Articles

A Biomimetic Approach to the Discorhabdin Alkaloids: Total Syntheses of Discorhabdins C and E and Dethiadiscorhabdin D

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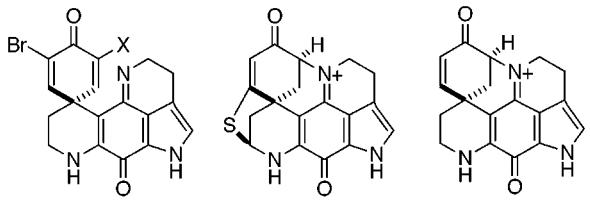
The characteristic spirodienone structure of the discorhabdin alkaloids is readily formed by reaction of the tyramine-substituted indoloquinonimines **26**, **35**, and **36** with cupric chloride, triethylamine, and oxygen. This cyclization provides a possibly biomimetic route to discorhabdins C and E (**41** and **42**). The unbrominated spirodienone **40** reacts with hydrogen over Pd/C to give enone **46**. Bromination at the α position gives a mixture of bromoenones that undergo smooth conversion to dethiadiscorhabdin D (**4**) upon treatment with basic alumina.

The pyrroloquinoline alkaloids known as the discorhabdins[1] are found in the sponges of the genus *Latrunculia* du Bocage along the New Zealand coast. These quinonimine alkaloids are responsible for the pigmentation possessed by the sponges, and many of the compounds in this class, along with the structurally related prianosins,[2] makaluvamines,[3] and epinardins,[4] demonstrate antitumor activity. Because of their cytotoxicity and unusual ring structures, the discorhabdins have attracted the synthetic interest of several groups,[5] two of which have completed total syntheses of discorhabdin C (**1**).[6] In this article, we report a biomimetic approach to the spirodienone core of the discorhabdin alkaloids, resulting in syntheses of discorhabdins C and E (**1** and **2**), and studies directed toward the synthesis of discorhabdin D (**3**), resulting in preparation of the dethia analogue **4**.



Inspection of the discorhabdin structures suggests a biosynthesis from tyrosine and tryptamine, derived from the amino acids phenylalanine and tryptophan, respectively. Indeed, Munro et al. showed that incubation of [U−^{14}C]-L-phenylalanine in tissue slices of *Latrunculia* sp. B produced discorhabdin B with elevated ^{14}C incorporation.[7] But how are these two biogenic amines converted into discorhabdin C and E and eventually into the bizarre structure of discorhabdin D? We believe that the early stages of this transformation might proceed along the lines indicated in Scheme 1. Beginning with an appropriately oxidized and functionalized tryptamine (**6**), coupling of tyramine (**5**) could occur by a Michael addition followed by autoxidation to the quinonimine (**8**). The regiochemistry of the 1,4-addition leading to **7** might be the result of enzymic intervention, or it might result from addition to protonated quinonimine **6**. Autoxidation of *p*-aminophenols to quinonimines is known to be quite facile.[8] Often, only catalytic base and air are needed for such oxidations, but metal ions and other quinones can

(1) (a) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1988**, *44*, 1727. (c) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4127. (d) Blunt, J. W.; Munro, M. H. G.; Battershill, C. N.; Copp, B. R.; McCombs, J. D.; Perry, N. B.; Princep, M.; Thompson, A. M. *New J. Chem.* **1990**, *14*, 761. (e) Copp, B. R.; Fulton, K. F.; Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1994**, *59*, 8233. (f) Yang, A.; Baker, B. J.; Grimwade, J.; Leonard, A.; McClintock, J. B. *J. Nat. Prod.* **1995**, *58*, 1596. (g) Six other discorhabdins were presented at the New Zealand Institute of Chemistry Conference, Auckland, New Zealand, December 7−10, 1993.

(2) (a) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Hirata, Y.; Sasaki, T.; Lu, H.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 4939. (b) Chemg, J.; Ohizumi, Y.; Walchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1988**, *53*, 4621.

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(4) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Tetrahedron* **1996**, *52*, 8899.

(5) (a) Sadanandan, E. V.; Pillai, S. K.; Lakshmikantham, M. V.; Billimoria, A. D.; Culpepper, J. S.; Cava, M. P. *J. Org. Chem.* **1995**, *60*, 1800. (b) Roberts, D.; Joule, J. A.; Bros, M. A.; Alvarez, M. *J. Org. Chem.* **1997**, *62*, 568. (c) White, J. D.; Yager, K. M.; Yakura, T. *J. Am. Chem. Soc.* **1994**, *116*, 1831. (d) Knolker, H. J.; Hartmann, K. *Synlett* **1991**, 428. (e) Kubiak, G. G.; Confalone, P. N. *Tetrahedron Lett.* **1990**, *31*, 3845. (f) Roberts, D.; Alvarez, M.; Joule, J. A. *Tetrahedron Lett.* **1996**, *37*, 1509.

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(7) Lill, R. E.; Major, D. A.; Blunt, J. W.; Munro, M. H. G.; Battershill, C. N.; McLean, M. G.; Baxter, R. L. *J. Nat. Prod.* **1995**, *58*, 306.

(8) (a) James, T. H.; Weissberger, A. *J. Am. Chem. Soc.* **1938**, *60*, 98. (b) James, T. H.; Snell, J. M.; Weissberger, A. *J. Am. Chem. Soc.* **1938**, *60*, 2084. (c) Schneider, F. *Ber.* **1899**, *32*, 689.

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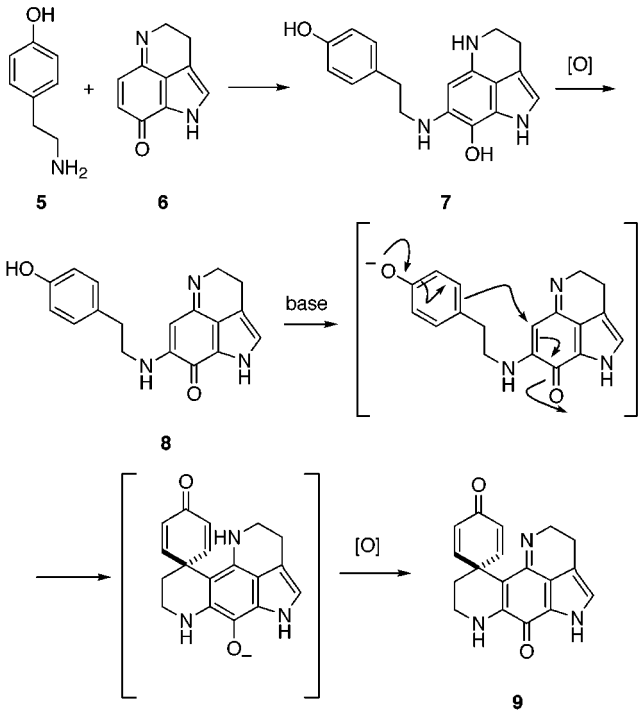
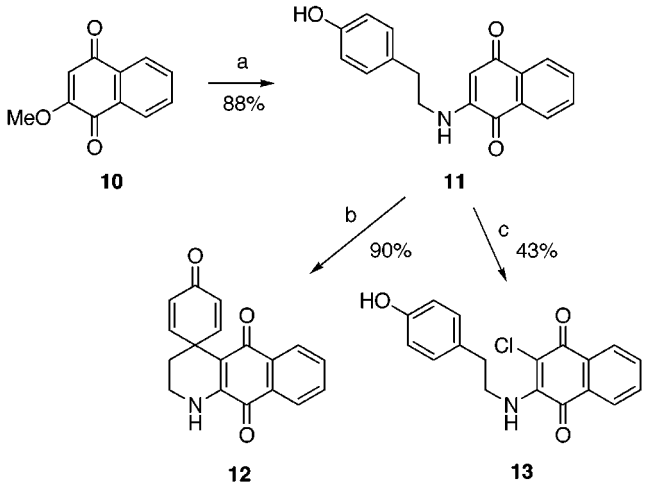
Scheme 1



catalyze the process.[9] Chemical oxidants such as iron(III) chloride, silver(I) oxide, and ceric ammonium nitrate (CAN) are also effective reagents for these transformations.[10] The key reaction in the hypothetical biomimetic process is a second Michael addition, occurring intramolecularly with the phenoxide of the tyramine side chain. This second addition, followed again by oxidation to the quinone, would form the spirodienone portion of the discorhabdin core (**9**).[11]

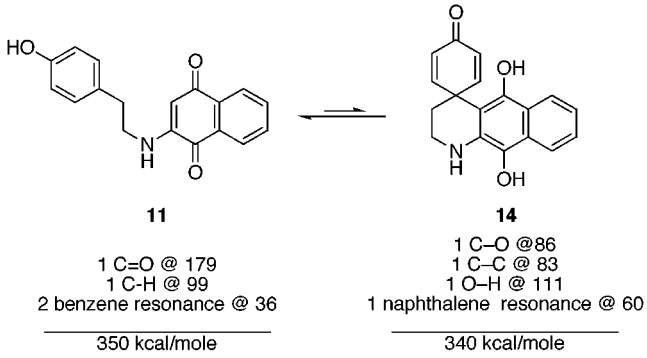
We set out to explore the feasibility of this intramolecular phenoxide Michael addition and autoxidation using aminonaphthoquinone **11** as a model substrate (Scheme 2). Compound **11** was prepared in good yield by reaction of tyramine and 2-methoxynaphthoquinone **10**.[12] Exposure of substrate **11** to various basic conditions, both with and without simultaneous aeration with O_2, resulted in recovered starting material. Conditions evaluated included $NaOCH_3$ in methanol, *tert*-BuOK in *tert*-butyl alcohol, *tert*-BuOK in DMF, K_2CO_3 in DMF, and triethylamine in DMF. However, when **11** was treated with cupric chloride and triethylamine in acetonitrile while the solution was oxygenated, spirodienone **12** was produced in very high yield. A series of control experiments showed that $CuCl_2$, O_2, and Et_3N are all required for effective conversion of **11** to **12**. With Et_3N/O_2 and no $CuCl_2$ only recovered starting material is obtained, and

Scheme 2



a. tyramine, EtOH. b. $CuCl_2 \cdot 2H_2O$, Et_3N, O_2, CH_3CN.
c. $CuCl_2 \cdot 2H_2O$, O_2, CH_3CN.

Scheme 3



with $CuCl_2/O_2$ and no Et_3N, chloroquinone **13** is produced in modest yield.

A possible rationale for these observations is as follows. The Michael addition itself would transform **11** into its isomer **14**. A simple thermodynamic approximation, using typical bond energies,[13] suggests that this isomerization is endothermic by about 10 kcal mol^{-1} (Scheme 3). Oxidation of the hydroquinone moiety of **14** provides a large driving force and makes the overall conversion of **11** to **12** quite exothermic. We think the role of $CuCl_2$ is to catalyze oxidation of **14** to **12**. Copper(II) salts are well-known catalysts for the autoxidation of hydroquinones to quinones, and these processes are implicated in many biogenetic pathways.[14] Another possible mechanistic explanantion is that Cu(II) forms the phenoxy radical, which undergoes cyclization to give a semiquinone that can then be fully oxidized to quinone **12** by air.[15]

(9) (a) LuValle, J. E.; Weissberger, A. *J. Am. Chem. Soc.* **1947**, *69*, 1821. (b) Lamer, V. K.; Temple, W. *Proc. Natl. Acad. Sci.* **1929**, *15*, 191.

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(11) For examples of *p*-phenolate alkylations, see: (a) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 4238. (b) Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1963**, *85*, 567. (c) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1996**, *118*, 2301.

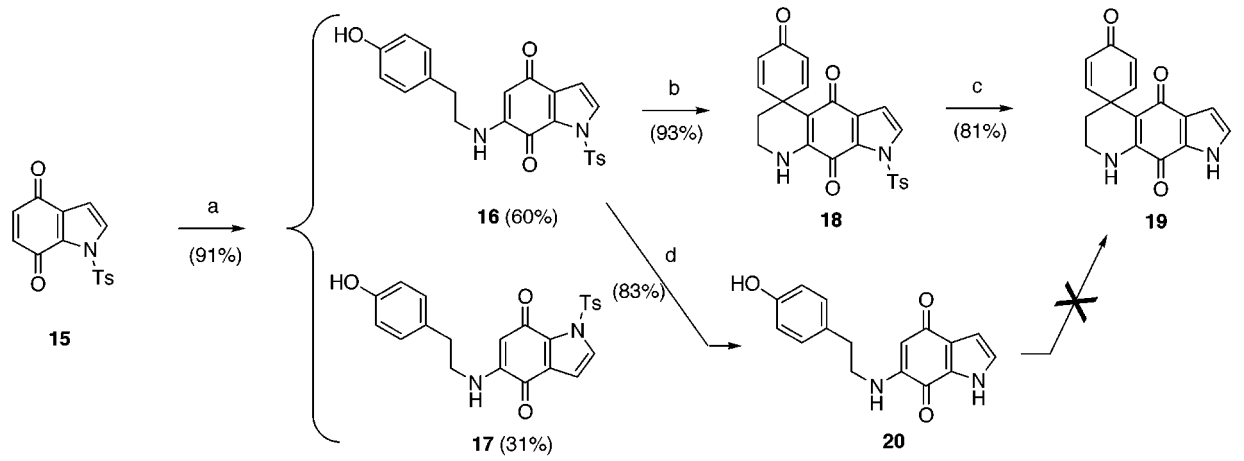
(12) (a) Smith, L. I.; Hoehn, H. H. *J. Am. Chem. Soc.* **1941**, *63*, 1178. (b) *Elsevier's Encyclopedia of Organic Chemistry*; Radt, F., Ed.; Elsevier Publishing Company: New York, 1952; Series III, Vol. 12b, p 3054.

(13) Streitwieser, A.; Heathcock, C. H.; Kosower, E. M. *Introduction to Organic Chemistry*; Macmillian Publishing Company: New York, 1992.

(14) (a) Janes, S. M.; Mu, D.; Wemmer, D.; Smith, A. J.; Kaur, S.; Maltby, D.; Burlingame, A. L.; Klinman, J. P. *Science* **1990**, *248*, 981. (b) Dooley, D. M.; McGuirl, M. A.; Brown, D. E.; Turowski, P. N.; McIntire, W. S.; Knowles, P. F. *Nature* **1991**, *349*, 262. (c) Li, Y.; Trush, M. A. *Arch. Biochem. Biophys.* **1993**, *300*, 346. (d) Duine, J. A.; Jongejan, J. A. In *Bioinorganic Catalysis*; Reedijk, J., Ed.; Marcel Dekker: New York, 1993; pp 447−468.

(15) (a) Walling, *Free Radicals in Solution*; Wiley and Sons: New York, 1957; pp 457−461. (b) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981; pp 369−386.

Scheme 4



a. tyramine, CH_3CN. b. $CuCl_2 \cdot 2H_2O$, Et_3N, O_2, CH_3CN. c. KOH, MeOH. d. NaOMe, MeOH.

To demonstrate that the oxidative cyclization was applicable to substrates other than naphthoquinone **11**, we decided to test these reaction conditions with an indole model system that would resemble the discorhabdins. To this end, 4,7-indoloquinone (**15**) was prepared by known methods[16] from 4,7-dimethoxyindole.[17] Addition of tyramine to quinone **15** under air produced aminoquinones **16** and **17** as a 2:1 mixture of regioisomers, from which **16** was isolated in 60% yield (Scheme 4). As with naphthoquinone **11**, treatment of indoloquinone **16** under basic conditions resulted in only recovered starting material, plus partial loss of the tosyl group in some cases. However, when triethylamine and $CuCl_2 \cdot 2H_2O$ were added to **16** under aerobic conditions, spirodienoneone **18** was isolated in high yield. This cyclization could also be performed on regioisomer **17**, also in good yield (81%). An attempt was made to cyclize deprotected indole **20**, but this attempt resulted in extremely poor mass recovery, perhaps because of strong complexation of copper by the more basic diaminoquinone. Nevertheless, spirodienone **18** can be easily deprotected with sodium methoxide in methanol to provide spiroindoloquinone **19** in 81% yield. The structure of quinone **19** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1), which therefore confirmed the regiochemistry of tyramine adducts **16** and **17**.

The next challenge in the synthesis was to elaborate the model indole system into a synthetically useful tryptamine substrate. Our initial attempts focused on placing an ethylamine side chain at the 3-position of the indole ring. A well-precedented and straightforward approach was to utilize an electrophilic aromatic substitution reaction with oxalyl chloride and an amine.[18] To this end, exposure of 4,7-dimethoxyindole (**21**) to oxalyl chloride followed by dibenzylamine provided the expected

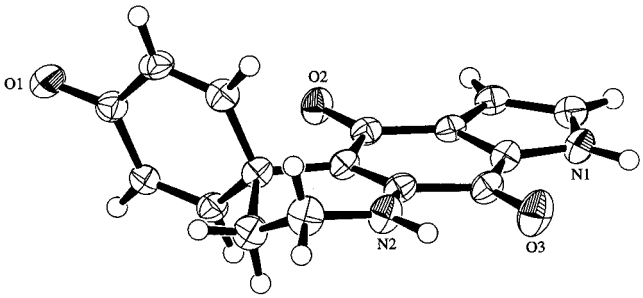


Figure 1. ORTEP representation of the X-ray crystal structure of spirodienone **19**.

ketoamide in 63% yield. Reduction of this compound with $LiAlH_4$ and tosylation of the indole nitrogen gave tryptamine **22** in 84% yield. Ceric ammonium nitrate oxidation[19] of dimethoxyindole **22** resulted in many side reactions, including loss of the ethylamine chain. Therefore, a protecting group swap was performed to improve the oxidation. After dibenzylamine **22** was hydrogenated over $Pd(OH)_2$, the resulting primary amine was protected as the Boc derivative by reaction with di-*tert*-butyl dicarbonate, and the dimethoxyindole was oxidized with ceric ammonium nitrate to obtain quinone **23** in 80% yield. Addition of tyramine in the presence of oxygen to quinone **23** produced a 3:2 mixture of regioisomers (**24a** and **24b**), similiar to the situation that had been observed in the addition of tyramine to quinone **15**. In this case, the isomeric product mixture was inseparable. In addition, all attempts to transform quinones **24** into iminoquinone **26**, after deprotection of the amine, failed. Likewise, all attempts to form iminoquinone **27** prior to tyramine addition also failed (Scheme 5).[20]

Because of these failures, we altered our synthetic plan to include a methoxy group at the site where we want to attach the tyramine unit. Such a compound has, in fact, been employed in previous syntheses of discorhabdin C.[5a−c,6] To this end, it was necessary to redesign the synthesis of our aromatic core. We also wanted to develop

(16) Jackson, Y.; Billimoria, A. D.; Sadanandan, E. V.; Cava, M. P. *J. Org. Chem.* **1995**, *60*, 3543.

(17) Cherif, M.; Cotelle, P.; Catteau, J. P. *Heterocycles* **1992**, *34*, 1749. We discovered discrepancies between the reported characterization data and our data. For full experimental details and full characterization data, please refer to the Supporting Information. For alternate routes to 4,7-dimethoxyindole, see: (a) Rodighiero, G.; Malesani, G.; Fornasiero, U. *Gazz. Chim. Ital.* **1961**, *91*, 742. (b) Rajeswari, S.; Drost, K. J.; Cava, M. P. *Heterocycles* **1992**, *34*, 1749.

(18) Speeter, M. E.; Anthony, W. C. *J. Am. Chem. Soc.* **1954**, *76*, 6208.

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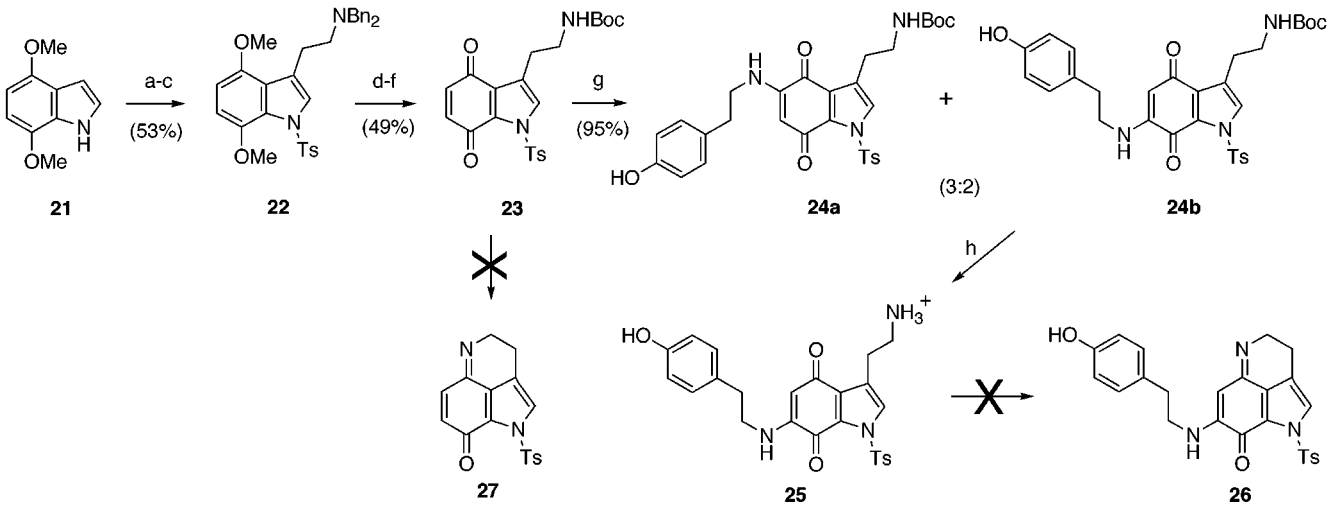
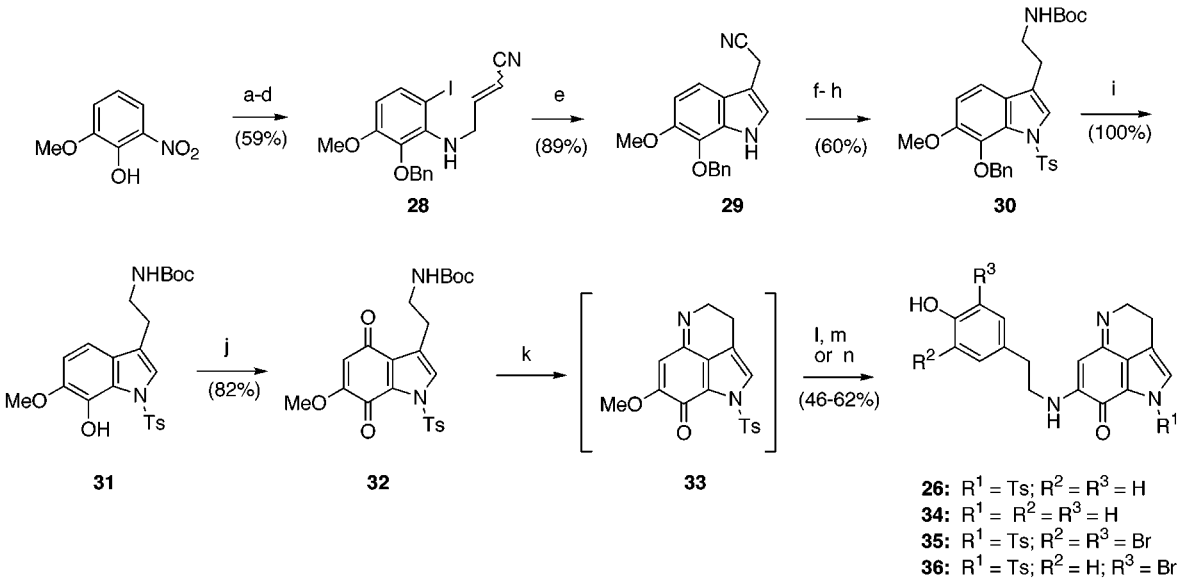
(20) Also, see: Szczepankiewicz, B. G. Ph.D. Thesis, Univerisity of California at Berkeley.

Scheme 5



a. $(COCl)_2$, $HNBn_2$, Et_2O. b. $LiAH_4$, Et_2O. c. NaH, TsCl, THF. d. H_2, $Pd(OH)_2$, EtOH. e. $(Boc)_2O$, CH_2Cl_2. f. ceric ammonium nitrate, CH_3CN, H_2O. g. **5**, O_2, CH_3CN h. CF_3CO_2H.

Scheme 6



a. BnBr, K_2CO_3, DMF. 2. Fe, HCl, H_2O. c. ICl, Et_2O, H_2O, Na_2CO_3. d. $BrCH_2CH{=}CHCN$, $NaHCO_3$, acetone, H_2O. e. 5 mol % $Pd(OAc)_2$, (o-$MeC_6H_4)_3P$, Et_3N, CH_3CN, reflux, 3 h. f. $LiAlH_4$, ether. g. $(Boc)_2O$, CH_2Cl_2. h. Ts_2O, NaH, DMF. i. H_2, Pd/C, MeOH. j. Fremy's salt, acetone/water. k. TFA, CH_2Cl_2. l. $NaHCO_3$, EtOH, tyramine•HCl. m. $NaHCO_3$, EtOH, bromotyramine•HCl. n. $NaHCO_3$, EtOH, dibromotyramine•HCl.

a new tryptamine synthesis that would be general for many possible substitution patterns on the benzene ring. We thought that a palladium(0) coupling such as the Heck reaction[21] might serve our purposes to rapidly establish the indole system with the ethylamine substituent intact. Although palladium-catalyzed indole syntheses are known, at that time there were no corresponding tryptamine syntheses.[22]

2-Nitroguaicol[23] **27** was chosen as our starting material (Scheme 6). Benzylation of the phenolic hydroxy group and reduction of the nitro group gave the corresponding aniline, which undergoes regioselective iodination with ICl to provide the ortho iodo derivative in 72% yield. A small amount of starting material always persists in the iodination reaction, even in the presence of excess ICl. Our next task was to attach a suitable side chain for the Heck cyclization. A convenient alkylating agent for our purpose was bromocrotononitrile, but alkylation of our aniline derivative with this bromide was surprisingly difficult. Conditions that were successful in model studies (NaH or LiHMDS in THF followed by allyl bromide) gave none of the desired product (**28**) when bromocrotononitrile was used as the electrophile. Eventually, the use of

(21) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(22) (a) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. *J. Org. Chem.* **1980**, *45*, 2709. (b) Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *12*, 1037. (c) Wensbo, D.; Annby, U.; Gronowitz, S. *Tetrahedron* **1995**, *51*, 10323. (d) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375. (e) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676. A similiar tryptamine system was reported concurrently with this work in the following: Zhang, H. C.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804.

(23) Thompson, M. J.; Zeegers, P. J. *Tetrahedron* **1990**, *46*, 2661.

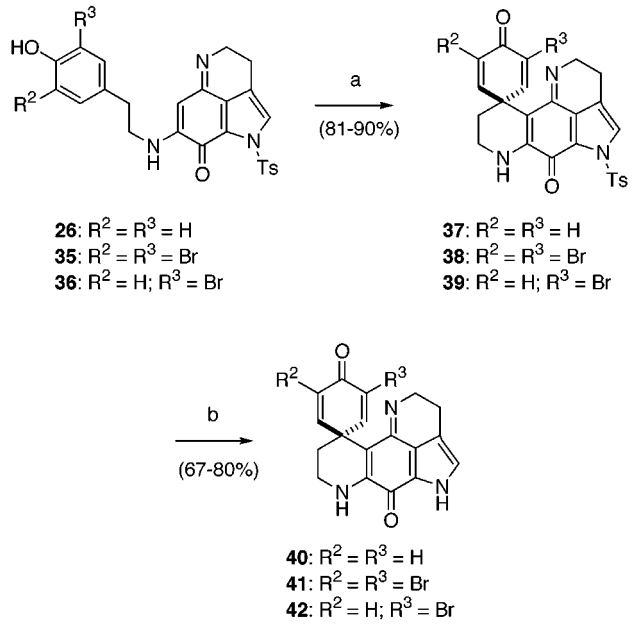
an acetone/water solvent pair in the presence of sodium bicarbonate was found to work very well, giving **28** in 86% yield. When this substrate was exposed to catalytic palladium acetate, tri-*o*-tolylphosphine, and stoichiometric base, indole **29** was smoothly produced in 89% yield. Lithium aluminum hydride reduction of the nitrile followed by treatment with di-*tert*-butyl dicarbonate and tosylation of the indole nitrogen resulted in formation of Boc-protected tryptamine **30**.

The remaining challenge at this point was to find conditions that would oxidize the indole to a *para*-indoloquinone. Hydrogenolysis of the benzyl ether provided phenol **31** uneventfully. Several oxidants, such as ceric ammonium nitrate, $FeCl_3$, and iodobenzene bis(trifluoroacetate), converted **31** into an *ortho*-quinone instead of the desired *para*-indoloquinone. However, freshly prepared Fremy's salt[24] was found to give exclusively *para*-quinone **32** in excellent yield. If previously prepared or commerically available Fremy's salt was used, the yield was greatly diminished. With the formation of quinone **32**, we had converged with a known intermediate used previously in the synthesis of makaluvamine D, which also constituted a formal synthesis of discorhabdin C.[5a] Treatment of **32** with trifluoroacetic acid, followed by tyramine hydrochloride and sodium bicarbonate, provided *N*-tosylmakaluvamine D (**26**) along with a small amount of makaluvamine D (**34**). Similar treatment of **32** with bromotyramine or dibromotyramine provided analogues **35** and **36** in modest but unoptimized yield (46−47%).

The smooth transformation of **32** into **26** upon treatment with tyramine is striking. Because **25** does not undergo closure to **26** (Scheme 5), the mechanism of formation of **26** presumably involves prior formation of **33**, which undergoes addition of tyramine and elimination of methanol, leading to **32**. However, it will be recalled that the amine derived from **23** also resists cyclization to **27** (Scheme 5). Therefore, we have the curious situation that, of three rather similar aminoethyl indoloquinones, the only one that undergoes cyclization to the indoloquinonimine is the one having a methoxy substituent at C-6; when there is a hydrogen or an amino substituent at this position, cyclization does not occur. We do not have a convincing explanation for this behavior.

With phenol **26** in hand, we were ready to attempt the spirocyclization that had been successful in our model studies. However, conditions identical to those that are effective for cyclization of **11** and **16** did not provide any of the desired discorhabdin core (**37**). Instead, extensive decomposition occurred, and no products could be isolated. Since the obvious difference between the model systems and quinone **16** is the additional imine functionality, we presumed that it was responsible for the change in reaction. This type of vinylogous guanidine would be expected to be rather basic and is most likely protonated under neutral conditions. Since each natural product isolated from this family of iminoquinones is reported as a salt, it seemed reasonable that copper ions could form a strong complex with this basic imine. An interaction of this type might limit the copper ion's ability to function oxidatively in the reaction. If so, the use of an excess of copper(II) chloride could still potentially

Scheme 7



a. 3 eq $CuCl_2$, Et_3N, O_2, CH_3CN. b. NaOMe, MeOH

produce the desired spirodienone. Indeed, when phenol **26** was treated with 3 equiv of $CuCl_2$ and 4 equiv of triethylamine, spiroquinone **37** was isolated in 90% yield (Scheme 7). Similar treatment of analogues **35** and **36** gave *N*-tosyldiscorhabdin C (**41**) and *N*-tosyldiscorhabdin E (**42**). The only remaining transformation required to complete the synthesis of the discorhabdin core was removal of the *N*-tosyl group. This was accomplished by treatment of spirodienone **37** with sodium methoxide in methanol, providing **40** in 80% yield. Similar deprotections gave discorhabdin C (**41**) and discorhabdin E (**42**). This deprotection was somewhat inconsistent, and sometimes yields were much lower (20−50%) due to extensive decomposition. In addition, inorganic salts often seemed to contaminate the product, so extra care was necessary to ensure that the product was pure.

With relatively efficient syntheses of discorhabdins C and E in hand, we turned our attention to the most complex member of the discorhabdin family, discorhabdin D (**3**). The unique feature of this alkaloid is the bond between C2 and N18. Our original attempts to create this bond were based on a possible biomimetic route, illustrated in Scheme 8. Reduction of the quinonimine to the *p*-aminophenol anion **43** should occur with ease.[25] Models show that the secondary amine hydrogen in **43** is well positioned for the postulated 1,5-hydride shift, which would convert **43** into enolate **44**, while effectively oxidizing the aminophenol back to the quinonimine oxidation state. The most problematic part of the proposal is the postulated 1,6-addition of the enolate to the nitrogen of the quinonimine, leading to the *p*-aminophenol **45** and creating the crucial C−N bond. However, this speculative step is precedented in a key step in the Steglich synthesis of nectarone.[26]

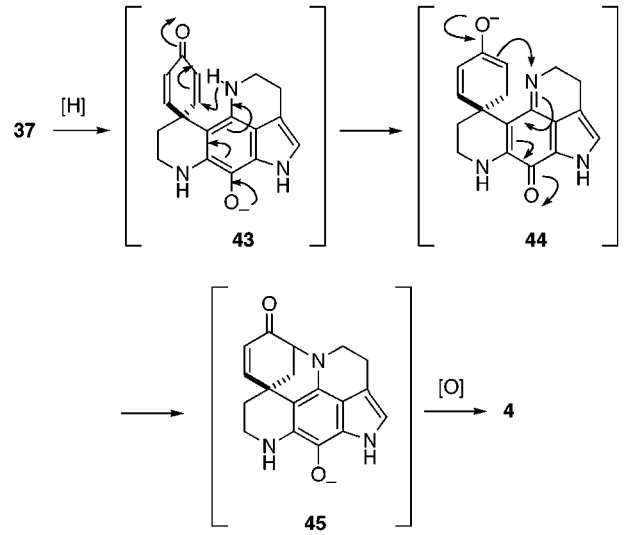
Nevertheless, many attempts to bring this possibly biomimetic plan to fruition were unsuccessful. Many mild

(24) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.

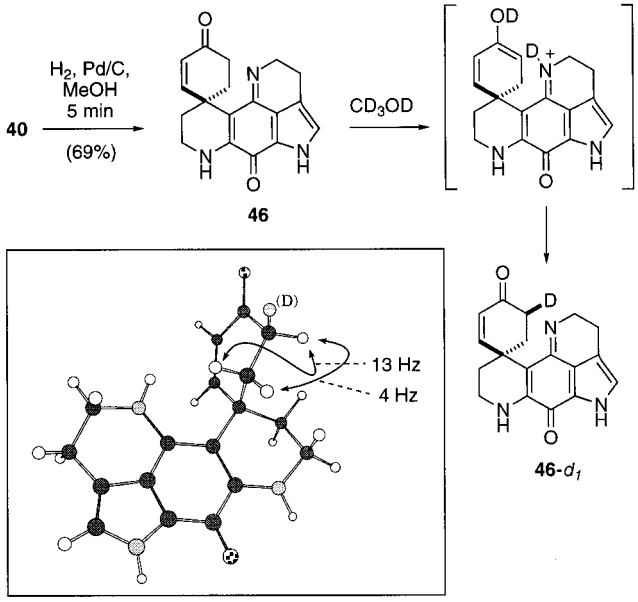
(25) Wölcke, U.; Kaiser, A.; Koch, W.; Scheer, M. *Helv. Chim. Acta* **1970**, *53*, 1704.

(26) Hilger, C. S.; Fugmann, B.; Steglich, W. *Tetrahedron Lett.* **1985**, *26*, 5975.

Scheme 8



Scheme 9



reducing agents quickly reduced iminoquinone **37**, as evidenced by disappearance of the characteristic red color of the indoloquinonimine. These included sodium dithionite, sodium cyanoborohydride, lithium borohydride, H_2 over Wilkinson's catalyst, H_2 over Rh/Al_2O_3, Zn/Ag couple, Mg in methanol, and Al/Hg amalgam. In all cases, either no further reaction occurred and aerobic oxidation regenerated starting quinonimine **37** or prolonged reaction times resulted in decomposition. Reaction with H_2 over Pd/C for 5 min did provide enone **46** in reasonable yield (Scheme 9). However, deuterium labeling studies showed that the reduction was simply a facile Pd-mediated hydrogenation of one of the dienone double bonds rather than the proposed 1,5-hydride shift. The structure of **46** was confirmed by single-crystal X-ray analysis (Figure 2).[27] In solutions of d_4-methanol, ketone **46** cleanly

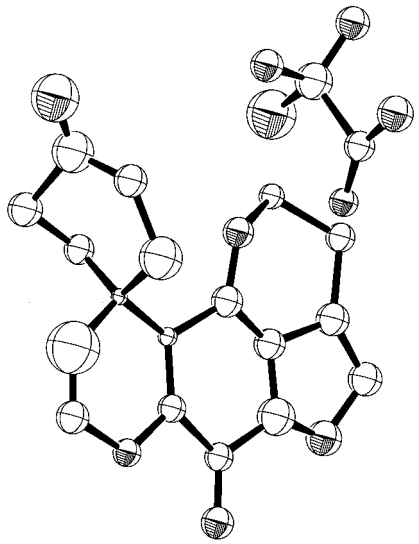


Figure 2. ORTEP representation of the X-ray crystal structure of spiroenone **46** (trifluoroacetate salt).

exchanged one of the C2 hydrogens for deuterium, providing **46**-d_1. The exchange is highly stereoselective, and analysis of the ^{1}H NMR spectrum showed that the remaining C2-hydrogen is a double doublet with geminal coupling constants of 4 and 13 Hz (with additional broadening due to the small vicinal H−D coupling). Thus, the deuterium must be equatorial and the remaining hydrogen axial. Molecular modeling of enone **46** revealed a bias for a conformation, shown in the insert in Scheme 9, such that the C2-hydrogen on the opposite face of the cyclohexenone ring from the imine nitrogen is axial. Thus, the deuterium incorporation results from intramolecular delivery of deuterium from the protonated imine to the enol, as shown in Scheme 9.

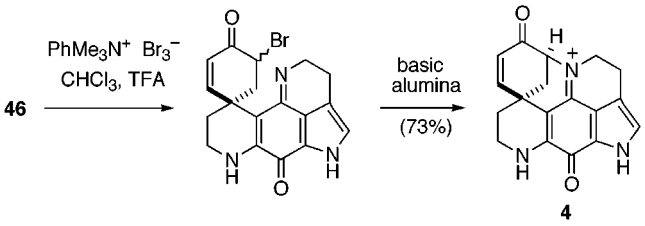
This discovery suggested an attractive alternative for formation of the C2−N18 bond of discorhabdin D—nucleophilic displacement of a C2 bromide by N18. We had previously considered and discarded this approach on the basis of our molecular modeling, which had suggested that a C2 bromide would prefer the equatorial position and therefore be positioned incorrectly for nucleophilic displacement. The deuterium incorporation results caused us to reconsider this approach, since the intramolecular enol protonation would ensure that the bromine atom would be in the correct positon for displacement.[28] To this end, we treated enone **46** with phenyltrimethylammonium tribromide[29] in a mixture of chloroform and trifluoroacetic acid (Scheme 10). The crude product was shown by ^{1}H NMR to be a mixture of bromides, along with some **4**. When this crude mixture was filtered through basic alumina and the filtrate was allowed to stand for 1 h, compound **4** was obtained in good yield. The spectral characteristics of imine **4** are similiar to those reported for discorhabdin D,[1c] with the hydrogen attached to C2 appearing as a triplet at 4.28 ppm with $J = 2.5$ Hz. The analogous proton in discorhabdin D gives rise to a triplet at 4.35 ppm with $J = 2.8$ Hz. Comparison of the ^{13}C NMR spectra shows C2 of **4**

(27) Figure 2 shows fairly large thermal factors for some of the atoms. The molecule is chiral because of the spiro stereocenter. Except for the cyclohexene double bond, the molecule would have a plane of symmtery. Because the CH_2-CH_2 and CH=CH groups are rather similar sterically, both enantiomers can occupy the same sites in the crystal cell, albeit with unequal populations.

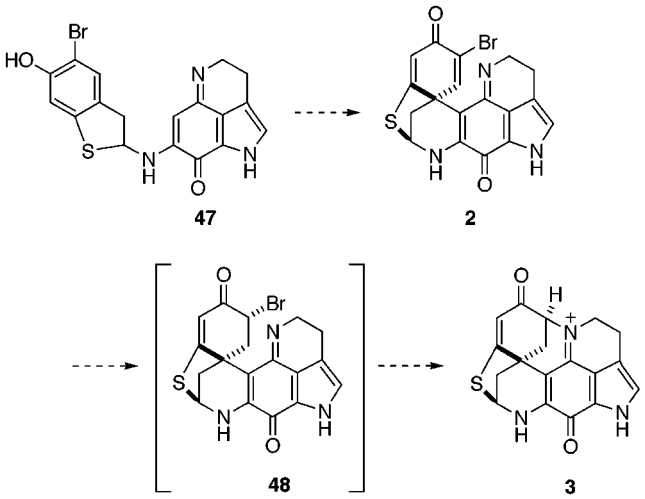
(28) In the conformation depicted in Scheme 9, it appears that an axial bromide is not in a position to undergo nucleophilic displacement by the imine nitrogen. However, another conformation that brings the halogenated carbon into good proximity for displacement appears to be easily available.

(29) Marquet, A.; Jaques, J. *Bull. Chim. Soc. Fr.* **1962**, 90.

Scheme 10



Scheme 11



appearing at 64.5 ppm, while C2 in discorhabdin D appears at 62.3 ppm.[1c] Compound **4** is presumably a trifluoroacetate salt. The nature of the counterion for discorhabdin D has never been reported, but it is probably chloride.

The isolation of compound **4** constitutes the first time this ring system has been successfully prepared by synthesis. To use this approach for the synthesis of discorhabdin D itself, it will be necessary to learn how to incorporate the sulfur atom. Our current working hypothesis (Scheme 11) is that discorhabdin D is biosynthesized by a series of reactions starting with makaluvamine F (**47**),[3a] which undergoes a cyclization similar to that demonstrated in this work to give discorhabdin B (**2**). Reduction of the dienone double bond that bears the bromine atom, perhaps in the manner proposed in Scheme 8 (but not yet demonstrated), would yield the unknown bromo ketone **48**, which would immediately cyclize to give discorhabdin D. Research aimed at duplicating this proposal is currently underway.

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Supporting Information Available: Experimental procedures and spectral data for all compounds and X-ray tables for compound **19** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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