Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 4959

www.rsc.org/obc

PAPER

The synthetic and biological studies of discorhabdins and related compounds†

Yasufumi Wada,[a] Yu Harayama,[a] Daigo Kamimura,[a] Masako Yoshida,[a] Tomoyuki Shibata,[c] Kousaku Fujiwara,[c] Koji Morimoto,[b] Hiromichi Fujioka*[a] and Yasuyuki Kita*[a,b]

Received 11th January 2011, Accepted 11th April 2011
DOI: 10.1039/c1ob05058c

Various analogues of the marine alkaloids, discorhabdins, have been synthesized. The strategy contains spirocyclization with phenyliodine(III) bis(trifluoroacetate) (PIFA), oxidative fragmentation of the β-amino alcohols with the hypervalent iodine reagent $C_6F_5I(OCOCF_3)_2$, the detosylation and dehydrogenation reaction of the pyrroloiminoquinone unit in the presence of a catalytic amount of NaN_3 and the bridged ether synthesis with HBr–AcOH as the key reactions. All the synthesized compounds were evaluated by *in vitro* MTT assay for cytotoxic activity against the human colon cancer cell line HCT-116. Furthermore, the discorhabdin A oxa analogues were also evaluated against four kinds of tumor model cells, a human colon cancer cell line (WiDr), a human prostate cancer cell line (DU-145) and murine leukemia cell lines (P388 and L1210). For the identification of the target, discorhabdin A and the discorhabdin A oxa analogue were evaluated by an HCC panel assay. In the test, discorhabdins could have a novel mode of action with the tumor cells.

Introduction

Discorhabdin alkaloids were isolated from marine sponges, such as New Zealand sponges of the genus *Latrunculia*, the Okinawan sponge *Prianos melanos*, the Fijian sponge *Zyzzya cf. Marsailis*, *etc*.[1–17] All of them have a unique structure of the azacarbocyclic spirocyclohexanone and pyrroloiminoquinone system. Among the various isolated discorhabdins (A–X), discorhabdin A (**1a**),[2,3] B (**1b**),[2,3] D (**1d**),[4] H,[61] I,[45] J,[46] L,[45] M,[46] N,[46] Q,[13] R[14] and X[17] have a sulfur-containing fused ring system. Discorhabdin S (**2**), T and U have a methyl sulfide moiety, while the others have no sulfur atom. The discorhabdins F,[6] Q, S,[16] T[16] and prianosin B (**1c**)[5] have the 16,17-dehydropyrroloiminoquinone moiety. Because of their prominent potent antitumor activity, the discorhabdins have attracted considerable attention (Fig. 1).

Many studies have reported the synthesis of the discorhabdins. Several partial and total syntheses of discorhabdin C (**3**) have appeared in the past decade by Knolker, Heathcock, Yamamura and our group, *etc*.[18–35] We have accomplished the first total syntheses of discorhabdin A (**1a**) in 2003 and prianosin B (**1c**) in 2009.[36–41] The discorhabdins have a strong cytotoxic activity *in vitro*. Currently, many discorhabdin alkaloids have been isolated and synthesized. However, only a few biological studies including structure activity relationships or the mode of action of the

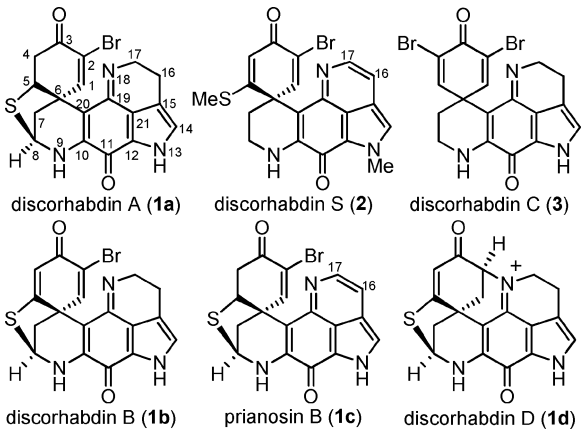


Fig. 1 The structure of the discorhabdins.

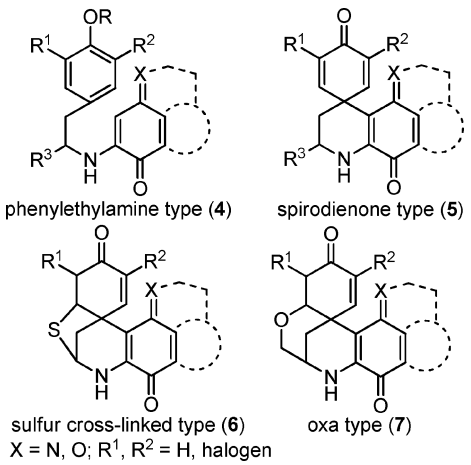


Fig. 2 Four types of discorhabdin analogues.

[a]*Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka, 565-0871, Japan*
[b]*College of Pharmaceutical Sciences, Ritsumeikan University, 1-1-1 Nojihi-gashi, Kusatsu, Shiga, 525-8577, Japan*
[c]*Shinagawa R&D Center, Daiichi Sankyo Co. Ltd., 1-2-58 Hiromachi, Shinagawa, Tokyo, 140-0005, Japan*

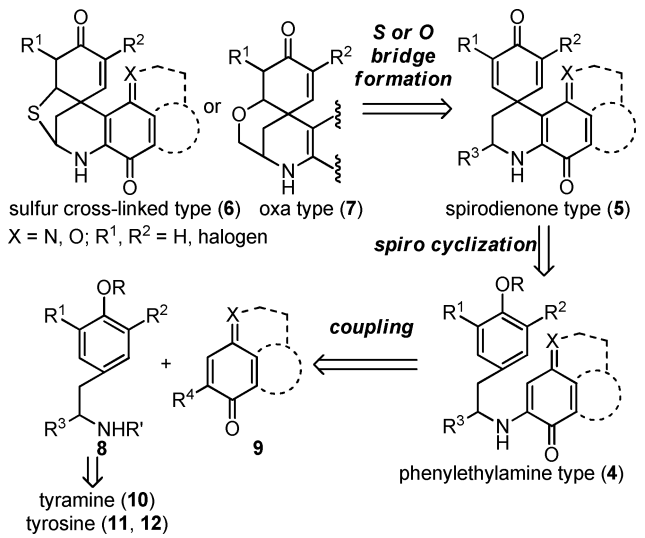
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/c1ob05058c

discorhabdins have been reported.[42–44] As part of our research program on new potential antitumor drugs, we focused our efforts on the preparation of the discorhabdin analogues which were categorized in four groups, *i.e.*, the phenylethylamine type (**4**), spirodienone type (**5**), sulfur cross-linked type (**6**) and oxa type (**7**) (Fig. 2).[45] To clarify the best location for the chemical modifications, we began to study the structure activity relationships (SAR) of the discorhabdin analogues.

Results and discussion

Chemistry

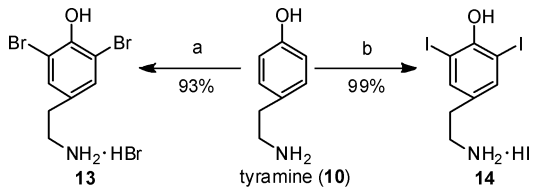
The retrosynthetic analysis to prepare the analogues is shown in Scheme 1. The coupling reaction between the tyramine or tyrosine derivative **8** and quinone or iminoquinone derivative **9** would give rise to the corresponding phenylethylamine type (**4**). The spirodienone type (**5**) could be synthesized from the phenylethylamine type (**4**) *via* the spirocyclization reaction. The *S* or *O* bridge formation reaction would produce the sulfur cross-linked type (**6**) and oxa type (**7**) from the spirodienone type (**5**) (Scheme 1).



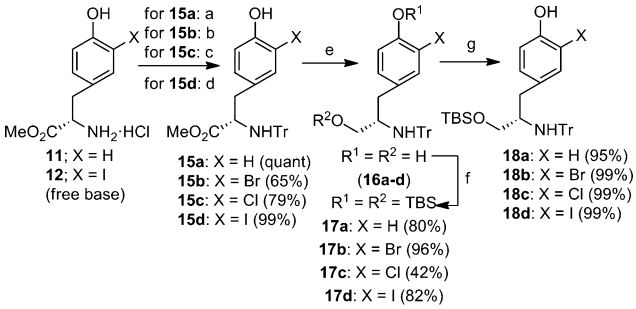
Scheme 1 Retrosynthetic analysis.

The syntheses of tyramine or the tyrosine derivatives **8** are shown in Schemes 2 and 3. The starting materials were the commercially available tyramine (**10**), L-tyrosine methyl ester hydrochloride (**11**) and 3-iodo-L-tyrosine (**12**). The preparations of dibromotyramine (**13**) and diiodotyramine (**14**) were achieved from tyramine (**10**) in a single step. Treatment of tyramine with I_2 and 30% H_2O_2 in H_2O for 3 h at 55 °C produced the diiodo compound **14** (yield 99%).

The preparations of the non- or monohalogenated tyrosine derivatives **18a–d** are shown in Scheme 3. *N*-Tritylation of the L-tyrosine methyl ester hydrochloride **11** with TrCl and Et_3N in DMF produced compound **15a**. *N*-Tritylation of **11** followed by *ortho*-bromination afforded the bromo compound **15b**. *ortho*-Chlorination of **11** followed by *N*-tritylation gave the chloro compound **15c**. The iodo compound **15d** was synthesized by esterification of the carboxyl group of 3-iodo-L-tyrosine **12** followed by *N*-tritylation. The aminoalcohols **16a–d** were obtained by the



Scheme 2 Syntheses of tyramine derivatives.

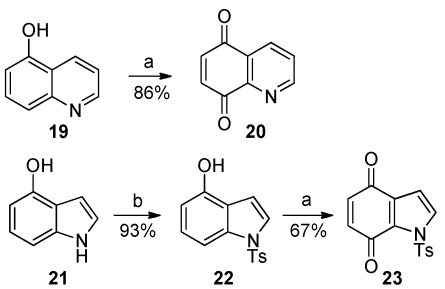


(a) TrCl, Et_3N, DMF, 0 °C, 3 h. (b)1) TrCl, Et_3N, DMF, 0 °C, 3 h. 2) NBS/DMF, DMF, rt, 2.5 h. (c)1) SO_2Cl_2, AcOH-Et_2O, 0 °C, 6 h. 2) TrCl, Et_3N, DMF, 0 °C, 3 h. (d)1) $SOCl_2$, MeOH, reflux, 3 h. 2) TrCl, Et_3N, DMF, 0 °C, 3 h. e) DIBAH, CH_2Cl_2, 0 °C, 5 h. f) TBSCl, DBU, CH_2Cl_2, 0 °C, 2.5 h. (g) TBAF, THF, 0 °C, 0.5 h.

Scheme 3 Syntheses of tyrosine derivatives.

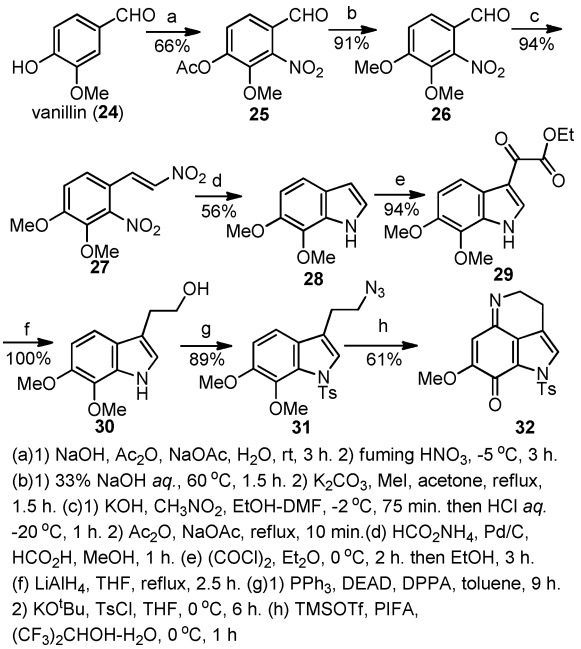
reduction of **15a–d** with diisobutylaluminium hydride (DIBAL). Disilylation of the phenolic and aliphatic hydroxyl groups of **16a–d** produced compounds **17a–d**. The syntheses of phenols **18a–d** were accomplished by selective desilylation of the phenolic silyl ether of **17a–d** with tetra-*n*-butylammonium fluoride (TBAF).

The syntheses of the quinones are shown in Scheme 4. Quinone **20** was synthesized from 5-hydroxyquinoline **19** according to Barret's method.[47] Quinone **23** was prepared from 4-hydroxyindole by the tosylation of **21** followed by oxidation with phenyliodine(III)diacetate (PIDA).



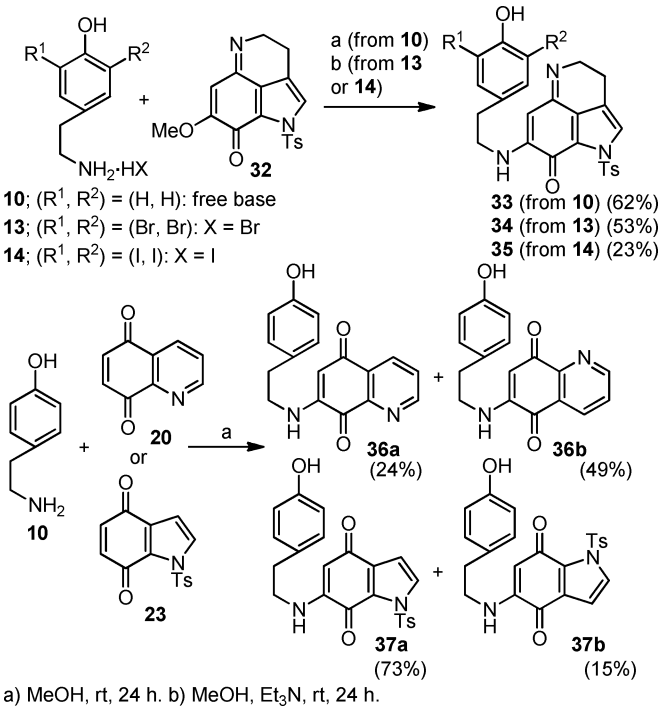
Scheme 4 Syntheses of quinones **20** and **23**.

Iminoquinone **32** was prepared by our previously developed PIFA-induced pyrroloiminoquinone formation (Scheme 5).[48] The starting material was commercially available vanillin **24**. The nitro compound **25** was prepared from **24** by acetylation of the hydroxyl group followed by selective nitration with fuming HNO_3. Deacetylation of compound **25** and the subsequent methylation of the resulting phenolic hydroxyl group gave the dimethoxy compound **26**. The nitro-aldol reaction of **26** with CH_3NO_2 under basic conditions afforded the dinitro compound **27**. The synthesis of indole **28** was accomplished by the reductive cyclization of

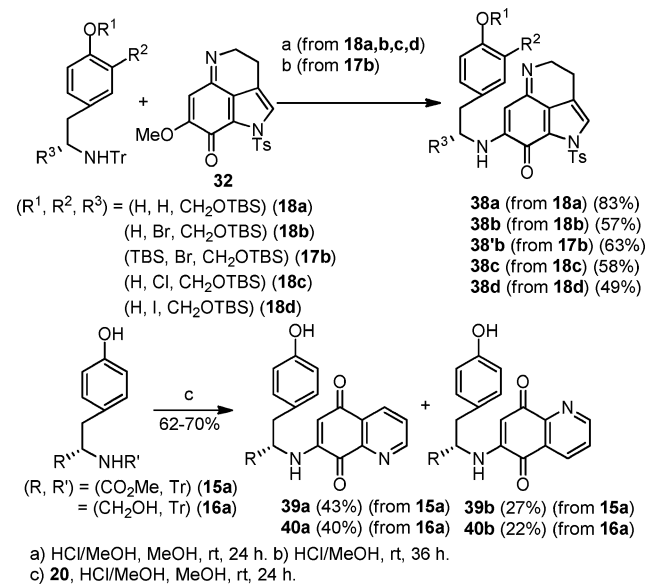


(a)1) NaOH, Ac_2O, NaOAc, H_2O, rt, 3 h. 2) fuming HNO_3, -5 °C, 3 h. (b)1) 33% NaOH *aq.*, 60 °C, 1.5 h. 2) K_2CO_3, MeI, acetone, reflux, 1.5 h. (c)1) KOH, CH_3NO_2, EtOH-DMF, -2 °C, 75 min. then HCl *aq.* -20 °C, 1 h. 2) Ac_2O, NaOAc, reflux, 10 min.(d) HCO_2NH_4, Pd/C, HCO_2H, MeOH, 1 h. (e) $(COCl)_2$, Et_2O, 0 °C, 2 h. then EtOH, 3 h. (f) $LiAlH_4$, THF, reflux, 2.5 h. (g)1) PPh_3, DEAD, DPPA, toluene, 9 h. 2) KO^{t}Bu, TsCl, THF, 0 °C, 6 h. (h) TMSOTf, PIFA, $(CF_3)_2CHOH$-H_2O, 0 °C, 1 h

Scheme 5 Synthesis of iminoquinone **32**.



Scheme 6 Syntheses of phenylethylamine type-1.



Scheme 7 Syntheses of phenylethylamine type-2.

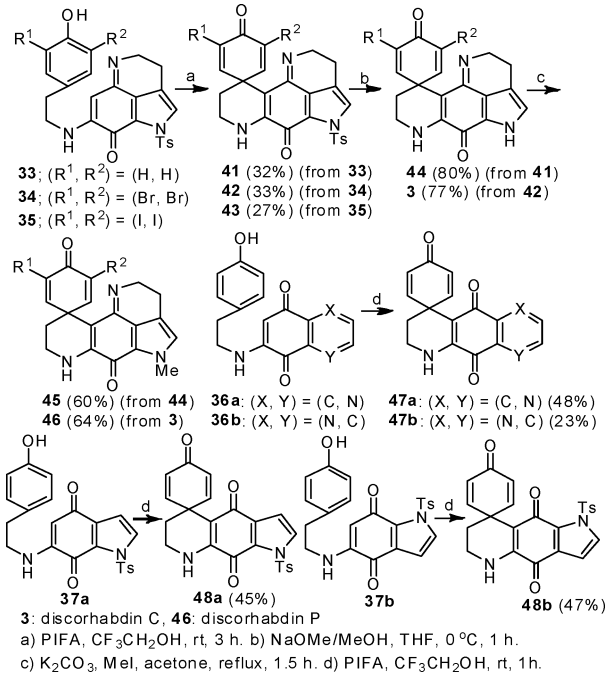
27 with HCO_2NH_4, Pd/C and HCO_2H.[49] Compound **29** was synthesized from the indole **28** by the reaction with oxalyl chloride and subsequent quenching by EtOH. The produced ketoester **29** was reduced to the ethylalcohol **30** by lithium aluminium hydride (LAH). Azide **31** was synthesized by a 2-step procedure, *i.e.*, Mitsunobu azidation followed by *N*-tosylation. The iminoquinone **32** was prepared by the PIFA-induced pyrroloiminoquinone formation. In this reaction, PIFA was activated by TMSOTf.

Coupling reactions of tyramine or the tyrosine derivatives with the quinones or iminoquinone to produce the phenylethylamine-type compounds are shown in Schemes 6 and 7. Syntheses of the phenylethylamine-type-1 reactions gently proceeded to produce the desired products in about 60% yields. The reaction conditions for the coupling reactions of tyramine or the tyrosine derivatives were different. In the case of the tyramine derivatives, *i.e.*, the *N*-H compound (for example **10**), the coupling reaction only proceeded in MeOH. The reactions of the tyramine ammonium salts **13** or **14** needed the addition of Et_3N. In the cases of the tyrosine derivatives *i.e.*, the *N*-3;Tr compounds, deprotection was carried out using HCl–MeOH before the coupling reaction. Iminoquinone **32** was so unstable that it decomposed within 1 day in air. The coupling reaction with the iminoquinone **32** selectively proceeded at the methoxyl position. However, in the case of the quinones **20** or **23**, two regioisomers were obtained in the ratio of *ca.* 2 : 1 (the major isomers were **36a**, **37a**, **39a** and **40a**).[35]

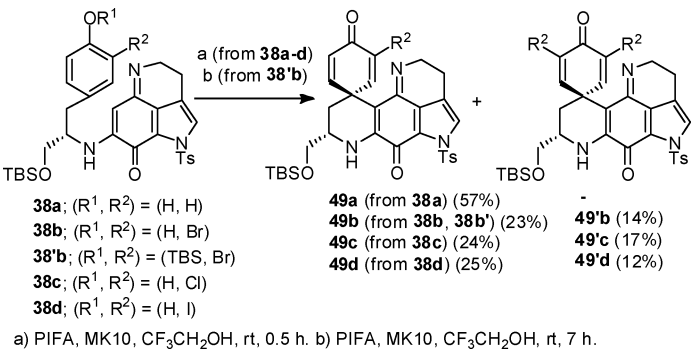
The PIFA-induced spirocyclization reaction of the phenylethylamine-type compounds gave the spiro-type compounds (Schemes 8 and 9). The spirocyclization reaction of the tyramine derivatives **33–37** proceeded with PIFA in CF_3CH_2OH to give the spirodienones **41–43** and **47–48**.[18,23,50] The reaction times of compounds **33–35**, having iminoquinone as the partial structure, were longer than those of compounds **36–37** containing the quinone (Scheme 8).

On the other hand, the spirocyclization of the tyrosine types needed MK10 as an additive and two spirodienones **49** and **49′** were obtained. For the phenols (**38a–d**), the reactions proceeded smoothly, but the diastereoselectivities were lower (dr = 1.5–1.0). The reactions of the silyl ether (**38′b**) proceeded slowly, but the diastereoselectivity was better (dr = ~4.8) (Scheme 9).[36,37]

The sulfur cross-linked-type compounds were synthesized from the spiro-type compounds. The desilylation reaction of compound **49b** by $BF_3{\cdot}Et_2O$ in CH_2Cl_2 afforded the aminoalcohol **50b**. The reaction using TBAF did not give good results because of its basicity. Compound **49b** or **50b** was unstable under the basic conditions. The *N*,*O*-acetal compound **51** was synthesized by the oxidative fragmentation reaction of **50b** with $C_6F_5I(OCOCF_3)_2$ in CH_3CN–MeOH.[38,39] The resulting *N*,*O*-acetal was a mixture



Scheme 8 Syntheses of spirodienone type-1.



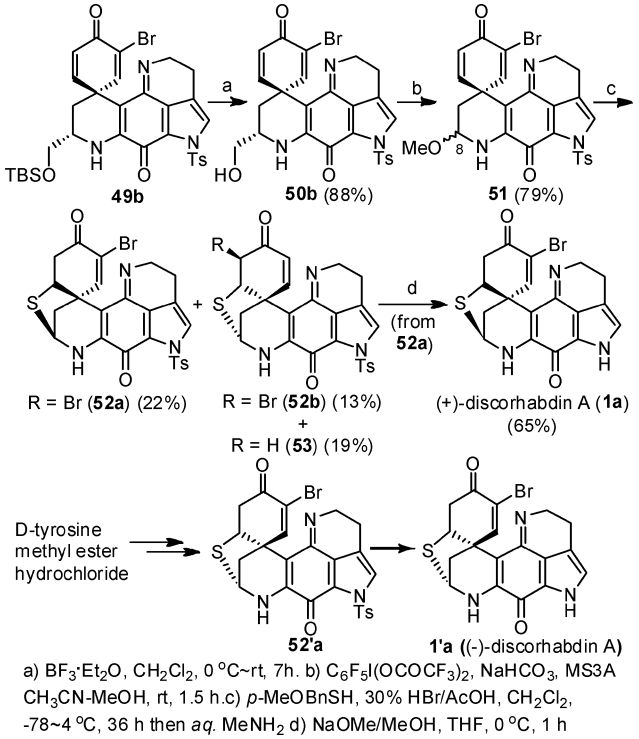
Scheme 9 Synthesis of spirodienone type-2.

of α- and β-methoxyl isomers due to the route *via* the iminium intermediate. The sulfur cross-linked reaction was carried out by the addition of *p*-MeOBnSH at the 8-position, Michael addition of the thioether to the dienone followed by the removal of the *p*-MeOBn group with *aq.* $MeNH_2$ to give the sulfur cross-linked type compounds **52a,b** and **53**.[37] Two constitutional isomers (**52a,b**) were produced by the addition of the thiol at the 8 position (dr = 1 : 1.5). Detosylation of **52a** was performed with NaOMe–MeOH in THF to give (+)-discorhabdin A (**1a**).

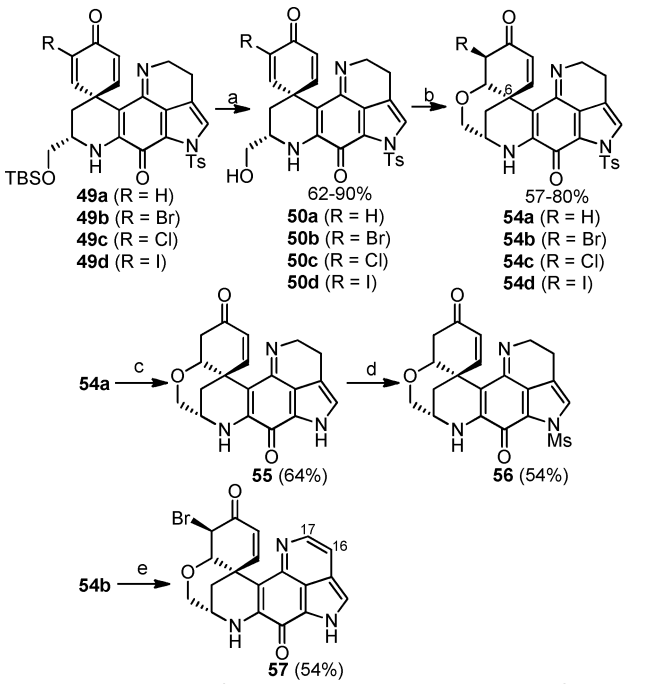
(–)-Discorhabdin A (**1′a**) was also synthesized from the D-tyrosine methyl ester hydrochloride (Scheme 10).

The syntheses of oxa-type compounds are shown in Schemes 11 and 12. Aminoalcohols **50a–d** were synthesized by desilylation of compounds **49a–d** using $BF_3{\cdot}Et_2O$. The ether bridged formation reactions were carried out with 30% HBr–AcOH, and the oxa-type compounds **54a–d** were obtained. The *N*-H and *N*-Ms oxa-type compounds **55** and **56** were synthesized from a non-halogen compound **54a**. The 16,17-dehydro oxa-type compound **57** was synthesized from compound **54b** (Scheme 11).

Compounds **54′b–d**, which are the constitutional isomers of **54b–d**, were also synthesized from compounds **50′b–d**. Compound



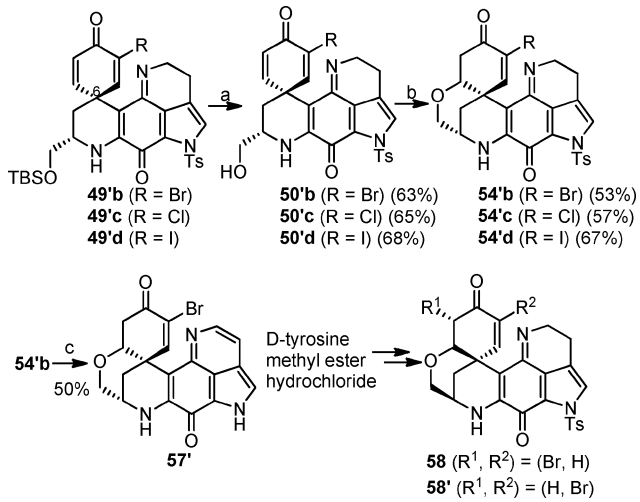
Scheme 10 Synthesis of sulfur cross-linked type.



Scheme 11 Synthesis of oxa type-1.

58 and its constitutional isomer **58′** were synthesized from the D-tyrosine methyl ester hydrochloride (Scheme 12).

The absolute configuration of the oxa-type compound **54d** was determined as follows. Although four stereoisomers would be possible for **54d**, the presence of the NOE effect between the



Scheme 12 Synthesis of oxa type-2.

hydrogen atoms at the C-5 and C-a positions suggested A or B for **54d**. We next determined the relative configuration between the C-4 and C-5 hydrogen atoms to be *trans*, because the coupling constant $J_{4,5}$ of **54d** was 13.0 Hz. It is reported that $J_{4,5}$ of the *trans* configuration was 13.5 Hz and $J_{4,5}$ of the *cis* configuration was 4.3 Hz in epinardin B.[51] Therefore, we determined that the absolute configuration of the oxa-type compound **54d** was **A** (Fig. 3).

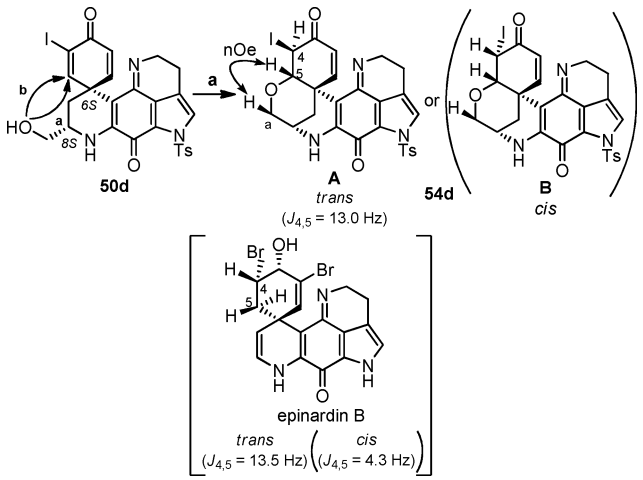
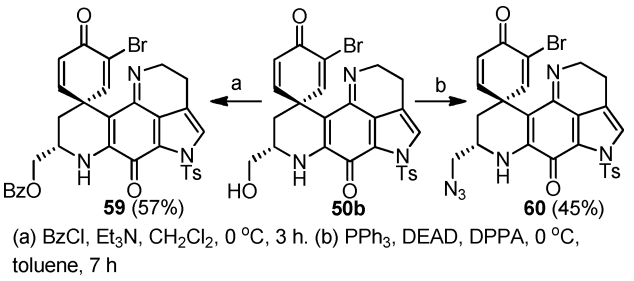


Fig. 3 Determination of absolute configuration of oxa type compound **54d**.

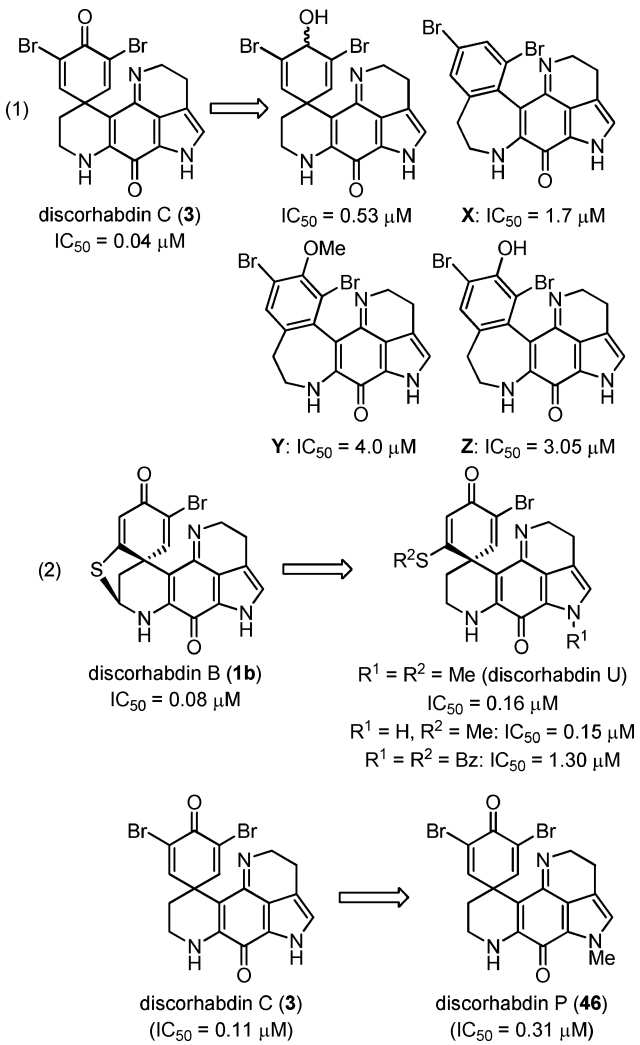
Compounds **59** and **60** were synthesized from the aminoalcohol **50b**. Protection of the aliphatic hydroxyl group of **50b** by BzCl and Et_3N gave the benzoate **59** in 57% yield. The Mitsunobu azidation of **50b** gave the azide compound **60** in 45% yield (Scheme 13).



Scheme 13 Synthesis of compounds **59** and **60**.

Biological activity

Although many synthetic studies of the discorhabdin alkaloids have been reported, the biological studies including the structure activity relationships or the mode of action in the discorhabdins did not significantly proceed.[42–44] Blunt *et al.* reported the structure activity relationships of the discorhabdins using the derivatives of the natural discorhabdin C (**3**) (Scheme 14 (1)).[6] They reported that the conversion of the dienone to a dienol caused a dramatic alteration in the cytotoxicity and confirmed the importance of the dienone/enone system in the observed biological properties of the discorhabdins. The azepine derivatives **X**, **Y**, **Z** were not effective. Copp *et al.* also reported the structure activity relationships using the derivatives of the natural discorhabdins B (**1b**) and C (**3**) (Scheme 14 (2)).[52]



Scheme 14 Structure activity relationships of discorhabdin derivatives against P388.

It is suggested that the sulfur cross-linked structure is important. However, the discorhabdin alkaloids were isolated in such small amounts that it was difficult to undergo more systematic and detailed biological studies. As for the mode of action of the discorhabdins, Ireland *et al.* reported that the inhibitive activity of DNA topoisomerase II by discorhabdin A was weak, whereas the makaluvamines, in the same class of pyrroloiminoquinone alkaloids as the discorhabdins, showed a cytotoxicity toward the tumor cell line by inhibition of topoisomerase II.[8] The inability of discorhabdin A to inhibit topoisomerase II is indicative of the fact that this potent cytotoxicity most probably acts by a different mechanism than the makaluvamines.[53–57]

in vitro MTT assay

The *in vitro* cytotoxic potency of the phenylethylamine-type compounds, type A to type C, against HCT-116 was first evaluated. The results are expressed as IC_{50} values. We examined the influence of the conversion of the pyrroloiminoquinone moiety to the quinone moiety and of the R substitution. The type B compounds (**36a**, **39a**, **40a**) showed a stronger cytotoxicity than the type C ones (**36b**, **39b**, **40b**). From the comparison of R = H, CO_2Me, CH_2OH, it can be seen that the strength of the biological activity was in the order of H (**36a**, **b**) > CO_2Me (**39a**, **b**) > CH_2OH (**40a**, **b**). However, overall, the phenylethylamine-type compounds showed a lower activity than discorhabdin A (**1a**). One of the reasons may be that it is the difference in the mode of action with discorhabdin A (**1a**) (Fig. 4).

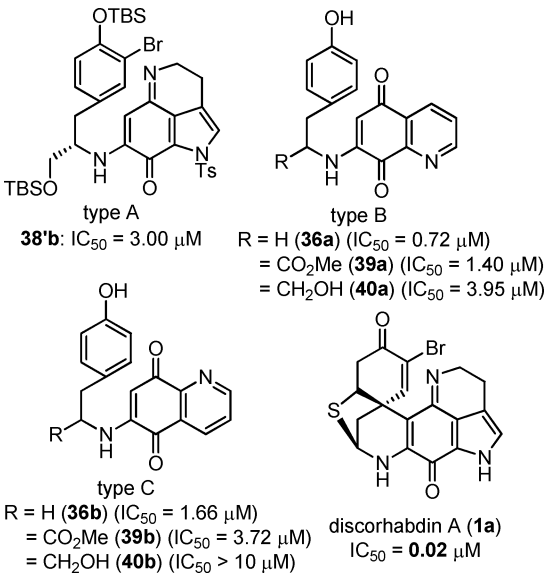
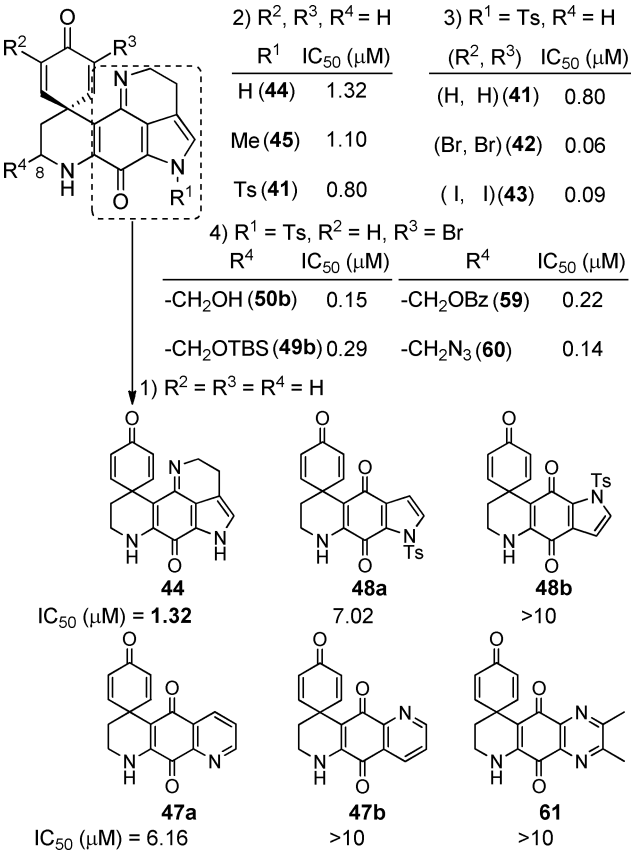


Fig. 4 SAR of phenylethylamine type compounds against HCT-116.

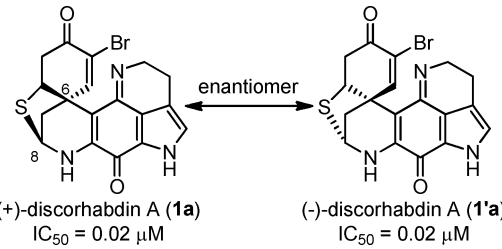
We next examined the spirodienone-type compounds. The activity and stability of the spirodienone-type compounds were better than the phenylethylamine-type compounds. We first examined the influence of the conversion of the pyrroloiminoquinone moiety to a variety of quinone moieties; see the results of **44**, **47a,b**, **48a,b** and **61**. If the quinone compounds have a strong cytotoxicity, it is ideal, because the quinone compounds are easily synthesized and stable. From the results, however, the pyrroloiminoquinone moiety had a significant biological activity. The effect of the *N*-substituted R^1 was next investigated; see the results of **44**, **45** and **41**. No notable effect of the *N*-substituent was observed, but it was the preferred electron-withdrawing group. The effect of the R^2 and R^3 substituent was next investigated. The presence of the halogen atom was necessary for the biological activity. Comparing the nonhalogen compound (**41**) to the dibromo compound (**42**) or the diiodo compound (**43**), compound **42** or **43** was about ten times stronger than **41**. Among the halogens, the natural-type bromo substituent, compound **42**, showed the strongest IC_{50} value. We think that the side chain at the 8-position, *i.e.*, the R^4 substituent, does not have a significant effect on the biological activity; see the results of **49b**, **50b**, **59** and **60** (Table 1).

Table 1 SAR of spirodienone type against HCT-116



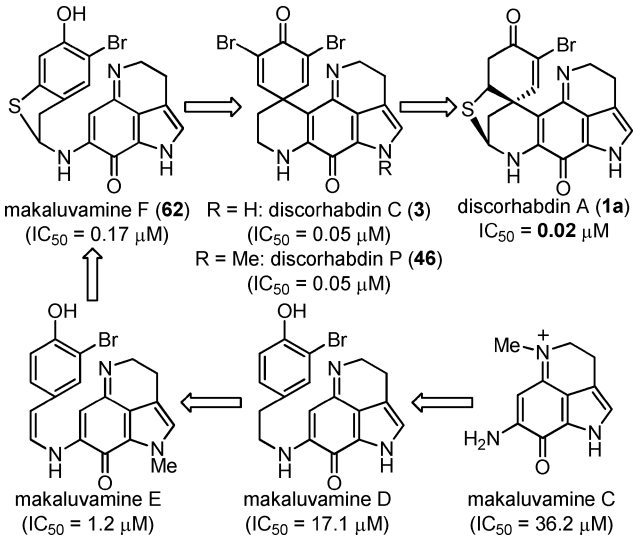
The stereochemistry of how the discorhabdins influenced the activity among the sulfur cross-linked-type compounds was investigated. (+)-Discorhabdin A (**1a**) had the same activity as (–)-discorhabdin A (**1′a**). From this result, the stereochemistry at the C-6 and C-8 positions did not affect the activity very much. In these compounds, the position of the carbonyl oxygen of the enone is similar. The bromo substituent may not have a steric effect, but an electronic effect on the biological activity (Scheme 15).[58–60]

From the structural comparison of makaluvamine F (**62**),[8,61] discorhabdins C (**3**),[1] P (**46**)[12] and discorhabdin A (**1a**),[2,3] the difference in the activity might come from the flexibility of the compounds. The order of strength of the activity was discorhabdin A, discorhabdins C and P then makaluvamine F. We estimated that one of the active sites is the spiro enone moiety. Discorhabdins C and P have flexible spiro-centers. On the other hand, discorhabdin



Scheme 15 SAR of sulfur cross-linked type against HCT-116.

A has a rigid spiro-center (Scheme 16). C. M. Ireland *et al.* also reported that the activity of makaluvamine C, D, E, F and discorhabdin A dramatically demonstrated an increasing cytotoxicity concurrent with the structural elaboration.[7,8,25]

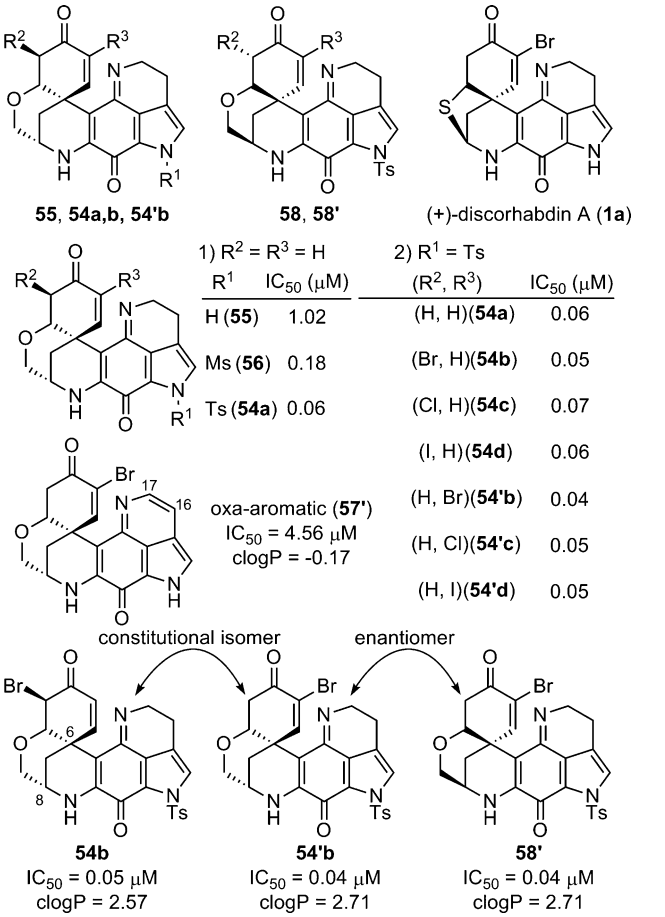


Scheme 16 Phenylethylamine *vs.* spiro *vs.* sulfur cross-linked type against HCT-116.

We then examined the oxa-type compounds (Table 2). Almost all the oxa-type compounds had strong activities. (1) From a comparison of R^1 (H (**55**), Ms (**56**) and Ts (**54a**)), it was shown that the electron-withdrawing groups as the *N*-substituent R^1 are better. (2) The presence of the halogen atom in the R^2 or R^3 substituent was preferable in the oxa-type compounds (**54a,b,c,d** and **54′b,c,d**). The activity of the compounds was not caused by the variation of the halogen, but the bromo substituent showed the highest activity. The stereochemistry at the C-6 and C-8 positions did not significantly affect the activity. It is interesting that the oxa-aromatic (**57′**) had a very weak activity. We think that the decrease in the value of *C*log*P* affects the shift of the drug into a tumor cell during the absorption process or weakens the hydrophobic interaction of the pyrroloiminoquinone unit and the target protein.[62–66]

With the oxa-type compounds in hand, we examined their cytotoxicity *in vitro* against four kinds of tumor model cells, WiDr (human colon adenocarcinoma), DU-145 (human prostate tumor cell), P388 and L1210 (murine leukemia). As a reference, the IC_{50} values of discorhabdin A *in vitro* for each cell, WiDr = 0.03 μM, DU-145 = 0.09 μM, P388 = 0.03 μM and L1210 = 0.04 μM, are shown. All the oxa-type compounds exhibited good IC_{50} values. Especially, compound **54′b** and its enantiomer **58′** gave the best

Table 2 SAR of oxa-type against HCT-116



The *c*log*P* values were calculated by ChemBioDraw Ultra 12.0.

results. Their IC_{50} values against HCT-116 (0.04 μM, 0.05 μM: see Table 2) are almost the same as that of discorhabdin A (0.03 μM). To our surprise, their IC_{50} values against L1210 (0.01 μM, 0.02 μM) are higher than that of discorhabdin A (**1a**) (0.06 μM) (Table 3).

These results indicated significant structural information about the biological activity. The spiro and pyrroloiminoquinone structures play an important role in the biological activity. It may be that these units are active sites. Next, the halogen substitution is significant, especially the bromo substitution on R^1 or R^2, and the electron-withdrawing group on R^3. The sulfur or oxa-bridged structure is necessary for fixing the spiro-enone structure. However, it does not significantly affect the stereochemistries at the 6- and 8-positions (Fig. 5).

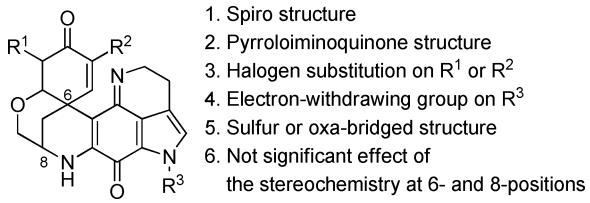


Fig. 5 Information on the structure for biological activity.

Table 3 Biological activity of oxa-type against tumor cells

Entry	Compound	R^1	R^2	R^3	IC_{50} values (μM)			
					WiDr	DU-145	P388	L1210
1	**55**	H	H	H	1.23	0.71	0.38	0.80
2	**54a**	Ts	H	H	0.22	0.18	0.13	0.14
3	**54b**	Ts	Br	H	0.06	0.38	0.13	0.12
4	**54′b**	Ts	H	Br	0.08	0.15	0.09	0.01
5	**58**	Ts	Br	H	0.30	0.33	0.14	0.12
6	**58′**	Ts	H	Br	0.18	0.17	0.29	0.02
7	discorhabdin A (**1a**)				0.03	0.09	0.03	0.04

In vivo assay

Acute toxicity test. On the basis of our favorable profile *in vitro*, compounds **54a** and discorhabdin P (**46**) were tested in the mouse *in vivo* assay.‡ We first evaluated the single-dose toxicity test. For the test, the model animal is BALB/c-nu/nu. The single-dose toxicity of compound **54a** was tested using two kinds of doses (a; 58 mg $kg^{-1} \times 2$, b; 58 mg kg^{-1}). The results are as follows: a; It was observed that the model mouse became pale, hypothermic and stertorous after a dose. It was also observed that the ability of the model mouse to exercise had decreased and it was confirmed dead. b; It was observed that the dose made the model mouse pale and hypothermic and it had a decreased ability to exercise. Next, the single-dose toxicity of compound **46** was tested using four kinds of doses (a; 100 mg kg^{-1}, b; 80 mg kg^{-1}, c; 60 mg kg^{-1}, d; 40 mg kg^{-1}). The results are as follows: a, b, c; The dose made the model mouse immediately go into rigor contraction. After 20 min, an abnormal behavior, for example the mouse was jumping up and down and a general stiffness, was observed. Paramyotonia was observed and the mouse was confirmed dead after 1 h. d; In this case, it was milder than for the cases with highest doses. The mortality rate was 50%. Suffering from diarrhea was not observed by the time of death.

Drug efficacy test. Next, we assessed the drug efficacy. The assessed model was the human colorectal tumor HCT-116 xenograft subcutaneously implanted in BALB/c-nu/nu mice. The compound administration was started when the tumor was established on day 7. Compound **54a** was injected by i.v. 40 mg kg^{-1} (5 times/week), 20 mg kg^{-1} (5 times/week) and 10 mg kg^{-1} (5 times/week). We assessed the drug efficacy for compound **46**. Compound **46** was injected by i.v. 20 mg kg^{-1}, 10 mg kg^{-1}, 5 mg kg^{-1} (3 times/week × 2w), 2 mg kg^{-1} (3 times/week × 2w) and 1 mg kg^{-1} (3 times/week × 2w). The changing of the tumor volumes are shown in Fig. 6. Regrettably, from these results, no effect by compound **54a** was observed. In the case of compound **46**, no shrinking of the tumor cell by the various administration methods was observed. A *temporary* decrease in body weight for the doses of 20 mg kg^{-1} and 10 mg kg^{-1} was observed. This may be the onset of the cell cytotoxicity against healthy cells (see supporting information†).

Pharmacokinetic test. We also examined the pharmacokinetic test. The examination conditions are as follows. The model animal was BALB/c-nu/nu (n = 2), i.v. The dose of compound **54a** was 10, 20 and 40 mg kg^{-1}. The blood collecting times were 5, 30, 60, 120 and 240 min. In the test, the detection limit was 0.3 μg mL^{-1}. The result was that only 0.36 mg mL^{-1} was detected at 5 min for the dose of 40 mg kg^{-1}. The dose of compound **46** was only 10 mg kg^{-1}. The blood collecting times were 15, 30, 60, 120 and 240 min. In the test, the detection limit was 0.1 μg mL^{-1}. The result was that there was no detection at every point.

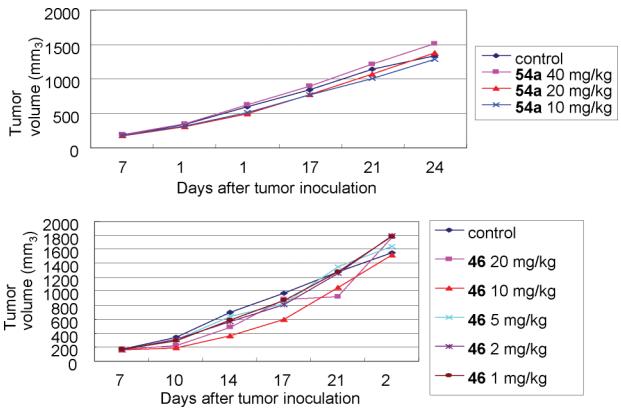


Fig. 6 Drug efficacy test.

From the *in vivo* testing, we reasoned that the oxa-type compound **54a** and discorhabdin P (**46**) were so unstable inside a living body that they were immediately decomposed

We think that this result was attributed to the iminoquinone structure, because the iminoquinone moiety was unstable. On the other hand, discorhabdin D (**64**) has an activity *in vivo*,[4] because the iminoquinone structure is stabilized by the cross-linking between the nitrogen atom of the iminoquinone and the α-carbon of the spiroenone.

Mode of action of discorhabdins

We estimated the HCC panel assay, the inhibition of protein kinase, histone deacetylase (HDAC), farnesyltransferase, telomerase and proteasome assays for discorhabdin A (**1a**) and the oxa-type compound (**54b**). We tried to determine the mode of action of the discorhabdins by comparison to the existing anticancer drugs.

(A) Inhibition of protein kinase assay. In the assay, we examined the selective inhibitive activity of the protein kinase. The activity of the multiprotein phosphoenzyme could be detected at the same time, which is connected to the intercellular signaling.[67] We also examined the inhibitive activity of the tyrosine kinase of the EGF receptor and VEGF receptor (Flt-1) by the easy-to-use

‡ All the animal care and experiments were conducted under the standard operational protocol of the former Sankyo Institutional Animal Care and Use Committee.

Table 4 Inhibition of protein kinase assay[a,b]

		assay result						
	Conc. (μM)	eEF2K	PKC	PTK	PKA	EGFR	Flt-1	Judgement positive; <1 μM
1a	100	+	—	+	—	—	2+	M1Y1F2 negative
	10	—	—	—	—	—	+	
	1						—	
54b	100	2+	—	+	—	—	2+	M1Y1F2 negative
	10	—	—	—	—	—	+	
	1						—	

[a] Controls: Herbimycin A (PTK), H89 (PKA), AG1478 (EGFR), SU4984 (Flt-1). Abbreviations: A (PKA), C (PKC), M (eEF2K), Y (PTK), E (EGFR), F (Flt-1). [b] >50% inh. At 0.01μM; 5+, 0.1μM; 4+, 1μM; 3+, 10μM; 2+, 100μM; 1+, 2+: >80% inhibition, +: 50~80% inhibition, −: <50% (not inhibition).

in vitro autophosphorylation reaction. The method determines the phosphorylated inhibition and the inhibitive pattern. The test compounds were drawn up to 100 μM. The test compounds having the inhibitive activity and selectivity were examined again by using a ten times diluted solution at three more levels. The case of more than a 50% inhibition activity at less than a 1 μM concentration was determined as positive. The result was that these compounds (**1a**, **54b**) were negative (Table 4).

(B) Inhibition of histone deacetylase (HDAC) assay. It is believed that the reason for the pathogenic mechanism of the cancer is the mutations of the oncogenes or antioncogenes. The control of the cell growth, adhesion and apoptosis are out of order because of the accumulation of changes in base sequence. On the other hand, impaired expression of genes without changing in base sequence was revealed; epigenetic alteration significantly contributes to the pathogenic mechanism of the cancer. Among them, the histone deacetylation, which controls the activity of the chromatin, plays an important role.[68] The HDAC controlling the level of histone acetylation is the focus of attention as a molecular target of an antitumor drug. The histone deacetylation occurs at the ε-amino group of the lysine residue which is in the core histone amino-terminal domain and affects the transcriptive activity by controlling the chromatin structure. The HDAC is the hydrolase of this acetylated lysine and is very involved in the impaired expression of genes during the carcinogenesis process. Therefore, the activity of the inhibition of the HDAC by compounds **1a** and **54b** was examined. The first test compounds were drawn up to 100 μM. The test compounds having an inhibitive activity were examined again using more diluted solutions at every level and the IC_{50} value determined. The results showed no activity (IC_{50} value > 100 μM) (Table 5).

Table 5 Inhibition of HDAC assay[a]

	Conc. (μM)	Fluorescence intensity	% Control
1a	0	58.15	100
	100	54.67	94.02
54b	0	58.15	100
	100	50.13	86.22

[a] Trichostatin A: IC_{50} value is 0.029 μM (as control). Very strong activity (+++); IC_{50} value < 0.1 μM. Strong activity (++); IC_{50} value 0.1–1 μM. Relatively strong activity (+); IC_{50} value 1–10 μM. No activity; IC_{50} value > 10 μM. Autogenic fluorescent compound cannot be measured.

Table 6 Inhibition of farnesyltransferase assay[a]

	Conc. (μM)	Radioactivity (dpm)	% Control
1a	0	1805	100
1a	10	945.5	52.4
54b	0	3528.5	100
54b	10	2770	78.5

[a] Strong activity; IC_{50} value < 100 nM. Relatively strong activity; IC_{50} value100 nM–10 μM. Weak activity; IC_{50} value >10 μM. Positive control; IC_{50} value 0.73 nM. Sample result; **1a**: IC_{50} value > 10 μM, **54b**: IC_{50} value > 10 μM.

(C) Inhibition of farnesyltransferase assay. The Ras is the low-molecular-weight G protein and is connected to cell growth and migration. This protein is activated by farnesylation, which is catalyzed by the farnesyltransferase (FPTase). Therefore, the FPTase inhibitor is expected to be an anticancer drug by controlling the overgrowth, metastasis and invasion of the cancer cells.[69] In the assay, the sample compound was added at 10 μM. In the case of IC_{50} value < 1 μM, it was positive. However, the results showed a weak activity (Table 6).

(D) The inhibition of telomerase assay. The telomerase (telomea synthetase) is activated in the cancer cells at the amount of 80–90% and supports the unlimited proliferation of cancer cells by means of resolving the problem of the genetic replication at the end of the liner DNA.[70] The cancer cells caused by the activity of the telomerase due to the aging and apoptosis with shortened telomeres. The inhibition activity of the telomerase by compounds **1a** and **54b** was examined. However, the results were negative (Table 7).

(E) The inhibition of proteasome assay. The proteasome is a selective degrading enzyme of the intracellular ubiquitinated protein and plays a main role in the cell cycle and the degradation of proteins which controls apoptosis.[71] There is clinical proof that VELCADE® (the inhibitor of the proteasome) has an anticancer efficacy against multiple myeloma. A great deal of attention has been focused on the inhibitor of the proteasome as a molecular target of antitumor drugs.[72] In this assay, the enzyme inhibition with the human origin 20S proteasome was examined. However, the results were negative (Table 8). From these results, the mode of action of **54a** or **1a** is not the inhibition of protein kinase, HDAC, farnesyltransferase, telomerase and proteasome.

(F) HCC panel assay. One of the accounts of the Human Cancer Cell Line (HCC) panel assay is that a drug having a similar

Table 7 Inhibition of telomerase assay[a]

	Conc. μM	Telomea product (**A**)	Internal standard (**B**)	A/B	% Control
	0	4252, 6048	5109, 5450	0.971	100
1a	10	4104, 3253	5850, 5742	0.634	65.3
54b	10	3562, 3574	5241, 5865	0.645	66.4
MST-204	1	729	5285	0.138	14.2

[a] IC_{50} value < 10 μM; positive, IC_{50} value ≥ 10 μM; negative **1a** and **54b** do not inhibit PCR. MST-204 was used as control.

Table 8 inhibition of proteasome assay[a]

[Chymotrypsin-like activity]			
	Conc. (μM)	% Control	IC_{50} (μM)
1a	10	106.1	> 10
54b	10	91.3	> 10
clasto-Lactacystin β-lactone	10	0	0.039
MG132	10	0	0.011
[Caspase-like activity]			
	Conc. (μM)	% Control	IC_{50} (μM)
1a	10	115.5	> 10
54b	10	98.1	> 10
[trypsin-like activity]			
	Conc. (μM)	% Control	IC_{50} (μM)
1a	10	95.5	> 10
54b	10	124.9	> 10

[a] Very strong activity (+++); IC_{50} value < 0.1 μM. Strong activity (++); IC_{50} value 0.1–1 μM. Relatively strong activity (+); IC_{50} value 1–10 μM. No activity; IC_{50} value > 10 μM.

mode of action statistically indicates a similar correlated fingerprint pattern.[73] The mean cytostatic and cytotoxic parameters of the oxa analogue **54b** and discorhabdin A (**1a**) were measured in a 39 human cancer cell line panel. The cytostatic parameters include GI_{50} and TGI, which are the concentrations of the drug required for a 50% growth inhibition and total growth inhibition, respectively. The cytotoxic parameter is the LC_{50}, which is the concentration required for a 50% cell kill. Also, the Table 9 range values, which represent the log of the maximum concentration difference between the least-sensitive and the most-sensitive cell line, are provided. This range parameter has been used to gain insights into the selectivity of the antitumor agents, because it provides a measure of histological specificity. The COMPARE analysis provided insights into what might be the molecular target of the active analogues exhibiting a high histologic selectivity. The COMPARE analysis correlates the mean graph data with the known molecular target levels in cell lines and thereby generates hypotheses concerning the agent's mechanism of action. First, the COMPARE correlations indicated that the cytostatic and cytotoxic parameters of the oxa analogue (**54b**) and discorhabdin A (**1**) represent three mechanistically distinct classes. The GI_{50}, TGI, and LC_{50} parameters of the two compounds correlate (correlation coefficient $r = 0.815$) with the same molecular target. The COMPARE correlations using the oxa analogue as a seed against the drug database (83 drugs: see supporting information) revealed no compound correlations. The third high ranking drugs which have similar r values of the oxa analogue, are vincristine ($r = 0.433$), actinomycin-D ($r = 0.430$) and vinblastine ($r = 0.392$).

Table 9 HCC panel assay for discorhabdin A (**1a**) and oxa analogue (**54b**)

		GI_{50}	TGI	LC_{50}
Discorhabdin A (**1a**)	MG-MID	–5.39	–4.94	–4.32
	Delta	0.43	0.55	0.87
	Range	1.25	1.31	1.19
Oxa analogue (**54b**)	MG-MID	–6.39	–5.94	–5.33
	Delta	1.12	0.96	0.99
	Range	2.01	1.77	2.32

However, the r value is < 0.5. As a result, the oxa analogue **54b** is estimated to have a novel mode of action (Fig. 7).

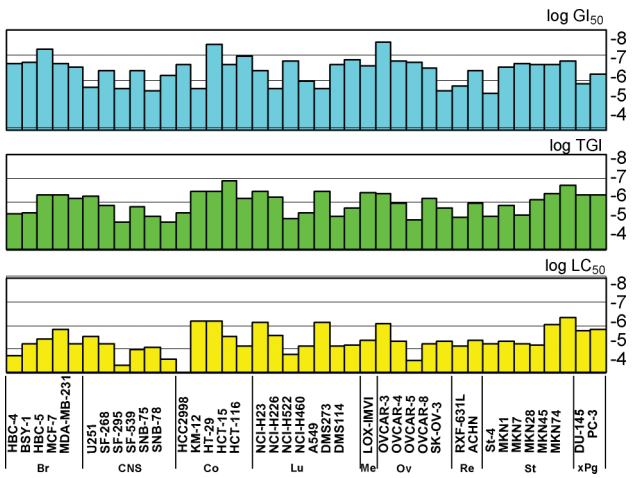


Fig. 7 The GI_{50}, TGI and LC_{50} values of oxa analogue **54b**.

Conclusions

We synthesized various discorhabdin analogues, *i.e.*, phenylethylamine (**4**), spirodienone (**5**), sulfur cross-linked (**6**) and the oxa-type (**7**). We designed and synthesized various stable oxa-type compounds with the oxygen cross-linked spiro-fused ring system. All compounds were evaluated by *in vitro* MTT assay for the structure activity relationships. The discorhabdin oxa analogues exhibited a strong activity against tumor model cells and some of them were the same as discorhabdin A (**1a**). However, the oxa analogue **54a** and discorhabdin P (**46**) were not active *in vivo*. For target identification of the discorhabdins, we evaluated discorhabdin A (**1a**) and the oxa analogue (**54b**) using six types of assays, *i.e.*, the inhibition of protein kinase, histone deacetylase, farnesyltransferase, telomerase, proteasome and the HCC panel assay. From these assays, it was revealed that the discorhabdin oxa analogue (**54b**) could have a novel mode of action in tumor cells.

Experimental section

General experimental procedures

Column chromatography was carried out on MERCK Kieselgel 60 (70–230 mesh ASTM), Fuji Silysia Chemical silica gel BW-300, Kanto Chemical silica gel 60 N (spherical, neutral, 40–50 μm) and Fuji Silysia Chromatography silica gel NH (100–200 mesh) using *n*-hexane/AcOEt or CH_2Cl_2/MeOH as an eluent. TLC analysis was carried out using aluminium sheet precoated with silica gel 60 F_{254} (Merck, Darmstadt, Germany). UV-Vis spectra were obtained on a SIMAZU UV-2200. Optical rotations were measured on a JASCO P-1020 polarimeter. HRMS were obtained on a JEOL JMS-D300 or JEOL JMS-600. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA500, JNM-ECS-400, JNM-AL300 and JNM-EX270. Samples were dissolved in $CDCl_3$, CD_3OD, $(CD_3)_2CO$ or DMSO-d_6. IR spectra were taken as KBr pellets using a SIMAZU FTIR-8400 spectrophotometer.

Total synthesis of prianosin B (1c). NaN_3 (1.1 mg, 0.0175 mmol) was added to a solution of compound **51b** (99.7 mg, 0.175 mmol) in DMF (0.3 mL) at rt under N_2. The mixture was allowed to warm to 70 °C and stirred for 1 h. The reaction mixture was quenched by H_2O and extracted by AcOEt. Organic phase was washed by H_2O (×3) and brine (×1). Organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 20/1) to give prianosin B (**1c**) (35.1 mg, 48%) as red solid; mp 253–255 °C; $[\alpha]_D^{23.0}$ +362 (*c* 0.405, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.87–2.94 (3H, m), 2.98 (1H, dd, *J* = 16.5, 4.0 Hz), 4.80 (1H, dd, *J* = 12.0, 6.5 Hz), 5.49–5.58 (1H, m), 6.30 (1H, br s), 7.54 (1H, d, *J* = 5.5 Hz), 7.78 (1H, s), 8.03 (1H, s), 8.49 (1H, d, *J* = 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 40.0, 45.6, 50.8, 56.5, 61.7, 113.7, 118.2, 119.6, 120.2, 125.3, 129.0 (2C), 143.0, 143.6, 146.1, 155.7, 167.6, 188.3; IR (KBr): 3057, 2924, 2853, 1682, 1645, 1595, 1472, 1303 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{13}BrN_3O_2S$ $[M+H]^+$: 413.9912, found 413.9920.

Methyl-3-(3chloro-4-hydroxyphenyl)-2-(tritylamino)propionate (15c). SO_2Cl_2 (0.38 mL, 4.74 mmol) was added to a solution of **11** (1.0 g, 4.32 mmol) in AcOH (7.7 mL) and Et_2O (0.86 mL) at 0 °C under N_2. The resulting solution was warmed to rt under stirring. Then the solution was filtered through a Celite pad, and washed with Et_2O. The filtrate was concentrated *in vacuo* to give **precursor 15c** (910 mg, 79%) as a colorless solid; mp 191–192 °C; ^{1}H NMR (500 MHz, CD_3OD) δ: 3.06 (1H, dd, *J* = 14.4, 7.5 Hz), 3.16 (1H, dd, *J* = 14.4, 6.0 Hz), 3.81 (3H, s), 4.26 (1H, dd, *J* = 7.5, 6.0 Hz), 6.90 (1H, d, *J* = 8.4 Hz), 7.01 (1H, dd, *J* = 8.4, 2.1 Hz), 7.22 (1H, d, *J* = 2.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 34.5, 52.6, 53.2, 116.7, 119.5, 126.0, 129.0, 130.8, 152.4, 169.4; IR (KBr): 3100, 1743, 1613, 1580, 1510 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{13}ClNO_3$ $[M+H]^+$: 230.0584, found 230.0565 (as free base).

Et_3N (103 μL, 0.750 mmol) was added to a solution of **precursor 15c** (100.0 mg, 0.375 mmol) in DMF (1.8 mL) at rt under N_2. After being stirred for 10 min, trityl chloride (TrCl) (104.5 mg, 0.375 mmol) was added to the resulting solution. The mixture was stirred at rt for 3 h. The reaction was quenched with H_2O and extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography using hexane/AcOEt (3/1) as the eluent to give **15c** (123 mg, 69%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.60 (1H, br s), 2.85 (2H, d, *J* = 6.6 Hz), 3.05 (3H, s), 3.47–3.55 (1H, m), 5.64 (1H, s), 6.91 (1H, d, *J* = 8.2 Hz), 6.99 (1H, d, *J* = 8.2 Hz), 7.09–7.23 (10H, m), 7.40 (6H, d, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 41.0, 51.4, 58.0, 70.9, 115.9, 126.3, 127.7, 128.7, 129.7, 130.1, 130.5, 145.7, 150.2, 174.8; IR (KBr): 3533, 3342, 1730, 1595, 1500 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{27}ClNO_3$ $[M+H]^+$: 472.1679, found 472.1686.

Methyl-3-(3-iodo-4-hydroxyphenyl)-2-(tritylamino)propionate (15d). $SOCl_2$ (0.52 mL, 7.16 mmol) was added dropwise to a solution of 3-iodo-L-tyrosine (**12**) (2.00 g, 6.51 mmol) in MeOH (13.0 mL). The suspension was heated at a reflux for 3 h. The mixture was evaporated *in vacuo* to give **precursor 15d** (2.30 g, 99%) as a colorless solid; mp 201–202 °C; ^{1}H NMR (300 MHz, CD_3OD) δ: 3.03 (1H, dd, *J* = 14.4, 7.5 Hz), 3.14 (1H, dd, *J* = 14.4, 6.0 Hz), 3.81 (3H, s), 4.24 (1H, dd, *J* = 7.5, 6.0 Hz), 6.82 (1H, d, *J* = 8.4 Hz), 7.07 (1H, dd, *J* = 8.4, 1.8 Hz), 7.22 (1H, d, *J* = 1.8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 34.3, 52.6, 53.2, 84.8, 115.0, 126.8, 130.5, 139.5, 156.0, 169.4; IR (KBr): 3200, 1741, 1600, 1570, 1502 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{13}INO_3$ $[M+H]^+$: 321.9940, found 321.9941 (as free base).

Et_3N (1.78 mL, 13.02 mmol) was added to a solution of **precursor 15d** (2.3 g, 6.51 mmol) in DMF (32 mL) at rt under N_2. After being stirred for 10 min, TrCl (1.8 g, 6.51 mmol) was added to the resulting solution. The mixture was stirred at rt for 3 h. The reaction was quenched with H_2O and extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography using hexane/AcOEt (3/1) as the eluent to give **15d** (3.62 g, quant.) as a colorless solid; mp 95–98 °C; $[\alpha]_D^{26.7}$ +15.2 (*c* 2.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.55 (1H, br s), 2.84 (2H, dd, *J* = 6.5, 2.6 Hz), 3.06 (3H, s), 3.50–3.55 (1H, m), 5.32 (1H, s), 6.92 (1H, d, *J* = 8.1 Hz), 7.07 (1H, dd, *J* = 8.1, 1.6 Hz), 7.17–7.24 (9H, m), 7.39 (6H, d, *J* = 7.2 Hz), 7.55 (1H, d, *J* = 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 40.6, 51.4, 57.9, 70.9, 85.2, 114.6, 126.4, 127.8, 128.7, 131.5, 131.6, 139.3, 145.7, 153.6, 174.7; IR (KBr): 3340, 3057, 3030, 2949, 2925, 2848, 1726, 1597, 1574, 1489, 1467, 1417 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{27}INO_3$ $[M+H]^+$: 564.1036, found 564.1043.

General procedure for the syntheses of 17a,c,d from 15a,c,d

Diisobutylaluminium hydride (DIBAL) (0.94 M solution in hexane, 3.23 equiv) was added dropwise to a solution of **15** (1.0 equiv) in dry CH_2Cl_2 (0.053 M solution) at –78 °C under N_2. The resulting solution was warmed to rt and stirred for 5 h. The mixture was cooled to 0 °C and quenched with H_2O. The precipitate was filtered through a Celite pad and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 and the mixture was washed with sat. *aq*. $NaHCO_3$ and brine, then dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography to give **16**.

16a (5.6 g, 95%) was obtained from **15a** (6.3 g, 14.4 mmol), DIBAL (50.5 mL, 47.5 mmol) and dry CH_2Cl_2 (280 mL). Eluent: hexane/AcOEt (2/1). **16a**: Colorless oil: ^{1}H NMR ($CDCl_3$): δ = 2.17 (dd, 1H, *J* = 13.2, 4.6 Hz), 2.42 (dd, 1H, *J* = 13.2, 9.5 Hz), 2.72–2.75 (m, 1H), 2.92 (dd, 1H, *J* = 10.8, 3.8 Hz), 3.11 (dd, 1H,

J = 10.8, 2.2 Hz), 4.92 (br s, 1H), 6.62 (d, 2H, J = 8.4 Hz), 6.76 (d, 2H, J = 8.4 Hz), 7.17–7.31 (m, 9H), 7.53 (d, 6H, J = 7.3 Hz).

16c (3.9 g, 51%) was obtained from **15c** (8.15 g, 17.3 mmol), DIBAL (64.0 mL, 60.5 mmol) and dry CH_2Cl_2 (86 mL). Eluent: hexane/AcOEt (2/1). **16c**: Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.14 (1H, dd, J = 13.2, 9.6 Hz), 2.41 (1H, dd, J = 13.2, 9.6 Hz), 2.64–2.80 (1H, m), 2.97 (1H, dd, J = 10.8, 3.9 Hz), 3.10 (1H, dd, J = 10.8, 2.5 Hz), 6.71 (1H, dd, J = 8.1, 1.5 Hz), 6.80 (1H, d, J = 8.1 Hz), 6.83 (1H, d, J = 1.5 Hz), 7.16–7.30 (9H, m), 7.55 (6H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.8, 55.2, 67.9, 71.3, 115.9, 119.5, 126.5, 127.9, 128.6, 129.3, 129.7, 132.1, 146.4, 149.7; IR (KBr): 3247, 1700, 1590, 1575, 1500 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{27}ClNO_2$ [M+H]$^+$: 444.1730, found 444.1721.

16d (680 mg, 90%) was obtained from **15d** (792 g, 1.40 mmol), DIBAL (4.46 mL, 4.20 mmol) and dry CH_2Cl_2 (7.0 mL). Eluent: hexane-AcOEt (2/1). **16d**: Colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.12 (1H, dd, J = 13.2, 4.5 Hz), 2.40 (1H, dd, J = 13.2, 9.5 Hz), 2.72–2.73 (1H, m), 2.98 (1H, dd, J = 10.9, 3.9 Hz), 3.10 (1H, dd, J = 10.9, 2.0 Hz), 6.73 (1H, d, J = 8.3 Hz), 6.78 (1H, dd, J = 8.3, 1.2 Hz), 7.22–7.34 (10H, m), 7.54 (6H, d, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.5, 55.2, 67.9, 71.3, 85.3, 114.6, 126.6, 127.9, 128.6, 131.0, 132.9, 138.9, 146.4, 153.3; IR (KBr): 3500, 3315, 3057, 3030, 2937, 2889, 1703, 1597, 1574, 1487, 1446 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{27}INO_2$ [M+H]$^+$: 536.1087, found 536.1082.

tert-Butyldimethylsilyl chloride (TBSCl) (3.0 equiv) was added to a solution of **16** (1.0 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.0 equiv) in dry CH_2Cl_2 (0.13 M solution) at 0 °C under N_2. The mixture was stirred at the same temperature for 2.5 h. The reaction was quenched with sat. *aq.* $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography to give **17**.

17a (7.3 g, 84%) was obtained from **16a** (5.6 g, 13.6 mmol), TBSCl (6.2 g, 40.8 mmol), DBU (10.2 mL, 68.0 mmol) and dry CH_2Cl_2 (90 mL). Eluent: hexane/AcOEt (20/1). **17a**: Colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.30 (s, 3H), –0.27 (s, 3H), 0.10 (s, 6H), 0.69 (s, 9H), 0.81 (s, 9H), 2.10 (br s, 1H), 2.36 (dd, 1H, J = 9.0, 3.0 Hz), 2.45–2.50 (m, 1H), 2.51 (m, 1H), 2.80 (dd, 1H, J = 9.6, 3.0 Hz), 6.52 (d, 2H, J = 8.1 Hz), 6.7 (d, 2H, J = 8.1 Hz), 7.00–7.14 (m, 9H), 7.43 (d, 6H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ = –5.6 (2C), –4.6, 18.0 (2C), 25.5, 25.7, 37.9, 55.3, 62.3, 70.9, 119.5, 126.0, 127.6, 128.6, 130.3, 132.2, 147.1, 153.5; IR (KBr): 2953, 2928, 1606, 1508, 1488, 1471 cm^{-1};HRMS (FAB) calcd for $C_{40}H_{56}NO_2Si_2$ (M+H$^+$) 638.3850. found 638.3834.

17c (4.9 g, 83%) was obtained from **16c** (3.9 g, 8.78 mmol), TBSCl (3.9 g, 26.3 mmol), DBU (3.9 mL, 26.3 mmol) and dry CH_2Cl_2 (44 mL). Eluent: hexane/AcOEt (20/1). **17c**: Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: –0.31 (3H, s), –0.29 (3H, s), 0.00 (6H, s), 0.67 (9H, s), 0.83 (9H, s), 1.99 (1H, br s), 2.31–2.39 (3H, m), 2.48–2.50 (1H, m), 2.73 (1H, d, J = 9.3 Hz), 6.52 (1H, d, J = 8.5 Hz), 6.57 (1H, d, J = 8.5 Hz), 6.81 (1H, s), 6.95–7.09 (9H, m), 7.38 (6H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –5.5, –5.4, –4.3, 18.1, 18.3, 25.7, 25.9, 37.8, 55.2, 62.3, 71.1, 120.2, 124.9, 126.3, 127.8, 128.6, 128.7, 131.2, 133.6, 147.2, 149.5; IR (KBr): 3327, 1596, 1494, 1471, 1462, 1448 cm^{-1}; HRMS (FAB) calcd for $C_{40}H_{55}ClNO_2Si_2$ [M+H]$^+$: 672.3460, found 672.3453.

17d (883 mg, 91%) was obtained from **16d** (680 mg, 1.27 mmol), TBSCl (564 mg, 3.81 mmol), DBU (0.564 mL, 3.81 mmol) and dry CH_2Cl_2 (12.7 mL). Eluent: hexane/AcOEt (20/1). **17d**: Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: –0.35 (3H, s), –0.33 (3H, s), 0.00 (6H, s), 0.61 (9H, s), 0.80 (9H, s), 2.26–2.34 (3H, m), 2.44–2.45 (1H, m), 2.66 (1H, dd, J = 9.6, 3.3 Hz), 6.42 (1H, d, J = 8.3 Hz), 6.61 (1H, dd, J = 8.3, 2.1 Hz), 6.90–7.04 (9H, m), 7.21 (1H, d, J = 2.1 Hz), 7.33 (6H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –5.4, –4.0, 18.1, 18.3, 25.8, 25.9, 34.6, 37.4, 55.2, 62.3, 71.1, 90.1, 117.8, 126.3, 127.8, 128.7, 130.3, 134.2, 140.5, 147.2, 153.2; IR (KBr): 3327, 1712, 1682, 1595, 1487, 1471, 1446 cm^{-1}; HRMS (FAB) calcd for $C_{40}H_{54}INNaO_2Si_2$ [M+Na]$^+$: 786.2662, found 786.2635.

General procedure for the syntheses of 38a,c,d from 17a,c,d

TBAF (1.0 M solution in THF, 1.0 equiv) was added to a solution of **17** (1.0 equiv) in dry THF (0.063 M solution) at 0 °C under N_2. The mixture was stirred at the same temperature for 0.5 h. The reaction was quenched with sat. *aq.* NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography to give **18**.

18a (818 mg, 95%) was obtained from **17a** (1.05 g, 1.64 mmol), TBAF (1.64 mL, 1.64 mmol) and dry THF (26 mL). Eluent: hexane/AcOEt (10/1). **18a**: Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ: –0.25 (3H, s), –0.22 (3H, s), 0.74 (9H, s), 2.12 (1H, br s), 2.37 (1H, dd, J = 9.6, 4.6 Hz), 2.44–2.52 (3H, m), 2.83 (1H, dd, J = 9.6, 3.1 Hz), 6.65 (2H, d, J = 8.4 Hz), 6.77 (2H, d, J = 8.4 Hz), 7.06–7.20 (9H, m), 7.46 (6H, d, J = 7.5 Hz).

18c (2.75 g, 99%) was obtained from **17c** (3.35 g, 4.98 mmol), TBAF (4.98 mL, 4.98 mmol) and dry THF (79 mL). Eluent: hexane/AcOEt (10/1). **18c**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ: –0.02 (3H, s), –0.01 (3H, s), 0.98 (9H, s), 2.23 (1H, br s), 2.60–2.68 (3H, m), 2.80–2.82 (1H, m), 3.00 (1H, dd, J = 9.3, 3.0 Hz), 6.91–6.97 (2H, m), 7.08 (1H, s), 7.26–7.40 (9H, m), 7.66 (6H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –5.4, 18.1, 25.9, 37.7, 55.1, 62.3, 71.1, 115.6, 119.3, 126.3, 127.8, 128.7, 129.6, 129.9, 132.9, 147.1, 149.4; IR (KBr): 3541, 3327, 3057, 3030, 2927, 2854, 1595, 1498, 1470, 1448 cm^{-1}.

18d (2.82 g, 99%) was obtained from **17d** (3.35 g, 4.39 mmol), TBAF (4.39 mL, 4.39 mmol) and dry THF (70 mL). Eluent: hexane-AcOEt (10/1). **18d**: Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: –0.02 (3H, s), –0.01 (3H, s), 0.98 (9H, s), 2.47–2.56 (3H, m), 2.80 (1H, m), 3.00 (1H, dd, J = 9.3, 3.0 Hz), 6.91–6.97 (2H, m), 7.08 (1H, s), 7.27–7.41 (9H, m), 7.66 (6H, d, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –5.4, 18.1, 25.9, 37.4, 55.1, 62.2, 71.1, 85.3, 114.4, 126.3, 127.8, 128.7, 131.3, 133.8, 139.1, 147.1, 152.9; IR (KBr): 3541, 3327, 3057, 3030, 2927, 2854, 1595, 1498, 1470, 1448 cm^{-1}; HRMS (FAB) calcd for $C_{34}H_{41}INO_2Si$ [M+Na]$^+$: 650.1951, found 650.1964.

A solution of **18** (1.2 equiv) in 0.1 M HCl/MeOH (1.44 equiv) was stirred at rt for 0.5 h under N_2. This solution was added dropwise to a solution of **32** (1.0 equiv) in MeOH (0.345 M solution). The mixture was stirred at rt for 16 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography to give **38**.

38a (228 mg, 83%) was obtained from **18a** (446 mg, 0.851 mmol), 0.1 M HCl/MeOH (9.3 mL), **32** (260 mg, 0.709 mmol) and MeOH (1.6 mL). Eluent: CH_2Cl_2/MeOH/Et_3N (100/5/0.1). **38a**: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.00 (3H, s), 0.01 (3H, s),

0.92 (9H, s), 2.44 (3H, s), 2.61 (2H, d, J = 6.9 Hz), 2.80 (2H, t, J = 7.2 Hz), 3.30–3.32 (1H, m), 3.47 (2H, d, J = 3.0 Hz), 4.14 (2H, t, J = 7.2 Hz), 5.63 (1H, s), 5.95 (1H, br s), 6.74 (2H, d, J = 8.4 Hz), 6.84 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.54 (1H, s), 8.06 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ: −5.5, −5.4, 17.9, 18.2, 21.7, 25.8, 34.2, 48.3, 54.9, 61.4, 94.6, 116.0, 118.0, 122.8, 125.9, 126.3, 128.3, 128.8, 129.7, 130.1, 134.4, 145.2, 145.8, 155.7, 156.1, 169.4; IR (KBr): 3375, 1666, 1614, 1579, 1531, 1514, 1494, 1462, 1380 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{40}N_3O_5SSi$ [M+H]$^+$: 606.2458, found 606.2465.

38c (128.1 mg, 58%) was obtained from **18c** (231.2 mg, 0.414 mmol), 0.1 M HCl/MeOH (4.97 mL), **32** (122.9 mg, 0.345 mmol) and MeOH (1.0 mL). Eluent: CH_2Cl_2/MeOH/Et_3N (100/5/0.1). **38c**: Red solid: ^{1}H NMR (270 MHz, CD_3OD) δ: 0.00 (6H, s), 0.91 (9H, s), 2.42 (3H, s), 2.61 (2H, d, J = 6.6 Hz), 2.77 (2H, t, J = 8.0 Hz), 3.33–3.36 (1H, m), 3.64–3.67 (2H, m), 4.11–4.12 (2H, m), 5.57 (1H, s), 6.75 (1H, d, J = 9.0 Hz), 6.82 (1H, d, J = 9.0 Hz), 7.03 (1H, s), 7.32 (2H, d, J = 8.9 Hz), 7.51 (1H, s), 8.03 (2H, d, J = 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.6, −5.5, 17.9, 18.2, 21.7, 25.8, 34.0, 48.1, 54.7, 61.3, 74.0, 86.1, 94.4, 107.4, 117.0, 117.9, 120.8, 122.7, 126.0, 126.3, 128.5, 128.8, 129.7, 130.0, 134.2, 145.9, 151.4, 156.0, 162.6, 166.8; IR (KBr): 3375, 3018, 2928, 2856, 1666, 1614, 1580, 1537, 1495, 1462, 1445, 1379 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{39}ClN_3O_5SSi$ [M+H]$^+$: 640.2068, found 640.2095.

38d (71.7 mg, 49%) was obtained from **18d** (171.3 mg, 0.264 mmol), 0.1 M HCl/MeOH (3.17 mL), **32** (78.4 mg, 0.200 mmol) and MeOH (0.5 mL). Eluent: CH_2Cl_2/MeOH/Et_3N (100/5/0.1). 3**8d**: Red solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.01 (3H, s), 0.13 (3H, s), 0.85 (9H, s), 2.32 (3H, s), 2.63 (2H, d, J = 6.3 Hz), 2.77 (2H, t, J = 8.1 Hz), 3.37–3.40 (1H, m), 3.48–3.54 (2H, m), 4.03 (2H, t, J = 8.1 Hz), 5.48 (1H, s), 6.79 (1H, d, J = 7.8 Hz), 6.89 (1H, d, J = 7.8 Hz), 7.28 (1H, s), 7.30 (2H, d, J = 9.0 Hz), 7.34 (1H, s), 8.00 (2H, d, J = 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.5, −5.4, 18.0, 18.2, 18.8, 21.8, 23.9, 25.9, 45.4, 45.6, 53.7, 56.4, 62.0, 97.1, 107.6, 117.2, 118.0, 119.3, 126.5, 128.7, 128.9, 129.8, 130.6, 131.0, 135.4, 137.0, 139.2, 158.1, 164.5, 175.7, 186.2; IR (KBr): 3368, 2953, 2928, 2856, 1709, 1666, 1616, 1578, 1558, 1534, 1491, 1464, 1443, 1379 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{39}IN_3O_5SSi$ [M+H]$^+$: 732.1424, found 732.1416.

General procedure for the syntheses of 49a, c–d, 49′c–d from 38a,c,d

PIFA (1.2 equiv) and montmorillonite K10 (1/4 mg of **38** (mg)) was added to a solution of **38** (1.0 equiv) in CF_3CH_2OH (0.03 M solution) at rt under N_2. The mixture was stirred at rt for 0.5 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography to give **49**.

49a (66.0 mg, 57%) was obtained from **38a** (115 mg, 0.190 mmol), PIFA (98 mg, 0.228 mmol), and CF_3CH_2OH(6.3 ml). Eluent: hexane/AcOEt/Et_3N (100/50/0.1). **49a**: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: –0.02 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 1.41 (1H, d, J = 13.2 Hz), 1.61 (1H, d, J = 13.2 Hz), 2.33 (3H, s), 2.52 (2H, t, J = 7.2 Hz), 3.43–3.45 (2H, m), 3.63–3.75 (3H, m), 3.99 (1H, t, J = 7.2 Hz), 5.99 (1H, br s), 6.12 (1H, dd, J = 9.9, 3.0 Hz), 6.13 (1H, dd, J = 9.9, 3.0 Hz), 6.80 (1H, dd, J = 9.9, 3.0 Hz), 6.89 (1H, dd, J = 9.9, 3.0 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.35 (1H, s), 7.95 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.4, −5.3, 17.5, 18.3, 21.7, 25.7, 37.5, 40.8, 49.5, 66.3, 105.5, 118.5, 121.9, 125.8, 126.4, 127.5, 128.6, 129.7, 134.6, 141.9, 145.7, 152.9, 157.3, 168.7, 186.1; IR (KBr): 3394, 1660, 1620, 1595, 1574, 1524, 1460, 1435, 1379 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{38}N_3O_5SSi$ [M+H]$^+$: 604.2301, found 604.2323.

49c (24.7 mg, 24%) and **49′c** (18.2 mg, 17%) were obtained from **38c** (105.6 mg, 0.165 mmol), PIFA (85.1 mg, 0.198 mmol), and CF_3CH_2OH (5.5 ml). Eluent: hexane/AcOEt/Et_3N (100/50/0.1). **49c**: Red solid: mp > 300 °C; $[\alpha]_D^{26.3}$ +225 (c 1.84, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.01 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 1.46–1.65 (2H, m), 2.33 (3H, s), 2.52 (2H, t, J = 7.3 Hz), 3.38–3.45 (2H, m), 3.64–3.76 (2H, m), 3.97–4.04 (1H, m), 6.19 (1H, d, J = 9.9 Hz), 6.88 (1H, dd, J = 9.9, 2.7 Hz), 6.93 (1H, d, J = 2.7 Hz), 7.22 (2H, d, J = 8.4 Hz), 7.36 (1H, s), 7.72 (1H, d, J = 8.4 Hz), 7.94 (1H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: −5.4, 17.5, 18.3, 21.7, 25.9, 36.6, 41.8, 42.9, 48.1, 49.5, 53.4, 66.1, 118.5, 121.8, 125.4, 126.1, 126.3, 128.6, 129.7, 130.2, 134.5, 145.8, 152.5, 153.2, 168.4, 179.3; IR (KBr): 3387, 3153, 2928, 1798, 1660, 1597, 1574, 1528, 1460, 1379 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{37}ClN_3O_5SSi$ [M+H]$^+$: 638.1912, found 638.1909.

49′c: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.00 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 1.45–1.62 (2H, m), 2.33 (3H, s), 2.52 (2H, t, J = 7.5 Hz), 3.40–3.46 (2H, m), 3.64–3.73 (2H, m), 3.94–3.41 (1H, m), 5.27 (1H, br s), 6.24 (1H, d, J = 9.6 Hz), 6.82 (1H, d, J = 9.6 Hz), 7.06 (1H, s), 7.23 (2H, d, J = 7.8 Hz), 7.36 (1H, s), 7.93 (2H, d, J = 7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.4, −5.4, 17.5, 18.3, 21.7, 25.9, 36.9, 43.0, 49.4 53.4, 66.1, 77.2, 125.4, 126.4, 128.6, 129.6, 129.7, 133.0, 134.6, 142.1, 143.5, 145.8, 148.2, 157.2, 179.2; IR (KBr): 3393, 3153, 2955, 2930, 2856, 1661, 1595, 1574, 1529, 1462, 1379 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{37}ClN_3O_5SSi$ [M+H]$^+$: 638.1912, found 638.1926.

49d (21.8 mg, 25%) and **49′d** (10.8 mg, 12%) were obtained from **38d** (88.4 mg, 0.121 mmol), PIFA (63.3 mg, 0.145 mmol), and CF_3CH_2OH (4.0 ml). Eluent: hexane/AcOEt/Et_3N (100/50/0.1). **49d**: Red solid: $[\alpha]_D^{27.4}$ −164 (c 4.50, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ: –0.23 (3H, s), 0.21 (3H, s), 0.84 (9H, s), 1.36–1.68 (2H, m), 2.33 (3H, s), 2.53 (2H, t, J = 7.1 Hz), 3.38–3.49 (2H, m), 3.63–3.82 (2H, m), 3.94–4.04 (1H, m), 5.99 (1H, br s), 6.19 (1H, d, J = 9.7 Hz), 6.90 (1H, dd, J = 9.7, 2.6 Hz), 7.23 (2H, d, J = 7.4 Hz), 7.36 (1H, s), 7.49 (1H, d, J = 2.6 Hz), 7.94 (2H, d, J = 7.4 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: −5.3, −5.2, 17.6, 18.4, 21.6, 21.8, 24.7, 25.9, 29.7, 36.7, 45.1, 49.6, 66.1, 104.0, 118.5, 121.7, 123.2, 124.1, 125.5, 126.0, 126.3, 128.5, 129.5, 129.6, 129.7, 134.4, 139.0, 143.3, 145.6, 152.7, 157.2, 160.1, 168.1, 179.5; IR (KBr): 3395, 2928, 2856, 1659, 1574, 1529, 1461 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{37}IN_3O_5SSi$ [M+H]$^+$: 730.1268, found 730.1266.

49′d: Red solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.03 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 1.60–1.65 (2H, m), 2.38 (3H, s), 2.55 (2H, t, J = 7.5 Hz), 3.43–3.46 (2H, m), 3.66–3.77 (2H, m), 3.97–4.04 (1H, m), 6.05 (1H, br s), 6.26 (1H, d, J = 9.6 Hz), 6.87 (1H, dd, J = 9.6, 2.5 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.38 (1H, s), 7.69 (1H, d, J = 2.5 Hz), 7.96 (2H, d, J = 8.4 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: −5.2 (2C), 17.7, 18.4, 21.8, 24.7, 26.0, 29.8, 36.7, 45.1, 49.4, 49.6, 66.1, 104.1, 118.5, 121.8, 123.3, 125.5, 126.0, 126.3, 128.6, 129.2, 129.6, 129.8, 134.4, 143.4, 145.7, 152.7, 157.1, 160.0, 168.1, 179.5; IR (KBr): 3391, 3153, 2928, 2856, 1794, 1655, 1575, 1528, 1462, 1382 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{37}IN_3O_5SSi$ [M+H]$^+$: 730.1268, found 730.1284.

General procedure for the syntheses of 50a, c–d, 50′c–d from 49a, c–d, 49′c–d

$BF_3{\cdot}Et_2O$ (9.4 equiv) was added to a solution of **49** (1.0 equiv) in dry CH_2Cl_2 (0.055 M solution) at 0 °C under N_2. The mixture was allowed to warm to rt for 7 h. The reaction was quenched with $NaHCO_3$ powder, filtered and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography to give **50**.

50a (35.3 mg, 87%) was obtained from **49a** (50.1 mg, 0.0829 mmol), $BF_3{\cdot}Et_2O$ (0.10 mL, 0.78 mmol), and dry CH_2Cl_2 (1.5 mL). Eluent: CH_2Cl_2/MeOH/Et_3N (100/5/0.1). **50a**: Red solid: ^{1}H NMR (270 MHz, $(CD_3)_2CO$) δ: 1.53 (1H, d, J = 12.0 Hz), 1.81 (1H, t, J = 12.0 Hz), 2.64 (3H, s), 2.83 (2H, m), 3.57–3.82 (4H, m), 4.32 (1H, m), 6.06 (2H, dd, J = 10.2, 2.2 Hz), 6.96 (1H, dd, J = 10.2, 2.2 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.63 (1H, s), 8.06 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ: 18.0, 21.5, 38.4, 41.6, 50.4, 65.5, 111.9, 119.6, 122.5, 126.8, 127.3, 127.8, 129.4, 130.7, 135.6, 140.0, 147.0, 153.8, 158.0, 169.4, 185.6; IR (KBr): 3305, 1659, 1614, 1595, 1573, 1525, 1487, 1461, 1375 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{24}N_3O_5S$ [M+H]$^+$: 490.1437, found 490.1429.

50c (9.0 mg, 65%) was obtained from **49c** (16.7 mg, 0.0262 mmol), $BF_3{\cdot}Et_2O$ (35 μL, 0.276 mmol), and dry CH_2Cl_2 (1.4 mL). Eluent: CH_2Cl_2/MeOH/Et_3N (100/5/0.1). **50c**: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.55 (1H, d, J = 12.0 Hz), 1.79 (1H, d, J = 12.0 Hz), 2.36 (3H, s), 2.57–2.62 (2H, m), 3.54–3.56 (2H, m), 3.78–3.83 (2H, m), 4.00–4.03 (1H, m), 6.03 (1H, br s), 6.22 (1H, d, J = 9.9 Hz), 6.92 (1H, dd, J = 9.9, 2.4 Hz), 6.98 (1H, d, J = 2.4 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.40 (1H, s), 7.95 (2H, d, J = 8.4 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 17.8, 21.7, 28.9, 29.6, 38.6, 44.2, 49.4, 59.6, 68.1, 77.2, 80.1, 118.6, 122.0, 123.3, 125.4, 126.0, 128.5, 129.8, 134.5, 145.9, 152.5, 157.4, 168.3, 191.2; IR (KBr): 3389, 2930, 1713, 1661, 1595, 1573, 1529, 1485, 1462, 1377 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{23}ClN_3O_5S$ [M+H]$^+$: 524.1047, found 524.1066.

50′c (5.5 mg, 65%) was obtained from **49′c** (11.9 mg, 0.0160 mmol), $BF_3{\cdot}Et_2O$ (21.4 μL, 0.169 mmol), and dry CH_2Cl_2 (0.86 mL). Eluent: CH_2Cl_2/MeOH/Et_3N (100/5/0.1). **50′c**: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.56–1.57 (1H, m), 1.80–1.84 (1H, m), 2.37 (3H, s), 2.57–2.62 (2H, m), 3.54–3.59 (2H, m), 3.79–3.85 (2H, m), 3.98–4.01 (1H, m), 4.72 (1H, br s), 6.29 (1H, d, J = 9.9 Hz), 6.86 (1H, d, J = 9.9 Hz), 7.10 (1H, s), 7.27 (2H, d, J = 7.8 Hz), 7.41 (1H, s), 7.95 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ: 18.0, 21.5, 37.6, 39.8, 42.4, 44.0, 47.9, 50.2, 65.2, 119.6, 125.8, 127.4, 129.4, 130.7, 131.7, 135.6, 147.0, 150.0, 158.7, 169.3, 178.9; IR (KBr): 3385, 3130, 1660, 1650, 1595, 1575, 1525, 1485, 1460, 1375 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{23}ClN_3O_5S$ [M+H]$^+$: 524.1047, found 524.1060.

50d (14.9 mg, 81%) was obtained from **49d** (22.1 mg, 0.030 mmol), $BF_3{\cdot}Et_2O$ (39.3 μL, 0.303 mmol), and dry CH_2Cl_2 (1.5 mL). Eluent: CH_2Cl_2/MeOH/Et_3N (100/5/0.1). **50d**: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65 (1H, d, J = 12.0 Hz), 1.78 (1H, d, J = 12.0 Hz), 2.36 (3H, s), 2.58 (2H, t, J = 7.2 Hz), 3.54–3.57 (2H, m), 3.79–3.85 (2H, m), 4.00–4.05 (1H, m), 6.23 (1H, d, J = 9.7 Hz), 6.94 (1H, dd, J = 9.7, 2.6 Hz), 7.27 (1H, d, J = 8.4 Hz), 7.41 (1H, s), 7.53 (1H, d, J = 2.6 Hz), 7.96 (2H, d, J = 8.4 Hz); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ: 18.0, 21.6, 37.1, 45.9, 50.0, 50.4, 65.4, 65.5, 119.6, 122.6, 124.3, 126.2, 127.4, 129.4, 130.2, 130.7, 135.6, 147.0, 153.8, 154.2, 166.4, 169.2, 179.7; IR (KBr): 3387, 2925, 2853, 1794, 1655, 1572, 1528, 1460, 1379 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{23}IN_3O_5S$ [M+H]$^+$: 616.0403, found 616.0403.

50′d (6.3 mg, 68%) was obtained from **49′d** (10.6 mg, 0.015 mmol), $BF_3{\cdot}Et_2O$ (16.7 μL, 0.145 mmol), and dry CH_2Cl_2 (0.7 mL). Eluent: CH_2Cl_2/MeOH/Et_3N (100/5/0.1). **50′d**: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.93–1.98 (1H, m), 2.15–2.22 (1H, m), 2.36 (3H, s), 2.53–2.62 (2H, m), 3.51–3.55 (3H, m), 3.79–3.84 (2H, m), 6.30 (1H, d, J = 9.8 Hz), 6.90 (1H, d, J = 9.8 Hz), 7.23 (1H, s), 7.28 (2H, d, J = 7.5 Hz), 7.71 (1H, s), 7.95 (2H, d, J = 7.5 Hz); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) δ: 18.0, 21.6, 37.6, 46.2, 46.7, 50.3, 50.4, 65.3, 104.2, 119.6, 123.5, 127.4, 128.3, 129.4, 130.2, 130.7, 131.3, 147.0, 153.9, 158.9, 162.1, 169.3; IR (KBr): 3370, 2924, 1655, 1574, 1528, 1458, 1377 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{23}IN_3O_5S$ [M+H]$^+$: 616.0403, found 616.0413.

General procedure for the synthesis of 54a, c–d, 54′c–d from 50a, c–d, 50′c–d

30% HBr–AcOH (0.75 mL/1.0 mmol of **50**) was added to a solution of **50** (1 equiv) in dry CH_2Cl_2 (0.02 M solution) at 0 °C under N_2. The mixture was stirred warming to rt for 36 h. The reaction was quenched with sat. *aq.* $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography to give **54**.

54a (23.5 mg, 66%) was obtained from **50a** (35.3 mg, 0.0721 mmol), 30% HBr-AcOH (67 μL), and dry CH_2Cl_2 (3.6 mL). Eluent: hexane/AcOEt (1/1). **54a**: Red solid: mp > 300 °C; $[\alpha]_D^{26.5}$ +956 (*c* 0.541, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.69 (1H, d, J = 12.9 Hz), 1.92 (1H, d, J = 12.9 Hz), 2.34 (3H, s), 2.53–2.58 (3H, m), 2.84 (1H, dd, J = 16.8, 12.9 Hz), 3.55 (1H, s), 3.73–3.79 (2H, m), 4.15 (1H, dd, J = 16.8, 6.0 Hz), 4.28 (1H, dd, J = 9.6, 6.0 Hz), 5.85 (1H, s), 5.89 (1H, d, J = 10.2 Hz), 7.03 (1H, d, J = 10.2 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.40 (1H, s), 7.95 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.8, 21.7, 27.9, 36.5, 37.5, 44.0, 44.5, 49.5, 53.4, 68.0, 75.0, 118.6, 122.1, 124.8, 125.5, 126.7, 128.6, 129.7, 134.6, 145.8, 148.3, 152.7, 157.6, 168.5, 174.9, 197.5; IR (KBr): 3392, 2941, 2842, 1660, 1595, 1569, 1523, 1488, 1458 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{24}N_3O_5S$ [M+H]$^+$: 490.1437, found 490.1439.

54c (3.5 mg, 71%) was obtained from **50c** (4.9 mg, 0.00935 mmol), 30% HBr-AcOH (7 μL), and dry CH_2Cl_2 (0.47 mL). Eluent: hexane/AcOEt (1/1). **54c**: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.91 (1H, d, J = 12.9 Hz), 2.34 (1H, dd, J = 12.9, 2.1 Hz), 2.44 (3H, s), 2.85–2.99 (2H, m), 3.67–4.15 (7H, m), 5.48 (1H, br s), 6.36 (1H, d, J = 10.6 Hz), 7.06 (1H, d, J = 10.6 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.91 (1H, s), 8.09 (2H, d, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.8, 21.7, 28.9, 29.6, 38.6, 44.2, 49.4, 59.6, 68.1, 77.2, 80.1, 118.6, 122.0, 123.3, 125.4, 126.0, 129.8, 134.5, 145.9, 152.5, 157.4, 168.3, 191.2; IR (KBr): 3395, 2928, 2853, 1682, 1658, 1574, 1526, 1487, 1462, 1379 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{23}ClN_3O_5S$ [M+H]$^+$: 524.1047, found 524.1057.

54′c (2.4 mg, 57%) was obtained from **50′c** (4.2 mg, 0.00801 mmol), 30% HBr-AcOH (6 μL), and dry CH_2Cl_2 (0.40 mL). Eluent: hexane/AcOEt (1/1). **54′c**: Red solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.87 (1H, d, J = 13.5 Hz), 2.38 (1H, dd, J = 13.5, 2.1 Hz), 2.44 (3H, s), 2.78 (1H, dd, J = 16.8, 4.8 Hz), 2.93–2.99 (2H, m), 3.36 (1H, dd, J = 16.8, 13.2 Hz), 3.65–4.02 (5H, m), 4.32 (1H, dd, J = 13.2, 5.3 Hz), 7.22 (1H, s), 7.45 (2H, d, J = 8.7 Hz), 7.91

(1H, s), 8.09 (2H, d, J = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.8, 21.7, 27.5, 29.7, 30.9, 37.7, 38.2, 44.3, 49.7, 68.2, 74.5, 118.6, 122.0, 125.9, 128.6, 129.8, 134.5, 140.8, 145.9, 152.4, 153.7, 174.9, 190.2; IR (KBr): 3400, 2928, 2853, 1682, 1659, 1595, 1574, 1526, 1489, 1462, 1377 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{23}ClN_3O_5S$ $[M+H]^+$: 524.1047, found 524.1071.

54d (2.8 mg, 76%) was obtained from **50d** (3.7 mg, 0.00601 mmol), 30% HBr-AcOH (9 µL), and dry CH_2Cl_2 (0.30 mL). Eluent: hexane/AcOEt (1/1). **54d**: Red solid: $[\alpha]_D^{21.0}$ +96.8 (c 0.322, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.78 (1H, d, J = 13.0 Hz), 2.00 (1H, d, J = 13.0 Hz), 2.43 (3H, s), 2.61–2.70 (2H, m), 2.92 (1H, dd, J = 16.8, 13.0 Hz), 3.61 (1H, s), 3.73 (1H, d, J = 12.5 Hz), 3.80–3.84 (1H, m), 3.88 (1H, d, J = 12.5 Hz), 4.23 (1H, dt, J = 17.5, 6.0 Hz), 4.36 (1H, dd, J = 13.0, 5.5 Hz), 5.89 (1H, br s), 5.97 (1H, d, J = 10.0 Hz), 7.11 (1H, d, J = 10.0 Hz), 7.33 (2H, d, J = 8.0 Hz), 7.48 (1H, s), 8.03 (2H, d, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.9, 21.7, 28.1, 36.6, 37.6, 44.5, 49.6, 68.1, 75.1, 109.4, 118.6, 122.2, 124.9, 125.5, 125.7, 128.7, 129.8, 134.7, 143.5, 145.8, 152.8, 157.6, 168.6, 198.5; IR (KBr): 2928, 2853, 2359, 2341, 2253, 1659, 1570, 1523, 1489, 1458; HRMS (FAB) calcd for $C_{26}H_{23}IN_3O_5S$ $[M+H]^+$: 616.0403, found 616.04011.

54′d (1.4 mg, 67%) was obtained from **50′d** (2.1 mg, 0.0341 mmol), 30% HBr-AcOH (3 µL), and dry CH_2Cl_2 (0.17 mL). Eluent: hexane/AcOEt (1/1). **54′d**: Red solid: mp > 300 °C; $[\alpha]_D^{22.0}$ –76.0 (c 0.626, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.79 (1H, d, J = 12.8 Hz), 2.04 (1H, d, J = 12.8 Hz), 2.41 (3H, s), 2.67 (2H, t, J = 7.5 Hz), 2.88 (1H, dd, J = 16.5, 6.0 Hz), 3.01 (1H, dd, J = 16.8, 13.0 Hz), 3.61 (1H, s), 3.72 (1H, d, J = 12.4 Hz), 3.82–3.99 (2H, m), 4.25 (1H, dt, J = 18.0, 6.5 Hz), 4.31 (1H, dd, J = 12.5, 5.0 Hz), 5.85 (1H, br s), 7.32 (2H, d, J = 8.3 Hz), 7.47 (1H, s), 7.74 (1H, s), 8.01 (2H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.8, 21.7, 27.1, 29.7, 36.3, 44.4, 49.8, 63.4, 68.2, 74.8, 98.4, 102.1, 118.5, 124.4, 125.9, 128.7, 129.8, 129.8, 145.8, 152.3, 154.1, 154.3, 165.5, 168.4, 185.0, 191.4; IR (KBr): 3018, 1710, 1659, 1526, 1487, 1460; HRMS (FAB) calcd for $C_{26}H_{23}IN_3O_5S$ $[M+H]^+$: 616.0403, found 616.0408.

Discorhabdin oxa-aromatic analogue (57). NaN_3 (0.248 mg, 0.00382 mmol) was added to a solution of **54b** (20.8 mg, 0.0366 mmol) in DMF (0.063 mL) at rt under N_2. The mixture was allowed to warm to 70 °C and stirred for 1 h. The reaction mixture was quenched by H_2O and extracted by AcOEt. Organic phase was washed by H_2O (×3) and brine (×1), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 20/1) to give **57** (8.15 mg, 54%) as a red solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.10 (1H, d, J = 11.7 Hz), 2.29 (1H, d, J = 11.7 Hz), 2.79–2.82 (2H, m), 4.01–4.06 (1H, m), 4.14 (1H, d, J = 10.4 Hz), 4.57 (1H, d, J = 10.4 Hz), 5.97 (1H, s), 6.56 (1H, d, J = 9.7 Hz), 6.57 (1H, br s), 7.04 (1H, d, J = 9.7 Hz), 7.34 (1H, d, J = 5.8 Hz), 7.90 (1H, s), 8.31 (1H, d, J = 5.8 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 26.0, 30.0, 35.5, 42.7, 57.7, 72.8, 80.6, 101.9, 114.9, 117.2, 117.3, 117.7, 119.3, 124.2, 132.5, 170.7, 178.1, 190.6, 191.8; IR (KBr): 2924, 1651, 1601, 1531, 1548, 1454 cm^{-1}.

Discorhabdin oxa-aromatic analogue (57′). NaN_3 (0.205 mg, 0.00315 mmol) was added to a solution of **54′b** (14.0 mg, 0.0246 mmol) in DMF (0.042 mL) at rt under N_2 atmosphere. The mixture was allowed to warm to 70 °C. and stirred for 1 h. The reaction mixture was quenched by H_2O and extracted by AcOEt. Organic phase was washed by H_2O (×3) and brine (×1). Organic phase was dried over Na_2SO_4. and evaporated *in vacuo*. Residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 20/1) to give **57′** (5.07 mg, 50%) as a red solid; mp >300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.10 (1H, d, J = 12.8 Hz), 2.25 (1H, d, J = 12.8 Hz), 2.97–3.00 (1H, m), 3.15–3.23 (1H, m), 3.86–4.05 (2H, m), 4.45–4.59 (1H, m), 5.23–5.30 (1H, m), 6.32 (1H, br s), 7.26–7.49 (2H, m), 7.87–7.94 (2H, m), 8.41 (1H, d, J = 5.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.4, 29.1, 39.7, 40.0, 52.4, 80.8, 110.6, 112.3, 118.0, 123.6, 125.0, 129.2, 142.9, 143.3, 146.2, 158.6, 165.3, 190.5, 191.0; IR (KBr): 3057, 2930, 2856, 1682, 1645, 1599, 1535, 1504, 1485, 1461 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{15}BrN_3O_3$ $[M+H]^+$: 412.0297, found 412.0293.

Discorhabdin oxa analogue (55). 5 M NaOMe in MeOH (9.60 µl, 0.0480 mmol) was added to a solution of **54a** in dry THF (1.6 ml) at 0 °C under N_2. The mixture was stirred at 0 °C for 0.5 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 5/1) to give **55** (10.3 mg, 64%) as a green solid: ^{1}H NMR (300 MHz, CD_3OD) δ: 2.09 (1H, d, J = 12.3 Hz), 2.44 (1H, d, J = 12.3 Hz), 2.63–2.66 (3H, m), 3.04–3.14 (1H, m), 3.60–3.66 (4H, m), 3.88 (1H, d, J = 10.8 Hz), 4.23 (1H, d, J = 8.4 Hz), 5.94 (1H, d, J = 9.6 Hz), 6.70 (1H, s), 7.08 (1H, d, J = 9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.4, 28.9, 37.7, 38.8, 46.6, 63.7, 67.7, 76.2, 103.2, 120.3, 124.1, 124.3, 124.8, 125.9, 128.5, 155.5, 156.7, 169.4, 200.5; IR (KBr): 3350, 2931, 2852, 1651, 1602, 1556, 1537, 1523, 1488, 1434 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{18}N_3O_3$ $[M+H]^+$: 336.1348, found 336.1370.

Discorhabdin oxa analogue (56). NaH (0.902 mg, 0.0228 mmol) was added to a solution of **55** (5.10 mg, 0.0152 mmol) in dry THF (0.75 ml) at 0 °C under N_2. The mixture was stirred at 0 °C for 10 min and MsCl (1.40 µl, 0.0182 mmol) was added to the mixture. The mixture was stirred at 0 °C for 30 min and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 20/1) to give **56** (3.40 mg, 54%) as red solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.78 (1H, d, J = 12.6 Hz), 1.99 (1H, d, J = 12.6 Hz), 2.61–2.66 (3H, m), 2.89 (1H, m), 3.57 (3H, s), 3.58–3.58 (2H, m), 3.71–3.89 (2H, m), 4.20 (1H,m), 4.35 (1H, dd, J = 12.9, 5.1 Hz), 5.89–5.92 (1H, br s), 5.94 (1H, d, J = 10.2 Hz), 7.08 (1H, d, J = 10.2 Hz), 7.26 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.7, 28.0, 31.8, 36.7, 37.6, 42.3, 44.6, 49.7, 68.1, 74.2, 109.8, 118.4, 122.1, 124.9, 125.5, 145.9, 152.8, 157.5, 159.4, 165.4, 198.5; IR (KBr): 3400, 2933, 2849, 1651, 1614, 1568, 1523, 1494, 1462 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{20}N_3O_5S$ $[M+H]^+$: 414.1124, found 414.1138.

Compound 59. BzCl (5.00 µl, 0.0450 mmol) was added to a solution of **50b** (17.0 mg, 0.0300 mmol) and Et_3N (6.30 µl, 0.0450 mmol) in dry CH_2Cl_2 (1.0 ml) at 0 °C under N_2. The resulting solution was warmed to rt for 3.0 h. The reaction was quenched with H_2O and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by NH column chromatography (*n*-hexane/AcOEt = 2/1) to give **59** (11.5 mg, 57%) as red solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00–2.07 (2H, m), 2.42 (3H, s), 2.66 (2H, t, J = 8.0 Hz), 3.63–3.66 (2H, m), 4.01 (2H, t, J = 8.0 Hz), 4.15–4.17 (1H, m), 6.12 (1H, d, J = 10.4 Hz), 7.14 (1H, dd, J = 10.4, 2.8 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.38 (1H, s), 7.47–7.56 (3H, m), 7.61 (1H, d, J = 7.2 Hz), 8.03 (2H, d, J = 8.4 Hz), 8.08 (2H, d,

J = 8.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.4, 22.3, 25.9, 29.7, 52.6, 72.5, 76.2, 93.4, 98.7, 102.0, 115.5, 117.6, 123.7, 129.3, 145.4, 145.8, 147.2, 147.8, 147.9, 148.3, 155.7, 157.9, 158.3, 163.7, 165.5, 169.3, 180.0, 191.7, 198.3; IR (KBr): 2963, 2924, 1719, 1655, 1595, 1481, 1458 cm^{-1}; HRMS (FAB) calcd for $C_{33}H_{26}BrN_3O_6S$ $[M]^+$: 671.0726, found 671.0690.

Compound 60. PPh_3 (19.4 mg, 0.0740 mmol), DEAD (33.6 µl, 0.0740 mmol) and DPPA (16.0 µl, 0.0740 mmol) were added to a solution of **50b** (28.0 mg, 0.0490 mmol) in toluene (1.0 ml) at 0 °C under N_2. The resulting solution was warmed to rt for 7.0 h and evaporated *in vacuo*. The residue was purified by NH column chromatography (CH_2Cl_2/MeOH = 20/1) to give **60** (13.1 mg, 45%) as red solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88 (1H, d, J = 12.8 Hz), 1.94 (1H, d, J = 12.8 Hz), 2.43 (3H, s), 2.66 (2H, t, J = 7.2 Hz), 3.67–3.85 (3H, m), 4.11–4.23 (2H, m), 5.07 (1H, d, J = 12.4 Hz), 5.94 (1H, br s), 6.01 (1H, d, J = 10.4 Hz), 7.14 (1H, d, J = 10.4 Hz), 7.33 (2H, d, J = 8.4 Hz), 7.49 (1H, s), 8.01 (2H, d, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ: 17.3, 21.2, 43.6, 49.2, 55.1, 67.5, 80.2, 100.1, 100.7, 111.0, 121.9, 126.2, 126.8, 128.0, 130.0, 143.9, 146.0, 152.0, 155.5, 157.2, 158.9, 168.1, 189.3, 195.0; IR (KBr): 1659, 1575, 1525, 1493, 1462, 1369 cm^{-1}.

Discorhabdin P (46). K_2CO_3 (16.3 mg, 0.118 mmol) and MeI (3.70 µl, 0.0593 mmol) was added to a solution of discorhabdin C (**3**) (5.50 mg, 0.0118 mmol) in dry acetone (0.50 ml). The mixture was stirred at 40 °C for 12 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 10/1) to give discorhabdin P (3.60 mg, 64%) as a red solid; mp > 300 °C; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.87–1.89 (2H, m), 2.51 (2H, t, J = 7.5 Hz), 3.43–3.47 (2H, m), 3.73 (2H, t, J = 7.5 Hz), 3.82 (3H, s), 6.79 (1H, s), 7.56 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.0, 35.4, 37.6, 43.1, 45.9, 71.1, 97.1, 99.2, 106.3, 128.2, 133.1, 141.2, 149.9, 155.3, 168.0, 186.0, 193.2; UV/Vis (MeOH) λmax = 488 (log ε 0.18), 341 (1.60), 246 (3.29), 211 (3.41) nm; IR (KBr): 3387, 2926, 2503, 1649, 1566, 1523, 1493 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{18}Br_2N_3O_2$ $[M+H]^+$: 477.9766, found 477.9581.

Compound 14. I_2 (8.20 g, 32.3 mmol) and 30% H_2O_2 (7.20 ml) were added to a solution of tyramine (**10**) (4.00 g, 29.2 mmol) in H_2O (140 ml). The resulting solution was warmed to 55 °C for 3.0 h. The reaction mixture was quenched by sat. *aq.* $Na_2S_2O_3$ and sat *aq.* $NaHCO_3$. The solid was filtered and washed with H_2O dried *in vacuo* to give **14** (10.8 g, 99%) as a brown solid; mp 208–212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.68 (2H, t, J = 7.8 Hz), 2.98 (2H, t, J = 7.8 Hz), 3.32 (1H, br s), 7.59 (2H, s), 8.01 (2H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 30.9, 40.0, 87.7, 132.7, 139.3, 154.8; IR (KBr): 3349, 3127, 2997, 1589, 1471, 1454, 1300 cm^{-1}; HRMS (FAB) calcd for $C_8H_{10}I_3NNaO$ $[M+Na]^+$: 539.7794, found 539.7800.

Compound 43. Et_3N (64.3 µl, 0.464 mmol) was added to a solution of **14** (240 mg, 0.464 mmol) in MeOH (5.5 ml) at rt for 10 min under N_2. This solution was added dropwise to a solution of **32** (138 mg, 0.387 mmol). The mixture was stirred at rt for 16 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH/Et_3N = 100/5/0.1) to give **35** (76.6 mg, 23%) as a red solid; ^{1}H NMR (270 MHz, CD_3OD) δ: 2.42 (3H, s), 2.88 (2H, t, J = 7.0 Hz), 3.04 (2H, d, J = 7.0 Hz), 3.09 (2H, d, J = 7.0 Hz), 3.62 (2H, t, J = 7.0 Hz), 5.48 (1H, s), 7.41 (2H, d, J = 8.6 Hz), 7.48 (2H, s), 7.72 (1H, s), 8.05 (2H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 19.7, 21.7, 42.5, 47.2, 54.9, 94.6, 115.0, 119.4, 125.5, 128.3, 128.7, 130.0, 130.7, 131.0, 135.2, 135.8, 146.1, 148.1, 150.1, 156.6, 170.8; IR (KBr): 3262, 3053, 2101, 1681, 1614, 1566, 1556, 1531, 1525, 1494, 1469, 1446 cm^{-1}.

PIFA (55.0 mg, 0.129 mmol) was added to a solution of **35** (1.0 equiv) in CF_3CH_2OH (4.0 ml) at rt under N_2. The mixture was stirred at rt for 3.0 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH/Et_3N = 100/1/0.1) to give **43** (20.6 mg, 27%) as a red solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.92–1.95 (2H, m), 2.43 (3H, s), 2.64 (2H, t, J = 7.5 Hz), 3.48–3.54 (2H, m), 3.99 (2H, t, J = 7.5 Hz), 5.81 (1H, br s), 7.33 (2H, d, J = 8.0 Hz), 7.48 (1H, s), 7.71 (2H, s), 8.01 (2H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.8, 29.7, 32.8, 37.5, 48.5, 49.8, 96.4, 102.2, 111.3, 118.6, 121.7, 125.6, 126.4, 126.5, 127.2, 128.6, 129.8, 134.6, 142.1, 145.9, 162.6, 168.4, 174.1; IR (KBr): 3391, 2926, 2853, 1659, 1574, 1528, 1495, 1460, 1435 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{20}I_2N_3O_4S$ $[M+H]^+$: 711.9264, found 711.9258.

Compounds 36a, 36b. Quinoline-5,8-dione (**20**) (25.1 mg, 0.158 mmol) was added to a solution of tyramine (**10**) (26.0 mg, 0.189 mmol) in MeOH (2.0 ml) at rt under N_2. The mixture was stirred at rt for 16 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 20/1) to give **36a** and **36b** (less polar; (13.3 mg, 24%), polar (27.3 mg, 49%).

36b (less polar): brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.92 (2H, t, J = 7.5 Hz), 3.46 (2H, t, J = 7.5 Hz), 5.83 (1H, s), 6.80 (2H, d, J = 8.4 Hz), 7.07 (2H, d, J = 8.4 Hz), 7.72 (1H, dd, J = 7.8, 4.5 Hz), 8.44 (1H, dd, J = 7.8, 1.8 Hz), 8.87 (1H, dd, J = 4.5, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.2, 43.5, 98.5, 114.9, 128.2, 128.6, 129.4, 130.0, 133.1, 146.3, 148.6, 152.3, 155.5, 179.4, 180.1; IR (KBr): 3297, 2982, 2947, 1769, 1759, 1703, 1605, 1581, 1564, 1514, 1454 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{15}N_2O_3$ $[M+H]^+$: 295.1083, found 295.1079.

36a (polar): brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.90 (2H, t, J = 6.9 Hz), 3.44 (2H, t, J = 6.9 Hz), 5.94 (1H, s), 6.11 (1H, br s), 6.80 (2H, d, J = 8.4, 2.1 Hz), 7.05 (2H, d, J = 8.4 Hz), 7.58 (1H, dd, J = 7.8, 4.8 Hz), 8.34 (1H, dd, J = 7.8, 1.8 Hz), 8.99 (1H, dd, J = 4.8, 1.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 33.5, 43.9, 101.7, 115.8, 126.4, 127.4, 128.6, 129.7, 134.3, 147.6, 149.2, 155.0, 155.7, 181.3, 181.4; IR (KBr): 3556, 2986, 2086, 1757, 1606, 1568 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{15}N_2O_3$ $[M+H]^+$: 295.1083, found 295.1089.

Compounds 47a, 47b. PIFA (74.3 mg, 0.173 mmol) was added to a solution of **36a**, **36b** (42.4 mg, 0.144 mmol) in CF_3CH_2OH (7.2 ml) at rt under N_2. The mixture was stirred at rt for 1.0 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 15/1) to give **47a**, **47b** (less polar: 9.80 mg, 23%. polar: 20.1 mg, 48%).

47b (less polar): brown solid; mp 246–249 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.99 (2H, t, J = 5.7 Hz), 3.65 (2H, t, J = 5.7 Hz), 6.42 (2H, d, J = 9.9 Hz), 6.57 (1H, br s), 6.96 (2H, d, J = 9.9 Hz), 7.64 (1H, dd, J = 7.8, 4.5 Hz), 8.35 (1H, dd, J = 7.8, 1.8 Hz), 8.91 (1H, dd, J = 4.5, 1.8 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 32.8, 37.0, 48.6, 107.0, 126.8, 128.6, 130.6, 133.6, 146.1, 146.7, 152.4, 154.7, 176.9, 179.0, 185.1; IR (KBr): 3242, 2928, 1693, 1659, 1595, 1556, 1514, 1437, 1404 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{13}N_2O_3$ $[M+H]^+$: 293.0926, found 293.0932.

47a (polar): brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.98 (2H, t, J = 5.7 Hz), 3.62 (2H, t, J = 5.7 Hz), 6.39 (2H, d, J = 9.9 Hz), 7.00 (2H, d, J = 9.9 Hz), 7.59 (1H, dd, J = 7.8, 4.8 Hz), 8.35 (1H, dd, J = 7.8, 1.8 Hz), 8.93 (1H, dd, J = 4.8, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 33.3, 37.3, 39.7, 126.3, 126.6, 127.9, 130.1, 133.9, 137.3, 148.7, 153.2, 155.0, 177.2, 180.2, 186.2; IR (KBr): 3265, 2927, 2860, 2359, 2341, 2248, 2067, 1655, 1618, 1593, 1566, 1517, 1434 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{12}N_2NaO_3$ [M+Na]$^+$: 315.0746, found 315.0735.

Compounds 39a, 39b. Et_3N (0.200 ml, 1.47 mmol) was added to a solution of **11** (340 mg, 1.47 mmol) in MeOH (7.5 ml) at rt for 10 min under N_2. This solution was added dropwise to a solution of quinoline-5,8-dione (**20**) (213 mg, 1.33 mmol) in MeOH (7.5 ml). The mixture was stirred at rt for 16 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 10/1) to give **39a** and **39b** (less polar; (140 mg, 27%), polar (223 mg, 43%)).

39b (less polar): brown solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.10 (1H, dd, J = 13.8, 6.6 Hz), 3.21 (1H, dd, J = 13.8, 5.4 Hz), 3.77 (3H, s), 4.29 (1H, dd, J = 13.8, 5.7 Hz), 5.74 (1H, s), 6.46 (1H, d, J = 7.8 Hz), 6.82 (2H, d, J = 8.4 Hz), 7.00 (2H, d, J = 8.4 Hz), 7.17 (1H, br s), 7.67 (1H, dd, J = 7.5, 4.5 Hz), 8.43 (1H, dd, J = 7.8, 1.8 Hz), 8.90 (1H, dd, J = 4.5, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 36.6, 52.9, 56.4, 101.5, 116.0, 126.0, 128.6, 130.3, 130.4, 134.6, 146.3, 147.0, 153.0, 155.9, 170.5, 179.3, 181.9; IR (KBr): 3306, 3015, 2926, 2853, 1742, 1693, 1607, 1566, 1514, 1443 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{17}N_2O_5$ [M+H]$^+$: 353.1137, found 353.1146.

39a (polar): brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.07 (1H, dd, J = 14.0, 7.0 Hz), 3.17 (1H, d, J = 14 Hz), 3.76 (3H, s), 4.28 (1H, dd, J = 14.0, 7.0 Hz), 5.82 (1H, s), 6.35 (1H, d, J = 8.0 Hz), 6.79 (2H, d, J = 8.0 Hz), 6.95 (2H, d, J = 8.0 Hz), 7.57 (1H, dd, J = 7.5, 4.5 Hz), 8.32 (1H, dd, J = 7.5, 1.5 Hz), 8.95 (1H, dd, J = 4.5, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 37.5, 53.6, 57.0, 103.5, 116.8, 126.7, 127.3, 128.0, 130.9, 135.2, 147.1, 149.4, 155.6, 156.6, 171.4, 181.4, 182.3; IR (KBr): 3252, 2953, 1741, 1682, 1607, 1572, 1514, 1443 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{17}N_2O_5$ [M+H]$^+$: 353.1137, found 353.1138.

Compounds 40a, 40b. Et_3N (0.120 ml, 0.893 mmol) was added to a solution of tyrosinol (182 mg, 0.893 mmol) in MeOH (4.5 ml) at rt for 10 min under N_2. This solution was added dropwise to a solution of quinoline-5,8-dione (**20**) (129 mg, 0.812 mmol) in MeOH (4.5 ml). The mixture was stirred at rt for 3.0 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH = 15/1) to give **40a** and **40b** (less polar; (63.7 mg, 22%), polar (116 mg, 40%))

40b (less polar): brown solid; ^{1}H NMR (500 MHz, CD_3OD) δ: 2.80 (1H, dd, J = 14.0, 8.0 Hz), 2.91 (1H, dd, J = 14.0, 6.0 Hz), 3.63–3.75 (3H, m), 5.76 (1H, s), 6.67 (2H, d, J = 8.5 Hz), 7.08 (2H, d, J = 8.5 Hz), 7.77 (1H, dd, J = 8.0, 5.0 Hz), 8.39 (1H, dd, J = 7.5, 1.5 Hz), 8.81 (1H, dd, J = 5.0, 1.5 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ: 36.8, 57.9, 63.5, 100.4, 102.0, 116.3, 126.6, 129.8, 130.0, 131.4, 135.5, 150.6, 153.5, 175.2, 179.6, 183.1; IR (KBr): 3287, 2922, 2853, 1730, 1693, 1605, 1566, 1556, 1514, 1462 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{17}N_2O_4$ [M+H]$^+$: 325.1188, found 325.1173.

40a (polar): brown solid; ^{1}H NMR (400 MHz, CD_3OD) δ: 2.70 (1H, dd, J = 13.6, 6.0 Hz), 2.81 (1H, dd, J = 13.6, 6.0 Hz), 3.53–3.65 (3H, m), 5.74 (1H, s), 6.57 (2H, d, J = 8.0 Hz), 6.97 (2H, d, J = 8.0 Hz), 7.56 (1H, dd, J = 7.2, 4.4 Hz), 8.28 (1H, d, J = 7.2 Hz), 8.76 (1H, d, J = 3.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 36.8, 57.8, 63.4, 101.4, 116.2, 116.3, 128.0, 129.7, 131.4, 135.8, 150.1, 150.3, 155.3, 157.2, 182.0, 182.6; IR (KBr): 3336, 2924, 2853, 1732, 1685, 1600, 1568, 1514, 1462 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{16}N_2NaO_4$ [M+Na]$^+$: 347.1008, found 347.1008.

Compound 48b. 1-(Toluene-4-sulfonyl)-1*H*-indole-4,7-dione (**23**) (228 mg, 0.755 mmol) was added to a solution of tyramine (**10**) (114 mg, 0.831 mmol) in MeOH (8.3 ml) at rt under N_2. The mixture was stirred at rt for 18 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (*n*-hexane/AcOEt = 3/1) to give **37a** (polar: 116 mg, 32%), **37b** (less polar: 60.7 mg, 17%).

PIFA (65.8 mg, 0.153 mmol) was added to a solution of **37b** (60.7 mg, 0.139 mmol) in CF_3CH_2OH (7.0 ml) at rt under N_2. The mixture was stirred at rt for 1.0 h and evaporated *in vacuo*. The residue was purified by SiO_2 column chromatography (n-hexane/AcOEt = 3/1) to give **48b** (28.3 mg, 47%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82 (2H, t, J = 6.0 Hz), 2.42 (3H, s), 3.46–3.50 (2H, m), 6.07 (1H, br s), 6.28 (2H, dd, J = 8.4, 1.6 Hz), 6.62 (1H, d, J = 4.0 Hz), 6.76 (2H, d, J = 8.4, 1.6 Hz), 7.27 (2H, d, J = 8.4 Hz), 7.63 (1H, d, J = 3.2 Hz), 7.95 (2H, dd, J = 8.4, 1.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.8, 34.0, 37.6, 39.4, 105.8, 106.7, 126.0, 127.8, 127.9, 129.3, 129.6, 132.7, 133.8, 143.8, 145.9, 153.2, 171.4, 177.8, 185.9; IR (KBr): 3372, 2359, 2341, 1658, 1620, 1589, 1541, 1510, 1462 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{19}N_2O_5S$ [M+H]$^+$ 435.1015, found 435.1021.

MTT assay. The cytotoxicity was tested against HCT-116 human colon cancer cells, WiDr human colon tumor cells, DU-145 human prostage tumor cells, P388 and L1210 mouse leukemia cells using the microculture tetrazolium (MTT) assay. Growing cells for HCT-116, WiDr and DU-145 were incubated for 24 h after seeding, and for 72 h in the presence of the test compounds in DMSO. The growing cells for P388 and L1210 were incubated in the presence of the test compounds in DMSO for 96 h.

HCC panel assay cell lines. Human breast cancer: HBC-4, BSY-1, HBC-5, MCF-7, MDA-MB-231. Central nervous system cancer: U251, SF-268, SF-295, SF-539, SNB-75, SNB-78. Colon cancer: HCC2998, KM-12, HT-29, HCT-15, HCT-116. Lung cancer: NCI-H23, NCI-H226, NCI-H522, NCI-H460, A549, DMS273, DMS114. Melanoma: LOX-IMVI. Ovarian cancer: OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, SK-OV-3. Renal cancer: RXF-631L, ACHN. Stomach cancer: St-4, MKN1, MKN7, MKN28, MKN45, MKN74. Prostate cancer: DU-145, PC-3.

Acknowledgements

This work was financially supported by a Grant-in-Aid for Scientific Research (A) and (B) and Scientific Research for Exploratory Research from the Japan Society for the Promotion of Science Y. W. We thank the Japan Society for the Promotion of Science (JSPS) for the Research Fellowship for Young Scientists. We thank Dr Takao Yamori of the Screening Committee of Anticancer Drugs supported by a Grant-in-Aid for Scientific Reserch on Priority Area "Cancer" from The Ministry of Education, Culture, Sports, Science and Technology, Japan, for the HCC panel assay.

Notes and references

1 N. B. Perry, J. W. Blunt, J. D. McCombs and M. H. G. Munro, *J. Org. Chem.*, 1986, **51**, 5476.
2 J. Kobayashi, J.-F. Cheng, M. Ishibashi, H. Nakamura, Y. Ohizumi, Y. Hirata, T. Sasaki, H. Lu and J. Clardy, *Tetrahedron Lett.*, 1987, **28**, 4939.
3 N. B. Perry, J. W. Blunt and M. H. G. Munro, *Tetrahedron*, 1988, **44**, 1727.
4 N. B. Perry, J. W. Blunt, M. H. G. Munro, T. Higa and R. Sasaki, *J. Org. Chem.*, 1988, **53**, 4127.
5 J.-F. Cheng, Y. Ohizumi, M. R. Wälchli, H. Nakamura, Y. Hirata, T. Sasaki and J. Kobayashi, *J. Org. Chem.*, 1988, **53**, 4621.
6 J. W. Blunt, M. H. G. Munro, C. N. Battershill, B. R. Copp, J. D. McCombs, N. B. Perry, M. R. Prinsep and A. M. Thompson, *New J. Chem.*, 1990, **14**, 761.
7 J. Kobayashi, J.-F. Cheng, S. Yamamura and M. Ishibashi, *Tetrahedron Lett.*, 1991, **32**, 1227.
8 D. C. Radisky, E. S. Radisky, L. R. Barrows, B. R. Copp, R. A. Kramer and C. M. Ireland, *J. Am. Chem. Soc.*, 1993, **115**, 1632.
9 T. F. Molinski, *Chem. Rev.*, 1993, **93**, 1825.
10 B. R. Copp, K. F. Fulton, N. B. Perry, J. W. Blunt and M. H. G. Munro, *J. Org. Chem.*, 1994, **59**, 8233.
11 A. Yang, B. J. Baker, J. Grimwade, A. Leonard and J. B. McClintock, *J. Nat. Prod.*, 1995, **58**, 1596.
12 S. P. Gunasekera, P. J. McCarthy, R. E. Longley, S. A. Pomponi, A. E. Wright, E. Lobkovsky and J. Clardy, *J. Nat. Prod.*, 1999, **62**, 173.
13 M.-G. Dijoux, W. R. Gamble, Y. F. Hallock, J. H. Cardellina, R. van Soest and M. R. Boyd, *J. Nat. Prod.*, 1999, **62**, 636.
14 J. Ford and R. J. Capon, *J. Nat. Prod.*, 2000, **63**, 1527.
15 G. Lang, A. Pinkert, J. W. Blunt and M. H. G. Munro, *J. Nat. Prod.*, 2005, **68**, 1796.
16 S. P. Gunasekera, I. A. Zuleta, R. E. Longley, A. E. Wright and S. A. Pomponi, *J. Nat. Prod.*, 2003, **66**, 1615.
17 M. El-Naggar and R. J. Capon, *J. Nat. Prod.*, 2009, **72**, 460.
18 For partial and total syntheses of discorhabdin C, see: Y. Kita, T. Yakura, H. Tohma, K. Kikuchi and Y. Tamura, *Tetrahedron Lett.*, 1989, **30**, 1119.
19 H.-J. Knölker, R. Boese and K. Hartmann, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1678.
20 G. G. Kubiak and P. N. Confalone, *Tetrahedron Lett.*, 1990, **31**, 3845.
21 H.-J. Knölker and K. Hartmann, *Synlett*, 1991, 428.
22 S. Nishiyama, J.-F. Cheng, X.-L. Tao and S. Yamamura, *Tetrahedron Lett.*, 1991, **32**, 4151.
23 Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka and T. Yakura, *J. Am. Chem. Soc.*, 1992, **114**, 2175.
24 T. Izawa, S. Nishiyama and S. Yamamura, *Tetrahedron*, 1994, **50**, 13593.
25 J. D. White, K. M. Yager and T. Yakura, *J. Am. Chem. Soc.*, 1994, **116**, 1831.
26 E. V. Sadanandan, S. K. Pillai, M. V. Lakshmikantham, A. D. Billimoria, J. S. Culpepper and M. P. Cava, *J. Org. Chem.*, 1995, **60**, 1800.
27 M. A. Ciufolni, Q. Dong, M. H. Yates and S. Schunk, *Tetrahedron Lett.*, 1996, **37**, 2881.
28 A. J. Peat and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 1028.
29 D. Roberts, J. A. Joule, M. A. Bros and M. Alvarez, *J. Org. Chem.*, 1997, **62**, 568.
30 R. Zhao and J. W. Lown, *Synth. Commun.*, 1997, **27**, 2103.
31 M. Makosza, J. Stalewski and O. S. Maslennikova, *Synthesis*, 1997, 1131.
32 Y. Kita, H. Watanabe, M. Egi, T. Saiki, Y. Fukuoka and H. Tohma, *J. Chem. Soc., Perkin Trans. 1*, 1998, 635.
33 G. A. Kraus and N. Selvakumar, *J. Org. Chem.*, 1998, **63**, 9846.
34 M. Iwao, O. Motoi, T. Fukuda and F. Ishibashi, *Tetrahedron*, 1998, **54**, 8999.
35 K. M. Aubart and C. H. Heathcock, *J. Org. Chem.*, 1999, **64**, 16.
36 For total synthesis of discorhabdin A, see: H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, M. Egi and Y. Kita, *Angew. Chem., Int. Ed.*, 2002, **41**, 348.
37 H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, Y. Kiyono, M. Egi and Y. Kita, *J. Am. Chem. Soc.*, 2003, **125**, 11235.
38 Y. Harayama, M. Yoshida, D. Kamimura and Y. Kita, *Chem. Commun.*, 2005, 1764.
39 Y. Harayama, M. Yoshida, D. Kamimura, Y. Wada and Y. Kita, *Chem.–Eur. J.*, 2006, **12**, 4893.
40 Y. Harayama and Y. Kita, *Curr. Org. Chem.*, 2005, **9**, 1567.
41 Y. Wada, K. Otani, N. Endo, Y. Harayama, D. Kamimura, M. Yoshida, H. Fujioka and Y. Kita, *Tetrahedron*, 2009, **65**, 1059.
42 R. E. Longley, O. J. McConnell, E. Essich and D. Harmody, *J. Nat. Prod.*, 1993, **56**, 915.
43 D. S. Swaffar, C. M. Ireland and L. R. Barrows, *Anti-Cancer Drugs*, 1994, **5**, 15.
44 K. Miller, B. Alvarez, C. Battershill, P. Northcote and H. Parthasarathy, *Mar. Biol.*, 2001, **139**, 235.
45 Y. Wada, K. Otani, N. Endo, Y. Harayama, D. Kamimura, M. Yoshida, H. Fujioka and Y. Kita, *Org. Lett.*, 2009, **11**, 4048.
46 J. A. Diers, H. K. Pennaka, J. Peng, J. J. Bowling, S. O. Duke and M. T. Hamann, *J. Nat. Prod.*, 2004, **67**, 2117.
47 R. Barret and M. Daudon, *Tetrahedron Lett.*, 1990, **31**, 4871.
48 Y. Kita, M. Egi, M. Ohtsubo, T. Saiki, A. Okajima, A. Takada and H. Tohma, *Chem. Pharm. Bull.*, 1999, **47**, 241.
49 S. Rajeswari, K. J. Drost and M. P. Cava, *Heterocycles*, 1989, **29**, 415.
50 Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka, K. Kikuchi and T. Yakura, *Tetrahedron Lett.*, 1991, **32**, 2035.
51 M. D'Ambrosio, A. Guerriero, G. Chiasera and F. Pietra, *Tetrahedron*, 1996, **52**, 8899.
52 T. Grkovic, B. Kaur, V. L. Webb and B. R. Copp, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1944.
53 M.-G. Dijoux, P. C. Schnabel, Y. F. Hallock, J. L. Boswell, T. R. Johnson, J. A. Wilson, C. M. Ireland, R. Soest, M. R. Boyd, L. R. Barrows and J. H. Cardellina, *Bioorg. Med. Chem.*, 2005, **13**, 6035.
54 B. A. Shinkre, K. P. Raisch, L. Fan and S. E. Velu, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2890.
55 D. Passarella, F. Belinghieri, M. Scarpellini, G. Pratesi, F. Zunino, O. M. Gia, L. D. Via, G. Santoro and B. Danieli, *Bioorg. Med. Chem.*, 2008, **16**, 2431.
56 B. A. Shinkre, K. P. Raisch, L. Fan and S. E. Velu, *Bioorg. Med. Chem.*, 2008, **16**, 2541.
57 D. A. Venables, G. P. Concepción, S. Matsumoto, L. R. Barrows and C. M. Ireland, *J. Nat. Prod.*, 1997, **60**, 408.
58 S. Roy, P. U. Maheswari, M. Lutz, A. L. Spek, H. Dulk, S. Barends, G. P. van Wezel, F. Hartl and J. Reedijk, *Dalton Trans.*, 2009, 10846.
59 A. D. Richards and A. Rodger, *Chem. Soc. Rev.*, 2007, **36**, 471.
60 S. Roy, K. D. Hagen, P. U. Maheswari, M. Lutz, A. L. Spek, J. Reedijk and G. P. van Wezel, *Chem. Med. Chem.*, 2008, **3**, 1427.
61 S. S. Matsumoto, H. M. Haughey, D. M. Schmehl, D. A. Venables, C. M. Ireland, J. A. Holden and L. R. Barrows, *Anti-Cancer Drugs*, 1999, **10**, 39.
62 S. H. van Rijt, A. Mukherjee, A. M. Pizarro and P. J. Sadler, *J. Med. Chem.*, 2010, **53**, 840.
63 S. M. Ansell, S. A. Johnstone, P. G. Tardi, L. Lo, S. Xie, Y. Shu, T. O. Harasym, N. L. Harasym, L. Williams, D. Bermudes, B. D. Liboiron, W. Saad, R. K. Prud'homme and L. D. Mayer, *J. Med. Chem.*, 2008, **51**, 3288.
64 M. Jelokhani-Niaraki, L. H. Kondejewski, L. C. Wheaton and R. S. Hodge, *J. Med. Chem.*, 2009, **52**, 2090.
65 M. St-Jean, T. Izard and J. Sygusch, *J. Biol. Chem.*, 2007, **282**, 14309.
66 Y. Li, X. Gao and L. Chen, *J. Biol. Chem.*, 2009, **284**, 4324.
67 S. M. Campos and S. Ghosh, *J. Oncol.*, 2010, 1.
68 P.-M. Yang, J.-H. Lin, W.-Y. Huang, Y.-C. Lin, S.-H. Yeh and C.-C. Chen, *Biochem. Biophys. Res. Commun.*, 2010, **391**, 1396.
69 A. N. Scott, C. Hetheridge, A. R. Reynolds, V. Nayak, K. Hodivala-Dilke and H. Mellor, *Angiogenesis*, 2008, **11**, 337.
70 W. C. Hahn, S. A. Stewart, M. W. Brooks, S. G. York, E. Eaton, A. Kurachi, R. L. Beijersbergen, J. H. M. Knoll, M. Meyerson and R. A. Weinberg, *Nat. Med.*, 1999, **5**, 1164.
71 M. Britton, M. M. Lucas, S. L. Downey, M. Screen, A. A. Pletnev, M. Verdoes, R. A. Tokhunts, O. Amir, A. L. Goddard, P. M. Pelphrey, D. L. Wright, H. S. Overkleeft and A. F. Kisselev, *Chem. Biol.*, 2009, **16**, 1278.
72 A. Fontanini, C. Foti, H. Potu, E. Crivellato, R. Maestro, P. Bernardi, F. Demarchi and C. Brancolini, *J. Biol. Chem.*, 2009, **284**, 8369.
73 T. Yamori, A. Matsunaga, S. Sato, K. Yamazaki, A. Komi, K. Ishizu, I. Mita, H. Edatsugi, Y. Matsuba, K. Takezawa, O. Nakanishi, H. Kohno, Y. Nakajima, H. Komatsu, T. Andoh and T. Tsuruo, *Cancer Res.*, 1999, **59**, 4042; K. D. Paull, R. H. Shoemaker, L. Hodes, A. Monks, D. A. Scudiero, L. Rubinstein, J. Plowman and M. R. Boyd, *J. Natl. Cancer Inst.*, 1989, **81**, 1088.

