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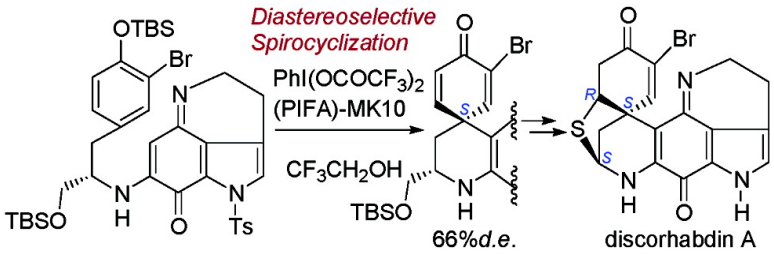

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The First Total Synthesis of Discorhabdin A

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Abstract: The first stereoselective total synthesis of a potent antitumor alkaloid, discorhabdin A (**1**), which is a unique sulfur-containing pyrroloiminoquinone alkaloid, is described. The key step in the stereocontrolled total synthesis of **1** involves both a diastereoselective oxidative spirocyclization using a hypervalent iodine(III) reagent and an efficient construction of the labile and highly strained *N*,*S*-acetal skeleton. These methodologies provide a breakthrough in the total syntheses of these promising new antitumor agents, discorhabdins and their analogues, which should serve as valuable probes for structure−activity studies.

Introduction

Discorhabdins and prianosins 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*, and so on. Among the various discorhabdins (A−R) isolated,[1] discorhabdins A (**1**),[1b,c] B,[1c] D,[1d] Q,[1m] and R[1n] have a unique sulfur-containing fused ring system incorporating the azacarbocyclic spirocyclohexadienone and pyrroloiminoquinone system (Chart 1) and show potent antitumor activity.[2] Because of their prominent biological activities and unusual ring structures, the discorhabdins have attracted considerable attention, and several partial and total syntheses of discorhabdin C have appeared in the past decade.[3] However, in most cases, synthetic efforts have been devoted only toward the diverse preparation of the pyrroloiminoquinone unit. To the best of our knowledge, the total syntheses of sulfur-containing discorhabdins have not yet been reported because construction of the labile and highly strained *N*,*S*-acetal (sulfur cross-linked) core was difficult. Furthermore, biosynthetically, the timing and insertion point for the introduction of sulfur in discorhabdins have not yet been clarified.[4]

As part of our continued studies on the total syntheses of discorhabdins and the related alkaloids, we have already reported the total synthesis of discorhabdin C[3f] via spirodienone formation using a hypervalent iodine(III) reagent, phenyliodine bis(trifluoroacetate) (PIFA), and, recently, using several hypervalent iodine(III)-induced reactions,[5] we achieved the first total synthesis of (±)-makaluvamine F (**2**),[6] which is assumed to be the biosynthetic precursor of sulfur-containing discorhabdins (Scheme 1).

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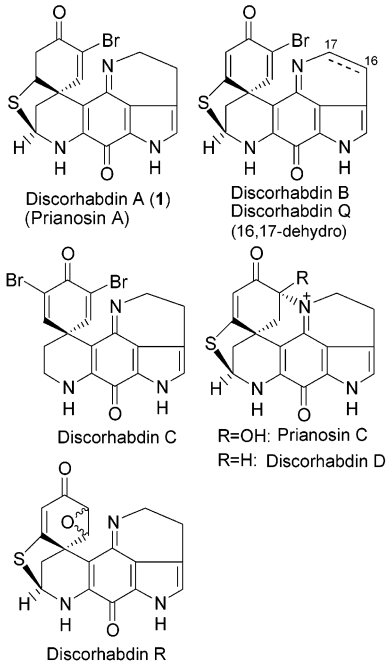
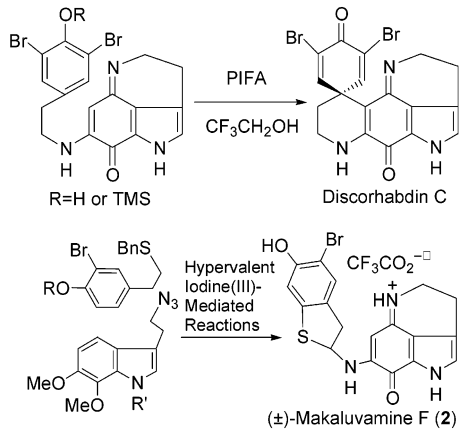
Chart 1. Discorhabdins and Prianosins



Scheme 1. Our Previous Synthetic Studies toward Pyrroloiminoquinone Alkaloids



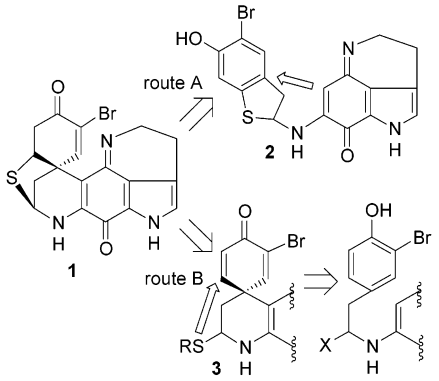
Very recently, we have briefly communicated a facile and efficient construction of the sulfur cross-linked spirocyclic system of discorhabdin A.[7] In this paper, we report a full account of the first total synthesis of discorhabdin A (**1**) as the optically pure form involving the stereoselective formation of its spirocyclic system as well as the construction of its sulfur cross-linked spirodienone skeleton.

Results and Discussion

Construction of a Sulfur Cross-Linked System: Synthesis of the Naphthoquinone Analogue of Discorhabdin A. The primary problem in synthesizing sulfur-containing discorhabdins is how to construct the highly strained sulfur cross-linked spiro-fused ring system. Retrosynthetic analyses of sulfur cross-linked system of **1** are shown in Scheme 2.

That is, one approach involves an oxidative spirocyclization of **2** (route A), and another involves an intramolecular 1,4-addition reaction of spirocyclohexadienone **3** (route B).

Scheme 2. Retrosynthetic Analyses of the Sulfur Cross-Linked Core of Discorhabdin A (**1**)



First, on the basis of a plausible hypothesis by Munro and co-workers,[4] we examined the biosynthetically plausible route A from makaluvamine F (**2**) using our previously developed oxidative spirocyclization reaction with PIFA.[3a,8] As a result, the oxidative cyclization of **2** as well as trimethylsilylated **2** using PIFA under various conditions yielded a complex mixture, probably due to the high reactivity of the iodine(III) reagent toward the sulfide group, the aminoiminoquinone skeleton, and the phenolic OH group in **2**. Incidentally, we also examined the spirodienone formation of **2** using the $CuCl_2/NEt_3/O_2$ system developed by Aubart and Heathcock,[3r] but obtained a complex mixture. Thus, we attempted to further investigate an oxidative spirocyclization using the naphthoquinone model of makaluvamine F after transformation of the sulfide group into the corresponding sulfoxide **5b** or sulfonium salt **5c** (Figure 1). However, the cyclization of **5b** with PIFA did not proceed at all. Furthermore, attempts to prepare **5c** from **5a** by known procedures were all unsuccessful due to the instability of **5a** under alkylation conditions.[9] After all, we encountered serious difficulties, such as high reactivity of the functional groups on **5a** (or **2**) toward oxidants and excessive strain required for the cyclization in constructing the sulfur cross-linked system.

Therefore, we altered the synthetic strategy. Retrosynthetic analysis of the highly strained part of **1**, the sulfur cross-linked spiro-fused ring system, is outlined in route B, Scheme 2. Key elements of our strategy include the preconstruction of the spirodienone system using the hypervalent iodine(III) reagent and the final introduction of the sulfur group leading to the cross-linked system.

We set out to explore the feasibility of constructing the sulfur cross-linked system of discorhabdins using aminonaphthoquinone **7** as a model substrate. Compound **7** was readily prepared from commercially available tyrosine methylester (**6**) and 1,4-naphthoquinone (Scheme 3). Oxidative spirocyclization of **7** using PIFA in CF_3CH_2OH[8] followed by acid hydrolysis (6 N HCl/dioxane$-H_2O$) yielded the corresponding spirodienone carboxylic acid **8**. We then attempted the direct transformation into *N*,*S*-acetal **9a** by oxidative decarboxylation of **8** in the presence of several thiols or AcSH. However, **8** was mostly recovered because of the high reactivity of sulfur nucleophiles toward oxidants and anodic oxidation. Thus, we examined an alternative route via *N*,*O*-acetal **10**, which could be readily

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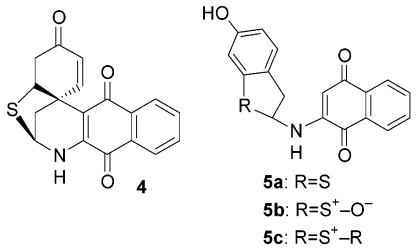
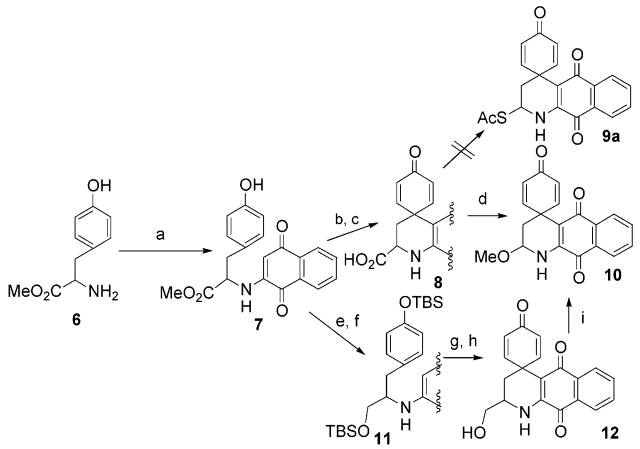


Figure 1. Naphthoquinone analogues.

Scheme 3. Synthesis of Naphthoquinone Analogue[a]



[a] (a) 1,4-Naphthoquinone, MeOH, 12 h, 57%; (b) PIFA, CF_3CH_2OH, 0.5 h, 42%; (c) 6 M HCl aq, 1,4-dioxane, 60 °C, 2.5 h, 76%; (d) −2e, NaOMe (5 mol %), MeOH, 60% [cf. $Pb(OAc)_4$, CH_2Cl_2−MeOH, 45%; $PhI(OAc)_2$, MeOH, 22%; PIFA, MeOH, 29%]; (e) $LiBH_4$, THF, 2 h; (f) TBSCl, DBU, CH_2Cl_2, 1 h, quant. (two steps); (g) PIFA, CF_3CH_2OH, 0.5 h, 71%; (h) TBAF, THF−H_2O, 1 h, 71%; (i) $Pb(OAc)_4$, CH_2Cl_2−MeOH, 61%.

prepared by oxidative decarboxylation of **8**. Consequently, the anodic oxidation reaction[10] (graphite anode−graphite cathode system in an undivided cell) of **8** proceeded smoothly in MeOH in the presence of 5 mol % NaOMe to give **10** in 60% yield. In contrast, chemical oxidation reactions using $Pb(OAc)_4$, $PhI(OAc)_2$ (PIDA), or PIFA afforded **10** only in low to moderate yields. An alternative approach to **10** via amino alcohol derivative **12** was also possible, that is, reduction of **7** using $LiBH_4$ followed by silylation with *tert*-butyldimethylsilyl chloride (TBSCl) to give bis-silylated compound **11**. PIFA-induced spirocyclization reaction[3a] of **11** and then desilylation with tetra *n*-butylammonium fluoride (TBAF) yielded the spirodienone **12**. Efficient transformation of **12** into **10** was performed by using $Pb(OAc)_4$[11] in CH_2Cl_2−MeOH (Scheme 3).

After an extensive survey of sulfur nucleophiles such as AcSR (R = H, TMS, K), $EtOCS_2K$, M_2S (M = Li, Na, Me_3Si), TrSH, $^iPr_3SiSH$, BnSH, *p*-$MeOC_6H_4CH_2SH$ (*p*-MeOBnSH), *i*-PrSH, *t*-BuSH, and PhCOSH, which may convert the methoxy group of **10** into a sulfur functional group, the thioacetyl group or *p*-methoxybenzylthio group was introduced efficiently when using AcSK or *p*-MeOBnSH (in the presence of $BF_3{\cdot}Et_2O$) to give **9a** or **9b** in 78% or 80% yield, respectively. Several thiol groups could also be substituted in low to moderate yields (Scheme 4). Next, we examined the construction of the sulfur cross-linked system from both *N*,*S*-acetals (**9a**,**b**). Treatment of **9a** with 2 M NH_3 in EtOH yielded the sulfur cross-linked compound (±)-**4** via thiol **13** in 51% yield (Scheme 4). On the other hand, transformation of the *p*-methoxybenzylthio group into thiol **13** using known procedures did not proceed and yielded a complex mixture. Thus, we planned a novel approach to **4** via sulfonium salt **14**,[12] which was assumed to be formed by intramolecular 1,4-addition of the sulfide group to the activated enone moiety under a variety of acidic conditions[13] (Scheme 4). Consequently, using 30% HBr−AcOH, **4** was also synthesized in 41% yield from **9b**. The structural features of **4** were supported by spectroscopic data and were compared to the data reported for **1** by Munro and co-workers.[1c]

The three-dimensional structure of **4** was deduced from difference nOe spectra recorded in $(CD_3)_2SO$. The observed enhancements, shown in Scheme 4, were in complete agreement with structure **4**.

Total Synthesis of Discorhabdin A. Next, we applied the model study to the total synthesis of discorhabdin A. We first examined the shorter path via amino acid derivative **18**, which is the same as that toward the naphthoquinone model compound **4**. Tritylation of **6**·HCl followed by mono-bromination with NBS yielded **15** in 65% yield (two steps; Scheme 5). A coupling reaction of **15** with pyrroloiminoquinone **16a**, which was prepared by our previously developed PIFA-induced pyrroloiminoquinone formation,[3o] provided **17** as its CF_3CO_2H salt (**17**·**TFA**) in 37% yield. We then examined the oxidative spirocyclization reaction of **17**·**TFA** using PIFA. Although various reaction conditions were tested, this reaction did not give the corresponding spirodienone **18**, but yielded a complex mixture probably because generation of the free base of **17**, which was reactive enough to cyclize, from **17**·**TFA** was difficult. This might be because **17**·**TFA** has an active methine proton and is readily decomposed under basic conditions (even in the presence of NEt_3). Thus, we modified the synthetic strategy into an alternative route via amino alcohol **21** as follows: reduction of **15** with DIBAH followed by silylation of the resulting alcohol with TBSCl gave the bis-silylated compound **19a**. Selective removal of the phenolic TBS of **19a** with TBAF in THF, followed by a coupling reaction with *N*-tosylated pyrroloiminoquinone **16b**, yielded **20a**. Spirodienone formation of **20a** using PIFA proceeded effectively in the presence of MK10 to give a diastereomeric mixture, **21a** and **21′a**.[14]

Both diastereomers were readily separated by column chromatography on silica gel to give the less polar isomer, **21a**, and the polar isomer, **21′a**, in 27% and 18% yields, respectively. The absolute configuration of the newly formed spirocenter of these isomers was determined by stereospecific chemical transformation of **21a** and **21′a** into cyclic ethers **23a** and **23b**, because we could not obtain crystals of **21a** and **21′a** suitable for X-ray crystal structure analysis. That is, desilylation of TBS ether of **21a** by $BF_3{\cdot}Et_2O$ followed by acid-induced intramolecular 1,4-addition of the OH group to the brominated enone side of cyclohexadienone moiety exclusively gives cyclic ether **23a**. In the same manner, **23b** was obtained stereospecifically from isomer **21′a**. These results show that the nucleophilic attack

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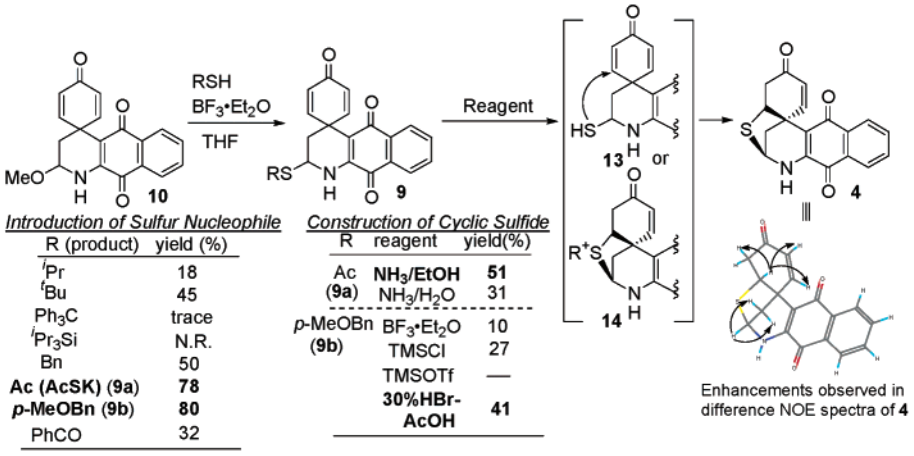
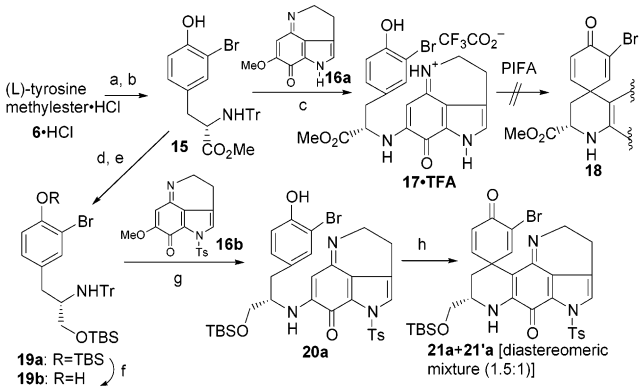
(12) Formation of sulfonium salt **14** could not be identified because of its unstability.
(13) (a) Schöberl, A.; Lange, G. *Liebigs Ann. Chem.* **1956**, *599*, 140−160. (b) Nenajdenko, V. G.; Lebedev, M. V.; Balenkova, E. S. *Tetrahedron* **2001**, *57*, 9017−9024.
(14) In the absence of MK10, spirodienones were obtained in 22% yield as a diastereomeric mixture of **21a** and **21′a** (1.5:1).

Scheme 4. Construction of a Sulfur Cross-Linked System

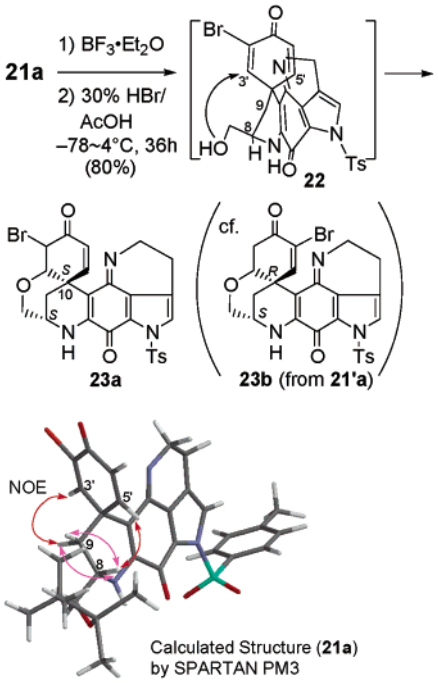


Scheme 5. Construction of the Spirocyclic System[a]



[a] (a) TrCl, Et_3N, DMF, quant.; (b) NBS, DMF, 65%; (c) 0.1 N HCl/MeOH, then **16a**, MeOH, 20 h, 37%; (d) DIBAH, CH_2Cl_2, −78 °C to room temperature, 5 h, 96%; (e) TBSCl, DBU, CH_2Cl_2, 0 °C, 1.5 h, 87%; (f) TBAF, THF, 0 °C, 0.5 h, quant.; (g) 0.1 N HCl/MeOH, then **16b**, MeOH, 16 h, 54%; (h) PIFA−MK10, CF_3CH_2OH, 0.5 h, 45% (cf. PIFA, CF_3CH_2OH, 22%).

Scheme 6. Determination of the Absolute Configuration of the Spirocenter of **21a** and **21′a**

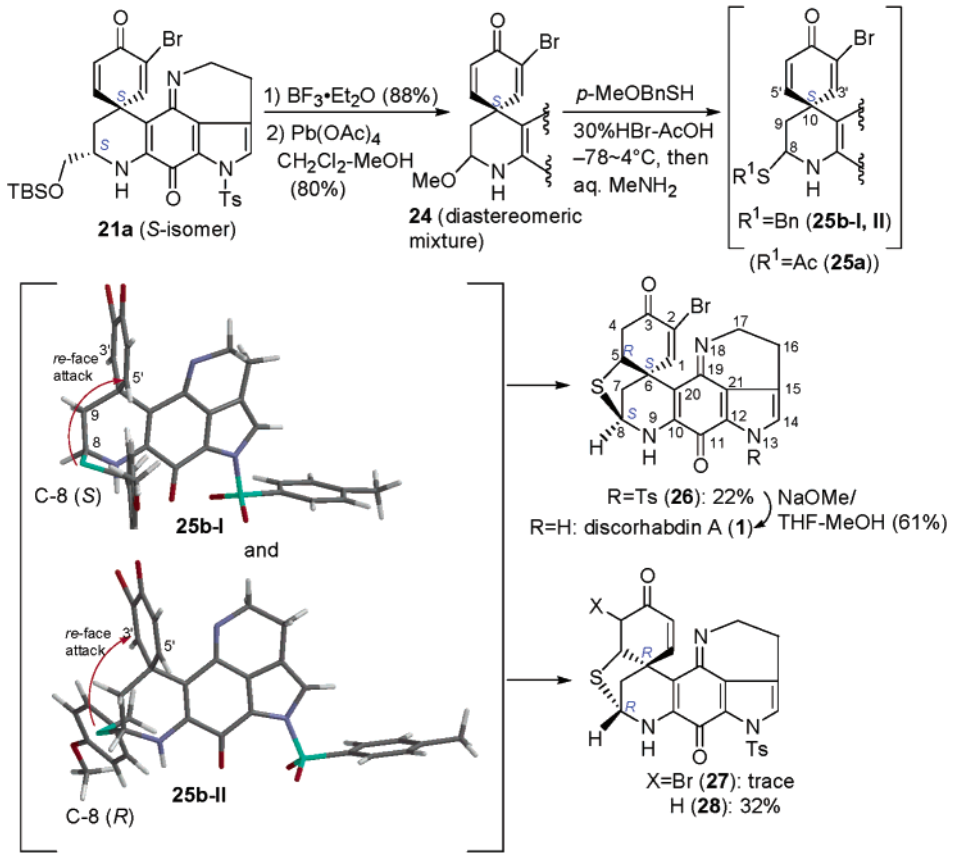


of the OH group of **22** specifically occurs on either C-3′ or C-5′, which is located on the same side as the hydroxymethyl group. Thus, the absolute configuration of the spirocenter [C-10 (C-4′)] of both isomers **21a** and **21′a** was determined to be *S* and *R*, respectively. This was also supported by ^{1}H NMR nOe analyses for **21a** and **21′a**. Specifically, nOe difference experiments showed the presence of an nOe between the hydrogen atoms at C-8 and C-5′ in **21a** but not in **21′a**[15] (Scheme 6).

The major isomer **21a**, whose absolute stereochemistry (*S* configuration) of the spirocenter (C-10) is the same as that of natural **1**, was desilylated and then converted into the methoxylated compound **24** by oxidative dealkylation with $Pb(OAc)_4$. The remaining challenge was to transform *N*,*O*-acetal **24** into cross-linked *N*,*S*-acetal **25** because of the instability of **24** toward both acidic and basic reaction conditions. We first examined the introduction of a thioacetyl group and applied the method for the preparation of model compound **9a** to compound **24**. However, **25a** (R^1 = Ac) was not obtained at all, but instead a complex mixture was yielded unexpectedly. On the other hand, a *p*-methoxybenzylthio group was introduced efficiently in the presence of BF_3•Et_2O to give unstable *N*,*S*-acetal **25b** (R^1 = *p*-methoxybenzyl) in 61% yield as a diastereomeric mixture. Thus, we applied the same procedure as that of the model study, involving an acid-induced 1,4-addition of a sulfide group to the cyclohexadienone moiety. Accordingly, we treated a diastereomeric mixture of **25b** with 30% HBr−AcOH followed by aqueous workup with $MeNH_2$ to give 11% yield of *N*-tosylated discorhabdin A (**26**). Ultimately, we found an efficient one-pot transformation procedure yielding **26** in 22% yield from **24**. The procedure used *p*-methoxybenzylthiol in 30% HBr−AcOH (36 h; −78 °C to 4 °C) followed by treatment with aqueous $MeNH_2$ and mainly gave **26** as well as the undesired cross-linked compound **28**, which was possibly formed by debromination after 1,4-addition to the brominated enone side. The stereochemistry in constructing the cross-linked sulfide **26** was predicted from the minimized conformation of the initially formed *N*,*S*-acetal **25b-I**, natural type conformer (C-8 (*S*)-configuration), according to the SPARTAN Parametric Method 3 (PM3) calculation (Scheme 7). Scheme 7 shows that intramolecular 1,4-addition of the sulfide group in **25b-I** most likely yields **26** exclusively by attack on C-5′ from the *re*-face of the cyclohexadienone ring, while in another diastereomer **25b-II**

(15) An nOe between the hydrogen atoms at C-8 and C-3′ in **21′a** was observed.

Scheme 7. Total Synthesis of Discorhabdin A (**1**)

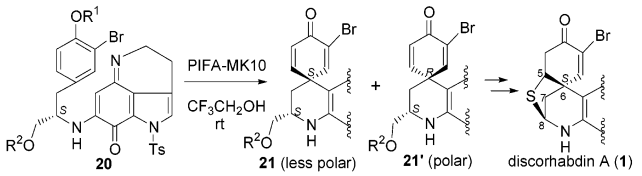


(C-8 (*R*)-configuration), the sulfide group was assumed to be introduced exclusively into C-3′ from the *re*-face of the cyclohexadienone ring to yield **28** via **27**. Thus, *N*-tosylated discorhabdin A **26**, which has the desired absolute and relative configuration, was obtained. The enantiomeric excess (ee) of **26** was confirmed to be >99% by HPLC analysis using a chiral column (DAICEL CHIRALCEL OD; *n*Hex/*i*PrOH = 65/35; 20 °C). Finally, removal of the tosyl group of **26** with NaOMe in THF gave discorhabdin A (**1**) as the optically pure form in 61% yield for the first time (Scheme 7).

The synthetic product as its HCl salt was in all respects identical to natural **1** including optical rotation {synthetic **1**·**HCl**: $[\alpha]_D$ +388° (c = 0.06, MeOH); natural **1**·**HCl**[1c]: $[\alpha]_D$ +400° (c = 0.05, MeOH)} and ^{1}H NMR nOe data.

Stereoselective Total Synthesis of Discorhabdin A. To secure the more efficient synthesis of **1**, we planned the stereoselective total synthesis of discorhabdin A (**1**). Because the lone spirostereocenter (C-6), which was formed in PIFA-induced spirocyclization, was found to define the absolute and relative stereochemistry of the remaining two stereogenic centers (C-5, C-8) of **1**, we attempted to improve the diastereoselectivity of the PIFA-induced spirocyclization reaction of **20**. First, we examined the cyclization reaction using several substrates **20a**−**c**, whose hydroxymethyl group was protected by sterically hindered silyl groups (entries 1−3, Table 1). However, these attempts were all unsuccessful even when using other iodine(III) reagents and additives. Furthermore, deprotection of the silyl ether moiety to the corresponding alcohol became more and more difficult as the silyl group became bulkier. After various efforts, we found that the diastereomeric excess slightly increased in the reaction of bis-silylated substrate **20d** with PIFA

Table 1. Diastereoselective Spirocyclization of **20** Using PIFA



entry	R^1	R^2	substrate	equiv (PIFA)	time (h)	ratio[a] (**21**:**21′**)	yield (%) (**21** + **21′**)
1	H	TBS	**20a**	1.2	0.5	1.5:1	45 (**21a** + **21′a**)
2	H	TIPS	**20b**	1.2	0.75	1.4:1	37
3	H	TBDPS	**20c**	1.2	0.75	1.5:1	25
4	TMS	TBS	**20d**	2.0	1	2.0:1	24[b] (**21a** + **21′a**)
5	TBS	TBS	**20e**	4.0	7	4.8:1	49 (**21a** + **21′a**)
6	TIPS	TBS	**20f**	4.0	7	4.1:1	49 (**21a** + **21′a**)
7	TBDPS	TBS	**20g**	5.0	24	2.6:1	34 (**21a** + **21′a**)

[a] The ratio was determined by HPLC (DAICEL CHIRALPAK AD-H). [b] Yield for two steps (silylation and spirocyclization).

in the same manner as in our report on the total synthesis of discorhabdin C,[3f] but the chemical yield of **21** decreased (entry 4, Table 1).

Thus, we investigated the spirocyclization of several silyl phenol ethers **20e**−**g** whose hydroxymethyl group was protected by TBS group to facilitate deprotection (Table 1). In the event, spirodienone formation did occur, giving rise to a 4.8:1 mixture of both diastereomers **21a** and **21′a** (66% diastereomeric excess (de)) with moderate chemical yield when using TBS phenol ether **20e** as the reaction substrate, while a longer reaction time (7 h) and excess PIFA (4 equiv) were required to complete the reaction (entry 5, Table 1).[16]

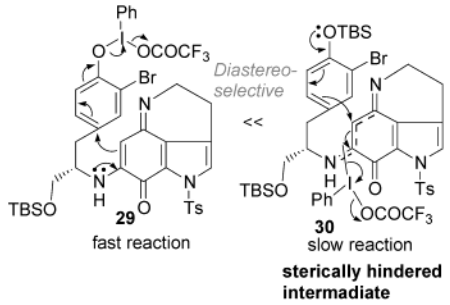


Figure 2. Possible mechanism for diastereoselective spirocyclization.

The mechanism for generation of the stereoselectivity in this reaction is still unclear, but the slower reaction via sterically more hindered intermediate **30**, whose enamino-imine moiety seems to react with PIFA, as compared to that via **29** is more likely to enhance the diastereoselectivity (Figure 2).

Through subsequent transformations from **21a** as described above, we achieved the first stereoselective total synthesis of **1**.

Conclusions

We developed a concise and efficient method for constructing the highly strained and unique sulfur-bridged portion of discorhabdins. Furthermore, the first total synthesis of discorhabdin A was accomplished by diastereoselective oxidative spirocyclization using PIFA. Construction of the three stereogenic centers have been achieved successfully by the use of commercially available (L)-tyrosine as the only chiral source and synthon. The synthesis of discorhabdin A will enable clinical examination of this or related promising new antitumor agents having a unique spiro-fused ring system. Toward this end, we plan to obtain a variety of analogues and derivatives of discorhabdin A as both their natural and their unnatural forms utilizing our procedures from (L)- or (D)-tyrosine as the starting material. In addition, the present results should give important clues on the biosynthetic path to sulfur-containing discorhabdins.

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Supporting Information Available: Complete experimental procedures and characterization data for all previously unreported compounds described herein, including chiral HPLC data for **26** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Although we also tried some other readily removable protective groups (R^1 and R^2 of **20**) such as acetyl (R^2), benzoyl (R^2), and MOM (R^1) in this reaction, both de and yields did not improve.