ORGANIC LETTERS

2001
Vol. 3, No. 24
3971−3974

Nodulisporic Acid A Synthetic Studies. 2. Construction of an Eastern Hemisphere Subtarget

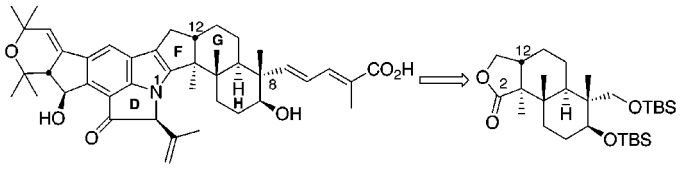
Amos B. Smith, III,* Young Shin Cho, and Haruaki Ishiyama

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

Received October 10, 2001

ABSTRACT



(+)-Nodulisporic acid A (**1**) (+)-**4**

In this, the second of two Letters, we describe an effective assembly of (+)-4, an eastern hemisphere subtarget comprising the FGH rings of (+)-nodulisporic acid A (1) (17 steps, 9% overall yield). Central to the synthesis is a Koga three-component conjugate addition–alkylation sequence which secures the *trans* orientation of the vicinal quaternary methyl groups.

In 1997 the Merck group reported the isolation and structure elucidation of (+)-nodulisporic acid A (**1**), a novel indole terpene, which displays potent oral systemic activity against fleas in dogs.[1] Further study on the mechanism of action demonstrated that nodulisporic acid A (**1**) acts as an insecticide by selectively modulating the invertebrate-specific glutamate-gated chloride ion channel.[2] Efforts to identify the key constituents of the nodulisporic acid A pharmacophore revealed that even minor changes to the polycyclic core lead to deleterious effects on the biological activity.[3] However, modifications of the C(8) side chain afforded several nodulisporic acid A derivatives which exhibit enhanced activity.[4]

(+)-Nodulisporic acid A (**1**) possesses an intriguing array of architectural features including a highly substituted indole core, nine stereogenic carbons, and an eight-ring fused array, including the unique, highly strained five-membered β-ketodihydropyrrole. Ring D, derived from isoprenylation of the indole moiety, is unprecedented among the indole mycotoxins.[1] Also of interest vis à vis the biogenetic origin of (+)-nodulisporic acid is the reversal of the ring fusion of the dihydropyran and cyclopentyl ring in the western hemisphere compared to the janthitrems[5] and shearinines.[6]

In the preceding Letter,[7] we outlined our convergent strategy for the construction of (+)-**1**, in conjunction with an efficient synthesis of the western subtarget (−)-**3**, exploit-

(1) (a) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809. (b) Shoop, W. L.; Gregory, L. M.; Zakson-Aiken, M.; Michael, B. F.; Haines, H. W.; Ondeyka, J. G.; Meinke, P. T.; Schmatz, D. M. *J. Parasitol.* **2001**, *87*, 419.

(2) (a) Smith, M. M.; Warren, V. A.; Thomas, B. S.; Brochu, R. M.; Ertel, E. A.; Rohrer, S.; Schaeffer, J.; Schmatz, D.; Petuch, B. R.; Tang, Y. S.; Meinke, P. T.; Kaczorowski, G. J.; Cohen, C. J. *Biochemistry* **2000**, *39*, 5543 (b) Kane, N. S.; Hirschberg, B.; Qian, S.; Hunt, D.; Thomas, B.; Brochu, R.; Ludmerer, S. W.; Zheng, Y.; Smith, M.; Arena, J. P.; Cohen, C. J.; Schmatz, D.; Warmke, J.; Cully, D. F. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 13949.

(3) Meinke, P. T.; Ayer, M. B.; Colletti, S. L.; Li, C.; Lim, J.; Ok, D.; Salva, S.; Schmatz, D. M.; Shih, T. L.; Shoop, W. L.; Warmke, L. M.; Wyvratt, M. J.; Zakson-Aiken, M.; Fisher, M. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2371.

(4) Berger, R.; Shoop, W. L.; Pivnichny, J. V.; Warmke, L. M.; Zakson-Aiken, M.; Owens, K. A.; deMontigny, P.; Schmatz, D. M.; Wyvratt, M. J.; Fisher, M. H.; Meinke, P. T.; Colletti, S. L. *Org. Lett.* **2001**, *3*, 3715.

(5) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 697.

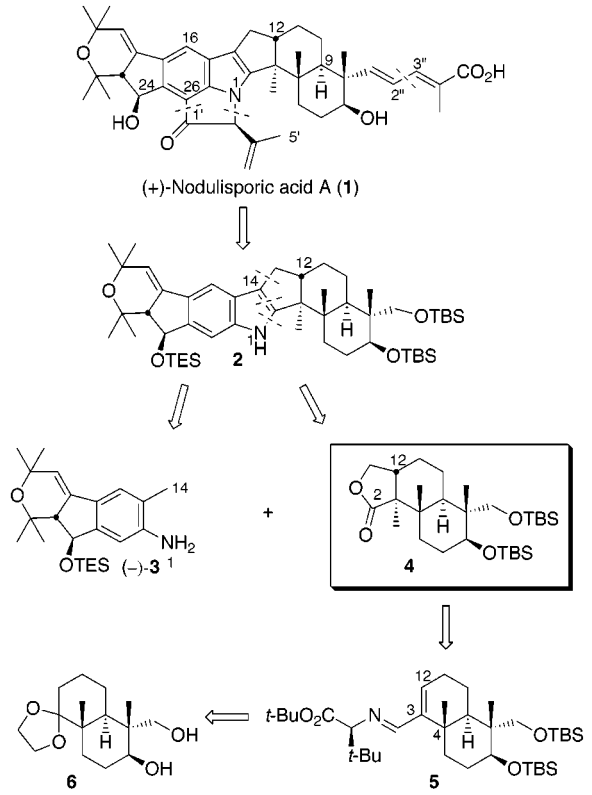
(6) Belofsky, G. N.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *Tetrahedron* **1995**, *51*, 3959.

(7) Smith, A. B., III; Ishiyama, H.; Cho, Y. S.; Ohmoto, K. *Org. Lett.* **2001**, *3*, 3967.

10.1021/ol016888t CCC: $20.00
Published on Web 11/03/2001

ing a Shibasaki−Mori transmetalation−cyclization.[8] Herein, we present an effective synthesis of eastern hemisphere **4**, highlighted by the tandem installation of a vinyl moiety and the C(3) quaternary methyl group exploiting a Koga three-component conjugate addition−alkylation protocol (Scheme 1).[9] Further disconnection of **5** leads to diol **6**, previously

Scheme 1

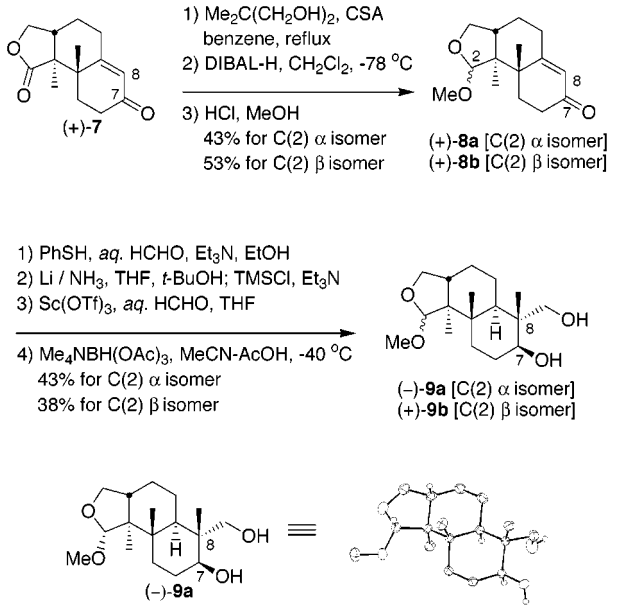


prepared during the Smith−Õmura synthesis of (+)-pyripyropene A.[10]

Initially, we investigated a route to the eastern subtarget (+)-**4**, beginning with lactone (+)-**7** (Scheme 2). Tricyclic lactone (+)-**7**, designed as a common building block for construction of a variety of indole tremorgens,[11] was derived from (−)-Wieland−Miesher ketone (16 steps; 8% overall yield).[11b] A three-step sequence then furnished individual acetals (+)-**8a** and -**8b**.[11c] Reductive alkylation via a method developed in our laboratory[12] in the 1980s followed by stereoselective reduction of the ketone[10] led to the diastereoselective generation of the C(7) and C(8) stereocenters

(8) Mori, M.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 3486.
(9) Kogen, H.; Tomioka, K.; Hashimoto, S.; Koga, K. *Tetrahedron* **1981**, *37*, 3951.
(10) Nagamitsu, T.; Sunazuka, T.; Obata, R.; Tomoda, H.; Tanaka, H.; Harigaya, Y.; Õmura, S.; Smith, A. B., III. *J. Org. Chem.* **1995**, *60*, 8126.
(11) (a) Smith, A. B., III; Nolen, E. G., Jr.; Shirai, R.; Blase, F. R.; Ohta, M.; Chida, N.; Hartz, R. A.; Fitch, D. M.; Clark, W. M.; Sprengeler, P. A. *J. Org. Chem.* **1995**, *60*, 7837. (b) Smith, A. B., III; Hartz, R. A.; Spoors, P. G.; Rainier, J. D. *Isr. J. Chem.* **1997**, *37*, 69. (c) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254.
(12) Smith, A. B., III; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685.

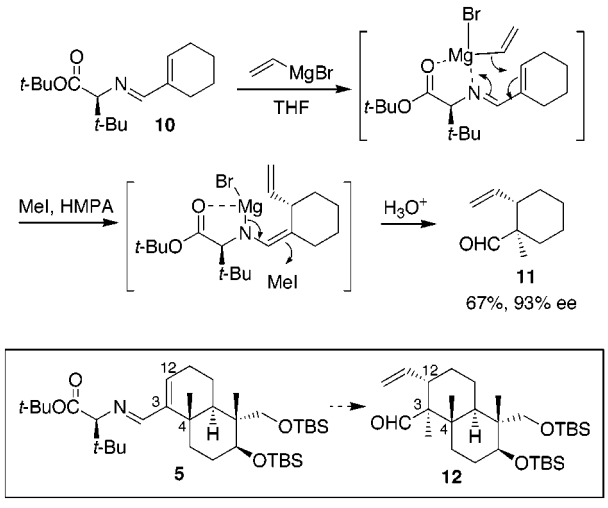
Scheme 2



with high efficiency. The configurations of the newly generated stereocenters were determined by single-crystal X-ray analysis of diol (−)-**9a**. Although diols (−)-**9a** and (+)-**9b** were appropriately functionalized for the eastern hemisphere construction, the overall length of this route [23 steps from (−)-Wieland−Miesher ketone] was not amenable to large-scale production. We therefore sought a more efficient strategy.

In redesigning the synthesis with (+)-**4** as the target, we recognized an opportunity for the tandem generation of the stereogenic centers at C(3) and C(12) (Scheme 3). Toward

Scheme 3



this end, Koga reported that addition of vinyl Grignard reagent to an α,β-unsaturated imine (e.g., **10**), possessing a stereogenic center α to the nitrogen, afforded an intermediate

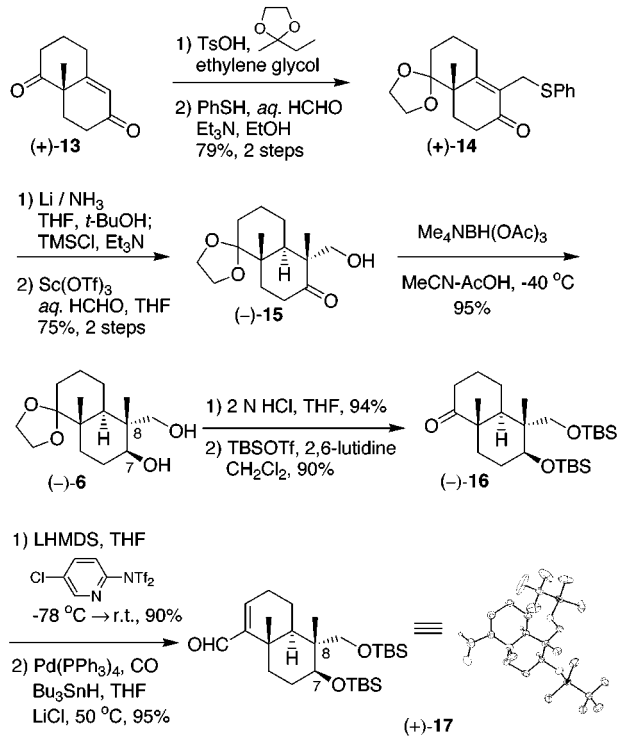
which yielded the 1,2-disubstituted cyclohexanecarboxaldehyde **11** after methylation and acidic hydrolysis.[9] We anticipated that aldehyde **12** could be prepared from imine **5** via a similar protocol.

The second-generation synthesis of (+)-**4** began with (+)-Wieland−Miesher ketone (**13**), available in >99% ee via the method of Fürst (Scheme 4).[13] Chemoselective transketalization followed by Kirk−Petrow (phenylthio)methylation[14] led to enone (+)-**14**. Reductive alkylation utilizing aqueous formaldehyde and $Sc(OTf)_3$ catalyst[15] afforded *β*-hydroxyketone (−)-**15**. Noteworthy, this reaction in aqueous media proceeded in higher yield [(1) Li/NH_3, THF; $TMSCl$, Et_3N; (2) $Sc(OTf)_3$, aqueous HCHO, THF, 75% yield for two steps] compared to our earlier one-pot anhydrous protocol [Li/NH_3, THF; $TMSCl$, Et_3N; HCHO(g), 42% yield].[12] Stereoselective reduction of (−)-**15** with tetramethylammonium triacetoxyborohydride furnished *trans* diol (−)-**6**, an intermediate in our (+)-pyripyropene A total synthesis.[10] Ketal hydrolysis [2 N HCl, THF] and disilylation [TBSOTf, 2,6-lutidine, CH_2Cl_2] then furnished (−)-**16** in 85% for the two steps. Sulfonylation with the Comins reagent [*N*-(5-chloro-2-pyridyl)triflimide][16] next led to the requisite enol triflate, which in turn underwent palladium-catalyzed carbonylation[17] to produce aldehyde (+)-**17** (86% yield, two steps). The relative stereochemistry at C(7) and C(8) was secured by single-crystal X-ray analysis.

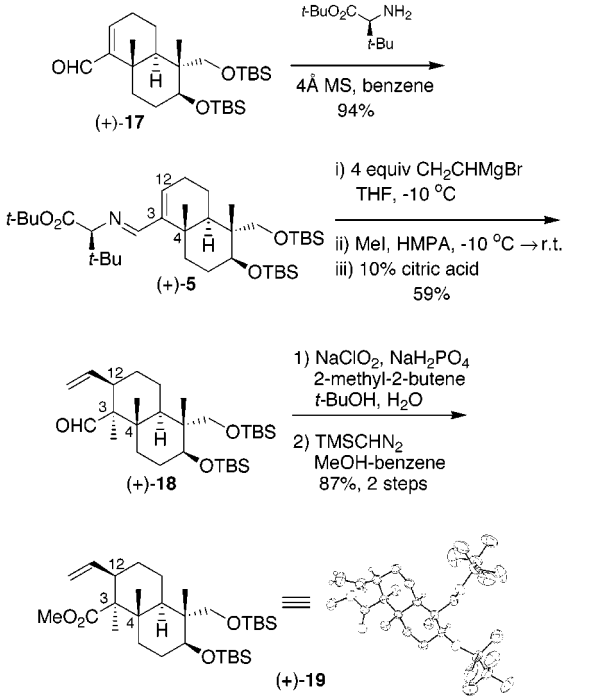
Imine (+)-**5** (Scheme 5), substrate for the Koga three-component conjugate addition−alkylation, was then prepared by condensation of aldehyde (+)-**17** with L-*tert*-leucine *tert*-butyl ester[18] in 94% yield. Addition of vinylmagnesium bromide to (+)-**5**, followed by quenching the resulting anion with methyl iodide in the presence of HMPA, afforded, after hydrolysis, aldehyde (+)-**18** in 59% yield.[9] Subsequent oxidation of the aldehyde to the carboxylic acid and esterification with trimethylsilyldiazomethane[19] then led to methyl ester (+)-**19**. Contrary to the expectation based on the Koga precedent,[9] the undesired stereochemistry at C(12) was obtained, as determined by single-crystal X-ray analysis. Importantly, the C(3) quaternary center, vicinal to the C(4) quaternary center, possessed the requisite stereochemistry for (+)-nodulisporic acid A (**1**).

The stereochemical issue at C(12) was easily corrected via ozonolysis and epimerization to afford aldehyde (+)-**20**, precursor to the targeted *γ*-lactone (Scheme 6).[20] Reduc-

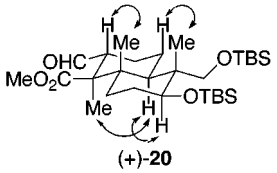
Scheme 4



Scheme 5

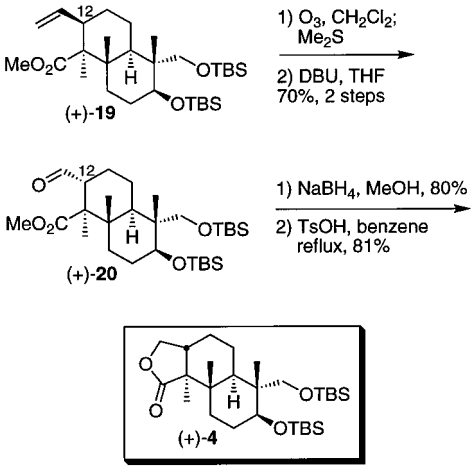


(13) Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis*, **1977**, 167.
(14) Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1962**, 1091.
(15) Kobayashi, S. *Chem. Lett.* **1991**, 2187.
(16) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(17) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. (b) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(18) Anderson, G. W.; Callahan, F. M. *J. Am. Chem. Soc.* **1960**, *82*, 3359.
(19) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.
(20) The structure of (+)-**20** was assigned by a 2D NOESY NMR experiment. Full analysis of the data is shown in the Supporting Information.



(+)-20

Scheme 6



tion of the aldehyde and treatment of the resulting alcohol with TsOH [benzene, at reflux][21] then furnished the eastern hemisphere γ-lactone (+)-**4** in 65% for the two steps.

(21) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957.

In summary, we have developed an effective synthesis of (+)-**4**, the eastern hemisphere FGH subtarget of (+)-nodulisporic acid A (**1**), via the Koga three-component conjugate addition−alkylation protocol. The synthesis proceeded in 17 steps and 9% overall yield. Studies directed toward the union of the eastern and western hemispheres [(+)-**4** and (−)-**3**] and final elaboration to (+)-nodulisporic acid A (**1**) will be reported in due course.

Acknowledgment. Financial support was provided by the National Institutes of Health (National Institute of General Medical Sciences) through Grant GM-29028 and by Merck Research Laboratories. We also thank Dr. G. Furst, Dr. R. K. Kohli, and Dr. P. J. Carroll, Directors of the University of Pennsylvania Spectroscopic Facilities, for assistance in obtaining NMR spectra, high-resolution mass spectra, and X-ray analysis, respectively.

Supporting Information Available: Spectroscopic and analytical data for compounds **4**, **5**, **6**, **9a**, **9b**, **15**, **16**, **17**, **18**, **19**, and **20** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016888T