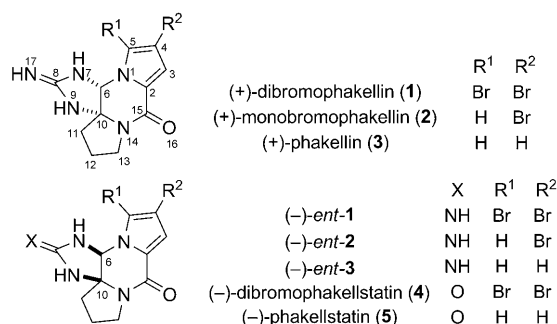


Total Synthesis of (+)-Dibromophakellin**

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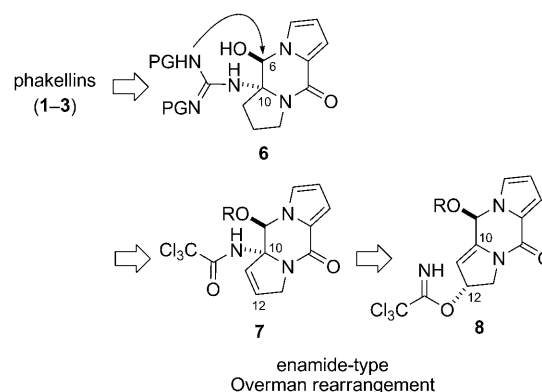
(+)-Dibromophakellin (**1**), a member of a family of pyrrole-imidazole marine alkaloids, was isolated from *Pseudoaxinyssa cantharella* in 1985^[1] as the enantiomer of natural (–)-dibromophakellin (*ent*-**1**)^[2] (Scheme 1). Neither enantio-



Scheme 1. Structures of the phakellins (**1–3**) and phakellstatins (**4, 5**).

mer of phakellin (**3**/*ent*-**3**) has yet been isolated; however, **3** and *ent*-**3** were obtained from **1** and *ent*-**1**, respectively, by hydrogenolysis.^[1,2b] A number of related compounds have been isolated, together with dimeric analogues of palauamine and related congeners.^[3] Most analogues of phakellin have characteristic complex spiro- and/or fused cyclic urea and guanidine functional groups, which have attracted the interest of synthetic chemists, who have devoted much effort to their synthesis.^[4] Foley and Büchi completed the first synthesis of (±)-dibromophakellin (**1**) on the basis of a proposed biosynthetic pathway.^[4a,5] Subsequently, (±)-phakellin (**3**) and phakellstatin alkaloids have been obtained through related oxidative cyclization strategies.^[4a–c,f,g] The first enantioselective synthesis of an alkaloid of this class was reported by Poullennec and Romo, who synthesized (+)-dibromophakellstatin (*ent*-**4**) and (+)-phakellstatin (*ent*-**5**) by employing a Hoffman rearrangement as a key reaction.^[6] The same research group also synthesized (+)-monobromophakellin (**2**) and (+)-phakellin (**3**) by using an oxidative cyclization with a hypervalent iodine reagent.^[7]

Herein we present total syntheses of (+)-phakellin (**3**) and (+)-dibromophakellin (**1**). The construction of the chiral aminals at C6 and C10 is one of the most challenging aspects of the enantioselective synthesis of phakellin (**3**) and related compounds. Poullennec and Romo addressed this issue by desymmetrization of a chiral diketopiperazine.^[6] Our approach was to introduce the chirality at C10 by means of a [3,3] sigmatropic rearrangement with transfer of the chirality at C12, as depicted retrosynthetically in Scheme 2.



Scheme 2. Retrosynthetic analysis of phakellins **1–3**. PG = protecting group.

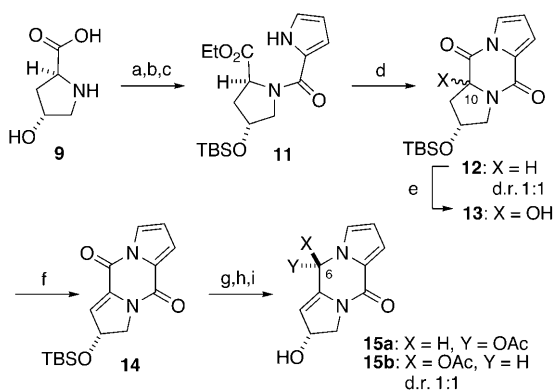
This rearrangement reaction, the so-called Overman rearrangement,^[8] is an effective method for the installment of an amino group at a tertiary carbon atom. It has been applied widely in the synthesis of complex natural products,^[9] but has not been used previously with an enamide substrate (conversion of **8** into **7** in Scheme 2). Since the nitrogen atom of the enamide has an electron-donating character, acceleration of this rearrangement reaction was expected.^[10]

To set the stage for the synthesis of **3**, we synthesized the optically active alcohol **15** (Scheme 3). First, piperazine **12** was prepared by the method developed by Al Mourabit and co-workers.^[11] The esterification of *trans*-4-hydroxy-L-proline (**9**) with ethanol in the presence of thionyl chloride, followed by protection of the hydroxy group with TBSCl and imidazole, gave the corresponding ethyl ester in 89% yield. Treatment of the ester with pyrrole-2-carboxylic acid (**10**) in the presence of EDCI and DMAP gave amide **11** in 92% yield, and subsequent treatment with sodium hydride in THF at 0°C gave piperazine **12** in 85% yield as a mixture of diastereomers at C10 (d.r. 1:1). Next, oxidation at C10 was conducted with IBX in a reaction that we developed recently for α-amino carbonyl compounds.^[12] Thus, the treatment of **12** with the complex IBX-trimethylamine *N*-oxide^[13] generated the α-hydroxy carbonyl compound **13** (d.r. 1:1), which reacted

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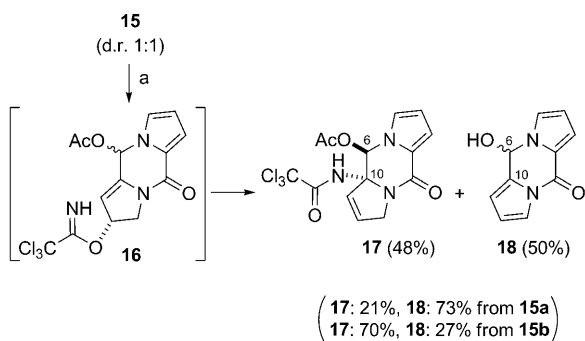
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.200806233>.



Scheme 3. Synthesis of alcohol **15a**: a) SOCl_2 , EtOH, reflux (98%); b) TBSCl, imidazole, CH_2Cl_2 , 25 °C (91%); c) pyrrole-2-carboxylic acid (**10**), EDCI, DMAP, CH_2Cl_2 , 25 °C (92%); d) NaH, THF, 0 °C (85%, d.r. 1:1); e) IBX-trimethylamine *N*-oxide, DMSO, 25 °C (d.r. 1:1); f) MsCl, Et_3N , CH_2Cl_2 , 25 °C (52% over two steps); g) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, EtOH/THF (1:1), 0 °C; h) Ac_2O , pyridine, CH_2Cl_2 , 25 °C (75% over two steps, d.r. 1:1); i) HF- Et_3N , THF, 25 °C (92%). DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, IBX = 2-iodoxybenzoic acid, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl.

subsequently with methanesulfonyl chloride in the presence of triethylamine with elimination to give the unsaturated cyclic amide **14** in 52 % yield from **12**. The C6 carbonyl group was reduced with sodium borohydride in the presence of cerium(III) chloride,^[14,15] and the resulting alcohol (1:1 diastereomeric mixture at C6) was protected with an acetyl group. The TBS ether was then cleaved with HF-triethylamine to give the alcohol **15** as a 1:1 mixture of diastereomers at C6 (**15a** and **15b**) in 69 % yield from **14**.

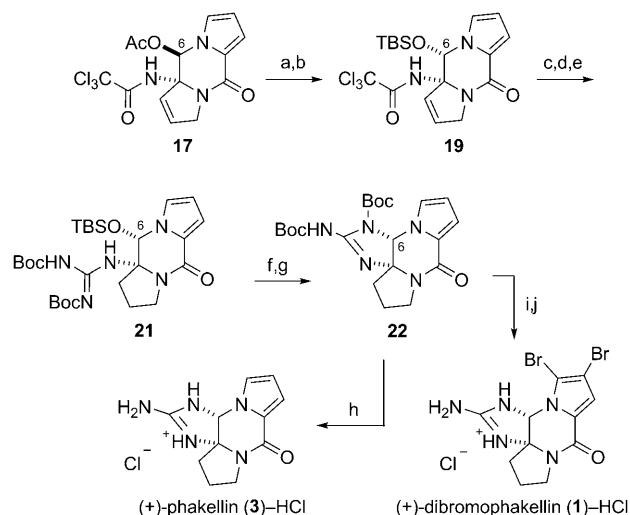
We next investigated the construction of the C10 aminal by an enamide-type Overman rearrangement (Scheme 4). To prepare the substrate for the rearrangement reaction, a trichloroacetimidoyl group was introduced at the hydroxy group in **15** (1:1 diastereomeric mixture of **15a** and **15b**) with trichloroacetonitrile and DBU in dichloromethane at room temperature. Surprisingly, the rearrangement reaction took place simultaneously at room temperature, and aminal **17** was obtained as a single diastereomer in 48 % yield. This reaction of an enamide substrate would be strongly accelerated



Scheme 4. Enamide-type Overman rearrangement: a) Cl_3CCN , DBU, CH_2Cl_2 , 0–25 °C. DBU = 1,8-diazabicycloundec-7-ene.

relative to the usual thermal Overman rearrangement owing to the neighboring electron-donating group. In this Overman rearrangement, pyrrole **18** was also obtained in 50 % yield. To gain insight into the nature of this reaction, the two diastereomers were separated, and each was subjected separately to the enamide-type Overman rearrangement. The β isomer **15b** was transformed into aminal **17** in 70 % yield, together with pyrrole **18** in 27 % yield. On the other hand, pyrrole **18** was obtained in 73 % yield from the α isomer **15a**.^[18] These observations show that the rearrangement reaction proceeds from the β isomer **15b** without steric repulsion at C6, whereas the other isomer affords pyrrole **18** by an elimination reaction. Moreover, the existence of an isomerization pathway between the α and β isomer of **15** during the trichloroacetimidate formation–Overman rearrangement reaction process is also suggested.

Following the successful construction of the chiral aminal at C10, we examined the synthesis of (+)-dibromophakellin **1** and (+)-phakellin (**3**; Scheme 5). The acetyl group in **17** was exchanged for a TBS group by hydrolysis with potassium carbonate in methanol, followed by treatment with TBS chloride and sodium hydride, to give **19** in 78 % yield from **17**. Two diastereomers (at C6) were generated upon hydrolysis; these two isomers converged to the thermodynamically stable α epimer (at C6) in the presence of NaH, presumably via the ring-opened system reported by Romo and co-workers.^[6,7] The trichloroacetyl group was removed with DIBAL-H.^[19] After reduction of the olefin with hydrogen in the presence of Raney nickel, *N*-Boc-protected guanidine was installed at the amine with 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (**20**) in the presence of silver(I) triflate to provide **21** in 91 % yield from **19**. The configuration at C6 in the guanidine



Scheme 5. Completion of the synthesis of (+)-**1** and (+)-**3**: a) K_2CO_3 , MeOH, 25 °C (96%); b) TBSCl, NaH, THF, 0 °C (82%); c) DIBAL-H, toluene, –80 °C (97%); d) H_2 , Raney nickel, EtOH, 25 °C (99%); e) NBoc = C(SMe)NHBoc (**20**), AgOTf , Et_3N , MeCN, 25 °C (95%); f) TBAF, THF, 0 °C (99%); g) MsCl, Et_3N , CH_2Cl_2 , reflux (91%); h) aqueous HCl, MeOH, 25 °C (99%); i) NBS, MeCN, 25 °C (85%); j) aqueous HCl, MeOH, 25 °C (99%). Boc = *tert*-butoxycarbonyl, DIBAL-H = diisobutylaluminum hydride, NBS = *N*-bromosuccinimide, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl.

21 was confirmed by an NOE experiment. The synthesis of **1** and **3** was completed as follows: The TBS ether was cleaved with TBAF, and during mesylation of the resulting alcohol (4:1 diastereomeric mixture at C6) with methanesulfonyl chloride and triethylamine, a cyclization reaction took place to give the cyclic guanidine **22** in 90% yield from **21**.^[18] Finally, the two Boc groups were removed with methanolic HCl to furnish (+)-phakellin (**3**) in 99% yield. (+)-Dibromophakellin (**1**) was synthesized from **22** by bromination with NBS, followed by deprotection with methanolic HCl. All spectroscopic data and optical rotation values of the products were consistent with reported data.^[1]

In conclusion, total syntheses of (+)-dibromophakellin (**1**) and (+)-phakellin (**3**) were completed in 19 and 18 steps, respectively, from **9**. Although the present synthesis still requires many steps, it features chiral aminal formation by means of the Overman rearrangement of an enamide. Further synthetic studies of this class of pyrrole–imidazole marine alkaloids on the basis of this strategy are in progress.

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