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A SYNTHETIC APPROACH TO DISCORHABDIN ALKALOIDS: HYPERVALENT IODINE OXIDATION OF p-SUBSTITUTED PHENOL DERIVATIVES TO AZACARBOCYCLIC SPIRODIENONES

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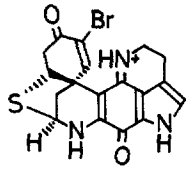
Summary: Hypervalent iodine oxidation of O-silylated p-substituted phenols by phenyliodosyl bis(trifluoroacetate) (PIFA) in 2,2,2-trifluoroethanol gave azacarbocyclic spirodienones in good yields.

Discorhabdins A-C (1-3) have been isolated as the major pigments from three sponge species of the genus Latrunculia du Bocage from New Zealand.[1] Discorhabdin A (1) has also been isolated independently from an Okinawan marine sponge Prianos melanos (named prianosin A)[2] and discorhabdin D (4) has been isolated from a Japanese sponge of the genus Prianos.[3] These discorhabdins (1-4) are strongly cytotoxic and antimicrobial, and have a new ring system, pyrrolo[1,7]phenanthroline with a spirocyclohexadienone or related spiro system. Their highly fused structures and the strong biological activities have proven to be challenging targets for organic synthesis. Although intramolecular spirocyclization of phenols to carbocyclic dienones by aryl participations of a neighboring phenoxy group,[4a] decomposition of phenolic diazoketones,[4b,c] oxidative phenol couplings,[4d] or phenoxy-enoxy radical couplings,[4e] have been well documented, effective synthesis of azacarbocyclic spirodienone systems is quite rare.[4c] We recently described a general route to p-benzoquinone monoacetals and spirolactones from p-substituted phenols by the hypervalent iodine reagent, phenyliodosyl bis(trifluoroacetate) (PIFA)[5] and now apply this method to an effective synthesis of the azacarbocyclic spirodienone, which is a significant system in discorhabdin alkaloids.

First, oxidative cyclization of the p-substituted phenol (5) prepared by condensation of tyramine and 2-methoxy-1,4-naphthoquinone in ethanol was examined with PIFA. The reaction of 5 and PIFA at room temperature (r.t.) for 10 min in CH_3CN in the presence of pyridine gave a spirodienone (6) in low yield (32%). In order to control the two reactive groups, phenolic OH and aminoquinone groups, we examined the oxidation of 5 after protection of OH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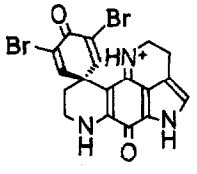
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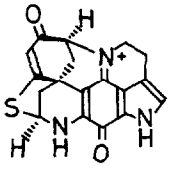
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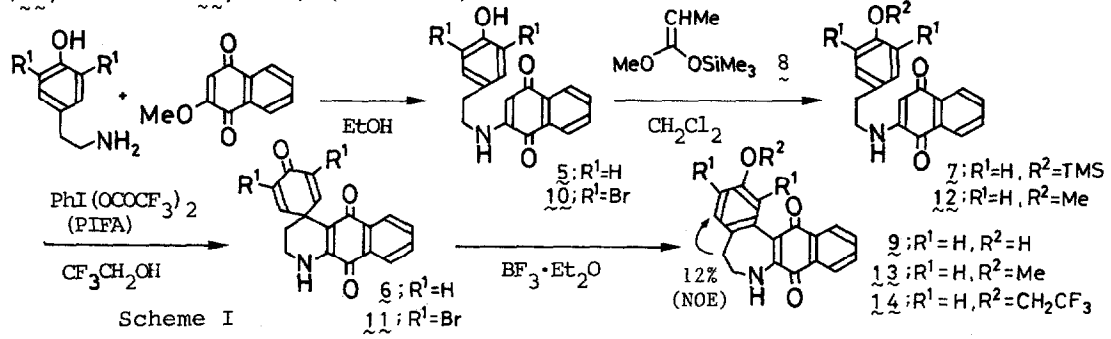
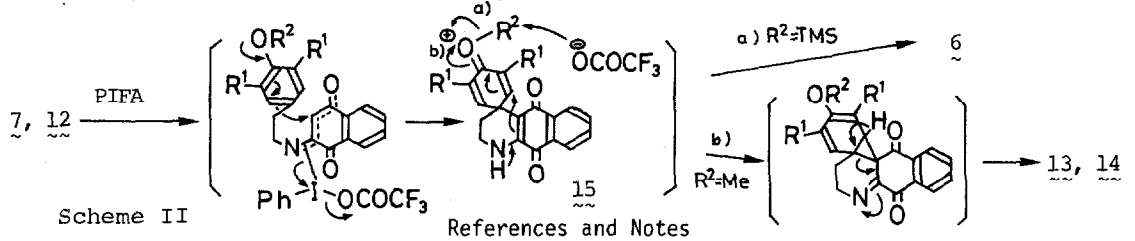
group. Compound (5) was treated with O-silylated ketene acetal (8)[6] in CH_2Cl_2 at 50°C for 5h under nitrogen to give 7 in a quantitative yield. The oxidation of 7 was performed with 1 eq. of PIFA in CF_3CH_2OH at r.t. for 15 min under nitrogen to give crude 6, which was purified by column chromatography to give pure 6[7] in 86% yield from 5. Treatment of 6 with $BF_3 \cdot Et_2O$ gave a phenol (9) via a dienone-phenol (D-P) rearrangement.[8] Similarly, silylation of dibromophenol (10) with 8 followed by oxidation with PIFA gave the spiro-dienone (11)[9] in 42% yield from 10. Oxidation of O-methyl ether (12) with PIFA under the same conditions gave a mixture of 6 (31%) and the D-P rearrangement products (13, 24% and 14, 29%) (Scheme I).



Scheme I

From these results, the reaction presumably proceeds with an initial formation of ipso-displacement intermediate (15). When R^2 is TMS, O-R^2 bond cleavage occurs readily to give 6. On the other hand, when R^2 is Me, O-R^2 bond cleavage is more difficult and the D-P rearrangement takes place competely to give 13 and 14 as shown in Scheme II. Synthetic approach to the discorhabdin alkaloids using the present novel efficient spirocyclization is in progress.



Scheme II

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7) 6: mp 268-270°C; IR ν 3375, 1670, 1660, 1650, 1615, 1595, 1560 cm^{-1}. NMR δ (CDCl3): 1.8-2.1 (m, 2H), 3.4-3.7 (m, 2H), 6.35 (d, 2H, J=10 Hz), 6.91 (d, 2H, J=10 Hz), 7.5-7.7 (m, 2H), 7.9-8.1 (m, 2H).
8) The result of NOE experiments on the O-acetate of 9 is in good accord with its structure.
9) 11: dp 244-245°C, IR 3340, 1670,1595, 1560 cm^{-1}.

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