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Enantioselective Total Synthesis and Structure Revision of Spirodihydrobenzofuranlactam 1. Total Synthesis of Stachybotrylactam

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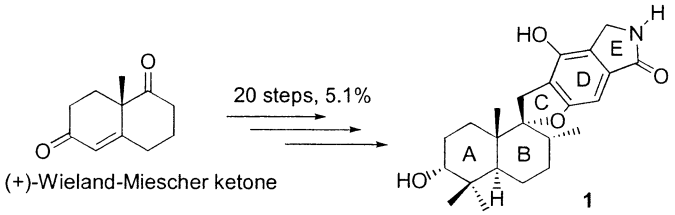
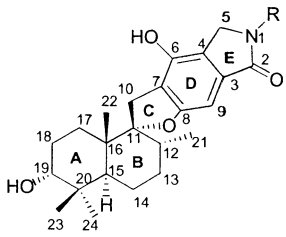
ABSTRACT

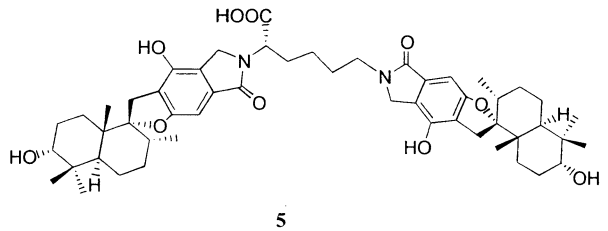


The enantioselective total synthesis and structure revision of spirodihydrobenzofuranlactam 1 and of its regioisomer 25 are presented. Optically pure (+)-Wieland–Miescher ketone was utilized to construct the AB bicyclic core in 10 steps. Introduction of the resorcylate D-ring unit was achieved by use of our *tert*-butyl ester metalation sequence. Subsequent stereoselective spirocyclization to form the C-ring was followed by regioselective ring cyanation and lactam formation to produce the pentacyclic structure 1 and its regioisomer 25.

A series of spirodihydrobenzofuranlactams, active as antagonists of endothelin and as inhibitors of HIV-1 protease, were isolated from the cultures of two different *Stachybotrys* species by Roggo et al. in 1996[1a,b] and assigned structures **1**−**5** on the basis of extensive NMR studies. The pseudosymmetric "dimer" **5** is the most potent representative of this series. These novel spirodihydrobenzofuranlactams were reported to contain the unique axial hydroxyl group at the C-19 position and the benzofuranlactam moiety. Their undetermined absolute configuration as well as their pharmacological activity[1a] encouraged us to develop the first synthetic access to these new compounds. We describe herein an enantioselective total synthesis of structure **1** and its regioisomer **25** as well as their comparisons with natural material.



1 R= H
2 R=$(CH_2)_2OH$
3 R=$(CH_2)_4COOH$
4 R= $CH(COOH)(CH_2)_2COOH$



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Our approach (Scheme 1) commenced with the preparation of the AB ring segment. *trans*-Decalone **6** was prepared by a published procedure[4−6] from enantiopure (+)-Wieland−Miescher ketone. Ketone **6** was then converted to the enol trimethylsilyl ether, which was reacted with methyl iodide and benzyltrimethylammonium fluoride (BTAF)[4] to give the α-methyl derivative **7** in 82% yield. Ketone **7** was treated with hydrazine in ethanol at reflux to afford the hydrazone **8** in 84% yield, followed by treatment with iodine and DBU

(1) (a) Roggo, B. E.; Petersen, F.; Sills, M.; Roesel, J. L.; Moerker, T.; Peter, H. H. *J. Antibiot.* **1996**, *49*, 13. (b) Roggo, B. E.; Hug, P.; Moss, S.; Stämpfli, A.; Kriemler, H.-P.; Peter, H. H. *J. Antibiot.* **1996**, *49*, 374.

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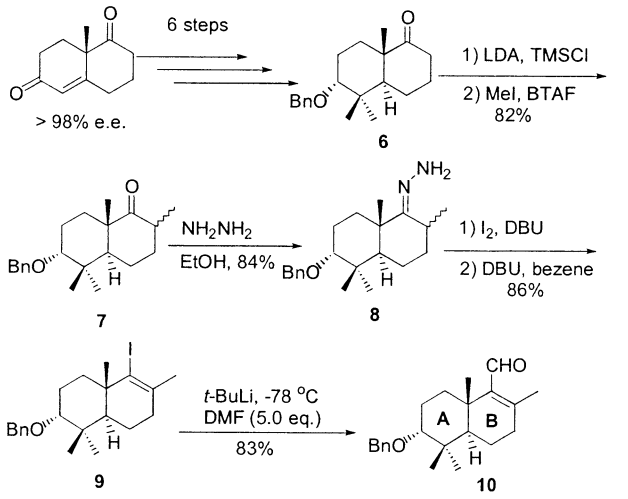
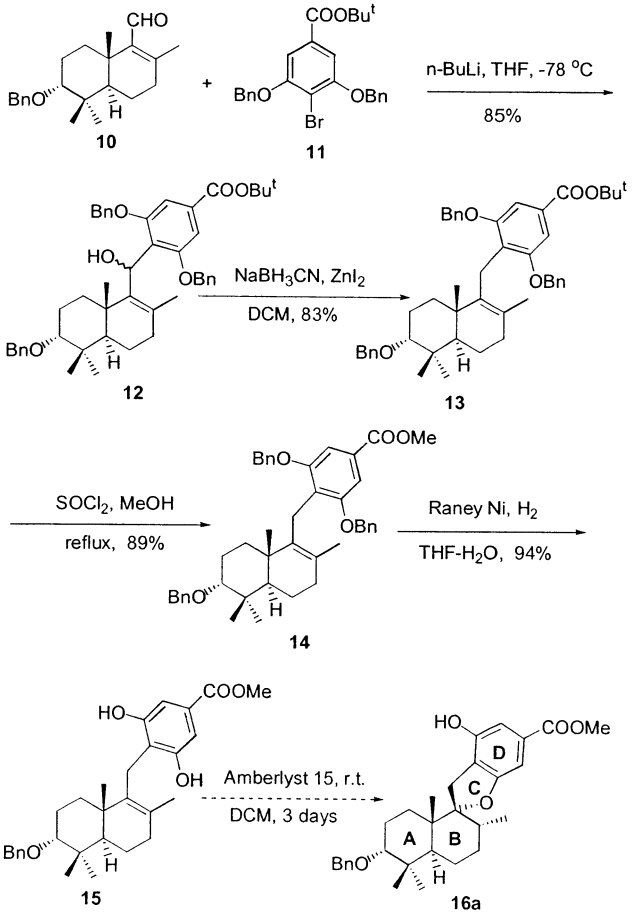
Scheme 1. Construction of AB-Ring Segment **10**



in anhydrous ethyl ether and then with DBU in benzene to produce the vinyl iodide **9** in 86% yield.[7] At this stage, lithiation of **9** was followed by treatment with methyl 4-formyl-3,5-dibenzyloxybenzoate,[3] but no reaction was observed, presumably due to the steric repulsion between the angular methyl and two benzyloxy groups on the benzene ring. Alternatively, a formyl group was installed on the AB ring by treatment of lithiated compound **9** with DMF in THF at −78 °C to furnish the α,β-unsaturated aldehyde **10** in 83% yield.

Bromine−lithium[3] exchange of *tert*-butyl-4-bromo-3,5-dibenzyloxybenzoate **11**[8] in THF at −78 °C, followed by quenching with α,β-unsaturated aldehyde **10**, gave rise to the carbinol **12** (Scheme 2). Removal of the secondary benzylic hydroxyl group to afford compound **13** was achieved using the $NaBH_3CN$ and ZnI_2 system.[9] Subsequent treatment of **13** with thionyl chloride in excess methanol produced the methyl ester **14** in 89% yield. Hydrogenation of compound **14** by employing either 10% Pd/C or $Pd(OH)_2$ resulted in mixtures due to cleavage of one to three benzyl groups and reduction of the alkene. In contrast, Raney nickel[9] selectively removed both benzyl groups on the benzene ring to give compound **15** in 94% yield. Compound **15** was then subjected to acid-catalyzed spiro-heteroannulation. Unfortunately, either no reaction or complicated mixtures were obtained by treatment of compound **15** using Corey's method (THF/ethylene glycol, 2 N HCl),[10] McMurry's method (Amberlyst 15/DCM),[11] or other acidic conditions (TFA/$CHCl_3$; $Hg(OCOCF_3)_2$/THF; PTS/benzene).

Scheme 2. Attempted Spiroannulation of C- and D-Rings

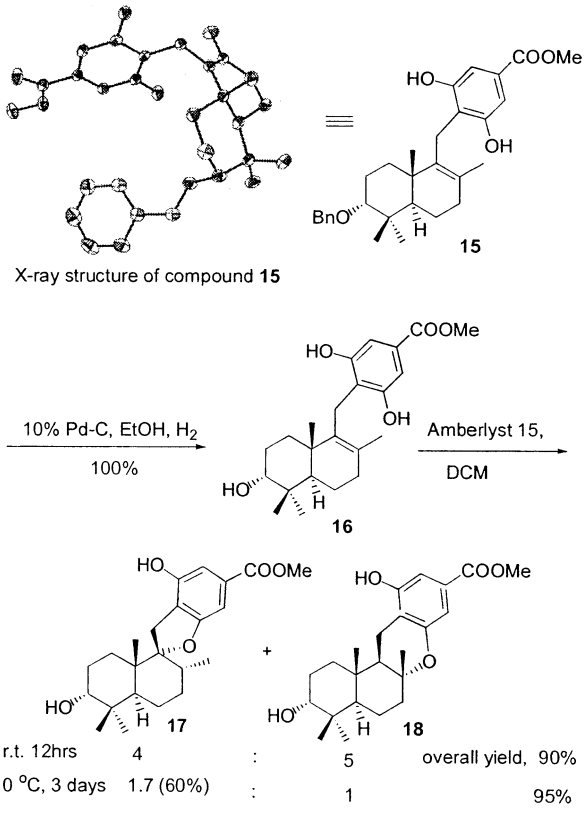


From the X-ray crystal structure of **15** (Scheme 3), two benzylic side chains were found to lie on the same side of the AB-bicyclic core, which indicates possible steric hindrance between these two benzylic side chains upon the spiroannulation. We considered that the "remote" axial benzyloxy group on the A-ring could be a factor in the failed spiroannulation. With this in mind, compound **16** was then prepared in quantitative yield by cleavage of the benzyl group in **15** using 10% Pd/C.

Spiroannulation now proceeded smoothly (Scheme 3) when compound **16** was treated with Amberlyst 15 in dichloromethane at room temperature, giving the chromatographically separable isomers benzofuran **17** and benzopyran **18** in a ratio of 4:5 (90% overall yield). A series of reaction conditions were screened including variation of solvents and temperatures to optimize the reaction. Finally, Amberlyst 15 with dichloromethane as solvent at 0 °C was found to afford benzofuran and benzopyran in a ratio of 1.7:1 (yield of benzofuran 60%), comparable to Corey's[10] and McMurry's[11] results in related systems. Protic solvents and dipolar aprotic solvents gave benzofuran as the major product (up to 3:1), but in low conversion (up to 30%); extension of the reaction time in these solvents led to gradual decomposition without increase of conversion. Control experiments showed the generation of **17** and **18** is irreversible under our optimum reaction conditions.

(2) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 368.
(3) Kende, A. S.; Zhong, M. *Synth. Commun.* **1999**, *29*, 3401.
(4) Smith, A. B., III; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685.
(5) (a) Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1962**, 1091. (b) Shimizu, T.; Hiranuma, S.; Hayashibe, S.; Yoshioka, H. *Synlett* **1991**, 833.
(6) Yusui, K.; Kawada, K.; Kagawa, K.; Tokura, K.; Kitadokoro, K.; Ikenishi, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1698.
(7) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989.
(8) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *41*, 4572.

Scheme 3. Construction of C-Ring

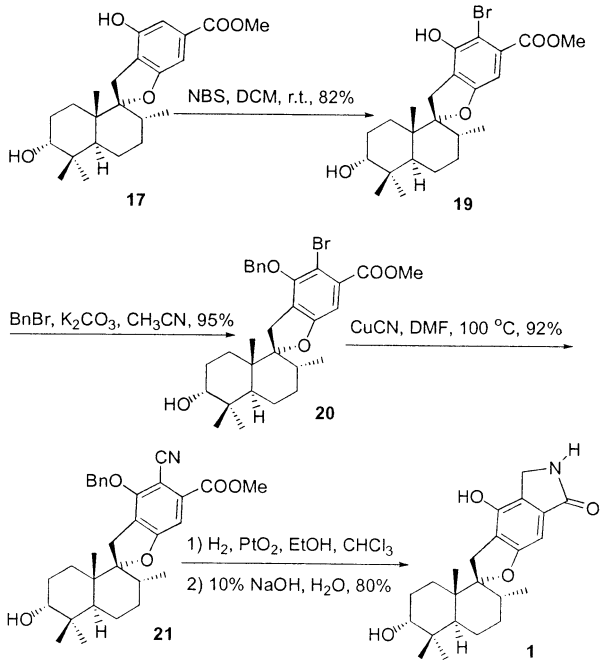


Regioselective aromatic bromination of benzofuran **17** using NBS in dichloromethane provided **19** in 82% yield, together with 5−10% of chromatographically unseparable dibromo compound. The structure of **19** was confirmed by single-crystal X-ray analysis of the derived compound **20**, which was chemoselectively obtained in 95% yield by treatment of **19** with benzyl bromide and K_2CO_3 in acetonitrile. Reaction of bromide **20** with cuprous cyanide (10 equiv) in DMF at 100 °C[10] gave nitrile **21** in 92% yield. Spirodihydrobenzofuranlactam **1** was then obtained in 80% yield by hydrogenation of nitrile **21** using PtO_2/EtOH/$CHCl_3$[12] and subsequent lactamization with base (Scheme 4), and the structure **1** was confirmed by single-crystal X-ray analysis.

To our surprise, the ^1H NMR and ^{13}C NMR spectra of our synthetic compound **1** were not identical to those reported for the natural spirodihydrobenzofuranlactam **1**.[13] A careful reading of the assignment of the structure of natural product **1** reported by Roggo[1b] revealed that they had placed the sole aromatic proton at C-9 based only on the absence of an NOE from that aromatic proton to the methylene protons at C-5 or C-10. Actually, the unique regioisomer **25** also would lack an NOE from that aromatic proton to the methylene protons

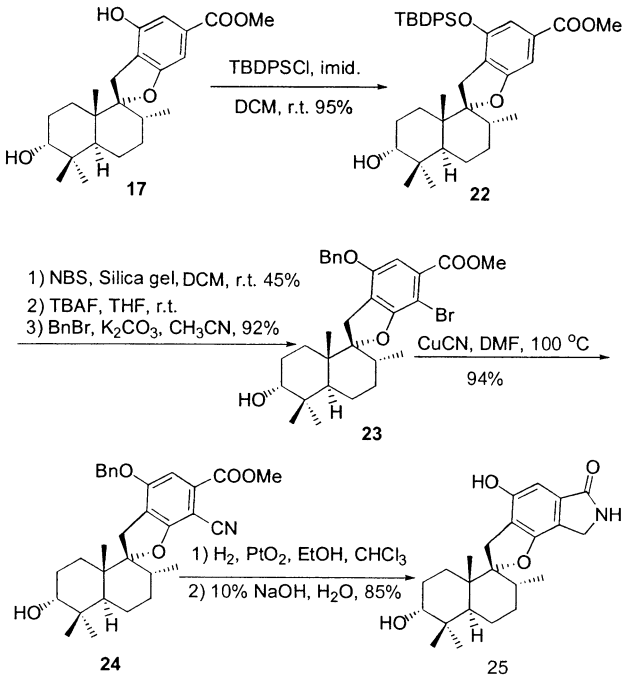
(9) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron* **1998**, *54*, 5635.
(10) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551.
(11) McMurry, J. E.; Erion, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 2712.
(12) Taishi, T.; Takechi, S.; Mori, S. *Tetrahedron Lett.* **1998**, *39*, 4347. (b) Wrobel, J.; Dietrich, A.; Gorham, B. J.; Sestanj, K. *J. Org. Chem.* **1990**, *25*, 2694.

Scheme 4. Construction of E-Ring



at C-5 or C-10. Therefore, we decided to test the possibility that the natural spirolactam reported by Roggo actually possessed structure **25** instead of **1**. Structure **25** corresponds to stachybotrylactam, a compound first isolated in 1995 by Jarvis et al.[14,15] With benzofuran **17** in hand, we could prepare the regioisomer **25** by redirecting the ring bromination so as to obtain the regioisomer **23** and then following the same sequence as was employed to make compound **1**. Since the

Scheme 5. Synthesis of Regioisomer **25**



phenol group in **17** directed exclusively to *ortho*-bromination, a bulky protecting group on the phenol might alter bromination regioselectivity. By using the bulky TBDPS ether **22**, we found that NBS and silica gel (excess) in DCM gave a 1:1 mixture of the two bromo compounds, which were easily separable by chromatography. In the absence of silica gel, or using other solvents or bromination reagents, inferior *para* regioselectivity was observed. Subsequent desilylation and benzyl ether formation after isomer separation gave **23**. Cyanation followed by nitrile reduction led to the lactam **25**.[16] Comparisons of ^{1}H NMR and ^{13}C NMR spectra of our synthetic **25** established the structural identity of the latter with the natural spirolactam isolated by Roggo et al.[1] reported to have structure **1** and with stachybotrylactam isolated by Jarvis.[15] The absolute configuration of the natural lactam could not be established because neither the Roggo group nor the Jarvis laboratories had reported its optical rotation. However, a very closely related spirobenzofuranlactam *N*-ethanol derivative reported by Jarvis has the negative sign of optical rotation ($[\alpha]^{20}_D = -16$, *c* 0.1, MeOH), which is very similar to that of our synthetic lactam **25** ($[\alpha]^{20}_D = -21.3$, *c* 1.10, MeOH). Thus, the absolute configuration of natural stachybotrylactam is most likely correctly represented by stereoformula **25**.

Acknowledgment. We thank Drs. John Huffman (Indiana University) and Rene Lachicotte (University of Rochester) for X-ray analyses and Prof. B. Jarvis (University of Maryland) and Dr. S. Roggo (Ciba-Geigy Ltd.) for kindly sending us copies of ^{1}H and ^{13}C NMR spectra of natural stachybotrylactam.

Supporting Information Available: Data including ^{1}H NMR and ^{13}C NMR spectra for **1**, **10**, **13**, **15**, **17**, **20**, **21**, and **23**−**25**. ORTEP plots of **1**, **15**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Data for **1**: colorless crystals; $[\alpha]^{20}_D = 0.5$ (c 1.01, MeOH); mp 255 °C dec (MeOH/EtOAc); IR (cm^{-1}) 3441, 3264, 2937, 1671; ^{1}H NMR (400 MHz, CD_3OD) δ 0.74 (3H, d, $J = 6.4$ Hz), 0.90 (3H, s), 1.00 (3H, s), 1.05 (3H, s), 1.05−1.09 (1H, m), 1.52−1.61 (5H, m), 1.83−1.97 (3H, m), 2.13−2.16 (1H, m), 2.86 (1H, AB, $J = 17.2$ Hz), 3.25 (1H, AB, $J = 17.2$ Hz), 3.35 (1H, br), 4.27 (2H, s), 6.66 (1H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 14.55, 15.08, 20.68, 21.50, 23.91, 24.57, 27.51, 30.80, 31.36, 37.16 (2C), 39.93, 42.04, 42.88, 75.00, 93.92, 96.97, 117.80, 122.73, 132.78, 148.16, 163.08, 172.81; APCI 386 ([MH]$^+$, 100). Anal. Calcd for $C_{23}H_{31}NO_4 \cdot {}^1/_2CH_3OH$ (shown by X-ray): C, 70.30; H, 8.28. Found: C, 70.26; H, 8.49.

(14) Direct comparison of Jarvis's spectroscopic data with Roggo's data was impossible due to the different solvent systems used in measuring the NMR spectra. Roggo et al. have recently independently concluded that their lactam **1** is structurally identical to the stachybotrylactam reported by Jarvis.[15] We have been unable to obtain actual reference samples of either the Roggo spirolactam or the Jarvis stachybotrylactam.

(15) Jarvis, B. B.; Salemme, J.; Morais, A. *Nat. Toxins* **1995**, *3*, 10.

(16) Data for **25**: amorphous solid; $[\alpha]^{20}_D = -21.3$ (*c* 1.10, MeOH); mp 210 °C dec (EtOAc); IR (cm^{-1}) 3460, 3264, 2935, 1681; ^{1}H NMR (400 MHz, DMSO-d_6) 0.64 (3H, d, $J = 6.4$ Hz), 0.80 (3H, s), 0.88 (3H, s), 0.95 (3H, s), 0.88−0.95 (1H, m), 1.35−1.52 (5H, m), 1.69−1.85 (3H, m), 2.01 (1H, m), 2.75 (1H, AB, $J = 16.8$ Hz), 3.10 (1H, AB, $J = 16.8$ Hz), 3.18 (1H, br), 4.09 (1H, AB, $J = 16.8$ Hz), 4.10 (1H, br), 4.20 (1H, AB, $J = 16.8$ Hz), 6.55 (1H, s), 8.35 (1H, br), 9.70 (1H, br); ^{13}C NMR (100 MHz, DMSO-d_6) 15.91, 16.016, 20.83, 22.78, 24.22, 25.29, 29.05, 31.15, 32.313, 36.85, 37.70, 39.62, 42.18, 42.41, 73.84, 98.08, 101.23, 114.38, 116.89, 134.61, 154.38, 156.49, 170.61; APCI 386 ([MH]$^+$, 100). Anal. Calcd: C, 71.66; H, 8.11. Found: C, 71.50; H, 7.92.