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Total synthesis of *ent*-(−)-azonazine using a biomimetic direct oxidative cyclization and structural reassignment of natural product

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ABSTRACT

A biomimetic approach has been investigated and developed for the total synthesis of azonazine, an unusual marine natural cyclopeptide containing a rigid transannular 10-membered ring. A hypervalent iodine-mediated direct oxidative cyclization was successfully developed and applied to construct the highly strained core, which was the key step in the first total synthesis of *ent*-(−)-azonazine. Based on the physical evidences of synthesized diastereomer and enantiomer of azonazine, both the relative and absolute configurations of the natural product were revised. Two fluorinated azonazine derivatives were also synthesized in short convenient steps utilizing the same intermediate in this work. The established total synthesis opens a potential opportunity to study the structure–activity relationship of natural azonazine.

1. Introduction

Fungi within the genus *Aspergillus* provides an abundant source of bioactive small molecules possessing diverse structures.[1] Azonazine (**1a**, Fig. 1) was recently reported as a novel hexacyclic dipeptide from *Aspergillus insulicola*, a Hawaiian marine sediment-derived fungus.[2] This compound was found to exhibit anti-inflammatory activity by inhibiting NF-κB luciferase (IC_{50} 8.37 μM) and nitrite production (IC_{50} 13.70 μM). The originally proposed structure of azonazine (**1a**) contains a benzofuranoindoline ring system bearing a quaternary center at C10 position, which presents similarity to the core of diazonamide A[3] (**2**, Fig. 1). However, a unique transannular 10-membered ring (**F**) connecting the tetracyclic moiety and the diketopiperazine unit (**E**) makes the skeleton of azonazine much more rigid than diazonamide A. It could be deduced that such tension would distorted the benzene ring of dihydrobenzofuran out of a planar structure. The unique challenging structure and interesting biological activity make azonazine an attractive target for total synthesis.[4–6] Bisai and co-workers recently developed a straightforward access to the core of azonazine (**1a**) by a Lewis acid catalyzed Friedel–Crafts reaction of electron rich aromatics with 3-alkyl-3-hydroxy-2-oxoindole.[5] Vincent and co-workers also reported a close method to construct the benzofuroindolines and chromenoindoline derivatives by $FeCl_3$-promoted regioselective hydroarylation of *N*-acetyl indoles with phenols, followed by an oxidation step.[6] Very recently, our group disclosed the first total synthesis of (−)-azonazine,[7] in which a hypervalent iodine-mediated biomimetic oxidative cyclization process was applied to construct the highly strained 10-membered ring. Both the relative and absolute structure of natural (+)-azonazine were reassigned by assistance of the synthetic compounds and their physical characterizations. Herein, we wish to detail our campaigns toward the original proposed structure (**1a**) as well as

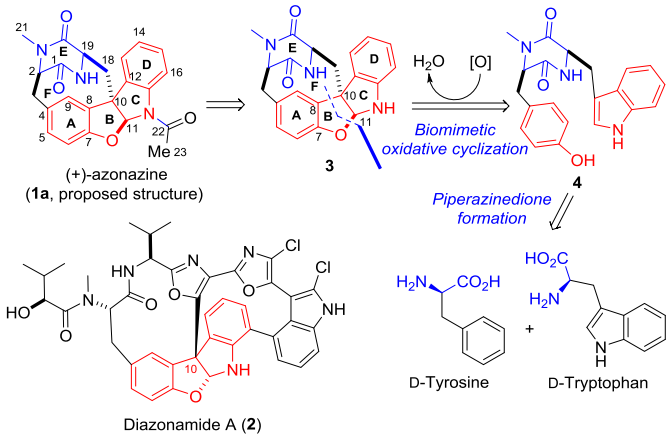

Fig. 1. Retrosynthetic analysis of the proposed azonazine (**1a**).

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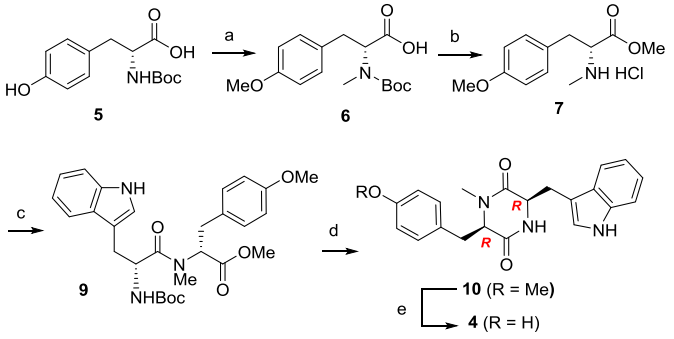
the structure revision, which finally led to first total synthesis of *ent*-(−)-azonazine.

2. Results and discussion

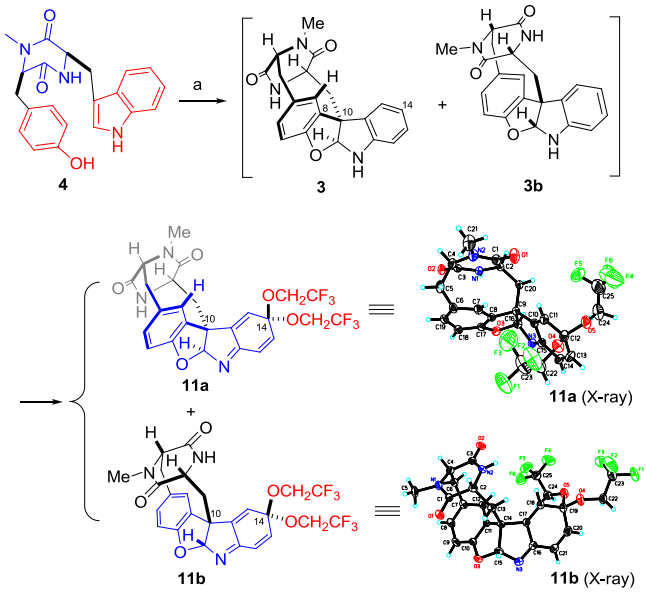
Construction of the benzofuranoindoline ring system (Fig. 1, A/B/C/D rings of azonazine **1a**) bearing a highly strained transannular 10-membered ring (F ring) is the most arduous task in the whole synthesis. In order to achieve a higher efficiency in our synthesis, an oxidative cyclization mimicking the biogenesis pathway[2,4b] was considered as a preferred method. According to our retrosynthesis (Fig. 1), the de-*N*-acetyl precursor indoline **3** could be prepared from the corresponding diketopiperazine **4**. The key C8–C10 bond were devised to form through a direct biomimetic oxidative cyclization of the indole and phenol functionalities. Diketopiperazine **4** could be conveniently prepared from commercially available D-Tyr and D-Trp derivatives.

D-Tyrosine derivative **5** and D-tryptophan derivative **8** were applied as the starting materials in our synthesis (Scheme 1). Double methylation of D-*N*-Boc-Tyr-OH (**5**) provided compound **6**,[8] which was then transformed to D-*N*-Me-Tyr(OMe)-OMe hydrochloride salt (**7**) by treatment with thionyl chloride in methanol. Coupling of D-*N*-Boc-Trp-OH (**8**) with **7** was carried out under BEP-mediated conditions,[9,10] providing the dipeptide **9**. Cyclization of **9** to diketopiperazine **10** was achieved by deprotection of *N*-Boc functionality with 3 M HCl in EtOAc and subsequent treatment with aqueous $NaHCO_3$. O-Demethylation of **10** was achieved by treatment with BBr_3 in dichloromethane, affording precursor **4** for examination of the key oxidative cyclization.



Scheme 1. Preparation of diketopiperazine **4**. Reagents and conditions: (a) MeI, NaH, THF, 0 °C to rt; (b) $SOCl_2$, MeOH, 0 °C, then reflux, 98% for two steps; (c) *N*-Boc-D-Trp-OH (**8**), BEP, DIEA, CH_2Cl_2, 0 °C to rt, 76%; (d) 3 M HCl in EtOAc, rt, then aqueous $NaHCO_3$; (e) BBr_3, CH_2Cl_2, 0 °C to rt, 90% for two steps. (BEP=2-bromo-1-ethyl pyridinium tetrafluoroborate.)

Oxidative construction of the benzofuranoindoline ring system of azonazine was then examined using diketopiperazine **4** as the substrate (Scheme 2). Among the available mild oxidants, hypervalent iodine reagents and their applications have attracted great attentions in organic synthesis in recent years. Various oxidative transformations mediated by hypervalent iodines have been successfully applied to the synthesis of complex organic molecules.[4b,11] Treatment of diketopiperazine **4** with 1 equiv of $PhI(OAc)_2$ in the presence of LiOAc in a cold trifluoroethanol solution was found to be workable. Two diastereomeric hexacyclic products **11a** and **11b**, whose structures were determined by NMR methods and confirmed by the X-ray single crystallographic analyses, were afforded in very low isolated yields (Scheme 2; and entry 1, Table 1). Several other hypervalent iodine (III) reagents were also examined in this study (Table 1). Unfortunately, all the attempts using PIFA or HTIB in either TFE or HFIP, or PIDA in HFIP gave undesirable results (entries 2–6). An iron(III) oxidant, $Fe(acac)_3$, was also examined in THF in



Scheme 2. Oxidative cyclization of diketopiperazine **4** with $PhI(OAc)_2$. Reagents and conditions: (a) $PhI(OAc)_2$ (1 equiv), LiOAc, TFE, −15 °C, 30 min, **11a** (<5% yield), **11b** (<5% yield).

Table 1
Optimization of oxidative cyclization of **4**[a]

	Conditions	Results or yield (%)		
		4	**11a**	**11b**
1	PIDA (1 equiv), LiOAc, TFE, −15 °C, 30 min	>30	<5	<5
2	PIFA (1 equiv), LiOAc, TFE, −15 °C, 30 min	Complicated		
3	HTIB (1 equiv), LiOAc, TFE, −15 °C, 30 min	Complicated		
4	PIDA (1 equiv), LiOAc, HFIP, −15 °C, 30 min	Complicated		
5	PIFA (1 equiv), LiOAc, HFIP, −15 °C, 30 min	Complicated		
6	HTIB (1 equiv), LiOAc, HFIP, −15 °C, 30 min	Complicated		
7	$Fe(acac)_3$ (2 equiv), *t*-BuOK, THF, −40 °C to rt	N.R.		
8	PIDA (2 equiv), LiOAc, TFE, −15 °C, 30 min	0	16	12
9	PIDA (2 equiv), LiOAc, TFE, −30 °C, 30 min	0	15	11

[a] PIDA: (diacetoxyiodo)benzene; PIFA: [bis(trifluoroacetoxy)iodo]-benzene; HTIB: [hydroxy(tosyloxy)iodo]benzene; TFE: 2,2,2-trifluoroethanol; HFIP: hexafluoroisopropanol.

the presence of *t*-BuOK, and no reaction was detected (entry 7). Final optimizations were achieved by increasing the amount of PIDA (up to 2 equiv) in TFE, affording the best results at −15 °C (entry 8). Further extending the reaction times or using more PIDA were not helpful to this reaction, giving more complicated situations.

The products **11a** and **11b** clearly mentioned that an over-oxidation happened at the C14 position. Though the detailed mechanism is unclear yet, intermediates **3** and **3b** (Scheme 2, a diastereomer of **3**) are possibly produced at the first stage of the oxidative cyclization (C, Fig. 2). Unfortunately, these two highly strained structures (**3** and **3b**) make a further $PhI(OAc)_2$-oxidation easily happen on the indoline nitrogen (D, Fig. 2). A subsequent TFE-addition takes place at the C14 position to release certain amount of molecular tension of the intermediates. As a net result, an *O*,*O*-di(trifluoroethoxy)-ketal was formed at the C14 position of **11a** and **11b** after these $PhI(OAc)_2$-mediated oxidations.

To avoid the above over-oxidation, modification of the functional group(s) on the indole moiety of diketopiperazine **4** was attempted. Four derivatives **12a**–**d** were thus designed and synthesized, either to change the electron density of the indole substructure (**12a**–**c**) or to block the C14 position where the previous over-oxidation took place (**12d**). N^{ind}-Ac diketopiperazine **12a** was

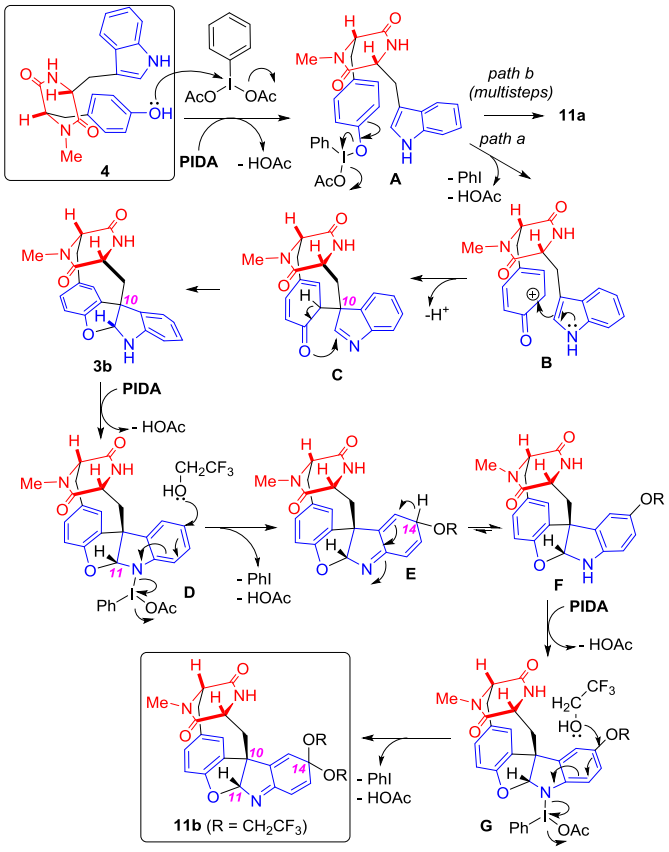
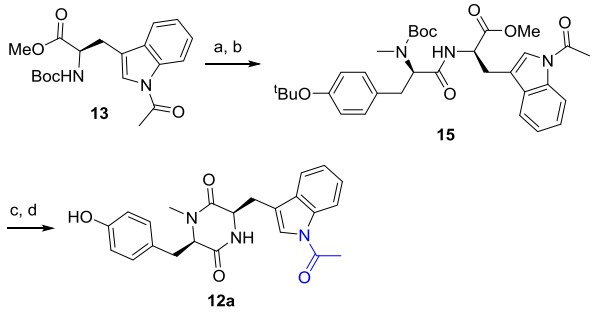


Fig. 2. A proposed mechanism for PIDA-oxidative generation of **11b**.

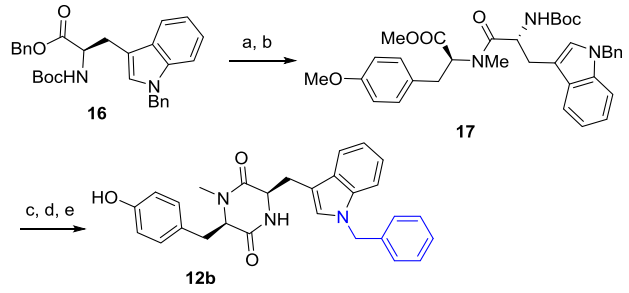
synthesized using N^{ind}-Ac-D-Trp derivative **13**[12] and *N*-Me-Boc-D-Try(^{t}Bu)-OH (**14**) as the starting materials. Compound **13** was deprotected and coupled with **14** to yield dipeptide **15**. Deprotection of the *N*-Boc functionality followed by ring-closing under microwave-assisted conditions[13] afforded **12a** in satisfactory yields (Scheme 3).



Scheme 3. Synthesis of diketopiperazine **12a**. Reagents and conditions: (a) 3 M HCl in EtOAc; (b) *N*-Me-Boc-D-Tyr(^{t}Bu)-OH (**14**), EDCI, HOBt, DIEA, CH_2Cl_2, 0 °C to rt, 76% for two steps; (c) 3 M HCl in EtOAc; (d) ^{n}BuOH/NMM/HOAc, MW, 100 °C, 83% for two steps.

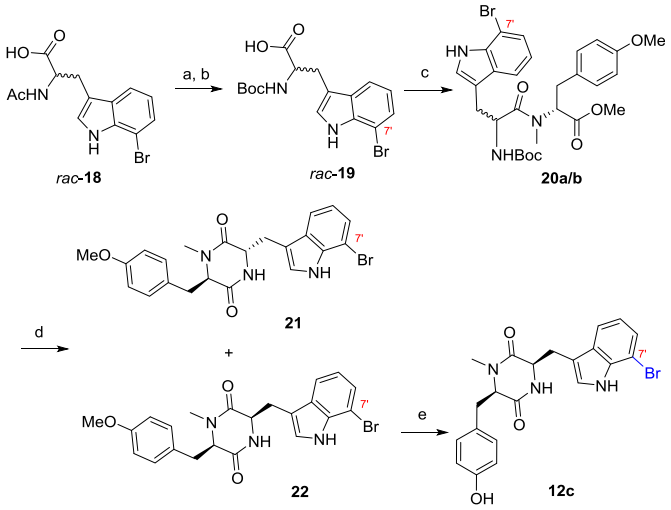
Accordingly, N^{ind}-Bn diketopiperazine **12b** was obtained using D-N^{ind}-Bn Trp derivative **16**[14] and D-Tyr derivative **7** as the starting materials. Hydrolysis of **16** followed by coupling with **7** gave dipeptide **17**, which was further transformed to **12b** by a sequence of deprotection, cyclization, and O-demethylation (Scheme 4).

A racemic material of *N*-Ac-(7′-Br-Trp)-OH (**18**)[15] was used as the starting material to synthesize 7′-Br substituted diketopiperazine **12c**. After amino-protecting group exchange, compound **18**



Scheme 4. Preparation of diketopiperazine **12b**. Reagents and conditions: (a) NaOH, H_2O/MeOH; (b) *N*-Me-D-Tyr(Me)-OMe HCl (**7**), BEP, DIEA, CH_2Cl_2, 0 °C to rt, 71% for two steps; (c) 3 M HCl in EtOAc; (d) $NaHCO_3$ (aqueous); (e) BBr_3, DCM, 0 °C to rt, 79% for three steps.

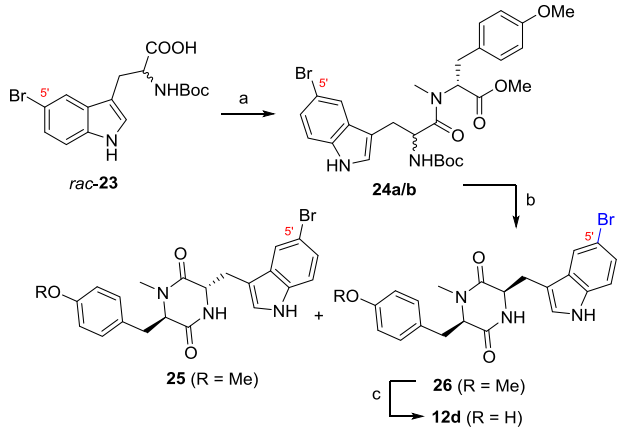
was transformed to *rac*-*N*-Boc-Trp derivative **19**, which was reacted with D-Tyr derivative **7** to yield a mixture of two dipeptide diastereomers **20a** and **20b**. Both of them were further converted into two separable diketopiperazine **21** and **22** by a sequence of acidic deprotection and alkalic cyclization. Diketopiperazine substrate **12c** was finally obtained by O-demethylation of **22** (Scheme 5).



Scheme 5. Preparation of diketopiperazine **12c**. Reagents and conditions: (a) 6 M HCl, reflux; (b) Boc_2O, NaOH, THF/H_2O, 70% for two steps; (c) *N*-Me-D-Tyr(OMe)-OMe HCl (**7**), BEP, HOBt, CH_2Cl_2, 65%; (d) 3 M HCl in EtOAc, then aqueous $NaHCO_3$, **21** (41%), and **22** (43%); (e) BBr_3, CH_2Cl_2, 0 °C to rt, 85%.

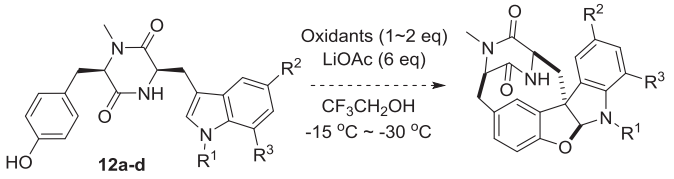
5′-Bromo-diketopiperazine **12d** was designed to block the C14 position where the over-oxidation happened. Starting with *rac*-*N*-Boc-(5′-Br-Trp)-OH (**23**)[16] and **7**, a mixture of two dipeptide diastereomers **24a** and **24b** were synthesized. After similar deprotection and cyclization, diketopiperazine **25** and **26** were obtained. O-Demethylation of **26** led to the desired substrate **12d** (Scheme 6).

All four cyclopeptide derivatives **12a**–**d** were examined under oxidative cyclization conditions, but the results turned out to be disappointing (Table 2). When the indole nitrogen was protected either by an electron-withdrawing group (Ac, entry 1, **12a**) or an electron-donating group (Bn, entry 2, **12b**), the corresponding substrates displayed no reactivity under the oxidation conditions. This indicated that the free indole nitrogen (NH) was an essential group for the oxidative cyclization process initiated by PIDA. When a bromine atom was introduced into 7′ position of the indole moiety to decrease the electron density (entry 3, **12c**), the reaction turned out to be very complicated. Furthermore, when 5′ position of the indole moiety was substituted by a bromine atom to block



Scheme 6. Preparation of diketopiperazine **12d**. Reagents and conditions: (a) *N*-Me-D-Tyr(Me)-OMe HCl (**7**), BEP, HOAt, DIEA, CH_2Cl_2, 85%; (b) 3 M HCl in EtOAc, then aqueous $NaHCO_3$, **25** (46%) and **26** (47%); (c) BBr_3, CH_2Cl_2, 0 °C to rt, 90%.

Table 2
Oxidative cyclization of diketopiperazine derivatives **12a–d**[a]



Entry	Substrate	Oxidant	Results
1	**12a** (R^1=Ac, R^2=H, R^3=H)	PIDA	NR
2	**12a** (R^1=Ac, R^2=H, R^3=H)	PIFA	NR
3	**12b** (R^1=Bn, R^2=H, R^3=H)	PIDA	NR
4	**12b** (R^1=Bn, R^2=H, R^3=H)	PIFA	NR
5	**12c** (R^1=H, R^2=H, R^3=Br)	PIDA	Complicated
6	**12d** (R^1=H, R^2=Br, R^3=H)	PIDA	Complicated

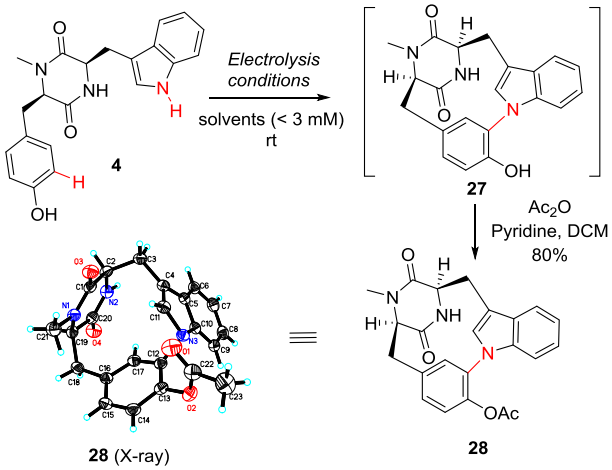
[a] PIDA: (diacetoxyiodo)benzene; PIFA: [bis(trifluoroacetoxy)iodo]benzene.

the over-oxidation site (entry 4, **12d**), no positive result was observed either.

Since all these substrate modifications couldn't improve the results, we further decided to attempt other oxidation methods, such as electrochemical oxidation reaction,[17] using the previous substrate **4**. Electrolysis of **4** with a constant voltage was examined under both acidic and basic conditions (Table 3). Under acidic conditions, only dimerized products were detected with different voltages (entries 1 and 2). When the reaction was performed under basic conditions at 0.8 V, no apparent reaction was found to happen (entry 3). But when the voltage of the electrolysis reaction was raised up to 1.0 V, an unexpected cyclization product **27** was observed, structure of which was further confirmed by X-ray diffraction analysis of its *O*-Ac derivative **28**. To our surprise, the carbocation generated by anode oxidation was intramolecularly captured by the indole nitrogen atom, instead of its 3′-position of the indole moiety. As the result, a new 12-membered ring was given via the newly formed C–N bond. More likely, the high strain within the molecule blocks the formation of the required 10-membered ring.

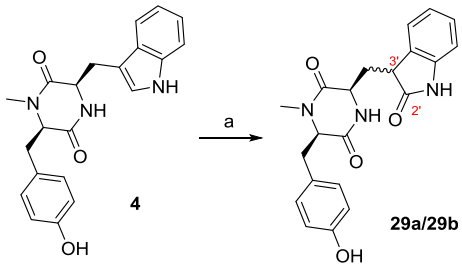
In order to further enhance the nucleophilicity of 3′-carbon of the indole moiety of **4**, we then oxidized the corresponding indole moiety to oxindole **29** (Scheme 7). It was expected that an oxidative coupling reaction would happen to construct the C10 stereocenter of azonazine (**1a**). Diketopiperazine **4** was oxidized by DMSO under acidic condition to yield a mixture of inseparable diastereomer **29a** and **29b** (~2:1 dr according to the ^1H NMR).

Table 3
Electrochemical oxidative cyclization of diketopiperazine **4**



Entry	Voltage	Electrolyte	Base/acid	Solvent	Results
1[a]	0.8 V	$LiClO_4$	HOAc	CH_3NO_2	dimerization
2[a]	1.0 V	$LiClO_4$	HOAc	CH_3NO_2	dimerization
3[b]	0.8 V	Et_4NClO_4	NaOH	CH_3CN/H_2O	N.R.
4[b]	1.0 V	Et_4NClO_4	NaOH	CH_3CN/H_2O	**27** (19%)

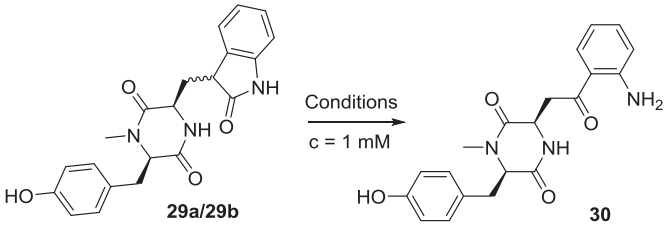
[a] $LiClO_4$ (3 M); HOAc (0.8 M).
[b] Et_4NClO_4 (0.15 M); NaOH (2–4 equiv); CH_3CN/H_2O=10:1.



Scheme 7. Preparation of oxoindole **29a**/**b**. Reagents and conditions: (a) DMSO, HOAc, concd HCl, 40% (dr ~2:1).

With **29a**/**29b** in hand, a variety of oxidative coupling conditions were then screened for the intramolecular cyclization (Table 4). Several different oxidants were firstly tested, including Fe(III), Ce(IV), Mn(IV), Mn(III), Cu(I), Ir(IV), I_2, and air. Under most

Table 4
Oxidative coupling of **29a**/**b**



	Oxidants	Solvent	Additive	Results (yield)
1[a]	$K_3Fe(CN)_6$	$H_2O/CHCl_3$	KOH	**30 (31%)**
2[a]	$K_3Fe(CN)_6$	HOAc	—	**30 (25%)**
3[a]	MnO_2	Toluene	KOH	**30 (ND)**
4[a]	$Mn(OAc)_3$,$Cu(OAc)_2$	HOAc	—	**30 (ND)**
5[a]	$[Cu(TMEDA)OHCl]_2$	CF_3CH_2OH	KOH	**30 (ND)**
6[a]	K_2IrCl_6	$H_2O/CHCl_3$	KOH	**30 (ND)**
7[a]	Air	H_2O	KOH	**30 (ND)**
8[a]	$(NH_4)_2Ce(NO_3)_6$	MeCN	—	Complicated
9[b]	I_2	THF	LiHMDS	Complicated

[a] Reaction was carried out from 0 °C to rt.
[b] Reaction was carried out from −40 °C to rt.

conditions, substrate **29a/29b** was transformed to a ring-opening product **30**, structure of which was confirmed by X-ray diffraction analysis (Table 4, entries 1–7). When Ce(IV) and I_2 (entries 8 and 9) were used as the oxidants, the reactions turned out to be very complicated. A probable mechanism of this transformation is shown in Fig. 3. The C3′ position of the oxindole is firstly oxidized to a 3′-hydroxy-2′-oxindole, which undergoes an intramolecular fragmentation leading to **30** after releasing one molecule of carbon monoxide.

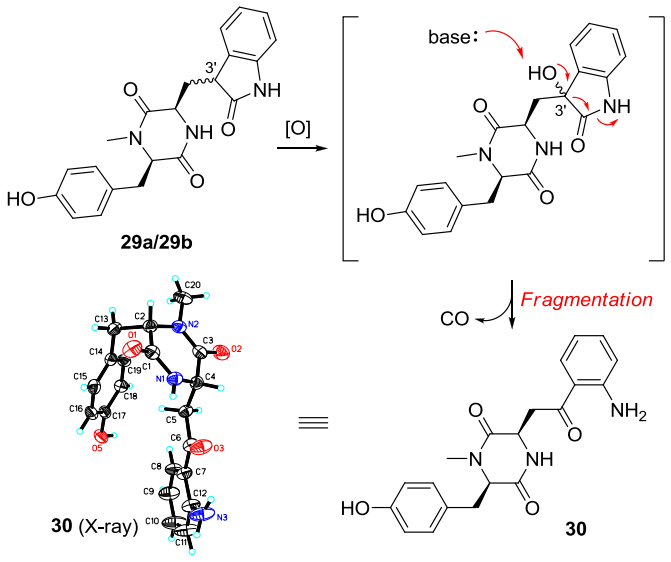


Fig. 3. A proposed mechanism for the oxidative fragmentation.

Since the previous attempts to avoid over-oxidation were unsuccessful, we turned back to the intermediate **11a**, which contains the similar hexacyclic ring system of natural product with the right stereochemistry at C10 position. Starting from **11a**, three possible sequences could reach the natural product (Fig. 4). Method 1 involves a ketal exchange of **11a** with 1,3-propanedithiol, giving dithioacetal **31a**. Further hydrogenation and acetylation of **31a** will afford **1a** finally. The imine functionality is reduced at first, by the second method, to yield C-14 trifluoroethoxy derivative **33a**. Reductive cleavage of the ether bond affords **32a**, which is further transformed to **1a** by N-acetylation. On the other hand, the ether group of **33a** can also be deprotected and triflated to yield **36a**, which can be converted to **1a** by hydrogenation and N-acetylation. In method 3, hydrolysis of **11a** would give quinone **34a** as a key intermediate. Azonazine **1a** could be provided by a sequence of reduction, phenol O-triflation, hydrogenation, and N-acetylation transformation from **34a**.

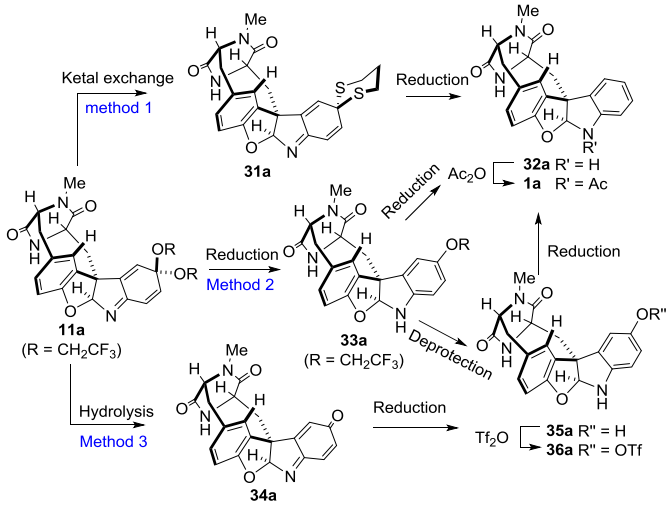
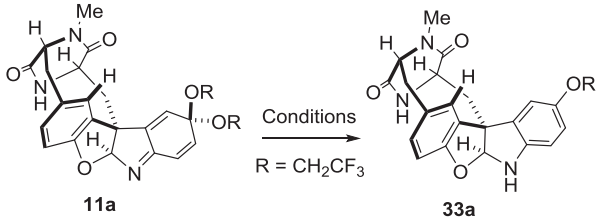


Fig. 4. Three possible methods to convert **11a** into azonazine (**1a**).

Ketal exchange of **11a** was attempted, and the results turned out to be disappointing. Under the catalysis of a variety of Lewis acids, including $Et_2O{\cdot}BF_3$, ZnI_2, and $Sc(OTf)_3$, the expected reaction didn't happen. We then had to move our attention to alternative methods. A number of different reductive conditions were screened (Table 5), and **11a** was finally reduced with activated zinc powder in the presence of Et_3SiH and HOAc in tetrahydrofuran, giving the desired product **33a** in 87% yield (entry 4).

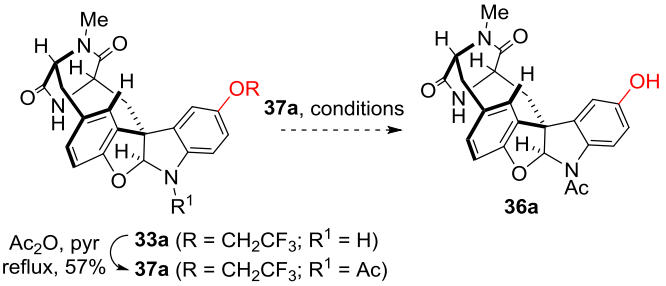
Table 5
Reduction of benzoquinone functionality of **11a**



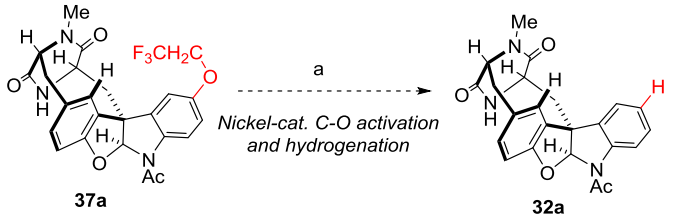
Entry	Conditions	Temp	Yield (%)
1	Zn (activated), HOAc	rt	52
2	SmI_2, THF	rt	34
3	$NaBH_4$, MeOH	0 °C to rt	42
4	Zn (activated)/Et_3SiH/HOAc, THF	rt	87

Considering the existence of a naked nitrogen atom on the indoline ring of **33a** might make it unstable, we decided to convert it into the *N*-Ac derivative **37a** at first. Unfortunately, further cleavage of the trifluoroethyl aryl ether of **37a** was proven to be problematic (Table 6). Substrate **37a** remained unchanged using Lewis acid BBr_3 or TMSI (entries 1–2) even at high temperatures. When EtSNa was applied as a nucleophilic reagent (entry 3), the reaction turned out to be complicated. When **37a** was exposed to NaOH in methanol (entry 4), only hydrolysis of *N*-acetyl group happened. Cleavage of the aryl ether bond of **37a** by nickel catalyzed C–O activation and hydrogenation[18] also gave negative results (Scheme 8).

Table 6
Attempts for conversion of **37a** into **36a**



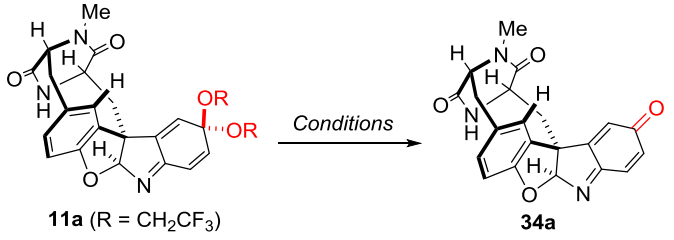
Entry	Conditions	Temp (°C)	Results
1	BBr_3, CH_2Cl_2	−40 to 40	N.R.
2	TMSI, DMF	rt to 100	N.R.
3	EtSNa, DMF	rt to 100	Complicated
4	NaOH (1 M), MeOH	rt	**33a**



Scheme 8. Failed attempts for aryl C–O reductive cleavage with nickel-catalyzed activation and hydrogenative reduction. Reagents and conditions: (a) Metal: Ni^{II}; ligands: Ph_3P, or Cy_3P; solvents: PhMe, or $^iPr_2O$, or THF, or $(EtO)_2CH_2$; H donors: Et_3SiH, or DIBAl-H, or 9-BBN, or BH_3, or Bu_3SnH.

Hydrolysis of the *O*,*O*-ditrifluoroethyl acetal of **11a** was eventually explored (Fig. 4, method 3; Table 7). While strong acids were used, slow decomposition of the substrate was observed during the reaction process (Table 7, entries 1–5). Careful adjustment of the combinations of Lewis acid and Brønsted acid found that the hydrolysis provided the best results when HOAc was employed as the solvent (entry 6). If it was carried out under microwave irradiation, the reaction was greatly accelerated (entries 9 and 10). Furthermore, addition of a small amount of water would facilitate the hydrolysis, but would lead to several side-products. The ratio of water and HOAc was therefore carefully optimized (entries 11–13). When HOAc/H_2O (15:1, v/v) was applied as the solvent, the reaction turned out to be fast and clean under microwave-assisted conditions, giving the desired quinone **34a** (59% yield).

Table 7
Hydrolysis of **11a** to quinone **34a**

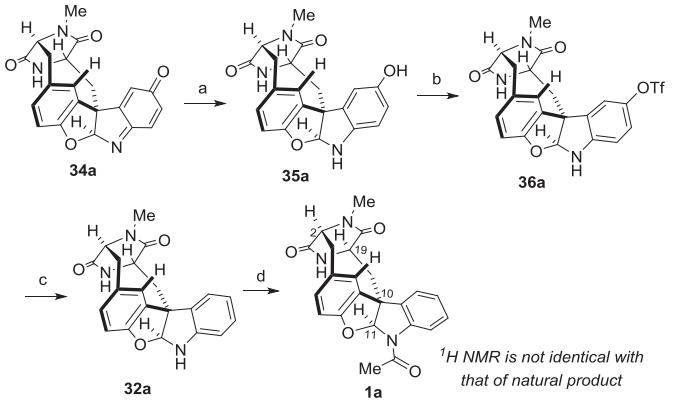


Entry	Conditions	Temp (°C)	Time (h)	Results (yield)
1	1 M HCl, MeOH	rt	2	Decomposition
2	PTSA, acetone	rt	2	Decomposition
3	PPTS, acetone	−30 to rt	2	Decomposition
4	HCOOH	rt	0.25	Decomposition
5	TFA	rt	0.16	Decomposition
6	HOAc	rt	7	**34a** (41%)
7	$Zn(OTf)_2$, acetone	rt to reflux	1	Decomposition
8	MgI_2, acetone	rt to reflux	1	Decomposition
9[a]	HOAc	70	0.033	**34a** (38%)
10[a]	HOAc	50	0.4	**34a** (40%)
11[a]	HOAc/H_2O(15:1)	50	0.1	**34a** (59%)
12[a]	HOAc/H_2O(5:1)	50	0.1	**34a** (42%)
13[a]	HOAc/H_2O(2:1)	50	0.1	**34a** (31%)

[a] Microwave irradiation.

Availability of quinone **34a** enabled us to continue our synthesis of azonazine (**1a**). As shown in Scheme 9, quinone **34a** was immediately reduced with $NaBH_4$ to afford stable phenol **35a**, which was then converted into the corresponding *O*-triflate **36a** under the optimized conditions (Tf_2O/Et_3N in EtOAc, −15 °C). Hydrogenative removal of the triflate functionality of **36a** (in the presence of catalytic amount of $Pd(OH)_2$ on charcoal) followed by N-acetylation finally afforded the originally proposed structure of (+)-azonazine (**1a**).

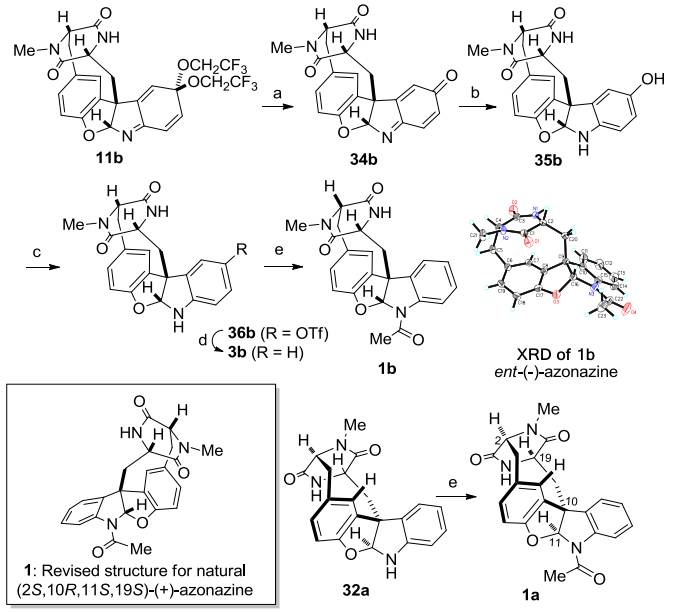
To our surprise, multiple apparent differences were found in the ^1H NMR spectrum of synthetic **1a** from those reported for the



Scheme 9. Synthesis of the proposed structure of azonazine. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 67%; (b) Tf_2O, Et_3N, EtOAc, −15 °C, 53%; (c) H_2, cat. $Pd(OH)_2$/C, Et_3N, MeOH/EtOAc, rt, 80%; (d) Ac_2O, pyridine, reflux, 25%.

natural product. After analyzing the original report carefully,[2] we found that the assignment of the relative configurations at C10 and C11 might be ambiguous.[19] We found the ^1H NMR of the previous intermediate **11b** was much more similar to that of natural product than its counterpart **11a**. Therefore, we decided to synthesize the other C10/C11 diastereomer **1b** from **11b** for further analysis.

The diastereomeric target **1b** was synthesized with similar steps as those for **1a** (Scheme 10). Hydrolysis of **11b** under microwave-assisted conditions followed by $NaBH_4$ reduction of quinone **34b** provided phenol **35b**. Deoxygenation of the C14 phenol group of **35b** was accomplished by O-triflation and subsequent hydrogenation, giving **3b** in good yield. However, problems were met in the final N-acetylation step. Previously used basic conditions (Ac_2O, pyridine, reflux) didn't work well in this substrate, leading to very low yield and several inseparable side-products. A variety of acetylation reagents, additives, and solvents were then screened (Table 8). Finally, we found the unusual acidic conditions (Ac_2O in HOAc at rt) provided much higher yield (89%) of the final product **1b**, whose stereochemical structure was determined by NMR



Scheme 10. Completion of the total synthesis of *ent*-(−)-azonazine (**1b**). Reagents and conditions: (a) HOAc, microwave irradiation, dioxane/H_2O, 65 °C, 45–55%; (b) $NaBH_4$, MeOH, 0 °C, 80%; (c) Tf_2O, Et_3N, EtOAc, −15 °C, 70%; (d) H_2, cat. $Pd(OH)_2$/C, Et_3N, MeOH/EtOAc, rt, 96%; (e) Ac_2O, HOAc, rt, **1b** (89%); **1a** (67%); see Table 8 for more details of optimization of the final N-acetylation step.

Table 8
Conditions for selective N-acetylation of **3b**

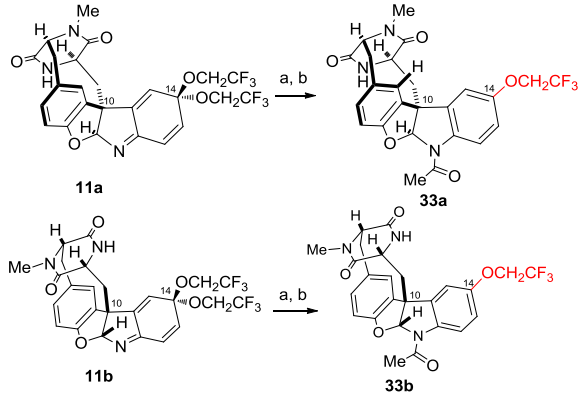
Entry	Conditions	Temp (°C)	**1b** (%)
1	Ac_2O, DCM/Py (5:1), 48 h	70	30
2	Ac_2O, Py, 4 h	70	40
3[a]	Ac_2O, Py, 30 min	90	33
4	Ac_2O, TEA, DCM, 11 h	Reflux	—[b]
5	AcCl, TEA, DMF	rt	Complicated
6	Ac_2O, TEA, DMF, DMAP (0.05 equiv)	−30 °C to rt	—[b]
7	HOAc, HATU, DIEA, DMF	0 °C to rt	N.R.
8	HOAc, BEP, DIEA, DMF	0 °C to rt	N.R.
9	1-Acetylimidazole, TEA, DMF	0 °C to rt	N.R.
10	Ac_2O, AcOH	rt	89

[a] Microwave irradiation.
[b] No desired product were found.

methods and further confirmed by an X-ray single crystal diffraction experiment. The optimized acidic N-acetylation conditions were also workable to convert **32a** into **1a** (previously in Scheme 9, 25% yield) in an improved yield (67%, Scheme 10).

With the above physical characterizations in hand, the absolute chemistry of **1b** was unambiguously assigned as (2*R*,10*S*,11*R*,19*R*) (Scheme 10). Except the opposite optical rotation {synthetic: $[\alpha]_D^{27}$ −299.3 (*c* 0.11, MeOH); natural: $[\alpha]_D^{23}$ +295.0 (*c* 0.1, MeOH)}, all other physical evidences of **1b** were in good agreement with those reported for the natural product.[2] Therefore, the absolute configuration of natural (+)-azonazine should be revised as (2*S*,10*R*,11*S*,19*S*)-**1**.

Advantages of modern natural product synthesis include its ability in the development of important derivatives, among which some are difficult to be achieved by traditional functionality modifications. Selective introduction of fluorine atom(s) to bioactive natural and unnatural products is of extreme interest in today's pharmaceutical research.[20] Some fluorine-containing intermediates accidentally generated in this synthesis undoudtedly provide us a particular opportunity to explore fluorinated analogues and derivatives of azonazine. As an extra income of this study, we easily synthesize the C14-trifluoroethoxy analogues **33a**/**33b** of *ent*-azonazine in two steps from the common ketal intermediates **11a**/**11b** by reduction with zinc/HOAc under mild conditions[21] and subsequent N-acetylation (Scheme 11).



Scheme 11. Convenient synthesis of fluorinated azonazine analogues **33a** and **33b**. Reagents and conditions: (a) Et_3SiH, Zn, HOAc, THF, rt; (b) Ac_2O, AcOH, rt. Compound **33a** (70% for two steps); **33b** (67% for two steps).

3. Conclusions

In summary, we have successfully accomplished the first total synthesis of *ent*-(−)-azonazine. A biomimetic direct oxidative cyclization has been successfully developed and applied as the key step to construct the highly strained hexacyclic core of azonazine. An unusual product **28** contains a 12-membered ring via new sp^2 C–N bond formation in the electrochemical oxidation further confirmed that high strain exists within the natural skeleton. By analysis of spectroscopic evidences and X-ray single crystal studies of the synthesized enantiopure diastereomers, the absolute stereochemistry of natural (+)-azonazine was unambiguously revised as (2*S*,10*R*,11*S*,19*S*)-**1**. In addition, two intermediates produced in this work were utilized to the synthesis of corresponding fluorinated azonazine derivatives in short convenient steps. Biological properties of these unnatural products including the two-fluorinated derivatives are currently under investigation in our laboratory and will be reported in due course.

4. Experimental section

4.1. General

All reactions were carried out in flame-dried glassware with magnetic stirring and monitored by thin-layer chromatography (TLC). THF was distilled from sodium; dichloromethane was distilled from CaH_2; and ethyl acetate was dried over K_2CO_3 and distilled. All melting points were uncorrected. ^1H NMR was recorded on a Varian instrument (300 or 500 MHz) and a Bruker instrument (400 or 600 MHz); ^{13}C NMR were recorded on a Varian instrument (75 or 125 MHz) and a Bruker instrument (100 or 150 MHz). IR spectra were recorded on Nicolet 380 FT-IR instrument. Optical rotations were measured on a Jasco P-1030 digital polarimeter. High resolution mass spectra (HRMS) were measured on an IonSpec 4.7 Tesla FTMS spectrometer. Flash column chromatographies were performed on silica gel H (10–40 μm). MPLC purification was performed using a Biotage Isolera system and KP-SIL SNAP flash cartridge column packed with silica gel (particle size 50–60 micron, 50–52 Å pore size). Microwave reactions were run on a CEM Discover S Microwave Synthesizer. X-ray intensity data were collected on a Bruker APEX-II CCD area detector employing graphite-monochromated Cu-Ka radiation (*l*=1.54178 Å) at a temperature of 296(2) K.

4.2. D-*N*-Me-Tyr(Me)-OMe·HCl (7)

To a solution of D-Boc-Tyr-OH (**5**) (50.0 g, 178 mmol) in 500 ml of dry THF under N_2 atmosphere at 0 °C was added sodium hydride (60% oil dispersion, 35.6 g, 890 mmol, 5 equiv) in portions. The resulting reaction mixture was stirred at 0 °C for 15 min, and methyl iodide (44.3 ml, 712 mmol, 4 equiv) was then added. The reaction was stirred overnight at rt. The excess sodium hydride was quenched by the careful addition of water, and the solvents were removed in vacuo. The residue was diluted with 300 ml of water and washed with Et_2O. The aqueous phase was then acidified with $KHSO_4$ (to pH 3) and was extracted with EtOAc. The combined extracts were successively washed with aqueous $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude compound **6** was used directly for the next step.

The above crude product was dissolved in methanol (400 ml) and cooled down to 0 °C under N_2 atmosphere. Thionyl chloride (14.3 ml, 196 mmol, 1.1 equiv) was slowly added to the reaction system. The resulting mixture was stirred at 0 °C for 0.5 h, and then refluxed for 2 h. The solvents were removed in vacuo to give **7** as white solid (45.3 g, 174 mmol, 98% for two steps). Mp: 152–155 °C. $[\alpha]_D^{25.2}$ −31.3 (*c* 1.0, MeOH); IR (KBr): 3417, 2954, 2834, 2691, 2433, 1745, 1612, 1514, 1249, 1029, 835 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.88 (br s, 2H), 7.22 and 7.16 (two d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 4.22 and 4.08 (two dd, *J*=7.5, 4.8 Hz, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 3.27 (m, 1H), 3.14 (m, 1H), 2.54 and 2.52 (two s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.45 and 168.62 (1C), 158.48 and

158.44 (1C), 130.61 and 130.47 (2C), 126.55 and 126.18 (1C), 114.00 and 113.91 (2C), 61.39 and 61.20 (1C), 55.07, 52.59, 33.91 and 33.84 (1C), 31.79 and 31.52 (1C); ESI-MS (*m*/*z*): 224 (M−HCl+H$^+$); HRMS (ESI) calcd for $C_{12}H_{18}NO_3$ (M−HCl+H$^+$) 224.1287, found 224.1281.

4.3. Dipeptide 9

To a solution of **7** (12.7 g, 49.0 mmol, 1.05 equiv), *N*-Boc-D-Trp-OH (**8**) (14.2 g, 46.7 mmol, 1 equiv), and BEP (16.6 g, 60.6 mmol, 1.3 equiv) in dry CH_2Cl_2 (500 ml) under N_2 atmosphere at 0 °C was added *N*-ethyldiisopropylamine (24.3 ml, 140 mmol, 3 equiv) slowly via a syringe pump (flow rate 25 ml/h). The resulting mixture was stirred at 0 °C for 0.5 h and then stirred at rt overnight. The organic solvent was removed in vacuo, and the resulting mixture was diluted with EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by MPLC on silica gel (MeOH in CH_2Cl_2: 0–5%) to give **9** (18.0 g, 76%) as a white foam. $[\alpha]_D^{25.8}$ +48.0 (*c* 1.02, $CHCl_3$). IR (KBr): 3337, 3005, 2976, 2952, 2834, 1738, 1701, 1641, 1513, 1247, 1032, 747 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34–8.20 (m, 1H), 7.68–7.50 (m, 1H), 7.34–7.27 (m, 1H), 7.16 (t, *J*=7.4 Hz, 1H), 7.12–7.08 (m, 1H), 7.03 (d, *J*=1.8 Hz, 1H), 6.94–6.76 (m, 2H), 6.72–6.62 (m, 2H), 5.16 (d, *J*=9.0 Hz, 1H), 5.02 (dd, *J*=9.9, 5.7 Hz, 1H), 4.92–4.78 (m, 1H), 3.73–3.59 (m, 6H), 3.29–3.13 (m, 2H), 3.09–3.03 (m, 1H), 2.87–2.81 (m, 1H), 2.88 and 2.66 (two s, 3H), 1.43–1.33 (d, *J*=21.6 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.17 and 172.75 (1C), 171.10 and 170.57 (1C), 158.63 and 158.48 (1C), 155.30 and 155.12 (1C), 136.28, 130.15 and 129.97 (2C), 128.97, 127.93, 123.44 and 122.67 (1C), 122.12 and 122.09 (1C), 119.69 and 119.60 (1C), 119.03 and 118.93 (1C), 114.25 and 114.03 (2C), 111.28 and 111.06 (1C), 110.52 and 110.15 (1C), 79.73, 61.19 and 59.64 (1C), 55.31, 52.56 and 52.32 (1C), 50.90 and 50.47 (1C), 34.61 and 33.92 (1C), 33.39, 29.18 and 29.11 (1C), 28.49 and 28.41 (3C); ESI-MS (*m*/*z*): 532 (M+Na$^+$); HRMS (ESI) calcd for $C_{28}H_{35}N_3O_6$ (M+Na$^+$) 532.2427, found 532.2418.

4.4. Diketopiperazine 4

To a solution of 3 M HCl in EtOAc (100 ml) was added **9** (17.9 g, 35.1 mmol) at rt. The mixture was stirred at rt for 2 h. The solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the organic layer was successively washed with aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The crude product **10** was used directly for the next step without further purification.

To a solution of crude **10** (13.0 g, 34.4 mmol, 1 equiv) in dry CH_2Cl_2 (400 ml) was added BBr_3 (1.9 M in CH_2Cl_2, 90 ml, 171 mmol, 5 equiv) at 0 °C. The resulting mixture was stirred at rt overnight. Water was slowly added at 0 °C to quench the reaction. The resulting solution was filtered, and the solid was washed with CH_2Cl_2. The organic phases were concentrated (to remove CH_2Cl_2), and then diluted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The residue combined with the previously filtered solid was purified by MPLC on silica gel (MeOH in CH_2Cl_2: 0–5%) to give **4** (11.3 g, 90% for two steps) as a white solid. Mp: 128–132 °C. $[\alpha]_D^{25}$ +157.1 (*c* 0.65, CH_3CN); IR (KBr): 3291, 2926, 2685, 2600, 2261, 1664, 1632, 1516, 1458, 1233, 1100, 746 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 9.15 (s, 1H), 7.44 (d, *J*=8.1 Hz, 1H), 7.38 (d, *J*=8.1 Hz, 1H), 7.13 (t, *J*=7.2 Hz, 1H), 7.05 (t, *J*=7.5 Hz, 1H), 6.96–6.84 (m, 4H), 6.78 (d, *J*=8.5 Hz, 2H), 6.19 (s, 1H), 4.02 (t, *J*=4.5 Hz, 1H), 3.92 (d, *J*=9.6 Hz, 1H), 2.95–2.81 (m, 5H), 2.73 (dd, *J*=14.3, 4.3 Hz, 1H), 1.56 (dd, *J*=14.3, 9.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 167.00, 166.96, 157.28, 137.63, 132.25 (2C), 128.14, 128.05, 125.12, 122.51, 119.89, 119.50, 116.41 (2C), 112.35, 110.48, 64.09, 56.45, 36.91, 33.41, 31.75; ESI-MS (*m*/*z*): 364 (M+H$^+$); HRMS (ESI) calcd for $C_{21}H_{22}N_3O_2$ (M+H$^+$) 364.1648, found 364.1656.

4.5. Ketals 11a and 11b

To a solution of $PhI(OAc)_2$ (3.86 g, 12.0 mmol, 2 equiv) and LiOAc (2.38 g, 6 equiv) in CF_3CH_2OH (550 ml) was added **4** (2.18 g, 6.0 mmol) in 50 ml CF_3CH_2OH slowly at −15 °C. The reaction mixture was stirred for 30 min and quenched with aqueous $Na_2S_2O_3$ (10 ml). The solvents were removed, and MeOH/CH_2Cl_2 (1:20) was added. The sediment was filtered and washed three times with MeOH/CH_2Cl_2 (1:20). The filtrates were concentrated in vacuo. The resulting residue was purified by MPLC on silica gel (MeOH in CH_2Cl_2: 0–5%) to give a mixture of **11a**/**b**, which was further purified by preparative TLC (EtOAc) to give **11a** (535 mg, 16%) and **11b** (401 mg, 12%) as slightly yellow solids.

Compound **11a**: Single crystal for X-ray analysis was prepared by slow evaporation from DMSO. Mp: >270 °C (decomposition); $[\alpha]_D^{25.0}$ −56.0 (*c* 1.0, THF). IR (KBr): 3445, 3218, 2945, 1678, 1621, 1580, 1483, 1282, 1170, 1107, 992 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 7.05 (s, 1H), 6.93 (d, *J*=8.2 Hz, 1H), 6.89 (s, 1H), 6.85 (d, *J*=10.2 Hz, 1H), 6.78 (d, *J*=8.1 Hz, 1H), 6.58 (dd, *J*=10.2, 2.4 Hz, 1H), 6.11 (s, 1H), 5.47 (s, 1H), 4.19–4.00 (m, 6H), 3.30 (d, *J*=14.0 Hz, 1H), 3.06 (s, 3H), 2.89 (dd, *J*=14.1, 4.3 Hz, 1H), 2.81 (dd, *J*=16.1, 3.2 Hz, 1H), 2.00 (dd, *J*=16.2, 3.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 168.76, 165.87, 164.86, 158.89, 148.41, 139.26, 133.55, 133.25, 128.13, 127.52, 126.05, 125.33 (q, *J*=275 Hz, 1C), 125.28 (q, *J*=275 Hz, 1C), 122.28, 116.86, 111.37, 98.84, 66.32, 62.08 (q, *J*=34.6 Hz, 2C), 57.42, 56.12, 38.38, 37.60, 33.86; ESI-MS (*m*/*z*): 558 (M+H$^+$); HRMS (ESI) calcd for $C_{25}H_{22}N_3O_5F_6$ (M+H$^+$) 558.1469, found 558.1458.

Compound **11b**: Single crystals for X-ray analysis was prepared by vapor diffusion (THF/hexanes). Mp: >250 °C (decomposition); $[\alpha]_D^{25.1}$ −20.4 (*c* 1.02, THF). IR (KBr): 3260, 2933, 1682, 1655, 1579, 1484, 1287, 1155, 1112, 988, 752 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 7.32 (s, 1H), 6.97 (dd, *J*=8.1, 1.7 Hz, 1H), 6.94 (s, 1H), 6.87 (d, *J*=10.2 Hz, 1H), 6.66 (d, *J*=8.1 Hz, 1H), 6.58 (dd, *J*=10.2, 2.4 Hz, 1H), 6.46 (d, *J*=2.4 Hz, 1H), 6.25 (s, 1H), 4.17–3.99 (m, 6H), 3.48 (d, *J*=14.0 Hz, 1H), 3.05 (dd, *J*=14.1, 6.4 Hz, 1H), 2.71 (dd, *J*=16.4, 3.9 Hz, 1H), 2.44 (s, 3H), 2.28 (dd, *J*=16.4, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 169.87, 165.19, 164.78, 159.56, 149.67, 139.18, 132.92, 132.31, 129.16, 127.40, 126.46, 125.37 (q, *J*=275 Hz, 1C), 125.23 (q, *J*=275 Hz, 1C), 121.23, 110.86, 118.18, 98.71, 66.84, 62.25 (q, *J*=35 Hz, 1C), 62.10 (q, *J*=35 Hz, 1C), 57.17, 55.62, 39.29, 38.66, 32.93; ESI-MS (*m*/*z*): 558 (M+H$^+$). HRMS (ESI) calcd for $C_{25}H_{22}N_3O_5F_6$ (M+H$^+$) 558.1472, found 558.1458.

4.6. Dipeptide 15

To a solution of 3 M HCl in dioxane (30 ml) was added compound **13** (1.62 g, 4.5 mmol) at rt. The mixture was stirred at rt for 3 h. The solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the organic layer was successively washed with aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The crude product was used directly for the next step without further purification.

To a solution of the above crude product in dry CH_2Cl_2 (40 ml) under N_2 atmosphere at 0 °C was added EDCI (0.920 g, 4.8 mmol), HOBt (0.648 g, 4.8 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, and then **14** (1.405 g, 4.0 mmol) was added. *N*-ethyldiisopropylamine (1.31 ml, 8.0 mmol)was slowly added. The resulting mixture was stirred at 0 °C for 0.5 h and then stirred at rt overnight. The organic solvent was removed in vacuo, and the resulting mixture was diluted with EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatograph on silica gel (EtOAc/PE: 0–1/2), to give **15** as a white foam (1.80 g, 76% for two

steps). $[\alpha]_D^{26}$ +31.75 (*c* 1.20, $CHCl_3$); IR (KBr): 3334, 2976, 2932, 1743, 1685, 1507, 1452, 1388, 1366, 1327, 1162, 1015, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J*=7.7 Hz, 1H), 7.48 (d, *J*=7.7 Hz, 1H), 7.28 (m, 3H), 7.05 (m, 2H), 6.88 (d, *J*=8.2 Hz, 2H), 6.70 (m, 1H), 4.83 (m, 2H), 3.66 (m, 3H), 3.23 (m, 3H), 2.88 (m, 1H), 2.64 (s, 3H), 2.56 (s, 3H), 1.28 (m 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.77, 170.88, 170.41, 168.66, 156.41, 155.14, 154.03, 135.83, 132.22, 129.49, 129.42 (2C), 125.51, 124.30 (2C), 123.79, 118.65, 116.80, 80.52, 78.39, 60.81, 52.60, 52.08, 33.64, 31.77, 28.90 (3C), 28.23 (3C), 27.61, 24.10. HRMS (MALDI): calcd for $C_{33}H_{43}N_3O_7Na$ ($M+Na^+$) 616.3003; found 616.2993.

4.7. Diketopiperazine 12a

To a solution of 3 M HCl in dioxane (5 ml) was added compound **15** (0.10 g, 0.17 mmol) at rt. The mixture was stirred at rt for 3 h. The solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the organic layer was successively washed with aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The crude product was used directly for the next step without further purification.

To a solution of the above crude product in *n*-butyl alcohol (1 ml) was added HOAc (0.15 ml) and *N*-methylmorpholine (0.1 ml). The resulting mixture was irradiated by microwave (150 W) at 100 °C for 15 min. The organic solvent was removed in vacuo, the crude residue was purified by MPLC on silica gel (MeOH in CH_2Cl_2: 0–6%) to give **12a** (57 mg, 83% for two steps) as a white solid. Mp: 179–185 °C. $[\alpha]_D^{23}$ +153.82 (*c* 0.50, MeOH); IR (KBr): 3250, 3016, 2938, 2814, 1676, 1637, 1612, 1452, 1329, 1245, 1227, 1017, 748 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 8.20 (m, 1H), 7.99 (s, 1H), 7.45 (m, 1H), 7.26 (m, 2H), 7.00 (m, 2H), 6.88 (dd, *J*=6.5, 2.0 Hz, 3H), 6.21 (s, 1H), 4.12 (t, *J*=4.0 Hz, 1H), 3.88 (dt, *J*=10.9, 2.8 Hz, 1H), 3.06 (s, 5H), 2.73 (ddd, *J*=14.1, 3.0, 1.1 Hz, 1H), 2.47 (s, 3H), 0.95 (dd, *J*=14.1, 11.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 169.76, 166.92, 166.52, 157.62, 136.84, 132.62 (2C), 130.69, 127.59, 125.83, 125.79, 124.04, 119.84, 117.25, 117.15, 116.44 (2C), 63.93, 55.28, 36.35, 33.34, 31.50, 24.37. HRMS (MALDI): calcd for $C_{233}H_{243}N_3O_4$ ($M+H^+$) 406.1770; found 406.1761.

4.8. Dipeptide 17

To a solution of **16** (300 mg, 0.62 mmol) in methanol (6 ml) was added 2 M NaOH solution (1 ml) at 0 °C. The resulting mixture was slowly warmed to rt and stirred until the consumption of the starting material (monitored by TLC). The resulting residue was diluted with EtOAc, and the water layer was acidified by 1 M HCl (to pH ~3). The organic layer was successively washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was used directly for the next step without further purification.

To a solution of the above crude product, **7** (169 mg, 0.65 mmol) and BEP (221.7 mg, 0.81 mmol) in dry CH_2Cl_2 (40 ml) under N_2 atmosphere at 0 °C was slowly added *N*-ethyldiisopropylamine (0.30 ml, 1.86 mmol), the reaction mixture was stirred at 0 °C for 0.5 h and then stirred at rt overnight. The organic solvent was removed in vacuo, and the resulting mixture was diluted with EtOAc. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatograph on silica gel (EtOAc/PE: 0–1/2), to give **17** as a white foam (227 mg, 71%). $[\alpha]_D^{26}$ +38.37 (*c* 1.75, $CHCl_3$). IR (KBr): 3430, 3302, 2999, 2976, 2932, 2831, 1740, 1707, 1647, 1513, 1364, 1247, 1227, 1175, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J*=7.7 Hz, 1H), 7.14 (m, 9H), 6.94 (d, *J*=8.6 Hz, 2H), 6.70 (d, *J*=8.6 Hz, 2H), 5.24 (t, *J*=10.4 Hz, 2H), 5.15 (d, *J*=9.1 Hz, 1H), 5.05 (dd, *J*=9.9, 5.7 Hz, 1H), 4.88 (m, 1H), 3.69 (d, *J*=32.1 Hz, 3H), 3.57 (d, *J*=14.7 Hz, 3H), 3.21 (m, 2H), 3.05 (dd, *J*=14.4, 6.0 Hz, 1H), 2.86 (m, 1H), 2.72 (s, 3H), 1.48 (d, *J*=77.5 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.66, 171.06, 158.45, 155.22, 137.71, 136.56, 129.93 (2C), 128.93, 128.80 (2C), 128.63, 127.63, 127.43, 126.88 (2C), 121.86, 119.42, 119.18, 113.98 (2C), 109.85, 109.74, 79.59, 59.39, 55.25, 52.23, 50.98, 50.07, 33.90, 33.28, 28.95, 28.42 (3C); HRMS (MALDI): calcd for $C_{35}H_{41}N_3O_6Na$ ($M+Na^+$) 622.2903; found 622.2888.

4.9. Diketopiperazine 12b

To a solution of 3 M HCl in dioxane (3 ml) was added compound **17** (163 mg, 0.27 mmol) at rt. The mixture was stirred at rt for 2 h. The solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the organic layer was successively washed with aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. To a solution of the crude product in CH_2Cl_2 (3 ml) under N_2 atmosphere at 0 °C was slowly added BBr_3 (1.9 M in CH_2Cl_2, 0.6 ml, 1.14 mmol). The resulting mixture stirred at rt overnight. The reaction was quenched by slow addition of water and extracted by DCM/MeOH (20:1). The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatograph on silica gel (DCM–DCM/MeOH=20:1) to give **12b** (97 mg, 79% for three steps) as a white solid. Mp: 122–125 °C; $[\alpha]_D^{26}$ +118.44 (*c* 1.60, MeOH); IR (KBr): 3340, 3245, 3062, 3028, 2926, 1669, 1637, 1515, 1466, 1331, 1234, 1026, 742 cm^{-1}, ^1H NMR (400 MHz, CD_3CN) δ 7.46 (d, *J*=7.8 Hz, 1H), 7.28 (tt, *J*=6.9, 6.1 Hz, 4H), 7.19 (m, 2H), 7.12 (m, 1H), 7.05 (m, 1H), 6.97 (s, 1H), 6.94 (s, 1H), 6.84 (m, 2H), 6.77 (m, 2H), 6.19 (s, 1H), 5.31 (s, 2H), 4.02 (t, *J*=4.5 Hz, 1H), 3.93 (dt, *J*=9.5, 3.1 Hz, 1H), 2.89 (m, 4H), 2.77 (ddd, *J*=34.0, 14.2, 4.6 Hz, 2H), 1.58 (dd, *J*=14.3, 9.6 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 167.08, 167.02, 157.47, 139.25, 137.62, 132.32 (2C), 129.63 (2C), 129.04, 129.01, 128.48, 128.09 (2C), 127.93, 122.62, 120.08, 120.06, 116.54 (2C), 110.99, 110.25, 64.13, 56.51, 50.52, 37.07, 33.52, 31.73. HRMS (MALDI): calcd for $C_{28}H_{28}N_3O_3$ ($M+H^+$) 454.2135; found 454.2125.

4.10. Compound *rac*-19

To a solution of *rac*-**18** in dioxane (60 ml) was added HCl (6 M, 60 ml). The reaction mixture was heated to reflux for 6 h before the solvent was removed in vacuo. The crude residue was dissolved in NaOH (aqueous, 3 M, 50 ml). Then water (100 ml), THF (150 ml), Boc_2O (9.2 g, 42.2 mmol) was added and the reaction mixture was stirred at rt overnight. The solvent was removed in vacuo and the resulting mixture was diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated to give *rac*-**19** (9.90 g, 70%) was brown solid. The crude residue used directly for the next step without further purification. Mp: 116–120 °C; IR (KBr): 3418, 3334, 2976, 2926, 1698, 1506, 1435, 1161, 1073, 1023, 823 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 12.62 (s, 1H), 11.08 (s, 1H), 7.55 (d, *J*=7.8 Hz, 1H), 7.29 (d, *J*=7.5 Hz, 1H), 7.23 (s, 1H), 7.04 (d, *J*=7.9 Hz, 1H), 6.95 (t, *J*=7.7 Hz, 1H), 4.15 (m, 1H), 3.14 (dd, *J*=14.4, 4.2 Hz, 1H), 2.98 (dd, *J*=14.3, 9.7 Hz, 1H), 1.26 (d, *J*=51.2 Hz, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.83, 155.41, 134.33, 129.00, 125.07, 123.48, 119.88, 117.84, 111.78, 104.21, 78.05, 54.43, 28.17, 26.78. HRMS (MALDI): calcd for $C_{16}H_{19}N_2O_4BrNa$ ($M+Na^+$) 405.0431; found 405.0420.

4.11. Diketopiperazines 21 and 22

To a solution of *rac*-**19** (3.1 g, 8.10 mmol) in dry CH_2Cl_2 (80 ml) under N_2 atmosphere at 0 °C was slowly added BEP (2.41 g, 8.8 mmol), HOAt (1.43 g, 8.8 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, then *N*-Me-D-Tyr(Me)-OMe HCl (2.18 g, 8.4 mmol) was added followed by slowly addition of *N*-ethyldiisopropylamine (4.42 ml, 26.8 mmol). The reaction mixture was stirred at rt overnight. The solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the organic layer was

successively washed with water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatograph on silica gel (PE–PE/EA=2:1) to give **20a**/**20b** (3.11 g, 65%) as a mixture of two diastereomers, which was used directly for the next step without further purification.

To a solution of 3 M HCl in EtOAc (30 ml) was added compounds **20a**/**20b** (2.3 g, 3.91 mmol) at rt. The mixture was stirred at rt for 2 h. The solvent was removed in vacuo. The above residue was dissolved in methanol (100 ml) and ammonium hydroxide (6 ml) was added. The reaction mixture was stirred at rt for 0.5 h before the solvent was removed in vacuo. The crude residue was purified by flash chromatograph on silica gel (DCM–MeOH/DCM=20:1) to give **21** (0.77 g, 43%) and **22** (0.73 g, 41%) as white foams.

Compound **21**: $[\alpha]_D^{27}$ −35.61 (*c* 0.95, MeOH); IR (KBr): 3256, 2928, 2830, 1676, 1653, 1511, 1437, 1325, 1248, 1111, 1030, 780 cm^{-1}, ^1H NMR (400 MHz, CD_3CN) δ 9.33 (s, 1H), 7.36 (d, *J*=7.9 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.07 (d, *J*=2.4 Hz, 1H), 6.96 (t, *J*=7.5 Hz, 3H), 6.77 (d, *J*=8.0 Hz, 2H), 6.07 (s, 1H), 3.93 (t, *J*=4.1 Hz, 1H), 3.74 (s, 3H), 3.13 (dd, *J*=11.0, 0.8 Hz, 1H), 3.03 (dd, *J*=5.9, 4.2 Hz, 2H), 2.89 (m, 5H). ^{13}C NMR (100 MHz, CD_3CN) δ 168.65, 167.35, 159.91, 135.70, 131.80 (2C), 129.82, 127.75, 126.20, 124.94, 121.12, 119.16, 114.59 (2C), 111.54, 105.21, 64.15, 55.74, 54.11, 36.26, 33.02, 29.05. HRMS (ESI): calcd for $C_{22}H_{23}N_3O_3Br$ ($M+H^+$) 456.0928; found 456.0917.

Compound **22**: $[\alpha]_D^{27}$ +129.54 (*c* 1.15, MeOH); IR (KBr): 3250, 2929, 2834, 1676, 1652, 1512, 1460, 1330, 1249, 1032, 832, 743 cm^{-1}. ^1H NMR (400 MHz, CD_3CN) δ 9.38 (s, 1H), 7.41 (d, *J*=7.9 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 6.99 (dd, *J*=5.0, 2.7 Hz, 2H), 6.95 (m, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 6.36 (s, 1H), 4.03 (t, *J*=4.5 Hz, 1H), 3.92 (m, 1H), 3.70 (s, 3H), 2.86 (m, 5H), 2.76 (dd, *J*=14.2, 4.3 Hz, 1H), 1.54 (dd, *J*=14.3, 9.6 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 165.53, 165.25, 158.67, 134.70, 130.88 (2C), 128.55, 127.91, 124.61, 123.81, 120.03, 117.85, 113.72 (2C), 111.14, 103.88, 62.76, 55.16, 54.62, 35.71, 32.03, 30.67. HRMS (ESI): calcd for $C_{22}H_{23}N_3O_3Br$ ($M+H^+$) 456.0904; found 456.0917.

4.12. Diketopiperazine 12c

To a solution of **22** in CH_2Cl_2 (60 ml) under N_2 atmosphere at 0 °C was slowly added BBr_3 (1.9 M in CH_2Cl_2, 10 ml). The resulting mixture stirred at rt for 12 h. The reaction was quenched by slow addition of water and extracted by DCM. The crude residue was purified by flash chromatograph on silica gel (DCM–DCM/MeOH=20:1) to give **12c** (4.20 g, 85%) as a white solid. Mp: 152–155 °C; $[\alpha]_D^{23}$ +136.95 (*c* 1.25, MeOH); IR (KBr): 3256, 3016, 2938, 2362, 1667, 1643, 1515, 1471, 1334, 1237, 1046, 1026, 835, 737 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 9.27 (s, 1H), 7.42 (d, *J*=7.9 Hz, 1H), 7.32 (d, *J*=7.6 Hz, 1H), 7.06 (s, 1H), 6.97 (dd, *J*=10.5, 5.1 Hz, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 6.21 (s, 1H), 4.04 (t, *J*=4.3 Hz, 1H), 3.89 (dt, *J*=9.8, 3.1 Hz, 1H), 2.92 (s, 3H), 2.83 (m, 3H), 1.47 (dd, *J*=14.3, 9.9 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 166.79, 166.68, 157.26, 135.98, 132.29, 129.74, 128.16, 125.93, 125.08, 121.29, 119.14, 116.40, 112.33, 105.14, 64.08, 56.43, 36.90, 33.34, 31.89. HRMS (MALDI): calcd for $C_{21}H_{21}N_3O_3Br$ ($M+H^+$) 442.0769; found 442.0761.

4.13. Diketopiperazines 25 and 26

To a solution of *rac*-**23** (3.1 g, 8.10 mmol) in dry CH_2Cl_2 (40 ml) under N_2 atmosphere at 0 °C was slowly added BEP (2.41 g, 8.8 mmol), HOAt (1.43 g, 8.8 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, then *N*-Me-D-Tyr(Me)-OMe HCl (2.18 g, 8.4 mmol) was added followed by slowly addition of *N*-ethyldiisopropylamine (4.42 ml, 26.8 mmol). The reaction mixture was stirred at rt overnight. The solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the organic layer was successively washed with water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatograph on silica gel (PE–PE/EA=2:1) to give **24a**/**24b** (4.05 g, 85%) as a mixture of two diastereomers, which was used directly for the next step without further purification.

To a solution of 3 M HCl in EtOAc (30 ml) was added compound **24a**/**24b** (2.3 g, 3.91 mmol) at rt. The mixture was stirred at rt for 2 h. The solvent was removed in vacuo. The above residue was dissolved in methanol (100 ml) and ammonium hydroxide (6 ml) was added. The reaction mixture was stirred at rt for 0.5 h before the solvent was removed in vacuo. The crude residue was purified by flash chromatograph on silica gel (DCM–MeOH/DCM=20:1) to give **25** (0.84 g, 47%) and **26** (0.80 g, 45%) as white foams.

Compound **25**: $[\alpha]_D^{23}$ −21.05 (*c* 0.68, MeOH); IR (KBr): 3266, 2932, 2829, 1674, 1644, 1511, 1455, 1397, 1248, 1180, 1107, 1030, 881, 793 cm^{-1}, ^1H NMR (400 MHz, CD_3CN) δ 9.39 (s, 1H), 7.62 (d, *J*=1.4 Hz, 1H), 7.29 (d, *J*=8.6 Hz, 1H), 7.19 (dd, *J*=8.6, 1.9 Hz, 1H), 7.01 (d, *J*=2.3 Hz, 1H), 6.97 (d, *J*=8.6 Hz, 2H), 6.78 (d, *J*=8.6 Hz, 2H), 6.40 (s, 1H), 3.87 (t, *J*=4.0 Hz, 1H), 3.71 (s, 3H), 3.01 (m, 4H), 2.96 (s, 1H), 2.88 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 168.30, 167.38, 160.12, 135.98, 131.94, 130.39, 128.05, 126.71, 125.05, 122.17, 114.66, 114.10, 112.75, 110.06, 64.18, 55.89, 54.44, 36.40, 32.99, 28.80. HRMS (MALDI): calcd for $C_{22}H_{23}N_3O_3Br$ ($M+H^+$) 456.0915; found 456.09173.

Compound **26**: $[\alpha]_D^{26}$ +80.20 (*c* 1.80, MeOH); IR (KBr): 3261, 2934, 2827, 1673, 1644, 1512, 1456, 1335, 1248, 1030, 882, 798 cm^{-1}, ^1H NMR (400 MHz, CD_3CN) δ 9.31 (s, 1H), 7.58 (d, *J*=1.8 Hz, 1H), 7.32 (d, *J*=8.6 Hz, 1H), 7.23 (dd, *J*=8.6, 1.8 Hz, 1H), 6.97 (d, *J*=2.4 Hz, 1H), 6.92 (q, *J*=8.8 Hz, 4H), 6.24 (s, 1H), 4.03 (t, *J*=4.6 Hz, 1H), 3.91 (dt, *J*==9.1, 3.2 Hz, 1H), 3.71 (s, 3H), 2.89 (s, 3H), 2.81 (dt, *J*=14.3, 3.5 Hz, 2H), 2.71 (dd, *J*=14.2, 4.4 Hz, 1H), 1.59 (dd, *J*=14.4, 9.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 166.80, 166.56, 159.93, 136.28, 132.13, 130.20, 129.28, 126.70, 125.14, 122.05, 115.02, 114.22, 112.77, 110.66, 64.08, 56.57, 55.93, 37.12, 33.37, 31.68. HRMS (MALDI): calcd for $C_{22}H_{23}N_3O_3Br$ ($M+H^+$) 456.0919; found 456.09173.

4.14. Diketopiperazine 12d

To a solution of **26** (5.84 g, 12.8 mmol) in CH_2Cl_2 (60 ml) under N_2 atmosphere at 0 °C was slowly added BBr_3 (1.9 M in CH_2Cl_2, 10 ml). The resulting mixture stirred at rt for 12 h. The reaction was quenched by slow addition of water and extracted by DCM. The crude residue was purified by flash chromatograph on silica gel (DCM–DCM/MeOH=20:1) to give **12d** (5.38 g, 95%) as a white solid. Mp: 161–165 °C; $[\alpha]_D^{27}$ +112.40 (*c* 0.65, MeOH). IR (KBr): 3272, 2935, 2825, 1670, 1639, 1515, 1460, 1341, 1233, 1046, 878 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 9.08 (s, 1H), 7.91 (s, 1H), 7.58 (s, 1H), 7.17 (m, 2H), 6.89 (d, *J*=8.4 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 2H), 6.75 (d, *J*=1.8 Hz, 1H), 6.24 (s, 1H), 4.04 (t, *J*=4.3 Hz, 1H), 3.80 (d, *J*=9.8 Hz, 1H), 2.95 (s, 3H), 2.90 (dd, *J*=14.3, 4.7 Hz, 1H), 2.79 (dd, *J*=14.3, 3.9 Hz, 1H), 2.71 (dd, *J*=14.2, 2.9 Hz, 1H), 1.23 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 167.21, 166.81, 157.44, 136.09, 132.29 (2C), 129.78, 127.79, 126.56, 124.90, 121.97, 116.49 (2C), 113.99, 112.59, 110.10, 64.02, 56.36, 36.73, 33.47, 31.36; HRMS (MALDI): calcd for $C_{21}H_{21}N_3O_3Br$ ($M+H^+$) 442.0775; found 442.0761.

4.15. Cyclopeptide 28

A solution of **4** (200 mg, 0.55 mmol), NEt_4ClO_4 (3 g, 13.1 mmol) in CH_3CN (70 ml) and aqueous NaOH (0.6 M, 10 ml) was transferred into an undivided electrolysis cell equipped with a graphite felt anode and a platinum cathode. Electrolysis with a constant voltage of 1.0 V was performed at rt, using a standard calomel electrode as a reference electrode. After the consumption of the starting material, the electrolysis was stopped and the reaction mixture was neutralized by $KHSO_4$ (aqueous) and the solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the

organic layer was successively washed with water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by preparative TLC (CH_2Cl_2/MeOH=20:1) to give **27** (38 mg, 19%).

To a solution of **27** (19 mg, 0.053 mmol) in CH_2Cl_2 (2 ml) was added pyridinium (0.2 ml) and acetic anhydride (20 mg, 0.20 mmol), the reaction mixture was heated to reflux until the consumption of the starting material. The solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the organic layer was successively washed with 1 M HCl, water, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by preparative TLC (CH_2Cl_2/MeOH=20:1) to give **28** (17 mg, 80%) as a white solid. Single crystals for X-ray analysis were prepared by vapor diffusion (THF/hexanes). Mp >270 °C (decomposition). $[\alpha]_D^{23}$ −93.54 (*c* 0.40, MeOH); IR (KBr): 3451, 3248, 2932, 1761, 1673, 1651, 1504, 1449, 1324, 1198, 1101, 1016, 910, 755 cm^{-1}, ^1H NMR (400 MHz, CD_3CN) δ 7.68 (d, *J*=7.7 Hz, 1H), 7.40 (d, *J*=7.8 Hz, 1H), 7.31 (td, *J*=7.5, 1.1 Hz, 1H), 7.25 (m, 1H), 7.05 (dd, *J*=8.3, 1.6 Hz, 1H), 7.01 (d, *J*=8.3 Hz, 1H), 6.48 (s, 1H), 6.45 (s, 1H), 5.54 (s, 1H), 4.41 (dd, *J*=4.5, 1.9 Hz, 1H), 4.17 (dd, *J*=5.9, 1.7 Hz, 1H), 3.50 (ddd, *J*=17.3, 15.7, 0.9 Hz, 2H), 3.05 (dd, *J*=14.8, 4.7 Hz, 1H), 2.93 (dd, *J*=16.5, 7.1 Hz, 1H), 2.41 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ 170.79, 168.12, 166.47, 153.49, 148.25, 144.33, 138.31, 138.26, 135.57, 130.42, 130.28, 126.01, 124.66, 124.06, 122.64, 120.93, 117.77, 61.26, 58.99, 34.22, 31.55, 26.69, 21.04. HRMS (MALDI): calcd for $C_{23}H_{22}N_3O_4$ ($M+H^+$) 404.1611; found 404.1605.

4.16. Compound 30

To a solution of **4** (100 mg, 0.27 mmol) in HCl (concd, 0.3 ml) and HOAc (2.7 ml) was slowly added DMSO (48.8 μl), the reaction mixture was stirred at rt until the consumption of the starting material. The solvent was removed in vacuo. The resulting residue was diluted with EtOAc, and the organic layer was successively washed with aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatograph on silica gel (DCM/MeOH=100:1–DCM/MeOH=20:1) to give a mixture of **29a**/**29b** (40 mg, 39%) as a yellow solid, which was used directly for the next step without further purification.

A solution of **29a**/**29b** in aqueous KOH (1 M, 0.15 ml) was diluted with water (6 ml). The above solution was added to aqueous solution of $K_3Fe(CN)_6$ (52 mg, 0.158 mmol) at 0 °C, then $CHCl_3$ (10 ml) was added and the reaction mixture was stirred at rt until the consumption of the starting material. The reaction mixture was neutralized by $KHSO_4$ (aqueous) and extracted with CH_2Cl_2 for two times. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated. The crude residue was purified by preparative TLC (CH_2Cl_2/MeOH=20:1) to give **30** (3 mg, 31%) as a slightly yellow solid. Single crystals for X-ray analysis was prepared by vapor diffusion (THF/hexanes). $[\alpha]_D^{27}$ +70.37 (*c* 0.20, MeOH); IR (KBr): 3444, 3345, 2923, 1675, 1638, 1617, 1590, 1515, 1450, 1338, 1253, 1026, 980, 832, 754 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.83 (d, *J*=2.1 Hz, 1H), 7.24 (t, *J*=7.2 Hz, 1H), 7.16 (d, *J*=9.1 Hz, 3H), 6.88 (d, *J*=8.4 Hz, 2H), 6.73 (t, *J*=8.1 Hz, 3H), 6.58 (t, *J*=7.5 Hz, 1H), 4.34–4.26 (m, 1H), 4.21 (s, 1H), 3.09–2.99 (m, 2H), 2.98 (s, 3H), 2.54 (d, *J*=3.4 Hz, 1H), 1.62 (dd, *J*=17.4, 8.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.35, 165.84, 165.54, 156.89, 151.10, 134.32, 131.35 (2C), 131.06, 125.36, 116.78, 115.95, 115.26 (2C), 114.65, 62.21, 50.18, 43.95, 34.80, 32.19. HRMS (MALDI): calcd for $C_{20}H_{22}N_3O_4$ ($M+H^+$) 368.1614; found 368.1605.

4.17. Quinone 34a

Ketal **11a** (60 mg, 0.108 mmol), HOAc (4.5 ml), and water (0.03 ml) were introduced into an oven-dried 20 ml CEM® vial. The vial was then sealed with a Teflon-lined septum. The resulting mixture was irradiated by microwave (50 W) at 50 °C for 15 min. Solvents were removed in vacuo, and the residue was diluted with EtOAc. The organic layer was washed by aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by MPLC on silica gel (MeOH in CH_2Cl_2: 0–5%) to give **34a** (24 mg, 59%) as a yellow solid. Mp: 135–137 °C; $[\alpha]_D^{24.8}$ −197.3 (*c* 0.50, THF); IR (KBr): 3244, 3062, 2922, 2851, 1679, 1638, 1481, 1235, 1030, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J*=10.0 Hz, 1H), 7.32 (s, 1H), 7.03 (d, *J*=8.0 Hz, 1H), 6.91 (d, *J*=8.2 Hz, 1H), 6.88 (s, 1H), 6.67 (d, *J*=9.9 Hz, 1H), 6.17 (s, 1H), 5.39 (s, 1H), 4.24 (s, 1H), 4.20 (d, *J*=3.7 Hz, 1H), 3.29 (d, *J*=13.9 Hz, 1H), 3.13 (s, 3H), 3.10–3.01 (m, 2H), 1.99 (d, *J*=15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.94, 166.97, 166.32, 165.74, 157.75, 154.02, 137.33, 133.39, 133.15, 131.76, 125.79, 125.17, 123.85, 115.62, 111.61, 65.35, 57.18, 54.95, 37.69, 36.08, 33.83; ESI-MS (*m*/*z*): 376 ($M+H^+$); HRMS (ESI): calcd for $C_{21}H_{18}N_3O_4$ ($M+H^+$) 376.1298; found 376.1292.

4.18. Quinone 34b

Ketal **11b** (40 mg, 0.072 mmol), HOAc (1 ml), and dioxane (1 ml), water (0.1 ml) were introduced into an oven-dried 10 ml CEM® vial. The vial was then sealed with a Teflon-lined septum. The resulting mixture was irradiated by microwave (50 W) at 65 °C for 1.2 h. Solvent was removed in vacuo, and the residue was diluted with EtOAc. The organic layer was washed by aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by MPLC on silica gel (MeOH in CH_2Cl_2: 0–5%) to give **34b** (13 mg, 48%) as a yellow solid. Mp: 160–165 °C; $[\alpha]_D^{25.6}$ −1.72 (*c* 0.275, $CHCl_3$); IR (KBr): 3473, 3223, 2928, 1672, 1637, 1483, 1274, 1027, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.46 (d, *J*=9.9 Hz, 1H), 7.36 (s, 1H), 7.08 (s, 1H), 6.99 (d, *J*=8.1 Hz, 1H), 6.83 (d, *J*=8.1 Hz, 1H), 6.63 (d, *J*=9.9 Hz, 1H), 6.40 (s, 1H), 4.28 (s, 1H), 4.16 (d, *J*=6.1 Hz, 1H), 3.90 (d, *J*=14.3 Hz, 1H), 3.06 (dd, *J*=14.4, 6.3 Hz, 1H), 2.97 (dd, *J*=16.4, 3.7 Hz, 1H), 2.56 (s, 3H), 2.48 (dd, *J*=16.3, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.77, 170.58, 165.65, 163.93, 158.51, 155.48, 136.79, 133.65, 131.31, 131.28, 126.34, 125.12, 122.11, 116.32, 110.58, 65.84, 56.86, 54.34, 38.54, 36.19, 32.62; ESI-MS (*m*/*z*): 376 ($M+H^+$); HRMS (ESI): calcd for $C_{21}H_{18}N_3O_4$ ($M+H^+$) 376.1295; found 376.1292.

4.19. Phenol 35a

To a solution of **34a** (86 mg, 0.23 mmol) in MeOH (5 ml) was added $NaBH_4$ (10 mg, 0.26 mmol, 1.14 equiv) at 0 °C. The reaction was monitored by TLC until the starting material was consumed. Silica gel was added and the solvent was removed in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:1–20:1) to give **35a** (58 mg, 67%) as a white solid. Mp: >240 °C (decomposition); $[\alpha]_D^{29}$ +193.7 (*c* 0.108, MeOH); IR (KBr): 3350, 2970, 2937, 2835, 1661, 1635, 1481, 1236, 1058, 925 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.52 (d, *J*=2.6 Hz, 1H), 6.93 (d, *J*=1.6 Hz, 1H), 6.85 (dd, *J*=8.0, 1.7 Hz, 1H), 6.71 (d, *J*=8.0 Hz, 1H), 6.53 (dd, *J*=8.3, 2.5 Hz, 1H), 6.49–6.44 (m, 2H), 6.08 (d, *J*=5.3 Hz, 1H), 5.50 (s, 1H), 5.27 (d, *J*=5.3 Hz, 1H), 4.10 (d, *J*=4.2 Hz, 2H), 3.26 (d, *J*=14.0 Hz, 1H), 3.08 (s, 3H), 2.96 (dd, *J*=16.1, 3.2 Hz, 1H), 2.86 (dd, *J*=14.0, 4.6 Hz, 1H), 1.91 (d, *J*=4.3 Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 168.18, 165.84, 158.50, 151.61, 142.54, 133.81, 132.57, 132.46, 130.61, 125.53, 115.18, 113.25, 110.87, 110.73, 110.32, 65.97, 59.95, 56.18, 41.15, 38.15, 33.86; ESI-MS (*m*/*z*): 378 ($M+H^+$); HRMS (ESI): calcd for $C_{21}H_{20}N_3O_4$ ($M+H^+$) 378.1459; found 378.1448.

4.20. Phenol 35b

To a solution of **34b** (110 mg, 0.29 mmol) in MeOH (5 ml) was added $NaBH_4$ (12 mg, 0.32 mmol, 1.1 equiv) at 0 °C. The reaction was monitored by TLC until consumption of the starting material.

Silica gel was added and the solvent was removed in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:1–20:1) to give **35b** (88 mg, 80%) as a white solid. Mp: >220 °C (decomposition); $[\alpha]_D^{24}$ −253.6 (*c* 0.33, MeOH); IR (KBr): 3336, 2935, 2852, 1662, 1632, 1482, 1454, 1200, 1019, 819 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 7.33 (d, *J*=1.5 Hz, 1H), 7.00 (s, 1H), 6.96 (d, *J*=2.3 Hz, 1H), 6.89 (dd, *J*=8.0, 1.7 Hz, 1H), 6.62–6.48 (m, 4H), 6.17 (d, *J*=4.6 Hz, 1H), 5.40 (d, *J*=4.1 Hz, 1H), 4.12 (s, 1H), 4.07 (d, *J*=6.5 Hz, 1H), 3.46 (d, *J*=14.0 Hz, 1H), 3.02 (dd, *J*=14.1, 6.6 Hz, 1H), 2.62 (dd, *J*=16.3, 4.5 Hz, 1H), 2.43–2.38 (m, 4H); ^{13}C NMR (125 MHz, CD_3CN) δ 169.94, 165.32, 159.23, 151.88, 142.32, 134.20, 132.19, 131.81, 130.82, 126.00, 115.60, 111.53, 111.00, 110.74, 110.12, 66.52, 59.88, 55.18, 42.19, 38.92, 32.76; ESI-MS (*m*/*z*): 378 ($M+H^+$); HRMS (ESI): calcd for $C_{21}H_{20}N_3O_4$ ($M+H^+$) 378.1455; found 378.1448.

4.21. Triflate 36a

To a solution of **35a** (50 mg, 0.13 mmol) in dry EtOAc (8 ml) under N_2 atmosphere was added triethylamine (0.3 ml). The solution was cooled down to −15 °C for 10 min, and Tf_2O (48 μl, 0.28 mmol, 2.15 equiv) was slowly added. The solution was stirred for 3 h at −15 °C until aqueous NH_4Cl solution was added. The resulting mixture was diluted with EtOAc and washed with water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatograph (CH_2Cl_2/MeOH, 100:1–20:1) to give **36a** (36 mg, 53%) as a white solid. Mp: >270 °C (dec); $[\alpha]_D^{28}$ +217.0 (*c* 0.16, MeOH); IR (KBr): 3285, 3053, 2928, 2845, 1673, 1654, 1488, 1418, 1213, 1060, 893 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.03 (d, *J*=2.7 Hz, 1H), 7.36 (d, *J*=3.7 Hz, 1H), 7.26 (d, *J*=1.6 Hz, 1H), 7.12 (dd, *J*=8.6, 2.7 Hz, 1H), 6.86 (dd, *J*=8.0, 1.6 Hz, 1H), 6.75 (dd, *J*=6.1, 4.8 Hz, 2H), 6.62 (d, *J*=8.6 Hz, 1H), 6.20 (d, *J*=3.8 Hz, 1H), 4.18 (d, *J*=4.2 Hz, 1H), 4.14 (s, 1H), 3.26 (d, *J*=13.8 Hz, 1H), 3.03 (s, 3H), 2.79 (dd, *J*=14.0, 4.6 Hz, 1H), 2.74 (dd, *J*=15.9, 3.6 Hz, 1H), 1.94 (dd, *J*=16.1, 3.9 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.41, 164.24, 156.49, 148.89, 141.32, 132.82, 131.60, 131.50, 128.47, 123.91, 121.09, 118.38 (q, *J*=319 Hz, 1C), 117.26, 109.93, 108.68, 107.95, 64.43, 58.13, 54.20, 39.09, 36.71, 32.67; ESI-MS (*m*/*z*): 510 ($M+H^+$); HRMS (ESI): calcd for $C_{22}H_{19}N_3O_6F_3S$ ($M+H^+$) 510.0957; found 510.0941.

4.22. Triflate 36b

To a solution of **35b** (28 mg, 0.074 mmol) in dry EtOAc (2 ml) under N_2 atmosphere was added triethylamine (0.05 ml). The solution was cooled down to −15 °C for 10 min, and Tf_2O (25 μl, 0.15 mmol, 2 equiv) was slowly added. The solution was stirred for 1 h at −15 °C until aqueous NH_4Cl solution was added. The resulting mixture was diluted with EtOAc and washed with water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash column chromatograph (CH_2Cl_2/MeOH, 100:1–20:1) to give **36b** (26.5 mg, 70%) as a white solid. Mp: >250 °C (decomposition); $[\alpha]_D^{25}$ −368.4 (*c* 0.115, MeOH); IR (KBr): 3444, 2934, 2848, 1673, 1636, 1490, 1419, 1217, 1137, 884 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 7.58 (d, *J*=2.6 Hz, 1H), 7.52 (d, *J*=3.1 Hz, 1H), 7.22 (d, *J*=1.5 Hz, 1H), 7.10 (dd, *J*=8.6, 2.6 Hz, 1H), 6.93 (dd, *J*=8.0, 1.7 Hz, 1H), 6.63 (d, *J*=3.7 Hz, 1H), 6.62 (d, *J*=3.1 Hz, 1H), 6.28 (d, *J*=3.2 Hz, 1H), 4.12 (d, *J*=6.5 Hz, 2H), 3.35 (d, *J*=13.7 Hz, 1H), 3.02 (dd, *J*=13.9, 6.4 Hz, 1H), 2.55 (dd, *J*=16.2, 4.5 Hz, 1H), 2.39–2.32 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.19, 164.00, 157.60, 148.64, 141.29, 133.21, 130.74, 130.15, 129.93, 124.52, 120.89, 118.28 (q, *J*=319 Hz, 1C), 116.78, 109.16, 108.58, 108.01, 64.83, 58.04, 53.41, 39.59 (DEPT, HMQC), 37.55, 31.62; ESI-MS (*m*/*z*): 510 ($M+H^+$); HRMS (ESI): calcd for $C_{22}H_{18}N_3O_6F_3SNa$ ($M+Na^+$) 532.0760; found 532.0761.

4.23. Compound 32a

A mixture of **36a** (35 mg, 0.069 mmol), triethylamine (30 μl, 0.22 mmol), and 15 mg $Pd(OH)_2/C$ (20% Pd) in MeOH (1.5 ml) and EtOAc (1.5 ml) was stirred at rt under hydrogen atmosphere (1 atm) at rt for 2 h. The reaction mixture was filtered through a pad of Celite. The solid was washed with 5% MeOH/CH_2Cl_2. The combined organic phases were concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:1–20:1) to afford **32a** (20 mg, 80%) as a white solid. Mp: >300 °C (decomposition); $[\alpha]_D^{29}$ +154.8 (*c* 0.14, $CHCl_3$); IR (KBr): 3330, 2925, 2848, 1670, 1650, 1485, 1316, 1233, 1057, 944, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J*=7.5 Hz, 1H), 7.12 (t, *J*=7.7 Hz, 1H), 6.97–6.89 (m, 3H), 6.83 (d, *J*=8.5 Hz, 1H), 6.67 (d, *J*=7.8 Hz, 1H), 6.14 (d, *J*=3.6 Hz, 1H), 5.44 (s, 1H), 4.91 (d, *J*=3.6 Hz, 1H), 4.22 (s, 1H), 4.17 (d, *J*=4.5 Hz, 1H), 3.29–3.24 (m, 2H), 3.16 (s, 3H), 3.02 (dd, *J*=14.0, 4.6 Hz, 1H), 1.89 (dd, *J*=16.2, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.95, 165.57, 156.95, 147.47, 131.93, 131.39, 130.82, 129.55, 128.51, 124.82, 124.75, 120.59, 110.94, 109.20, 109.07, 65.35, 58.93, 55.48, 40.58, 37.61, 33.84; ESI-MS (*m*/*z*): 362 ($M+H^+$); HRMS (ESI): calcd for $C_{21}H_{20}N_3O_3$ ($M+H^+$) 362.1496; found 362.1499.

4.24. Compound 3b

A mixture of **36b** (62.6 mg, 0.123 mmol), triethylamine (34 μl, 0.246 mmol), and 15 mg $Pd(OH)_2/C$ (20% Pd) in MeOH (3 ml) and EtOAc (1 ml) was stirred at rt under hydrogen atmosphere (1 bar) at rt for 2 h. The reaction mixture was filtered through a pad of Celite. The solid was rinsed with 5% methanol/dichloromethane. The combined filtrates were concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH, 100:1–20:1) to afford **3b** (43.0 mg, 96%) as a white solid. Mp: >300 °C (dec); $[\alpha]_D^{28.7}$ −416.2 (*c* 0.125, MeOH); IR (KBr): 3430, 2979, 2858, 1664, 1634, 1479, 1055, 1012, 810, 744 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.44 (d, *J*=7.2 Hz, 1H), 7.22 (d, *J*=1.4 Hz, 1H), 7.14 (d, *J*=3.5 Hz, 1H), 7.03 (td, *J*=7.7, 1.2 Hz, 1H), 6.88 (dd, *J*=8.0, 1.7 Hz, 1H), 6.73 (td, *J*=7.4, 0.8 Hz, 1H), 6.60–6.54 (m, 2H), 6.19 (d, *J*=3.6 Hz, 1H), 4.12 (m, 2H), 3.36 (m, 1H), 2.99 (dd, *J*=14.0, 6.4 Hz, 1H), 2.55 (m, 1H), 2.41–2.34 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ 168.28, 164.18, 157.70, 148.45, 131.67, 131.11, 130.30, 129.66, 127.96, 124.51, 122.92, 118.20, 108.87, 108.58, 108.06, 64.92, 58.02, 53.60, 40.47, 37.49, 31.63; ESI-MS (*m*/*z*): 362 ($M+H^+$); HRMS (ESI): calcd for $C_{21}H_{20}N_3O_3$ ($M+H^+$) 362.1504; found 362.1499.

4.25. Azonazine diastereomer 1a (the originally proposed structure)

To a solution of **32a** (14 mg, 0.039 mmol) in HOAc (2 ml) was added Ac_2O (0.01 ml, 0.106 mmol) at rt. The resulting mixture was stirred at rt for 6 h. The solvent was removed, and the residue was diluted by EtOAc. The organic layer was washed with aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by preparative TLC (EtOAc/MeOH, 50:1) to afford **1a** (10.5 mg, 67%) as a white solid. Mp: >300 °C (dec); $[\alpha]_D^{28.2}$ +342.7 (*c* 0.175, MeOH); IR (KBr): 3518, 3232, 3012, 2928, 2848, 1677, 1649, 1485, 1391, 1241, 971, 756 cm^{-1}; ^1H NMR (500 MHz, CD_3CN) δ 8.10 (s, 1H), 8.06 (d, *J*=7.1 Hz, 1H), 7.26 (t, *J*=7.3 Hz, 1H), 7.19 (t, *J*=7.4 Hz, 1H), 7.01 (s, 1H), 6.91 (d, *J*=8.1 Hz, 1H), 6.80 (d, *J*=8.1 Hz, 1H), 6.46 (s, 1H), 5.61 (s, 1H), 4.18 (s, 1H), 4.14 (d, *J*=4.5 Hz, 1H), 3.29 (d, *J*=14.1 Hz, 1H), 3.13 (dd, *J*=16.3, 2.8 Hz, 1H), 3.09 (s, 3H), 2.89 (dd, *J*=14.1, 4.7 Hz, 1H), 2.41 (s, 3H), 2.18 (dd, *J*=16.3, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_3CN) δ 171.74, 168.24, 165.77, 157.67, 142.95, 134.78, 133.77, 132.82, 130.35, 129.28, 125.35 (2C), 124.95, 116.52, 111.25, 107.01, 65.97, 58.79, 56.18, 40.98, 38.20,

33.94, 24.37; ESI-MS (m/z): 404 ($M+H^+$); HRMS (ESI): calcd for $C_{23}H_{21}N_3O_4Na$ ($M+Na^+$) 426.1429; found 426.1424.

4.26. *ent*-(−)-Azonazine (1b)

To a solution of **3b** (13 mg, 0.036 mmol) in HOAc (1.5 ml) was added Ac_2O (0.01 ml, 0.106 mmol) at rt. The resulting mixture was stirred at rt for 4 h. The solvent was removed and the residue was diluted by EtOAc. The organic layer was washed with aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by preparative TLC (EtOAc/MeOH, 50:1) to afford **1b** (13 mg, 89%). The single crystal for X-ray analysis was prepared by slow evaporation from CH_3CN. Mp: >350 °C (dec); $[\alpha]_D^{26.5}$ −299.3 (c 0.11, MeOH); IR (KBr): 3430, 3219, 2926, 2849, 1661, 1626, 1485, 1394, 1283, 1027, 740 cm^{-1}; ^1H NMR (600 MHz, CD_3CN) δ 8.13 (s, 1H), 7.60 (dd, J=7.5, 0.8 Hz, 1H), 7.51 (d, J=1.6 Hz, 1H), 7.29 (td, J=7.8, 1.3 Hz, 1H), 7.19 (td, J=7.5, 1.1 Hz, 1H), 6.96 (m, 2H), 6.67 (d, J=8.1 Hz, 1H), 6.59 (s, 1H), 4.27 (d, J=5.1 Hz, 1H), 4.09 (d, J=6.5 Hz, 1H), 3.50 (d, J=14.2 Hz, 1H), 3.08 (dd, J=14.2, 6.9 Hz, 1H), 2.84 (dd, J=16.5, 5.8 Hz, 1H), 2.49 (dd, J=16.5, 2.2 Hz, 1H), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, CD_3CN) δ 171.29, 169.43, 165.49, 159.05, 142.52, 135.37, 133.22, 132.02, 131.51, 129.62, 126.46, 125.71, 124.15, 117.31, 110.84, 106.98, 66.32, 59.08, 54.84, 43.41, 39.24, 32.83, 24.17; ESI-MS (m/z): 404 ($M+H^+$); HRMS (ESI): calcd for $C_{23}H_{22}N_3O_4$ ($M+H^+$) 404.1610; found 404.1605.

4.27. Azonazine analogue 33a

To a solution of **11a** (26 mg, 0.047 mmol) in THF (3 ml) was added Zn powder (9.0 mg, 0.14 mmol), Et_3SiH (29 μl, 0.19 mmol), and AcOH (30 μl, 0.52 mmol) at rt under N_2 atmosphere. The reaction mixture was stirred at rt until consumption of the starting material (monitored by TLC). The reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The solid was washed with EtOAc. The organic layers were washed with aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The crude residue was directly used for the next step without further purification.

The above crude product was treated with HOAc (1.5 ml) and Ac_2O (0.01 ml, 0.106 mmol), and the resulting mixture was stirred at rt for 10 h. The mixture was concentrated in vacuo, and the residue was then diluted by EtOAc. The solution was washed with aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by preparative TLC (EtOAc/MeOH, 50:1) to afford **33a** (16 mg, 70% for two steps) as a white solid. $[\alpha]_D^{27}$ +282.10 (c 0.20, THF); IR (KBr): 3224, 2924, 2854, 1677, 1651, 1619, 1490, 1390, 1261, 1162, 1066, 971, 818 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 8.05 (s, 1H), 7.83 (d, J=2.7 Hz, 1H), 7.00 (s, 1H), 6.92 (d, J=8.1 Hz, 1H), 6.84 (m, 2H), 6.45 (s, 1H), 5.63 (s, 1H), 4.58 (q, J=8.4 Hz, 2H), 4.19 (s, 1H), 4.15 (d, J=4.3 Hz, 1H), 3.28 (d, J=14.0 Hz, 1H), 3.07 (m, 4H), 2.89 (dd, J=14.1, 4.6 Hz, 1H), 2.39 (s, 3H), 2.12 (s, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ 171.37, 168.37, 165.76, 157.59, 155.33, 138.00, 133.81, 131.38 (q, J=329 Hz), 125.37, 123.71, 118.38, 117.26, 114.37, 112.57, 111.29, 106.99, 66.7 (q, J=35 Hz), 65.97, 65.93, 58.84, 56.10, 40.60, 38.19, 34.95, 33.93, 30.44, 24.12. HRMS (MALDI): calcd for $C_{25}H_{22}N_3O_5Na$ ($M+Na^+$) 524.1428; found 524.1404.

4.28. Azonazine analogue 33b

To a solution of **11b** (20 mg, 0.036 mmol) in THF (1 ml) was added Zn powder (5.0 mg, 0.077 mmol), Et_3SiH (22.9 μl, 0.14 mmol), and AcOH (23 μl, 0.40 mmol) at rt under N_2 atmosphere. The reaction mixture was stirred at rt until consumption of the starting material (monitored by TLC). The reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The solid was washed with EtOAc. The organic layers were washed with aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The crude residue was directly used for the next step without further purification.

The above crude product was treated with HOAc (2.0 ml) and Ac_2O (0.01 ml, 0.106 mmol), and the resulting mixture was stirred at rt for 10 h. The mixture was concentrated in vacuo, and the residue was then diluted by EtOAc. The solution was washed with aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by preparative TLC (EtOAc/MeOH, 50:1) to afford **33b** (12.6 mg, 70% for two steps) as a white solid. Mp: >270 °C (dec); $[\alpha]_D^{26}$ −251.4 (c 0.725, THF); IR (KBr): 3451, 2964, 2917, 2844, 1673, 1656, 1492, 1391, 1259, 1154, 1077, 1018, 797 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.00 (d, J=8.7 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J=2.5 Hz, 1H), 6.99 (s, 1H), 6.97 (d, J=1.8 Hz, 1H), 6.74–6.68 (d, J=8.5 Hz, 2H), 4.87–4.71 (m, 2H), 4.25 (s, 1H), 4.16 (d, J=6.3 Hz, 1H), 3.40 (d, J=13.9 Hz, 1H), 3.06 (dd, J=14.0, 6.6 Hz, 1H), 2.80 (dd, J=16.2, 5.1 Hz, 1H), 2.50–2.43 (m, 1H), 2.38 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.64, 168.07, 164.17, 157.14, 153.98, 135.95, 135.82, 131.76, 130.44, 129.98, 124.92, 124.02 (q, J=277 Hz, 1C), 116.20, 113.55, 110.82, 109.49, 105.49, 65.13 (q, J=34 Hz, 1C), 64.73, 57.37, 53.33, 40.64, 37.73, 31.67, 23.36; ESI-MS (m/z): 502 ($M+H^+$); HRMS (ESI): calcd for $C_{25}H_{23}N_3O_5F_3$ ($M+H^+$) 502.1576; found 502.1584.

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Supplementary data

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