

Tetrahedron Letters 40 (1999) 7501-7505

TETRAHEDRON LETTERS

A concise total synthesis of (\pm) -A80915G, a member of the napyradiomycin family of antibiotics

Shunji Takemura, Aya Hirayama, Junko Tokunaga, Fumie Kawamura, Kyoko Inagaki, Kimiko Hashimoto and Masaya Nakata *

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Received 19 July 1999; accepted 12 August 1999

Abstract

 (\pm) -A80915G, a member of the napyradiomycin family of antibiotics, has been synthesized from 1-amino-2,5dimethoxy-4-nitrobenzene via the sequential palladium-catalyzed cross-coupling reactions (the Stille reaction) of aryl halides with allyltins and the Diels-Alder reaction of the chloroquinone with the Danishefsky-Brassard diene. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: napyradiomycins; Stille reactions; Diels-Alder reactions; Danishefsky-Brassard dienes.

Napyradiomycins (A1, A2, B1, B2, B3, B4, C1, C2) were isolated from the culture broth of Chainia rubra MG802-AF1.¹ They inhibit the growth of gram-positive bacteria including drug-resistant strains. The absolute structures of napyradiomycins B2 and B4 were determined by X-ray crystallography (Fig. 1). The structures of other napyradiomycins were elucidated by NMR analyses. Following the isolation of the napyradiomycins, structurally related antibiotics have been isolated: SF2415 (A1, A2, A3, B1, B2, B3),² A80915 (A, B, C, D, G),³ naphthomevalin,⁴ WS9558 (A=napyradiomycin A1, B=napyradiomycin B1),⁵ and phosphatoquinones (A, B).⁶ Naphthomevalin was easily converted to A80915G by alkaline treatment (NaOH, MeOH).⁴ Recent biological evaluation shows that napyradiomycin B1 (WS9558 B) is the non-steroidal estrogen-receptor antagonist⁵ and phosphatoquinones A and B are the protein tyrosine phosphatase inhibitors.⁶ The absolute structures of naphthomevalin and phosphatoguinone A were based on their CD spectra.^{4,6} Interestingly, A80915G (2,3-epoxynaphthomevalin) has the opposite absolute configuration to that of phosphatoquinone A. Among these compounds, A80915G has the basic structure of the napyradiomycin family of antibiotics. We now report in this letter a concise total synthesis of (\pm) -A80915G. We anticipated that the geranyl and prenyl side chains would be incorporated via the palladium-catalyzed cross-coupling reactions (the Stille reaction) of aryl halides with allyltins and the dihydroxynaphthoquinone nucleus would be obtained via the Diels-Alder reaction of the quinone

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^{*} Corresponding author. Tel: +81-45-563-1141; fax: +81-45-563-0446; e-mail: msynktxa@applc.keio.ac.jp



Figure 1.

with the Danishefsky-Brassard diene. In order to realize this strategy, it was necessary to prepare the 1,4-dimethoxybenzene derivative substituted with three different halogen atoms; the iodo and bromo substituents were used for the sequential Stille reactions and the chloro substituent was used for the regioselective Diels-Alder reaction.

The synthesis of the requisite 1,4-dimethoxybenzene derivative substituted with three different halogen atoms (I, Br, and Cl) began with the commercially available starting material, 1-amino-2,5-dimethoxy-4nitrobenzene (1) (Scheme 1). Diazotization of 1 (NaNO₂, conc. H₂SO₄, AcOH, 40°C, 0.5 h)⁷ followed by chlorination (CuCl, conc. HCl, 80°C, 20 min)⁷ afforded **2** in 70% yield. Reduction of **2** with NH₂NH₂·H₂O in the presence of a catalytic amount of FeCl₃·6H₂O (active carbon, MeOH, 65°C, 0.5 h)^{8,9} and the resulting amine **3** was regioselectively brominated [(*n*-Bu)₄NBr₃, 3:2 CH₂Cl₂:MeOH, rt, 2 h]¹⁰ to afford **4**¹¹ in 77% yield (two steps) as the sole product. The structure of **4** was confirmed by ¹H NMR analysis ($J_{a,b}$ =3.0 Hz) of **5**¹¹ derived from **4** (NaNO₂, aq. HCl, THF, 0°C, 1 h, then NaBH₄, rt, 1 h). Diazotization of **4** (NaNO₂, aq. HCl, 0°C, 20 min)⁹ followed by iodination (aq. KI, rt, 3 days)⁹ afforded the desired trihalogenated compound **6**¹¹ in 87% yield.





With the trihalogenated compound **6** in hand, we turned our attention to the palladium-catalyzed crosscoupling reactions (Scheme 2). After extensive optimization of the solvent, temperature, and catalyst, we found that this Stille reaction proceeded smoothly using **6** (1 equiv.), geranyl tributyltin (**7**)¹² (3 equiv.), and PdCl₂(dppf)¹³ (0.1 equiv.) in DMF at 125°C for 24 h, affording the desired coupling product **8**¹¹ in 73% yield. The minor by-product was the only de-iodinated compound **5** (4% yield). Under almost the same reaction conditions, the second Stille reaction of **8** (1 equiv.) afforded **10**¹¹ in 67% yield using prenyl tributyltin (9)^{12,14} (3 equiv.), and PdCl₂(dppf) (0.2 equiv.). The minor by-product in this case was the de-brominated compound 11 (29% yield).¹⁵



The next crucial step was the Diels-Alder reaction (Scheme 3). The requisite quinone 12 was obtained from 10 by oxidative demethylation with AgO-nitric acid (dioxane, rt).¹⁶ Because of the instability to silica gel column purification, the crude quinone 12 was directly subjected to the Diels-Alder reaction using several dienes (13a,¹⁷ 13b,¹⁸ 13c,¹⁹ and $13d^{20}$). Among them, only 13a was found to be a suitable diene; to a solution of the crude quinone 12 (1 equiv.) in THF was added diene 13a (3 equiv.) at rt. After 1 h at rt, 1 M aq. HCl was added and the mixture was worked up. The residue was dissolved in DMF and heated at 140°C for 1.5 h. The desired adduct 14^{11} was obtained in 38% yield from 10. The Diels-Alder reaction of 12 with other dienes (13b, 13c, and 13d) resulted in decomposition.





Although the obtained hydroxynaphthoquinone 14 completely resisted the epoxidation (aq. H_2O_2 , aq. Na_2CO_3 , EtOH, 70°C),²¹ the methoxymethyl (MOM) ether 15¹¹ obtained from 14 (MOMCl, (*i*-Pr)₂NEt, CH₂Cl₂, 0°C, 20 min, 99%) underwent smooth epoxidation (aq. H_2O_2 , aq. Na_2CO_3 , EtOH, 70°C, 5 min),²¹ affording 16¹¹ in 88% yield. Finally, deprotection of 16 with BCl₃ in CH₂Cl₂ at -100°C for

15 min afforded the desired (\pm)-A80915G in 20% yield along with the de-MOM product 17 in 37% yield.²² The obtained synthetic (\pm)-A80915G²³ was identical with the natural A80915G based on a spectroscopic comparison except for optical rotation. Studies toward the chiral syntheses of A80915G and other napyradiomycins are now in progress.

Acknowledgements

We wish to thank Drs. J. S. Mynderse and M. J. Martinelli, Eli Lilly and Company, for their kind gifts of the spectral data of the natural A80915G. We also thank Professor A. Zeeck, Universität Göttingen, for his generous gifts of the NMR spectra of naphthomevalin.

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- 22. The amount of an as yet unidentified by-product increased as the reaction time was elongated.
- 23. (±)-A80915G: reddish-brown oil; *R_f*=0.40 (5:1 hexane:ethyl acetate); UV (MeOH) 208.5 nm (ε 9500), 250.5 nm (ε 6060), 363.0 nm (ε 2480) [lit.³ (EtOH) 253 nm (ε 11000), 301 nm (ε 6720), 368 nm (ε 5240). Lit.⁴ (MeOH) 201 nm (ε 10200), 253 nm (ε 8100), 368 nm (ε 4200)]; IR (neat) 3380, 2960, 2930, 2860, 1700, 1640, 1620, 1585, 1500, 1450, 1380, 1320, 1280, 1240, 1160, 1110, 1045, 1010, 940, 860, 840, 750 cm⁻¹ [lit.³ (CHCl₃) 1697, 1637, 1618 cm⁻¹. Lit.⁴ (KBr) 1695, 1640, 1620, 1590 cm⁻¹]; ¹H NMR (300 MHz, CDCl₃) δ (TMS=0.00)=1.58 (3H, s), 1.64 (3H, s), 1.72 (3H, s), 1.73 (6H, 2×s), 1.95–2.15 (4H, m), 2.41 (1H, dd, *J*=15.5, 6.9 Hz), 2.54 (1H, dd, *J*=15.5, 6.9 Hz), 3.10 (1H, dd, *J*=15.5, 6.9 Hz), 3.23 (1H, dd, *J*=15.5, 6.9 Hz), 5.05 (1H, br t-like, *J*=ca. 6.9 Hz), 5.10–5.20 (2H, m), 6.47 (1H, br), 6.63 (1H, d, *J*=2.1 Hz), 7.02 (1H, d, *J*=2.1 Hz), 11.82 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ (CHCl₃=77.00)=16.56, 17.68, 18.21, 25.28, 25.53, 25.68, 25.86, 26.48, 39.74, 67.44, 67.62, 107.99, 108.65, 109.28, 116.83, 116.97, 124.00, 131.60, 134.39, 135.51, 138.90, 162.98, 164.56, 191.24, 195.51. Found: *m/z* 410.2094. Calcd for C₂₅H₃₀O₅: M⁺, 410.2093.