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

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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-1065[1] and duocarmycins[2] (A,[3,4] B_1,[5] B_2,[5] C_1,[4,6] C_2,[4,6] D,[2] SA[7]) 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 hetroaromatic 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 $XCOCH_2$ 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.

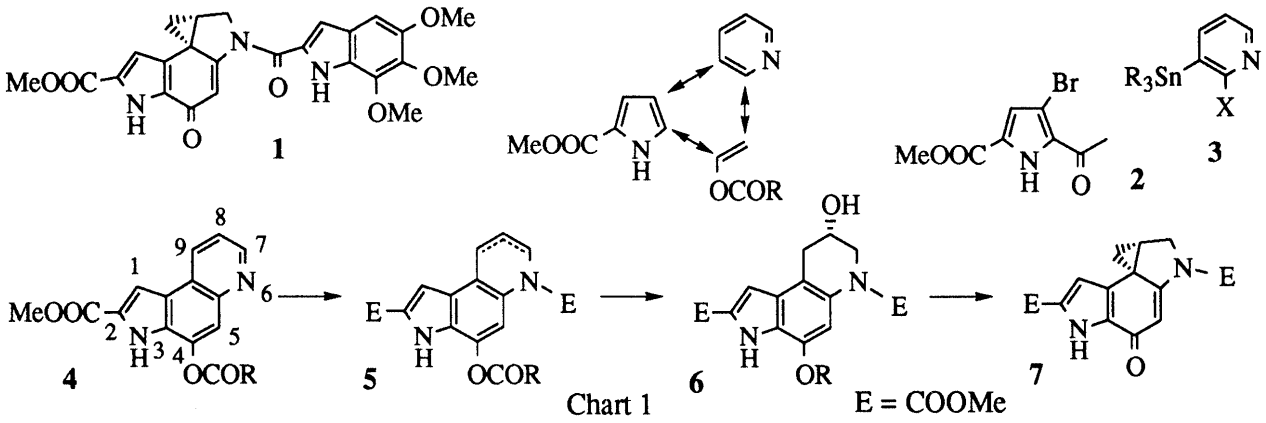

Chart 1

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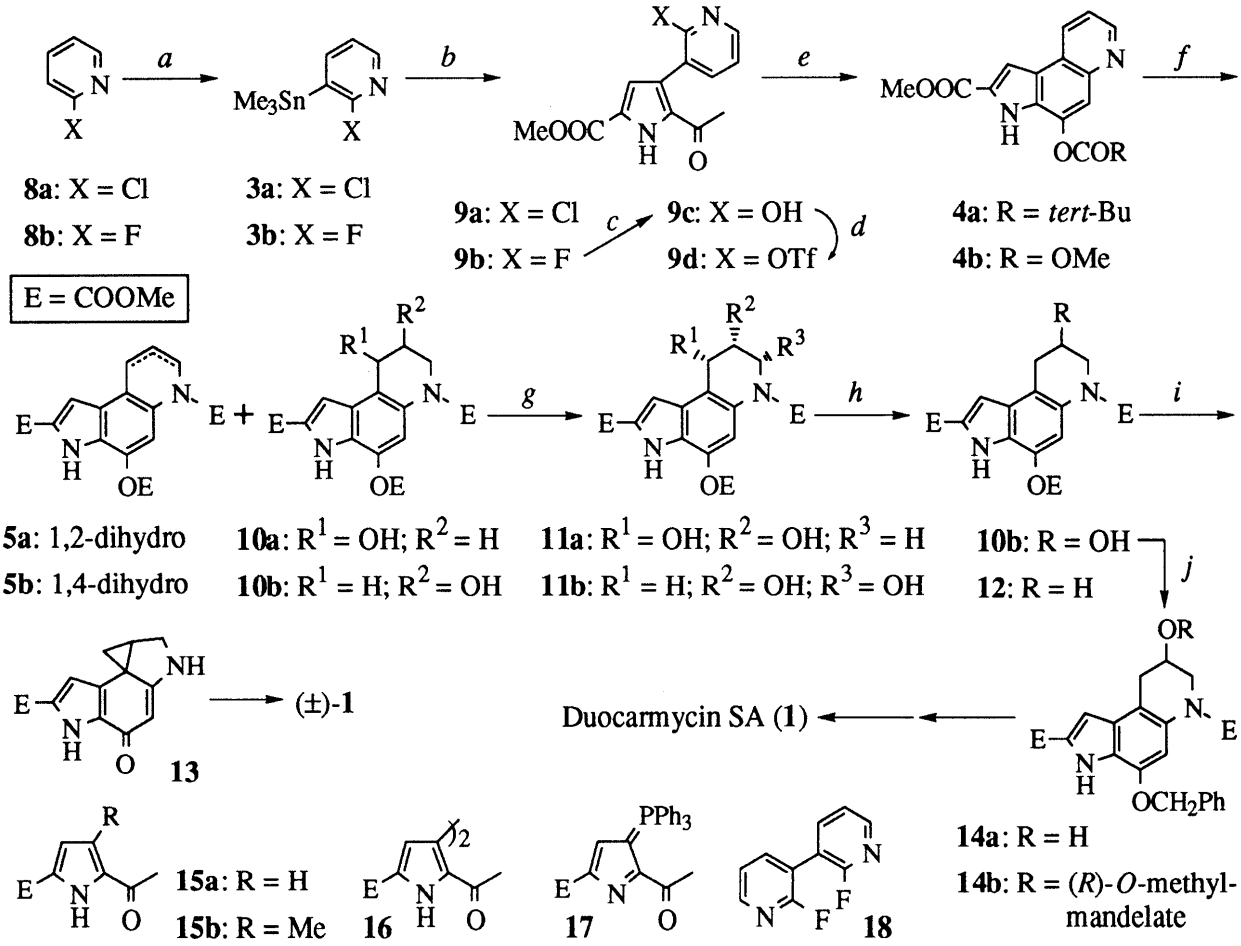
Actual synthesis was started with preparation of 2-chloro and 2-fluoro-3-(trimethylstannyl)pyridines [**3a** (50%), **3b** (89%)] from **8a** and **8b**, according to the method reporpted in the literature.[12] Either of these was coupled with **2** using a catalytic amount of a palladium-phosphine complex 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 conditions[13] of palladium chemistry to the silyl enol ether derived from **9d**. Thus the *tert*-BuMe$_2$Si enol ether of **9d** was heated in xylene at 160°C with Bu$_3$SnF and LiCl in the presence of a catalytic amount of PdCl$_2$(Ph$_3$P)$_2$ 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 NaBH$_4$ 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 OsO$_4$ to produce diols **11a** and **11b**, followed by Lewis acid-mediated reduction with Et$_3$SiH, 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) Me$_3$SnCl, *ca.* –70—0°C. *b*: **2**, 10 mol % PdCl$_2$(Ph$_3$P)$_2$ in xylene or 5 mol % PdCl$_2$[(*o*-tol)$_3$P]$_2$ in toluene, reflux, *c*: 5% HCl in DME–H$_2$O (1:1), 60°C. *d*: Tf$_2$O, pyridine, CH$_2$Cl$_2$, 0—25°C. e: i) *tert*-BuMe$_2$SiOTf, Et$_3$N, CH$_2$Cl$_2$, 0°C; ii) 3 mol % PdCl$_2$(Ph$_3$P)$_2$, Bu$_3$SnF, LiCl, Ar, xylene, 160°C, iii) *tert*-BuCOCl or ClCOOMe, pyridine. *f*: NaBH$_4$, ClCOOMe, THF–2-propanol (1:2), rt. *g*: cat. OsO$_4$, Me$_3$N→O, Me$_2$CO–H$_2$O. *h*: Et$_3$SiH, BF$_3$·OEt$_2$, CH$_2$Cl$_2$, 0°C. *i*: i) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0°C; ii) K$_2$CO$_3$, MeOH, rt. *j*: i) Et$_3$N, MeOH, rt; ii) PhCH$_2$Br, K$_2$CO$_3$, Me$_2$CO, 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. (±)-Duocarmycin SA [(±)-**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 itermediate **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]

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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)