CHEMISTRY LETTERS, pp. 1591-1594, 1990.

Synthetic Studies on Novel Sulfur-Containing Alkaloids, Prianosins Isolated from the Marine Sponge *Prianos melanos.* Synthesis of the Spirodienone Moiety by Phenolic Oxidation

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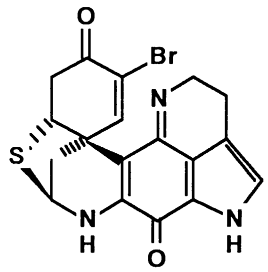
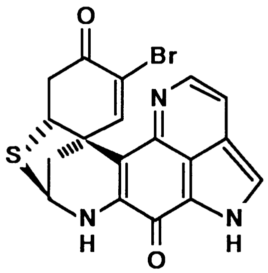
In connection with sulfur-containing alkaloids, prianosins, a spiro derivative has been synthesized by phenolic oxidation of a phenol precursor with thallium (III) oxidation or electrochemical oxidation media.

Marine natural products have offered challenging targets to synthetic chemists for their complicated structures exhibiting remarkable biological activities. Among them, a family of derivatives carrying spiro moiety has been quite attractive to us from view points of biomimetic phenolic oxidations using thallium (III) salts [thallium trinitrate (TTN) or thallium trifluoroacetate (TTFA)] or anodic oxidation.$^{1)}$ Along our research direction, we have planned synthesis of prianosins A, B, C,and D, isolated by Kobayashi et al. from the marine sponge *Prianos melanos.*$^{2)}$ Closely related natural products, discorhabdins A (= prianosin A), B, C and D were also isolated by Munro et al. from *Latrunculia* du Bocage and *Prianos melanos.*$^{3)}$ In these natural products, a pyrro-1,7-phenanthroline and a spirodienone constitute a highly fused ring system exhibiting a potent antineoplastic activity. Although several synthetic groups have reported their efforts toward total synthesis of prianosins or dicorhabdins,$^{4)}$ we have independently started synthesis of these natural products involving above-mentioned phenolic oxidation. We describe herein our research process.



Prianosin A



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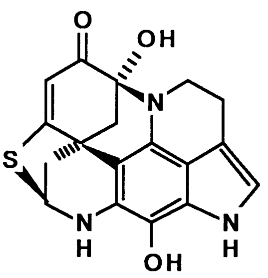

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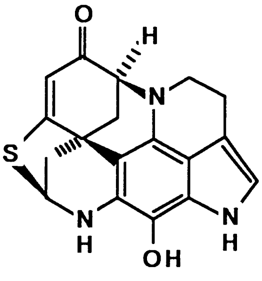
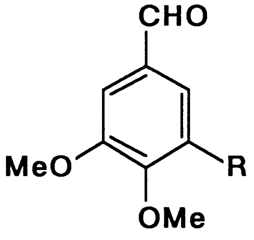


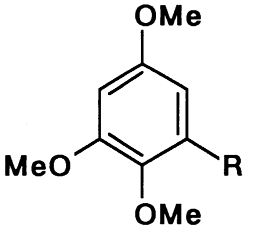
Prianosin D

When the known nitrobenzaldehyde (1)$^{5)}$ was subjected to selective reduction (Fe - concd HCl / refluxing MeOH) followed by benzoylation (BzCl - pyr.), the corresponding benzamide (2)$^{6)}$ was obtained in 88% yield. Upon Baeyer - Villiger oxidation, 2 was converted into a formyl derivative, which was treated with MeI - K_2CO_3 in MeOH to yield directly a methyl ether (3)$^{6)}$ in 78% yield from 2. Conversion of the benzoyl group in 3 to a benzyl group was undertaken with BH_3-SMe_2 in THF at refluxing temperature to give 4$^{6)}$ in 98% yield. Reaction of 4 with ethyl chloroacetoacetate in EtOH at refluxing temperature provided an indole (5)$^{6)}$ in 80% yield. This compound (5) was then transformed into an azide (6)$^{6)}$ in three steps (1. $LiAlH_4$ /

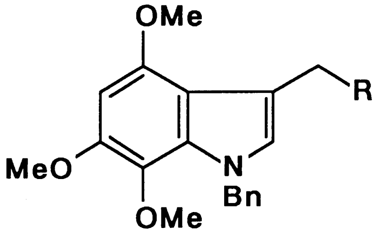
THF, room temp, quantitative; 2. MsCl - Et_3N / CH_2Cl_2, 0 °C; 3. NaN_3 / DMF, 60 °C, 99% in two steps). Oxidation of **6** with CAN in 50% aq. CH_3CN effected a quinone formation to **7**6) in 68% yield. Reaction of **7** with 3,5-dibromotyrosine hydrobromide in the presence of $NaHCO_3$ in refluxing EtOH provided a phenol derivative (**8**)6) in 69% yield.



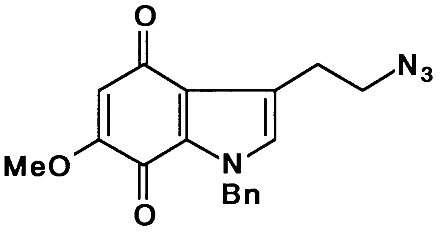
1 R = NO_2
2 R = NHBz



3 R = NHBz
4 R = NHBn



5 R = COOEt
6 R = CH_2N_3



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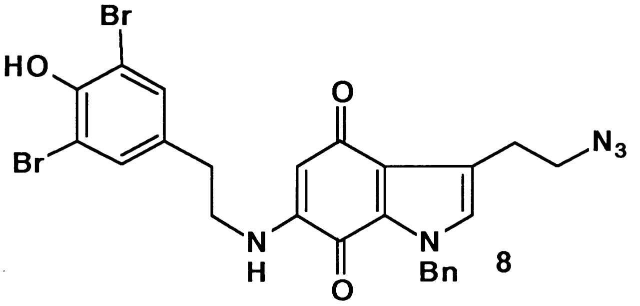

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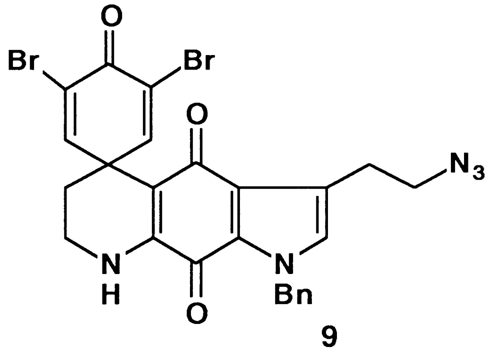

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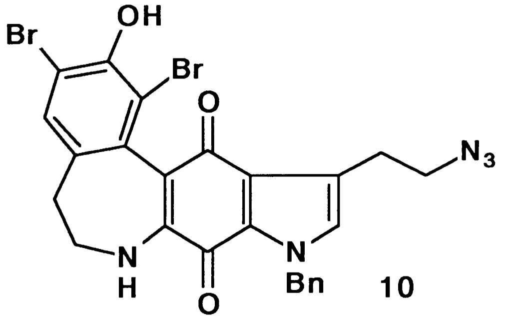

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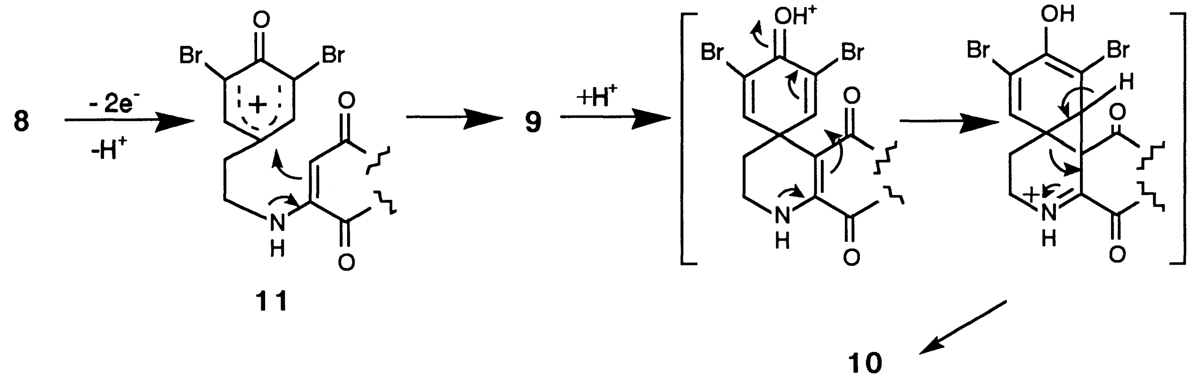
Oxidation of the phenol (**8**) so far obtained was evaluated under such conditions as thallium (III) salts and electrochemical oxidation media, as follows. Compound **8** was converted into a mixture of **9**6) and **10**6) in 24 and 9% yields by anodic oxidation7) at a constant current [7 mA (+1600 → 1700 mV *vs.* SCE)] in MeOH in the presence of $LiClO_4$ as a supporting electrolyte. A similar result was also obtained under TTN oxidation [TTN (2 equiv. mol) / MeOH, 0 °C, 5 h], which afforded a mixture of **9** and **10** in 10 and 28% yields, while TTFA oxidation [TTFA (1 equiv. mol) / CH_2Cl_2, 0 °C → room temp, overnight] provided **10** in 14% yield as only isolable product. Thus, the two electron oxidation might proceed as shown in Scheme 1, via a cation intermediate (**11**) to give **9**, and these acidic conditions might cause an unexpected transformation of **9** into a sterically delivered phenol (**10**).

In conclusion, related to total synthesis of prianosins, the spiro derivative could be synthesized by phenolic oxidation of the corresponding phenol using thallium salts or anodic oxidation. Further synthetic studies on these natural products are still in progress.8)



J.-F. C. thanks the Ministry of Education, Science and Culture as well as the Fujisawa Foundation for their fellowships.

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4) Y. Kita, T. Yakura, H. Tohma, K. Kikuchi, and Y. Tamura, *Tetrahedron Lett.*, **30**, 1119 (1989); P. N. Confalone, *J. Heterocycl. Chem.*, **27**, 31 (1990).

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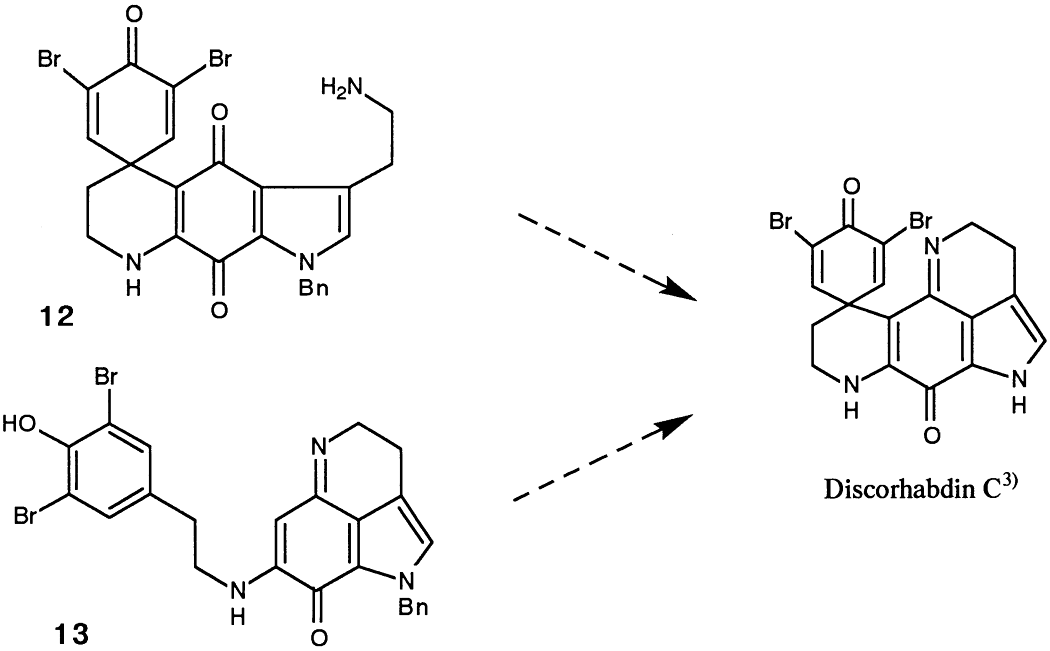
6) **2**: $C_{16}H_{15}NO_4$ [m/z 285.1004 (M^+)]; mp 137 - 138 °C (hexane - EtOAc); IR (KBr): 3450, 1685, 1595, and 1540 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.96 (3H, s), 4.05 (3H, s), 7.31 (1H, d, J= 1.8 Hz), 7.56 (3H, complex), 7.90 (2H, complex), 8.68 (1H, broad s), 8.75 (1H, d, J= 1.8 Hz), and 9.95 (1H, s). **3**: $C_{16}H_{17}NO_4$ [m/z 287.1169 (M^+)]; mp 69 - 71 °C (hexane - EtOAc); IR (KBr): 3450, 1680, 1610, and 1530 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.84 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 6.31 (1H, d, J= 3 Hz), 7.54 (3H, complex), 7.85 (1H, d, J= 3 Hz), 7.89 (2H, complex), and 8.65 (1H, broad s). **4**: $C_{16}H_{19}NO_5$ [m/z 273.1368 (M^+)]; IR (film): 3450, 1610, and 1520 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.70 (3H, s), 3.76 (3H, s), 3.83 (3H, s), 4.33 (2H, s), 4.75 (1H, broad s), 5.86 (1H, d, J= 2.9 Hz), 5.90 (1H, d, J= 2.9 Hz) and 7.35 (5H, complex). **5**: $C_{22}H_{25}NO_4$ [m/z 383.1731 (M^+)]; IR (film): 1730, 1620, and 1510 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (3H, t, J= 6.8 Hz), 3.58 (3H, s), 3.83 (3H, s), 3.84 (2H, d, J= 1 Hz), 3.88 (3H, s), 4.17 (2H, q, J= 6.8 Hz), 5.50 (2H, s), 6.23 (1H, s), 6.79 (1H, s), 7.09 (2H, dd, J= 6.8, 1.5 Hz), and 7.28 (3H, complex). **6**: $C_{20}H_{22}N_4O_3$ [m/z 366 (M^+)]; IR (film): 2950, 2850, 2100, 1620, and 1510 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.09 (2H, t, J= 7.8 Hz), 3.50 (2H, t, J= 7.8 Hz), 3.59 (3H, s), 3.899 (3H, s), 3.902 (3H, s), 5.50 (2H, s), 6.26 (1H, s), 6.70 (1H, s), 7.08 (2H, complex), and 7.25 (3H, complex). **7**: UV (MeOH): λ_{max} 438 (ε 2000), 334 (22000), 287 (30000), and 227 (44000)

nm; IR (film): 2950, 2850, 2100, 1660, 1640, 1600, and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.00 (2H, t, J= 6.8 Hz), 3.53 (2H, t, J= 6.8 Hz), 3.81 (3H, s), 5.51 (2H, s), 5.67 (1H, s), 6.86 (1H, s), 7.25 (2H, complex), and 7.32 (3H, complex). **8**: $C_{25}H_{21}N_5O_3Br_2$ [m/z 597 (M^+)]; IR ($CHCl_3$): 3400, 2100, 1680, 1590, and 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.82 (2H, t, J= 6.8 Hz), 3.02 (2H, t, J= 6.8 Hz), 3.33 (2H, dt, J= 5.4, 6.8 Hz), 3.56 (2H, t, J= 6.8 Hz), 5.26 (1H, s), 5.48 (2H, s), 5.71 (1H, t, J= 5.4 Hz), 5.88 (1H, broad s), 6.85 (1H, s), 7.20 (2H, complex), 7.29 (2H, s), and 7.33 (3H, complex). **9**: $C_{25}H_{19}N_5O_3Br_2$ [m/z 595 (M^+)]; IR ($CHCl_3$): 3360, 2100, 1660, and 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.94 (2H, t, J= 5.9 Hz), 2.96 (2H, t, J= 5.9 Hz), 3.54 (4H, complex), 5.48 (2H, s), 6.19 (1H, broad s), 6.89 (1H, s), 7.36 (2H, s), and 7.19 - 7.37 (5H, complex). **10**: $C_{25}H_{19}N_5O_3Br_2$ [m/z 595 (M^+)]; IR ($CHCl_3$): 3350, 2100, 1660, 1590, and 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.88 (2H, t, J= 5.9 Hz), 3.00 (2H, t, J= 5.9 Hz), 3.56 (2H, t, J= 6.0 Hz), 4.00 (2H, broad t, J= 6.0 Hz), 5.46 (2H, s), 5.99 (1H, broad s), 6.86 (1H, s), 7.30 (2H, s), and 7.19 - 7.35 (5H, complex).

7) As usual, a glassy carbon beaker and a Pt wire were used as an anode and a cathode, respectively.

8) Intramolecular cyclization of an amine (**12**) derived from **9** to the corresponding imine has been up to now unsuccessful, therefore, an alternative approach involving phenolic oxidation of the imine-containing phenol derivative (**13**) is more favorable and also undertaken. These results will be published elsewhere.



12

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Discorhabdin C[3)]

(Received June 18, 1990)