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Total Synthesis of (+)-Dibromophakellin and (+)-Dibromophakellstatin

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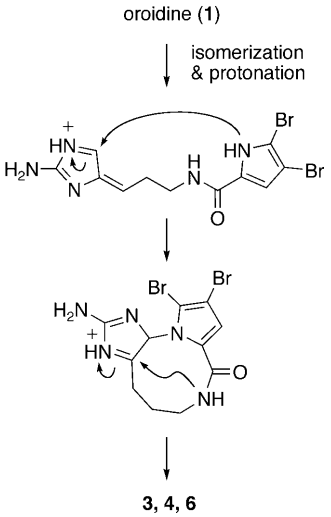
Abstract: A new method for the preparation of quaternary chiral aminals has been developed that employs an enamide-type Overman rearrangement process. This methodology was applied to enantioselective total syntheses of (+)-dibromophakellin and (+)-dibromophakellstatin.

Keywords: aminals · enamides · natural products · Overman rearrangement · total synthesis

Introduction

Phakellins and phakellstatins, isolated from marine sponges, are members of the pyrrole–imidazole alkaloid family.[1,2] Members of this family possess characteristic spiro and/or fused tetracyclic skeletons that contain cyclic guanidine or urea moieties and chiral vicinal aminal centers. The biosynthetic pathway for construction of these natural products has been proposed to involve cyclization of oroidine (**1**) through an isomerization and protonation process (Scheme 1).[2] Interestingly, both enantiomers of dibromophakellin (**4**) have been isolated from natural sources. A number of related compounds have also been isolated, together with a dimeric analogue of palau′amine and its related congener.[3] In spite of their structural similarities, members of this family possess a variety of biological activities.[1,4]

The characteristic structure of this alkaloid family, its unique biosynthetic pathway, as well as its wide range of biological activities has stimulated the interest of synthetic chemists. The first synthetic approach, described by Foley and Büchi in 1982, was targeted at (+/−)-dibromophakellin (**4**) and mimicked the biosynthetic pathway.[5a] Following this early report, several total syntheses of phakellins and phakellstatins have been described.[5] Although these alkaloids possess only two asymmetric centers at C6 and C10, their construction is made difficult because of problems with instability and epimerization. Consequently, only a few successful routes have been developed for the syntheses of members of this alkaloid family in its enantiomerically pure form. In 2003, the first enantioselective syntheses of (+)-phakellstatin (**5**) and (+)-dibromophakellstatin (**6**) were described by Romo and co-workers (Figure 1).[6] In their route, the chiral centers at C10 were enantioselectively installed using a Hofmann rearrangement of the achiral amide, which takes place with retention of configuration. Recently, Romo and Wang reported the syntheses of (+)-phakellin (**2**) and (+)-monobromophakellin (**3**) that employ an oxidative cyclization process promoted by a hypervalent iodine reagent.[7] In this pathway, the C6 stereocenter was established by an isomerization process that is regulated by the chiral center at C10.



Scheme 1. Proposed biosynthetic pathway for formation of the oroidine derived alkaloids **3**, **4**, and **6**.

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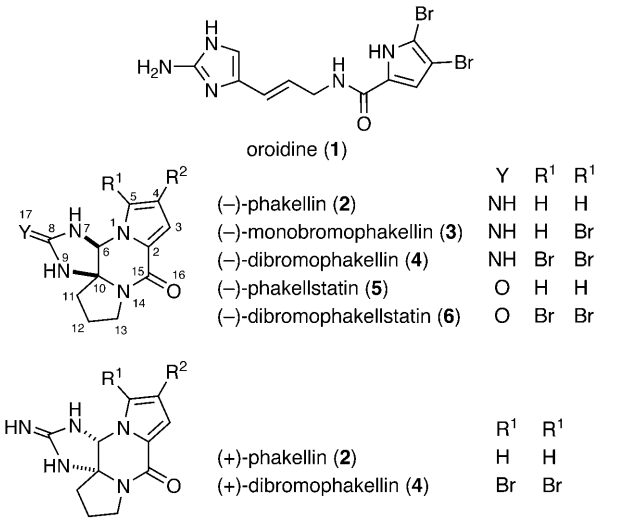


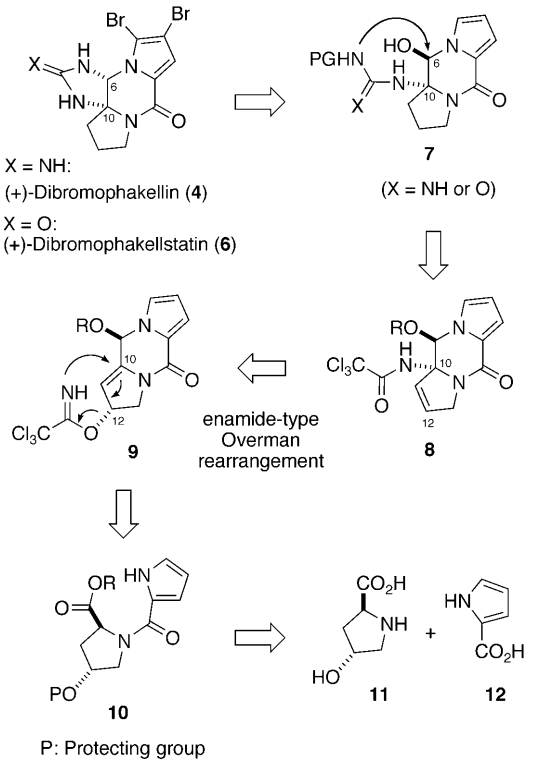
Figure 1. Structures of oroidine (**1**) and representative oroidine derived tetracyclic alkaloids related to the phakellins and phakellstatins.

We recently developed a synthetic approach for the enantioselective preparation of (+)-phakellin (**2**) and (+)-dibromophakellin (**4**) that relies on the use of an Overman rearrangement[8] of an enamide to construct the chiral *N,N*-aminal quaternary center at C10.[9] Herein, we report the full details of the routes we have developed for the synthesis of (+)-phakellins (**2** and **4**), including the methodology used in the key construction of the chiral *N,N*-aminal structure. A synthesis of (+)-phakellstatins (**5** and **6**) based upon the enamide-type Overman rearrangement strategy is also described.

Results and Discussion

Retrosynthetic Analysis of Phakellins and Phakellstatins

The synthetic strategy used for the preparation of (+)-phakellins and (+)-phakellstatins is illustrated in a retrosynthetic fashion in Scheme 2. We envisaged that the unique fused-spiro-ring system present in these targets could be constructed by cyclization of a guanidine or urea moiety in intermediate **7**. The presence in **7** of a quaternary asymmetric center at C10, which exists as an *N,N*-aminal, represents a significant challenge for the enantioselective synthesis of these alkaloids. To access the quaternary *N,N*-aminal structure in its



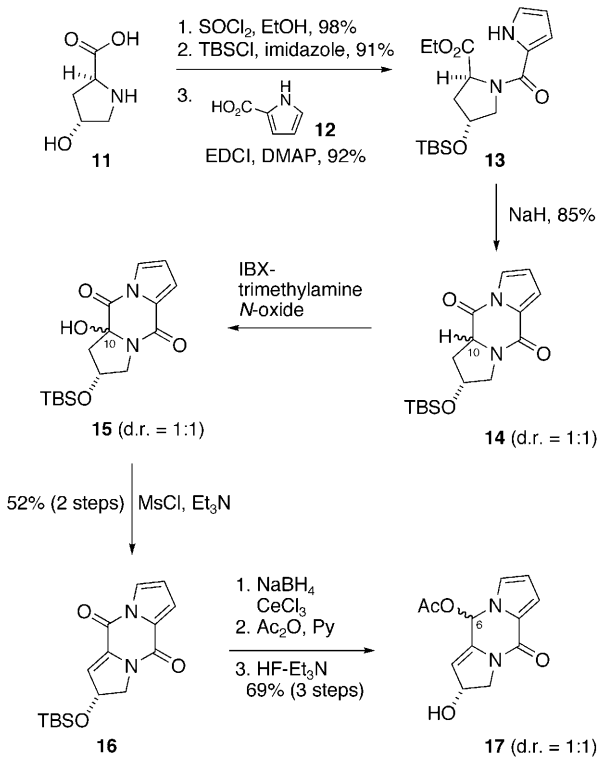
Scheme 2. Retrosynthetic analysis of phakellins and phakellstatins.

enantiomerically enriched form, we planned to construct the C10 center by a process in which chirality is transferred from the C12 position in **9** using an Overman-type [3,3]-sigmatropic rearrangement.[8] The Overman rearrangement is a powerful method for formation of C–N bonds and has been widely applied in the synthesis of complex natural products.[10] However, to date there are no reports of the use of enamide-type substrates in this rearrangement, as exemplified in the conversion of **9** into **8** (Scheme 2). In contrast to typical Overman rearrangements, which usually require high temperatures and long reaction times, we anticipated that reaction of the enamide substrate **9** would take place under mild conditions owing to the rate-accelerating effect of the electron-donating enamine moiety. Finally, we postulated that the optically active imidate ester **9**, together with the required absolute configuration at C12, could be generated through a condensation reaction between 4-hydroxy-L-proline (**11**) and pyrrole-2-carboxylic acid (**12**).

Synthesis of (+)-Phakellin (2) and (+)-Dibromophakellin (4)

In the plan described in Scheme 2, optically active allylic alcohol **17** serves as the substrate for the Overman rearrangement. This substance was synthesized by a route involving the piperazine intermediate **14** (Scheme 3).[11] Esterification of *trans*-4-hydroxy-L-proline (**11**) with ethanol in the presence of thionyl chloride followed by protection of the hydroxyl group with *tert*-butyldimethylsilylchloride (TBSCl) in

Abstract in Japanese:
ピロールイミダゾールアルカロイドに属する dibromophakellin 及び dibromophakellstatin の不斉全合成を達成した。本合成では、エナミドを基質とした Overman 転位反応を用いることで、これらのアルカロイドに共通する C10 位 *N,N*-アミナール不斉炭素を温和な条件下、効率よく構築する手法を確立した。

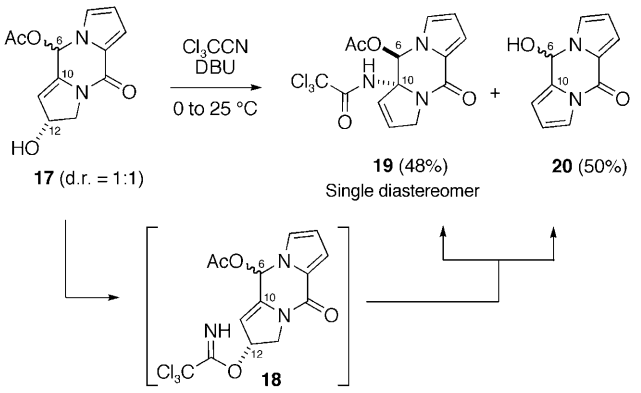


Scheme 3. Synthesis of the precursor for the Overman rearrangement of **17**.

the presence of imidazole gave the corresponding ethyl ester, which was coupled with pyrrole-2-carboxylic acid (**12**) using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) and 4-(dimethylamino) pyridine (DMAP) to give the amide **13** (82% from **11**). Cyclization of **13** was promoted by treatment with sodium hydride in THF to give the key piperazine **14** in 85% yield as a 1:1 mixture of C10 epimers. Oxidation at C10 in **14** was carried out using 2-iodoxybenzoic acid (IBX), using a process that we recently developed for the preparation of α-hydroxy-amino carbonyl compounds.[12] In the oxidation reaction, the IBX trimethylamine *N*-oxide reagent developed by Nicolaou and co-workers[13] was more effective than IBX alone, cleanly giving the α-hydroxyl carbonyl **15** (d.r. = 1:1).

The hydroxyl group at C10 in **15** was then subjected to elimination conditions using methanesulfonyl chloride in the presence of triethylamine. This process produced the enamide **16** in 52% yield (from **14**). The alcohol, obtained by reduction of carbonyl group at C6 in **16** using sodium borohydride in the presence of cerium (III) chloride,[14] was protected as an acetate. Removal of the TBS protecting group on the acetate with HF/triethylamine gave the desired alcohol **17** as a 1:1 C6 epimeric mixture (69% from **16**).

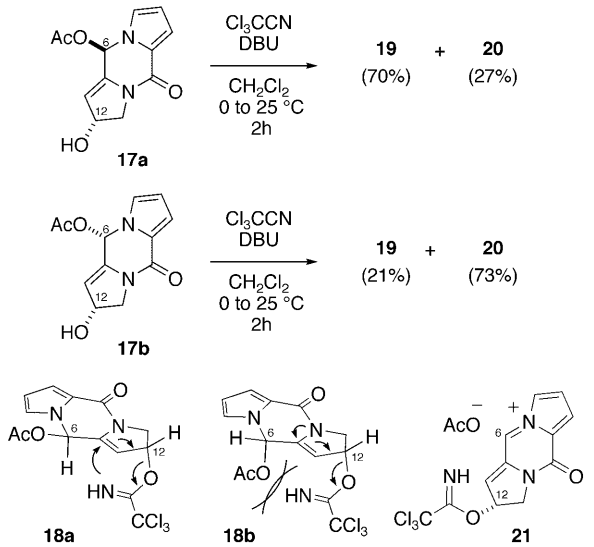
With the desired allylic alcohol **17** in hand, the Overman rearrangement was explored (Scheme 4). When the allylic alcohol **17** was treated with trichloroacetonitrile and DBU (1,8-diazabicycloundec-7-ene) at room temperature in order to obtain the corresponding trichloroacetoimidate **18**, a rearrangement reaction took place to generate the aminal **19** as



Scheme 4. Overman rearrangement of allylic alcohol **17**.

a single diastereomer in 48% yield.[15] In this process, pyrrole **20** was also generated in 50% yield.[16] Thus, it appears that the enamide-type Overman rearrangement of **18** was drastically accelerated, a phenomenon that we attribute to the presence of the electron-donating enamide group.

We believed that the C6 stereocenter in **17** would have an important impact on the product distribution generated in this reaction. To test this proposal, the two diastereomers **17a** and **17b** were separated[17] and individually subjected to the Overman rearrangement reaction conditions (Scheme 5). The rearrangement product **19** was obtained in



Scheme 5. Overman rearrangement from **17a** and **17b**.

70% yield together with the pyrrole **20** (27%) from the reaction of β-isomer **17a**, whilst pyrrole **20** was produced in 73% yield from the reaction of α-isomer **17b**. The reason for the different reactivity profiles stems from steric hindrance in **17b**, which can be observed between the acetyl group at C6 and the hydroxyl group at C12 in the X-ray structure.[17] As a result, the rearrangement of the trichloroacetoimidate **18b** derived from the α isomer is hindered,

CHEMISTRY
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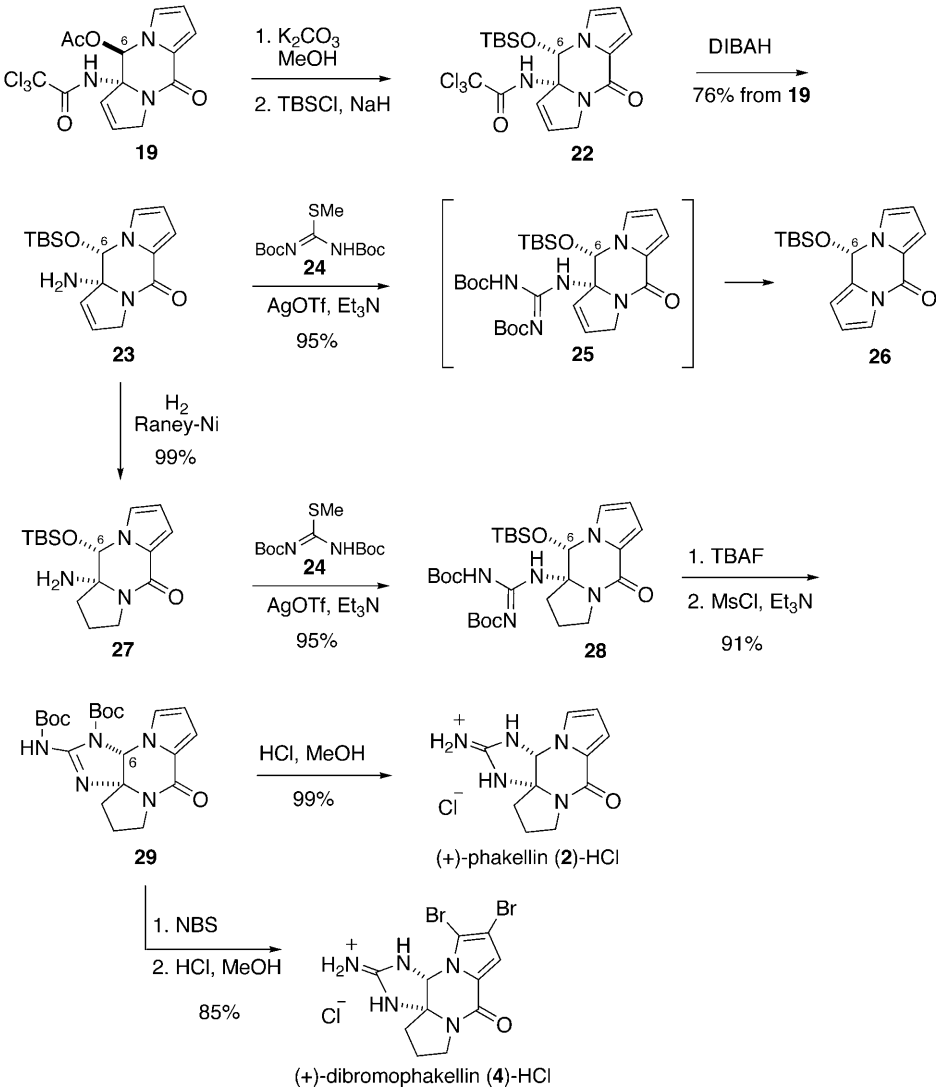
and instead, elimination takes place almost exclusively to generate **20** (Scheme 5). As the rearrangement product **19** and elimination product **20** are formed in reactions of both **17a** and **17b**, it is likely that an isomerization pathway via iminium cation intermediate **21** (Scheme 5) exists for the interconversion between isomeric trichloroacetoimidates **18a** and **18b**.

With the chiral aminal **19** in hand, the final steps in the syntheses of (+)-phakellin (**2**) and (+)-dibromophakellin (**4**) were examined (Scheme 6). Hydrolysis of **19** with potassium carbonate in methanol followed by silylation with TBSCl and NaH in tetrahydrofuran gave the silyl ether **22**. In this process, isomerization at C6 took place to exclusively form the thermodynamically more stable pseudoequatorial α isomer.[6,7,18] Removal of the trichloroacetyl group in **22** was carried out using diisobutylaluminium hydride (DIBAL) to give amine **23** (76% from **19**). Our initial attempt to install the guanidine group in **23** was not successful owing to an elimination–aromatization process that generated pyrrole **26**. To avoid this secondary aromatization reaction, the alkene moiety in **23** was reduced using hydrogen in the presence of Raney-Nickel to give **27**. Guanidination of the amine group in **27** employing bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (**24**) in the presence of silver (I) triflate led to the clean production of guanidine **28** (94% from **23**). The cyclic guanidine ring in **29** was constructed by removal of the TBS-ether protecting group in **28** with TBAF, followed by reaction of the resulting alcohol with methanesulfonyl chloride in the presence of triethylamine (91% from **28**). Finally, both *tert*-butoxycarbonyl (Boc) groups in **29** were removed using methanolic HCl to give (+)-phakellin (**2**) in 99% yield. The preparation of (+)-dibromophakellin (**4**) was achieved by a route involving dibromination of **29** at C4 and C5 with *N*-bromosuccinimide (NBS) followed by removal of the guanidine Boc groups with methanolic HCl (85%).

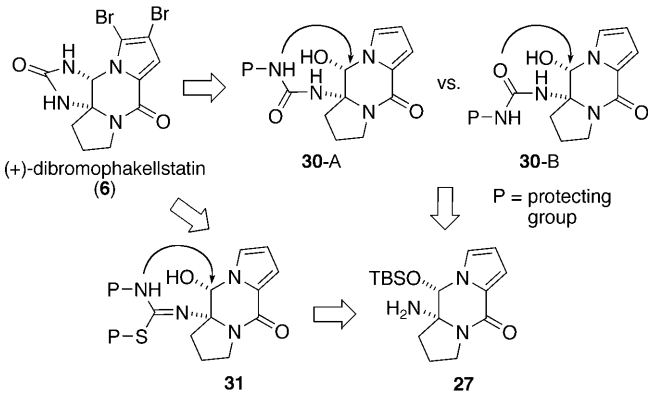


Scheme 6. Synthesis of (+)-phakellin (**2**) and (+)-dibromophakellin (**4**).

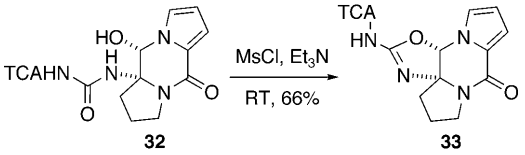
Synthesis of (+)-Phakellstatin (5) and (+)-Dibromophakellstatin (6)

Phakellstatins share a common basic skeleton with the phakellins, the only difference being the presence of a cyclic urea rather than a guanidine moiety spanning the C6 and C10 positions in the phakellstatins. Urea **30** is a key intermediate in the synthesis of phakellstatins, which relies on the strategy we have developed for preparation of the phakellins. Two cyclization modes, represented as **30**-A and **30**-B in Scheme 7, could be considered for constructing the cyclic urea group in **6** from **30**. Preliminary investigations showed that it was difficult to control these reaction modes (Scheme 8). In fact, cyclization of urea **32** by treatment with methanesulfonyl chloride gave the undesired isourea **33** exclusively in 66% yield.[6,19] The use of alternative reaction conditions, including those employing Lewis acids as reported by Taguchi and co-workers, were found not to be effective.[20]

We postulated that a thiopseudourea, like **31** in Scheme 7, would be a superior equivalent to urea **30** for the synthesis of phakellstatins. An appropriate thiopseudourea **35**



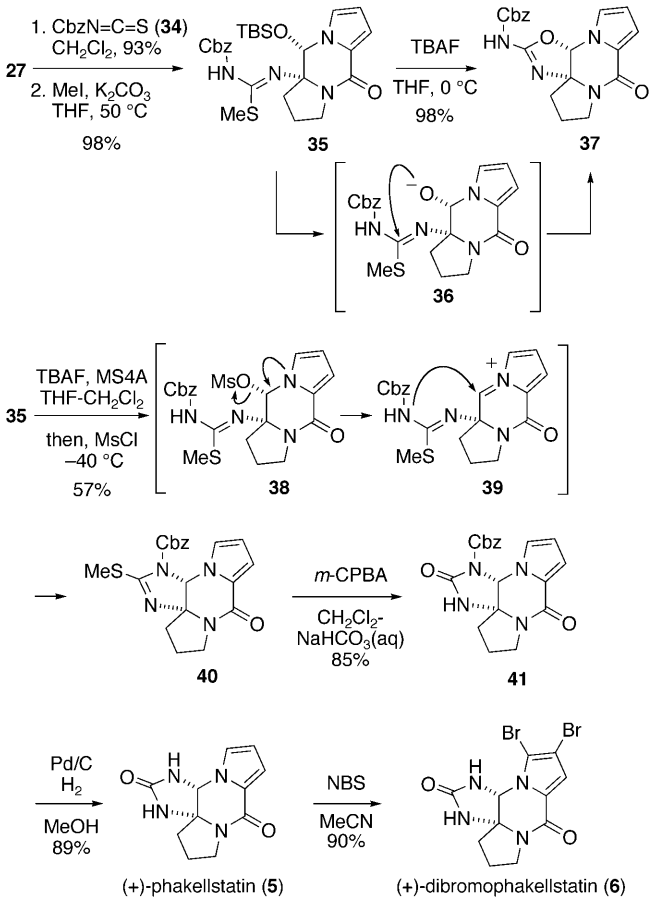
Scheme 7. Retrosynthetic analysis of phakellstatins.



Scheme 8. Cyclization of urea **32**. TCA = trichloroacetyl.

was prepared in 91% yield from the enantiomerically enriched amine **27** by treatment with benzyloxycarbonyl isothiocyanate (**34**) followed by methyliodide in the presence of potassium carbonate. In an attempt to remove the TBS-ether by reaction with TBAF at 0°C in tetrahydrofuran, the isourea **37** was unexpectedly generated in 99% yield, presumably by acyl nucleophilic substitution by the resulting alcohol in **36** on the pseudourea. A variety of conditions were investigated for this deprotection process (e.g., HF/pyridine, HF/triethylamine, and TBAF with an acetic acid buffer) but in each case only the isourea **37** was produced.

As the hydroxyl group at C6 in **36** was unexpectedly highly reactive toward intramolecular cyclization, a one-pot procedure involving sequential deprotection and hydroxyl functionalization was examined. Thus, reaction of **36** with TBAF was carried out at −40°C in the presence of 4 Å M.S., followed by addition of methanesulfonyl chloride to the resulting reaction mixture. Under these conditions, the desired cyclization reaction took place predominantly to generate the cyclic thiopseudourea **40** (57% from **35**); formation of isourea **37** was suppressed, being produced in only 11% yield. In this process, the iminium ion **39**, generated by elimination of the mesylate at C6, participates as an electrophile in the cyclization reaction. The final steps in the syntheses of (+)-phakellstatin (**5**) and (+)-dibromophakellstatin (**6**) were achieved in the following manner (Scheme 9). Oxidation of **40** with *meta*-chloroperbenzoic acid (*m*-CPBA) gave urea **41** in 85% yield. Removal of the carboxybenzyl (Cbz) group in **41** by using hydrogen in the presence of Pd/C furnished (+)-phakellstatin (**5**) in 89% yield. Finally, bromine introduction at the C4 and C5 positions of **5** took place selectively upon treatment with two equivalents of NBS to generate (+)-dibromophakellstatin



Scheme 9. Synthesis of (+)-phakellstatin (**5**) and (+)-dibromophakellstatin (**6**).

(**6**) in 90% yield. The ^{1}H and ^{13}C NMR spectra, mass spectra, and optical rotations of synthetic **5** and **6** matched those previously reported.

Conclusions

In the study described above, we have developed a new synthetic method for introduction of quaternary chiral aminals by means of an enamide-type Overman rearrangement. This strategy was successfully applied to the total syntheses of (+)-dibromophakellin (**5**) and (+)-dibromophakellstatin (**6**). In the approach to (+)-phakellstatins, a cyclic urea was constructed by cyclization of the corresponding thiopseudourea. Investigations of synthetic approaches to members of the pyrrole–imidazole alkaloid family, following the strategy developed in this work, are continuing.

Experimental Section

General: Flash column chromatography was performed on Silica gel 60 (spherical, particle size 0.040–0.100 mm; Kanto) or Chromatorex NH (particle size 100–200 mesh; Fuji Silysia). Optical rotations were measured on a JASCO P-2200 polarimeter, using a sodium lamp (589 nm).

^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECA 500, JNM-ECX 400, or JMTC 300 spectrometers. The spectra were referenced internally according to residual solvent signals of $CDCl_3$ (^{1}H NMR; δ = 7.26 ppm, ^{13}C NMR; δ = 77.0 ppm), [D_6]DMSO (^{1}H NMR; δ = 2.54 ppm, ^{13}C NMR; δ = 40.45 ppm) and CD_3OD (^{1}H NMR; δ = 3.30 ppm, ^{13}C NMR; δ = 49.0 ppm). Data for ^{1}H NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s singlet, d doublet, t triplet, m multiplet, br broad), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Mass spectra were recorded on JEOL JMS-T100X spectrometer with ESI-MS mode using methanol as solvent.

Thiopseudourea 35: Benzyloxycarbonyl isothiocyanate (**34**; 330 mg, 1.71 mmol) was added to a solution of amine **27** (365 mg, 1.14 mmol) in CH_2Cl_2 (20 mL) at 0 °C under an argon atmosphere. After stirring for 1.5 h at room temperature, the reaction mixture was concentrated in vacuo. The crude product was recrystallized from CH_2Cl_2 and hexane to give the isothiocyanate (546 mg, 93 %). Methyliodide (108 μL, 1.74 mmol) and potassium carbonate (482 mg, 3.48 mmol) were added to a solution of thiourea (449 mg, 0.87 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 3 h at 50 °C, quenched with H_2O, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:1) to give thiopseudourea **35** (450 mg, 98 %). $[\alpha]_D^{20} = +37.3$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.54 (br s, 1H), 7.33 (m, 5H), 6.92 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.88 (dd, *J* = 2.4, 1.7 Hz, 1H), 6.22 (dd, *J* = 3.8, 2.4 Hz, 1H), 5.54 (s, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 5.05 (d, *J* = 12.4 Hz, 1H), 4.05 (m, 1H), 3.64 (m, 1H), 2.37 (m, 1H), 2.29 (s, 1H), 2.12 (m, 3H), 1.09 (s, 9H), 0.28 ppm (d, *J* = 7.6 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.5, 157.3, 136.8, 128.5, 128.2, 127.8, 123.1, 120.8, 115.1, 110.5, 84.0, 80.2, 77.4, 77.0, 76.6, 67.1, 47.0, 39.2, 25.5, 21.7, 18.0, 14.2, −4.1, −4.4 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{26}H_{36}N_4NaO_4SSi$ 551.21242, found 551.21181.

Thiopseudourea 40: TBAF (419 mg, 1.60 mmol) was added to a solution of thiopseudourea **35** (424 mg, 0.80 mmol) and 4 Å M.S. (802 mg) in CH_2Cl_2/THF (1:1, 20 mL) at −40 °C under an argon atmosphere. After stirring for 10 min at −40 °C, methanesulfonyl chloride (186 μL, 2.40 mmol) was added to the reaction mixture, which was stirred for a further 1 h at −40 °C then allowed to stir at room temperature for 30 min, after which it was quenched with sat. NH_4Cl aq., and extracted with ethyl acetate. The organic layer was separated and washed with sat. $NaHCO_3$ aq. and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel that had been washed with Et_3N (hexane/ethyl acetate = 2:1 to 1:2) to give cyclic thiopseudourea **40** (183 mg, 57 %) and isourea **37** (34 mg, 11 %). $[\alpha]_D^{22} = -74.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.43 (m, 5H), 6.90 (m, 2H), 6.23 (t, *J* = 3.4, 1H), 6.18 (s, 1H), 5.41 (d, *J* = 12.0, 1H), 5.33 (d, *J* = 12.0, 1H), 3.93 (m, 1H), 3.80 (m, 1H), 2.35 (s, 3H), 2.11 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.0, 150.6, 134.2, 129.1, 128.8, 128.7, 124.4, 122.4, 113.0, 111.9, 89.0, 72.2, 69.3, 44.5, 40.1, 20.3, 15.2 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{20}H_{20}N_4NaO_3S$ 419.11538, found 419.11564.

Urea 41: *m*-CPBA (126 mg, 0.56 mmol) was added to a stirred solution of cyclic thiopseudourea **40** (111 mg, 0.28 mmol) in CH_2Cl_2/sat. $NaHCO_3$ aq. (2:1, 6 mL) at room temperature. After 1.5 h, the reaction mixture was quenched with sat. $Na_2S_2O_3$ aq. and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1:3) to give cyclic urea **41** (87 mg, 85 %). $[\alpha]_D^{23} = -151.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (m, 5H), 7.00 (dd, *J* = 2.8, 1.7 Hz, 1H), 6.96 (br s, 1H), 6.94 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.25 (dd, *J* = 3.8, 2.8 Hz, 1H), 5.44 (d, *J* = 12.0 Hz, 1H), 5.38 (d, *J* = 12.0 Hz, 1H), 2.21 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.4, 152.0, 150.3, 134.7, 128.7, 128.6, 128.2, 123.5, 123.2, 114.2, 112.2, 76.5, 69.6, 69.0, 44.6, 39.8, 19.6 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{19}H_{18}N_4NaO_4$ 389.12257, found 389.125851.

(+)-Phakellstatin 5: To a solution of cyclic urea **41** (87 mg, 0.24 mmol) in MeOH (5 mL) was added a catalytic amount of Pd/C. The suspension was vigorously stirred for 2 h under a H_2 atmosphere (balloon) at room temperature, after which it was filtered through a pad of Celite. The filtrates were concentrated in vacuo, and the residue was purified by column chromatography on silica gel (ethyl acetate/MeOH = 19:1) to give (+)-phakellstatin (**5**) (49 mg, 89 %). $[\alpha]_D^{18} = +104.7$ (*c* 0.3, DMF); ^{1}H NMR (125 MHz, [D_6]DMSO) δ = 8.11 (br s, 1H), 7.77 (br s, 1H), 7.13 (m, 1H), 6.65 (dd, *J* = 4.0, 1.7 Hz, 1H), 6.27 (dd, *J* = 4.0, 2.9 Hz, 1H), 5.75 (s, 1H), 3.52 (m, 1H), 3.43 (m, 1H), 2.23 (m, 1H), 2.10 (m, 2H), 1.97 ppm (m, 1H); ^{13}C NMR (500 MHz, [D_6]DMSO) δ = 160.1, 157.2, 124.3, 123.3, 112.8, 112.2, 80.0, 68.9, 45.6, 39.8, 20.6 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{11}H_{12}N_4NaO_2$ 255.08579, found 255.08323.

(+)-Dibromophakellstatin 6: NBS (15.3 mg, 0.086 mmol) was added to a stirred solution of (+)-phakellin (**5**) (10 mg, 0.043 mmol) in CH_3CN (1 mL) at room temperature. After 3 h at 40 °C, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 19:1) to give (+)-dibromophakellstatin (**6**) (15.3 mg, 91 %). $[\alpha]_D^{17} = +85.1$ (*c* 0.55, MeOH); ^{1}H NMR (500 MHz, [D_6]DMSO) δ = 8.29 (br s, 1H), 7.98 (br s, 1H), 6.91 (s, 1H), 5.75 (d, *J* = 2.3 Hz, 1H), 3.55 (m, 1H), 3.42 (m, 1H), 2.29 (m, 1H), 2.10 (m, 2H), 1.98 ppm (m, 1H); ^{13}C NMR (125 MHz, [D_6]DMSO) δ = 158.9, 155.1, 126.4, 114.8, 106.6, 102.1, 80.0, 69.6, 45.1, 39.8, 19.8 ppm; HRMS (ESI, $M+Na^+$) calcd for $C_{11}H_{10}Br_2N_4NaO_2$ 410.90682, found 410.9029.

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[16] No optical rotation was observed for **20**.

[17] The stereochemistry of **17b** was confirmed by using X-ray diffraction analysis. See the Supporting Information.

[18] The stereochemistry at C6 in **22** was determined using NOE analysis of **28** (Supporting Information).

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