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The Efficient Direct Synthesis of N,O-Acetal Compounds as Key Intermediates of Discorhabdin A: Oxidative Fragmentation Reaction of α-Amino Acids or β-Amino Alcohols by Using Hypervalent Iodine(III) Reagents

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Abstract: Hypervalent iodine(III) reagents are readily available, easy to handle, and have a low toxicity and similar reactivities to those of heavy metal reagents, and hence they are used for various oxidative reactions. The oxidative cleavage of alkynes or carbonyl compounds by using bis(trifluoroacetoxy)iodo(III) pentafluorobenzene ($C_6F_5I(OCOCF_3)_2$) has been reported.[1] Herein, the efficient direct synthesis of N,O-acetal compounds as key intermediates of discorhabdin A, by the oxidative fragmentation reaction of α-amino acids or β-amino alcohols by using $C_6F_5I(OCOCF_3)_2$, is described.

Keywords: discorhabdin A · hypervalent iodine reagents · N,O-acetal · natural products · synthetic methods

Introduction

N,O-Acetal compounds **A** are important intermediates as they are relatively stable, but readily generate unstable N-imines **B**, which are attacked by various nucleophiles to produce functionalized amine and amino acid derivatives **C**.

α-Amino acids and β-amino alcohols have recently attracted attention because they are easily available and constitute versatile building blocks as well as chiral auxiliaries. Therefore, the synthesis of N,O-acetal compounds from α-amino acids or β-amino alcohols facilitates the synthesis of functionalized natural and unnatural amine or amino acid derivatives and natural products containing a nitrogen atom (Scheme 1).[2]

Several methods have appeared for the synthesis of N,O-acetal compounds from α-amino acids and β-amino alcohols, for example, the electrochemical oxidation of α-amino acids,[3] the oxidation by lead tetraacetate[4] or the oxidative radical reaction[5] by phenyliodine(III) diacetate (PIDA) and iodine. However, these methods are problematic with regards to the use of highly toxic reagents, side reactions by iodine, generality and yield.

Over the past two decades, hypervalent iodine(III) reagents have received significant attention due to their low toxicity, ready availability, easy handling, and reactivities similar to those of heavy metal reagents. As a continuation of our studies on hypervalent iodine chemistry, we have already reported various oxidative reactions of carbonyl, alkynyl, phenol, and phenyl ether derivatives[6] by using phenyliodine(III) bis(trifluoroacetate) (PIFA) and PIDA. We have also accomplished the first diastereoselective total synthesis of the marine anticancer alkaloid (+)-discorhabdin A.[7] The key step in the stereocontrolled total synthesis of (+)-discorhabdin A involves the diastereoselective oxidative spirocyclization with PIFA. It has been clarified that the N,O-acetal compound is an important intermediate in the synthesis of (+)-discorhabdin A. However, up to this point we had only converted the β-amino alcohol into the N,O-acetal intermediate by using highly toxic lead tetraacetate (Scheme 2).

We recently succeeded in the novel and efficient direct synthesis of N,O-acetal compounds by the oxidative fragmentation reaction of α-amino acids or β-amino alcohols with the hypervalent iodine(III) reagent, bis(trifluoroacetoxy)iodo(III) pentafluorobenzene ($C_6F_5I(OCOCF_3)_2$) and communicated that this reaction could be applied to the improved synthesis of the N,O-acetal discorhabdin intermediate, which contains functionalized and unstable pyrro-

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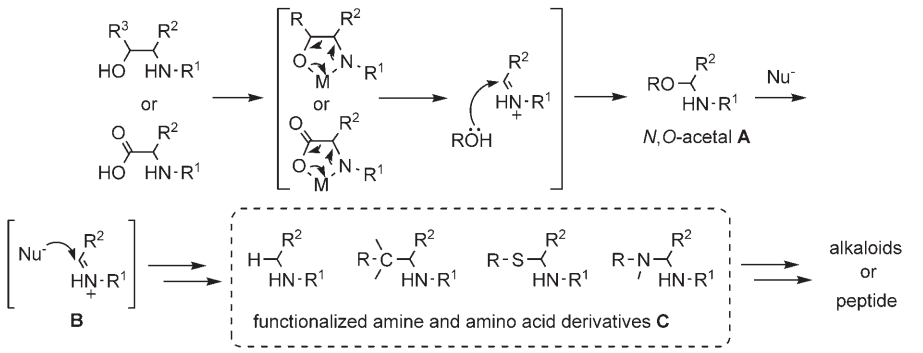
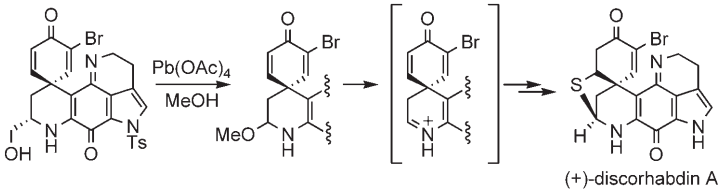
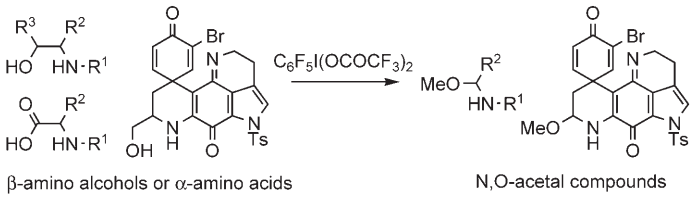


Scheme 1. Synthesis and efficient use of N,O-acetals.



Scheme 2. First total synthesis of (+)-discorhabdin A.

loiminoquinone moieties.[8] We now report the details of the composition of these N,O-acetal compounds and the application to the total synthesis of (+)- and (−)-discorhabdin A (Scheme 3).



Scheme 3. Fragmentation reaction by $C_6F_5I(OCOCF_3)_2$.

Results and Discussion

To optimize the reaction conditions, we first examined the MeO-introduction reaction via the iminium salt with the N-Fmoc serine methyl ester (**1a**, Table 1, Fmoc = fluorenylmethoxycarbonyl). Almost no reaction occurred when PIDA and PIFA were used, well-known hypervalent iodine(III) reagents, (entries 10 and 11) or when lead tetraacetate or $NaIO_4$ were used (entries 12–15), while surprisingly, the reaction proceeded smoothly with $C_6F_5I(OCOCF_3)_2$ to give the desired N,O-acetal compounds (entries 1–7). Specifically, the reaction employing CH_3CN/MeOH 10:1 (slightly diluted conditions) produced the N,O-acetal compound **2a** in good yield (entry 6).

Similarly, by using these reaction conditions (entry 6, Table 1), the reactions of other *N*-protected-β-amino alcohols (**1a–h**) with $C_6F_5I(OCOCF_3)_2$ were investigated (Table 2). Although the protecting groups on nitrogen were changed from the carbamates to Cbz and Bz groups (entries 6–8), most reactions produced good yields of the N,O-acetal compounds (**2a–h**).

Next, we applied this method to the α-amino acid derivatives (**3a–d**) to produce the N,O-acetal compounds (**4a–d**) and examined its application to intramolecular reaction in the absence of MeOH (Table 3). The formation of **4e** (entry 5) is reasonably explained by supposing that **3e** initially produces the iminium intermediate by treatment with $C_6F_5I(OCOCF_3)_2$ followed by an intramolecular cyclization involving the carboxyl group (Scheme 4).

A plausible reaction mechanism for the formation of N,O-acetal compounds from β-amino alcohols or α-amino acids is shown in Scheme 5. It is possible that the reaction proceeds by a radical pathway, but no signal corresponding to this was found in our ESR spectroscopic studies. We rather propose that the reaction proceeds via the five-membered ring intermediate as proposed in the reaction with lead tetraacetate.[9]

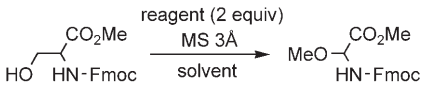
At the end of this reaction, we examined the application of this methodology to the synthesis of (+)- and (−)-discorhabdins (Table 4). Almost no reaction of the naphthoquinone (**5a**) occurred when the optimized conditions were used (entry 1). An explanation for this could be that the N,O-acetal compound (**6a**) may be undergoing disintegration as a result of the acidic reaction conditions. The reaction with $NaHCO_3$ proceeded smoothly (entry 2) to give the N,O-acetal compound (**6a**) in almost the same yield as that when lead tetraacetate was used (entry 3). Similarly, without $NaHCO_3$ almost no reaction of the β-amino alcohol compound, (+)-**5b** occurred (entry 4). When $NaHCO_3$ was added, the N,O-acetal intermediate of (+)-discorhabdin A, (+)-**6b** was produced in high yield (entries 5 and 8). The N,O-acetal compound (−)-**6b** was also produced in 93% yield under the same conditions (entry 9).

The N,O-acetal (−)-**6b** was converted to (−)-dicorhabdin A by a similar series of reactions as those for (+)-discorhabdin A, derived from (L)-tyrosine methyl ester (Scheme 6).

Conclusion

We have found a mild and efficient fragmentation method for α-amino acids and β-amino alcohols by using the hypervalent iodine(III) reagent $C_6F_5I(OCOCF_3)_2$ in place of toxic lead tetraacetate. This method facilitates the synthesis of functionalized amine or amino acid derivatives. The present fragmentation method of β-amino alcohols could be success-

Table 1. Examination of the reaction conditions with N-Fmoc serine methyl ester.

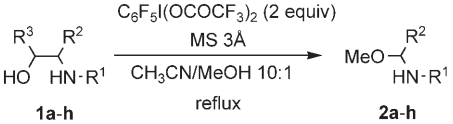


1a 2a

Entry	Reagent	Solvent	T [°C]	c [M]	t [h]	Yield [%]
1[a]	$C_6F_5I(OCOCF_3)_2$	CH_3CN/MeOH 2:1	50	0.1	24	13[b]
2	$C_6F_5I(OCOCF_3)_2$	CH_3CN/MeOH 50:1	50	0.1	24	26[b]
3	$C_6F_5I(OCOCF_3)_2$	CH_3CN/MeOH 10:1	50	0.1	24	41[b]
4	$C_6F_5I(OCOCF_3)_2$	CH_3CN/MeOH 10:1	reflux	0.1	24	58[b]
5	$C_6F_5I(OCOCF_3)_2$	CH_3CN/MeOH 10:1	reflux	0.1	5	66[b]
6	$C_6F_5I(OCOCF_3)_2$	CH_3CN/MeOH 10:1	reflux	0.02	5	89
7	$C_6F_5I(OCOCF_3)_2$ (1.2 equiv)	CH_3CN/MeOH 10:1	reflux	0.02	5	41[b]
8	$C_6F_5I(OCOCF_3)_2$	AcOEt/MeOH 10:1	reflux	0.02	5	76
9	$C_6F_5I(OCOCF_3)_2$	AcOEt/MeOH 10:1	reflux	0.1	5	43[b]
10	$C_6H_5I(OCOCF_3)_2$(PIFA)	CH_3CN/MeOH 10:1	reflux	0.02	24	trace[b]
11	$C_6H_5I(OCOCH_3)_2$(PIDA)	CH_3CN/MeOH 10:1	reflux	0.02	24	trace[b]
12	$Pb(OAc)_4$	CH_3CN/MeOH 10:1	reflux	0.02	24	trace[b]
13	$Pb(OAc)_4$	AcOEt/MeOH 10:1	reflux	0.02	24	trace[b]
14	$Pb(OAc)_4$	CH_2Cl_2/MeOH 10:1	RT	0.02	24	trace[b]
15	$NaIO_4$	MeOH	RT→reflux	0.02	24	trace[b]

[a] Without MS 3 Å. [b] Starting materials remained.

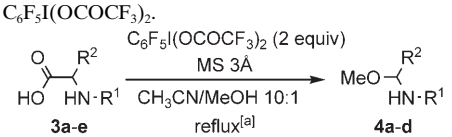
Table 2. Synthesis of N,O-acetals by oxidative fragmentation of β-amino alcohols with $C_6F_5I(OCOCF_3)_2$.



1a-h 2a-h

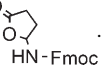
Entry	Reactant	R^1	R^2	R^3	t [h]	Yield [%]
1	**1a**	Fmoc	CO_2Me	H	5	89
2	**1b**	Fmoc	CO_2Me	CH_3	1	98
3	**1c**	Fmoc	H	H	3	90
4	**1d**	Fmoc	CH_3	H	0.5	63
5	**1e**	Fmoc	$CH(CH_3)_2$	H	0.5	76
6	**1f**	Cbz	CO_2Me	H	7	80
7	**1g**	Cbz	CO_2Bn	CH_3	1	quant.
8	**1h**	Bz	CO_2Me	CH_3	2	47

Table 3. Synthesis of N,O-acetals by oxidative fragmentation of α-amino acids with $C_6F_5I(OCOCF_3)_2$.



3a-e 4a-d

Entry	Reactant	R^1	R^2	t [h]	Yield [%]
1	**3a**	Fmoc	H	1	73
2	**3b**	Fmoc	CH_3	0.25	54
3	**3c**	Fmoc	$CH_2CH_2CO_2Me$	0.25	55
4	**3d**	Cbz	CO_2Et	1	46
5	**3e**	Fmoc	$CH_2CH_2CO_2H$	0.5	73[b]

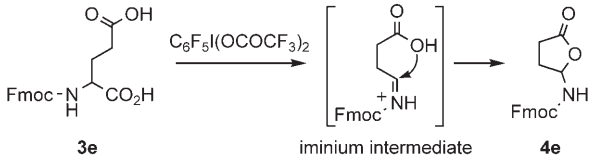
[a] The reaction does not proceed at room temperature. [b] Without MeOH. Product = **4e** 

fully applied to an improved synthesis of (+)- and (−)-discorhabdin A.

Experimental Section

^1H and ^{13}C NMR spectra were measured at 300 or 270 MHz with TMS as the internal standard. IR spectra were recorded by a diffuse reflectance measurement of samples dispersed in KBr powder. Elemental analyses and HRMS were performed by the Elemental Analysis Section of Osaka University. Merck silica gel 60 for column chromatography and Merck precoated TLC plates, silica gel F_{254}, for preparative TLC were used, respectively.

Materials: N-Fmoc[10] and N-Cbz[11] amino acids or amino alcohols were prepared according to the reported procedure. Phenyliodine(III) bis(trifluoroacetate) (PIFA) was prepared from commercially available phenyliodine diacetate (PIDA) and trifluoroacetic acid.[12] Bis(trifluoroacetoxy)iodo(III) pentafluorobenzene ($C_6F_5I(OCOCF_3)_2$) was prepared from pentafluoroiodobenzene and nitric acid.[13]



3e iminium intermediate 4e

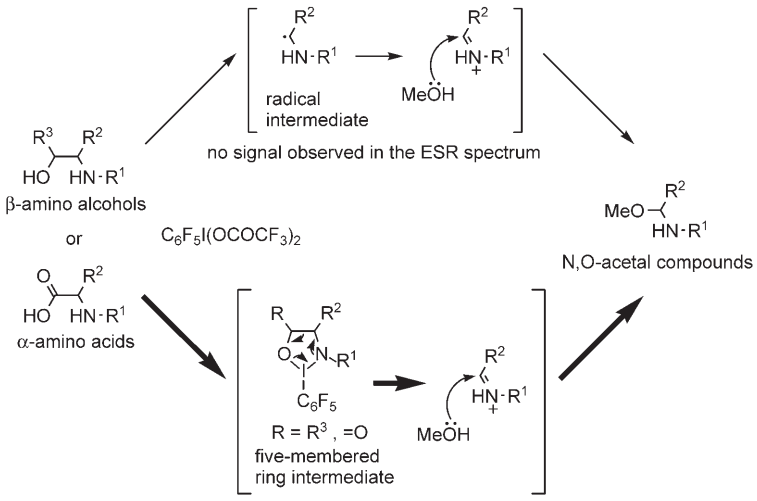
Scheme 4. Plausible reaction mechanism for the formation of **4e**.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxypropionic acid methyl ester (1a): ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J = 7.2$ Hz, 2H), 7.53 (br s, 2H), 7.33 (t, $J = 7.2$ Hz, 2H), 7.24 (t, $J = 7.5$ Hz, 2H), 5.90 (d, $J = 7.8$ Hz, 1H), 4.41–4.29 (m, 3H), 4.15 (t, $J = 6.6$ Hz, 1H), 3.93 (dd, $J = 10.2$, 3.0 Hz, 1H), 3.82 (dd, $J = 9.7$, 2.7 Hz, 1H), 3.69 (s, 3H), 2.78 ppm (br s, 1H); ^{13}C NMR (67.8 MHz $CDCl_3$): $\delta = 171.06$, 156.27, 143.69, 143.56, 141.20, 141.17, 127.65, 126.99, 124.98, 119.89, 67.09, 32.97, 55.96, 52.63, 46.98 ppm; IR (KBr): $\tilde{\nu} = 3350$, 2953, 2251, 1693, 1504 cm^{-1}; HRFABMS: calcd for $C_{19}H_{19}NO_5Na$: 364.12 $[M+Na]^+$; found: 364.12.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxybutyric acid methyl ester (1b): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J = 7.5$ Hz, 2H), 7.54 (d, $J = 6.9$ Hz, 2H), 7.33 (t, $J = 7.2$ Hz, 2H), 7.24 (td, $J = 7.5$, 1.2 Hz, 2H), 5.59 (d, $J = 9.0$ Hz, 1H), 4.36 (d, $J = 6.9$ Hz, 2H), 4.28 (d, $J = 9.3$ H, 2H), 4.17 (t, $J = 6.9$ Hz, 1H), 3.70 (s, 3H), 2.01 (br s, 1H), 1.18 ppm (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 171.65$, 156.71, 143.81, 143.65, 141.28, 127.70, 127.05, 125.06, 119.96, 67.93, 67.18, 59.02, 52.63, 47.12, 19.82 ppm; IR (KBr): $\tilde{\nu} = 3433$, 2953, 2253, 1713, 1514 cm^{-1}; HRFABMS: calcd for $C_{20}H_{22}NO_5$: 356.15 $[M+H]^+$; found: 356.15.

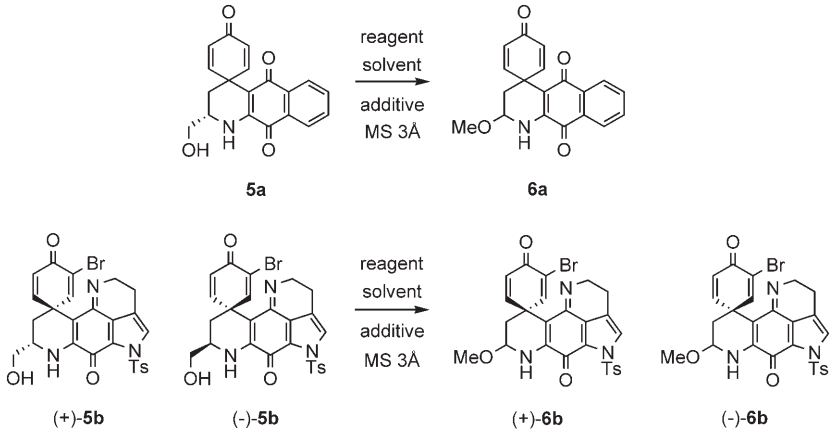
(2-Hydroxyethyl)carbamic acid 9*H*-fluoren-9-yl methyl ester (1c): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 7.5$ Hz, 2H), 7.57 (d, $J = 7.5$ Hz, 2H), 7.39 (t, $J = 7.5$ Hz, 2H), 7.30 (td, $J = 7.8$, 1.2 Hz, 2H), 5.13 (br s, 1H), 4.42 (d, $J = 6.6$ Hz, 2H), 4.20 (t, $J = 6.6$ Hz, 1H), 3.70 (t, $J = 4.5$ Hz, 2H), 3.34 ppm (t, $J = 5.4$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 143.84$, 141.31, 127.69, 127.04, 124.99, 119.97, 47.22 ppm; IR (KBr): $\tilde{\nu} = 3477$, 3352, 1672, 1537 cm^{-1}; HRFABMS: calcd for $C_{17}H_{17}NO_3Na$: 306.11 $[M+Na]^+$; found: 306.11.

(2-Hydroxy-1-methylethyl)carbamic acid 9*H*-fluoren-9-yl methyl ester (1d): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 7.2$ Hz, 2H), 7.58 (d, $J = 7.5$ Hz, 2H), 7.39 (t, $J = 7.5$ Hz, 2H), 7.30 (td, $J = 7.5$, 1.2 Hz, 2H), 4.83 (br s, 1H), 4.42 (d, $J = 6.6$ Hz, 2H), 4.20 (t, $J = 6.6$ Hz, 1H), 3.81 (br s,



Scheme 5. Plausible reaction mechanism for the formation of the N,O-acetals.

Table 4. Synthesis of N,O-acetal compounds by oxidative fragmentation of amino alcohol compounds of discorhabdins with $C_6F_5I(OCOCF_3)_2$.



Entry		Reagent (equiv)	Solvent	Additive (equiv)	T [°C]	t [h]	Yield [%]
1	**5a**	$C_6F_5I(OCOCF_3)_2$ (2.0)	CH_3CN/MeOH 10:1	none	RT→reflux	5.0	3
2	**5a**	$C_6F_5I(OCOCF_3)_2$ (2.0)	CH_3CN/MeOH 10:1	$NaHCO_3$ (7.0)	RT	4.0	50
3	**5a**	$Pb(OAc)_4$ (4.0)	CH_2Cl_2/MeOH 2:1	none	RT	5.0	61
4	(+)-**5b**	$C_6F_5I(OCOCF_3)_2$ (2.0)	CH_3CN/MeOH 10:1	none	RT→reflux	1.0	trace
5	(+)-**5b**	$C_6F_5I(OCOCF_3)_2$ (2.0)	CH_3CN/MeOH 10:1	$NaHCO_3$ (7.0)	RT	1.0	79
6	(+)-**5b**	$C_6F_5I(OCOCF_3)_2$ (4.0)	CH_3CN/MeOH 10:1	$NaHCO_3$ (7.0)	RT	24	26
7	(+)-**5b**	$C_6F_5I(OCOCF_3)_2$ (2.0)	CH_2Cl_2/MeOH 2:1	$NaHCO_3$ (7.0)	RT	1.5	51
8	(+)-**5b**	$Pb(OAc)_4$ (2.0)	CH_2Cl_2/MeOH 2:1	none	0	1.5	80
9	(−)-**5b**	$C_6F_5I(OCOCF_3)_2$ (2.0)	CH_3CN/MeOH 10:1	$NaHCO_3$ (7.0)	RT	0.75	93

1H), 3.67–3.64 (m, 1H), 3.54–3.52 (m, 1H), 1.16 ppm (d, J=6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=156.55, 143.83, 143.81, 141.27, 127.65, 127.01, 124.93, 119.93, 66.58, 48.89, 47.18, 17.21 ppm; IR (KBr): $\tilde{\nu}$=3321, 2945, 1693, 1537 cm^{-1}; HRFABMS: calcd for $C_{18}H_{20}NO_3$: 298.14 $[M+H]^+$; found: 298.15.

(1-Hydroxy-methyl-2-methylpropyl)carbamic acid 9*H*-fluoren-9-ylmethyl ester (1e): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.75 (d, J=7.5 Hz, 2H), 7.58 (d, J=7.5 Hz, 2H), 7.39 (t, J=7.2 Hz, 2H), 7.30 (td, J=7.8, 1.2 Hz, 2H), 4.85 (d, J=7.8 Hz, 1H), 4.44 (t, J=6.3 Hz, 2H), 4.21 (t, J=6.6 Hz, 1H), 3.66 (dd, J=9.6, 3.0 Hz, 2H), 3.47–3.45 (m, 1H), 1.87–1.80 (m, 1H), 0.94 (d, J=8.1 Hz, 3H), 0.91 ppm (d, J=7.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=143.90, 143.86, 141.34, 127.66, 127.04, 124.97, 119.95, 66.57, 63.79, 58.57, 47.34, 29.19, 19.47, 18.63 ppm; IR (KBr): $\tilde{\nu}$=3331, 2961, 1697, 1514 cm^{-1}; HRFABMS: calcd for $C_{20}H_{24}NO_3$: 326.18 $[M+H]^+$; found: 326.18.

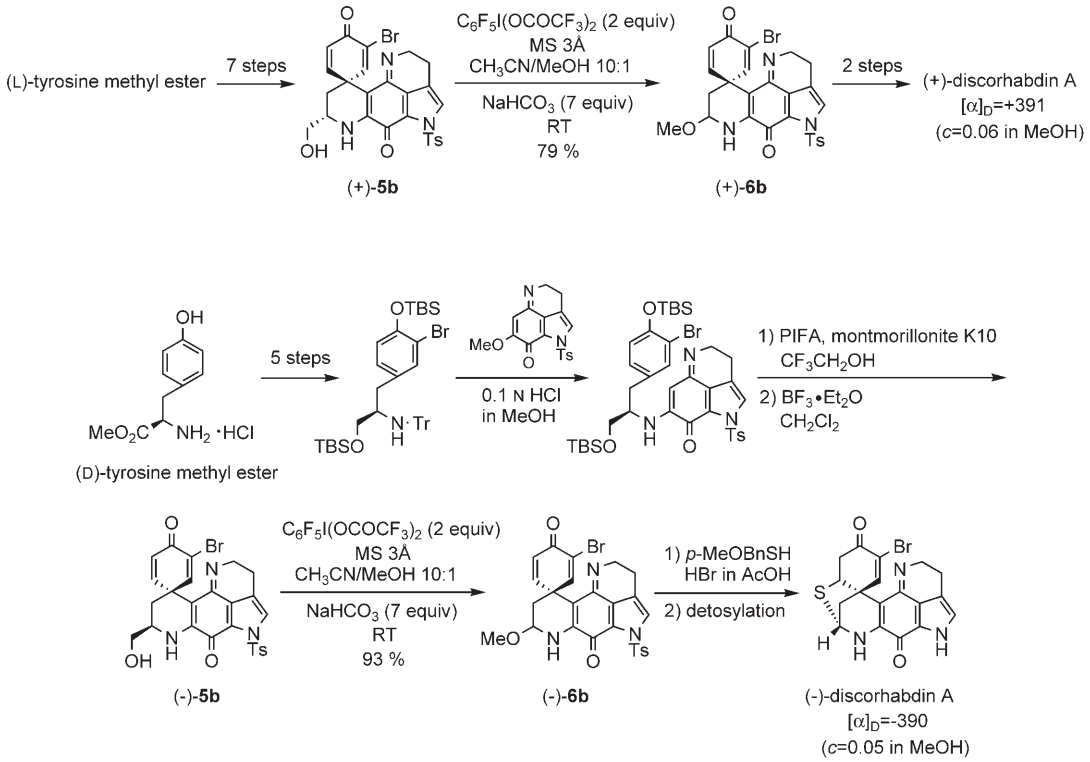
2-Benzyloxycarbonylamino-3-hydroxy-propionic acid methyl ester (1f): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.26 (s, 5H), 5.77 (d, J=6.2 Hz, 1H), 5.03 (s, 2H), 4.36 (t, J=3.6 Hz, 1H), 3.90 (dd, J=11.1, 3.0 Hz, 1H), 3.81 (dd, J=11.1, 2.7 Hz, 1H), 3.68 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.03, 156.24, 135.99, 128.49, 128.20, 128.07, 67.15, 63.11, 56.01, 52.67 ppm; IR (KBr): $\tilde{\nu}$=3364, 2955, 1693, 1504 cm^{-1}; HRFABMS: calcd for $C_{12}H_{16}NO_5$: 254.10 $[M+H]^+$; found: 254.10.

2-Benzyloxycarbonylamino-3-hydroxy-butyric acid benzyl ester (1g): ^{1}H NMR (270 MHz, $CDCl_3$): δ=7.24 (s, 5H), 5.57 (d, J=8.6 Hz, 1H), 5.09 (s, 1H), 5.02 (s, 1H), 4.29–4.24 (m, 1H), 1.94 (brs, 1H), 1.12 ppm (d, J=6.48 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=170.99, 156.70, 136.09, 135.15, 128.60, 128.49, 128.44, 128.16, 128.00, 68.00, 67.32, 67.16, 59.21, 19.88 ppm; IR (KBr): $\tilde{\nu}$=3427, 2978, 1715, 1520 cm^{-1}; HRFABMS: calcd for $C_{19}H_{22}NO_5$: 344.15 $[M+H]^+$; found: 344.15.

2-Benzoylamino-3-hydroxybutyric acid methyl ester (1h): Benzoyl chloride (0.34 mL, 2.95 mmol) and Et_3N (0.82 mL, 5.90 mmol) were added to a solution of 2-amino-3-hydroxy-butyric acid methyl ester (500 mg, 2.95 mmol) in DMF (15 mL) at room temperature. The reaction mixture was stirred for 10 h, quenched with water and extracted with AcOEt. The combined organic layers were then washed with brine and dried over Na_2SO_4. The product was isolated by silica-gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.77 (d, J=7.2 Hz, 2H), 7.44 (t, J=6.9 Hz, 1H), 7.35 (t, J=6.9 Hz, 2H), 7.00 (d, J=8.7 Hz, 1H), 4.74 (dd, J=8.7, 2.1 Hz, 1H), 4.41–4.34 (m, 1H), 3.70 (s, 3H), 1.20 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=171.59, 167.97, 133.58, 131.88, 128.56, 127.18, 68.12, 57.64, 52.62, 19.99 ppm; IR (KBr): $\tilde{\nu}$=3358, 2976, 1745, 1651, 1537 cm^{-1}; HRFABMS: calcd for $C_{12}H_{16}NO_4$: 238.11 $[M+H]^+$; found: 238.11.

(9*H*-Fluoren-9-ylmethoxycarbonylamino)acetic acid (3a): ^{1}H NMR (270 MHz, CD_3OD): δ=7.79 (d, J=7.0 Hz, 2H), 7.67 (d, J=7.6 Hz, 2H), 7.38 (t, J=7.3 Hz, 2H), 7.30 (td, J=7.6, 1.4 Hz, 2H), 4.34 (t, J=6.2 Hz, 2H), 4.24 (d, J=6.8 Hz, 1H), 3.83 ppm (s, 2H); ^{13}C NMR (75.5 MHz, CD_3OD): δ=173.58, 159.10, 145.23, 142.53, 128.75, 128.13, 126.23, 120.89, 68.15, 43.07 ppm; IR (KBr): $\tilde{\nu}$=3319, 3047, 1737, 1697, 1549 cm^{-1}; HRFABMS: calcd for $C_{17}H_{16}NO_4$: 298.11 $[M+H]^+$; found: 298.11.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)propionic acid (3b): ^{1}H NMR (300 MHz, CD_3OD): δ=7.79 (d, J=7.2 Hz, 2H), 7.67 (t, J=6.9 Hz, 2H), 7.38 (t, J=7.5 Hz, 2H), 7.30 (td, J=7.2, 1.2 Hz, 2H), 4.39–4.14 (m, 4H),



Scheme 6. Improved synthesis of (+)- and (−)-discorhabdin A.

1.39 ppm (d, J=7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, CD_3OD): δ=176.52, 145.33, 145.17, 142.54, 128.75, 128.15, 128.12, 126.27, 126.21, 120.88, 67.96, 50.81, 17.78 ppm; IR(KBr): $\tilde{\nu}$=3310, 2924, 1693, 1537 cm^{-1}; HRFABMS: calcd for $C_{18}H_{18}NO_4$: 312.12 $[M+H]^+$; found: 312.12.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)pentanedioic acid 5-methyl ester (3c): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.65 (d, J=7.5 Hz, 2H), 7.47 (d, J=3.3 Hz, 2H), 7.29 (t, J=7.2 Hz, 2H), 7.19 (t, J=7.2 Hz, 2H), 5.65 (brs, 1H), 4.39 (brs, 1H), 4.29 (d, J=6.6 Hz, 2H), 4.10 (t, J=6.6 Hz, 1H), 3.55 (s, 3H), 3.40 (s, 1H), 2.37–2.34 (m, 2H), 2.18–2.16 (m, 1H), 2.00–1.92 ppm (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=173.61, 163.50, 156.31, 143.80, 143.58, 141.20, 127.64, 127.00, 125.03, 119.89, 67.09, 51.81, 47.00, 36.90, 31.79, 30.05, 27.26 ppm; IR (KBr): $\tilde{\nu}$=3323, 1951, 1713, 1531 cm^{-1}; HRFABMS: calcd for $C_{21}H_{22}NO_6$: 384.14 $[M+H]^+$; found: 384.15.

2-Benzyloxycarbonylaminomalonic acid monoethyl ester (3d): ^{1}H NMR (270 MHz, $CO(CD_3)_2$): δ=7.34 (m, 5H), 6.92 (d, J=6.8 Hz, 1H), 5.11 (s, 2H), 4.99 (d, J=8.1 Hz, 1H), 4.22 (q, J=7.1 Hz, 2H), 1.25 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=206.35, 129.17, 128.71, 128.65, 67.18, 62.58, 14.21 ppm; IR (KBr): $\tilde{\nu}$=2982, 1732, 1520 cm^{-1}; HRFABMS: calcd for $C_{13}H_{16}NO_6$: 282.10 $[M+H]^+$; found: 282.10.

2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)pentanedioic acid (3e): ^{1}H NMR (300 MHz, CD_3OD): δ=7.79 (d, J=7.2 Hz, 2H), 7.69–7.65 (m, 2H), 7.38 (t, J=7.2 Hz, 2H), 7.30 (td, J=7.5, 1.5 Hz, 2H), 4.35 (d, J=7.8 Hz, 2H), 4.25–4.18 (m, 2H), 2.41 (t, J=7.5 Hz, 2H), 2.24–2.12 (m, 1H), 1.96–1.85 ppm (m, 1H); ^{13}C NMR (75.5 MHz, CD_3OD): δ=176.39, 175.38, 158.69, 145.32, 145.18, 142.55, 130.11, 128.77, 128.16, 126.27, 120.89, 68.01, 54.63, 32.22, 27.88 ppm; IR (KBr): $\tilde{\nu}$=3000, 2253, 1713 cm^{-1}; HRFABMS: calcd for $C_{20}H_{20}NO_6$: 370.13 $[M+H]^+$; found: 370.13.

General procedure for the oxidative fragmentation reaction of α-amino acids or β-amino alcohols with $C_6F_5I(OCOCF_3)_2$: Under a nitrogen atmosphere, $C_6F_5I(OCOCF_3)_2$ (0.2 mmol) and molecular sieves (3 Å, 850 mg mmol^{-1}) were added to a stirred solution of the amino acid or amino alcohol (0.1 mmol) in CH_3CN (4.5 mL) and CH_3OH (0.5 mL) at room temperature. The reaction mixture was refluxed at 95 °C with stirring for 0.25–7 h. The solution was then quenched with aqueous saturated $NaHCO_3$ and extracted with AcOEt. The combined organic layers were washed with brine, dried, and concentrated in vacuo. Purification of the residue by silica-gel column chromatography gave the corresponding N,O-acetal compounds.

[(9*H*-Fluoren-9-ylmethoxycarbonylamino)]methoxyacetic acid methyl ester (2a): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.67 (d, J=7.5 Hz, 2H), 7.50 (d, J=6.9 Hz, 2H), 7.29 (t, J=7.2 Hz, 2H), 7.22 (t, J=7.2 Hz, 2H), 5.85 (d, J=9.0 Hz, 1H), 5.27 (d, J=9.6 Hz, 1H), 4.31–4.45 (m, 2H), 4.14 (t, J=6.6 Hz, 1H), 3.72 (s, 3H), 3.34 ppm (s, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=167.69, 155.39, 143.29, 143.16, 141.03, 140.99, 127.46, 126.81, 126.77, 126.76, 126.70, 124.61, 119.75, 119.69, 80.27, 66.92, 55.88, 52.60, 46.71 ppm; IR (KBr): $\tilde{\nu}$=3325, 2953, 1715, 1504 cm^{-1}; HRFABMS: calcd for $C_{19}H_{19}NO_5Na$: 364.12 $[M+Na]^+$; found: 364.12.

Methoxymethylcarbamic acid 9*H*-fluoren-9-yl methyl ester (2c): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.67 (d, J=7.5 Hz, 2H), 7.50 (d, J=7.5 Hz, 2H), 7.31 (t, J=7.2 Hz, 2H), 7.22 (t, J=7.2 Hz, 2H), 5.50 (brs, 1H), 4.53 (d, J=7.4 Hz, 2H), 4.37 (d, J=6.9 Hz, 2H), 4.14 (t, J=6.9 Hz, 1H), 3.22 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=156.37, 143.68, 141.27, 127.69, 127.01, 124.90, 119.95, 73.51, 66.74, 55.54, 53.40, 47.06 ppm; IR (KBr): $\tilde{\nu}$=3346, 2943, 1697, 1537 cm^{-1}; HRFABMS: calcd for $C_{17}H_{17}NO_3Na$: 306.11 $[M+Na]^+$; found: 306.11.

(1-Methoxy-ethyl)carbamic acid 9*H*-fluoren-9-ylmethyl ester (2d): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.69 (d, J=7.2 Hz, 2H), 7.52 (d, J=7.5 Hz, 2H), 7.33 (t, J=7.2 Hz, 2H), 7.23 (t, J=7.5 Hz, 2H), 4.97 (brs, 1H), 4.44 (dd, J=6.9, 10.5 Hz, 1H), 4.32 (dd, J=6.6, 10.5 Hz, 1H), 4.15 (t, J=6.3 Hz, 1H), 3.22 (s, 3H), 1.27 ppm (t, J=2.4 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=155.80, 143.78, 143.68, 141.31, 127.70, 127.04, 127.01, 124.97, 124.89, 124.72, 119.98, 80.00, 66.54, 55.26, 47.17, 21.70 ppm; IR(KBr): $\tilde{\nu}$=3317, 2932, 1713, 1514 cm^{-1}; HRFABMS: calcd for $C_{18}H_{19}NO_3Na$: 320.13 $[M+Na]^+$; found: 320.13.

(1-Methoxy-2-methylpropyl)carbamic acid 9*H*-fluoren-9-ylmethyl ester (2e): ^{1}H NMR (270 MHz, $CDCl_3$): δ=7.69 (d, J=7.6 Hz, 2H), 7.52 (d,

J=7.8 Hz, 2H), 7.32 (t, J=7.3 Hz, 2H), 7.24 (t, J=7.6 Hz, 2H), 4.85 (d, J=10.26 Hz, 1H), 4.56–4.33 (m, 3H), 4.15 (t, J=6.48, 1H), 3.21 (s, 3H), 1.77–1.67 (m, 1H), 0.87 (d, J=6.8 Hz, 3H), 0.83 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=156.21, 143.69, 143.59, 141.23, 127.60, 126.94, 126.92, 124.86, 124.82, 119.91, 87.73, 66.44, 55.72, 47.34, 33.15, 17.93, 17.26 ppm; IR (KBr): $\tilde{\nu}$=3296, 2960, 1693, 1537 cm^{-1}; HRFABMS: calcd for $C_{20}H_{23}NO_3Na$: 348.16 $[M+Na]^+$; found: 348.16.

Benzyloxycarbonylaminomethoxyacetic acid methyl ester (2f): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.30 (s, 5H), 5.78 (brs, 1H), 5.29 (d, J=9.3 Hz, 1H), 5.08 (s, 2H), 3.74 (s, 3H), 3.39 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=167.95, 167.93, 135.70, 128.53, 128.31, 128.13, 80.62, 80.58, 67.34, 67.32, 56.19, 52.86 ppm; IR (KBr): $\tilde{\nu}$=3425, 2955, 1730, 1504 cm^{-1}; HRFABMS: calcd for $C_{12}H_{16}NO_5$: 254.10 $[M+H]^+$; found: 254.10.

Benzyloxycarbonylaminomethoxyacetic acid benzyl ester (2g): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.28 (s, 5H), 5.79 (brs, 1H), 5.30 (d, J=9.0 Hz, 1H), 5.14 (s, 2H), 5.07 (s, 2H), 3.37 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=136.30, 135.28, 129.27, 129.20, 129.05, 128.98, 128.80, 81.40, 68.49, 68.14, 68.11, 57.08, 57.05 ppm; IR (KBr): $\tilde{\nu}$=3323, 2936, 1730, 1514 cm^{-1}; HRFABMS: calcd for $C_{18}H_{20}NO_5$: 330.13 $[M+H]^+$; found: 330.14.

Benzoylaminomethoxyacetic acid methyl ester (2h): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.79 (dd, J=6.0, 0.9 Hz, 2H), 7.51–7.39 (m, 3H), 7.15 (d, J=8.7 Hz, 1H), 5.71 (d, J=9.0 Hz, 1H), 3.77 (s, 3H), 3.46 ppm (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=168.56, 167.46, 133.04, 132.30, 128.69, 127.23, 78.64, 56.86, 53.00 ppm; IR (KBr): $\tilde{\nu}$=3333, 2953, 1755, 1666 cm^{-1}; HRFABMS: calcd for $C_{11}H_{14}NO_4$: 224.09 $[M+H]^+$; found: 224.09.

The spectral data of methoxymethyl-carbamic acid 9*H*-fluoren-9-ylmethyl ester (**4a**) and (1-methoxyethyl)carbamic acid 9*H*-fluoren-9-ylmethyl ester (**4b**) are in good accordance with those of **2c** and **d**, respectively.

4-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4-methoxybutyric acid methyl ester (4c): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.75 (d, J=7.5 Hz, 2H), 7.57 (d, J=6.9 Hz, 2H), 7.39 (t, J=7.5 Hz, 2H), 7.30 (t, J=7.5 Hz, 2H), 5.10 (d, J=9.6 Hz, 1H), 4.89–4.86 (m, 1H), 4.48 (t, J=7.2 Hz, 1H), 4.40 (t, J=6.3 Hz, 1H), 4.20 (t, J=6.6 Hz, 1H), 3.65 (s, 3H), 3.28 (s, 3H), 2.44–2.35 (m, 2H), 1.98–1.91 ppm (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=201.98, 173.51, 156.00, 150.47, 143.73, 143.67, 141.33, 127.72, 127.03, 124.90, 119.98, 84.39, 66.61, 55.55, 51.74, 47.20, 30.43, 29.48 ppm; IR(KBr): $\tilde{\nu}$=3327, 2951, 1719, 1528 cm^{-1}; HRFABMS: calcd for $C_{21}H_{23}NO_5Na$: 392.15 $[M+Na]^+$; found: 392.15.

Benzyloxycarbonylaminomethoxyacetic acid ethyl ester (4d): ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.32–7.23 (m, 5H), 5.80 (d, J=8.4 Hz, 1H), 5.26 (d, J=9.6 Hz, 1H), 5.09 (s, 2H), 4.19 (q, J=6.3 Hz, 2H), 3.39 (s, 3H), 1.25 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=167.31, 155.50, 135.63, 128.46, 128.24, 128.06, 80.67, 67.38, 62.23, 56.21, 14.11 ppm; IR (KBr): $\tilde{\nu}$=3329, 2939, 1732, 1520 cm^{-1}; HRFABMS: calcd for $C_{13}H_{18}NO_5$: 268.12 $[M+H]^+$; found: 268.12.

(5-Oxo-tetrahydrofuran-2-yl)carbamic acid 9*H*-fluoren-9-yl methyl ester (4e): ^{1}H NMR (270 MHz, $CDCl_3$): δ=7.69 (d, J=7.3 Hz, 2H), 7.50 (d, J=7.3 Hz, 2H), 7.34 (t, J=7.0 Hz, 2H), 7.25 (td, J=7.6, 1.4 Hz, 2H), 5.92 (d, J=5.7 Hz, 1H), 5.5 (d, J=9.7 Hz, 1H), 4.41 (d, J=5.1 Hz, 2H), 4.15 (t, J=6.5 Hz, 1H), 2.66–2.45 (m, 3H), 1.97 ppm (brs, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=143.44, 141.28, 127.83, 127.13, 124.91, 120.02, 83.31, 46.90, 28.12 ppm; IR (KBr): $\tilde{\nu}$=1715, 1537 cm^{-1}; HRFABMS: calcd for $C_{19}H_{18}NO_4$: 324.12 $[M+H]^+$; found: 324.12.

General procedure for the oxidative fragmentation reaction of β-amino alcohol compounds of discorhabdins with $C_6F_5I(OCOCF_3)_2$: Under a nitrogen atmosphere, $C_6F_5I(OCOCF_3)_2$ (0.2 mmol) and molecular sieves (3 Å, 850 mg mmol^{-1}) were added to a stirred solution of the amino alcohol compounds of discorhabdins (0.1 mmol) and $NaHCO_3$ (0.7 mmol) in CH_3CN (4.5 mL) and CH_3OH (0.5 mL) at room temperature. The reaction mixture was stirred for 1–5 h. After this time, the solution was concentrated in vacuo. Purification of the residue by silica-gel column chromatography gave the corresponding N,O-acetal compounds. Spectral data of compounds, **5a**, **6a**, (+)-**5b**, and (+)-**6b** are in good agreement with those of the reported data.[7]

Compound (−)-**5b** was prepared from (D)-tyrosine methyl ester by a similar method to that used for the synthesis of (+)-discorhabdin A from (L)-tyrosine methyl ester.

5-(Toluene-4-sulfonyl)-3,5,7,8,9,10-hexahydro-2*H*-1,5,7-triazaacephenanthrylen-6-one-8-(hydroxymethyl)-10-spiro-4′-(2′-bromo)cyclohexa-2′,5′-dien-1′-one ((−)-5b): ^{1}H NMR (300 MHz, CD_3OD): δ=8.00 (d, J=8.4 Hz, 2H), 7.41 (d, J=2.7 Hz, 1H), 7.36 (d, J=8.1 Hz, 2H), 7.09 (dd, J=2.7, 9.6 Hz, 1H), 6.34 (d, J=9.9 Hz, 1H), 3.54–3.80 (m, 5H), 3.11 (m, 1H), 2.81 (m, 2H), 2.34 (s, 3H), 1.91 (t, J=6.9 Hz, 1H), 1.68 ppm (dd, J=13.5 Hz, 1H); IR (KBr): $\tilde{\nu}$=3240, 3465, 1938 cm^{-1}; HRFABMS: calcd for $C_{26}H_{23}BrN_3O_5S$: 568.05 $[M+H]^+$; found: 568.05.

5-(Toluene-4-sulfonyl)-3,5,7,8,9,10-hexahydro-2*H*-1,5,7-triazaacephenanthrylen-6-one-8-methoxy-10-spiro-4′-(2′-bromo)cyclohexa-2′,5′-dien-1′-one ((−)-6b): ^{1}H NMR (300 MHz, $CO(CD_3)_2$): δ=7.95 (d, J=8.3 Hz, 4H), 7.64 (d, J=2.8 Hz, 1H), 7.53 (d, J=0.75 Hz, 1H), 7.30–7.37 (m, 7H), 7.21–7.25 (m, 2H), 6.90–6.93 (m, 1H), 6.08 (d, J=9.9 Hz, 1H), 5.98 (d, J=9.9 Hz, 1H), 4.84 (s, 2H), 3.91–3.93 (m, 4H), 3.63–3.80 (m, 2H), 3.24 (s, 3H), 3.22 (s, 3H), 2.51–2.60 ppm (m, 4H); HRFABMS: calcd for $C_{25}H_{20}BrN_3O_5S$: 553.03 $[M+H]^+$; found: 553.03.

(−)-Discorhabdin A: ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.00 (brs, 1H), 7.55 (s, 1H), 6.86 (s, 1H), 5.91 (brs, 1H), 5.33 (brs, 1H), 4.70 (dd, J=7.5, 11.5 Hz, 1H), 4.26 (td, J=6.5, 18.0 Hz, 1H), 3.95 (td, J=8.5, 17.5 Hz, 1H), 2.70–2.89 ppm (m, 6H); ^{13}C NMR (75.5 MHz, $(CD_3)_2SO$): δ=188.3, 170.0, 157.5, 154.2, 141.4, 124.1, 122.5, 121.1, 118.1, 117.4, 115.2, 61.2, 55.9, 50.3, 50.2, 45.2, 39.0, 17.9 ppm; IR (KBr): $\tilde{\nu}$=3345, 1680, 1650, 1605, 1555, 1525, 1475, 1445, 1400, 1385, 1310 cm^{-1}; HRFABMS: calcd for $C_{18}H_{15}BrN_3O_2S$: 416.01 $[M+H]^+$; found: 416.01; $[\alpha]_D$=−390 (c=0.05 in MeOH).

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