ORGANIC LETTERS

2002
Vol. 4, No. 8
1291−1294

Synthesis of Side Chain Truncated 3″-Aldehyde, 3″-Carboxylic Acid, and 1″-Aldehyde from Nodulisporic Acid A

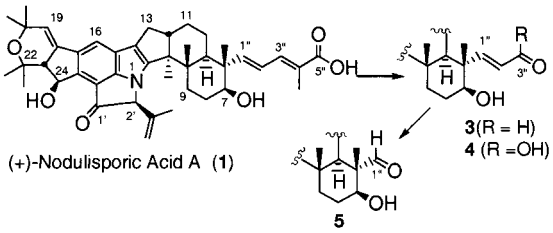
Prasun K. Chakravarty,* Sriram Tyagarajan, Thomas L. Shih, Steve Salva, Christine Snedden, Matthew J. Wyvratt, Michael H. Fisher, and Peter T. Meinke

Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co., Inc., P.O. Box 2000, Rahway, New Jersey 07065-0900

prasun_chakravarty@merck.com

Received February 22, 2002

ABSTRACT



An efficient synthesis of the truncated 3″-aldehyde (3) from nodulisporic acid A (1) under mild conditions is described. Further oxidation of 3 to 3″-carboxylic acid (4) and its subsequent oxidative degradation produced 1″-aldehyde (5). These new derivatives are versatile intermediates for the preparation of new, side chain modified derivatives of nodulisporic acid A.

In 1997, a new family of structurally complex natural products now known as the nodulisporic acids were discovered at Merck Research Laboratories.[1,2] These fermentation-derived indole diterpenes, of which (+)-nodulisporic acid A (NsA A, **1**) is the predominant product, exhibit potent insecticidal activity.[3] More recently, **1** was found to exhibit unusual systemic efficacy against fleas following ingestion of drug-treated bovine blood.[4] The insecticidal activity of **1** has been traced to its ability to selectively modulate a subset of the[1] invertebrate-specific glutamate-gated chloride channels targeted by ivermectin.[5] A systematic structural modification of **1** led to the identification of the key constituents that are responsible for the biological activity and delineated the molecule into so-called "permissive" and "nonpermissive" regions, as illustrated below (Figure 1).[6a,b] In addition, a series of amide derivatives (**2**) of **1** with significantly improved efficacy against fleas was also identified.[6,7] Furthermore, formation of two truncated aldehydes **3** and **5** in small quantities was observed during preliminary chemical degradation of **1**, resulting from the oxidative cleavage at 3″,4″- and 1″,2″-double bonds, respectively. It was envisaged that an adequate supply of aldehyde **3** would permit ready access to structurally diverse, side chain modified analogues of NsA A with potentially improved biological activity and/

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

(3) Ostlind, D. A.; Felcetto, T.; Misura, A.; Ondeyka, J.; Smith, S.; Goetz, M.; Shoop, W.; Mickle, W. *Med. Vet. Entomol*. **1997**, *11*, 407.

(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.

(5) 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.

(6) (a) Meinke, P. T.; Ayer, M. B.; Colletti, S. L.; Li, C.; Lim, J.; Ok, D.; Salva, S.; Shih, T. L.; Wyvratt, M. J.; Shoop, W. L.; Gregory, L. M.; Schmatz, D. M.; Fisher, M. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2371. (b) While chemical modifications at the permissive region of NsA A could be tolerated, the nonpermissive region of the molecule appeared to be essential for the maintenance of the biological activity.

(7) Shoop, W. L.; Gregory, L. M.; Zakson-Aiken, M.; Michael, B. F.; Pivnichny, J.; Meinke, P. T.; Fisher, M. H.; Wyvratt, M. J.; Schmatz, D. M. *J. Parasitol.* **2001**, *87*, 1150.

10.1021/ol025766d CCC: $22.00
Published on Web 03/20/2002

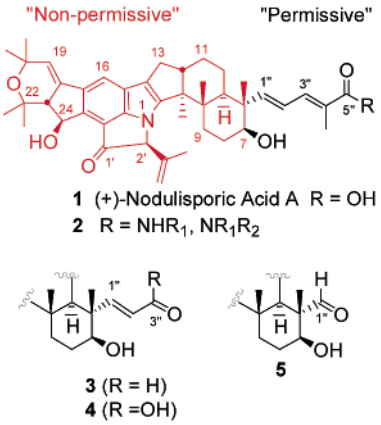


Figure 1.

or an altered spectrum thereof.[8] Since **1** was only available in limited quantities, the development of a synthesis of **3** was critical to success.

Nodulisporic acid A is oxidatively labile with multiple sites of unsaturation and, consequently, is prone to deleterious over-oxidation. Indeed, it was known that during the course of NMR studies in CD_3CN, the indole 2,3-double bond (NsA numbering: C_2,C_{14}) was oxidatively cleaved to yield the corresponding biologically inactive keto-amide.[1] Similar over-oxidation of **1** was also observed during attempted epoxidation, ozonolysis, and oxidation reactions using ruthenium catalysts.[9] In addition, the molecule is extremely sensitive to strong acids and undergoes spontaneous dehydration to form biologically inactive 23,24-dehydro NsA A. Strongly basic conditions are also deleterious, inducing epimerization at the 2′-center of **1**.[6] Therefore, it became apparent that oxidation methods requiring only neutral or weakly acidic conditions[14,15] could be used for a selective oxidation of **1** at the 3″,4″-double bond.[16] In this report, we describe the results of the oxidative degradation of **1** that led to the development of a highly efficient synthesis of the 3″-aldehyde **3** and its subsequent transformation into the corresponding 3″-carboxylic acid **4** and 1″-aldehyde **5**.

Because of the milder reaction conditions required, OsO_4-mediated bis-hydroxylation followed by oxidative cleavage of the resulting diols **8** offered a plausible strategy for the synthesis of **3** from **1**. Toward this end, the OsO_4 reaction was probed using a series of different reaction conditions with **1** or its chromatographically more tractable methyl ester **6**,[6,17] including a study of solvent and/or cosolvent effects on yields. No significant improvements in the yield of diols **9** were observed with substitution of **6** for NsA A in these reactions. Using alternate reaction conditions including exogenous ligands[18] (pyridine, quinuclidine, $MeSO_2NH_2$, $K_3Fe(CN)_6$, and DHQD) that are known to accelerate OsO_4-mediated transformations did not improve the reaction. Indeed, the best yields of **9** obtained were only 40% using catalytic OsO_4 (0.024 M OsO_4/hexane, 0.1 equiv) with *N*-methylmorpholine-*N*-oxide as the cooxidant. Stoichiometric osmium tetroxide or use of other cooxidants had little beneficial effect on this reaction. However, substitution of the more electron-rich *N*-alkyl nodulisporamide **7**[6,19] for **1** or **6** in our "optimized" dihydroxylation reaction led to formation of a diastreoisomeric mixture of diols **10** at an accelerated rate (4 h)[20] in excellent yields (80%) (Scheme 1).[21] Subsequent oxidation of diols **10** (without purification) proceeded smoothly under Corey's conditions[22] [$Pb(OAc)_4$, pyridine, MeOH, 0 °C] in near quantitative yields to form the 3″-aldehyde **3**.[23−25]

(8) (a) Tyagarajan, S.; Chakravarty, P. K.; Wyvratt, M. J.; Fisher, M. H.; Meinke, P. T.; Schmatz, D. M.; Shoop, W. L.; Warmke, L. M.; Zakson-Aiken, M. *Abstracts of Papers*, The 221st National Meeting of the American Chemical Society, San Diego, CA, April 1−5, 2001; American Chemical Society: Washington, DC; Abstract 245. (b) Ayer, M. B.; Chakravarty, P. K.; Meinke, P. T.; Shih, T. L.; Wyvratt, M. J.; Fisher, M. H.; Warmke, L. M.; Zakson-Aiken, M.; Shoop, W. L.; Schmatz, D. M. *Abstracts of Papers*, The 222nd National Meeting of the American Chemical Society, Chicago, IL, August 26−30, 2001; American Chemical Society: Washington, DC; Abstract 245. (c) Berger, R.; Shoop, W. L.; Pivnichny, J. V.; Warmke, L. M.; Zackson-Aiken, M.; Owens, K. A.; Demontgney, P.; Schmatz, D. M.; Wyvratt, M. J.; Fisher, M. H.; Meinke, P. T.; Colletti, S. L. *Org. Lett.* **2001**, *3*, 3715.

(9) All epoxidation reagents (MCPBA, AcOOH, H_2O_2, tBuOOH, dimethyldioxirane) failed completely due to the lability of the indole ring, as did ozonolyses[10] (using either stoichiometric or excess ozone) and use of ozonide−phosphine complexes[11] such as $(PhO)_3P{\cdot}O_3$. Similarly, the use of ruthenium catalysts (i.e., $RuCl_3{\cdot}3H_2O$, RuO_4, and RuO_2)[12,13] under a variety of conditions was also unsuccessful due to the rapid and complete degradation of **1**.

(10) Iwata, C.; Takemoto, Y.; Nakamura, A.; Imanishi, T. *Tetrahedron Lett.* **1985**, *26*, 3227.

(11) Wolfe, S.; Hasan, S. K.; Campbell, J. R. *J. Chem. Soc., Chem. Comm.* **1970**, 1420.

(12) Chakraborti, A. K.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2605.

(13) Martin, V. S.; Palazon, J. M.; Rodriguez, C. M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; John Wiley & Sons: New York, 1995; Vol. 6, pp 4415−4422,

(14) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(15) Viski, P.; Sezeverenyi, Z.; Simandi, L. I. *J. Org. Chem.* **1986**, *51*, 3213.

(16) The internal 1″,2″-double bond is less reactive than the corresponding 3″,4″-olefin presumably due to steric effects of the C_8 methyl group.

(17) (a) Treatment of **1** with stoichiometric OsO_4 gave a ∼1:1 mixture of diastereoisomeric diols **8** in modest yield (∼30%) along with a low level of the 3″-aldehyde **3** (10%). The major byproducts were a mixture of unidentified over-oxidation products along with some unreacted **1**. (b) The use of catalytic OsO_4 in the presence of $NaIO_4$ under standard conditions produced a mixture of two aldehydes **3** and **5**, separable by chromatography, in 24 and 2% yields, respectively, along with a mixture of unidentified over-oxidation products.

(18) Herrman, W. A.; Eder, S.; Scherer, W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1345.

(19) A facilitated coordination of OsO_4 to the 3″,4″-double bond was anticipated in the case of electron-rich amide **7**.

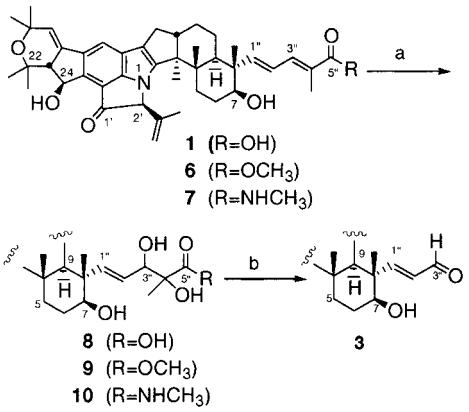
(20) An extended reaction time (>8 h) produced a small amount (∼10%) of the tetrahydroxy analogue of **10** (due to hydroxylation of the electron-rich styrenyl C_{18}−C_{19} double bond) along with the desired products.

(21) **Preparation of Diols 10 from the Amide 7.** To a solution of **7** (0.27 mmol) in CH_2Cl_2 (15 mL) were added *N*-methylmorpholine *N*-oxide (1.64 mmol) and a 4% aqueous solution of OsO_4 (0.055 mmol). After stirring for 4 h at 25 °C, the mixture was poured into 10% aqueous Na_2SO_3 and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The crude diols **10** (190 mg) (containing ∼10% **3**) obtained were used in the next step without purification. The diastereoisomers of **10** could be separated by silica gel chromatography using EtOAc−hexane (2:1).

(22) Corey, E. J.; Xiang, Y. B. *Tetrahedron Lett.* **1988**, *29*, 995.

(23) To a solution of crude diols **10** (190 mg, 0.245 mmol) in methanol (12 mL) was added pyridine (0.12 mL) at 0 °C followed by $Pb(OAc)_4$ (110 mg, 0.245 mmol). After 15 min of stirring at ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and poured into aqueous saturated $Na_2S_2O_3$. The organic phase was separated and washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The pure

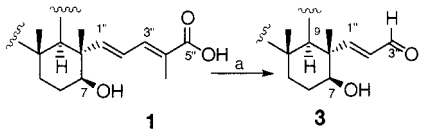
Scheme 1[a]



[a] Reaction conditions: (a) OsO_4, *N*-methylmorpholine-*N*-oxide, CH_2Cl_2, 25 °C, 4 h (80%); (b) $Pb(OAc)_4$, pyridine, MeOH, 0 °C, 15 min (92%).

While the use of amide **7** improved yields, ideally, preparation of **3** directly from **1** still represented the most attractive strategy requiring minimal synthetic manipulations. Since the use of $KMnO_4$ under neutral conditions,[26] particularly $KMnO_4$ in THF−H_2O systems,[15] is known to stop the oxidation of an olefin at the aldehyde stage, a two-phase oxidation system consisting of NsA A in CH_2Cl_2 and $KMnO_4$ in water was examined. The reaction was surprisingly clean; the aldehyde **3** was produced in modest yield (30−35%) as the only TLC mobile product, while the baseline material accounted for much of the unconverted starting material. Further optimization of the reaction using phase transfer catalysts[27] such as 18-crown-6 in a two-phase system or anhydrous *n*-$C_{16}H_{33}N(Me)_3{\cdot}MnO_4$ (CTAP)[28] in a homogeneous system (CH_2Cl_2) did improve the yield of **3** somewhat, but the reaction failed to go to completion.[29] Ultimately, a key breakthrough in the selective oxidation of **1** occurred using $KMnO_4$ adsorbed on various solid supports, especially moist alumina.[30] To this end, treatment of a CH_2Cl_2 solution of **1** with $KMnO_4$ adsorbed on moist, weakly acidic alumina for 20 min at room temperature provided **3** in a near quantitative yield (Scheme 2).[31]

Scheme 2[a]



[a] Reaction conditions: (a) $KMnO_4$, alumina (weakly acidic), water, CH_2Cl_2, 25 °C, 20 min (94%).

This mild single-step procedure provided the most efficient conversion of NsA A into **3** and was readily applied toward the synthesis of **3** in multigram quantities with minimal purification of the final product. Indeed, purification simply entailed direct filtration of the crude reaction without workup through a short pad of Celite followed by evaporation of the solvent.

With the ready availability of **3**, attention was directed toward the synthesis of 3″-carboxylic acid **4** and, subsequently, to 1″-aldehyde **7** (Scheme 3).

These truncated analogues of NsA A, in addition to being useful synthetic intermediates, were also considered to be important for understanding the structure−activity relationship of the dienoic acid side chain. For the synthesis of **4**, a direct oxidation of **3** using sodium chlorite[32] was clearly a method of choice. Treatment of **3** with sodium chlorite (*t*-BuOH, NaH_2PO_4, 2-methylbutene, 25 °C) smoothly formed **4** in 76% yield.[33] This procedure was also extended to the synthesis of bis-silyl-protected derivatives **12a** and **12b**. For

aldehyde **3** (0.14 g, 92%) was obtained following purification by silica gel flash chromatography using acetone−hexane (1:2). ^1H NMR (500 MHz, $CDCl_3$): δ 9.62 (d, J = 7.5 Hz, 1H), 7.72 (s, 1H), 6.66 (d, J = 15.8 Hz, 1H), 6.19 (dd, J_1 = 7.6 Hz, J_2 = 15.8 Hz, 1H), 6.07 (d, J = 2.8 Hz, 1H), 5.26 (d, J = 6.2 Hz, 1H), 5.23 (s, 1H), 5.09 (s, 1H), 5.02 (br s, 1H), 3.54 (br s, 1H), 3.20 (s, 1H), 2.90 (dd, J_1 = 3.4 Hz, J_2 = 6.1 Hz, 1H), 2.82 (m, 1H), 2.77 (dd, J_1 = 6.6 Hz, J_2 = 13.9 Hz, 1H), 2.34 (dd, J_1 = 13.5 Hz, J_2 = 13.4 Hz, 1H), 2.01 (br s, 1H), 1.40−1.90 (m, 8H), 1.51 (s, 3H), 1.46 (br s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.17 (s, 6H), 1.12 (s, 3H), 0.98 (s, 3H). MS *m/e*: 624.4 (M + 1).

(24) Cleavage of diols **10** with sodium periodate was also probed under a variety of conditions, but in all instances, the yields were inferior.

(25) All new nodulisporic acid analogues were characterized by ^1H NMR and mass spectrometry.

(26) For a review of oxidative cleavages of C=C bonds, see: Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society; Washington, DC, 1990; pp 77, 96.

(27) (a) Sam, D. J.; Simmons, H. E. *J. Am. Chem. Soc.* **1972**, *94*, 4024. (b) Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1978**, *43*, 1532.

(28) (a) Hazra, B. G.; Kumar, T. P.; Joshi, P. L. *Liebigs Ann./Recl.* **1997**, 1029. (b) Bhushan, V.; Rathore, R.; Chandrasekaran, S. *Synthesis* **1984**, *5*, 431. (c) Reischl, W.; Zbiral, E. *Tetrahedron* **1979**, *35*, 1109.

(29) Reaction of **1** with CTAP gave **3** in 40% yield along with unreacted **1** (~50%), which was readily recycled. While this reaction failed to go to completion, the nonpolar **3** was readily separable from unreacted acid **1**. Low levels of the corresponding 1″-aldehyde **5** (<5 %) was also obtained from this reaction, presumably via the intermediacy of the 1″,2″3″,4″-tetra-ol of **1**.

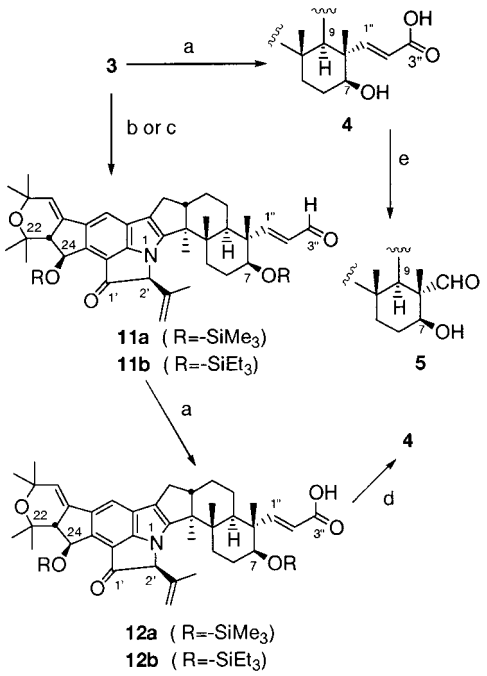
(30) (a) Quici, S.; Regen, S. L. *J. Org. Chem.* **1979**, *44*, 3436. (b) Menger, F. M.; Lee, D. G. *J. Org. Chem.* **1979**, *44*, 2446. (c) Ferreira, J. T.; Cruz, W. O.; Vieira, P. C.; Yonashiro, M. *J. Org. Chem.* **1987**, *52*, 3698. (d) Lee, D. J.; Chen, T.; Wang, Z. *J. Org. Chem.* **1993**, *58*, 2918.

(31) **Preparation of 3 from 1.** $KMnO_4$ (3 g) was dissolved in water (5 mL), and the solution was cooled to 0 °C. Al_2O_3 (weakly acidic, 10.8 g) was added, and the solution was stirred for 5 min until thoroughly mixed. A solution of **1** (3 g) in CH_2Cl_2 (300 mL) was added dropwise via an addition funnel over 20 min under rapid stirring. The solution was aged for an additional 20 min at 25 °C and then filtered through a pad of Celite using CH_2Cl_2 as an eluant followed by EtOAc. The solvents were removed under reduced pressure at ambient temperature to yield pure **3** (2.6 g, 94%).

(32) (a) Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 470. (b) Gorgen, G.; Boland, W.; Preiss, U.; Simon, H. *Helv. Chem. Acta*. **1989**, *72*, 917.

(33) **Preparation of 4.** To a solution of **3** (0.14 g) in *t*-BuOH (3 mL) at 25 °C was added 2-methyl-2-butene (1 mL), and the mixture was stirred for 5 min. A solution of $NaOCl_2$ (0.08 g) and $NaH_2PO_4{\cdot}2H_2O$ (0.09 g) in water (1.5 mL) was then added. After 4 h of stirring, the solution was poured into saturated NH_4Cl (aqueous), extracted with CH_2Cl_2 (3×), and dried (Na_2SO_4). The solution was filtered and concentrated under reduced pressure. Pure 3″-acid **4** (0.11 g, 76%) was obtained following flash chromatography on silica gel using 60% acetone in hexane. ^1H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 1H), 6.89 (d, J = 15.8 Hz, 1H), 6.07 (d, J = 2.7 Hz, 1H), 5.89 (d, J = 16 Hz, 1H), 5.26 (d, J = 6.2 Hz, 1H), 5.22 (s, 1H), 5.09 (s, 1H), 5.02 (br s, 1H), 3.54 (br s, 1H), 2.90 (dd, J_1 = 3.4 Hz, J_2 = 6.1 Hz, 1H), 2.82 (m, 1H), 2.77 (dd, J_1 = 6.6 Hz, J_2 = 13.9 Hz, 1H), 2.34 (dd, J_1 = 13.5 Hz, J_2 = 13.4 Hz, 1H), 2.01 (br s, 1H), 1.40−1.90 (m, 8H), 1.51 (s, 3H), 1.46 (br s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H), 0.96 (s, 3H). MS *m/e*: 640.6 (M + 1).

Scheme 3[a]



[a] Reaction conditions: (a) $NaClO_2$, $Me_2C{=}CHMe$, NaH_2PO_4, *t*-BuOH, H_2O, 25 °C, 4 h (76%); (b) $(Me_3Si)_2NH$, CH_3CN, 25 °C, 12 h (100%); (c) Et_3SiCl, $^iPr_2NEt$, CH_2Cl_2, from 0 to 25 °C, 2 h (100%); (d) pyridinium-*p*-toluenesulfonate, EtOH, 25 °C, 2 h; (e) $KMnO_4$, alumina (weakly acidic), water, CH_2Cl_2, 25 °C, 20 min (24%).

the synthesis of **12a** and **12b**, both C_7 and C_{24} hydroxyls of **3** were silylated using either hexamethyldisilazane (CH_3CN, 25 °C) or triethylsilyl chloride ($^iPr_2NEt$, CH_2Cl_2, 25 °C) to produce **11a** and **11b**, respectively, in near quantitative yields.[34,35] These aldehydes **11a** and **11b** were then oxidized with sodium chlorite to afford **12a** and **12b** in high yields under mild conditions.[36] Removal of the protecting groups (PPTS, EtOH, 25 °C)[37] generated **4** in near quantitative yields. Finally, the 1″,2″-olefinic bond in **4** was oxidized using $KMnO_4$ adsorbed on moist, weakly acidic alumina (CH_2Cl_2, 25 °C, 12 h), in a manner similar to the synthesis of **3**, to produce **5** in 24% yield.[38]

In conclusion, nodulisporic acid A (**1**) was selectively oxidized in a single step under mild conditions using $KMnO_4$ adsorbed on weakly acidic Al_2O_3 to produce the corresponding side-chain truncated 3″-aldehyde **3** in near quantitative yields. Alternatively, **3** was also prepared from the amide **7** in two steps using OsO_4 followed by $Pb(OAc)_4$. Further oxidation of **3** with sodium chlorite produced the 3″-carboxylic acid **4** in high yields, which upon oxidative degradation using $KMnO_4$ on a solid support formed 1″-aldehyde **5**. Both the 3″- and 1″-aldehydes **3** and **5**, respectively, along with carboxylic acid **4** represent potentially important intermediates for the preparation of new, side chain modified derivatives of **1**.

Acknowledgment. We gratefully thank Ms. Amy Bernick for providing mass spectral data and Mr. John Ondeyka for providing nodulisporic acid A.

OL025766D

(34) **Preparation of 11a.** To a solution of **3** (0.56 g) in CH_3CN (10 mL) at 25 °C was added $((CH_3)_3Si)_2NH$ (1.8 mL), and the solution was aged for 12 h. Additional $((CH_3)_3Si)_2NH$ (1.5 mL) and CH_3CN (3 mL) were then added. After 3 h, the solvent was removed under reduced pressure and the residue dried in vacuo for 1 h to yield to pure 7,24-bis-*O*-trimethylsilyl 3″-aldehyde **11a** (0.87 g, 100%), which required no purification.

(35) Hart, T. W.; Metcalf, D. A.; Scheinmann, F. *J. Chem. Soc. Chem. Commun.* **1979**, 156.

(36) **Preparation of 12b.** To a solution of **11b** (1 g) in *t*-BuOH (25 mL) at 25 °C was added 2-methyl-2-butene (6 mL), and the mixture was stirred for 5 min. A solution of $NaOCl_2$ (0.954 g) and $NaH_2PO_4{\cdot}2H_2O$ (1.28 g) in water (10 mL) was then added. After 4 h of stirring, the solution was poured into saturated NH_4Cl (aqueous), extracted with CH_2Cl_2 (3×), and dried (Na_2SO4). The solution was filtered and concentrated under reduced pressure. Pure bis-OTES-3″-acid **12b** (0.73 g) was obtained following flash chromatography on silica gel using gradient elution with 5−25% EtOAc in hexane.

(37) Askin, D.; Joe, D.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1990**, *55*, 5451.

(38) **Preparation of 5.** To a well-stirred mixture of $KMnO_4$ (0.2 g), water (0.2 mL), and Al_2O_3 (weakly acidic, 10.8 g) was added a solution of **4** (0.2 g) in CH_2Cl_2 (20 mL) at 25 °C. The mixture was aged for 12 h at 25 °C and then filtered through a pad of Celite. The residue was washed with CH_2Cl_2 (100 mL); the combined filtrate was removed under reduced pressure at ambient temperature, and the crude product was purified by flash chromatography using 50% EtOAc in hexane to give pure aldehyde **5** (0.045 g, 24%). ^1H NMR (500 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.72 (s, 1H), 6.07 (d, J = 2.8 Hz, 1H), 5.26 (d, J = 6.4 Hz, 1H), 5.22 (s, 1H), 5.09 (s, 1H), 5.02 (br s, 1H), 3.54 (br s, 1H), 3.20 (s, 1H), 2.90 (dd, J_1 = 3.0 Hz, J_2 = 6.0 Hz, 1H), 2.82 (m, 1H), 2.76 (dd, J_1 = 6.6 Hz, J_2 = 13.9 Hz, 1H), 2.6 (s.1H), 2.34 (dd, J_1 = 13.5 Hz, J_2 = 13.4 Hz, 1H), 2.20 (s, 1H), 1.40−1.90 (m, 8H), 1.51 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 0.99 (s, 3H). MS *m*/*e*: 598.5 (M + 1).