An Efficient Entry to Amino-Substituted Resorcylic Acid Derivatives for the Synthesis of Platensimycin and Analogues

Philipp Heretsch, Athanassios Giannis*

Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax +49(0341)9736599; E-mail: giannis@uni-leipzig.de

Received 21 May 2007

Abstract: An efficient entry to protected amino-substituted resorcylic acid derivatives, methyl 3- or 5-amino-2,4-bis(methoxymethoxy)benzoate, is reported. Both derivatives can be used for the synthesis of platensimycin and its analogues.

Key words: amino-resorcylic acid, antibiotic, arene, natural products, platensimycin

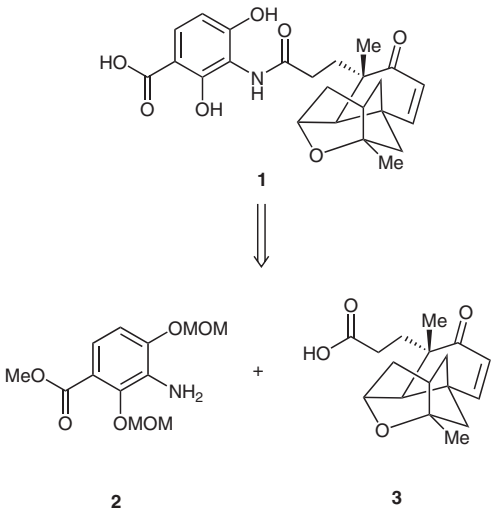
The recently discovered antibiotic (–)-platensimycin (**1**) exhibits remarkable broad-spectrum activity against gram-positive pathogens, among them strains of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecalis* (VRE), and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Its mechanism of action entails inhibition of bacterial fatty acid synthesis by affecting β-ketoacyl-[acyl-carrier-protein (ACP)] synthase I/II (Fab F/B). Hence, it acts by the same mechanism as the long known, but much weaker, inhibitors cerulenine and thiolactomycin.[1,2]

The first total synthesis of racemic platensimycin by Nicolaou and co-workers[3] applied a retrosynthetic scission to form an arene **2** and a ketolide subunit **3** (Scheme 1); this route was later used in the formal racemic[4] as well as in the enantioselective[5] syntheses by Nicolaou's group and a formal racemic synthesis by the Snider group.[6]

The aromatic subunit of platensimycin was synthesized by Nicolaou and co-workers in five steps from commercially available 2-nitroresorcinol (**4**) and its key features were directed *ortho*-metalation to attach the carboxylic acid moiety and microwave-assisted *tert*-butoxycarbonyl (Boc) deprotection (Scheme 2).

Much to our surprise there are no other procedures reported in literature for the synthesis of such tetrasubstituted amino-resorcylic acids or their derivatives.

Since a facile and efficient synthetic pathway to multigram quantities of appropriately protected **2** and derivatives was required for our ongoing work on platensimycin analogues, a strategy starting from commercially available methyl 2,4-dihydroxybenzoate (**6**) making use of a nitration to form the appropriately substituted arene was examined.

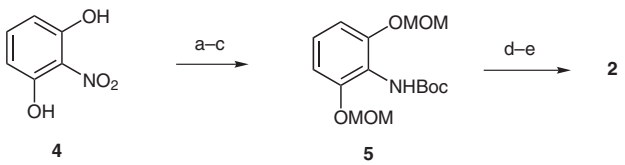


Scheme 1 The retrosynthetic approach to platensimycin

Several nitration and nitrosation/oxidation procedures were carefully investigated (such as $NaNO_2$ in AcOH, $NaNO_2$ in Ac_2O–AcOH,[7] $NaNO_2$ in Ac_2O–AcOH and concd HNO_3–H_2SO_4). Eventually we decided to use in situ formed acetyl nitrate[8] (by adding fuming HNO_3 in AcOH to a soln of the arene in Ac_2O–AcOH) as a suitable nitration agent.

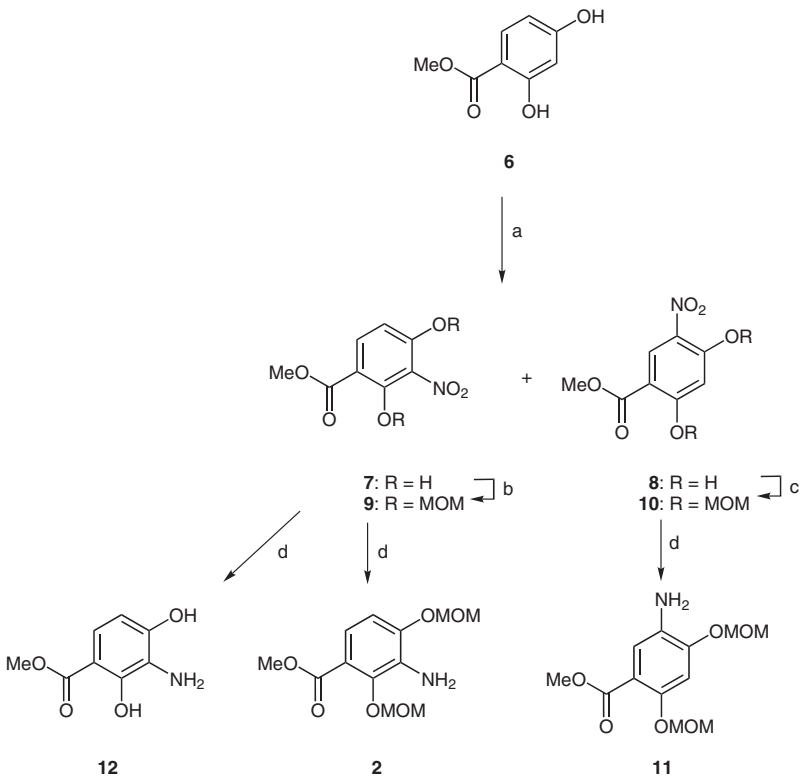
Although **7** and its known isomer **8**[9] were formed in almost 1:1 ratio in the reaction, separation was easily effected by complete precipitation of **8** by addition of water to the reaction mixture followed by isolation of **7** by extraction and chromatography. The use of 1.1 equivalents of nitric acid therein represents a compromise between complete conversion of the substrate and formation of undesired dinitration products.

Nitro-substituted dihydroxybenzoates **7** and **8** were now converted in two steps into the bis(methoxymethyl)-protected amino-substituted resorcylic acid derivatives **9** and **10**, respectively. Methoxymethyl-protection of **7** proceed-



Scheme 2 Nicolaou's synthesis of the aromatic subunit **2** of platensimycin. *Reagents and conditions*: (a) NaH, MOMCl; (b) H_2, Pd/C; (c) Boc_2O; (d) BuLi, TMSCl, then BuLi, methyl cyanoformate; (e) 1,2-dichlorobenzene, 205 °C.

SYNTHESIS 2007, No. 17, pp 2614–2616
Advanced online publication: 08.08.2007
DOI: 10.1055/s-2007-983843; Art ID: P06007SS



Scheme 3 Synthesis of platensimycin's aromatic subunit **2**, isomer **11** and parent arene **12**. *Reagents and conditions*: (a) HNO_3, Ac_2O–AcOH; (b) MOMCl, NaI, DIPEA; (c) NaH, MOMCl; (d) H_2, Pd/C.

ed smoothly to give **9** when using an excess of methoxymethyl chloride and sodium iodide in a DME–DMF mixture; hydrogenation of **9** using 10% palladium on carbon and an ambient pressure of hydrogen furnished the desired arene **2** in 34% yield over three steps. Furthermore isomer **8** was protected and hydrogenated in a total yield of 28%. Finally the unknown parent compound **12** was obtained by hydrogenation of **7** in nearly quantitative yield.

In summary, we have developed an efficient entry to protected amino-substituted resorcylic acid derivatives **2** and **11**. Compound **2** is a crucial intermediate for platensimycin synthesis. Both derivatives will facilitate the synthesis of this unique antibiotic and its analogues.

All reagents were commercially obtained from Acros, Aldrich, Alfa Aesar [methyl 2,4-dihydroxybenzoate (**6**)] and Fluka and used without further purification. Melting points were measured with a Boetius-micro hot stage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 (300 MHz for ^1H NMR; 75 MHz for ^{13}C NMR) and Bruker Avance-DRX 400 (400 MHz for ^1H NMR; 100 MHz for ^{13}C NMR); the residual solvent peak was used as an internal reference. HRMS were obtained on a Bruker Daltonics APEX II (for ESI). Reactions involving moisture-sensitive reactants were performed in flame-dried glassware under an argon atmosphere; reactants were added via syringe. Flash column chromatography was performed on silica gel (Acros 60 A, 0.035–0.070 mm) and analytical TLC on pre-coated silica gel plates (Merck 60 F_{254}, 0.25 mm).

Methyl 2,4-Dihydroxy-3-nitrobenzoate (7) and Methyl 2,4-Dihydroxy-5-nitrobenzoate (8)

Methyl 2,4-dihydroxybenzoate (**6**, 9.15 g, 54.4 mmol) was dissolved in a mixture of glacial AcOH (66 mL) and Ac_2O (34 mL) using ultrasonication. After cooling the clear soln to 0 °C (ice bath), a mixture of fuming HNO_3 (100%) (3.80 g, 60 mmol, 1.1 equiv) in glacial AcOH (30 mL) was added over 1 min. When addition was complete, the temperature of the light brown soln was allowed to rise to 22 °C and stirring was continued for a further 15 min after which an ochre-colored suspension had formed. H_2O (130 mL) was added, whereupon the mixture was aged for another 30 min without stirring. The precipitate was filtered, rinsed with small amounts of H_2O, and dried under vacuum to give crude **8**, which was recrystallized (MTBE, 250 mL) to give pure **8** (3.10 g, 33% based on recovered **6**) as pale yellow cubes.

The clear brown soln and combined washings were extracted with Et_2O (3 × 150 mL) and the solvents were removed under reduced pressure to give crude **7** as an deeply orange colored solid. Purification was carried out by chromatography (silica gel, *n*-hexane–EtOAc, 1:1) to yield pure **7** (3.40 g, 35% based on recovered **6**) as bright yellow needles and recovered starting material (1.40 g, 8.3 mmol).

Methyl 2,4-Dihydroxy-5-nitrobenzoate (8)

Mp 167–168 °C, R_f = 0.42 (*n*-hexane–EtOAc, 1:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.00 (s, 3 H, CH_3), 6.62 (s, 1 H, arom), 8.74 (s, 1 H, arom), 11.00 (s, 1 H, OH), 11.45 (s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.1, 105.9, 106.9, 127.5, 129.8, 160.5, 168.0, 169.1.

HRMS-ESI: *m*/*z* $[M - H]^-$ calcd for $C_8H_6NO_6$: 212.02006; found: 212.02002.

Methyl 2,4-Dihydroxy-3-nitrobenzoate (7)

Mp 125–126 °C, R_f = 0.48 (*n*-hexane–EtOAc, 2:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, CH_3), 6.63 (d, ^3J = 9.3 Hz, 1 H, arom), 7.99 (d, ^3J = 9.3 Hz, 1 H, arom), 11.17 (s, 1 H, OH), 12.87 (s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.0, 105.9, 109.4, 129.5, 136.9, 160.3, 160.9, 170.0.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_8H_7NO_6Na$: 236.01656; found: 236.01652.

Methyl 2,4-Bis(methoxymethoxy)-3-nitrobenzoate (9); Typical Procedure

To a stirred solution of NaH (9.00 g, 60.0 mmol) in anhyd DME (100 mL) was added MOMCl (90%, technical, 6.0 mL, 70.0 mmol), a solution of **7** (3.20 g, 15.0 mmol) in anhyd DMF (50 mL) and DIPEA (13.7 mL, 80.0 mmol) consecutively. The yellow suspension was heated to 55 °C for 1 h. After this time the reaction mixture was diluted with H_2O (150 mL) and sat. aq $NaHCO_3$ (300 mL) and extracted with Et_2O (4 × 150 mL). The organic phase was washed with 1 M HCl (50 mL) and brine (50 mL) and was dried with $MgSO_4$ and filtered. The solvent was removed in vacuo and the resulting yellow oil was filtered through a short plug of silica gel (*n*-hexane–EtOAc, 3:1) yielding pure **9** (4.40 g, 14.6 mmol, 98%) as a pale yellow solid; mp 66–68 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 3.89 (s, 3 H, $COOCH_3$), 5.15 (s, 2 H, OCH_2O), 5.28 (s, 2 H, OCH_2O), 7.06 (d, ^3J = 9.0 Hz, 1 H, arom), 7.97 (d, ^3J = 9.0 Hz, 1 H, arom).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.6, 57.0, 58.0, 95.1 (2 ×), 102.3, 110.8, 118.2, 134.1, 150.9, 152.4, 164.4.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{15}NO_8Na$: 324.06899; found: 324.06923.

Methyl 2,4-Bis(methoxymethoxy)-5-nitrobenzoate (10)

To a stirred suspension of NaH (60% in paraffin oil, 1.20 g, 30.0 mmol), which was previously washed with anhyd *n*-petane (2 × 5 mL), in anhyd DMF (30 mL) was added dropwise a solution of **8** (2.13 g, 10.0 mmol) in anhyd DMF (30 mL) at 0 °C (ice bath). The deep-red solution was stirred until no more hydrogen evolution could be detected (20 min). Then, MOMCl (90%, technical, 1.85 g, 23.0 mmol) was added dropwise. After complete addition the ice bath was removed and stirring at r.t. was continued for 1 h. After this time the reaction mixture was diluted with H_2O (100 mL) and stirred for 1 h. The mixture was extracted with Et_2O (200 mL) and the organic phase was washed with H_2O (2 × 200 mL) and brine (50 mL). The organic phase was dried with $MgSO_4$ and filtered, the solvent was removed in vacuo to yield pure **10** (2.57 g, 8.5 mmol, 85%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.55 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.90 (s, 3 H, $COOCH_3$), 5.34 (s, 2 H, OCH_2O), 5.36 (s, 2 H, OCH_2O), 7.12 (1 H, arom), 8.54 (1 H, arom).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4, 57.0, 57.2, 95.2, 95.5, 103.5, 110.8, 113.9, 130.5, 155.3, 161.7, 164.1.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{12}H_{16}NO_8$: 302.08704; found: 302.08709.

Methyl 3-Amino-2,4-bis(methoxymethoxy)benzoate (2); Typical Procedure

Methyl 2,4-bis(methoxymethoxy)-3-nitrobenzoate (**9**, 1.51 g, 5.0 mmol) was hydrogenated with ambient pressure of H_2 using 10% Pd/C (530 mg, 10 mol%) in EtOAc (100 mL) for 16 h. The resulting suspension was filtered through a pad of Celite and washed with EtOAc and the solvent was removed under reduced pressure to give pure **2** (1.36 g, quantitative) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.85 (s, 3 H, $COOCH_3$), 4.20 (br, 2 H, NH_2), 5.10 (s, 2 H, OCH_2O), 5.24 (s, 2 H, OCH_2O), 6.50 (d, ^3J = 8.7 Hz, 1 H, arom), 7.25 (d, ^3J = 8.7 Hz, 1 H, arom).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.0, 56.5, 57.8, 94.9, 101.3, 109.6, 118.1, 120.2, 131.8, 145.6, 148.7, 166.4.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{12}H_{17}NO_6Na$: 294.09481; found: 294.09506.

Methyl 5-Amino-2,4-bis(methoxymethoxy)benzoate (11)

Using the typical procedure for **2** with methyl 3-amino-2,4-bis(methoxymethoxy)benzoate (**10**, 301 mg, 1.0 mmol) gave pure **11** (271 mg, quantitative) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.49 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 3.84 (s, 3 H, $COOCH_3$), 5.12 (s, 2 H, OCH_2O), 5.23 (s, 2 H, OCH_2O), 6.89 (1 H, arom), 7.23 (1 H, arom).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.9, 56.4, 56.6, 95.0, 97.3, 105.9, 115.1, 117.5, 131.6, 148.8, 150.9, 166.3.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{12}H_{18}NO_6$: 272.11286; found: 272.11327.

Methyl 3-Amino-2,4-dihydroxybenzoate (12)

Methyl 2,4-dihydroxy-3-nitrobenzoate (**7**, 300 mg, 1.4 mmol) was hydrogenated with ambient pressure of H_2 using 10% Pd/C (150 mg, 10 mol%) in EtOAc (30 mL) for 16 h. The resulting suspension was filtered through a pad of Celite and washed with EtOAc and the solvent was removed under reduced pressure to give pure **12** (250 mg, 97%) as colorless prisms; mp 215 °C (dec.).

^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD): δ = 3.85 (s, 3 H, $COOCH_3$), 4.29 (br, 2 H, NH_2), 6.33 (d, ^3J = 8.8 Hz, 1 H, arom), 7.19 (d, ^3J = 8.8 Hz, 1 H, arom).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 52.0, 103.9, 107.2, 117.8, 123.5, 149.0, 149.5, 170.4.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_8H_9NO_4Na$: 206.04238; found: 206.04237.

Acknowledgment

Philipp Heretsch is grateful for a Ph.D. fellowship from Fonds der Chemischen Industrie (VCI).

References

(1) (a) Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarathy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C.; Hernandez, L.; Allocco, J.; Basilio, ; Tormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B. *Nature* **2006**, *441*, 358. (b) Singh, S. B.; Jayasuriya, H.; Ondeyka, J. G.; Herath, K. B.; Zhang, C.; Zink, D. L.; Tsou, N. N.; Ball, R. G.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Pelaez, F.; Young, K.; Wang, J. *J. Am. Chem. Soc.* **2006**, *128*, 11916. (c) Häbich, D.; von Nussbaum, F. *ChemMedChem* **2006**, *1*, 951.

(2) Giannis, A. *Chem. Eng. News* **2006**, *84*, 8.

(3) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7086; *Angew. Chem.* **2006**, *118*, 7244.

(4) Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 1922.

(5) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 3942; *Angew. Chem.* **2007**, *119*, 4016.

(6) Zou, Y.; Chen, C.-H.; Taylor, C. D.; Foxman, B. M.; Snider, B. B. *Org. Lett.* **2007**, *9*, 1825.

(7) Behnisch, R. In *Houben–Weyl - Methods of Organic Chemistry*, 4th ed., Vol. E 16c; Klamann, D., Ed.; Thieme: Stuttgart, **1992**, 16–20.

(8) Maleski, R. J.; Kluge, M.; Sicker, D. *Synth. Commun.* **1995**, *25*, 2327.

(9) Jadhav, G. V.; Deshpande, V. N. *J. Indian Chem. Soc.* **1952**, *29*, 773.