# Combined Directed *Ortho*-, Remote-Metalation and Cross-Coupling Strategies. Concise Syntheses of the Kinamycin Biosynthetic Grid Antibiotics Phenanthroviridin Aglycon and Kinobscurinone

Shin-ichiro Mohri, Marijan Stefinovic, and Victor Snieckus*

*Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1*

*Received June 20, 1997*

The kinamycins constitute a class of polyketide-derived[1] antitumor antibiotics first isolated from *Streptomyces murayamaensis*,[2] in which the already considerable biosynthetic and synthetic interest has been accelerated by their recent structural revision from *N*-cyanamides of benzo[*b*]carbazole to 5-diazobenzo[*b*]-fluorenes **1**.[3,4] Extensive biosynthetic studies by Gould and co-workers have placed a number of diverse condensed aromatics and heteroaromatics along the biosynthetic grid to the kinamycins, including the benz[*a*]-anthraquinone dehydrorabelomycin,[5a] WS-5995A (from *S. auranticolor*),[5b] the phenanthroviridins **2**[6] and **3**,[6,7] the benzo[*b*]fluorenone, kinobscurinone (**4a**)[8] and the corresponding aminobenzo[*b*]fluorene, stealthin C,[9] and prekinamycin (**4b**).[10] Structural uniqueness (**2**, **3**) and challenging biosynthetic questions[8,9] have fueled synthetic studies and have led to the synthesis of **3**,[11] **4b**,[12] and the benzofluorenone **5**[11] by Gould, Echavarren, and Hauser, respectively. We report short and efficient syntheses of phenanthroviridin aglycon (**3**) and kinobscurinone (**4a**) which demonstrate the evolving utility of strategies which link directed *ortho*-[13] and remote-metalation[14a] with transition metal catalyzed cross-coupling reactions.[14] Since **5** has been previously converted into **4a**,[8] prekinamycin **4b**,[9,10,12] and stealthin C,[9] this work also constitutes total synthesis of these natural products.

The synthesis of phenanthroviridin aglycon (**3**), the first naturally-occurring benzo[*b*]phenanthridine, was initiated by the preparation of the oxaborole **7**[15] from the readily available benzyl alcohol **6**[16] using a directed *ortho*-metalation−trimethylborate quench protocol (Scheme 1).

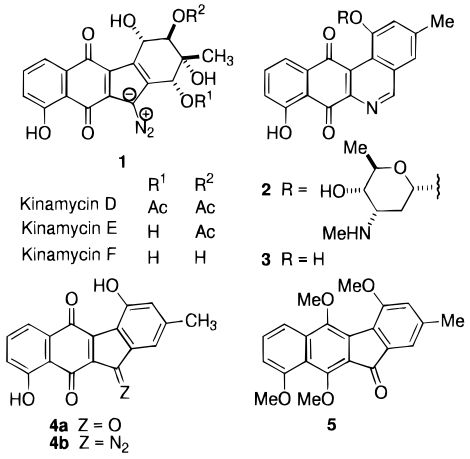
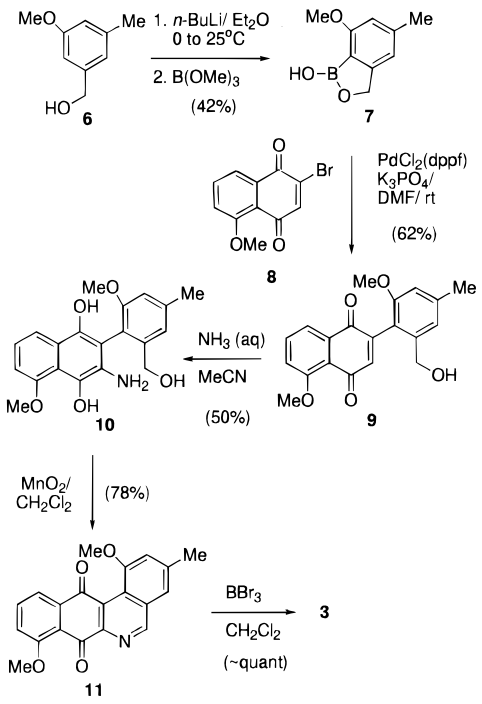



**Figure 1.**

**Scheme 1**



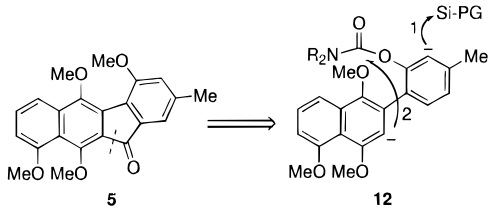

Suzuki−Miyaura cross-coupling[17] of **7** with the versatile bromojuglone **8**[18] under anhydrous conditions[19] furnished the biaryl **9** in good yield. Simple dissolution of **9** in aqueous ammonia[20] led directly to the hydroquinone **10** in modest yield which, upon treatment with $MnO_2$, was converted into **11** by an oxidative cyclization which appears to be unprecedented. Deprotection with $BBr_3$ concluded the synthesis of the phenanthroviridin aglycon **3** in five steps from **7** and 15% overall yield which compares favorably with the previous route achieved by Gould.[10,21]

The construction of the benzofluorenone **5** was formulated on the basis of a key remote-metalation−carbamoyl migration reaction (Scheme 2, **12**, step 2) which, perforce, necessitates prior silicon protection[14b](step 1).

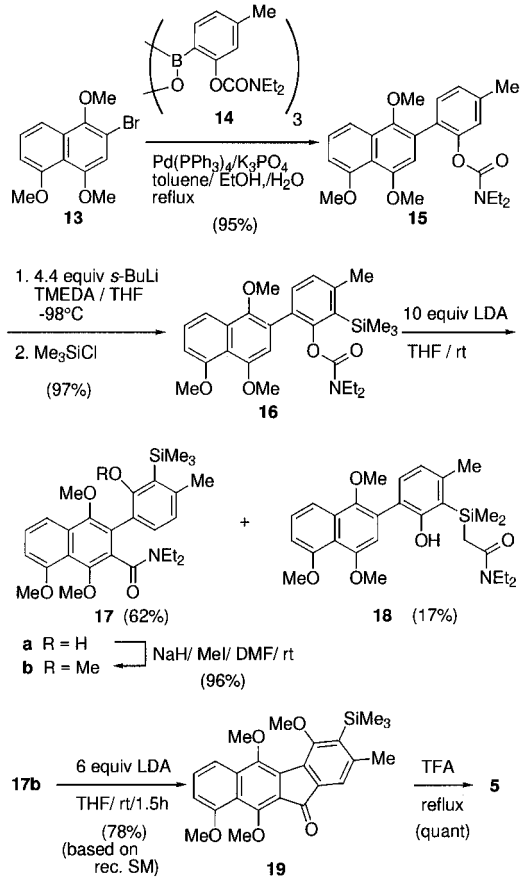
(1) Gould, S. J.; Tamayo, N.; Melville, C. R.; Cone, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 2207.
(2) Mithani, S.; Weeratunga, G.; Taylor, N. J.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1994**, *116*, 2209.
(3) Sato, Y.; Gould, S. J. *Tetrahedron Lett.* **1985**, *26*, 4023.
(4) Sato, Y.; Gould, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 4625.
(5) (a) Seaton, P. J.; Gould, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5282. (b) Watanabe, M.; Date, M., Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37* (2), 292.
(6) Fendrich, G.; Zimmermann, W.; Gruner, J.; Auden, J. A. L. Eur. Pat. Appl. EP 304, 400 (Cl.C07D221/18), 1989.
(7) Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1992**, *57*, 2774.
(8) Cone, M. C.; Hassan, A. M.; Gore, M. P.; Gould, S. J.; Borders, D. B.; Alluri, M. R. *J. Org. Chem.* **1994**, *59*, 1923.
(9) (a) Gould, S. J.; Melville, C. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 51. (b) For a recent synthesis of Stelathins A and B see: Koyama, H.; Kamikawa, T. *Tetrahedron Lett.* **1997**, *38*, 3973.
(10) Gould, S. J.; Melville, C. R.; Cone, M. C.; Chen, J.; Carney, J. R. *J. Org. Chem.* **1997**, *62*, 320.
(11) (a) Gould, S. J.; Chen, J.; Cone, M. C.; Gore, M. P.; Melville, C. R.; Tamayo, N. *J. Org. Chem.* **1996**, *61*, 5720. (b) de Frutos, O.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 8953.
(12) Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722.
(13) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(14) (a) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424. (b) Fu, J.; Zhao, B.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683.
(15) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1988**, *29*, 2517.
(16) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(17) Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889.
(18) Brown, A. G.; Crimmin, M. J.; Edwards, P. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 123.
(19) Fu, J.-M. Ph. D. Thesis, University of Waterloo, **1990**. Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221. Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.
(20) Echavarren, A. M.; Tamayo, N.; Cardenas, D. J. *J. Org. Chem.* **1994**, *59*, 6075. Gore, M. P.; Gould, S. J.; Weller, D. D. *J. Org. Chem.* **1992**, *57*, 2774.

S0022-3263(97)01123-7 CCC: $14.00 

**Scheme 2**



**Scheme 3**



Towards testing this approach, the AB/D ring system **15** (Scheme 3) was prepared in high yield by cross-coupling of bromonaphthalene **13**[15] with the 2-carbamoyloxy phenylboronic acid **14**.[22] Protection of the most reactive metalation site and avoidance of the anionic *ortho*-Fries rearrangement[14b] in **15** was accomplished by low temperature metalation−silylation and afforded **16** in quantitative yield. The critical O → C ring-to-ring carbamoyl transfer was achieved with excess LDA to give **17a** in 62% yield accompanied by **18**, a minor product arising from α-silyl methyl deprotonation−carbamoyl migration.[23,24] Phenol **17a** was methylated to give biarylamide[25,29] **17b** which, under the optimized conditions shown, underwent a second remote-metalation−cyclization[14a] to furnish fluorenone **19** in 78% yield based on recovered starting material. The synthesis was concluded by treatment of **19** with TFA at reflux to afford benzofluorenone **5** (quantitative yield) which was shown to be identical with authentic material by spectral comparison.[12]

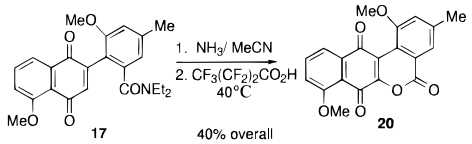
In conclusion, phenanthroviridin aglycone **3** (five steps, 15% overall yield based on **7**) and benzofluorenone **5** (five steps, 43% overall yield based on **13**) have been prepared which provide access to key and diverse kinamycin antibiotic intermediates for biosynthetic studies and demonstrate the continuing advantages of combined directed metalation−cross-coupling regimens in natural product synthesis.[28]

**Acknowledgment.** We are grateful to NSERC Canada and Monsanto/Searle/Ceregen for continuing support of our synthetic efforts under the Industrial Research Chair Program. V.S. and S.M. extend their warm thanks to Dr. M. Kasai and Kyowa Hakko Kogyo Sakai Research Laboratories for a leave of absence to Mr. S.-i. Mohri and for support. We are grateful to Professor S. Gould for provision of spectral data and for collegial interaction. We thank Jan Venne for assistance with NMR experiments and C. Kendall, W. Iwema Bakker, R. Britton, and B.-p. Zhao for considerable work which set the stage for the present accomplishments.

**Supporting Information Available:** Full experimental procedure with listings of $^{13}C$, $^{1}H$, and IR, and MS spectral lines (11 pages).

JO971123D

(21) An alternate route to phenanthroviridin led instead to lactone **20** whose conversion into WS-5995A has been previously reported: Zhao, B.-P. Ph. D. Thesis, University of Waterloo, 1993.

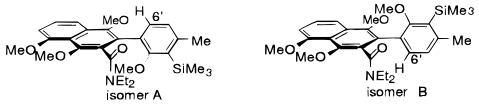


(22) Prepared in 49% yield from *N,N*-diethyl methylphenyl *O*-3-carbamate: (1) *s*-BuLi/TMEDA/THF/−78 °C; (2) $B(OMe)_3$; (3) aqueous $NH_4Cl$.

(23) Brough, P. A.; Fisher, S.; Zhao, B.-p.; Thomas, R. C.; Snieckus, V. *Tetrahedron Lett.* **1996**, *37*, 2915.

(24) As expected,[14b] the corresponding triethylsilyl (TES) derivative of **16** did not undergo this type of rearrangement; however, formation of the TES derivative in poorer yield (53%) due to slower reactivity of the anion with TESCl, thus allowing competitive anionic Fries rearrangement, made its use in the synthesis unattractive.

(25) Compound **17b** was isolated as a mixture of two atropisomers which were easily separated by silica gel chromatography but underwent rapid equilibration in eluent solvent EtOAc−hex (3:1), $CHCl_3$ (1:1, first order kinetics, $\Delta G^{\ddagger}_{298} = 24.7$ kcal/mol, no coalescence of selected signals at >130 °C in DMSO-$d_6$). Careful concentration at 0 °C *in vacuo* gave stable atropisomer **A** ($^{1}H$ NMR $\delta$ 7.32, H-6′) and **B** ($\delta$ 6.79, H-6′) whose structural assignments are also supported by molecular mechanics calculations. (Minimization of aryl−aryl and aryl−amide bond rotational barriers, MacSpartan *Plus* using SYBYL force field). Interestingly, when the **17b** isomer **A/B** mixture (1:1) was treated with LDA, only **A** was transformed into the fluorenone **18**. Competitive unknown side reaction(s) precluded a more efficient conversion of into **18** by **17b A/B** equilibration. At lower temperatures the reaction did not proceed at significant rates, thus preventing the study of individual isomers while at 45 °C (5 h) it gave poor yields (38%) of **19** and no recovery of **17b**. The possibility of thermodynamic preference for cyclization of lithiated species of both isomers **A** and **B** appears unlikely since TMSCl quench of the reaction mixture after consumption of isomer **A** resulted in the isolation of unsilylated **B**. We rationalize these observations as follows. Assuming the involvement of CIPE[26] and minimum aryl−amide bond rotation, isomer **A**−LDA complex (or its aggregate) leads to productive deprotonation and cyclization to **18** while isomer **B**−complex cannot achieve the transition state for analogous deprotonation. The rate of equilibration of **B** or its LDA complex with the equivalent species of isomer **A** is then slow relative to their decomposition pathways, thus precluding higher conversion into **18**. Further work may lead to development of systems for atropisomer control central to chiral conversions.[27]



| Dihedral angles: Ph-Ph′: 80° (100°) | Ph-Ph′: 110° (90°) |
|---|---|
| Am-Ph: 78° | Am-Ph: 80° |
| $\Delta H_f$ = -111.34 kcal/mol | $\Delta H_f$ = -109.94 kcal/mol |

(26) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(27) Bringmann, G.; Walter, R.; Weirich R. *Angew. Chem., Int. Ed. Engl.* **1992**, *29*, 977.

(28) All new compounds show analytical and spectral (IR, NMR, MS) data consistent with their depicted structures.

(29) Cladden, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 949.