Pergamon

Tetrahedron Letters, Vol. 35, No. 11, pp. 1695-1698, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0139-O

Indoloquinones, Part 2[1]

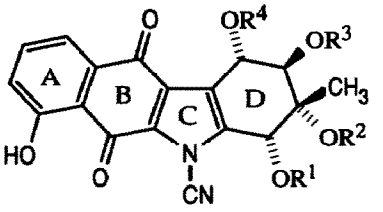
Palladium-Promoted Synthesis of a 7-Deoxyprekinamycin Isomer

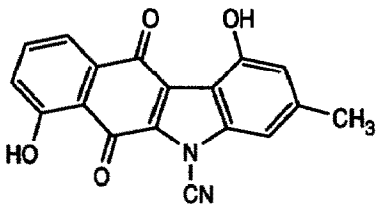
Hans-Joachim Knölker* and ***Noeleen O' Sullivan***

Institut für Organische Chemie, Universität Karlsruhe
Richard-Willstätter-Allee, 76131 Karlsruhe, Germany

Abstract: We have developed a four-step synthesis of the prekinamycin analogue **3** based on a palladium-promoted oxidative coupling as the key step.

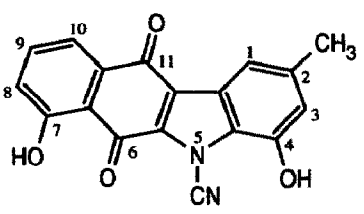
The kinamycins represent a novel class of antibiotic alkaloids which have been isolated from *Streptomyces murayamaensis* ATCC 21414[2,3] and, more recently, from other actinomycetes.[4] These antibiotics exhibit potent activity against Gram-positive and, to a lesser extent, against Gram-negative bacteria. They also possess weak antitumor activity.[2] The characteristic structural features of the kinamycins are a benzo[*b*]carbazole framework and a *N*-cyano moiety, both of which are highly unusual among natural products. Extensive studies on the biosynthesis of the kinamycins have been performed by Gould and coworkers who demonstrated that they derive from a single-chain decaketide.[5] The key intermediate in the biosynthesis of the kinamycins, which differ only in the oxygen substituents, was shown to be prekinamycin with an aromatic D ring. Prekinamycin has also been isolated from *S. murayamaensis* by Gould and its structure has been assigned as **1**.[3]





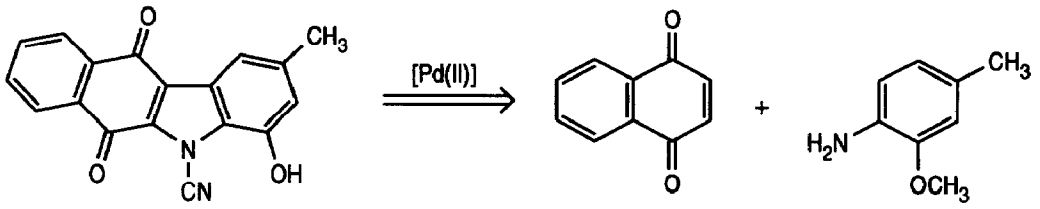
1

	R^1	R^2	R^3	R^4
Kinamycin A	Ac	Ac	Ac	H
Kinamycin B	H	Ac	H	H
Kinamycin C	Ac	H	Ac	Ac
Kinamycin D	Ac	H	Ac	H
Kinamycin E	Ac	H	H	H
Kinamycin F	H	H	H	H



2

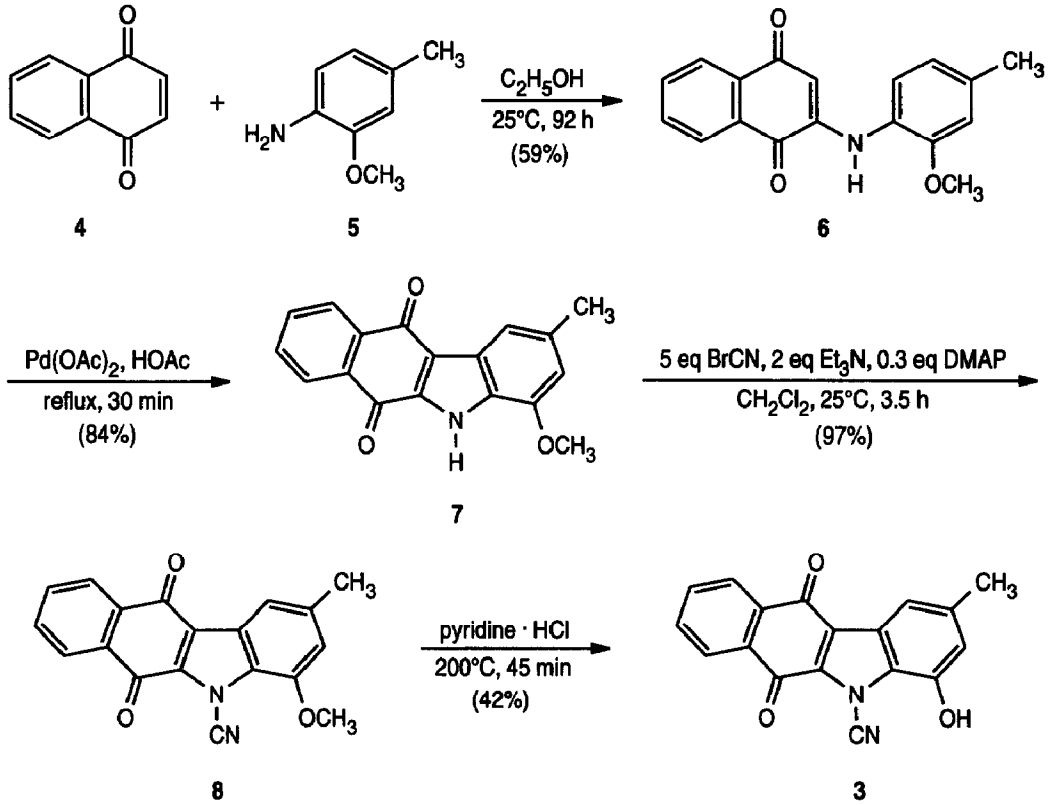
Because of the unprecedented structures and the potent biological activities several approaches have been described towards the total synthesis of the kinamycins.[6] Most recently, Echavarren and coworkers have reported the synthesis of compound **1**.[7] However, the spectral data of the synthetic material were not in agreement with those described by Gould for the natural product. Therefore, it has been proposed that prekinamycin must have a structure different from **1**.[7]



3 **4** **5**

Scheme 1

The isomeric compound **2** represents a possible structural alternative for prekinamycin. In this paper we report on an efficient palladium-promoted coupling leading to the 7-deoxyprekinamycin isomer **3**. Formal disconnections suggested that **3** could be derived from 1,4-naphthoquinone **4** and the arylamine **5** (Scheme 1).



4 **5** **6**

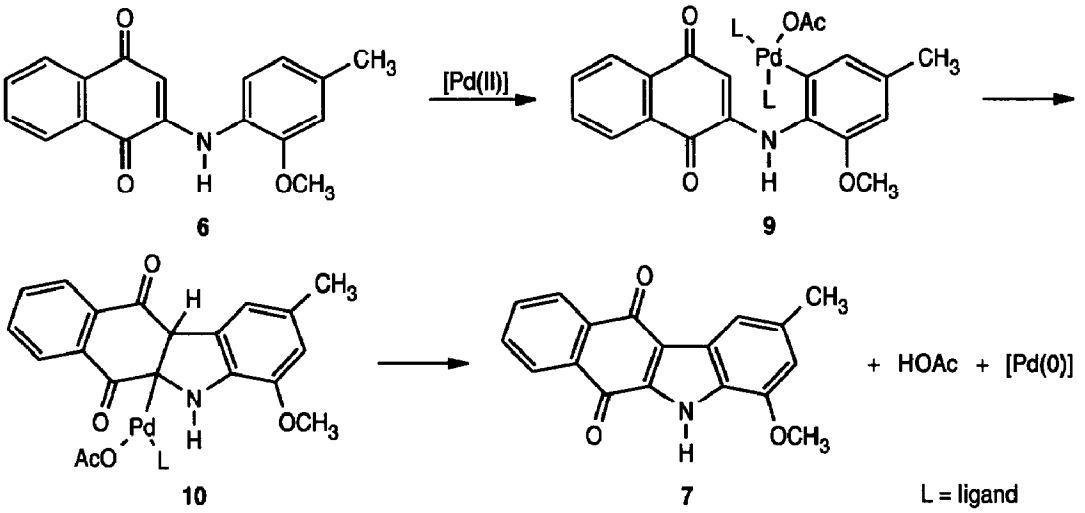
7

8 **3**

Scheme 2

Transition metal-mediated reactions lead to the possibility of convergent total syntheses of carbazole alkaloids.[8] Palladium-promoted cyclizations of diarylamines have frequently been used for the synthesis of the carbazole framework.[9] It has been demonstrated that a related Pd-promoted cyclization of 2-anilino-1,4-benzoquinones can be utilized for the synthesis of carbazoloquinones.[10] Therefore, we decided to elaborate a brief synthesis of the 7-deoxyprekinamycin isomer **3** based on a Pd-promoted C-C bond formation as the key step (Scheme 2). The arylamine **5** has already been used as a starting material in our iron-mediated total synthesis of the cytotoxic carbazole alkaloid koenoline.[11] Addition of **5** to 1,4-naphthoquinone **4** gave the corresponding 2-anilino-1,4-naphthoquinone **6**. Treatment of **6** with stoichiometric amounts palladium(II) acetate in refluxing glacial acetic acid under argon for 30 min provided the desired benzo[*b*]carbazole **7** in 84% yield. Reaction of **7** with sodium hydride and phenyl cyanate in DMF[6a] failed to afford the corresponding cyanamide **8**. However, when **7** was reacted with an excess of cyanogen bromide and triethylamine in the presence of *p*-dimethylaminopyridine in dry dichloromethane for 3.5 h at 25°C[7b] the cyanamide **8** was obtained in 97% yield. Finally, selective cleavage of the methyl ether in the presence of the *N*-cyano moiety with pyridine hydrochloride[12] transformed compound **8** to the 7-deoxyprekinamycin isomer **3**.[13]

The mechanism which we propose for the C-C coupling by analogy with related Pd-promoted reactions[14] has been supported by additional experiments (Scheme 3). Electrophilic attack of a Pd(II) species at the aromatic ring of **6** affords the σ-arylpalladium(II) complex **9**. Insertion of the quinone double bond generates the σ-alkylpalladium(II) complex **10** which on reductive β-elimination provides the benzo[*b*]carbazole **7**.



Scheme 3

In summary we have completed the synthesis of the 7-deoxyprekinamycin isomer **3** in four steps by using a palladium-promoted cyclization of a 2-arylamino-1,4-naphthoquinone to the parent benzo[*b*]carbazole framework. Investigations to extend this methodology to the synthesis of fully oxygenated prekinamycin isomers by employing 5-hydroxy-1,4-naphthoquinone (juglone) are in progress.

Acknowledgement: Financial support of this work by the *Fonds of Chemical Industry* and the *Royal Society* (postdoctoral fellowship to N. O' S.) is gratefully acknowledged.

References and Notes

1. Part 1: H.-J. Knölker, K. Hartmann, *Synlett* **1993**, 755.
2. S. Ito, T. Matsuya, S. Omura, M. Otani, A. Nakagawa, Y. Iwai, M. Ohtani, T. Hata, *J. Antibiotics* **1970**, *23*, 315. T. Hata, S. Omura, Y. Iwai, A. Nakagawa, M. Otani, S. Ito, T. Matsuya, *J. Antibiotics* **1971**, *24*, 353. S. Omura, A. Nakagawa, H. Yamada, T. Hata, A. Furusaki, T. Watanabe, *Chem. Pharm. Bull.* **1973**, *21*, 931.
3. M. C. Cone, P. J. Seaton, K. A. Halley, S. J. Gould, *J. Antibiotics* **1989**, *42*, 179. P. J. Seaton, S. J. Gould, *J. Antibiotics* **1989**, *42*, 189.
4. K. Isshiki, T. Sawa, H. Nakagawa, N. Matsuda, S. Hattori, M. Hamada, T. Takeuchi, M. Oosono, M. Ishizuka, Z. Yang, B. Zhu, W. Xu, *J. Antibiotics*, **1989**, *42*, 467. T. A. Smitka, R. Bonjouklian, T. J. Perun, A. H. Hunt, R. S. Foster, J. S. Mynderse, R. C. Yao, *J. Antibiotics* **1991**, *45*, 581.
5. Y. Sato, M. Geckle, S. J. Gould, *Tetrahedron Lett.* **1985**, *26*, 4019. Y. Sato, S. J. Gould, *Tetrahedron Lett.* **1985**, *26*, 4023. Y. Sato, S. J. Gould, *J. Am. Chem. Soc.* **1986**, *108*, 4625. P. J. Seaton, S. J. Gould, *J. Am. Chem. Soc.* **1987**, *109*, 5282. P. J. Seaton, S. J. Gould, *J. Am. Chem. Soc.* **1988**, *110*, 5912. M. P. Gore, S. J. Gould, D. D. Weller, *J. Org. Chem.* **1991**, *56*, 2289. M. P. Gore, S. J. Gould, D. D. Weller, *J. Org. Chem.* **1992**, *57*, 2774. M. C. Cone, C. R. Melville, M. P. Gore, S. J. Gould, *J. Org. Chem.* **1993**, *58*, 1058.
6. a) G. I. Dmitrienko, K. E. Nielsen, C. Steingart, N. S. Ming, J. M. Willson, G. Weeratunga, *Tetrahedron Lett.* **1990**, *31*, 3681. G. Weeratunga, G. K. B. Prasad, J. Dilley, N. J. Taylor, G. I. Dmitrienko, *Tetrahedron Lett.* **1990**, *31*, 5713.
   b) K. Kobayashi, H. Takeuchi, S. Seko, H. Suginome, *Helv. Chim. Acta* **1991**, *74*, 1091.
   c) P. J. O' Sullivan, R. Moreno, W. S. Murphy, *Tetrahedron Lett.* **1992**, *33*, 535.
7. a) A. M. Echavarren, A. M. Castano, M. Pérez, N. Tamayo, presentation at the CERC 3 *Workshop on Selective Synthesis*, Gent, Belgium, 25-28 April 1993, Abstract No. 27.
   b) A. M. Echavarren, N. Tamayo, M. C. Paredes, *Tetrahedron Lett.* **1993**, *34*, 4713.
8. For reviews, see: H.-J. Knölker in *Organic Synthesis via Organometallics*; K. H. Dötz, R. W. Hoffmann, Eds.; Vieweg: Braunschweig, 1991; p. 119. H.-J. Knölker, *Synlett* **1992**, 371.
9. B. Åkermark, L. Eberson, E. Jonsson, E. Pettersson, *J. Org. Chem.* **1975**, *40*, 1365. R. B. Miller, T. Moock, *Tetrahedron Lett.* **1980**, *21*, 3319. D. E. Ames, A. Opalko, *Tetrahedron* **1984**, *40*, 1919. H. Furukawa, C. Ito, M. Yogo, T.-S. Wu, *Chem. Pharm. Bull.* **1986**, *34*, 2672.
10. H. Furukawa, M. Yogo, C. Ito, T.-S. Wu, C.-S. Kuoh, *Chem. Pharm. Bull.* **1985**, *33*, 1320. S. Bittner, P. Krief, T. Massil, *Synthesis* **1991**, 215. M. Yogo, C. Ito, H. Furukawa, *Chem. Pharm. Bull.* **1991**, *39*, 328.
11. H.-J. Knölker, M. Bauermeister, *Chem. Commun.* **1990**, 664. H.-J. Knölker, M. Bauermeister, *Tetrahedron* **1993**, *49*, 11221.
12. F. W. Bachelor, A. A. Loman, L. R. Snowdon, *Can. J. Chem.* **1970**, *48*, 1554. M. V. Bhatt, S. U. Kulkarni, *Synthesis* **1983**, 249.
13. Selected spectral data of the 7-deoxyprekinamycin isomer **3**. IR (KBr): ν 3305 (br, OH), 2252 (CN); ^{1}H-NMR (400 MHz, $[CD_3]_2SO$): δ 2.36 (s, 3 H, CH_3), 6.84 (s, 1 H, 3-H), 7.50 (s, 1 H, 1-H), 10.91 (s, 1 H, OH); HRMS calcd for $C_{18}H_{10}N_2O_3$ (M^+): 302.0691, found: 302.0675.
14. L. S. Hegedus, *Angew. Chem.* **1988**, *100*, 1147; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1113.

(*Received in Germany* 23 *December* 1993; *accepted* 13 *January* 1994)