[14] Factors influencing configurational stability of binaphthyl systems are not entirely predictable: A. K. Yudin, J. P. Martyn, S. Pandiaraju, J. Zheng, A. Lough, *Org. Lett.* **2000**, *2*, 41.

[15] Data were corrected for Lorentz and polarization effects, and equivalent reflections were averaged using the Bruker SAINT software as well as utility programs from the XTEL library. The structure was solved using SHELXTL and Fourier techniques, and refined by least squares against $|F^2|$ using a combination of SHELXTL and the XTEL library. All hydrogen atoms were included as fixed isotropic contributors in the final cycles of refinement. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-173110 (*rac*-**2a**) and CCDC-173109 (*rac*-**2b**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[16] Crystal data for *rac*-**2a**: crystal dimensions $0.30 \times 0.10 \times 0.03$ mm, monoclinic, space group $C2c$, $a = 21.404(4)$, $b = 12.253(3)$, $c = 18.103(4)$ Å, $\beta = 96.27(3)^\circ$; $V = 4719.58$ Å3, $Z = 4$, $\rho = 1.160$ mg mm$^{-3}$; $\mu = 0.71073$ mm$^{-1}$, $F(000) = 1720$, Bruker Smart6000 CCD diffractometer, $1.92 < \theta < 26.37^\circ$, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, Ω scans, $T = 112(2)$ K, 36 868 reflections measured, 4813 unique, 1668 with $I > 2\sigma(I)$, $-26 \le l \le 25$, $-15 \le k \le 14$, $-22 \le l \le 22$; $R = 0.0667$, $wR = 0.0644$, GOF = 1.565, $\Delta\rho_{max} = 0.31$ e Å$^{-3}$.

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[18] For an example of metal-associated ligand atropisomerization, see: a) M. T. Ashby, G. N. Govindan, A. K. Grafton, *J. Am. Chem. Soc.* **1994**, *116*, 4801; b) M. D. Tudor, J. J. Becker, P. S. White, M. R. Gagné, *Organometallics* **2000**, *19*, 4376.

[19] *Rac*-**1** (14.6 mg, 74.6 μmol) and lithium dimethylamide (3.8 mg, 74.5 μmol) were dissolved in toluene and allowed to stir at room temperature for 30 min. The volatiles were removed in vacuo from the violet solution to leave a residue that was redissolved in toluene, treated with $ZrCl_4$ (8.7 mg, 37.3 μmol), and stirred at room temperature. An orange precipitate formed over the course of 12 hours, from which single crystals could be retrieved for analysis.

[20] Crystal data for *rac*-**2b**: crystal dimensions $0.15 \times 0.12 \times 0.10$ mm, monoclinic, space group $P2_1/c$, $a = 20.4685(12)$, $b = 17.3030(10)$, $c = 21.1452(13)$ Å, $\beta = 118.062(2)^\circ$; $V = 6608.52$ Å$^3$, $Z = 8$, $\rho = 1.465$ mg mm$^{-3}$; $\mu = 0.71073$ mm$^{-1}$, $F(000) = 2976$, Bruker Smart6000 CCD diffractometer, $2.24 < \theta < 27.50^\circ$, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, Ω scans, $T = 111$ K, 48 532 reflections measured, 15 184 unique, 6638 with $I > 2\sigma(I)$, $-24 \le l \le 26$, $-21 \le k \le 22$, $-27 \le l \le 23$; $R = 0.0322$, $wR = 0.0241$, GOF = 0.627, $\Delta\rho_{max} = 0.36$ e Å$^{-3}$.

[21] A full discussion of the solid-state structure will be provided elsewhere.

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# Synthetic Studies on the Sulfur-Cross-Linked Core of Antitumor Marine Alkaloid, Discorhabdins: Total Synthesis of Discorhabdin A**

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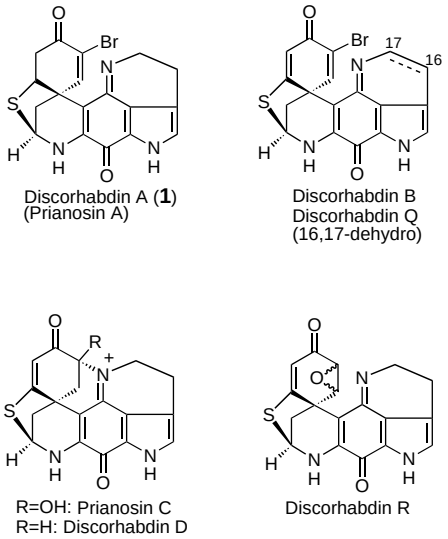
Discorhabdins and prianosins have been isolated from marine sponges such as New Zealand sponges of the genus *Latrunculia*, Okinawan sponge *Prianos melanos*, and Fijian sponge *Zyzzya cf. Marsailis*. Among the various discorhabdins (A–R) isolated, discorhabdins A (**1**),[1a,b,d] B,[1b] D,[1c] Q,[1e] and R[1f] have a unique sulfur-containing fused-ring system incorporating an azacarbocyclic spirocyclohexadienone and a pyrroloiminoquinone system (Scheme 1), and show potent antitumor activity.[2] The discorhabdins have




Scheme 1. Sulfur-containing discorhabdins.

attracted the synthetic interest of several groups including ours because of their cytotoxicity and unusual ring structures.[3] However, 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, the timing and insertion point for the introduc-

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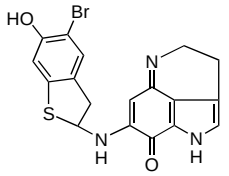
tion of sulfur in discorhabdins have not yet been clarified biosynthetically.[4]

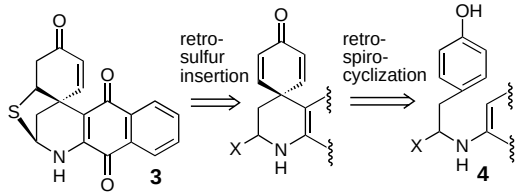
We report herein synthetic studies on the sulfur-cross-linked spirodienone core of discorhabdin alkaloids, which results in the first total synthesis of (±)-discorhabdin A (**1**).

First, on the basis of a plausible hypothesis by Munro and co-workers,[4] we examined the biosynthetically potential route from makaluvamine F (**2**)[1d, 3h] using our previously developed oxidative spirocyclization reaction with phenyliodine(III) bis(trifluoroacetate) (PIFA).[3d, 5]



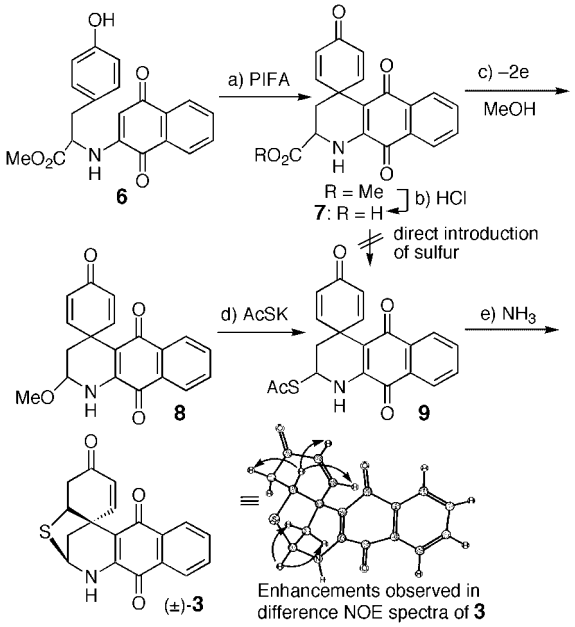
Makaluvamine F (**2**)

The spirocyclization of **2** using PIFA under various conditions yielded a complex mixture. We also examined the formation of a spirodienone from **2** using the $CuCl_2$/$NEt_3$/$O_2$ system developed by Aubart and Heathcock,[3i] but obtained a complex mixture. Therefore, we altered the synthetic strategy. Retrosynthetic analysis of the highly strained core of **1**, namely, the sulfur-cross-linked spiro-fused ring system **3**, is outlined in Scheme 2. Key elements of our strategy include the iodine(III)-induced oxidative spirocyclization of **4** and the final introduction of the sulfur group leading to the cross-linked core.




Scheme 2. Retrosynthetic analysis of sulfur-cross-linked core (**3**) of discorhabdin A.

We set out to explore the feasibility of constructing the sulfur-cross-linked core of discorhabdins using aminonaphthoquinone **6** as a model substrate. Compound **6** was readily prepared from commercially available (L)-tyrosine methyl ester (**5**) and 1,4-naphthoquinone (Scheme 3). Oxidative spirocyclization of **6** using PIFA/montmorillonite K10 (MK10), followed by acid hydrolysis (6N HCl/dioxane-$H_2O$) yielded the corresponding spirodienone carboxylic acid **7**. The use of MK10[6] improved the yield of this spirocyclization step compared to our previous procedure.[3d, 5] We then attempted the direct introduction of a sulfur functional group by oxidative decarboxylation of **7** in the presence of several thiols or AcSH. However, **7** was mostly recovered because of the high reactivity of sulfur nucleophiles towards oxidants and anodic oxidation. Thus, we examined an alternative route via *N*,*O*-acetal **8**, which could be readily prepared by oxidative decarboxylation of **7**. Consequently, the anodic oxidation[7] (graphite anode/graphite cathode system in a nondivided cell) of **7** proceeded smoothly in MeOH in the presence of 5 mol% NaOMe to give **8** in 60% yield. In contrast, chemical oxidation reactions using $Pb(OAc)_4$, $PhI(OAc)_2$ (PIDA), or PIFA afforded **8** only in low to moderate yields. After an extensive survey of sulfur nucleophiles, such as AcSR (R = H, TMS, K), $EtOCS_2K$, $M_2S$ (M = Li, Na, $Me_3Si$), TrSH, PhCOSH, and *t*BuSH, which may convert the methoxy group of **8** into a sulfur group, the thioacetyl group was introduced efficiently using AcSK in the presence of $BF_3 \cdot Et_2O$ to give **9** in 78% yield. Several thiol groups could also be substituted in low to moderate yields. Treatment of **9** with 2M $NH_3$ in EtOH yielded the sulfur-cross-linked compound (±)-**3** in 51% yield (Scheme 3). The structural features of **3** were supported by spectroscopic data[8] and was compared with the data reported for **1** by Munro and co-workers.[1b] The three-dimensional structure of **3** was deduced from difference NOE spectra recorded in $(CD_3)_2SO$. The observed enhancements (Scheme 3) were in complete agreement with structure **3**.




Scheme 3. Construction of sulfur-cross-linked core **3**. a) PIFA-MK 10, $CF_3CH_2OH$, 0.5 h, 42%; b) 6M aq HCl, 1,4-dioxane, 60°C, 2.5 h, 76%; c) −2e, NaOMe (5 mol%), MeOH, 60% ($Pb(OAc)_4$, $CH_2Cl_2$-MeOH, 45%; $PhI(OAc)_2$, MeOH, 22%; PIFA, MeOH, 29%); d) AcSK-$BF_3 \cdot Et_2O$, THF, −78→4°C, 24 h, 78%; e) 2M $NH_3$/EtOH, 12 h, 51%.

Thus, we applied this model study to the total synthesis of discorhabdin A. We first examined the same path as that towards the naphthoquinone model compound **3**. Tritylation of **5** followed by monobromination with NBS yielded **10** in 65% yield (2 steps; Scheme 4). A coupling reaction of **10** with pyrroloiminoquinone **11a**, which was prepared by our previously developed PIFA-induced pyrroloiminoquinone formation,[9] provided **12** in 46% yield. We then examined the oxidative spirocyclization reaction of **12** using PIFA. Although various reaction conditions were tested, this reaction did not give the corresponding spirodienone, but unexpectedly yielded a complex mixture. Thus, we modified the synthetic strategy as follows: reduction of **10** with DIBAH followed by silylation of the resulting alcohol with TBSCl gave the bissilylated compound **13**. Selective desilylation of **13** with TBAF in THF, followed by a coupling reaction with 1-tosylated pyrroloiminoquinone derivative **11b** yielded **14**. Spirodienone formation using PIFA proceeded effectively in the presence of MK10 to give **15** as a mixture of two diastereomers in 45% yield.

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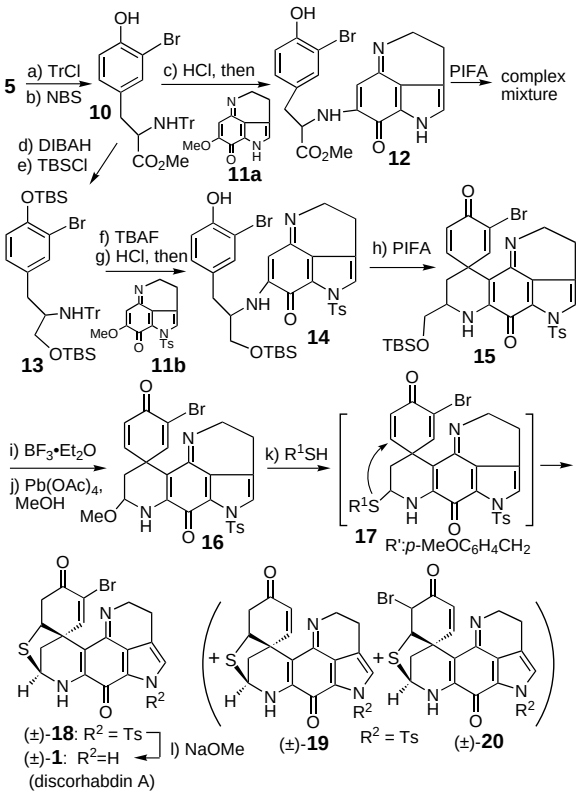


Scheme 4. Total synthesis of discorhabdin A (**1**). a) TrCl, $Et_3N$, DMF, quant.; b) NBS, DMF, 65%; c) 0.1N HCl/MeOH, then **11a**, MeOH, 20 h, 46%; d) DIBAH, $CH_2Cl_2$, $-78\,^{\circ}C \rightarrow$RT, 5 h, 96%; e) TBSCl, DBU, $CH_2Cl_2$, 0 °C, 1.5 h, 87%; f) TBAF, THF, 0 °C, 0.5 h, quant.; g) 0.1N HCl/MeOH, then **11b**, MeOH, 16 h, 54%; h) PIFA-MK 10, $CF_3CH_2OH$, 0.5 h, 45%; i) $BF_3 \cdot Et_2O$, $CH_2Cl_2$, 0 °C $\rightarrow$RT, 7 h, 90%; j) $Pb(OAc)_4$, $CH_2Cl_2$/MeOH (2/1), 0 °C, 1.5 h, 88%; k) *p*-$MeOC_6H_4CH_2SH$, 30% HBr-AcOH, $CH_2Cl_2$, $-78 \rightarrow 4\,^{\circ}C$, 15 h, **18**(22%), **19**(19%), **20**(13%); l) NaOMe, THF-MeOH, 0 °C, 1 h, 65%. Tr = triphenylmethyl; NBS = *N*-bromosuccinimide; DIBAH = diisobutylaluminum hydride; TBS = *tert*-butyldimethylsilyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBAF = tetrabutylammonium fluoride; Ts = toluene-4-sulfonyl.

The diastereomeric mixture **15** was desilylated, and then converted into the methoxy compound **16** by oxidative dealkylation with $Pb(OAc)_4$. The remaining challenge was to transform *N*,*O*-acetal **16** to *N*,*S*-acetal **17** because of the instability of **16** towards both acidic and basic reaction conditions. We first examined the introduction of a thioacetyl group, and applied the best method for the preparation of a model compound **9** to compound **16**. However, **17** ($R^1$ = Ac) was not obtained at all, but instead a complex mixture was yielded. Thus, we re-investigated various sulfur nucleophiles, such as $Na_2S$, $(R_3Si)_2S$, TrSH, (*p*-MeO)BnSH, and *t*BuSH to obtain **17**. As a result, a *p*-methoxybenzylthiol group was introduced efficiently in the presence of $BF_3 \cdot Et_2O$ to give **17**. Debenzylation of **17**, a labile and highly functionalized compound, also required the mildest possible reaction conditions. Our initial strategy was to perform a mild debenzylation on the *p*-methoxybenzylsulfonium salt formed by 1,4-addition of a sulfide group. Accordingly, we treated **17** with 30% HBr-AcOH followed by workup with $NaHCO_3$ but obtained only a trace amount of *N*-tosylated discorhabdin A (**18**). Ultimately, we found an efficient one-pot transformation procedure yielding **18** in 22% yield from **16**. The procedure used *p*-methoxybenzylthiol in 30% HBr-AcOH followed by treatment with aqueous $MeNH_2$ and gave **18**[10] as well as the undesired debrominated compounds **19** and **20**, which were formed by 1,4-addition to the bromo-enone side. Removal of the Ts group of **18** with NaOMe provided (±)-discorhabdin A (**1**) in 65% yield (Scheme 4).

The spectral data of synthetic **1** was identical to those reported for the natural product.[1a,b] Further improvement of the overall yield and an investigation into the total synthesis of optically active discorhabdin A are now underway.

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[8] Characterization of (±)-**3**: orange solid; $R_f = 0.20$ (silica gel, *n*-hexane/AcOEt 2/1); m.p. 255–257 °C (from AcOEt); $^1H$ NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.07$ (d, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 7.75 (t, $J = 8.0$ Hz, 1H), 7.64 (t, $J = 8.0$ Hz, 1H), 7.05 (d, $J = 10.5$ Hz, 1H), 6.49 (br s, 1H), 6.19 (d, $J = 10.5$ Hz, 1H), 5.29–5.33 (m, 1H), 4.60 (dd, $J = 12.0$, 7.5 Hz, 1H), 2.61–2.83 (m, 4H); $^{13}C$ NMR (75.5 MHz, $[D_6]$DMSO, 25 °C): $\delta = 195.7$, 180.6, 178.4, 154.9, 144.9, 135.0, 133.0, 132.4, 129.8, 125.7, 125.4, 124.9, 118.8, 59.5, 55.7, 46.8, 45.3, 39.4; IR (KBr): $\tilde{\nu} = 1680$, 1675, 1595, 1565, 1495 $cm^{-1}$; UV/Vis (MeOH): $\lambda_{max}$ ($\varepsilon$) = 473 (1300), 270 (10900), 245 nm (10000); HR-MS: calcd for $C_{18}H_{13}NO_3S$ [$M^+$]: 323.0616, found: 323.0621.

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[10] Characterization of (±)-**18**: red solid; $R_f = 0.70$ (silica gel, $CH_2Cl_2$/MeOH 40/1); m.p. > 300 °C; $^1H$ NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.02$ (d, $J = 8.4$ Hz, 2H), 7.49 (s, 1H), 7.43 (s, 1H), 7.33 (d, $J = 8.4$ Hz, 2H), 5.93 (d, $J = 3.9$ Hz, 1H), 5.28 (t, $J = 3.9$ Hz, 1H), 4.62 (dd, $J = 11.7$, 7.8 Hz, 1H), 4.29 (dt, $J = 18.3$, 6.0 Hz, 1H), 3.89 (dt, $J = 18.3$, 9.0 Hz, 1H), 2.80–2.86 (m, 2H), 2.61–2.77 (m, 4H), 2.42 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$, 25 °C): $\delta = 188.0$, 168.3, 154.8, 152.8, 146.0, 140.6, 134.5, 129.8, 128.7, 126.1, 125.1, 121.9, 119.6, 118.4, 116.2, 61.3, 55.9, 50.0, 50.0, 45.5, 39.9, 21.7, 17.7; IR (KBr): $\tilde{\nu} = 3365$, 1680, 1660, 1610, 1595, 1565, 1525, 1455, 1375 $cm^{-1}$; UV/Vis ($CHCl_3$): $\lambda_{max}$ ($\varepsilon$) = 483 (1400), 326 (12200), 265 (14400), 242 nm (18200); HR-FAB-MS: calcd for $C_{25}H_{21}BrN_3O_4S_2$ [$M+H^+$]: 570.0157, found: 570.0171.


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