

Construction of 4-Hydroxy-2-pyridinones. Total Synthesis of (+)-Sambutoxin

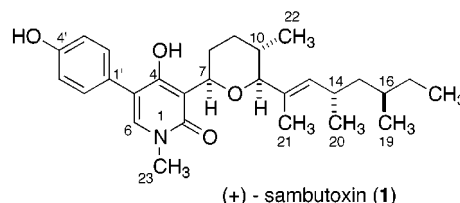
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Received August 2, 2000

ABSTRACT



Total synthesis of (+)-sambutoxin has been achieved, establishing the relative and absolute stereochemistry of the naturally occurring mycotoxin. Efforts feature methodology for enantiocontrolled construction of 1,3-*anti*-dimethyl arrays and a novel Saegusa oxidation to provide a pyridinone methide leading to formation of the central dihydropyran ring.

In 1995, Lee and co-workers reported the isolation of the mycotoxin designated as sambutoxin (**1**) from wheat cultures of *Fusarium sambucinum* PZF-4.¹ This metabolite is structurally representative of a small class of natural products featuring the central 4-hydroxy-2-pyridinone linked to two additional ring systems at the C-3 and C-5 positions.² Examples such as funiculosin,^{2a} oxysporidinone,^{2b} apiosporamide,^{2c} and related natural products^{2d} display a range of biological activities including antibiotic, antiinsecticidal, antifungal, and antitumor properties. On the other hand, sambutoxin was found to be a potentially lethal contaminant in the feed sources of livestock producing hemorrhagic lesions of the gastrointestinal tract. While the previous efforts for structure determination of **1** were able to establish the connectivity and relative stereochemistry of

the substituted tetrahydropyran ring, the stereochemistry of the 1,3-dimethyl array at C-14 and C-16 and the absolute configuration have remained undefined. In connection with our previous syntheses of pyridone metabolites tenellin³ and ilicicolin H,⁴ and our continuing interests in devising methodology toward funiculosin,⁵ a successful strategy for preparation of **1** has been developed. Herein we report a convergent asymmetric synthesis of (+)-sambutoxin, which has also established the assignments of relative and absolute stereochemistry.

The development of an efficient, enantioselective synthesis of the acyclic 1,3-dimethyl (C₁₄–C₁₆) arrangement poses a significant problem for natural product chemistry.⁶ Recognizing the structural similarities of sambutoxin and funiculosin, we theorized that the trimethylheptenyl array of **1** would display the *anti*-1,3-dimethyl relationship as previously

(1) (a) Kim, J.-C.; Lee, Y.-W. *Appl. Environ. Microbiol.* **1994**, *60*, 4380. (b) Kim, J.-C.; Lee, Y.-W.; Tamura, H. T.; Yoshizawa, T. *Tetrahedron Lett.* **1995**, *36*, 1047.

(2) (a) Ando, K.; Matsuura, I.; Nawata, Y.; Endo, H.; Sasaki, H.; Okyotomi, T.; Saehi, T.; Tamura, G. *J. Antibiot.* **1978**, *31*, 533. (b) Breinholt, J.; Ludvigsen, S.; Rassing, B. R.; Rosendahl, C. N.; Nielsen, S. E.; Olsen, C. E. *J. Nat. Prod.* **1997**, *60*, 33. (c) Alfatafta, A. A.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **1994**, *57*, 1696. (d) Takahashi, S.; Kakinuma, N.; Uchida, K.; Hashimoto, R.; Yanagisawa, T.; Nakagawa, A. *J. Antibiot.* **1998**, *51*, 1051. Fujimoto, H. Ikeda, M.; Yamamoto, K.; Yamazaki, M. *J. Nat. Prod.* **1993**, *56*, 1268.

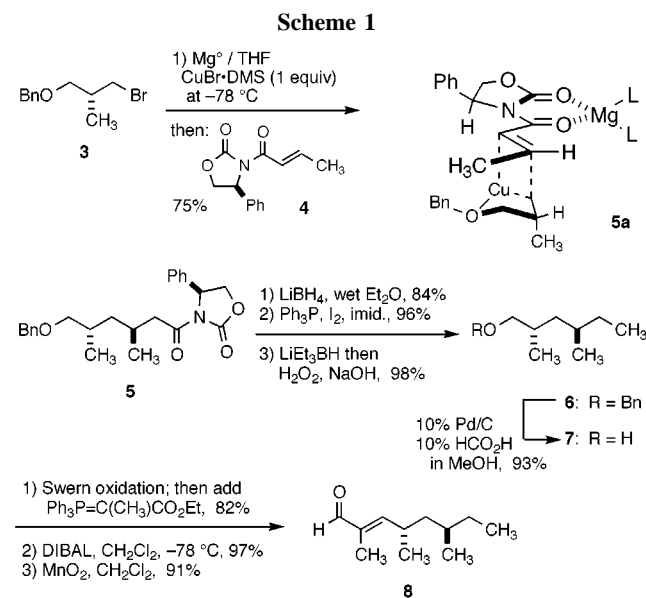
(3) Williams, D. R.; Sit, S.-Y. *J. Org. Chem.* **1982**, *47*, 2846. See also: Rigby, J. H.; Qabar, M. J. *J. Org. Chem.* **1989**, *54*, 5852.

(4) Williams, D. R.; Bremmer, M. L.; Brown, D. L.; D'Antuono, J. J. *Org. Chem.* **1985**, *50*, 2807.

(5) Williams, D. R.; Lowder, P. D.; Gu, Y.-G. *Tetrahedron Lett.* **1997**, *38*, 327.

(6) For an overview of conformational analyses, see: Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054. For a summary of synthesis strategies, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

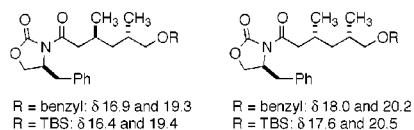
demonstrated by X-ray crystallography for tetrahydrofuniculosin.^{2a} Aided by the expertise gained in stereocontrolled preparations of 1,3-*syn*- and *anti*-dimethyl arrays for myxovirescin synthesis,^{7,8} we examined the asymmetric conjugate addition of Yamamoto copper reagents utilizing the Hruby 4-phenyloxazolidinone auxiliary.⁹ Thus, addition of the organocopper complex derived from bromide **3**¹⁰ provided for outstanding diastereofacial selectivity as shown in **5** (Scheme 1). Chelation in the *syn-s-cis* conformer as depicted



in **5a** facilitated a process of double induction stemming from the existing asymmetry of the homochiral copper species. Benzyl ether **6** was obtained as a single diastereomer in 79% overall yield following reductive conversion from *N*-acyloxazolidinone **5**. Hydrogenolysis of **6** and homologation to aldehyde **8** was achieved in a straightforward fashion.¹¹

To develop a flexible route for construction of the vicinal C₁₀ and C₁₁ stereochemistry irrespective of the 1,3-dimethyl

(7) Williams, D. R.; Li, J. *Tetrahedron Lett.* **1994**, 35, 5113. In the course of our total synthesis efforts, we prepared and characterized the individual 1,3-*syn*- and 1,3-*anti*-diastereomers of the imides below. Distinguishing features can be found in the carbon NMR spectra for chemical shifts of the methyl groups of the asymmetric array as tabulated below. Signals for *syn*-isomers were consistently found slightly downfield relative to the corresponding *anti*-arrangement.

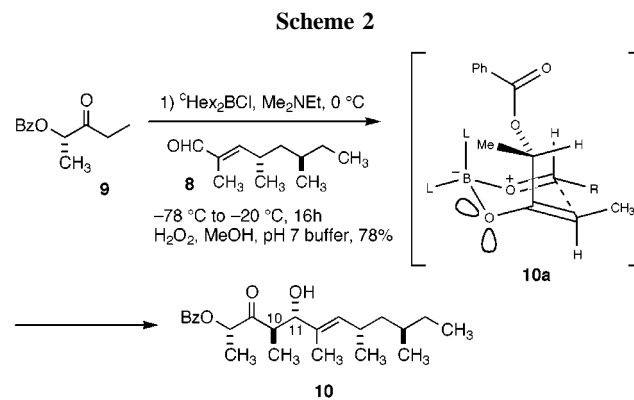


(8) An attempt to calculate ¹³C NMR chemical shifts on Boltzmann-weighted MM3 geometries for 1,3-dimethyl arrays has been applied to sambutoxin. Stahl, M.; Schopfer, U.; Frenking, G.; Hoffmann, R. W. *J. Org. Chem.* **1996**, 61, 8083.

(9) (a) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, 58, 766. (b) Williams, D. R.; Kissel, W. S.; Li, J. *Tetrahedron Lett.* **1998**, 39, 8593, and references therein.

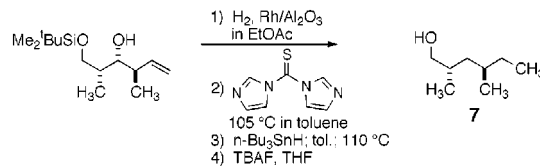
(10) The optically pure bromide **3** and its corresponding Grignard reagent were prepared from (2*R*)-methyl 3-hydroxy-2-methylpropionate (Aldrich) via reaction with benzyl 2,2,2-trichloroacetimidate, LiAlH₄ reduction, tosylation, and exchange with LiBr in DMF at 50 °C (D'Antuono, J. Ph.D. Thesis, Indiana University, 1988. Earley, J. Ph.D. Thesis, Indiana University, 1996).

stereogenicity in **1**, we chose to pursue an asymmetric *anti*-aldol process.¹² While a number of chiral auxiliaries and procedures have been examined for this purpose, a general solution for the *anti*-aldol reaction is not widely practiced.¹³ However, methodology previously described by Paterson and co-workers,¹⁴ which has incorporated chirality in the starting ketone **9** as derived from (*S*)-ethyl lactate, has proven most effective for our purposes (Scheme 2). Thus, the *E*(*O*)-boron



enolate of **9** was generated with dicyclohexylboron chloride and dimethylethylamine in ether at -78 °C with warming to 0 °C (2 h). Upon cooling to -78 °C and introduction of aldehyde **8**, the reaction mixture was stirred at -20 °C overnight leading to the isolation of β -hydroxyketone **10** in 78% yield as a single, crystalline diastereomer (mp 83–84 °C; [α]_D²³ +42.3° (*c* = 1.1, CHCl₃)). Our observations are consistent with the Paterson model of the preorganized six-membered transition state from **10a**. The minimization of A(1,3)strain in the *E*(*O*)-enolate, in addition to lone pair repulsion of the benzoate and enolate oxygens, imposes facial discrimination by avoiding steric interactions with the methyl

(11) Unambiguous confirmation of our 1,3-stereochemistry was established by an independent synthesis using asymmetric allylation methodology to produce the homoallylic alcohol below. See: Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem.* **1987**, 52, 316. Conversion to primary alcohol **7** was accomplished in four steps (65% overall yield).



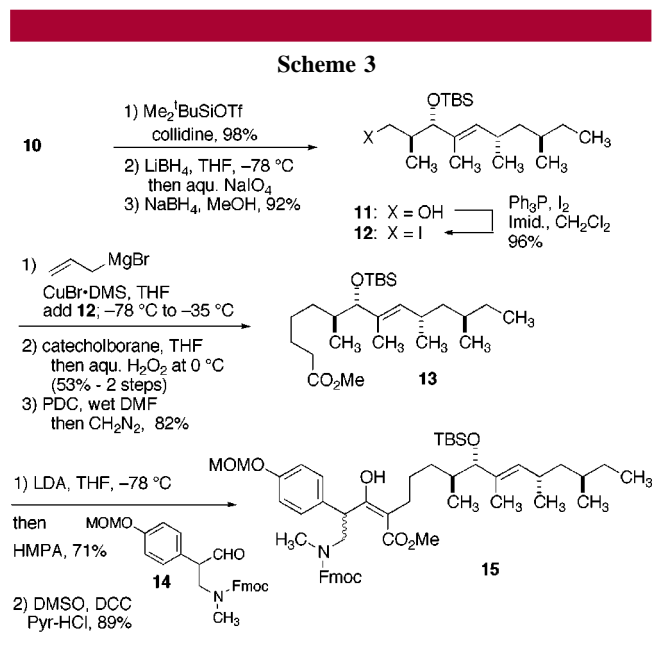
(12) For some leading references, see: (a) Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T. -H. *J. Org. Chem.* **1996**, 61, 2038. (b) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, 56, 5747. (c) Braun, M.; Sacha, H. *Angew. Chem., Int. Ed. Engl.* **1991**, 30, 1318. (d) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, 32, 61.

(13) Our efforts to utilize the Heathcock protocol (see ref 12b) of *N*-propionyl-4-isopropyl and 4-phenyloxazolidinones with aldehyde pre-complexation using Et₂AlCl led to modest yields (55–65%) of inseparable mixtures of aldol adducts (ratios ~2:1). Adoption of the Yan procedure (see ref 12a) afforded excellent $\geq 99:1$ *anti*-diastereoselectivity in our case. However, numerous methods for removal of the auxiliary resulted solely in cleavage of the oxazolidinone ring.

(14) (a) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, 35, 9083. (b) For a review: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, 51, 1.

group of the lactate auxiliary. Adoption of this model warrants careful consideration. For example, the corresponding benzyl ether derivative of **9** leads to formation of the *Z*(*O*)-enolate under the same conditions. In the latter case, postulation of bridging chelation of the benzyloxy substituent with the boron–carbonyl complex is proposed to account for *syn*-product formation.^{14,15} Additionally, calculations have suggested that *E*(*O*)-enolates leading to *anti*-products can be invoked from boat transition states without a substantial cost in energy.¹⁶ The observation of a large coupling constant in the proton NMR spectrum of **10** ($J = 9.4$ Hz) for the vicinal C₁₀–C₁₁ hydrogens is characteristic of the *anti*-relationship.¹⁷

Silyl ether formation, oxidative cleavage of the chiral auxiliary, and elongation of the carbon chain was accomplished using a sequence of standard transformations leading to the construction of the heterocyclic pyridinone as illustrated in Scheme 3. Formation of the enolate of **13** and



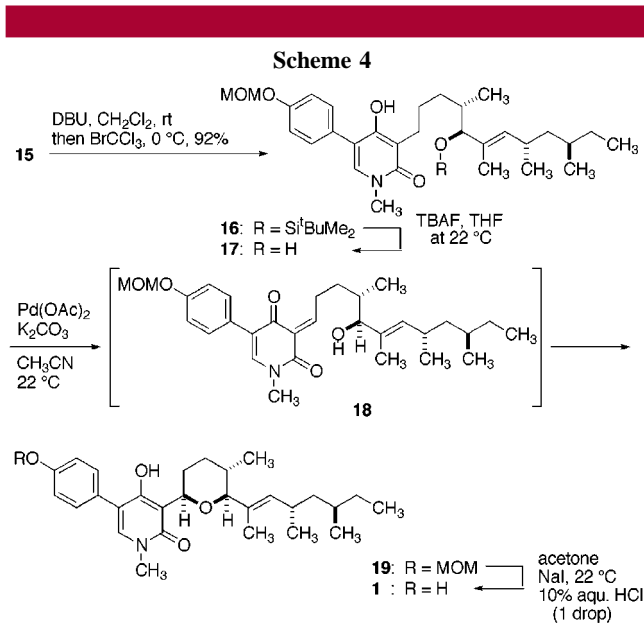
condensation with the protected amino aldehyde **14**¹⁸ was immediately followed by oxidation to provide enol ester **15**.

Removal of the Fmoc protecting group with DBU spontaneously triggered cyclization to the intermediate 5,6-dihydropyridinone which underwent oxidation in situ to pyridone **16** upon addition of bromotrichloromethane in overall 92% yield (Scheme 4).¹⁹ Sluggish removal of the TBS silyl ether of **16** with tetra-*n*-butylammonium fluoride provided the key intermediate **17** for oxidation under buffered Saegusa conditions with palladium acetate.²⁰ These conditions led exclusively to formation of the tetrahydropyran **19**

(15) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499.

(16) (a) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685. (b) Myers has described a restricted auxiliary which requires a boat transition state: Myers, A. G.; Widdowson, K. L.; Kukkola, P. *J. Am. Chem. Soc.* **1992**, *114*, 2765.

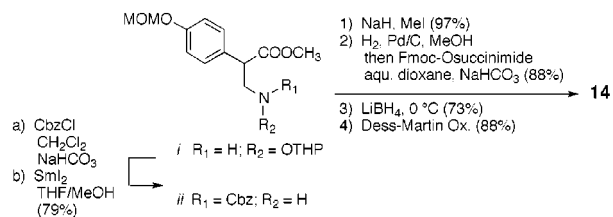
(17) This is due to conformational preferences in **10** for internal hydrogen bonding. House, H. O.; Crumrine, D. S.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.



(48% yield) via formation of the pyridinone methide **18** followed by intramolecular conjugate addition.²¹ Analysis of the proton NMR spectrum of **19** indicated a 2,6-diequatorial substitution pattern, exhibiting diaxial coupling of 10.2 and 9.9 Hz for methine hydrogens at C₇ and C₁₁, respectively. Hydrolytic removal of the β -methoxymethyl ether of **19** yielded (+)-sambutoxin (**1**), which proved to be identical via direct comparisons with exception of opposite optical rotation with a sample of the natural product.^{22,23}

In conclusion, we have achieved the enantiocontrolled total synthesis of (+)-sambutoxin, which has been identified as the antipode of the natural mycotoxin. These efforts have resolved the assignments of relative stereochemistry and absolute configuration for the metabolite. Key elements of

(18) The availability of the amino aldehyde **14** followed from a route described in our tenellin synthesis (ref 3) using the methyl ester *i*, *N*-methylation, Fmoc protection, and adjustment of the oxidation state led to **14** as summarized.



(19) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331.

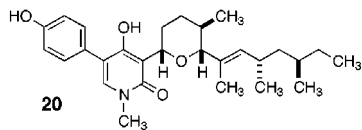
(20) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(21) Examples of pyridinone methides as reactive intermediates: (a) Asherson, J. L.; Young, D. W. *J. Chem. Soc., Chem. Commun.* **1977**, 916. (b) Girotra, N. N.; Wendler, N. L. *Heterocycles* **1978**, *9*, 417. (c) Tietze, L. F.; Brand, S.; Brumby, T.; Fennen, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 665. (d) Snider, B. B.; Lu, Q. *J. Org. Chem.* **1996**, *61*, 2839.

(22) We thank Professor Yin-Won Lee (Department of Agricultural Biology, College of Agriculture and Life Sciences, Seoul National University, Suwon 441–744 Korea) for a sample of (–)-sambutoxin for our direct comparisons. We have noted a discrepancy in the reported optical rotation of the natural material $[\alpha]_D^{25} -200^\circ$ ($c = 0.1$; CH_3OH) compared to data obtained from our sample $[\alpha]_D^{25} = -153^\circ$ ($c = 0.1$, CH_3OH) following flash chromatography. Synthetic **1** provided a rotation of $[\alpha]_D^{23} +143^\circ$ ($c = 0.6$; CH_3OH).

our synthesis route have included the development of the asymmetric conjugate addition reaction, the Paterson *anti*-aldol process, and the tandem Saegusa oxidation–cyclization strategy.

(23) We have also synthesized the diastereomer **20** ($[\alpha]_{D}^{27} -156^{\circ}$ ($c = 0.1; \text{CH}_3\text{OH}$)) which exhibits significantly different proton NMR data compared to those of the natural metabolite.



Acknowledgment. The authors gratefully acknowledge the National Institutes of Health (GM-41560) for generous support of our work.

Supporting Information Available: Experimental procedures and spectral data for compounds **5**, **6**, **10**, **11**, **16**, **19**, and **1** and a proton NMR spectra for **1** and authentic (–)-sambutoxin. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL006410+