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Nodulisporic Acid A Synthetic Studies. 1. Overall Strategy and Construction of a Western Hemisphere Subtarget

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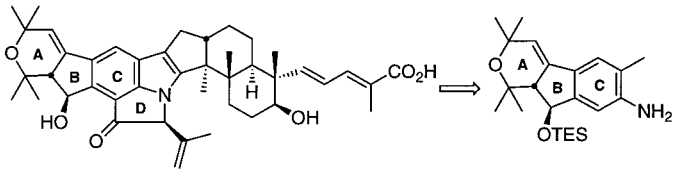
ABSTRACT

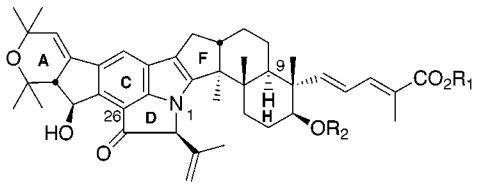


(+)-Nodulisporic acid A (**1**) (–)-**6**

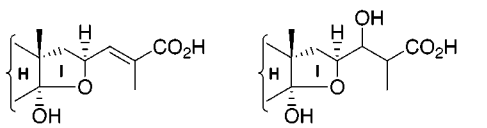
In this, the first of two Letters, we outline our overall strategy for the construction of (+)-nodulisporic acid A (1), a representative member of a new class of indole diterpenes. In addition, we describe the efficient assembly of (–)-6, an advanced western hemisphere subtarget, comprising the ABC rings of (+)-nodulisporic acid A (1). The synthesis proceeded in 9% overall yield (longest linear sequence, 11 steps), exploiting a Shibasaki–Mori tandem transmetalation–cyclization to construct ring B.

(+)-Nodulisporic acid A (**1**, Figure 1), a novel insecticide recently isolated by Ondeyka and co-workers from the fermentation extract of the fungus *Nodulisporium* sp.[1] possesses unique architecture as deduced initially from spectroscopic evidence, including the Dunkel computerized 2D INADEQUATE protocol.[2] The relative stereochemistry was subsequently confirmed by single-crystal X-ray diffraction analysis of the *p*-bromobenzoate methyl ester derivative (**2**, Figure 1); the absolute stereochemistry was established by the advanced Mosher ester method.[3]

Nodulisporic acid A (**1**) proved to be a potent insecticide, discovered while screening the natural product extract against the larvae of the blowfly (*Lucilia seracata*; LC_{50} of 0.3 ppm).[1] Further study revealed that (+)-**1** has an LC_{50} of 0.5 ppm against *Aedas aegypti* (the larvae of the mosquito) and is more active than paraherquamide (LC_{50} of 50 ppm in both



1 (+)-Nodulisporic acid A R_1 = H, R_2 = H
2 R_1 = CH_3, R_2 = *p*-BrC_6H_4CO



3 (–)-Nodulisporic acid A_1 **4** (–)-Nodulisporic acid A_2

Figure 1.

(1) 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.

(2) (a) Dunkel, R.; Mayne, C. L.; Curtis, J.; Pugmire, R. J.; Grant, D. M. *J. Magn. Reson.* **1990**, *90*, 290. (b) Dunkel, R.; Mayne, C. L.; Pugmire, R. J.; Grant, D. M. *Anal. Chem.* **1992**, *64*, 3133. (c) Dunkel, R.; Mayne, C. L.; Foster, M. P.; Ireland, C. M.; Li, D.; Owen, N. L.; Pugmire, R. J.; Grant, D. M. *Anal. Chem.* **1992**, *64*, 3150.

(3) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

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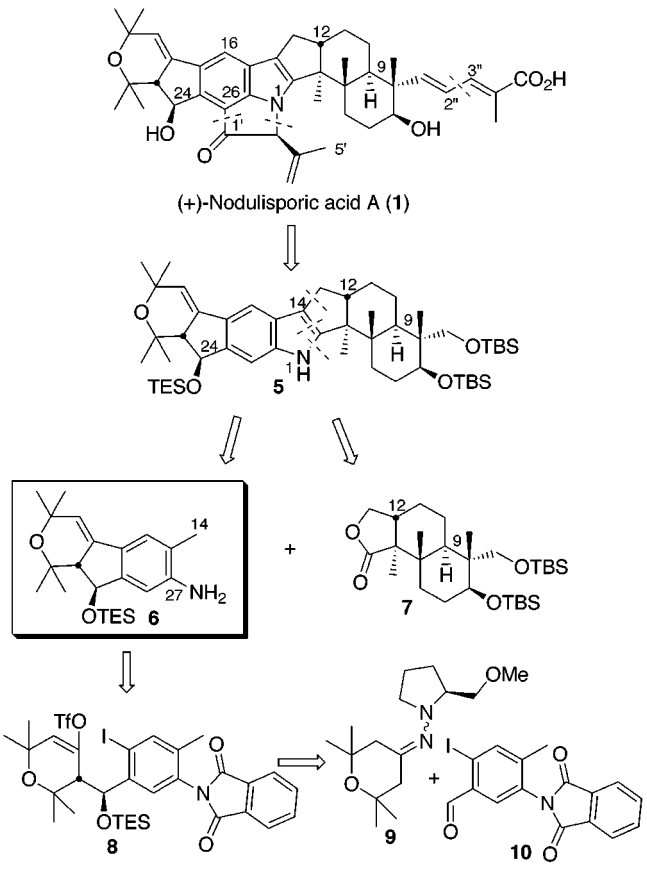
assays) but less active than ivermectin, which displays an LC_{50} of 0.02 and 0.045 ppb, respectively.[1] Importantly, nodulisporic acid A was shown by the Merck group to possess potent oral activity in dogs for the control of fleas.[4] Subsequent research on the mechanism of action suggests that the insecticidal activity of (+)-**1** arises via modulation of the glutamate-gated chloride channels,[5] vital to insect neurotransmission. Interruption of the glutamate-gated chloride channels results in insect paralysis and death. Since glutamate-gated chloride channels are not found in mammals, nodulisporic acid A (**1**) holds considerable promise as a systemic insecticidal agent. Interestingly, despite the resemblance between nodulisporic acid A (**1**) and other complex indole tremorgens, such as janthitrem G[6a] and the shearinines,[6b] lolitrems,[6c,d] paspalitrems,[6e] and penitrems,[6f] (+)-**1** does not possess tremorgenic activity, presumably due to the lack of the C(9) axial hydroxyl group, as is known for the simple indole diterpenes paspline and paspalicine.[7] Currently, (+)-nodulisporic acid A (**1**) is under development by the Animal Health Division at Merck & Co.

More recently (1999), Hensens and co-workers at Merck disclosed the isolation and structure determination of two fermentation congeners, nodulisporic acid A_1 (**3**, Figure 1) and A_2 (**4**, Figure 1), which exhibit similar biological profiles;[8] nodulisporic acid A_1 (**3**) has an LD_{50} of 0.4−1.5 ppm against *Lucilia seracata*, similar to that of (+)-**1**, while nodulisporic acid A_2 (**4**) was slightly less active with an LD_{50} of 0.8−2.2 ppm.

Although nodulisporic acid A (**1**) resembles other indole diterpenes,[6] the unprecedented N1−C26 bridge with a readily epimerizable isoprenyl side chain, the A ring dihydropyran, and the cyclopentyl ring possessing a labile secondary benzylic hydroxyl conspire to make (+)-nodulisporic acid A (**1**) a most formidable synthetic target. Intrigued by the architectural complexity and the outstanding antiparasitic activity, we recently mounted an investigation with a view toward both total synthesis and analogue preparation. In this the first of two Letters,[9] we disclose our overall synthetic strategy in conjunction with an efficient assembly of tricyclic aniline (−)-**6**, complete with appropriate functionality for further elaboration, that embodies the ABC western hemisphere rings of (+)-nodulisporic acid A (**1**). In the following Letter,[9] we describe an effective synthesis of the eastern hemisphere lactone **7**.

From the retrosynthetic perspective, initial scission between C(2″) and C(3″) and removal of the five-membered-ring isoprenyl moiety reveals indole **5** (Scheme 1), which,

Scheme 1



in turn, is envisioned to arise via union of the western hemisphere **6** with the eastern hemisphere **7**, exploiting an indole ring synthetic protocol[10] that proved highly effective in our recent total synthesis of (−)-penitrem D.[10d] For **6**, the cyclopentane ring was expected to arise via a palladium-catalyzed tandem transmetalation−cyclization of **8**.[11] Asymmetric addition of SAMP hydrazone **9**[12] to aldehyde **10** in turn would provide, after removal of the chiral auxiliary and hydroxyl protection (TESCl), the requisite precursor for enol triflate **8**.

Assembly of western hemisphere (−)-**6** began with commercially available 3-amino-4-methylbenzyl alcohol **11**

(4) 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.

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(6) (a) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 697. (b) Belofsky, G. N.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *Tetrahedron* **1995**, *51*, 3959. (c) Gallagher, R. T.; Hawkes, A. D.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem. Commun.* **1984**, 614. (d) Ede, R. M.; Miles, C. O.; Meagher, L. P.; Munday, S. C.; Wilkins, A. L. *J. Agric. Food Chem.* **1994**, *42*, 231 and references therein. (e) Dorner, J. W.; Cole, R. J.; Cox, R. H.; Cunfer, B. M. *J. Agric. Food Chem.* **1984**, *32*, 1069 and references therein. (f) de Jesus, A. E.; Steyn, P. S.; van Heerden, F. R.; Vleggaar, R.; Wessels, P. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1857 and references therein.

(7) Dorner, J. W.; Cole, R. J.; Cox, R. H.; Cunfer, B. M. *J. Agric. Food Chem.* **1984**, *32*, 1069.

(8) Hensens, O. D.; Ondeyka, J. G.; Dombrowski, A. W.; Ostlind, D. A.; Zink, D. L. *Tetraheron Lett.* **1999**, *40*, 5455.

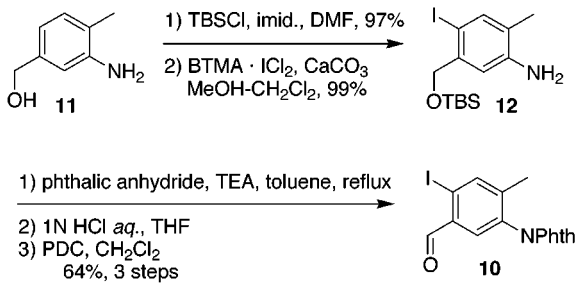
(9) Smith, A. B., III; Cho, Y. S.; Ishiyama, H. *Org. Lett.* **2001**, *3*, 3971.

(10) (a) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757. (b) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957. (c) Smith, A. B., III; Kanoh, N.; Minakawa, N.; Rainier, J. D.; Blase, F. R.; Hartz, R. A. *Org. Lett.* **1999**, *1*, 1263. (d) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254.

(11) Mori, M.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 3486.

(12) (a) Enders, D.; Zamponi, A.; Raabe, G.; Runsink, J. *Synthesis* **1993**, 725. (b) Enders, D.; Whitehouse, D. L. *Synthesis* **1996**, 621.

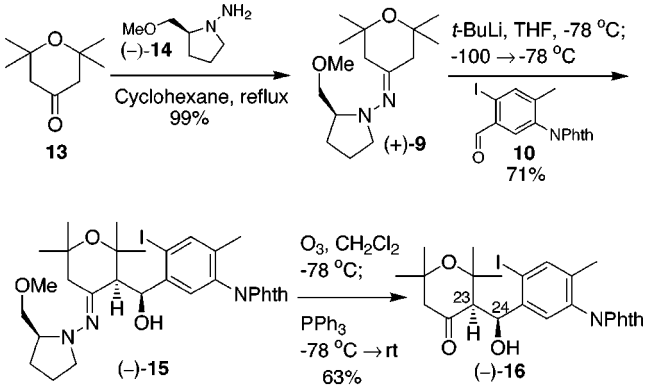
Scheme 2



(Scheme 2). Hydroxyl protection followed by regioselective iodination with benzyltrimethylammonium dichloroiodate (BTMA·ICl_2)[13] afforded amine **12**. Protection of the amino group as the phthalimide, hydrolytic removal of the TBS group, and oxidation of the resulting hydroxyl led to aldehyde **10** in 64% overall yield for the three steps.

Continuing with the synthesis, treatment of the Enders SAMP hydrazone (+)-**9**,[12] derived from known ketone **13**,[14] with *t*-BuLi at −78 °C in THF, followed by addition of aldehyde **10** at −100 °C, afforded a diastereomeric mixture of β-hydroxyhydrazones (11:2) in a combined yield of 84%; separation via flash chromatography provided (−)-**15** in 71% yield (Scheme 3). Ozonolysis then afforded β-hydroxyketone (−)-**16**.

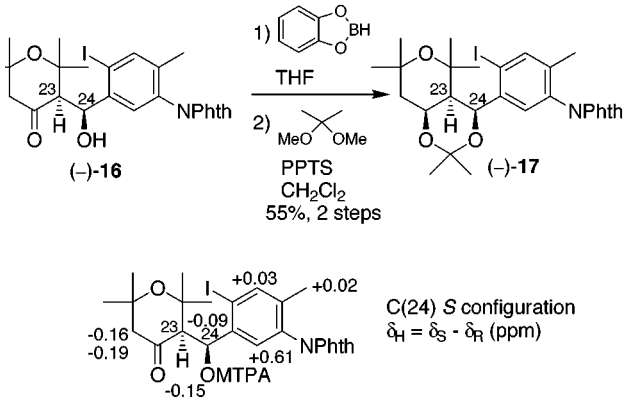
Scheme 3



The relative configurations of the newly generated stereocenters were assigned by conversion of (−)-**16** to the corresponding acetonide (−)-**17** (catecholborane;[15] 2,2-methoxypropane, PPTS); NOESY spectral data revealed the 23*R**/24*S** relative configurations (Scheme 4).[16] The absolute configuration of (−)-**16** was then assigned by advanced Mosher ester analysis.[3,17] The pertinent data from the Kakisawa test of (−)-**16** are illustrated in Scheme 4.

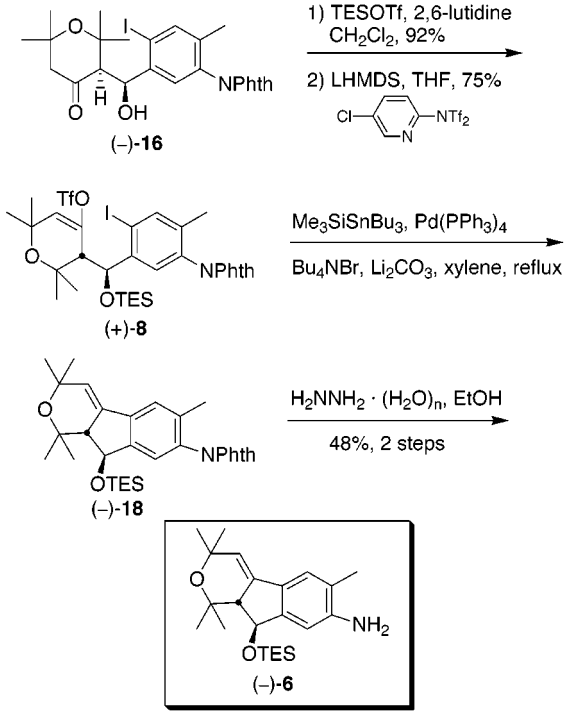
(13) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 600.
(14) Magnus, P.; Mansley, T. E. *Tetrahedron Lett.* **1999**, *40*, 6909.
(15) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.
(16) Analysis of NOESY spectral data is shown in the Supporting Information.

Scheme 4



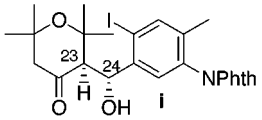
Protection of the secondary hydroxyl in (−)-**16** (TESOTf, 2,6-lutidine), followed by formation of the enol triflate with the Comins reagent [*N*-(5-chloro-2-pyridyl)triflimide],[18] provided vinyl triflate (+)-**8** in 69% for the two steps (Scheme 5). The Shibasaki−Mori protocol[11] for tandem transmetala-

Scheme 5



tion−cyclization (i.e., conversion of the vinyl triflate to the vinylstannane and subsequent cyclization with aryl iodide)

(17) The minor product **i** was identified as below by Mosher ester analysis and NOESY experiment of its acetonide derivative.



then furnished (−)-**18**. Unmasking the aniline moiety with hydrazine completed the synthesis of western hemisphere (−)-**6**.[19]

In summary, we have designed and executed an efficient synthesis of (−)-**6**, a western subtarget for (+)-nodulisporic acid A (**1**), by exploiting an asymmetric aldol reaction utilizing a SAMP hydrazone followed by a Shibasaki−Mori tandem transmetalation−cyclization. The synthesis proceeded in 11 steps and 9% overall yield. Importantly, the synthesis of (−)-**6** is highly competitive, compared to the recent synthesis by Magnus et al. of a racemic ABC model.[14] Studies to unite the western and eastern subtargets and complete the total synthesis of (+)-nodulisporic acid A (**1**) are currently ongoing in our laboratory.

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Supporting Information Available: Spectroscopic and analytical data for compounds **6**, **8**, **9**, **10**, **12**, **15**, **16**, **17**, and **18** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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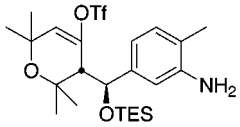
(18) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(19) We also observed as much as 27% of a reduced product, **ii**.



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