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SYNTHETIC STUDIES ON NOVEL SULFUR-CONTAINING ALKALOIDS, PRIANOSINS AND DISCORHABDINS: TOTAL SYNTHESIS OF DISCORHABDIN C

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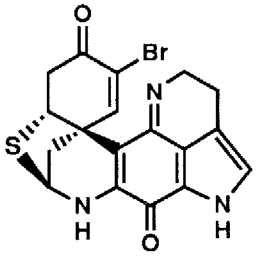
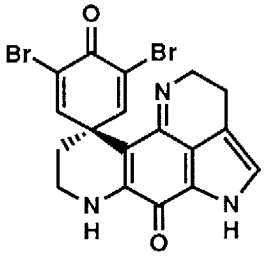
The first total synthesis of discorhabdin C, related to the cytotoxic sulfur-containing alkaloids prianosins and discorhabdins is described The crucial phenolic oxidation of the appropriate phenol carrying no protective group was achieved by electrochemical methodology.

Sulfur-containing alkaloids, prianosins[1] and discorhabdins[2] isolated from the marine sponges *Prianos melanos* and *Latrunculia* du Bocage have highly fused ring structures consisting of pyrro[1,7]phenanthroline and spirodienone moieties, which exhibit potent antineoplastic activities The novel structures and physiological properties of these natural products have prompted us to initiate their syntheses. In the preceding paper,[3] we reported the successful biomimetic synthesis of the spirodienone which was constructed by phenolic oxidations of the corresponding phenol using electrochemical methodology or thallium (III) salts We disclose herein total synthesis of the highly cytotoxic discorhabdin C (**1**), the major pigment of the sponge *Latrunculia* du Bocage.[2a,b] To the best of our knowledge, this is the first synthesis of a member of the prianosin family, although several groups have reported synthetic approaches to these natural products [4]

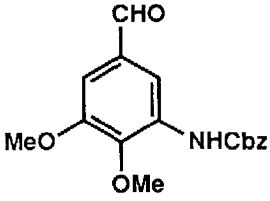


Prianosin A (Discorhabdin A)



Discorhabdin C (1)

The carbobenzyloxy (Cbz) derivative (**2**)[5] was prepared from 3,4-dimethoxy-5-nitrobenzaldehyde using essentially the same procedure as previously described[3] [1 Fe / refluxing HCl - MeOH; 2. CbzCl, Na_2CO_3 (67% in two steps)]. Transformation of **2** to **3**[5] was achieved in four steps [1 Jones oxid.; 2. Imd_2CO / THF, room temp., then NaN_3, 3 refluxing in toluene, 30 min, 4. $TMSCH_2CH_2OH$, 60 °C] in 81% overall yield Selective removal of the Cbz group in **3**, followed by N-benzylation [1. H_2, 10% Pd-C (100%); 2. PhCHO, AcOH, 3 $NaBH_3CN$ / CH_3CN, 50 → 60 °C (81% in two steps)] afforded **4**[5], which was then reacted with



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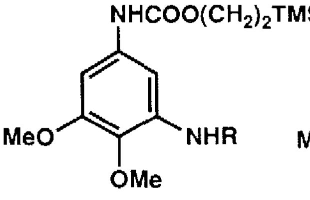
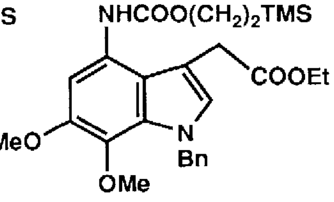


3 R = Cbz
4 R = Bn



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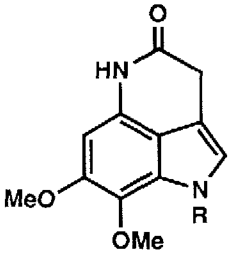
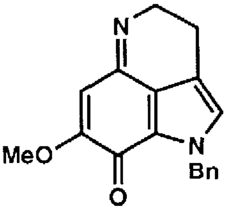


6 R = Bn
11 R = H



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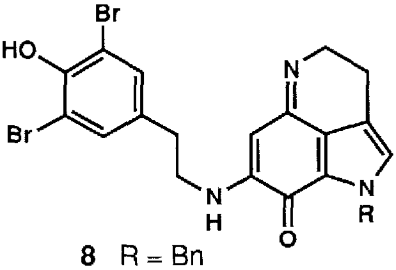
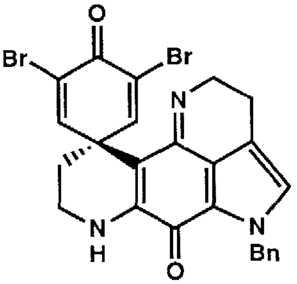


8 R = Bn
12 R = H



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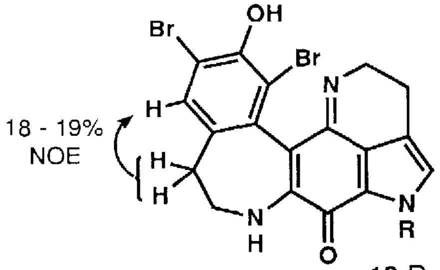
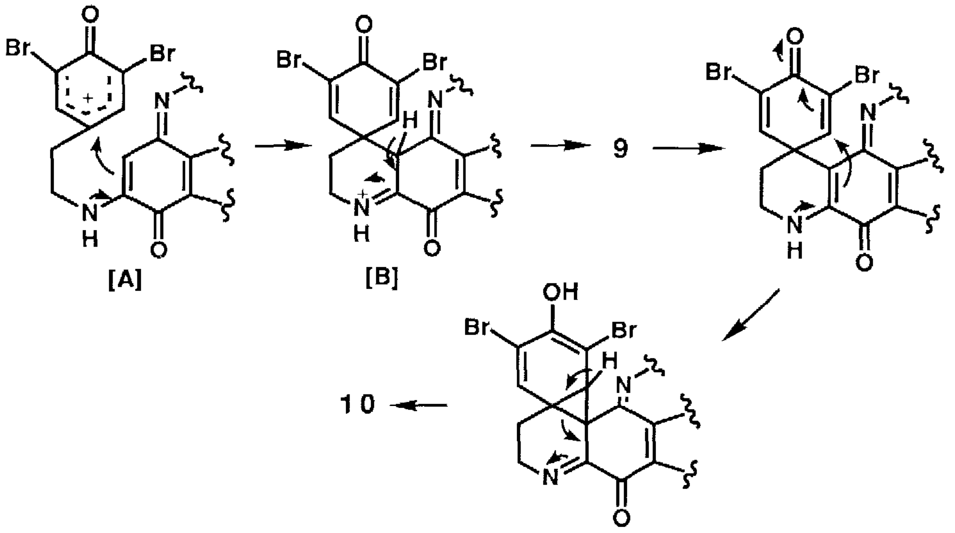


10 R = Bn
13 R = H

ethyl chloroacetoacetate in refluxing EtOH to give the indole (**5**)[5] in 85% yield. Considering the instability of the bisbromodienone moiety in **5**, particularly in basic conditions, we chose to construct the iminodienone skeleton before the phenolic oxidation. Thus, **5** was subjected to stepwise deprotection, followed by lactam formation[6] [1. ^{n}Bu$_4$NF / THF, room temp. (75%); 2. KOH / aq.MeOH, then neutralized with HCl; 3. DCC / THF, overnight (42% in two steps)] to provide a lactam (**6**)[7]. Reduction of **6** with $BH_3 \cdot Me_2S$ (THF, room temp.) gave the corresponding amine, which on CAN oxidation in 60% aq.CH_3CN yielded a rather unstable iminodienone (**7**)[7] in 50% overall yield. Coupling of **7** with 3,5-dibromotyramine hydrobromide in the presence of $NaHCO_3$ in EtOH provided the phenolic product (**8**)[7] in 78% yield. Anodic oxidation of **8** at a constant current [3 mA (+1700 → 1800 mV *vs* SCE)][8] in CH_3CN in the presence of $LiClO_4$ under an argon atmosphere yielded N-benzyl discorhabdin C (**9**)[7] and the ring expanded product (**10**)[7] in 19 and 9.2% yields, respectively. In the reaction mechanism, the two electron oxidation effected a cationic intermediate [A],



followed by cyclization to **[B]**, which on proton abstraction provided **9**, however, this condition might cause an undesirable ring expansion to a sterically delivered phenol (**10**).[9] Unfortunately in the last step, all efforts[10] made to remove the benzyl protective group in **9** were unsuccessful To circumvent such a difficulty, anodic oxidation was attempted without any protective group, as follows.

According to this synthetic plan, **5** was converted to the lactam (**11**)[7] in three steps [1. H_2, Pd black / AcOH - $HClO_4$, 2. KOH / aq.MeOH, then neutralized with HCl, 3 DCC / THF (36% in three steps)] Compound **11** was then subjected to essentially the same procedure as described above to afford **12** in 38% overall yield. Upon anodic oxidation of **12** [3 mA (+1200 → 1800 mV *vs* SCE)][8] the target discorhabdin C (**1**) was obtained in 24% yield together with the ring-expanded product (**13**)[7,9] in 6.2% yield. The synthetic product (**1**) was superimposable with an authentic sample in all respects of the spectral data

On the basis of these results, synthetic studies on other congeners containing sulfur atom are in progress.

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2) a) N. B. Perry, J. W. Blunt, J. D. McCombs, and M. H. G. Munro, *J. Org. Chem.*, **51**, 5478 (1986); b) J. W. Blunt, V. L. Calder, G. D. Fenwick, R. J. Lake, J. D. Mccombs, M. H. G. Munro, and N. B. Perry, *J. Nat. Prod.*, **50**, 290 (1987); c) N. B. Perry, J. W. Blunt, and M. H. G. Munro, *Tetrahedron*, **44**, 1727 (1988), d) N. B. Perry, J. W. Blunt, M. H. G. Munro, T. Higa, and R. Sasaki, *J. Org. Chem.*, **53**, 4127 (1988).

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4) Synthetic efforts by other groups: Y. Kita, T. Yakura, H. Tohma, K. Kikuchi, and Y. Tamura, *Tetrahedron Lett.*, **30**, 1119 (1989); P. N. Confalone, *J. Heterocyc. Chem.*, **27**, 31 (1990); G. G. Kublak and P. N. Confalone, *Tetrahedron Lett.*, **31**, 3845 (1990).

5) **2**: $C_{17}H_{17}NO_5$ [m/z 315.1138 (M^+)]; mp 97 - 98 °C (hexane - EtOAc); IR (nujol): 1735, 1695, 1595, and 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.92 (3H, s), 3.95 (3H, s), 5.23 (2H, s), 7.20 (1H, d, J= 2 Hz), 8.34 (1H, d, J= 2 Hz),), and 9.88 (1H, s). **3**: $C_{22}H_{30}N_2O_6Si$ [m/z 446.1862 (M^+)]; IR (film): 1725, 1610, and 1535 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.05 (9H, s), 1.01 (2H, complex), 3.79 (3H, s), 3.86 (3H, s), 4.20 (2H, complex), 5.19 (2H, s), 7.25 (1H, d, J= 3 Hz), and 7.48 (1H, d, J= 3 Hz). **4**: $C_{21}H_{30}N_2O_4Si$ [m/z 402.1991 (M^+)]; IR (film): 1705, 1610, and 1520 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.04 (9H, s), 1.00 (2H, complex), 3.77 (3H, s), 3.83 (3H, s), 4.20 (2H, complex), 4.30 (2H, s), 6.16 (1H, d, J= 2 Hz), and 6.62 (1H, d, J= 2 Hz). **5**: $C_{27}H_{36}N_2O_6Si$ [m/z 512.2347 (M^+)]; IR (film): 1720, 1620, and 1520 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.06 (9H, s), 1.10 (2H, complex), 1.27 (3H, t, J= 7 Hz), 3.61 (3H, s), 3.73 (2H, s), 3.90 (3H, s), 4.0 - 4.3 (4H, complex), 5.50 (2H, s), and 6.80 (1H, s).

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7) **6**: $C_{19}H_{18}N_2O_3$ [m/z 322.1319 (M^+)]; IR (film): 1665, 1645, 1615, and 1520 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.67 (3H, s), 3.87 (3H, s), 3.95 (2H, d, J= 2Hz), 5.46 (2H, s), 6.16 (1H, s), and 6.61 (1H, t, J= 2 Hz). **7**: IR (film): 1655, 1610, 1565, and 1545 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.71 (2H, t, J= 8 Hz), 3.82 (3H, s), 4.13 (2H, t, J= 8 Hz), 5.47 (2H, s), 6.08 (1H, s), and 6.72 (1H, s). **8**: $C_{25}H_{21}N_3O_2{}^{79}Br^{81}Br$ [m/z 553 (M^+)]; IR (film): 1665, 1620, 1595, and 1545 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.88 (2H, t, J= 7.2 Hz), 2.97 (2H, t, J= 7.6 Hz), 3.58 (2H, t, J= 7.2 Hz), 3.87 (2H, t, J= 7.6 Hz), 5.42 (1H, s), 5.53 (1H, s), 7.32 (1H, s), and 7.40 (2H,s). **9**: $C_{25}H_{19}N_3O_2{}^{79}Br^{81}Br$ [m/z 552.9816 (M^+)]; IR (film): 3370, 1650, 1565, and 1530 cm^{-1}; ^1H NMR (CD_3OD): δ 2.03 (2H, t, J= 5.6 Hz), 2.72 (2H, t, J= 7.6 Hz), 3.63 (2H, t, J= 5.6 Hz), 3.86 (2H, t, J= 7.6 Hz), 5.53 (2H, s), 7.16 (1H, broad s), 7.33 (5H, complex), and 7.71 (2H, s). **10**: $C_{25}H_{19}N_3O_2{}^{79}Br^{81}Br$ [m/z 551 (M^+)]; IR (film): 3300, 1655, 1595, and 1535 cm^{-1}; ^1H NMR (CD_3OD): δ 2.83 (2H, t, J= 6.7 Hz), 2.86 (2H, t, J= 7.6 Hz), 3.99 (2H, t, J= 7.6 Hz), 4.12 (2H, t, J= 6.7 Hz), 5.49 (2H, s), 7.16 (1H, s), and 7.36 (1H, s). **11**: $C_{12}H_{12}N_2O_3$ [m/z 232.0842 (M^+)]; IR (film): 1640, 1620, and 1525 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.91 (3H, s), 3.95 (3H, s), 3.99 (2H, t, J= 1.8 Hz), 6.18 (1H, s), 6.79 (1H, d, J= 1.8 Hz), 7.77 (1H, broad s), and 8.23 (1H, broad s). **12**: IR (film): 3300, 1665, 1620, 1595, and 1545 cm^{-1}; ^1H NMR (CD_3OD): δ 2.90 (2H, t, J= 7.1 Hz), 3.00 (2H, t, J= 7.3 Hz), 3.60 (2H, t, J= 7.1 Hz), 3.90 (2H, t, J= 7.3 Hz), 5.43 (1H, s), 7.20 (1H, s), and 7.42 (2H,s). **13**: $C_{18}H_{13}N_3O_2{}^{79}Br^{81}Br$ [m/z 463 (M^+)]; IR (film): 3300, 1660, 1620, 1590, and 1540 cm^{-1}; ^1H NMR (CD_3OD): δ 2.93 (2H, t, J= 6.8 Hz), 3.00 (2H, t, J= 7.6 Hz), 3.98 (2H, t, J= 7.6 Hz), 4.25 (2H, t, J= 6.8 Hz), 7.19 (1H, s), and 7.39 (1H,s).

8) Anodic oxidation was carried out using a 30 ml glassy carbon beaker as the anode and a platinum wire as the cathode respectively, and stopped at ca. 2 F/mol.

9) The structure was unambiguously determined by NOE experiment.

10) H_2, Pd-C or Pd-black or $Pd(OH)_2$ / MeOH or AcOH-$HClO_4$. Hydrogen transfer conditions (Pd-black - HCOOH or cyclohexene under refluxing temp.). DDQ / CH_2Cl_2 - H_2O.

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