

ALTERNATIVE SYNTHESIS OF DUOCARMYCIN SA USING A TRICYCLIC HETEROAROMATIC INTERMEDIATE PREPARED BY PALLADIUM-CATALYZED COUPLING REACTIONS

Hideaki MURATAKE, Miyuki TONEGAWA, and Mitsutaka NATSUME*

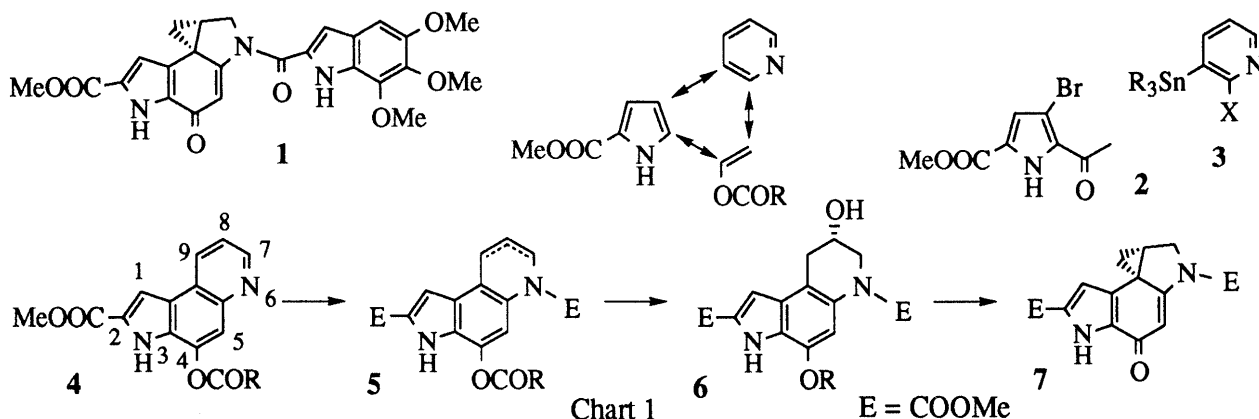
Research Foundation Itsuu Laboratory, 2-28-10 Tamagawa, Setagaya-ku, Tokyo 158, Japan

Alternative synthesis of duocarmycin SA (**1**) was achieved by developing a novel preparation method using palladium catalysts for a tricyclic heteroaromatic compound **4b**, followed by transformation into the previously reported intermediates **13** and **14a** by way of the alcohol **10b**.

KEY WORDS duocarmycin SA; antitumor antibiotic; formal synthesis; palladium-catalyzed coupling; 3*H*-pyrrolo[3,2-*f*]quinoline derivative

CC-1065¹⁾ and duocarmycins²⁾ (A,^{3,4)} B₁,⁵⁾ B₂,⁵⁾ C₁,^{4,6)} C₂,^{4,6)} D,²⁾ SA⁷⁾) are antitumor antibiotics isolated from culture broths of the *Streptomyces* species, and exhibit their biological activities by alkylating mostly the adenine portion of duplex DNA in a sequence-selective manner.⁸⁾ Among these antibiotics, duocarmycin SA (**1**) shows extremely potent cytotoxic activity, ten times or more stronger than CC-1065.⁹⁾ This is the reason why we have already reported two types of total synthesis of **1**,¹⁰⁾ and still continue the study to improve the synthesis methodology for achieving efficient synthesis not only of **1** itself but also of various compounds structurally related to **1** for the purpose of biological evaluation. In this communication, we report the third-generation synthesis of duocarmycin SA (**1**) on the basis of a novel preparation procedure of key intermediates with a tricyclic heteroaromatic structure **4** by making effective use of two palladium-catalyzed reactions.

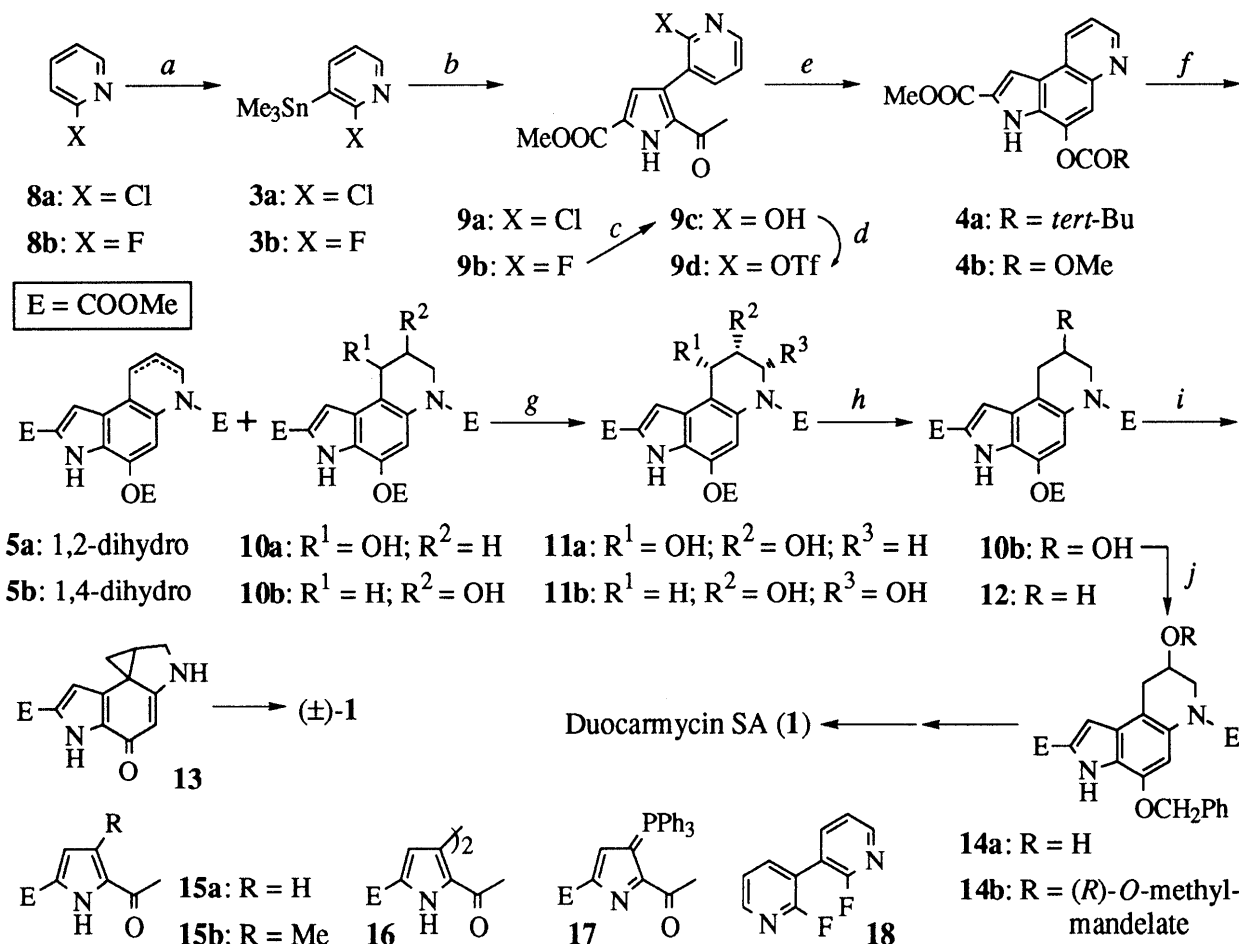
Adoption of **4** for the synthesis of duocarmycin SA stems from their possibilities of partial reduction to dihydropyridine derivatives **5**, whose alicyclic double bonds are so conveniently situated that the hydroxyl group can be introduced to the essential C-8 position of **6** (R = acyl) for construction of the cyclopropano-indolinone structure **7** of **1**. The latter transformation [**6** (R = H) → **7**] has been characteristic of our synthesis strategy and established as pivotal in our previous syntheses of **1**.¹⁰⁾ Retrosynthetically, **4** would be divided into three parts: methyl pyrrole-2-carboxylate, pyridine, and a two carbon unit corresponding to acyloxyethylene. For planning of starting materials, the latter two carbon unit would be an acetyl group attached to the pyrrole part rather than a XCOCH₂ residue connected to the pyridine part. We hoped that the bond formation between the pyrrole and pyridine units might be substantiated by the Stille coupling reaction,¹¹⁾ and therefore selected **2**^{10c)} and **3** as starting compounds. A substituent X was placed in **3** so as to restrict the bond connection between the terminal methyl group and the C-2 position of the pyridine ring.



* To whom correspondence should be addressed.

Actual synthesis was started with preparation of 2-chloro and 2-fluoro-3-(trimethylstannyl)pyridines [**3a** (50%), **3b** (89%)] from **8a** and **8b**, according to the method reported in the literature.¹²⁾ Either of these was coupled with **2** using a catalytic amount of a palladium-phosphine complex as shown in Chart 2 to obtain **9a** or **9b** in 21% or 65% yield. Pyrrole derivatives **15a** (12% or 3%), **15b** (16% or 8%), and **16** (15% or 6%) as well as **17** (6%) for **9a** and **18** (14% from used **3b**) for **9b** were isolated as by-products. The pyridylpyrrole **9b**, obtained in a good yield, was hydrolyzed to a pyridone derivative **9c** (96%) and then converted to its triflate **9d** (95%). The next crucial step for making a carbon-carbon bond connection between the acetyl methyl and the C-2 position of pyridine was achieved by applying Kuwajima conditions¹³⁾ of palladium chemistry to the silyl enol ether derived from **9d**. Thus the *tert*-BuMe₂Si enol ether of **9d** was heated in xylene at 160°C with Bu₃SnF and LiCl in the presence of a catalytic amount of PdCl₂(Ph₃P)₂ for 1 h, and the reaction product was isolated in the form of its pivalate **4a** or methyl carbonate **4b** in 91% or 89% yield.

With the required heteroaromatic compounds in hand, **4b** was reduced with NaBH₄ in the presence of ClCOOMe to a mixture of **5a** (52%) and **5b** (21%), together with **10a** (2%) and **10b** (2%).¹⁴⁾ When **5a** and **5b** were separately treated with OsO₄ to produce diols **11a** and **11b**, followed by Lewis acid-mediated reduction with Et₃SiH, the same **10b** was formed in 74% yield from **5a** and in 79% yield from **5b**. In practice, when **4b** was submitted to these three operations (*f*, *g*, *h*) successively without isolation of intermediary compounds **5a**,



a: i) LDA, THF, *ca.* -70°C; ii) Me₃SnCl, *ca.* -70—0°C. *b:* **2**, 10 mol % PdCl₂(Ph₃P)₂ in xylene or 5 mol % PdCl₂[(*o*-tol)₃P]₂ in toluene, reflux, *c:* 5% HCl in DME-H₂O (1:1), 60°C. *d:* Tf₂O, pyridine, CH₂Cl₂, 0—25°C. *e:* i) *tert*-BuMe₂SiOTf, Et₃N, CH₂Cl₂, 0°C; ii) 3 mol % PdCl₂(Ph₃P)₂, Bu₃SnF, LiCl, Ar, xylene, 160°C, iii) *tert*-BuCOCl or ClCOOMe, pyridine. *f:* NaBH₄, ClCOOMe, THF-2-propanol (1:2), rt. *g:* cat. OsO₄, Me₃N→O, Me₂CO-H₂O. *h:* Et₃SiH, BF₃·OEt₂, CH₂Cl₂, 0°C. *i:* i) MsCl, Et₃N, CH₂Cl₂, 0°C; ii) K₂CO₃, MeOH, rt. *j:* i) Et₃N, MeOH, rt; ii) PhCH₂Br, K₂CO₃, Me₂CO, reflux.

Chart 2

5b, **10a**, **10b**, **11a**, and **11b**, the desired product **10b** was obtained in 58% yield from **4b**, along with **12** (6%) originating from **10a** by reduction with Et_3SiH . Finally, **10b** was mesylated (97%) and the mesylate was treated with K_2CO_3 in MeOH. Methanolysis of the carbonate, formation of the cyclopropane ring, and subsequent removal of the *N*-COOMe group occurred in a single operation, and **13** was directly produced in 93% yield. ($\pm$)-Duocarmycin SA [($\pm$)-**1**] was synthesized from **13** as in the previous method.^{10a,10c)}

For completion of the synthesis of optically active **1**, the COOMe group in **10b** was removed (95%), and the product was benzylated as usual to obtain phenolic *O*-benzyl ether **14a** in 91% yield, accompanied by the *N,O*-dibenzyl derivative (5%). As this compound **14a** was optically resolved by way of its (*R*)-*O*-methylmandelate **14b**,^{10c)} duocarmycin SA (**1**) became available by a new sequence of reactions making use of the tricyclic heteroaromatic intermediate **4b**. Cyclopropanoindolinone **13** is the key compound for preparation of variously *N*-substituted substances for biological tests, and prepared in 28% overall yield from the pyrrole derivative **2**.¹⁵⁾

REFERENCES AND NOTES

- 1) a) Hanka L. J., Dietz A., Gerpheide S. A., Kuentzel S. L., Martin D. G., *J. Antibiot.*, **31**, 1211—1217 (1978); b) Martin D. G., Biles C., Gerpheide S. A., Hanka L. J., Krueger W. C., McGovern J. P., Mizsak S. A., Neil G. L., Stewart J. C., Visser J., *ibid.*, **34**, 1119—1125 (1981); c) Chidester C. G., Krueger W. C., Mizsak S. A., Duchamp D. J., Martin D. G., *J. Am. Chem. Soc.*, **103**, 7629—7635 (1981).
- 2) Yasuzawa T., Muroi K., Ichimura M., Takahashi I., Ogawa T., Takahashi K., Sano H., Saitoh Y., *Chem. Pharm. Bull.*, **43**, 378—391 (1995).
- 3) Takahashi I., Takahashi K., Ichimura M., Morimoto M., Asano K., Kawamoto I., Tomita F., Nakano H., *J. Antibiot.*, **41**, 1915—1917 (1988).
- 4) Yasuzawa T., Iida T., Muroi K., Ichimura M., Takahashi K., Sano H., *Chem. Pharm. Bull.*, **36**, 3728—3731 (1988).
- 6) a) Ichimura M., Muroi K., Asano K., Kawamoto I., Tomita F., Morimoto M., Nakano H., *J. Antibiot.*, **41**, 1285—1288 (1988). Isolated as pyrindamycins B and A; b) Ohba K., Watabe H., Sasaki T., Takeuchi Y., Kodama Y., Nakazawa T., Yamamoto H., Shomura T., Sezaki M., Kondo S., *ibid.*, **41**, 1515—1519 (1988); c) Ishii S., Nagasawa M., Kariya Y., Yamamoto H., Inouye S., Kondo S., *ibid.*, **42**, 1713—1717 (1989).
- 7) a) Ichimura M., Ogawa T., Takahashi K., Kobayashi E., Kawamoto I., Yasuzawa T., Takahashi I., Nakano H., *J. Antibiot.*, **43**, 1037—1038 (1990); b) Yasuzawa T., Saitoh Y., Ichimura M., Takahashi I., Sano H., *ibid.*, **44**, 445—447 (1991); c) Ichimura M., Ogawa T., Katsumata S., Takahashi K., Takahashi I., Nakano H., *ibid.*, **44**, 1045—1053 (1991).
- 8) a) Hurley L. H., Needham-VanDevanter D. R., *Acc. Chem. Res.*, **19**, 230—237 (1986); and references cited therein; b) Boger D. L., Ishizaki T., Zarrinmayeh H., Kitos O. A., Suntornwat O., *J. Org. Chem.*, **55**, 4499—4502 (1990); c) Boger D. L., Ishizaki T., Zarrinmayeh H., Munk S. A., Kitos P. A., Suntornwat O., *J. Am. Chem. Soc.*, **112**, 8961—8971 (1990); d) Sugiyama H., Ohmori K., Chan K. L., Hosoda M., Asai A., Saito H., Saito I., *Tetrahedron Lett.*, **34**, 2179—2182 (1993); e) Boger D. L., Yun W., *J. Am. Chem. Soc.*, **115**, 9872—9873 (1993); f) Boger D. L., *Acc. Chem. Res.*, **28**, 20—29 (1995).
- 9) Ichimura M., Ogawa T., Takahashi K., Mihara A., Takahashi I., Nakano H., *Oncol. Res.*, **5**, 165—171 (1993).
- 10) a) Muratake H., Abe I., Natsume M., *Tetrahedron Lett.*, **35**, 2573—2576 (1994); b) Muratake H., Matsumura N., Natsume M., *Chem. Pharm. Bull.*, **43**, 1064—1066 (1995); c) Muratake H., Abe I., Natsume M., *ibid.*, **44**, 67—79 (1996).
- 11) Review: a) Stille J. K., *Angew. Chem., Int. Ed. Engl.*, **25**, 508—524 (1986); b) Mitchell T. N., *Synthesis*, **1992**, 803—815.
- 12) Comins D. L., Myoung Y. C., *J. Org. Chem.*, **55**, 292—298 (1990).
- 13) Kuwajima I., Urabe H., *J. Am. Chem. Soc.*, **104**, 6831—6833 (1982).
- 14) Alcohols **10a** and **10b** were formed by addition of borane generated *in situ* to **5a** and **5b**, followed by oxidation with air. cf. Brown H. C., Midland M. M., Kabalka G. W., *J. Am. Chem. Soc.*, **93**, 1024—1025 (1971).
- 15) Thanks are due to the Ministry of Education, Science, and Culture of Japan for financial support.

(Received May 31, 1996; accepted June 23, 1996)