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HYPERVALENT IODINE OXIDATION OF *O*-SILYLATED PHENOL DERIVATIVES TO AZACARBOCYCLIC SPIRODIENONES; SYNTHETIC APPROACH TO THE ANTICANCER MARINE ALKALOID, DISCORHABDIN C

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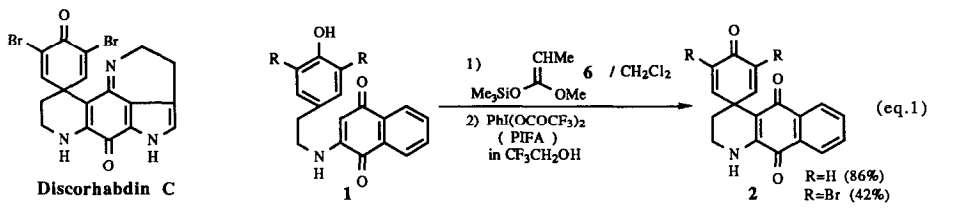
Summary: Hypervalent iodine oxidation of *O*-silylated phenols bearing various types of aminoquinones at the *p*-position in 2,2,2-trifluoroethanol gave azacarbocyclic spirodienones in good yields and application of this reaction to the synthetic approach to discorhabdin C was also described.

Discorhabdin C, isolated as the active cytotoxic principle from the sponge *Latrunculia* du Bocage, exhibits extreme toxicity toward tumor cells (P388 and L1210 leukemia)[1] and has a unique molecular skeleton, pyrrolo[1,7]phenanthroline nucleus incorporating azacarbocyclic spirodienone system. Recently, much attention has been paid for the total synthesis of this challenging target.[2] As part of our continuous studies on hypervalent iodine chemistry,[3] we have reported a general route to the azacarbocyclic spirodienones (**2**) incorporating benzoquinone moiety from *O*-silylated phenol derivatives (**1**) by using phenyliodine(III) bis(trifluoroacetate) (PIFA) as exemplified in eq 1.[2a] We now report a general synthesis of azacarbocyclic spirodienone systems from *O*-silylated phenol derivatives (**3a-f**) bearing both electron-poor and electron-rich aminoquinones at the *p*-position and could apply this spiroannulation to an efficient synthesis of the significant intermediate for discorhabdin C.

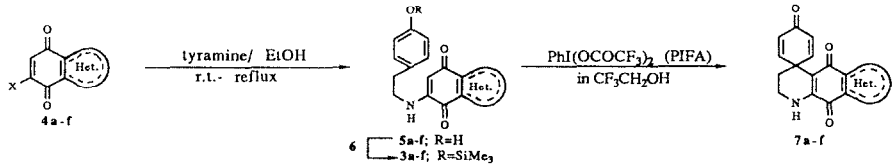
The starting *O*-silylated phenol derivatives (**3a-f**) were readily prepared[4] by the reaction of tyramine with the corresponding quinone derivatives (**4a-f**) followed by the treatment of the resulted *p*-substituted phenols (**5a-f**) with *O*-silylated ketene acetal (**6**)[5] in CH_2Cl_2 under nitrogen in 51-86% overall yields.

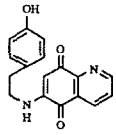
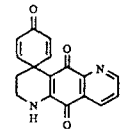
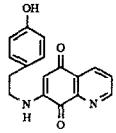
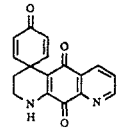
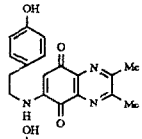
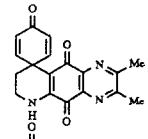
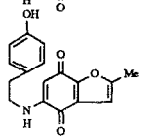
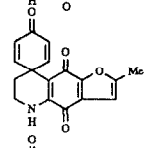
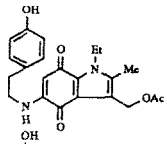
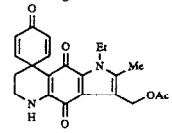
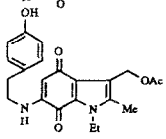
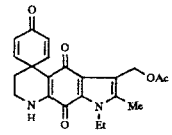


(eq.1)

Hypervalent iodine oxidation of **3** in CF_3CH_2OH gave good yields of the azacarbocyclic spirodienones (**7**). A typical experimental procedure is illustrated in the reaction of **3a** with PIFA. A solution of **3a**, obtained from the phenol (**5a**) and **6** in CH_2Cl_2 at room temperature for 30 min under nitrogen, was treated with PIFA in CF_3CH_2OH at room temperature for 10 min under nitrogen. Usual work-up and purification by column chromatography gave pure **7a** in 51% overall yield from **5a** (run 1). Other phenol derivatives (**5b-f**) bearing electron-poor (runs 2 and 3) and electron-rich quinones (runs 4-6) at the *p*-position similarly reacted with **6** and were subsequently treated with PIFA to give the corresponding azacarbocyclic spirodienones (**7b-f**). The results are listed in Table I.

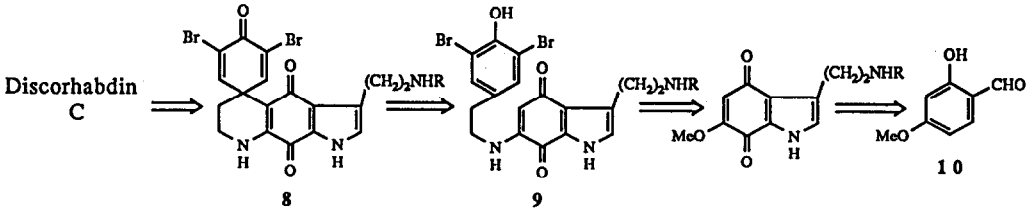
Table I. Synthesis of Azacarbocyclic Spirodienones



Run	Substrate		Conditions	Product		Yield (%)
1		**5a**	r.t., 10 min		**7a**	51
2		**5b**	r.t., 10 min		**7b**	63
3		**5c**	r.t., 10 min		**7c**	57
4		**5d**	r.t., 10 min		**7d**	53
5		**5e**	r.t., 15 min		**7e**	71
6		**5f**	r.t., 15 min		**7f**	86

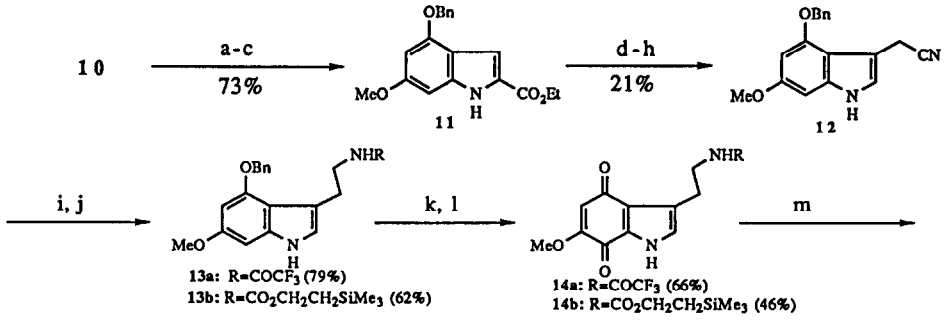
Finally, our attention was focused on the total synthesis of discorhabdin C. Given the success of the model study (run 6),[6] our approach to discorhabdin C required the indoloquinone intermediate (**8**), which might be obtained from *O*-silylated phenol derivative (**9**) by the hypervalent iodine oxidation with PIFA. A reasonable starting material for the synthesis of **9** is 4-methoxysalicyl aldehyde (**10**). Our synthetic strategy is shown in Scheme 1.

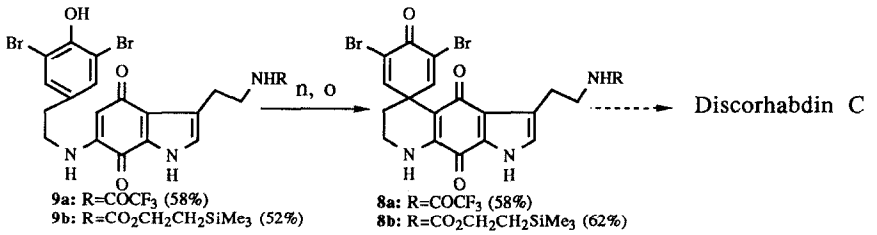
Scheme 1. Retrosynthesis of Discorhabdin C



Benzylation of **10** followed by condensation with ethyl azidoacetate in ethanolic sodium ethoxide gave the vinyl azide, which was decomposed in boiling xylene to give the 2-ethoxycarbonylindole (**11**).[7] Hydrolysis of the ester group of **11** and subsequent decarboxylation under thermal condition gave the 2-unsubstituted indole. Treatment of the indole with dimethyl(methylene)ammonium iodide[8] gave the 3-(dimethylamino)methyl derivative. The dimethylamino group was replaced by cyano group with NaCN via the quarternary salt to give the 3-cyanomethylindole (**12**). Catalytic hydrogenation of the cyano group followed by protection of the resulted amino group afforded **13a,b**. Debenzylation of **13a,b** followed by oxidation with the Fremy's salt gave the corresponding quinones (**14a,b**). Treatment of **14a,b** with 2,6-dibromotyramine gave the phenol derivatives (**9a,b**). Silylation of **9a,b** with **6** followed by oxidation with PIFA gave the desired intermediates (**8a,b**). Final cyclodehydration of **8a,b** towards discorhabdin C under deprotecting conditions is in progress. All new compounds were characterized by microanalyses and IR and NMR spectral data.

Scheme 2. Synthetic Approach to Discorhabdin C





Reagents a: $C_6H_5CH_2Br$/ K_2CO_3/ EtOH/ reflux. b: $N_3CH_2CO_2Et$/ NaOEt/ EtOH/ -15°C. c: xylene/ reflux. d: KOH/ EtOH/ reflux. e: Cu-chromite/ quinoline/ 215°C. f: $CH_2=N^+(CH_3)_2I^-/CH_2Cl_2$/ r.t. g: CH_3I/ 0°C. h: NaCN/ H_2O/ 80°C. i: H_2/ Raney Ni/ NH_3/ EtOH/ 3.3 atm. j: CF_3COSEt/ NaOMe/ MeOH/ 0°C; $O_2NC_6H_4OCO_2(CH_2)_2SiMe_3$/ NaOEt/ EtOH/ 0°C. k: H_2/ 10% Pd-C/ EtOH/ 3.3 atm. l: Fremy's salt/ KH_2PO_4/ acetone-H_2O. m: 2, 6-dibromotyramine/ EtOH/ reflux. n: **6**/ CH_2Cl_2/ r.t. o: $PhI(OCOCF_3)_2$ (PIFA)/ CF_3CH_2OH/ r.t.

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4) Details of the preparation of *O*-silylated phenol derivatives (**3a-f** and **9a,b**) will be published in a full paper.

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6) This work was presented at the 109th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April, 1989.

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