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Enantioselective constructions of quaternary carbons and their application to the asymmetric total syntheses of fredericamycin A and discorhabdin A*

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Abstract: An efficient enantioselective construction of quaternary carbons including spiro carbons is an area of intense interest due to the importance of these units as components of biologically active natural products. Prominent methods are presented for the synthesis of chiral, nonracemic quaternary carbon centers by (i) stereospecific rearrangement of optically active epoxides, (ii) enzyme-catalyzed resolution, and (iii) hypervalent iodine reagent-induced *ipso*-substitution of *para*-substituted phenol derivatives. These methods were applied to the total syntheses of fredericamycin A and discorhabdin A.

Keywords: asymmetric synthesis; quaternary carbons; spiro carbons; fredericamycin A; discorhabdin A.

INTRODUCTION

In the past two decades, we have been interested in the enantioselective constructions of quaternary carbons and their application to the total syntheses of natural products, which have chiral, nonracemic quaternary carbons or spiro centers. We will describe here the enantioselective constructions of quaternary carbons and their application to the total syntheses of fredericamycin A and discorhabdin A (Fig. 1).

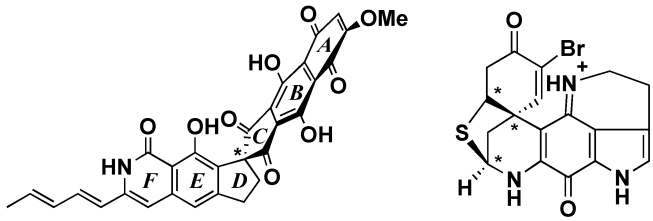

Fig. 1 Fredericamycin A and discorhabdin A.

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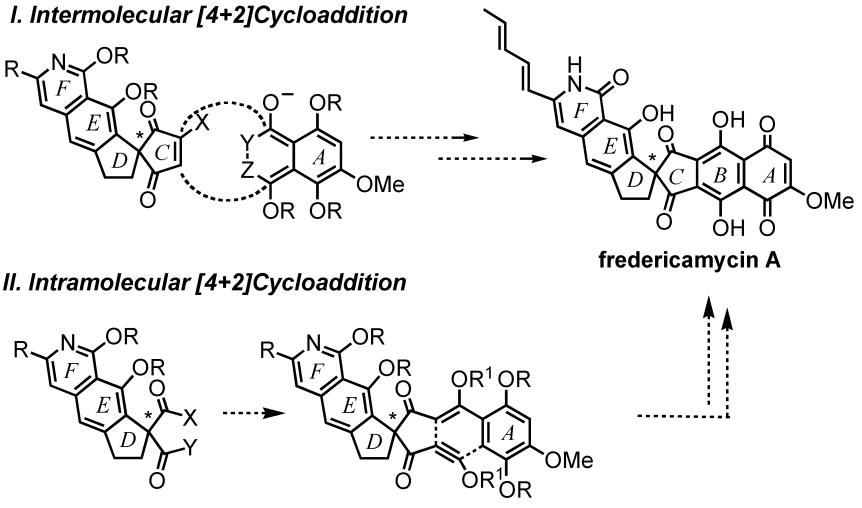
TOTAL SYNTHESIS OF FREDERICAMYCIN A

Fredericamycin A was isolated in 1981 by Pandey, who determined its structure in 1982 [1]. Fredericamycin A has strong in vitro and vivo cytotoxicities. It has a unique structure involving a single chiral spiro carbon center in the CD ring system. The chirality is based on the methoxy group in the ring A. Therefore, many chemists are much interested in the total synthesis of this compound. The first total synthesis of the optically active fredericamycin A was achieved by Boger [2], using a chiral high-performance liquid chromatography (HPLC) separation during the final stage of the synthesis. However, the absolute configuration still remained unknown. We planned to synthesize the optically active fredericamycin A by two different approaches and then determine its absolute configuration. One is an intermolecular approach, and the other is an intramolecular approach (Scheme 1).

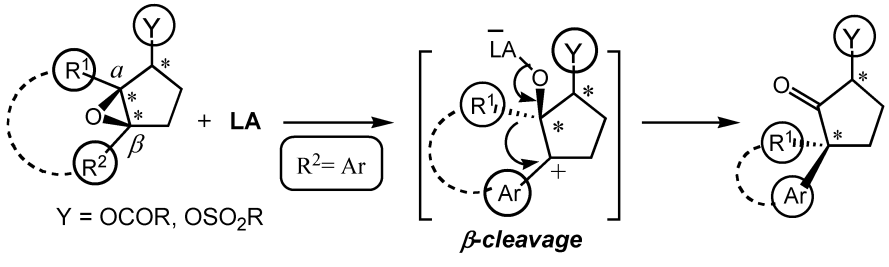


Scheme 1 Our approaches to synthesis of fredericamycin A.

Intermolecular synthesis of fredericamycin A

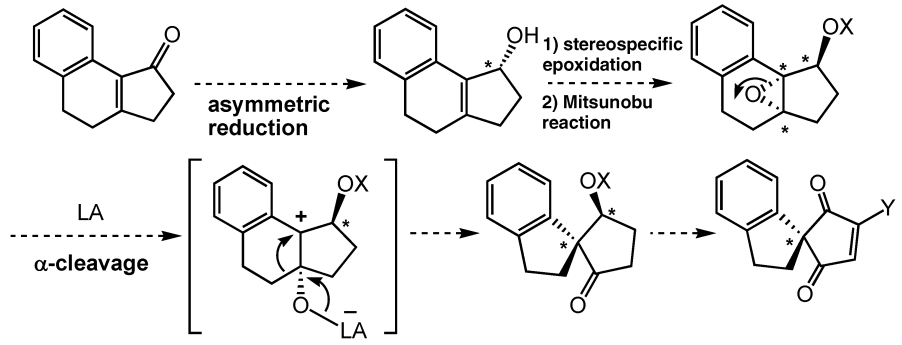
Model studies

One of our key reactions for the synthesis of the chiral, nonracemic quaternary carbon center is the Lewis acid (LA)-induced stereospecific rearrangement of α,β-epoxy alcohol derivatives with electron-withdrawing protecting groups. Thus, α-phenyl substituted epoxy alcohol derivatives selectively cleave at the α-position and the β-phenyl substituted epoxy alcohol derivatives selectively cleave at the β-position to produce the corresponding quaternary carbon centers in optically active form (Scheme 2) [3].



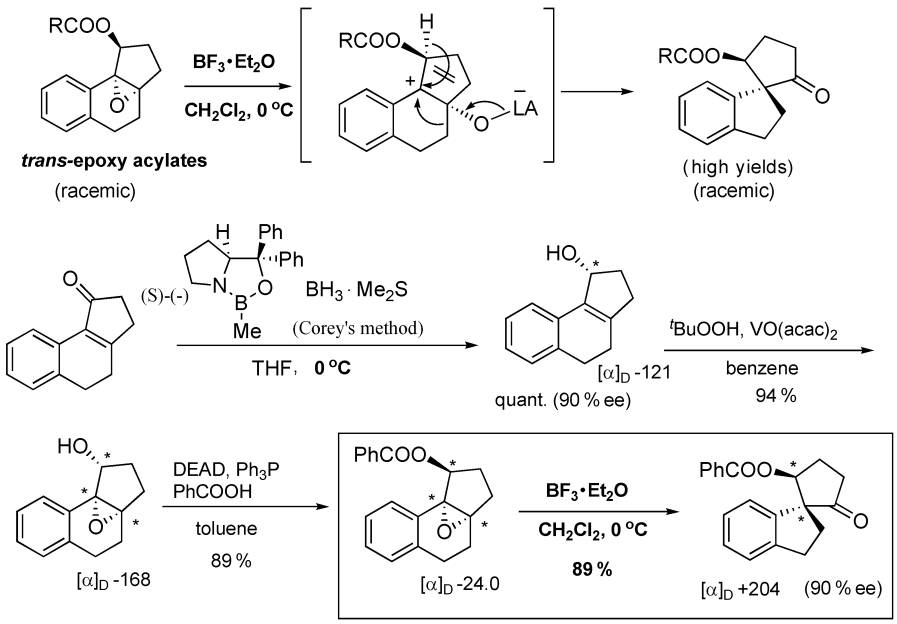
Scheme 2 Stereospecific rearrangement of α,β-epoxy alcohol derivatives having aromatic substituent at β-position.

The synthetic plan for the chiral spiro CDE ring of fredericamycin A is shown in Scheme 3. The LA treatment of the epoxy alcohol derivative may produce a benzyl cation intermediate, which may cause the subsequent ring contraction to produce the spiro keto compound. The asymmetric reduction of the enone followed by a Sharpless oxidation should give the optically pure α,β-epoxy alcohol. The stereoselective formation of the benzyl cation species from the α,β-epoxy alcohol derivatives and successive skeletal rearrangement would afford the optically active spiro compound, which could be converted to the desired optically active spiro halo diketo olefin.



Scheme 3 Synthetic plan for chiral spiro CDE ring.

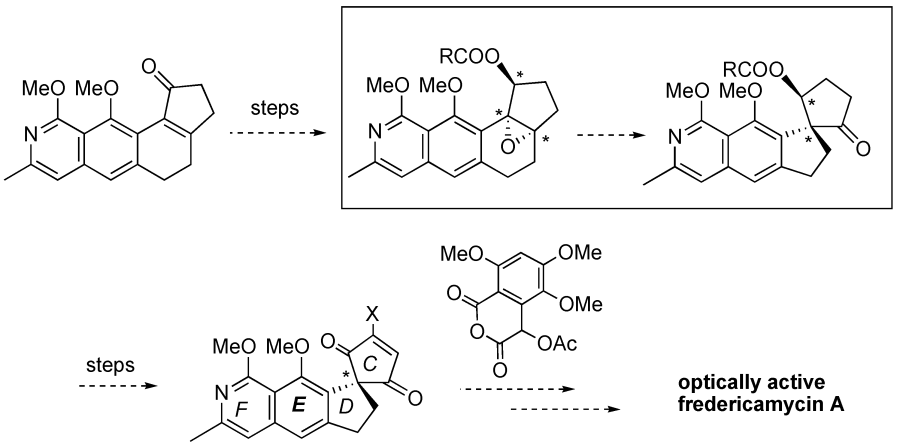
First, we examined the reaction of racemic *trans*-epoxy acylates. Thus, treatment of the *trans*-epoxy acylates with boron trifluoride-diethyl etherate gave the desired spiro compounds in good yields. The cleavage of the epoxide ring selectively occurs at the benzylic position. Although the electron-donating group such as alcohol, alkoxy, and siloxy groups accelerated the hydride shift rather than the skeletal rearrangement, the electron-withdrawing acyloxy groups decreased the tendency of the hydride shift. Thus, the hydride lays syn to the cleaving epoxide ring and the hydride shift is prevented, and then a skeletal rearrangement predominantly occurs. We next applied this method to the optically active system. The asymmetric reduction of the enone by Corey's method [4] afforded the optically active allyl alcohol in 90 % ee. Epoxidation of the alcohol by the stereoselective Sharpless method [5] gave the *cis*-epoxide as the sole product. The Mitsunobu reaction [6] of the alcohol gave the *trans*-epoxy benzoate in 90 % ee. Treatment of the *trans*-epoxy benzoate with boron trifluoride-diethyl etherate afforded the spiro compound in 89 % yield with complete retention of the optical purity. Therefore, a 90 % optical yield of the keto benzoate was obtained. This means that the rearrangement is completely stereospecific (Scheme 4).



Scheme 4 Asymmetric synthesis of spiro compound.

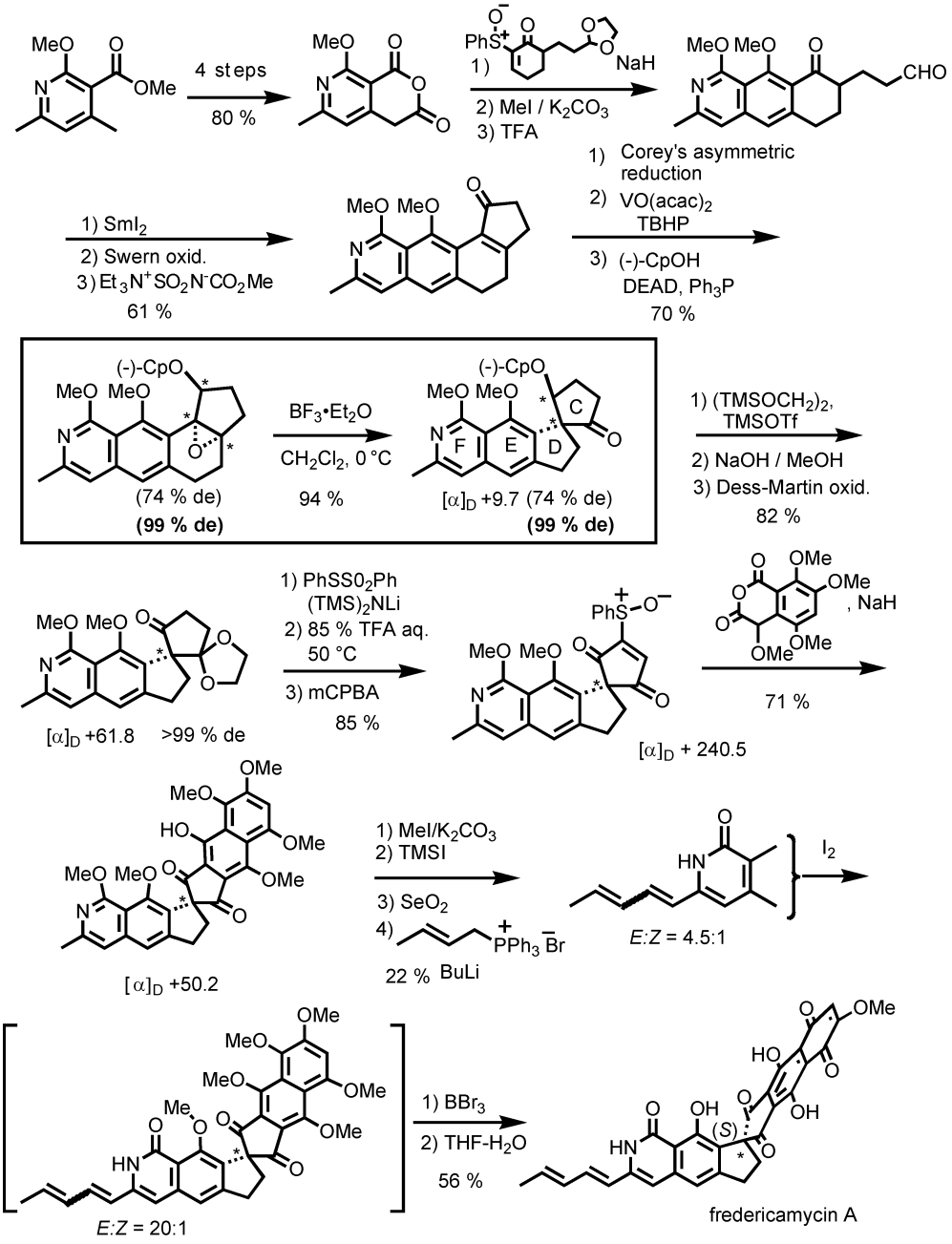
Total synthesis of fredericamycin A

With the stereospecific conversion of the *trans*-epoxy acylates to the chiral spiro compounds in hand, the reaction was next applied to the total synthesis of fredericamycin A. Scheme 5 shows our synthetic plan. Asymmetric reduction of the enone followed by Sharpless oxidation should give the optically pure α,β-epoxy alcohol. The stereoselective formation of the benzylic cation intermediate from the epoxy acylate and successive skeletal rearrangement would afford the chiral, nonracemic spiro ketone, which should be converted to the desired optically active spiro halo diketo olefin. The coupling reaction with suitably substituted homophthalic anhydride followed by some transformations would give the optically active fredericamycin A.



Scheme 5 Synthetic approach to optically active fredericamycin A.

The starting enone was prepared from the known pyridine derivative in 10 steps. Commercially available pyridine carboxylate was converted to the hetero homophthalic anhydride in 4 steps. The strong base-induced cycloaddition [7] of this anhydride with α-sulfinylenone provided the tricyclic compound. Methylation of the phenolic hydroxy function followed by deacetalization gave the formyl keto compound. The intramolecular pinacol coupling of the formyl keto compound with samarium iodide gave the diol, which was oxidized by Swern's method to afford the hydroxy ketone. Dehydration of the hydroxy ketone by the Burgess reagent [8] afforded the enone. Corey's asymmetric reduction of the enone followed by Sharpless epoxidation stereoselectively afforded the *cis*-epoxy alcohol, which was treated with (–)-camphanoic acid (>98 % ee) under Mitsunobu conditions to give the *trans*-epoxy camphanoate in 74 % de. The rearrangement reaction of the epoxy camphanoate with boron trifluoride-diethyl etherate proceeded at 0 °C to provide the optically active spiro compound. The rearrangement reaction of 99 % de of the epoxy camphanoate gave a 99 % de of the spiro compound. This means that the rearrangement proceeded with perfect stereoselectivity. Direct alkaline hydrolysis caused a retro-aldol and aldol condensation, which resulted in the racemization of the spiro center. Therefore, the keto camphanoate was acetalized by Noyori's method prior to the alkaline hydrolysis, and Dess–Martin oxidation gave the chiral nonracemic keto acetal. The chiral nonracemic keto acetal was converted to the α-sulfinyl olefin since the α-sulfinyl group was estimated to be a powerful directing and activating group in the strong base-induced cycloaddition of the homophthalic anhydride. Treatment of the keto acetal with lithium bis(trimethylsilyl)amide and $PhSSO_2Ph$ afforded the α,α-diphenylsulfenyl compound. Acid treatment of the disulfenyl compound caused deacetalization and elimination of the thiophenol to give the diketovinyl sulfide, which was oxidized with *m*-chloro peroxybenzoic acid (*m*-CPBA). Thus, the desired optically active CDEF-ring unit was obtained. Intermolecular cyclo condensation of the optically active CDEF-ring unit with enolate anion from homophthalic anhydride and sodium hydride gave the hexacyclic product. Methylation of the hydroxyl group, selective demethylation of the methyl ether on the F-ring, SeO_2 oxidation of the methyl function, then Wittig reaction with *trans*-2-butenyl triphenylphosphonium bromide afforded a 4.5 to 1 mixture of (*E,E*)- and (*E,Z*)-side chain isomers. Isomerization of the side chain, deprotection with the BBr_3, and subsequent auto-oxidation afforded natural fredericamycin A with (*S*)-spiro center (Scheme 6) [9].

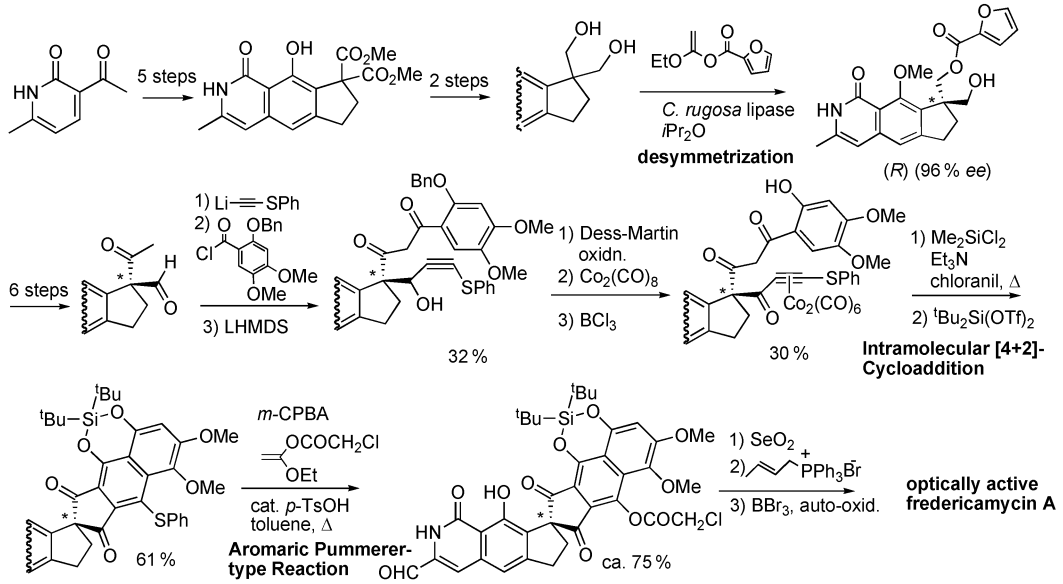


Scheme 6 Total synthesis of optically active fredericamycin A (intermolecular synthesis).

Intramolecular synthesis of fredericamycin A

The enantioselective desymmetrization of the prochiral 2,2-disubstituted 1,3-propane diols by lipase using vinyl esters often causes racemization due to acyl group migration during chromatography, storage, and subsequent transformations. We then developed an excellent solution of the racemization problem using the ethoxyvinyl aroyl ester. Thus, enzymatic enantioselective desymmetrization of the *meso*-cycloalkane-1,3-diols using the ethoxyvinyl aroyl ester afforded the racemization-resistant products

with high optical purity [10]. This desymmetrization method was successfully applied to the asymmetric total synthesis of fredericamycin A (Scheme 7). Enantioselective desymmetrization of the tricyclic prochiral 1,3-propane diol derived from pyridone derivative gave the tricyclic hydroxyl ester with high optical putrity. This optically active hydroxyl ester was transformed to the formyl ketone in six steps. Treatment of lithium acetylide to the formyl ketone followed by acid treatment gave the keto ethynyl carbinol. C-Acylation under basic conditions gave the *ortho*-acylated phenol ether, which was converted to the keto cobalt complex. This keto cobalt complex was subjected to our newly developed silylene-protected intramolecular [4+2]cycloaddition [11] to give the hexacyclic compound. The sulfinyl aromatic compound was then subjected to our newly developed aromatic Pummerer-type reaction [12] to give the *para*-acyloxy compound. Elongation of the side chain and desilylation, demethylation, and enol-keto transformation of this compound led to the formation of the desired optically active fredericamycin A [13].

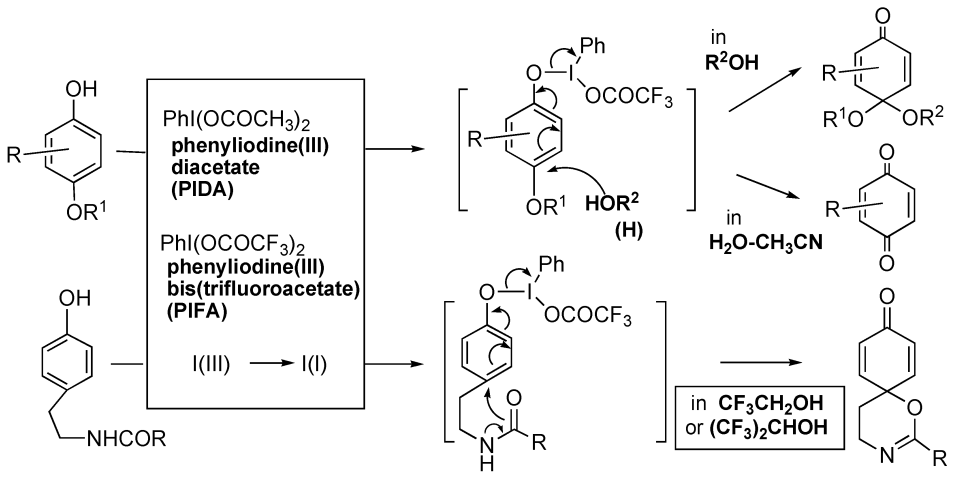


Scheme 7 Total synthesis of optically active fredericamycin A (intramolecular synthesis).

TOTAL SYNTHESIS OF DISCORHABDIN A

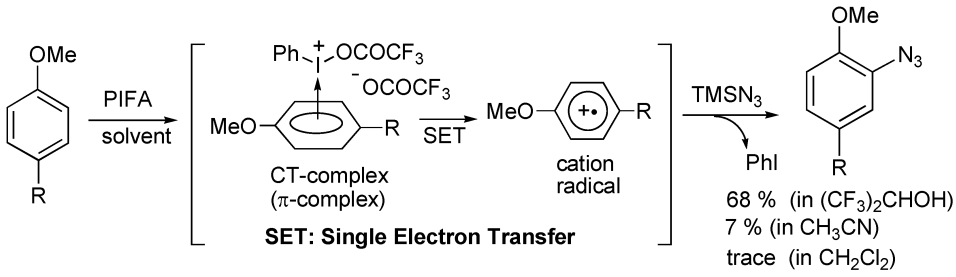
The second effective construction of the chiral nonracemic carbon centers is the chiral transfer *ipso*-substitution of *para*-substituted phenols and phenyl ethers using a hypervalent iodine reagent [14]. By using this construction method, we succeeded in the total synthesis of discorhabdin A having a chiral spiro center.

The development of the key reactions using hypervalent iodine reagents is summarized in Scheme 8. We found that phenyliodine bistrifluoro acetate (PIFA) reacted with *para*-substituted phenols in alcohol to afford the *O*-iodonium intermediate, which caused *ipso*-substitution with the alcohol to give the *para*-benzoquinone monoacetals [15]. In the presence of water, PIFA reacted with *para*-alkoxy phenols to give the *p*-benzoquinones [16]. *p*-Amidoalkyl-substituted phenols similarly caused intramolecular *ipso*-cyclization to give the spiro dienone compounds [17]. We found that a polar and less nucleophilic trifluoroethanol or hexafluoro isopropanol was the best solvent for the PIFA-induced substitution reaction of the *para*-substituted phenol derivatives [18].



Scheme 8 Development of key reactions.

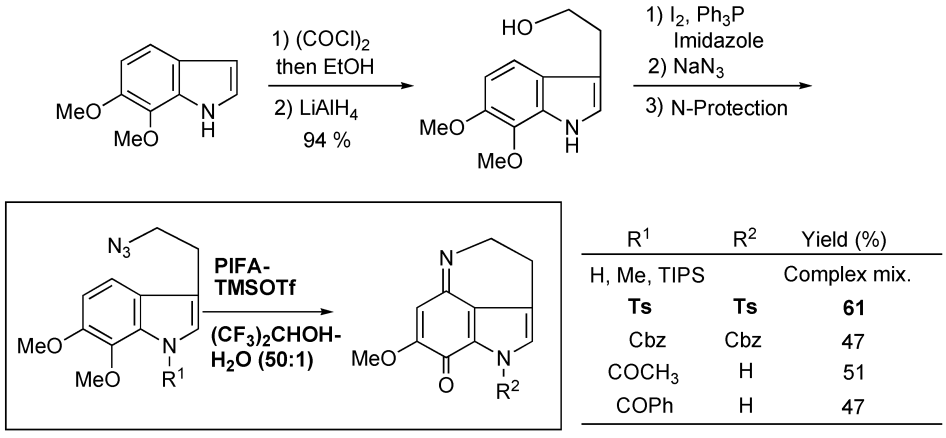
The PIFA-induced intramolecular substitution of phenyl derivatives was applied to the synthesis of the biologically quite important sulfur-containig discorhabdin A, which has three chiral centers and unstable *N*,*S*-acetal and indoloquinone imine moieties. To date, no one has succeeded in the total synthesis of this compound except us. The developed key reactions are that PIFA reacts with the phenolic oxygen and gives this kind of *O*-iodonium intermediate, and the inter- or intramolecular nucleophile attacks the *para*-position with production of the phenyl iodine to give the dienones or spirodienones. When the phenol was protected by an alkyl group, no reaction was observed in standard organic solvents. However, in trifluoroethanol or in hexafluoroisopropanol, trimethylsilyl azide was reacted with *para*-substituted phenyl ethers to give the corresponding 2-azide-substituted phenyl ethers in considerable yields [19]. Based on the UV and electron spin resonance (ESR), PIFA is thought to react with phenyl ethers to give the cation radicals, which react with azide nucleophile to give the 2-azide substituted phenyl ethers. Not only the azide nucleophile, but also other nucleophiles react with dimethoxybenzene in significant yields. The *N*-, *O*-, and *C*-nucleophiles reacted with phenyl ethers in the presence of PIFA in trifluoroethanol or in hexafluoroisopropanol to give the corresponding *ortho*-substituted phenyl ethers (Scheme 9) [20].



Scheme 9 Azidation of phenyl ethers via cation radical intermediates.

When the alkyl side chains with the terminal azide group were present at the *para*-positions, the intramolecular imine formation occurred, and in the presence of water, the corresponding quinone monoimines were obtained in good yields [21]. This is the best method to obtain the quinone monoimines. The treatment of dimethoxyindole with oxalyl chloride followed by the reaction with

ethanol and reduction with lithium aluminum hydride gave 3-hydroxyethylindole. The terminal hydroxyl group was converted to the iodo group, and then the azide group by the treatment with triphenyl phosphine-iodine and then with sodium azide. *N*-protection of the azidoethylindole followed by the PIFA-induced indoloquinone formation gave the desired pyrroloiminoquinones. The *N*-carboalkoxy compounds gave the *N*-carboalkoxy indoloquinone imines, and *N*-acyloxy ones gave the *N*-unsubstituted indoloquinoneimines in moderate yields (Scheme 10) [22].

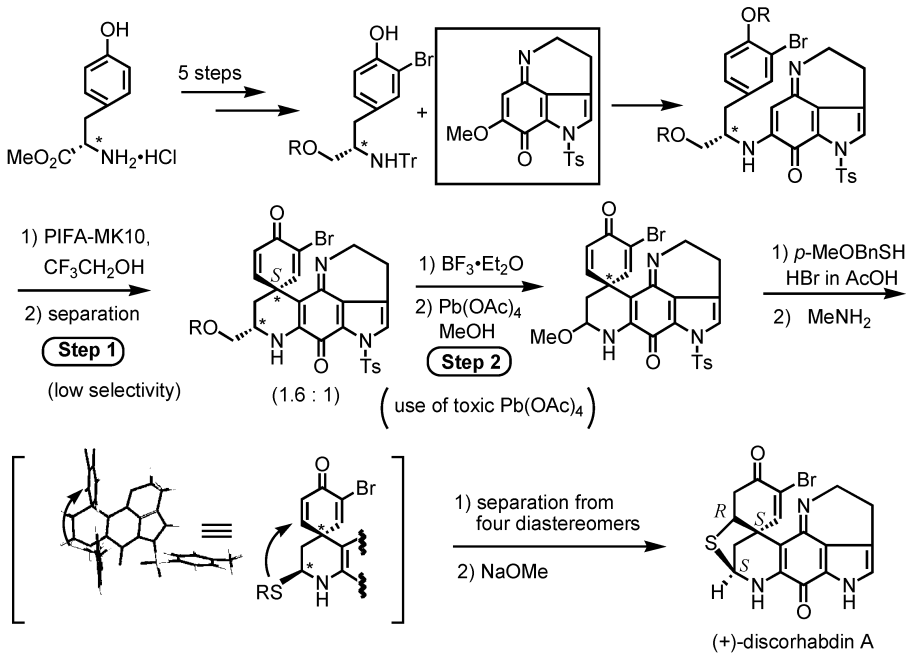


R^1	R^2	Yield (%)
H, Me, TIPS		Complex mix.
Ts	**Ts**	**61**
Cbz	Cbz	47
$COCH_3$	H	51
COPh	H	47

Scheme 10 Synthesis of pyrroloiminoquinone unit.

First total synthesis of discorhabdin A

The first total synthesis of discorhabdin A was achieved by the initial construction of the spirodienone moiety followed by the introduction of a sulfur group (Scheme 11). Commercially obtainable L-tyrosine was used as the starting material. The tyrosine derivative was treated with the indoloquinone imine to give the condensed compound. The PIFA-induced spiro cyclization of the corresponding compound gave the spirodienone. The chirality from L-tyrosine was transferred to the spiro carbon center. The alkoxyethyl group was converted to the methoxy group, which was replaced by the *para*-methoxybenzylthio group. 30 % Hydrobromic acid in acetic acid and treatment with methyl amine caused the Michael-type cyclization, and the produced sulfonium salt was readily converted to discorhabdin A [23]. All spectral data of the synthetic product were completely identical with those of the natural discorhabdin A [24].

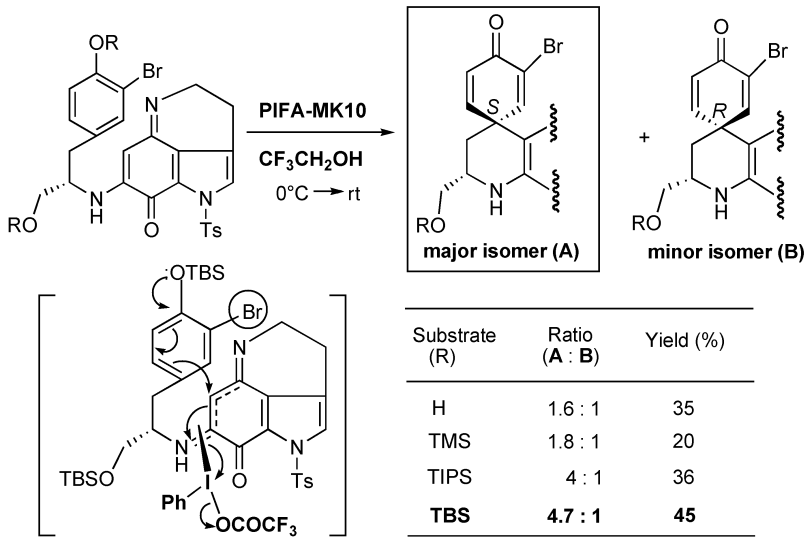


Scheme 11 First total synthesis of (+)-discorhabdin A.

Improved total synthesis of discorhabdin A

The above-mentioned first total synthesis of discorhabdin A had a few problems. One was the low selectivity of the spirodienone formation (step 1), and the other was the use of the toxic lead tetraacetate for the oxidative fragmentation (step 2). We then improved our synthetic method.

The stereoselective spiroannulation was accomplished by the use of the bulky tertiary buthyldimethylsilyl group. The hypervalent iodine reagent attacks the opposite site of the bulky siloxy group. Thus, the reagent goes to the β-side. Therefore, the less hindered side of the siloxybenzene selectively attacks the intermediate (Scheme 12).

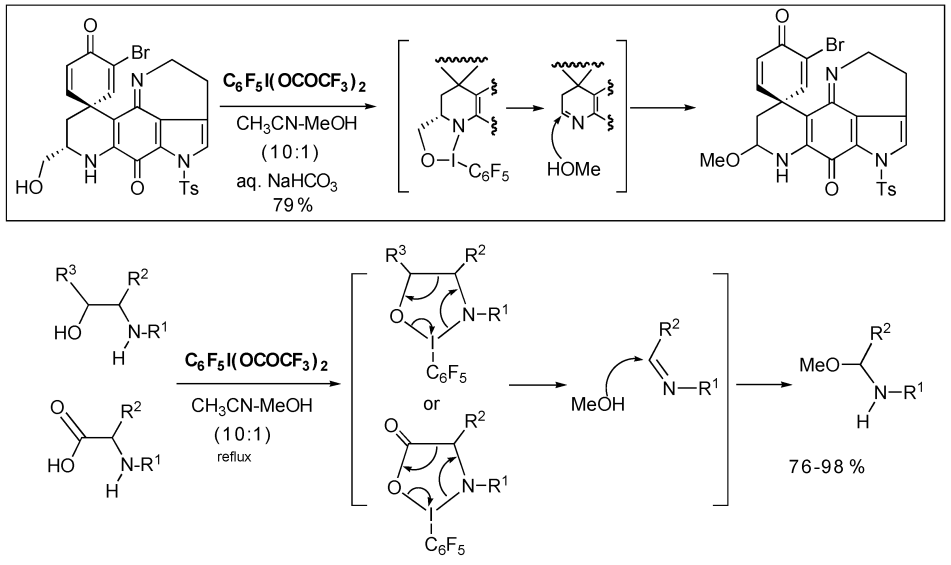


Substrate (R)	Ratio (**A** : **B**)	Yield (%)
H	1.6 : 1	35
TMS	1.8 : 1	20
TIPS	4 : 1	36
TBS	**4.7 : 1**	**45**

Scheme 12 Stereoselective spiroannulation (step 1).

The oxidative fragmentation of the β-amino alcohol was cleanly performed using pentafluorophenyliodine bistrifluoroacetate (Scheme 13) [25]. The improved total synthesis of (+)-discorhabdin A was accomplished, and the result is summarized below. The (–)-discorhabdin A was similarly prepared from D-tyrosine by the same method [26].

The oxa analogs of discorhabdin A were prepared in a similar manner.



Scheme 13 Oxidative fragmentation of β-amino alcohol with $C_6F_5I(OCOCF_3)_2$ (step 2).

Biological activities of the discorhabdins and related compounds

The biological activities of the discorhabdins and related compounds are listed in Fig. 2. As expected, the sulfur-containing (+)-discorhabdin A shows the strongest reactivity. Furthermore, we have found that (–)-discorhabdin A and its oxa analogs also show considerably strong cytotoxic activities [27].

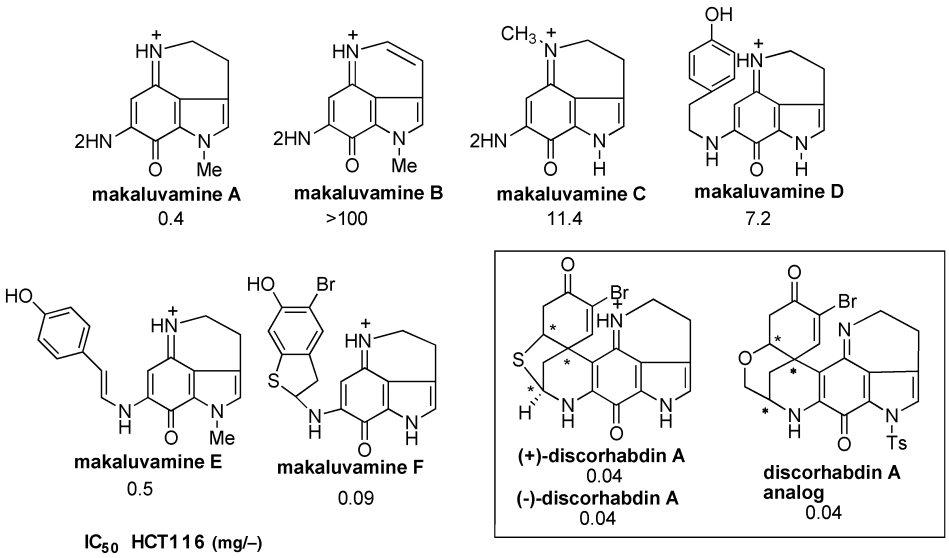


Fig. 2 Biological activities of discorhabdins and related compounds (cytotoxicity).

CONCLUSION

We developed three effective methods for the construction of chiral, nonracemic spiro carbon centers and their applications to efficient total syntheses of antitumor natural products, fredericamycin A and discorhabdin A.

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