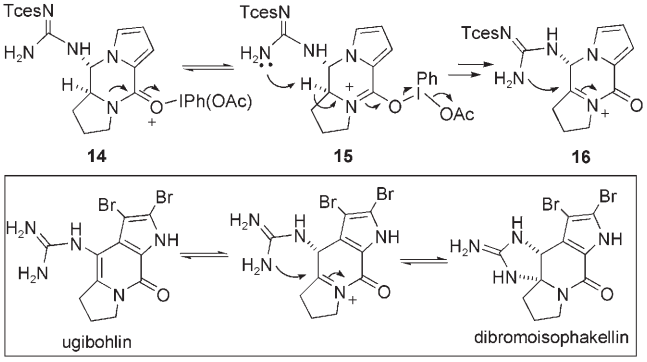
Table 1: Oxidative cyclization conditions for conversion of tricyclic guanidine **5**/**12** into phakellin compounds **11**/**13**.



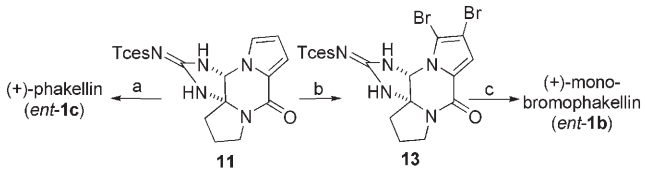
Entry	Reagents	Conditions	Yield [%][a]
1	$[Rh_2(tfa)_4]$ $PhI(OAc)_2$, MgO	65 °C, 8 h	≈10
2	$PhI(OAc)_2$	65 °C, 8 h	<30[b]
3	$PhI(OAc)_2$, MgO	MW, 150 W, 10 min	30–38
4	$PhI(O_2CCF_3)_2$	50 °C, 12 h	decomp
5	IBX	60 °C, 12 h	recovered **5**
6	$PhI(OAc)_2$	MW, 150 W, 10 min[c]	trace **13**

[a] Yield of isolated products. [b] Estimated by ^{1}H NMR spectroscopy (500 MHz) of the crude product. [c] Dibromoguanidine **12** was employed as substrate. NBS = *N*-bromosuccinimide, TFA = trifluoroacetyl, Ac = acetyl, IBX = 2-iodoxybenzoic acid, MW = microwave.

Deprotection of *N*-Tces-phakellin (**11**) afforded (+)-phakellin (*ent*-**1c**) following purification by preparative reverse-phase HPLC (Scheme 5). The synthetic material



Scheme 4. Proposed mechanism for oxidative cyclization and a related, proposed biomimetic interconversion of ugibohlin and dibromoisophakellin by Al-Mourabit and co-workers.



Scheme 5. a) Zn, AcOH, MeOH, 40 °C, 30 min, 85 %; b) NBS, CH_3CN, 20 °C, 16 h, 84 %; c) Zn, AcOH, MeOH, 40 °C, 40 min, 67 %.

exhibited spectroscopic and optical rotation data that correlated well with those reported for the naturally derived product (synthetic: $[\alpha]_D = +5.6\ deg\,cm^3\,g^{-1}\,dm^{-1}$; lit.[3]: $[\alpha]_D = +5\ deg\,cm^3\,g^{-1}\,dm^{-1}$). Bromination of **11** cleanly provided *N*-Tces-dibromophakellin (**13**) and subsequent reduction, resulting in cleavage of the Tces group and selective cleavage of the C5 bromo substituent, gave (+)-monobromophakellin (*ent*-**1b**).[15] The spectroscopic and optical rotation data for our synthetic material correlated well with the published data for (−)-monobromophakellin·HCl (synthetic: (+)-**1b**·HCl: $[\alpha]_D = +112.5\ deg\,cm^3\,g^{-1}\,dm^{-1}$; lit.[2]: $[\alpha]_D = -123\ deg\,cm^3\,g^{-1}\,dm^{-1}$) with the exception of the sign of rotation.

In summary, the first enantioselective synthesis of tetracyclic pyrrole–imidazole marine alkaloids from the phakellin family has been accomplished. The synthesis relies on a unique oxidative cyclization from a chiral tricyclic guanidine precursor and results in a highly concise, enantioselective route to these target compounds starting from L-proline (9 steps to give (+)-phakellin; 10 steps to give (+)-monobromophakellin). The optical antipodes of these natural products would be accessible using D-proline as the starting material. Importantly, this annulation process has a bearing on synthetic efforts toward palau'amine as it provides an expedient annulation strategy for advanced spiro-cyclopentane precursors.[16]

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