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Total Synthesis of the Cytostatic Marine Natural Product Dibromophakellstatin via Three-Component Imidazolidinone Anellation

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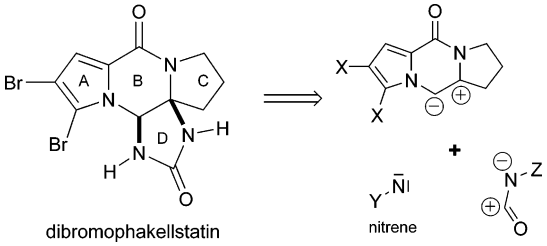

The tetracyclic pyrrole−imidazole alkaloid dibromophakellstatin from the marine sponge *Phakellia mauritiana* has been synthesized within seven steps from pyrrole in an 18% overall yield. The key step is a three-component assembly of a tricyclic enamide, a nitrene, and a carbamoyl building block, affording the imidazolidinone ring of dibromophakellstatin in one step. Notably, it is possible to employ the reagent $EtO_2CNHOTs$ in a double function as a source of the electrophilic nitrene and of a dipolar carbamoyl component. Use of debrominated precursor dipyrrolopyrazinones leads to much higher anellation yields and allowed us to develop a second generation synthesis. The cytostatic activity of dibromophakellstatin is confirmed.

Introduction

Pyrrole−imidazole alkaloids constitute a unique family of natural products exclusively found in marine sponges. Structures[1] and total syntheses[2] have been reviewed. We started a program on the total synthesis of the phakellin-type pyrrole−imidazole alkaloid dibromophakellstatin (**1**) from *Phakellia mauritiana*, because **1** is among the relatively few family members for which cytostatic activity has been reported in the course of its isolation in 1997.[3] Nothing is known on the mechanism of action. An efficient total synthesis of **1** should allow for the confirmation of that biological activity and pave the way toward functionalization of dibromophakellstatin for studies in chemical biology.

The key problem associated with the total synthesis of dibromophakellstatin originates in the ring strain of the tetracycle. Ring D obtains a 70° angle referred to as the almost planar ABC tricycle. While the approaches by Horne[4] and Feldman[5] adapt the biomimetic synthesis of *rac*-dibromophakellin reported by Büchi,[6] the "ABC strategy" (Figure 1) employs tricyclic pyrrolopyrazinones as precursors.[7−10]

In the biomimetic strategy, rings C and B are formed in one step starting from open-chain precursors where rings A and D are connected by an amide-containing chain. Our strategy toward the synthesis of dibromophakellstatin aimed at the installation of the imidazolidinone ring D in one step from an ABC tricyclic precursor. Ideally, a three-component assembly should include

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(3) Pettit, G. R.; McNulty, J.; Herald, D. L.; Doubek, D. L.; Chapuis, J. C.; Schmidt, J. M.; Tackett, L. P.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 180−183.
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(7) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344−6345.
(8) Chung, R.; Yu, E.; Incarvito, C. D.; Austin, D. J. *Org. Lett.* **2004**, *6*, 3881−3884.
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(10) Travert, N.; Martin, M.-T.; Bourguet-Kondracki, M.-L.; Al-Mourabit, A. *Tetrahedron Lett.* **2005**, *46*, 249−252.

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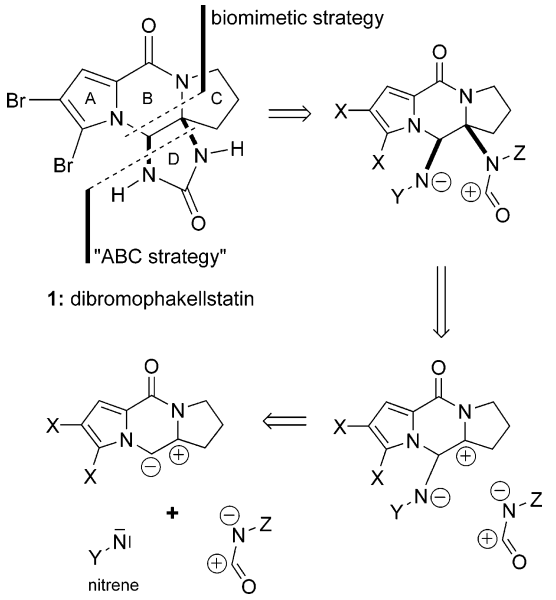


FIGURE 1. Retrosynthesis of dibromophakellstatin (**1**).

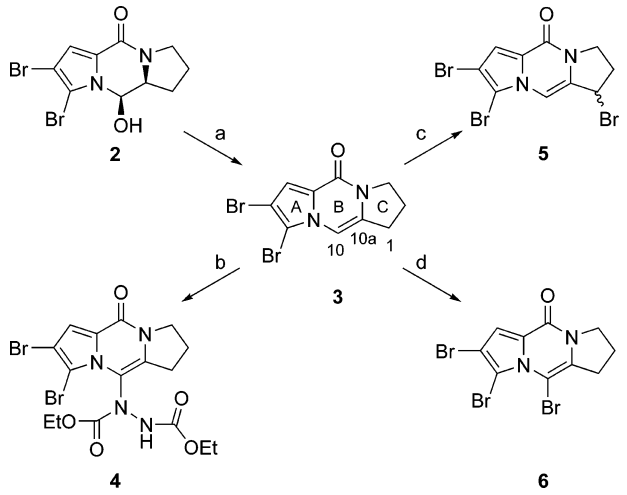
an enamide, a nitrene, and a carbamoyl building block (Figure 1). Use of an electrophilic nitrene offers the advantage of partially defining the order by which the condensation would take place. In the beginning, the nitrene is neutral. After being attacked by the enamide component, a negatively charged nitrogen would arise, capable of reacting with an activated carbamoyl component (Figure 1). Of course, the stereochemical course of our planned condensation was unclear in the beginning of our studies. The choice of reagents and variation in the pyrrole bromination would have some influence. In this paper, we will show that it is possible to anellate the imidazolidinone ring (D) in one step.

Results and Discussion

Orienting Experiments. We decided to first investigate reactions between a tricyclic enamide and various electrophiles. Scheme 1 outlines a few experiments on the reactivity of the tricyclic dipyrrolopyrazinone **3**, which was synthesized in five steps from pyrrole via the *N*,*O*-acetal **2**.[11]

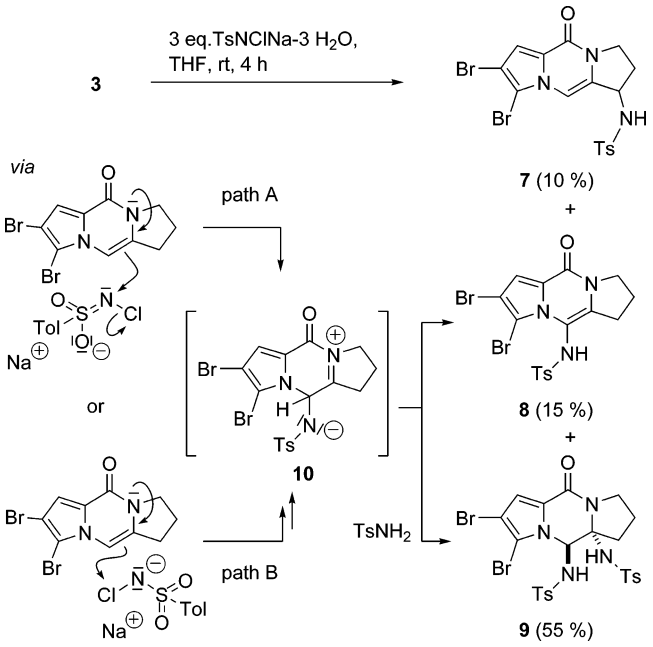
On treatment of **3** with *m*CPBA in the presence of water, we observed anti dihydroxylation of the C10,C10a double bond.[11] Deuteration of **3** on reaction with D_2O/D^+ at room temperature takes place first at C10, quantitatively, and then at the pyrrole ring. Deuteration of C1 was not observed. On reaction of **3** with NBS in pyridine at 0 °C, position C10 is brominated, affording **6** in 85% yield. Pyridine acts as an HBr scavenger and suppresses the radical process favoring an ionic mechanism. Changing the solvent to dichloromethane at 0 °C leads to exclusive radical substitution in the allylic position C1 (97% of **5**). Introduction of a nitrogen-containing substituent at C10 was possible on reaction of **3** with diethyl azodicarboxylate (DEAD) in refluxing $CHCl_3$ providing hydrazine **4** in 95% yield. The tendency of our proton-poor pyrrolopyrazinone intermediates to crystallize is fortunate for structural assignments.[12]

SCHEME 1. Functionalization of the Dipyrrolopyrazinone 3[a]



[a] (a) $POCl_3$ (1.5 equiv), pyridine, 0 °C, 2 h, 85%. (b) DEAD (1 equiv), $CHCl_3$, 70 °C, sealed tube, 12 h, 95%. (c) NBS (1 equiv), DCM, 0 °C, 1 h, 97%. (d) NBS (1.1 equiv), pyridine, 0 °C, 90 min, 85%.

SCHEME 2. Diamination of the Enamide 3 with Chloramine T



Diamination. A total synthesis of dibromophakellstatin (**1**) would require the introduction of two nitrogen substituents at C10 and C10a of enamide **3**. In a model study, reaction of **3** with chloramine T trihydrate ($TosNClNa\cdot 3H_2O$, 1.5 equiv) in THF at room temperature afforded the C10,C10a diaminated product **9** (55%), together with the C10 monoamination product **8** (15%, Scheme 2). The anti stereochemistry of **9** was determined by X-ray analysis.[12] With dry chloramine T, monoaminated **8** (45%) and the C1 allylic amination product **7** (20%) were formed and the diaminated product **9** was absent.

Bis-adduct **9** is formed by nucleophilic attack of toluene sulfonamide at C10a of the intermediate acyliminium ion **10**. It is known that, in the presence of water, chloramine T exists in equilibrium with toluene sulfonamide and hypochlorite.[13] For the formation of **9**, $TosNClNa\cdot 3H_2O$ should act as water source,

(11) Jacquot, D. E. N.; Hoffmann, H.; Polborn, K.; Lindel, T. *Tetrahedron Lett.* **2002**, *43*, 3699−3702.

(12) CCDC numbers: 614045 (**4**), 614046 (**8**), 614047 (**9**), 614042 (**12**), 614041 (**13**), 252066 (**15**), 252067 (**16**), 252091 (**18**), 252090 (**19**), 614040 (**20**), 614039 (**32**), 614044 (**33**), 614043 (**37**).

because reaction of **3** with dry TosNClNa does not lead to the formation of **9**.

In a competitive process, **10** would undergo deprotonation, affording the monoaminated product **8**. Amination in the allylic position C1, affording **7**, may arise from a radical process, paralleling allylic bromination. Chloramine T forms *N*-centered radicals at pH 5 in aqueous solutions at room temperature.[14] Allylic aminations of olefins by chloramine T have also been observed as side reactions of metal-mediated aziridination reactions.[15]

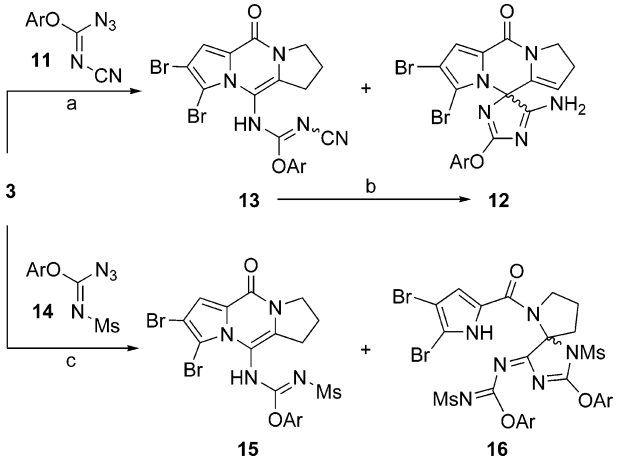
The most facile ionic process (path A, Scheme 2) would arise if the nitrogen of chloramine T acted as the electrophile with displacement of chloride. In the crystal, TosNClNa·$3H_2O$ is a chloroimine rather than a chloroamine,[16] and it is difficult to judge on the polarization of that N—Cl bond. After attack by C10, deprotonation would immediately afford intermediate **10**.

A more complicated ionic mechanism may commence with the chlorination of C10 via a chloronium intermediate (path B). Because we did not observe any chlorinated products, a C10 chloro substituent would have to be displaced by a tosylamino group that would first attack at the intermediate acyliminium ion (C10a), followed by intramolecular aziridine formation, ring opening, and either deprotonation or attack of a second equivalent of $TosNH_2$. A 1,2-rearrangement of the amino group of enamines on treatment with chloramine T has been observed even in the absence of metals.[17] In our case, the tosylamino group would have to migrate. Stradi et al. explored related reactions of *N*-chlorocarbamates with 1,2-diaminoalkenes affording imidazolidines and with 1-aminoalkenes leading to aminochlorinations with the chloro substituent in the β position.[18]

Although diamination of **3** was achieved with chloramine T, the anti stereochemistry of the product **9** prevented its use as a starting material for the assembly of the imidazolidinone ring D of dibromophakellstatin (**1**). We did not observe any syn product.

Reaction with Isourea Precursors. We turned to the isourea-derived nitrene sources **11** and **14**[19] anticipating that, after electrophilic attack, a zwitterionic intermediate would be formed that could undergo ring closure to an imidazoline. On irradiation of **3** in the presence of **11** or **14** employing a medium-pressure Hg lamp for 48 h, monoamination at C10 took place, affording **13** and **15** in low yields (Scheme 3). We went to thermal conditions and treated tricycle **3** with 1 equiv of *N*-cyanoisourea **11** in refluxing 1,4-dioxane. To our surprise, we obtained the unprecedented *spiro*-imidazoline **12** (structure confirmed by X-ray analysis[12]) in 55% yield, together with 15% of its putative precursor **13**. It was possible to cyclize the *N*-cyanoisourea **13** to **12** on treatment with HOAc—TFA (9:1) at 50 °C. Compound **12** is formed from **13**[12] by nucleophilic attack of the enamide portion at the cyano carbon. The percentage of **13** could be enhanced to 25% when the reaction time was reduced from 12 to 4 h.

SCHEME 3. Reaction of 3 with the Bis-Functional Reagents 11 and 14 (Ar = 2-*m*-Xylyl)[a]



[a] (a) **11** (1 equiv), 1,4-dioxane, reflux, 12 h, 55% (**12**), 15% (**13**). (b) HOAc—TFA (9:1), 50 °C, 24 h, 35%. (c) **14** (1.1 equiv), 1,4-dioxane, reflux, 8 h, 35% (**15**), 10% (**16**).

On treatment of tricycle **3** with 1 equiv of the mesylated isourea derivative **14** under thermal conditions, the desired cyclization to an imidazolidinone ring indeed occurred but with the cost of ring B opening. We obtained the ring B-opened *spiro*-tricycle **16**[12] incorporating a second equivalent of reagent **14** as a side product (10%), together with the C10-aminated product **15**.[12]

Reaction of 3 with Ethyl-*N*-tosyloxycarbamate. In our hands, it was not possible to cyclize enamines like **13** and **15** by formation of a bond between C10a and an the isourea nitrogen. Alternatively, the final step of ring D formation could be a condensation reaction to the urea unit.

We decided to investigate ethyl-*N*-tosyloxycarbamate (**17**)[20] for electrophilic amination of C10,[21] because we expected the anion of **17** to undergo α-elimination slowly enough to use the reagent as an electrophilic nitrene and as an *N*-nucleophile in the same reaction. For the synthesis of **17**, regioselective tosylation of the distilled *N*-hydroxycarbamate proceeded best in the presence of $NaHCO_3$ as the base (95% yield) when formation of the *N*,*O*-bistosylated side product was suppressed.

Reaction of the dibrominated pyrrolopyrazinone **3** was performed under conditions reported by Tardella et al. employing 7 equiv of CaO as a heterogeneous base in dichloromethane, together with 7 equiv of **17** (Scheme 4).[22] Reagent **17** can also be applied in two-phase aqueous systems in the presence of phase-transfer catalysts with $NaHCO_3$ as the base.[23] We observed that addition of water led to rapid initiation of the reaction without influencing the yield or the composition of the product mixture. The three stable products **18** (25%), **19** (20%), and **20** (5%) were isolated, together with a fourth, less stable product. For the workup, partitioning between saturated aqueous

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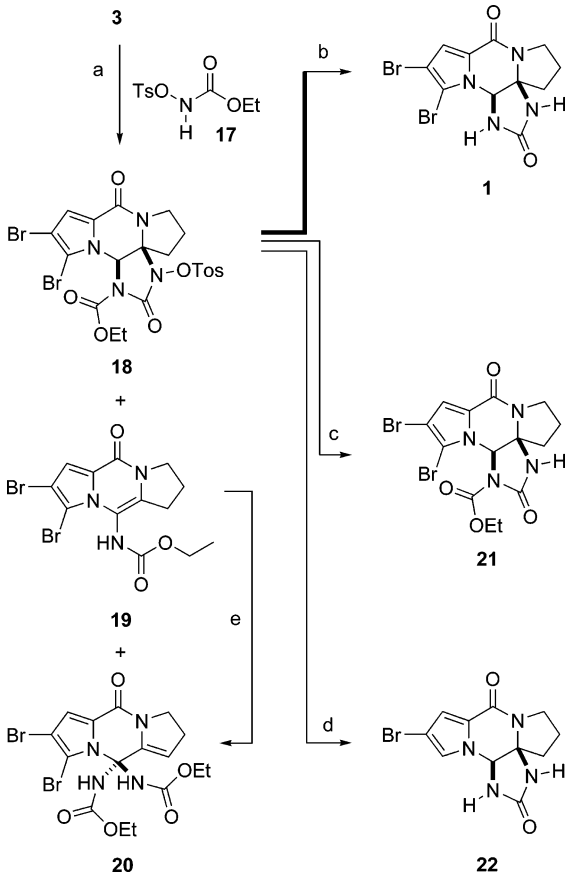
(21) For a review on electrophilic amination of carbonyl compounds, see: Erdik, E. *Tetrahedron* **2004**, *60*, 8747—8782.

(22) (a) Barani, M.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1994**, *50*, 3829—3834. (b) Fioravanti, S.; Colantoni, D.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2005**, *70*, 3296—3298, and references cited therein.

(23) Seno, M.; Namba, T.; Kise, H. *J. Org. Chem.* **1978**, *43*, 3345—3348.

SCHEME 4. Synthesis of *rac*-Dibromophakellstatin (1)[a]



[a] (a) **17** (7 equiv), CaO (7 equiv), DCM, 23 °C, 24 h, 25% (**18**), 20% (**19**), 5% (**20**). (b) SmI_2 (5 equiv), THF, 23 °C, 24 h, then MeOH, 23 °C, 12 h, 76%. (c) SmI_2 (2.5 equiv), THF, 23 °C, 15 min, 99%. (d) SmI_2 (7.5 equiv), THF, 23 °C, 24 h, then MeOH, 23 °C, 12 h, 60%. (e) **17** (7 equiv), CaO (7 equiv), DCM, 23 °C, 24 h, 50%.

$NaHCO_3$ and dichloromethane was preferred over tedious filtration.

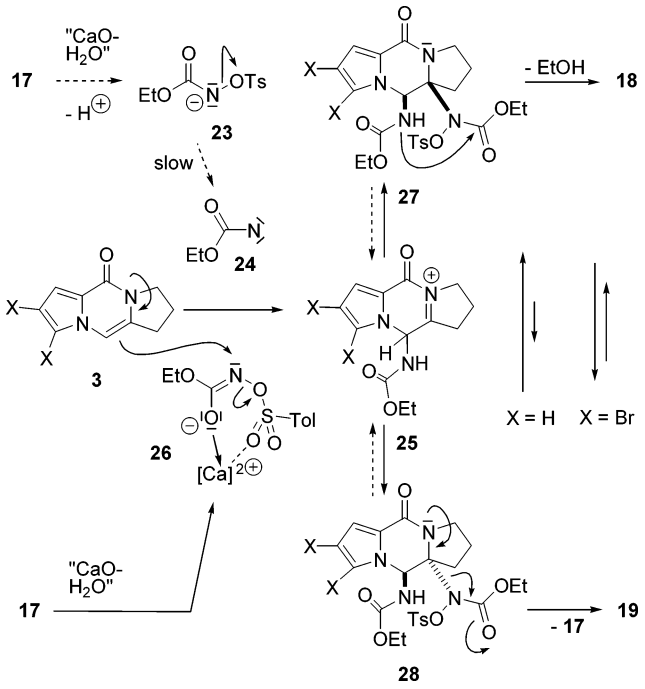
The structures of products **18**, **19**, and **20** were secured by crystal structure analysis.[12] We did not succeed in characterizing the fourth reaction product, which presumably is the open anti adduct (Scheme 5), which, on treatment with aqueous ammonia, afforded the alkenylcarbamate **19** by elimination.

On addition of 2.5 equiv of SmI_2 to a solution of **18** in THF, exclusive reduction of the N—O—bond occurs, affording tetracycle **21**. The ethoxycarbonyl group is cleaved off on treatment with an additional 2.5 equiv of SmI_2 and methanolic workup, affording dibromophakellstatin (**1**). With 7.5 equiv of SmI_2, the bromo substituent in the pyrrole α-position can be removed selectively, providing monobromophakellstatin (**22**).

The minor product **20** (Scheme 4) is formed after a second attack at C10, followed by deprotonation generating the C10a═C1 double bond. Indeed, we were able to independently convert **19** to **20** in 50% yield on treatment with 7 equiv of **17**.

Mechanism. *β*-Enaminoesters have been α-aminated employing $NsONHCO_2Et$,[24] and trialkylenamines may react as ambident N/C nucleophiles.[25] However, enamides have not been

SCHEME 5. Possible Mechanisms for the Formation of the Tetracycle 18[a]



[a] With NEt_3 as base, no tetracycle is formed.

investigated. It is likely that the acyliminium ion **25** (Scheme 5) is an intermediate of this novel three-component reaction, which itself could be formed by electrophilic attack of a nitrene at C10.

Interestingly, no reaction took place on replacing CaO by NEt_3, although it has been shown that NEt_3 is capable of generating nitrenes from **17** by slow α-elimination.[20] Nitrenes are probably not involved in the reaction of **3** with **17** in the presence of CaO. The acyliminium ion may alternatively be formed by direct nucleophilic attack of C10 of **3** at an sp^2-hybridized nitrogen and substitution of the tosyloxy group. There is precedence for the bimolecular reaction of enamines with tosyloximes.[26] A tosyloxime complex like **26** could be formed from reagent **3** and Ca^{2+} liberated from CaO and traces of water. NEt_3H^+ would fail to activate **17** toward direct attack by the nucleophilic enamide **3**.

Tetracycle **18** would be formed by nucleophilic syn attack of the reagent **17** at the acyliminium ion **25**, followed by condensation to the imidazolidinone with loss of ethanol (Scheme 5). It cannot be expected that an anti adduct (**28**) would cyclize to an imidazolidinone, which would be about 20 kcal/mol higher in energy than **18**. Instead, competing elimination of the tosyloxycarbamate **17** from **28** will occur, affording the alkenyl carbamate **19**. Although there is no direct proof of an equilibrium between the anomeric syn and anti adducts, exchange of nucleophiles at C10a has been shown for several alcohols and for water.[11]

Isolation of Bis-Adducts. We wondered whether it would be possible to characterize ring-opened syn and anti bis-adducts related to the putative intermediates **27** and **28** (Scheme 6).

An *N*-mesylated compound obtained from *rac*-longamide A (**29**)[27] did not react at all with the *N*-tosyloxycarbamate **17** in

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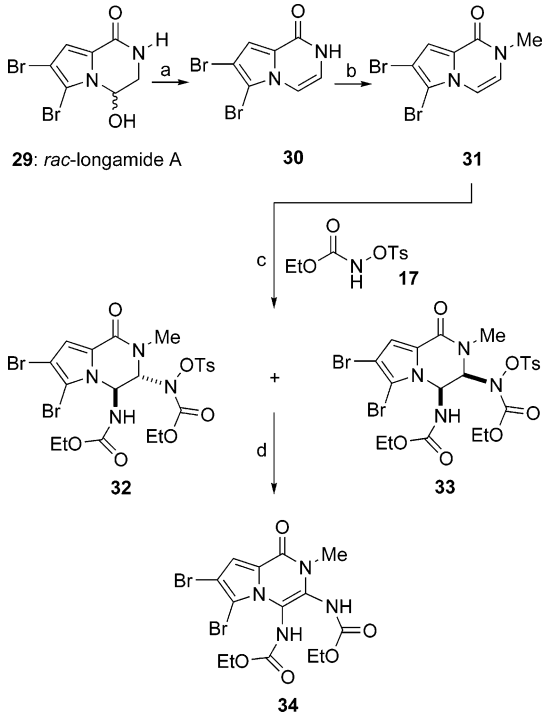
SCHEME 6. Model Study with Bicyclic Pyrrolopyrazinones[a]



[a] (a) TosCl (2 equiv), DCM, NEt_3 (6 equiv), rt, 24 h, 53%. (b) NaH (2 equiv), MeI (2 equiv), DMF, 0 °C to rt, 40 h, 73%. (c) **17** (7 equiv), CaO (7 equiv), DCM, rt, 24 h, **32** (44%), **33** (11%). (d) DMAP (1 equiv), pyridine, rt, 16 h, 80%.

the presence of CaO. Therefore, we investigated the behavior of the *N*-methylated AB system **31**, which was obtained in two steps from **29** (Scheme 6). On treatment of **31** with **17**, we obtained the diastereomers **32** (44%) and **33** (11%), which were separated by column chromatography and whose structures were both confirmed by crystal structure analyses.[12] However, there was neither an alkenyl carbamate formed that would be an analog of **19** (Scheme 4) nor any ABD tricycle that would correspond to the tetracycle **18**.

The absence of an alkenyl carbamate suggests that nucleophilic attack at C10a is faster at the bicycle AB than at the ABC tricyclic acyliminium ion and overwhelms competing deprotonation. The absence of an ABD tricycle reflects the sterically more relaxed situation in the bicyclic compared to the tricyclic system.

It was not possible to cyclize **32** or **33** to an ABD tricycle. Competing β-elimination of TsOH occurs in DMAP/pyridine, followed by tautomerization, affording the tetraaminoalkene **34** (Scheme 6).

Debromination Is the Key. The short total synthesis shown in Scheme 4 already allowed the production of more than 200 mg of dibromophakellstatin (**1**). However, the low yield of 25% of tetracycle **18** prompted us to investigate the effect of pyrrole bromination on the imidazolidinone anellation. Molecular modeling indicates that the energy differences between the syn and anti adducts should be close to 1 kcal/mol for the di- and nonbrominated compounds. Thus, we anticipated that subtle effects such as pyrrole bromination might influence the syn/anti ratio and perhaps even favor the syn adduct.

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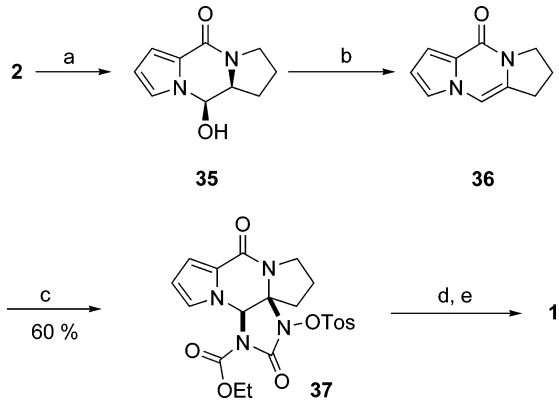
SCHEME 7. Access to *rac*-Dibromophakellstatin (1) via Nonbrominated Intermediates.[a]



[a] (a) H_2, Pd−C (5 mol %), NEt_3 (2 equiv), MeOH−DCM (1:1), 6 h, 98%. (b) MsCl (2 equiv), DBU (4 equiv), DCM, 0 °C to rt, 24 h, 60%. (c) **17** (7 equiv), CaO (7 equiv), DCM, rt, 24 h, 60%. (d) NBS (2 equiv), DCM, 0 °C, 4 h, 92%. (e) SmI_2 (5 equiv), THF, rt, 24 h, then MeOH, rt, 12 h, 85%.

The nonbrominated ABC tricycle **36** can be obtained from pyrrole in four steps.[8,10] However, because of the greater stability of the dibrominated vs the non-brominated intermediates, we chose to start from dibrominated *N*,*O*-acetal **2**, which was hydrogenated and then dehydrated.[8] The reaction of **36** with the $TsONHCO_2Et$ (**17**)/CaO proceeded completely, but the ratio of products was different from the nonbrominated case. We were pleased to observe that the yield of the nonbrominated tetracycle **37** was 60%, much higher than that for the dibrominated tetracycle **22**. We conclude that, fortunately, the absence of pyrrole bromination indeed favors the syn over the anti anomer (see Scheme 5). *rac*-phakellstatin was obtained on treatment of **37** with 5 equiv of SmI_2. *rac*-dibromophakellstatin (**1**) was synthesized from **37** by dibromination and deprotection with SmI_2 in the final step. Overall, our second generation synthesis provides *rac*-dibromophakellstatin (**1**) in an 18% yield over 7 steps, calculated starting from readily available 4,5-dibromopyrrolyltrichloromethylketone[28] as a precursor of tricycle **2**.[11] Our procedure gives access to gram quantities of the natural product. We probably would not have found this special synthesis if we had first focused on the development of a general method.

Related Work with Carbamates. Pellacani et al. reported the formation of structurally different imidazolidinones on reaction of $NsONHCO_2{}^tBu$ with β-ketoesters in the presence of CaO.[29] Mechanistically, Pellacani's reaction is different from the formation of our tetracycles **18** and **37** and presumably involves a diaziridinone intermediate formed from *tert*-butoxyisocyanate and an unchanged reagent.

The dependence of the behavior of arylsulfonyloxycarbamates on the reaction conditions may further be illustrated by the α-carbamoylation of β-ketoesters in the presence of NaH instead of CaO, as discovered by Hanessian.[30] *tert*-Butoxyisocyanate, formed via a Lossen rearrangement, is assumed to be the reacting species. Representing another mode of reactivity, α-amination of carbonyl compounds may occur (Genet had earlier identified BocNLiOTs,[31] crystallized by Boche,[32] as a reagent for this).

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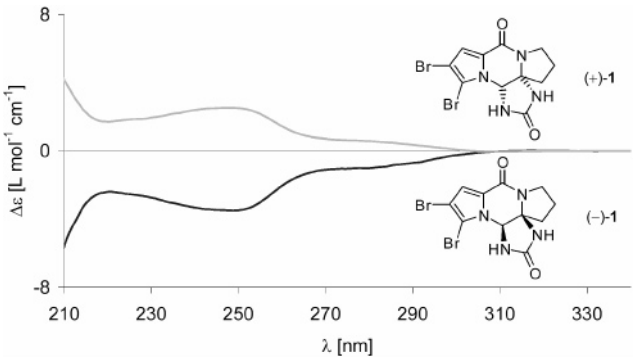

FIGURE 2. CD spectra and assignment of both enantiomers of dibromophakellstatin (**1**).

Biological Activity. When it comes to biological activity of the pyrrole−imidazole alkaloids, knowledge is still limited. Publications on the isolation and structure elucidation of the pyrrole−imidazole alkaloids contain more information on their biological activity than those reporting total syntheses. In theory, total synthesis should overcome problems associated with limited quantities of a natural product. We were pleased to confirm the cytostatic activity reported by Pettit et al. for (−)-dibromophakellstatin obtained by isolation from *Phakellia mauritiana*. In a preliminary investigation, our synthesized sample of *rac*-dibromophakellstatin (**1**) showed cytotstatic effects against the cell lines SF-268 (brain cancer, ED_{50} 1.4 μM), NCI-H460 (large cell lung cancer, 2.1 μM), and KM20L2 (colon cancer, 0.4 μM). This is important for the further development of the pyrrole−imidazole alkaloids at the border between the chemical and biological sciences.

Separation of Enantiomers. Baseline separation of the enantiomers was possible on a Chiralpak AD-H/45 HPLC column.

By comparing the circular dichroism (CD) spectra with those of other pyrrolopyrazinones,[33] we identified the later eluting compound as (−)-dibromophakellstatin ((−)-**1**). In 2,2,2-trifluoroethanol, (−)-**1** shows a trough at 248 nm ($\Delta\epsilon = -3.5$), together with a negative shoulder at 278 nm ($\Delta\epsilon = -1.0$, Figure 2). As expected, the CD spectra of the urea (−)-dibromophakellstatin and guanidine analogue (−)-dibromophakellin are very similar above 240 nm, because the negative helicity and syn position of substituents of the pyrrolopyrazinone partial structure strongly dominate over the influence of more distant functionalities. The values of optical rotations ($[\alpha_D^{20}] = -74.1°$ for (−)-**1**) were in agreement with our assignment.

Experimental Section

7,8-Dibromo-2,3-dihydro-1*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-one (3). To a stirred solution of *N,O*-acetal **2** (8.0 g, 22.9 mmol)[11] in pyridine (180 mL) was slowly added $POCl_3$ (3.2 mL, 34.3 mmol) at 0 °C under an argon atmosphere. After 2 h, water (10 mL) was added and the reaction mixture was diluted with 6 N HCl (250 mL). The aqueous layer was extracted with DCM (3 × 300 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. Recrystallization from MeOH provided dipyrrolopyrazinone **3** (6.61 g, 85%) as a colorless solid. Mp: 156 °C. R_f (silica gel, EtOAc): 0.55. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.20 (qi, 2H, $^3J = 7.1$ Hz), 3.01 (dt, 2H, $^3J = 7.1$, 7.1 Hz, $^4J = 1.4$ Hz), 4.04 (t, 2H, $^3J = 7.1$ Hz), 6.98 (s, 1H), 7.14 (br s, 1H). ^{13}C NMR ($CDCl_3$, 63 MHz): δ 22.5, 28.6, 46.8, 100.8, 101.0, 103.3, 111.0, 124.8, 131.3, 153.1. MS (EI, 70 eV): *m*/*z* (%) 330/332/334 (50.0/100/50.0) [M^+], 329/331/333 (10.0/25.0/20.0), 251/253 (27.1/20.9). IR (KBr): $\tilde{\nu}$ 3421, 3105, 2961, 2924, 1635, 1406, 1327, 1096, 795, 733. UV (CF_3CH_2OH): λ_{max} (log ϵ) 198 (4.00), 236 (4.67), 294 (4.31). Anal. Calcd for $C_{10}H_8Br_2N_2O$: C, 36.18; H, 2.43; N, 8.44. Found: C, 36.15; H, 2.58; N, 8.37.

(2,3-Dibromo-10-oxo-7,8-dihydro-6*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl)-hydrazine-1,2-dicarboxylic Acid Diethyl Ester (4). To a stirred solution of **3** (332 mg, 1.0 mmol) in $CHCl_3$ (10 mL) was added DEAD (454 μL, 1.0 mmol, 40% in toluene). The mixture was heated to 70 °C in a sealed tube for 12 h. After the reaction was complete, the solution was evaporated to yield a yellow crude product. After chromatography (silica gel, EtOAc/isohexane, 1:1), **4** (481 mg, 95%) was obtained as yellow crystals. Mp: 183 °C. R_f (silica gel, EtOAc): 0.80. The data for the major rotamer follow. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (t, 3H, $^3J = 7.1$ Hz), 1.29 (t, 3H, $^3J = 7.1$ Hz), 2.13−2.23 (m, 2H), 3.00−3.08 (m, 1H), 3.63−3.73 (m, 1H), 4.00−4.06 (m, 1H), 4.09−4.16 (m, 1H), 4.23 (q, 2H, $^3J = 7.1$ Hz), 4.26 (q, 2H, $^3J = 7.1$ Hz), 6.89 (br s, 1H), 7.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3, 14.6, 22.0, 29.1, 47.9, 62.6, 64.1, 97.4, 105.9, 113.1, 113.3, 126.6, 133.5, 152.5, 154.6, 155.9. The data for the minor rotamer follow. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29 (t, 3H, $^3J = 7.1$ Hz), 1.34 (t, 3H, $^3J = 7.1$ Hz), 2.13−2.23 (m, 2H), 3.10−3.17 (m, 1H), 3.58−3.63 (m, 1H), 4.00−4.06 (m, 1H), 4.09−4.16 (m, 1H), 4.26 (q, 2H, $^3J = 7.1$ Hz), 4.32 (q, 2H, $^3J = 7.1$ Hz), 6.96 (br s, 1H), 7.24 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 14.5, 21.9, 28.9, 47.9, 62.5, 64.1, 97.0, 105.9, 113.0, 113.2, 126.7, 134.1, 152.5, 154.1, 155.3. MS (EI, 70 eV): *m*/*z* (%) 503.9/505.9/507.9 (54.3/100/53.4) [M^+], 415.9/417.9/419.9 (27.1/55.7/28.0), 343.9/345.9/347.9 (40.4/74.2/38.6), 328.9/330.9/332.9 (44.0/76.1/37.1), 308/310 (31.5/44.0). IR (ATR): $\tilde{\nu}$ 3330, 3030, 2957, 2872, 1790, 1700, 1650, 1350, 1300, 1194, 1180, 1001, 804, 710. UV ($CHCl_3$): λ_{max} (log ϵ) 244 (4.53), 287 (3.87). HRMS (EI) calcd for $C_{16}H_{18}Br_2N_4O_5$: 503.9644. Found: 503.9650.

1,7,8-Tribromo-2,3-dihydro-1*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-one (5). To a stirred solution of **3** (332 mg, 1.0 mmol) in DCM (30 mL) was added NBS (187 mg, 1.05 mmol) at 0 °C. After 1 h, the reaction mixture was quenched with 2 N NaOH (25 mL) and extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (silica gel, EtOAc) and obtained as a colorless solid (400 mg, 97%). Mp: 69 °C. R_f (EtOAc): 0.75. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.53−2.69 (m, 2H), 4.08−4.15 (m, 1H), 4.30−4.35 (m, 1H), 5.38−5.40 (m, 1H), 7.23 (s, 1H), 7.30 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 35.2, 44.7, 44.8, 102.6, 103.8, 104.8, 112.5, 124.9, 132.4, 152.6. MS (EI, 70 eV): *m*/*z* (%) 407.9/409.9/411.9/413.9 (35.5/100/96.5/33.3) [M^+], 330/332/334 (24.5/36.6/15.1), 329/331/333 (55.4/97.9/50.6), 250/252 (15.6/17.1). IR (KBr): $\tilde{\nu}$ 3445, 3118, 2925, 1684, 1639, 1408, 1366, 1290, 1172, 967, 539. UV (EtOH): λ_{max} (log ϵ) 200 (3.97), 252 (4.45), 290 (4.23). HRMS (EI) calcd for $C_{10}H_7Br_3N_2O$: 407.8108. Found: 407.8096.

7,8,10-Tribromo-2,3-dihydro-1*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-one (6). To a stirred solution of **3** (664 mg, 2.0 mmol) in pyridine (5 mL) was added NBS (392 mg, 2.2 mmol) at 0 °C. After 90 min, a second portion of NBS (178 mg, 1.0 mmol) was added, and the mixture was stirred for 30 min and evaporated to dryness. The crude product was purified by column chromatography (silica gel, EtOAc). **6** (698 mg, 85%) was obtained as a colorless solid. Mp: 101−102 °C. R_f (EtOAc): 0.63. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.17−2.25 (m, 2H), 3.01−3.05 (m, 2H), 4.11−4.14 (m, 2H), 7.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 32.0, 48.5, 90.3, 102.4, 107.4,

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113.5, 127.5, 131.7, 152.3. MS (EI, 70 eV): *m*/*z* (%) 407.9/409.9/411.9/413.9 (35.4/100/96.6/33.5) [M^+], 330/332/334 (24.3/36.2/14.9), 329/331/333 (54.4/98.7/49.7), 250/252 (15.6/17.0). IR (ATR): $\tilde{\nu}$ 3200, 2957, 2872, 1650, 1445, 1376, 1241, 1160, 1107, 806, 710. UV (EtOH): λ_{max} (log ϵ) 202 (3.91), 248 (4.36). HRMS (EI) calcd for $C_{10}H_7Br_3N_2O$: 407.8108. Found: 407.8099.

***N*-(7,8-Dibromo-5-oxo-2,3-dihydo-1*H*,5*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-1-yl)-4-methylbenzenesulfonamide (7), *N*-(2,3-Dibromo-10-oxo-7,8-dihydro-6*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl)-4-methylbenzenesulfonamide (8), and Diaminated Product 9**. To a stirred solution of **3** (332 mg, 1.0 mmol) in THF (10 mL) was added chloramine T trihydrate (844 mg, 3.0 mmol) at room temperature. After 4 h, the reaction was quenched by the addition of aqueous sodium carbonate (30 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered off, and evaporated to yield a yellow crude product. Chromatography (silica gel, EtOAc/isohexane, 1:1) gave the diaminated product **9** (369 mg, 55%), alkenylsulfonamide **8** (75 mg, 15%), and sulfonamide **7** (50 mg, 10%) as colorless solids. Mp: >190 °C decomposition (**7**), >240 °C decomposition (**8**), >130 °C decomposition (**9**). R_f (silica gel, EtOAc): 0.77 (**9**), 0.58 (**8**), 0.63 (**7**). Data for **7** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.85−1.96 (m, 1H), 2.14−2.22 (m, 1H), 2.37 (s, 3H), 3.70 (m, 1H), 3.93−4.00 (m, 1H), 4.84−4.90 (m, 1H), 6.60 (s, 1H), 7.12 (s, 1H), 7.41 (d, 2H, ^3J = 8.0 Hz), 7.75 (d, 2H, ^3J = 8.0 Hz), 8.51 (d, 1H, ^3J = 8.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.8, 29.9, 44.1, 53.7, 101.3, 101.4, 102.8, 110.3, 124.6, 126.2 (2C), 129.7 (2C), 132.2, 138.3, 143.0, 151.6. MS (ESI+, FT): *m*/*z* (%) 499.9/501.9/503.9 (51.5/100/43.9) [M + H^+]. IR (KBr): $\tilde{\nu}$ 3436, 2923, 2854, 1634, 1435, 1409, 1392, 1339, 1159, 1090, 812, 739, 667, 546. UV ($CHCl_3$): λ_{max} (log ϵ) 285 (3.78). HRMS (ESI) calcd for $C_{17}H_{15}{}^{79}Br^{81}BrN_3O_3S$ + H: 501.9259. Found: 501.9256. Data for **8** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.33−1.58 (m, 1H), 1.65−1.79 (m, 2H), 2.30−2.40 (m, 1H), 2.41 (s, 3H), 3.78−3.82 (m, 2H), 7.19 (s, 1H), 7.42 (d, 2H, ^3J = 8.3 Hz), 7.65 (d, 2H, ^3J = 8.3 Hz), 10.2 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.9, 21.6, 27.5, 47.2, 100.5, 105.3, 108.5, 111.5, 126.3, 126.8 (2C), 129.8 (2C), 132.3, 137.7, 143.6, 151.3. MS (EI, 70 eV): *m*/*z* (%) 498.9/500.9/502.9 (0.97/2.32/1.08) [M^+], 343.9/345.9/347.9 (51.1/88.2/45.3), 249.9/251.9/253.9 (21.2/39.8/20.8), 91.1 (100). IR (ATR): $\tilde{\nu}$ 3030, 3000, 2957, 2871, 1615, 1430, 1376, 1324, 1156, 1074, 804, 668. UV (DMSO): λ_{max} (log ϵ) 293 (3.95). HRMS (EI) calcd for $C_{17}H_{15}{}^{79}Br^{81}BrN_3O_3S$ + H^+: 501.9259. Found: 501.9256. Data for **9** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.30−1.42 (m, 1H), 1.70−1.72 (m, 1H), 1.90−1.97 (m, 1H), 2.00−2.08 (m, 1H), 2.37 (s, 6H), 3.23−3.32 (m, 1H), 3.44−3.52 (m, 1H), 6.30 (d, 1H, ^3J = 9.5 Hz), 6.75 (s, 1H), 7.31−7.35 (m, 4H), 7.54−7.57 (m, 4H), 8.57 (s, 1H), 9.29 (d, 1H, ^3J = 9.5 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.8, 20.8, 20.9, 33.1, 44.3, 66.6, 80.4, 100.5, 107.4, 114.4, 125.1, 125.7 (2C), 126.0 (2C), 129.2 (2C), 129.3 (2C), 138.5, 139.4, 142.6, 142.8, 153.9. MS (ESI+, FT): *m*/*z* (%) 668.9/670.9/672.9 (66.9/100/53.0) [M + H^+]. IR (KBr): $\tilde{\nu}$ 3434, 3219, 1648, 1432, 1408, 1340, 1326, 1159, 1089, 812, 668, 555. UV (DMSO): λ_{max} (log ϵ) 287 (3.96). HRMS (ESI−) calcd for $C_{24}H_{23}Br_2N_4O_5S_2$ − H: 668.9477. Found: 668.9441.

***spiro*-Tetracycle 12 and 1-(2,3-Dibromo-10-oxo-7,8-dihydro-6*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl)-2-(2,6-dimethylphenyl)-3-cyanoisourea (13).** To a stirred solution of **3** (332 mg, 1.0 mmol) in 1,4-dioxane (10.0 mL) was added **11** (215 mg, 1.0 mmol)[19] at room temperature. The reaction mixture was refluxed for 12 h. The solvent was evaporated to yield a brown precipitate, which was purified by column chromatography (silica gel, EtOAc/isohexane, 8:2). *spiro*-Tetracycle **12** (286 mg, 55%) and alkenylisourea **13** (78 mg, 15%) were obtained as colorless solids. Mp: >199 °C decomposition (**12**), >186 °C decomposition (**13**). R_f (silica gel, EtOAc): 0.23 (**12**), 0.40 (**13**). Data for **12** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.14 (s, 6H), 2.56−2.76 (m, 2H), 3.83−4.00 (m, 2H), 5.13−5.14 (m, 1H), 6.98 (s, 1H), 7.00−7.07 (m, 3H), 8.67 (br s, 1H), 9.03 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 16.0, 27.1, 44.3, 84.0, 103.0, 106.1, 108.1, 113.7, 125.4, 126.4, 128.4 (2C), 129.4 (2C), 138.9, 149.9, 151.5, 175.1, 183.2. MS (EI, 70 eV): *m*/*z* (%) 516.9/518.9/520.9 (45.0/90.8/44.1) [M^+], 438.0/440.0 (88.8/89.0), 439.0/ 441.0 (39.9/24.0), 369.9/371.9/373.9 (16.8/30.0/13.0), 307.0/309.0 (36.9/36.9), 268.1 (82.6), 175.0 (100). IR (KBr): $\tilde{\nu}$ 3434, 3064, 2925, 1640, 1556, 1474, 1436,1414, 1376, 1329, 1302. UV (DMSO): λ_{max} (log ϵ) 236 (3.32), 249 (2.92). HRMS (EI) calcd for $C_{20}H_{17}Br_2N_5O_2$: 516.9749. Found: 516.9759. Data for *E*-/*Z*-isomers of **13** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.95−2.08 (br s, 3H), 2.13−2.20 (m, 2H), 2.24 (s, 3H), 2.89−3.08 (m, 2H), 3.91−4.07 (m, 2H), 7.09−7.18 (m, 3H), 7.25/7.27 (s, 1H), 11.0/11.4 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 15.9 (br), 21.3/21.6, 27.7/28.0, 47.6/47.7, 98.6/99.1, 105.2/105.3, 106.8/107.8, 111.1/113.1, 111.9/112.0, 126.1/126.3, 126.5/126.5, 128.8/128.8 (2C), 129.4/129.7 (2C), 131.4/132.7, 147.9/148.1, 151.4/151.6, 159.6/161.1. MS (EI, 70 eV): 516/518/520 (2.88/7.04/5.02) [M^+], 438/440 (20.3/25.4), 329/331/333 (15.2/27.5/20.9), 330/332/334 (55.9/100/55.9). IR (KBr): $\tilde{\nu}$ 3468, 3126, 2956, 2923, 2198, 1692, 1621, 1586, 1474, 1406, 1379, 1327, 1272, 1243. UV ($CHCl_3$): λ_{max} (log ϵ) 243 (3.52), 286 (2.94). HRMS (EI) calcd for $C_{20}H_{17}Br_2N_5O_2$: 516.9749. Found: 516.9767.

***N*-[1-(2,3-Dibromo-10-oxo-7,8-dihydro-6*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-ylamino)-1-(2,6-dimethylphenoxy)methylidene]-methanesulfonamide (15) and *spiro*-Cycle 16.** Compound **3** (332 mg, 1.0 mmol) was suspended in dioxane (5 mL) and heated to 60 °C until the solution became clear. A solution of azide **14** (289 mg, 1.08 mmol)[19] in dioxane (2 mL) was added. After refluxing for 8 h, the reaction mixture was cooled to room temperature and poured into brine (10 mL). The resulting solution was extracted with DCM (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography on silica gel, $CHCl_3$/MeOH, (40:1). **15** (140 mg, 35%) and **16** (50 mg, 10%) were obtained as yellowish solids. Mp: 210 °C (**15**), 130 °C (**16**). R_f ($CHCl_3$/MeOH (9.75:0.25)): 0.43 (**15**), 0.82 (**16**). Data for **15** follow. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.06 (br s, 6H,), 2.25 (qi, 2H, ^3J = 7.3 Hz), 2.97 (s, 3H), 3.12 (dddd, 1H, ^2J = 9.9 Hz, ^3J = 8.1, 7.3 Hz, ^5J = 1.5 Hz), 3.16 (dddd, 1H, ^2J = 9.9 Hz, ^3J = 8.1, 7.3 Hz, ^5J = 1.1 Hz), 4.12 (t, ^3J = 8.1 Hz, 2H), 7.00−7.07 (m, 3H), 7.28 (s, 1H), 8.96 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.7, 22.2, 28.8, 43.1, 47.8, 99.2, 106.5, 107.7, 113.5, 126.6, 126.7, 128.9 (2C), 130.1 (2C), 131.5, 148.0, 152.4, 155.5. MS (EI, 70 eV): *m*/*z* (%) 570/572/574 (11.4/22.5/9.5) [M^+], 491/493 (7.1/11), 369/371/373 (63.2/100/49.4), 370/372/374 (13.7/21.3/7.3). IR (KBr): $\tilde{\nu}$ 3436, 3260, 3120, 2926, 1692, 1654, 1618, 1587, 1476, 1369, 1328, 1283, 1165, 1133, 1091, 970, 900, 792, 770, 738, 623, 605, 562, 527. UV ($CHCl_3$): λ_{max} (log ϵ) 242 (1.45), 287 (0.86). HRMS (EI) calcd for $C_{20}H_{20}Br_2N_4O_4S$: 569.9572. Found: 569.9575. Data for **16** follow. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.87 (br s, 6H), 2.25−2.33 (m, 1H), 2.27 (s, 3H), 2.37 (s, 3H), 2.39−2.48 (m, 1H), 2.71 (s, 3H), 2.82−2.87 (m, 1H), 2.94−3.05 (m, 1H), 3.29 (s, 3H), 3.94−4.01 (m, 1H), 4.11−4.15 (m, 1H), 6.74 (d, 1H, ^4J = 2.5 Hz), 6.89−6.96 (m, 3H), 7.09−7.18 (m, 3H), 9.51 (d, 1H, ^4J = 2.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.9, 16.1, 16.4, 23.6, 36.3, 41.9, 43.1, 49.8, 89.6, 100.6, 106.8, 116.4, 125.6, 125.8, 127.2, 128.3 (2C), 128.9, 129.0, 129.6, 129.9, 130.5 (2C), 148.7, 149.9, 158.4, 165.9, 170.9 175.6. MS (EI, 70 eV): *m*/*z* (%) 810/812/814 (0.27/0.53/0.34) [M^+], 811/813/815 (0.06/0.14/0.0.07), 731/733/735 (0.22/0.34/0.12), 732/734 (0.13/0.21), 689/691/693 (2.16/4.17/2.68), 367/369/370 (31.3/44.6/18.1), 368/370 (10.2/12.9), 121/122/123 (41.4/100/8.5), 107 (40.6), 77 (30.3). IR (KBr): $\tilde{\nu}$ 3405, 3189, 3144, 3007, 2958, 2926, 2888, 1710, 1622, 1598, 1581, 1528, 1475, 1417, 1367, 1305, 1274, 1238, 1171, 1144, 1096, 1057, 968, 808, 780, 764, 616, 564, 540, 528, 502. UV ($CHCl_3$): λ_{max} (log ϵ) 283 (0.85). HRMS (EI) calcd for $C_{30}H_{32}Br_2N_6O_7S_2$: 810.0141. Found: 810.0141.

(2,3-Dibromo-10-oxo-7,8-dihydro-6*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl)carbamic Acid Ethyl Ester (19), *rac*-*N*-Ethoxy-

carbonyl-*N*′tosyloxydibromophakellstatin (18), and (2,3-Dibromo-5-ethoxycarbonylamino-10-oxo-7,8-dihydro-5*H*,10*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-yl)carbamic Acid Ethyl Ester (20). CaO (1.06 g, 19.0 mmol) was added to a solution of pyrazinone **3** (0.9 g, 2.7 mmol) and urethane **17** (4.90 g, 19.0 mmol)[20] in DCM (250 mL) under an argon atmosphere. Within 15 min, the suspension became orange. After stirring at room temperature for 24 h, the reaction mixture was filtered off and the precipitate was washed with DCM. The combined organic layers were evaporated to a yield a yellow solid. Chromatography (silica gel, EtOAc/isohexane, 7:3) gave tetracycle **18** (427 mg, 25%), carbamate **19** (226 mg, 20%), and orthoamidine **20** (68 mg, 5%) as colorless solids. Mp: 193 °C (**18**), 187 °C (**19**), 196 °C (**20**). R_f (silica gel, EtOAc): 0.49 (**18**), 0.38 (**19**), 0.33 (**20**). Data for **18** follow. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (t, 3H, ^3J = 7.2 Hz), 2.09 (ddd, 1H, ^2J = 12.4 Hz, ^3J = 8.0, 4.0 Hz), 2.24−2.39 (m, 2H), 2.42 (s, 3H), 2.43−2.50 (m, 1H), 3.70−3.78 (m, 1H), 3.87 (ddd, 1H, ^2J = 12.0 Hz, ^3J = 8.0, 4.0 Hz), 4.36 (qd, 1H, ^2J = 10.6 Hz, ^3J = 7.2 Hz), 4.43 (qd, 1H, ^2J = 10.6 Hz, ^3J = 7.2 Hz), 6.27 (s, 1H), 7.12 (s, 1H), 7.22 (d, 2H, ^3J = 8.2 Hz), 7.57 (d, 2H, ^3J = 8.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 20.8, 21.8, 34.1, 46.1, 65.1, 68.3, 86.0, 104.4, 105.6, 117.0, 126.7, 129.3 (2C), 129.9 (2C), 146.9, 149.9, 150.4, 153.9. MS (FAB, NBA): *m*/*z* (%) 631/633/635 (30/60/30) [M + H$^+$]. IR (KBr): $\tilde{\nu}$ 3436, 2983, 1803, 1743, 1670, 1552, 1388, 1273, 1015, 722, 545. UV (CH_3OH): λ_{max} (log ϵ) 289 (3.92), 231 (4.27). HRMS (FAB) calcd for $C_{21}H_{20}Br_2N_4O_7S$ + H: 629.9420. Found: 629.9429. Data for **19** follow. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (t, 3H, ^3J = 7.2 Hz), 2.19 (qi, 2H, ^3J = 7.3 Hz), 2.97 (t, 2H, ^3J = 7.3 Hz), 4.08 (t, 2H, ^3J = 7.3 Hz), 4.28 (q, 2H, ^3J = 7.2 Hz), 6.29 (s, 1H), 7.23 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.6, 21.9, 28.3, 47.8, 62.5, 106.1, 109.0, 111.2, 113.0, 117.1, 126.6, 152.7, 154.4. MS (EI, 70 eV): *m*/*z* (%) 417/419/421 (45/85/42) [M$^+$], 344/346/348 (30/59/30), 339/341 (27/24), 338/340 (48/49), 250/252/254 (33/60/31), 106 (30), 95 (100), 83 (44), 41 (26). IR (KBr): $\tilde{\nu}$ 3411, 3264, 2981, 1737, 1622, 1525, 1414, 1382, 1330, 1236, 1067, 738. UV (CH_3CN): λ_{max} (log ϵ) 283 (3.66), 236 (4.11). HRMS (EI) calcd for $C_{13}H_{13}Br_2N_3O_3$: 416.9324. Found: 416.9298. Data for **20** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.00−1.20 (m, 6H), 2.61−2.66 (m, 2H), 3.90−3.94 (m, 6H), 5.41 (t, 1H, ^3J = 2.8 Hz), 6.80 (s, 1H), 8.64 (br s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 14.0, 26.8, 44.4, 60.8, 75.9, 102.6, 102.7, 108.4, 111.7, 128.9, 142.5, 150.8, 152.4. MS (FAB, NBA): *m*/*z* (%) 505.3/507.3/509.3 (6.52/8.67/4.32) [M + H$^+$]. IR (KBr): $\tilde{\nu}$ 3422, 3286, 2981, 1742, 1629, 1561, 1481, 1377, 1252. UV (DMSO): λ_{max} (log ϵ) 266 (4.08), 231 (4.08), 300 (4.05). HRMS (FAB) calcd for $C_{16}H_{18}Br_2N_4O_5$ + H: 504.9692. Found: 504.9722.

***rac*-*N*-Ethoxycarbonyldibromophakellstatin (21).** To a solution of **18** (63 mg, 0.1 mmol) in dry THF (10 mL) was added SmI_2 (2.5 mL, 0.1 M solution in THF) at room temperature under an argon atmosphere. The reaction mixture was stirred for 10 min and then quenched with MeOH (1.0 mL). The reaction mixture was evaporated to dryness, and the crude product was purified by flash chromatography (silica gel, $CHCl_3$/MeOH, 9:1), yielding *rac*-*N*-ethoxycarbonyldibromophakellstatin (**21**, 46 mg, 99%) as a colorless solid. Mp: 201 °C. R_f (silica gel, $CHCl_3$/MeOH, 9:1): 0.36. Data for **21** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.28 (t, 3H, ^3J = 7.2 Hz), 1.97−2.05 (m, 2H), 2.19−2.24 (m, 1H), 2.26−2.35 (m, 1H), 3.37−3.44 (m, 1H), 3.58−3.63 (m, 1H), 4.23−4.33 (m, 2H), 6.69 (d, 1H, ^4J = 0.7 Hz), 7.00 (s, 1H), 9.06 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.9, 18.9, 37.7, 44.8, 62.7, 71.3, 77.5, 102.7, 105.6, 114.6, 126.4, 150.1, 150.8, 153.4. MS (EI, 70 eV): *m*/*z* (%) 464/462/460 (10.9/22.3/10.2) [M$^+$], 421/419/417 (27.3/58.4/29.6), 375/373/371 (11.4/19.2/9.85), 95.1 (100). IR (KBr): $\tilde{\nu}$ 3430, 3195, 3133, 2991, 1767, 1727, 1637, 1556, 1408, 1303, 1124, 1016, 738. UV (DMSO): λ_{max} (log ϵ) 283 (6.90). HRMS (EI) calcd for $C_{14}H_{14}Br_2N_4O_4$: 459.9382. Found: 459.9370.

***rac*-Dibromophakellstatin (*rac*-1).** To a solution of **18** (380 mg, 0.60 mmol) in dry THF (60 mL) was added SmI_2 (30 mL, 0.1 M in THF) at room temperature under an argon atmosphere. The reaction mixture was stirred for 36 h and then quenched with MeOH (5.0 mL). After an additional 4 h, the reaction mixture was evaporated to dryness. Purification by flash chromatography (silica gel, $CHCl_3$/MeOH, 9:1) afforded *rac*-dibromophakellstatin (*rac*-**1**, 179 mg, 76%) as a colorless solid. R_f (silica gel, $CHCl_3$/MeOH, 9:1): 0.28. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.93−2.01 (m, 1H), 2.07−2.14 (m, 2H), 2.26−2.33 (m, 1H), 3.39−3.46 (m, 1H), 3.53−3.58 (m, 1H), 5.99 (d, 1H, ^3J = 2.2 Hz), 6.91 (s, 1H), 7.98 (br s, 1H), 8.28 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 18.7, 38.7, 44.0, 68.5, 78.9, 101.0, 105.4, 113.7, 125.3, 153.9, 157.7. MS (EI, 70 eV): *m*/*z* (%) 388/390/392 (10.9/22.5/10.0) [M$^+$], 317/319/321 (2.25/6.07/2.69), 250/252/254 (4.02/7.36/4.30), 139 (100). HRMS (EI) calcd for $C_{11}H_{10}Br_2N_4O_2$: 387.9170. Found: 387.9154.

***rac*-Monobromophakellstatin (22).** To a solution of **18** (63 mg, 0.1 mmol) in THF (10 mL) was added SmI_2 (7.5 mL, 0.1 M in THF) at room temperature under an argon atmosphere. The reaction mixture was stirred for 36 h and then quenched with MeOH (1.0 mL). After an additional 4 h, the reaction mixture was evaporated to dryness. Purification by flash chromatography (silica gel, $CHCl_3$/MeOH, 9:1) yielded monobromophakellstatin (**22**, 18 mg, 60%) as a colorless solid. Mp: 185 °C. R_f (silica gel, $CHCl_3$/MeOH, 9:1): 0.22. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.93−2.01 (m, 1H), 2.07−2.14 (m, 2H), 2.26−2.33 (m, 1H), 3.39−3.46 (m, 1H), 3.53−3.58 (m, 1H), 5.77 (br s, 1H), 6.71 (d, 1H, ^4J = 1.8 Hz), 7.24 (d, 1H, ^4J = 1.8 Hz), 7.88 (br s, 1H), 8.08 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 19.1, 38.4, 44.4, 67.9, 78.4, 97.1, 112.4, 121.1, 124.0, 154.3, 158.3. MS (EI, 70 eV): *m*/*z* (%) 310/312 (62.9/60.5) [M$^+$], 282/284 (5.64/5.17), 293/241 (9.69/9.68), 172/174 (21.7/21.0), 139 (100). IR (KBr): $\tilde{\nu}$ 3422, 3255, 2926, 1724, 1627, 1551, 1481, 1438, 1188, 926. UV (DMSO): λ_{max} (log ϵ) 275 (7.26). HRMS (EI) calcd for $C_{11}H_{11}BrN_4O_2$: 310.0065. Found: 310.0072.

6,7-Dibromo-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (30). *rac*-Longamide A (**29**, 7.10 g, 22.9 mmol)[27] was suspended in dry DCM (190 mL) and treated with *p*-TsCl (8.80 g, 46.2 mmol) at room temperature. Triethylamine (15.6 mL, 112 mmol) was added via a dropping funnel within 30 min at 0 °C. After 24 h at room temperature, the solvent was evaporated. Purification by column chromatography (silica gel, $CHCl_3$/MeOH, 20:1) yielded **30** as colorless crystals (3.54 g, 53%). Mp: 140−142 °C. R_f (silica gel, $CHCl_3$/MeOH, 10:1): 0.43. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.78 (dd, 1H, ^3J = 5.7, 5.7 Hz), 7.15 (s, 1H), 7.16 (d, 1H, ^3J = 5.6 Hz), 10.88 (br s, 1H). ^{13}C NMR (DMSO-d_6, 63 MHz): δ 101.6, 102.8, 105.6, 111.0, 116.5, 125.6, 154.1. MS (EI, 70 eV): *m*/*z* (%) 290.0/292.0/294.0 (51.9/100.0/49.3) [M$^+$], 235.0/237.0/239.0 (5.31/10.0/5.22). IR (KBr): $\tilde{\nu}$ 3116, 3048, 2956, 2908, 1656, 1441, 1416, 1376, 1356, 1285, 1202, 1130, 973, 903, 806, 719. UV ($CHCl_3$): λ_{max} (log ϵ) 204 (3.82), 234 (4.35), 278 (3.95). HRMS (EI) calcd for $C_7H_4{}^{79}Br^{81}BrN_2O$: 291.8670. Found: 291.8669.

6,7-Dibromo-2-methyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (31). To a stirred suspension of **30** (1.50 g, 5.14 mmol) in DMF (15.0 mL) was added NaH (250 mg, 10.3 mmol, 60% in mineral oil) at 0 °C under an argon atmosphere. After 30 min, MeI (650 μL, 10.3 mmol) was added via cannula. The reaction mixture was stirred for an additional 40 h at room temperature. It was quenched by the addition of water (50 mL). The suspension was extracted with DCM (3 × 150 mL), and the combined organic layers were evaporated to dryness. The crude product was suspended in water (10 mL). Filtration gave **31** (1.10 g, 73%) as a colorless solid. Mp: 145−146 °C. R_f (silica gel, $CHCl_3$/MeOH (10:1)): 0.78. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.33 (s, 3H), 7.03 (d, 1H, ^3J = 5.9 Hz), 7.15 (d, 1H, ^5J = 0.7 Hz), 7.27 (dd, 1H, ^3J = 5.9 Hz, ^5J = 0.7 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 34.5, 100.9, 102.9, 105.4, 110.6, 121.0, 124.9, 153.4. MS (EI, 70 eV): *m*/*z* (%) 304.1/306.1/308.0 (48.9/100/45.0) [M$^+$], 225.1/227.1 (26.4/25.7). IR (KBr): $\tilde{\nu}$ 3118, 1709, 1665, 1448, 1406, 1381, 1364, 1245, 1077, 730. UV (DMSO): λ_{max} (log ϵ) 285 (3.89). HRMS (EI) calcd for $C_8H_6Br_2N_2O$: 303.8847. Found: 303.8841.

***Syn*-AB-Adduct (33) and *anti*-AB-Adduct (32).** To a stirred solution of **31** (800 mg, 2.62 mmol) in DCM (43 mL) was added

$EtO_2CNHOTs$ (**17**, 4.67 g, 18.3 mmol) at room temperature. After 20 min, CaO (1.03 g, 18.3 mmol) was added and the suspension was stirred for an additional 24 h. Filtration and evaporation of the mixture yielded a pale yellow crude product, which was purified by column chromatography (silica gel, EtOAc/isohexane, 1:1). Products **32** (752 mg, 44%) and **33** (188 mg, 11%) were obtained as colorless foams. Mp: 156−158 °C (**32**), 159−161 °C (**33**). R_f (silica gel, DCM/EtOAc, 9:1): 0.45 (**33**), 0.15 (**32**). Data for **32** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.95 (t, 3H, ^3J = 7.0 Hz), 1.18 (t, 3H, ^3J = 7.0 Hz), 2.42 (s, 3H), 2.93 (s, 3H), 3.89−4.15 (m, 4H), 5.81 (s, 1H), 6.05 (br s, 1H), 6.90 (s, 1H), 7.47 (d, 2H, ^3J = 8.5 Hz), 7.65 (d, 2H, ^3J = 8.5 Hz), 8.75 (br d, 1H, ^3J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.3, 14.2, 21.1, 32.2, 60.6, 61.6, 64.3, 77.9, 100.8, 105.4, 114.3, 125.3, 127.8, 128.8 (2C), 129.9 (2C), 146.5, 154.4, 155.3, 155.8. MS (ESI+, FT): *m*/*z* (%) 651/653/655 (50.0/100/47.3) [M^+]. IR (KBr): $\tilde{\nu}$ 3192, 2983, 1732, 1704, 1651, 1521, 1435, 1394, 1370, 1313, 1237, 1194, 1048, 660. UV (DMSO): λ_{max} (log ϵ) 278 (4.01). HRMS (ESI+) calcd for $C_{21}H_{24}Br_2N_4O_8S$ + H: 652.9741. Found: 652.9736. Data for **33** follow. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.91 (t, 3H, ^3J = 7.1 Hz), 1.19 (t, 3H, ^3J = 7.1 Hz), 2.43 (s, 3H), 2.96 (s, 3H), 3.81 (q, 2H, ^3J = 7.1 Hz), 4.11 (q, 2H, ^3J = 7.1 Hz), 5.91 (d, 1H, ^3J = 5.8 Hz), 6.51 (dd, 1H, ^3J = 10.1, 5.8 Hz), 6.89 (s, 1H), 7.49 (d, 2H, ^3J = 8.4 Hz), 7.77 (d, 2H, ^3J = 8.4 Hz), 7.83 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.3, 14.2, 21.1, 30.5, 58.5, 60.8, 62.1, 102.3, 105.4, 112.7, 123.7, 127.8, 125.3 (2C), 127.8 (2C), 146.4, 154.4, 154.6, 154.9. MS (ESI+, FT): *m*/*z* (%) 651/653/655 (52.0/100/49) [M + H^+]. IR (KBr): $\tilde{\nu}$ 3233, 2980, 1723, 1650, 1593, 1530, 1422, 1435, 1387, 1371, 1296, 1193, 1180, 1053, 812, 724, 652. UV (DMSO): λ_{max} (log ϵ) = 282 (3.71). HRMS (ESI+) calcd for $C_{21}H_{24}Br_2N_4O_8S$ + H: 652.9741. Found: 652.9738.

(6,7-Dibromo-4-ethoxycarbonylamino-2-methyl-1-oxo-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3-yl)-carbamic Acid Ethyl Ester (34). To a stirred solution of the 1:4 mixture of **32** and **33** (100 mg, 0.15 mmol) in pyridine (2 mL) was added DMAP (18.3 mg, 0.15 mmol) at room temperature. After 16 h, the mixture was diluted with 2 N HCl and then extracted with DCM (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and filtered off. The solvent was evaporated under reduced pressure, and a brown precipitate was obtained as crude product. Chromatography (silica gel, EtOAc/isohexane, 1:1) gave **34** (58 mg, 80%) as a colorless solid. Mp: 190−193 °C. R_f (silica gel, EtOAc): 0.80. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24−1.38 (m, 6H), 3.41 (s, 3H), 4.17−4.27 (m, 4H), 6.71 (br s, 1H), 6.87 (br s, 1H), 7.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.4, 14.1, 28.3, 58.3, 59.1, 92.1, 101.2, 103.1, 108.3, 114.3, 127.9, 152.3, 153.1, 158.2. MS (ESI+, FT): *m*/*z* (%) 478.9/480.9/482.9 (55.4/100/45.5) [M + H^+]. IR (KBr): $\tilde{\nu}$ 3233, 2980, 1723, 1650, 1593, 1530, 1422, 1435, 1387, 1371, 1296, 1193, 1180, 1053, 812, 724, 652. UV ($CHCl_3$): λ_{max} (log ϵ) 251 (4.13). HRMS (ESI+) calcd for $C_{14}H_{16}Br_2N_4O_5$ + H: 478.9566. Found: 478.9557.

10-Hydroxy-2,3,10,10a-tetrahydro-1*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-one (35). To a stirred solution of **2** (4.0 g, 11.4 mmol)[33] in DCM/MeOH (200 mL, 1:1) was added NEt_3 (3.2 mL, 22.8 mmol) and 10% Pd/C (600 mg, 0.57 mmol, 5 mol %) at room temperature. The mixture was kept under hydrogen until the reaction was complete (ca. 6 h). Brine (150 mL) was added, followed by extraction with DCM (3 × 300 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. Recrystallization of the crude product from MeOH yielded **35** (2.15 g, 98%) as colorless crystals. Mp: 180−181 °C. R_f (silica gel, EtOAc): 0.25. $[\alpha]_D^{23}$ = +116° (*c* = 10.0 mg/mL, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.76−2.26 (m, 4H), 3.30−3.44 (m, 1H), 3.50−3.58 (m, 1H), 3.98 (m, 1H), 5.56 (dd, 1H, ^3J = 7.0, 2.8 Hz), 6.13−6.15 (m, 1H), 6.58−6.60 (m, 1H), 6.64 (d, 1H, ^3J = 7.0), 7.01−7.05 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 22.6, 26.7, 43.8, 60.4, 75.4, 109.1, 110.9, 122.7, 124.1, 156.5. MS (EI, 70 eV): *m*/*z* (%) 192.0 (56) [M^+], 95 (14), 94 (47), 70 (100). IR (KBr): $\tilde{\nu}$ 3125, 2967, 2887, 1610, 1547, 1446, 1368, 1329, 1269, 1220, 1155, 1112, 1061, 1026, 963, 744, 653. UV (CF_3CH_2OH): λ_{max} (log ϵ) 198 (3.90), 230 (3.92), 278 (3.98). HRMS (EI) calcd for $C_{10}H_{12}N_2O_2$ 192.0899. Found: 192.0904.

2,3-Dihydro-1*H*-dipyrrolo[1,2-*a*;1′,2′-*d*]pyrazin-5-one (36). To a stirred suspension of the *N*,*O*-acetal **35** (750 mg, 3.9 mmol) in dry DCM was added MsCl (604 μL, 7.8 mmol) at 0 °C. DBU (2.32 mL, 15.6 mmol) was added within 30 min, and the solution was allowed to warm to room temperature. After 24 h, 2 N HCl (50 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (3 × 100 mL) and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent gave a brown crude product, which was purified by column chromatography (silica gel, EtOAc) to yield dipyrrolopyrazinone **36** (407 mg, 60%)[8] as colorless crystals. Mp: 143 °C. R_f (silica gel, EtOAc): 0.34. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.16 (q, 2H, ^3J = 7.3 Hz), 2.93 (dt, 2H, ^3J = 7.3 Hz, ^4J = 1.4 Hz), 4.02 (t, 2H, ^3J = 7.1 Hz), 6.50−6.52 (m, 1H), 6.91 (br s, 1H), 7.03−7.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.8, 28.2, 46.3, 102.6, 108.8, 112.0, 117.7, 123.9, 129.8, 155.2. MS (EI, 70 eV): *m*/*z* (%) 174/175 (100/14) [M^+], 145 (7), 118 (12). IR (KBr): $\tilde{\nu}$ 3432, 3013, 2971, 1691, 1630, 1372, 1284, 1183, 1022, 876, 729, 595. UV (CF_3CH_2OH): λ_{max} (log ϵ) 200 (4.76), 228 (4.64), 284 (3.94). EA calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.75; H, 5.77; N, 15.99.

***rac*-*N*-Ethoxycarbonyl-*N*′-tosyloxyphakellstatin (37).** CaO (1.68 g, 30 mmol) was added to a solution of pyrazinone **36** (870 mg, 5.0 mmol) and $EtO_2CNHOTs$ (**17**, 7.77 g, 30.0 mmol)[20] in DCM (150 mL) at room temperature, followed by water (270 μL, 15.0 mmol). Within 15 min, the suspension became orange. After stirring at room temperature for 24 h, a saturated solution of $NaHCO_3$ (200 mL) was added. The separated aqueous layer was extracted with DCM (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to a yellow solid. The crude product was purified by column chromatography (silica gel, EtOAc/isohexane, 1:1) to give tetracycle **37** (1.42 g, 60%) as a light yellow solid. Mp: 197−199 °C. R_f (silica gel, EtOAc): 0.65. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39 (t, 3H, ^3J = 7.1 Hz), 2.04−2.14 (m, 1H), 2.27−2.37 (m, 2H), 2.41 (s, 3H), 2.48−2.54 (m, 1H), 3.66−3.73 (m, 1H), 3.78−3.84 (m, 1H), 4.36−4.47 (m, 2H), 6.08 (s, 1H), 6.32−6.34 (m, 1H), 6.84−6.85 (m, 1H), 7.02−7.04 (m, 1H), 7.21 (d, 2H, ^3J = 8.4 Hz), 7.58 (d, 2H, ^3J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 21.0, 21.9, 35.1, 45.7, 65.0, 67.0, 84.1, 112.0, 114.3, 122.4, 124.1, 129.3 (2C), 129.4, 129.9 (2C), 146.7, 149.6, 151.1, 155.7. MS (ESI+, FT): *m*/*z* (%) 576.2/577.2 (100/26.4) [M + TEA + H^+]. IR (KBr): $\tilde{\nu}$ 3123, 2985, 1785, 1720, 1600, 1553, 1338, 1275. UV (DMSO): λ_{max} (log ϵ) 229 (4.28), 276 (3.96). HRMS (ESI+) calcd for $C_{14}H_{16}Br_2N_4O_5$+$C_6H_{15}N$ + H: 576.2492. Found: 576.2472.

Conversion of 37 to 18. To a solution of **37** (475 mg, 1.0 mmol) in DCM (10 mL) was added NBS (365 mg, 2.05 mmol) at 0 °C. After 4 h, the reaction mixture was evaporated to dryness and the crude product was purified by column chromatography (silica gel, EtOAc/isohexane, 6:4). Tetracycle **18** (578 mg, 92%) was obtained as a colorless solid. For characterization data, see above.

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Supporting Information Available: Complete experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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