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Postulated Biogenesis of WS9885B and Progress toward an Enantioselective Synthesis

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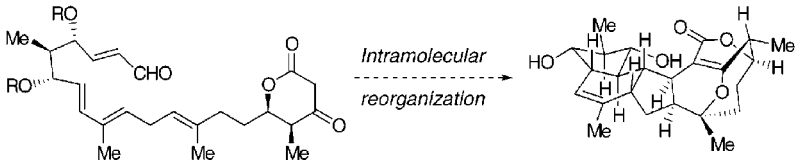
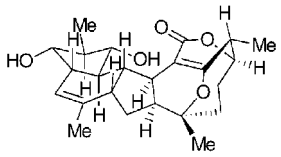
ABSTRACT



WS9885B

WS9885B promotes the assembly of microtubules *in vitro* and displays cytotoxicity as potent as paclitaxel against several cancer cell lines. In this Letter, we propose a biogenesis for this architecturally complex bacterial metabolite from a much simpler, polyunsaturated precursor. We also present significant progress toward a convergent, enantioselective synthesis of WS9885B. Our work features a chemoselective palladium-catalyzed cross-coupling of two advanced building blocks and an uncommon Claisen-like cyclization.

Scientists from the Fujisawa Pharmaceutical Company recently described the constitution, relative stereochemistry, and pronounced cytotoxicity of WS9885B (**1**), a substance isolated from the fermentation broth of *Streptomyces* sp. No9885.[1] This compound possesses an unprecedented hexacyclic architecture, a bridgehead alkene, and 12 stereocenters. Against several cancer cell lines in vitro, WS9885B displays cytotoxicity as potent as paclitaxel (Taxol®), an established drug for the treatment of ovarian and breast cancers.[2] Like paclitaxel,[3] **1** stabilizes cellular microtubules *in vitro* and warrants serious attention as a potential chemotherapeutic agent for the treatment of cancer.



1: WS9885B

WS9885B combines the important elements of novel structure with high biological activity and provides a powerful incentive for research in organic synthesis. An enantioselective synthesis of **1** would establish its absolute stereochemistry and permit a systematic study of the relationship between its constitution and microtubule-stabilizing properties and cytotoxicity.

While the biosynthesis of **1** is not yet known, *we propose that the architecturally and stereochemically complex structure of WS9885B could evolve from a substantially less complex substance by spontaneous intramolecular reorganization*. The essence of our biogenetic postulate and strategy for synthesis is that a structure of type **3** (Scheme 1), which could arise via an intramolecular Diels−Alder reaction[4] of

(1) Muramatsu, H.; Miyauchi, M.; Sato, B.; Yoshimura, S. 40th Symposium on The Chemistry of Natural Products, Fukuoka, Japan, 1998, Paper 83, p 487.

(2) Rowinsky, E. K.; Donehower, R. C. *New Engl. J. Med.* **1995**, *332*, 1004.

(3) (a) Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665. (b) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561.

(4) (a) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (b) Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893. (c) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S. *Tetrahedron Lett.* **1987**, *28*, 2447. (d) Roush, W. R. In *Advances in Cycloaddition*; JAI Press: Greenwich, CT, 1990; Vol. 2, p 91.

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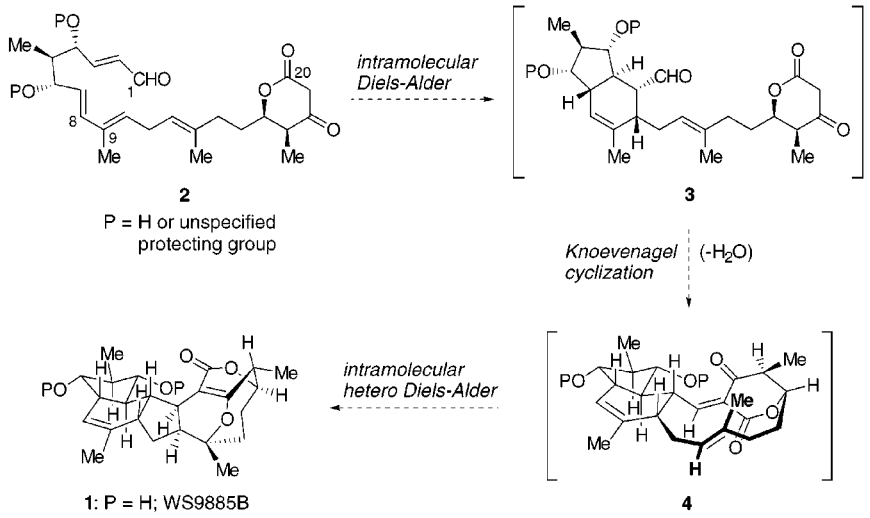
Scheme 1. Postulated Biogenesis of WS9885B (**1**)



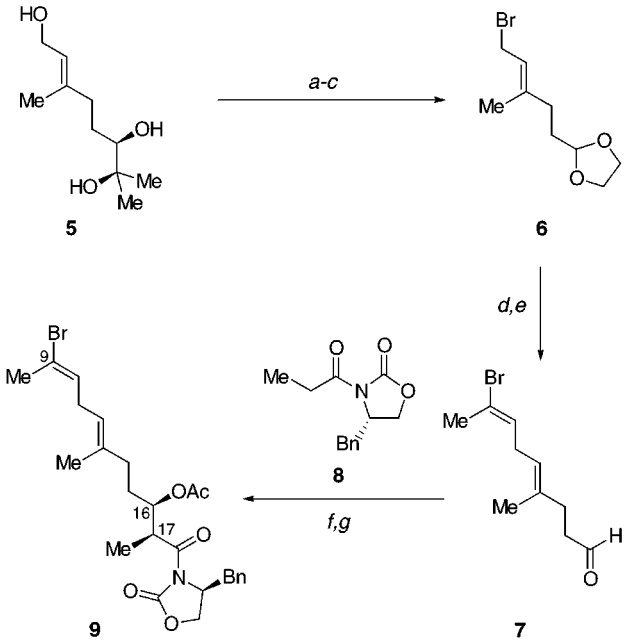
2, may be well-suited for a Knoevenagel cyclization[5] to a structure of type **4**. In the particular context of **4**, proximity between electron-deficient 4π and electron-rich 2π systems is a circumstance that may well favor the occurrence of a transannular inverse electron demand Diels−Alder reaction to give WS9885B (**1**) directly or in protected form.[6,7]

Our goal is to test the chemical basis of the hypothesis put forth in Scheme 1, and we set compound **2**—or a sufficiently stable surrogate—as a preliminary objective for synthesis. In this disclosure, we describe a convergent, enantioselective synthesis of tetraenal **15** by a pathway that features a chemoselective palladium-catalyzed cross-coupling of appropriately functionalized C1−C8 and C9−C20 domains. We also show that a Claisen-like cyclization of an acetate ester potassium enolate provides a reliable solution to the problem of constructing a β-keto lactone of the type found in **2**.

From the abundant terpene geraniol, we have established an expeditious eight-step synthesis of vinyl bromide **9**, an advanced intermediate comprising carbons 9−20 (see Scheme 2). Although standard dihydroxylation of geraniol is not highly site-selective, Sharpless and co-workers have shown that triol **5** can be prepared efficiently by asymmetric dihydroxylation of geraniol.[8] Reaction of **5** with sodium periodate supported on silica gel[9] provided an aldehyde that was immediately protected as a dioxolane acetal. Conversion of the allylic alcohol to bromide **6** was then smoothly achieved as shown in Scheme 2.

In the course of our recent synthesis of fumagillol,[10] we benefited from Corey's outstanding one-flask method for the

Scheme 2. Synthesis of Vinyl Bromide **9**[a]



[a] Reagents and conditions: (a) $NaIO_4/SiO_2$, CH_2Cl_2, 100%. (b) $HO(CH_2)_2OH$, CSA, CH_2Cl_2, 83%. (c) Et_3N, MsCl, THF, -45 °C; then LiBr, THF, 0 °C, 93%. (d) acetone 2,4,6-tri-isopropylbenzenesulfonylhydrazone, *s*-BuLi (2.2 equiv), THF, -78 °C; then **6**; *s*-BuLi (1.1 equiv); -78 → 0 °C; $Br(CH_2)_2Br$, -78 °C, 51%. (e) *p*-TsOH, acetone/H_2O, reflux, 100%. (f) **8**, Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C; **7**, -78 °C, 89%. (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 100%. CSA = camphorsulfonic acid; MsCl = methanesulfonyl chloride; *p*-TsOH = *p*-toluenesulfonic acid; DMAP = 4-(dimethylamino)pyridine.

(5) For reviews of the Knoevenagel reaction, see: (a) Jones, G. *Org. React. (N.Y.)* **1967**, *15*, 204. (b) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, p 341.

(6) For an excellent review of inverse electron demand and hetero Diels−Alder reactions, see: Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 451.

(7) The concept of performing tandem Knoevenagel−hetero Diels−Alder reactions derives strong precedent from the substantial studies of Tietze and co-workers. For reviews, see: (a) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(8) Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495.

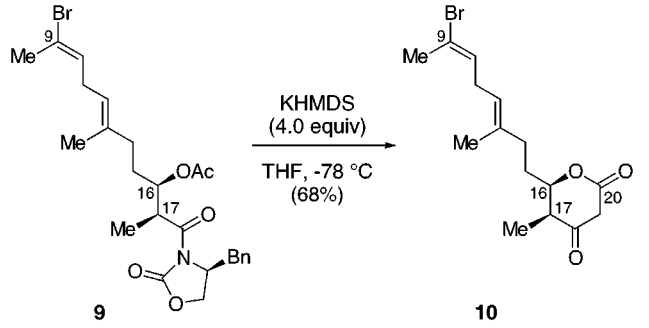
(9) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

controlled construction of dienyl halides of type **7**.[11] By this procedure and a subsequent deprotection step, large quantities of aldehyde **7** were obtained from allylic bromide **6**.

While we could not transform aldehyde **7** to β-keto lactone **10** in a stereocontrolled fashion via the catalytic asymmetric dienolate aldol chemistry of Sato,[12] we found Evans's asymmetric aldol methodology[13] to be optimal for the task of establishing the *syn* C16−C17 stereorelationship in a rigorous way. As expected, aldehyde **7** reacted efficiently with the boron enolate derived from the known propionimide **8**.[14] When the reaction temperature was maintained at −78 °C, we observed a single aldol adduct, which was subsequently acetylated to give imide acetate **9** in excellent yield.

Our intention was to transform **9** directly to β-keto lactone **10** via a somewhat uncommon Claisen-like cyclization (see Scheme 3).[15] Gratifyingly, treatment of **9** with 4 equiv of

Scheme 3. Claisen-like Cyclization of Imide Acetate **9**

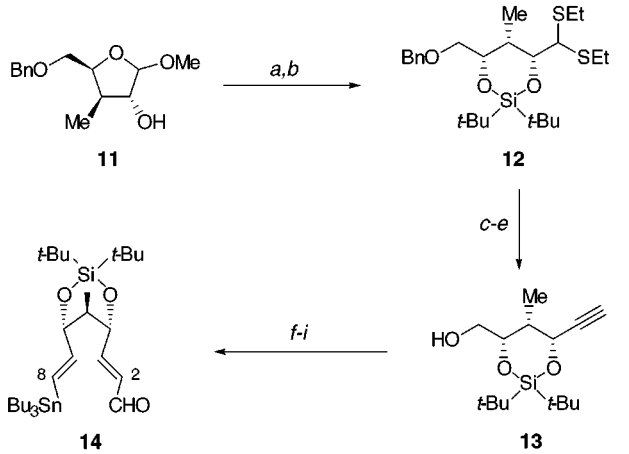


9 **10**

potassium hexamethyldisilazide[16] at −78 °C led to the rapid expulsion of the oxazolidinone auxiliary, which was recovered in quantitative yield, and provided the desired compound **10** in 68% yield following mild acidic workup.[17] This reliable and easily executed intramolecular carbon−carbon bond-forming reaction may prove generally useful for the facile preparation of optically active γ-alkyl-β-keto-δ-lactones.

As our studies matured, vinylstannane **14** emerged as an appropriately functionalized C1−C8 sector, and we could achieve an enantiospecific synthesis of this substance from the known D-xylose-derived lactol methyl ether **11**[18] through the high-yielding sequence shown in Scheme 4. Compound

Scheme 4. Synthesis of Vinyl Stannane **14**[a]



11 **12** **14** **13**

[a] Reagents and conditions: (a) EtSH, HCl, rt, 99%. (b) 2,6-lutidine, $(t\text{-Bu})_2Si(OTf)_2$, CH_2Cl_2, 65 °C, 84%. (c) NBS, 2,6-lutidine, MeCN/H_2O, 0 °C, 100%. (d) Ag(0), Et_2O; H_2, $Pd(OH)_2$, EtOH, 100%. (e) K_2CO_3, $CH_3COC(N_2)PO(OMe)_2$, MeOH, 90%. (f) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; Et_3N, 100%. (g) NBS, $AgNO_3$, acetone. (h) n-Bu_3SnH, $(Ph_3P)_4Pd$, THF, 80% (two steps). (i) $Ph_3P{=}CHCHO$, toluene, 70 °C, 62%. NBS = *N*-bromosuccinimide.

11 is an ideal starting material for a synthesis of **14** because it possesses the requisite stereotriad and differentiated oxidation states at its terminal carbon atoms. Reaction of **11** with ethanethiol in the presence of a catalytic amount of HCl gave rise to an acyclic 1,3-diol which was subsequently protected as di-*tert*-butylsilylene ketal **12**.[19] *N*-Bromosuccinimide-mediated hydrolysis of the dithioacetal function proceeded smoothly, affording the corresponding aldehyde. After treatment with elemental silver to remove residual thiol, the benzyl ether was hydrogenolyzed to produce a mixture of δ-lactol and hydroxy aldehyde tautomers[20] that reacted smoothly with dimethyl 1-diazo-2-oxopropylphosphonate in basic methanol[21] to give terminal alkyne **13**.

After Swern oxidation of alcohol **13**, application of Pattenden's two-stage alkyne hydrostannylation procedure[22] accomplished the introduction of the desired (*E*)-vinylstannane moiety. Our synthesis of key intermediate **14** was completed by a Wittig reaction of the alkynyl aldehyde with (triphenylphosphoranylidene)acetaldehyde. It is noteworthy

(10) Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 971.

(11) (a) Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256. (b) Corey, E. J.; Lee, J.; Roberts, B. E. *Tetrahedron Lett.* **1997**, *38*, 8915. (c) Corey, E. J.; Roberts, B. E. *Tetrahedron Lett.* **1997**, *38*, 8919.

(12) (a) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995**, *41*, 1435. (b) Sato, M.; Sugita, Y.; Abiko, Y.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 1157.

(13) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (d) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

(14) Gage, J. R.; Evans, D. A. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 339.

(15) (a) Brandänge, S.; Leijonmarck, H. *Tetrahedron Lett.* **1992**, *33*, 3025. (b) Leijonmarck, H. K. E. *Chem. Commun.* (Stockholm) **1992**, *3*, 1.

(16) The potassium counterion is important, as lithium and sodium acetate enolates reportedly give 11-membered rings resulting from competitive attack on the oxazolidinone carbonyl; see ref 15.

(17) In the base-induced Claisen-like cyclization of **9**, β-elimination of the C16 acetate group was not observed. Presumably, transition state 1,3-allylic strain discourages deprotonation at C17 (see: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001).

(18) (a) Anderson, C. D.; Goodman, L.; Baker, B. R. *J. Am. Chem. Soc.* **1958**, *80*, 5247. (b) Ireland, R. E.; Liu, L.; Roper, T. D. *Tetrahedron* **1997**, *53*, 13221.

(19) (a) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871. (b) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.

(20) ^{1}H NMR analysis at 25 °C revealed a ca. 9:1 ratio of lactol:hydroxy aldehyde tautomers.

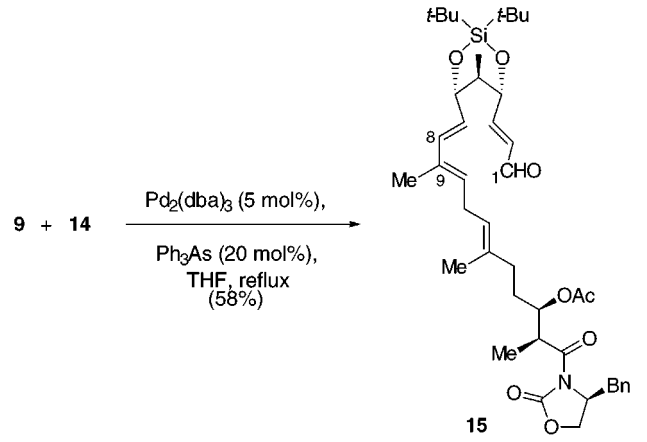
(21) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

(22) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417.

that the latter two reactions afforded the desired products as single geometrical isomers.

Having defined enantiocontrolled pathways to key intermediates **9** and **14**, we addressed the task of joining them through a Stille reaction.[23] Despite the proven utility of the Stille reaction, we approached the problem of joining **9** and **14** through this process with some trepidation because **14**, a substance bearing vinylstannane and electron-deficient enal moieties, could conceivably react with a transitory organopalladium(II) intermediate via a Stille and/or a Heck reaction.[24] In practice, however, exposure of a solution of compounds **9** and **14** in THF to $Pd_2(dba)_3$ (5 mol %) and triphenylarsine (20 mol %) at reflux[25] afforded the desired compound **15** in 58% yield (see Scheme 5); a Heck reaction,

Scheme 5. Chemoselective Cross-Coupling of **9** and **14**



which would have created a bond between C9 of **9** and C3 of **14**, was not observed. The chemoselective palladium-mediated union of compounds **9** and **14** is most gratifying because it establishes a crucial carbon−carbon bond and affords a substance possessing all of the carbon atoms of WS9885B (**1**). Incidentally, β-keto lactone **10** and its derived *tert*-butyldimethylsilyl enol ether are less stable than acetate imide **9** and were found to be unsuitable as substrates in Stille reactions with vinylstannane **14**.

In summary, we propose a biogenesis for WS9885B (**1**), a structurally complex natural product that stabilizes cellular microtubules and displays pronounced cytotoxicity. On the basis of our biogenetic proposal and the convergent strategy described herein, we are seeking an enantioselective laboratory synthesis of **1**. WS9885B is an ideal objective for research in organic synthesis because significant questions about the relationship between its constitution and cytotoxicity persist.

Acknowledgment. We are very grateful to Dr. Seiji Yoshimura from the Fujisawa Pharmaceutical Co. for NMR spectra of natural WS9885B (**1**). We thank Drs. D. H. Huang and L. B. Pasternack for NMR spectroscopic assistance and Dr. G. Siuzdak for mass spectrometric assistance. This work was supported by The Skaggs Institute for Chemical Biology and by predoctoral fellowships from the National Science and Engineering Research Council of Canada (C.D.V.) and the National Science Foundation (D.A.V.).

Supporting Information Available: Characterization data for compounds **9**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) For reviews of the Stille reaction, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React. (N.Y.)* **1997**, *50*, 1.

(24) For a review of the Heck reaction, see: de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379.

(25) The reagents and reaction conditions that we employed for this Stille coupling were reported to be effective in the following disclosure (see entry 17 of Table 1): Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.