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THE PREPARATION OF THE AZA-SPIROBICYCLIC SYSTEM OF DISCORHABDIN C *VIA* AN INTRAMOLECULAR PHENOLATE ALKYLATION

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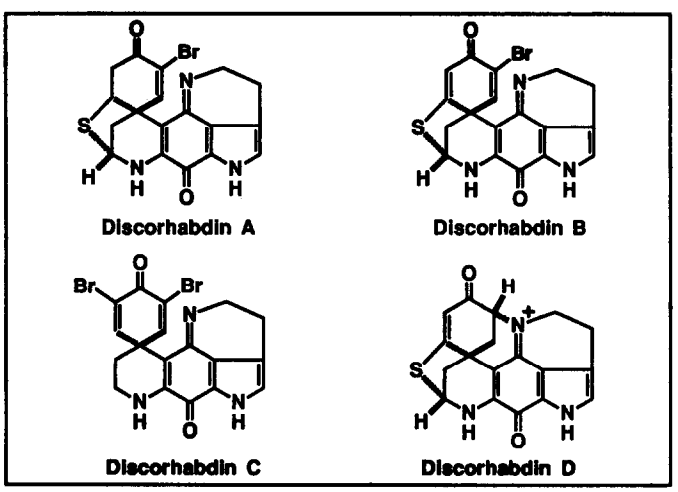
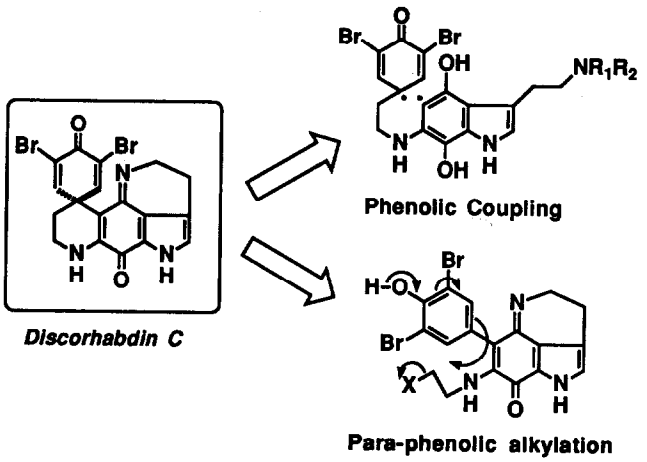
Abstract: *A model study designed for the synthesis of the discorhabdin alkaloids is presented. The key reaction is the intramolecular para-phenolate alkylation of the mesyloxy aminonaphthoquinone 10 to afford the target tetracyclic system 11.*

The discorhabdin alkaloids A-D were discovered by Perry and co-workers during bioassay-directed screenings of New Zealand marine invertebrates for antiviral and antitumor activities.[1] Some of the most cytotoxic extracts were found in the green and brown sponges of the genus *Latrunculia* du Bocage.



Discorhabdin C was the first of the discorhabdin alkaloids to be reported and is toxic to tumor cells (P388 leukemia) with an ED_{50} of 0.03 μg/mL, *in vitro*.[2] This novel molecule contains a unique molecular skeleton incorporating the first example of the pyrrolo[1,7]phenanthrolone nucleus in a naturally occurring system. These potent biological activities observed in compounds of relative inaccessibility render this class of materials attractive targets for total synthesis. We report herein a model study directed toward the preparation of the key spirobicyclic system characteristic of the discorhabdins.

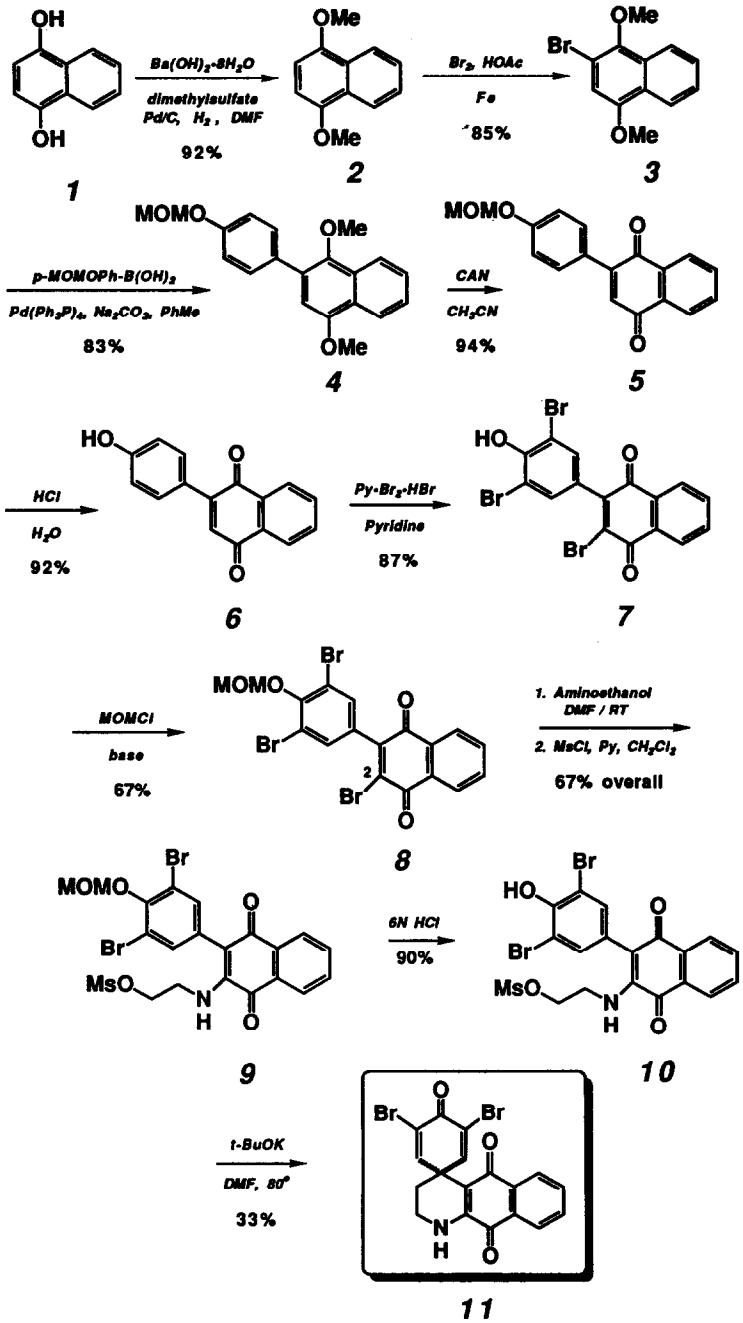
Retrosynthetic considerations revealed several approaches involving either oxidative phenolic coupling[3] or intramolecular phenolate alkylation[4] as key sequences.

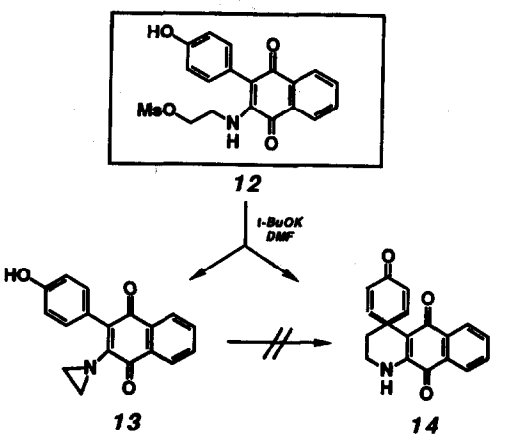


A recent disclosure by Kita[5] describing the former approach employing hypervalent iodine oxidation of O-silylated p-substituted phenols has prompted this report which utilizes the latter approach. Our synthesis begins with 1,4-dihydroxynapthalene (1) which is dimethylated under reducing conditions to avoid quinone formation to afford the dimethoxy derivative (2). Bromination of 2 in the presence of iron affords 2-bromo-1,4-dimethoxynapthalene[6] (3) which undergoes a Suzuki coupling[7] to p-(methoxymethyloxy)- phenylboronic acid[8] to yield the 2-aryl-1,4-dimethoxynapthalene 4 which is then oxidatively demethylated with ceric ammonium nitrate in acetonitrile.[9] The resulting napthoquinone 5, obtained in 94% yield, is deprotected (aqueous HCl/THF), and the resulting phenol 6 is treated with pyridinium bromide perbromide (3.5 eq, O°->rt) in pyridine to yield the desired tribromophenol 7. Addition-elimination of the 2-bromo substituent by nitrogen nucleophiles did not occur on the free phenol 7. However, after reprotection as its MOM ether 8, a ready conversion to the amino mesylate 9 is achieved by treatment with ethanolamine in dimethylforamide followed by mesyl chloride in pyridine. Deprotection of 9 yields the desired mesyloxy phenol 10, the key substrate for the spirocyclization reaction. Finally, treatment of 10 with potassium t-butoxide in DMF at 120°C affords the desired spirocyclic product 11 in 34% yield.

Interestingly, when the desbromo analog 12 is treated under identical conditions, the corresponding spirobicyclic compound 14 is the minor product. In this case, the phenolic aziridine 13 predominates. Although in principle the aziridine 13 might be an intermediate en route to the desired product; in practice, subjection of pure 13 to the reaction conditions for extended times did not afford a trace of the spirocycle 14. This stability of the aziridine toward spirocyclization presumably reflects a lack of favorable displacement trajectories for the phenolate nucleophile, a problem not present in the mesylate precursor.

Scheme


OH
OH
1
Ba(OH)2·8H2O
dimethylsulfate
Pd/C, H2, DMF
92%
OMe
OMe
2
Br2, HOAc
Fe
~85%
OMe
Br
OMe
3
p-MOMOPh-B(OH)2
Pd(Ph3P)4, Na2CO3, PhMe
83%
MOMO
OMe
OMe
4
CAN
CH3CN
94%
MOMO
O
O
5
HCl
H2O
92%
HO
O
O
6
Py·Br2·HBr
Pyridine
87%
Br
HO
Br
O
Br
O
7
MOMCl
base
67%
Br
MOMO
Br
O
2
Br
O
8
1. Aminoethanol
DMF / RT
2. MsCl, Py, CH2Cl2
67% overall
Br
MOMO
Br
MsO
N
H
O
O
9
6N HCl
90%
Br
HO
Br
MsO
N
H
O
O
10
t-BuOK
DMF, 80°
33%
O
Br
Br
O
N
H
O
11



With this model study successfully completed, efforts to employ the approach of para-phenolic alkylation to the total synthesis of the discorhabdins is currently in progress and will be reported in due course.

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2. See reference 1f: Although Discorhabdin C was active *in vitro*, it exhibited no activity when tested *in vivo*. Discorhabdin C was toxic to mice at *ca* 2 mg/kg of body weight. Discorhabdin C also exhibited antimicrobial activity.

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8. p-(Methoxymethyloxy)phenyl boronic acid was prepared by the method of Thompson (see ref. 7b); m.p. 152-153°C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.38(3H,s), 5.21(2H,s), 7.00(2H,d,J=9.5), 7.78(2H,d,J=8.5), 7.59(2H,br s); ^{13}C NMR (75.4MHz, DMSO-d_6) 55.50, 93.59, 114.96, 135.68, 158.44)

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