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

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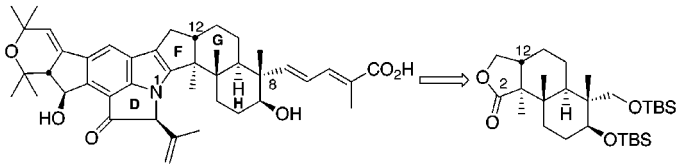
ABSTRACT



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.

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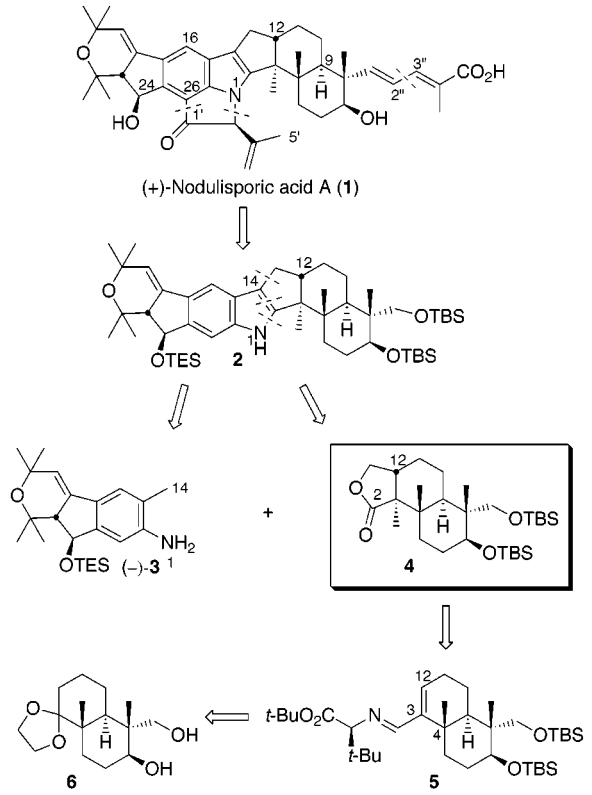
ing a Shibasaki−Mori transmetalation−cyclization.[8] Herein, we present an effective synthesis of eastern hemisphere **4**, highlighted by the tandem installation of a vinyl moiety and the C(3) quaternary methyl group exploiting a Koga three-component conjugate addition−alkylation protocol (Scheme 1).[9]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

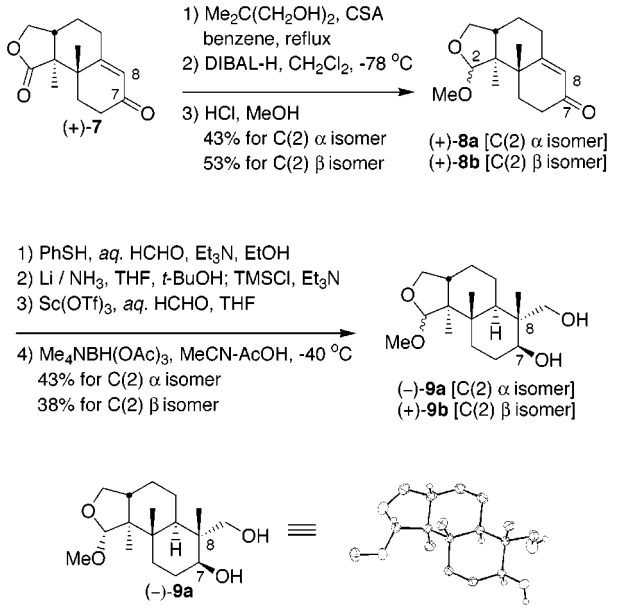
Scheme 1



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

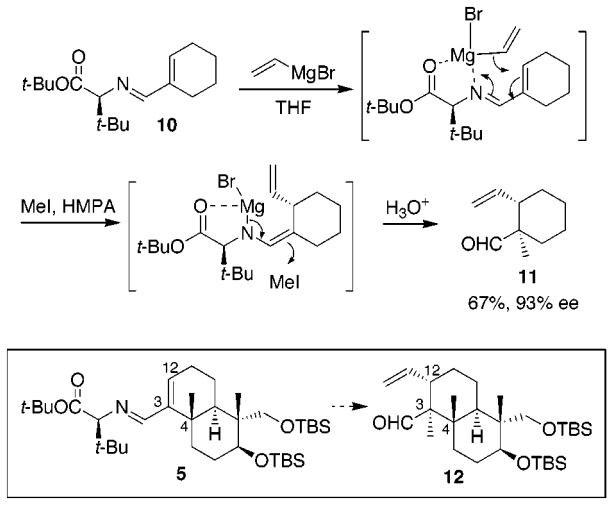
Scheme 2



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

(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.

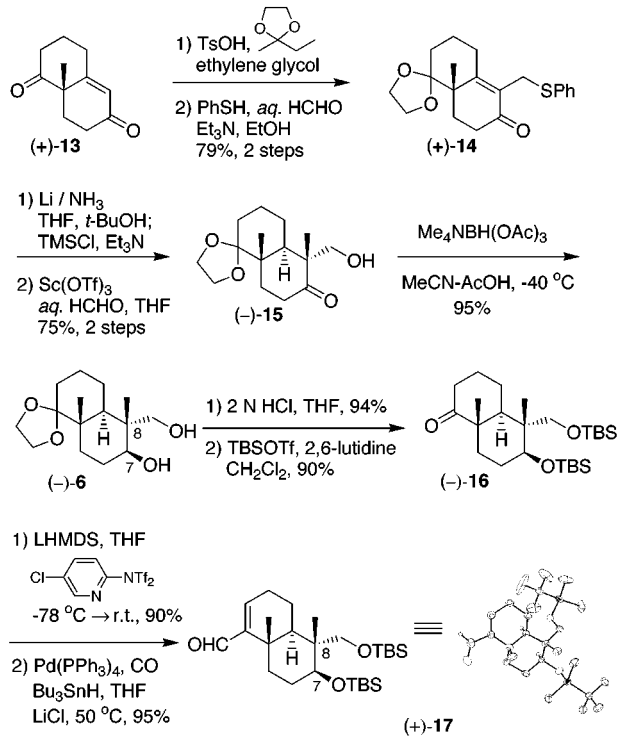
which yielded the 1,2-disubstituted cyclohexanecarboxaldehyde **11** after methylation and acidic hydrolysis.[9] We anticipated that aldehyde **12** could be prepared from imine **5** via a similar protocol.

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.

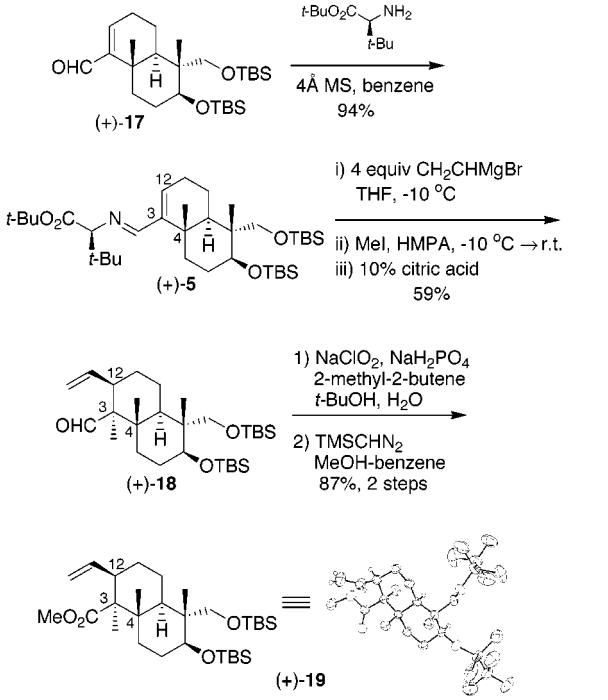
Imine (+)-**5** (Scheme 5), substrate for the Koga three-component conjugate addition−alkylation, was then prepared by condensation of aldehyde (+)-**17** with L-*tert*-leucine *tert*-butyl ester[18] in 94% yield. Addition of vinylmagnesium bromide to (+)-**5**, followed by quenching the resulting anion 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

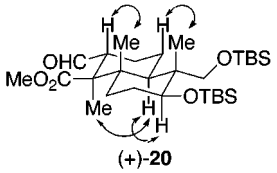


Scheme 5



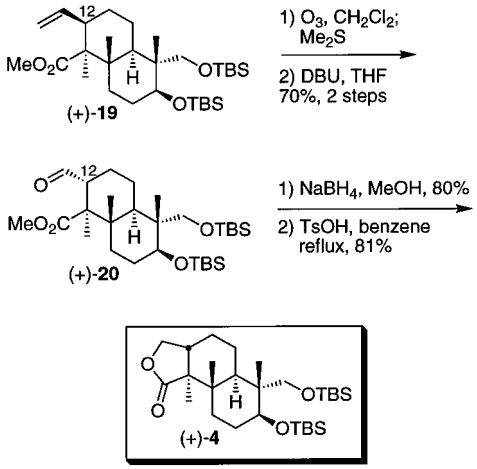
(13) Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis*, **1977**, 167.
(14) Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1962**, 1091.
(15) Kobayashi, S. *Chem. Lett.* **1991**, 2187.
(16) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(17) (a) Scott, W. J.; Crisp, G. T.; Stille, 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.

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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.

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