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New Synthetic Method for Indole-2-carboxylate and Its Application to the Total Synthesis of Duocarmycin SA

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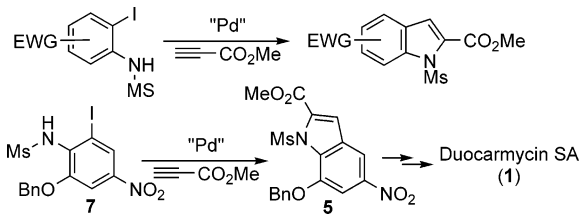
ABSTRACT



The sequential coupling and cyclization reactions between aryl halides and methyl propiolate were investigated. The electron-withdrawing groups on the aromatic ring are essential for producing the methyl indole-2-carboxylate derivatives. On the other hand, the presence of an extra methyl propiolate and $Pd(PPh_3)_4$ were required to provide an efficient catalytic system for the cyclization reactions. This reaction was used for the total synthesis of duocarmycin SA.

Because compounds containing indole ring systems possess unique biological activities, the synthetic methods for these compounds have attracted many organic chemists.[1] In our efforts directed toward the development of a new synthetic method for heterocyclic compounds, we have already published the Cu(II) salt catalyzed cyclization reaction of the 2-ethynylaniline derivatives. [2] Herein, we report a new synthetic method of the indole-2-carboxylate derivatives using the sequential coupling and cyclization reaction between the 2-haloaniline derivatives and methyl propiolate using the modified Negishi's reaction conditions [3] and its application to total synthesis of duocarmycin SA.

The palladium-catalyzed cross-coupling reaction between aryl halides and alkynes (Sonogashira reaction) has been applied to a wide range of substrates.[4] However, it is also well-known that a major drawback of this reaction is the difficulty of reaction with electron-deficient alkynes such as methyl propiolate. In 2001, Anastasia and Negishi published an elegant breakthrough of this problem using alkynylzinc derivatives as a counterpart.[3] At that time, we had just started a synthetic study of duocarmycin SA (**1**) according to the plan shown in Scheme 1. As we wanted to use the Cu(II)-catalyzed indole cyclization reaction as a key step for duocarmycin SA synthesis, we had to synthesize **6** as the substrate for this reaction. The synthesis of **7** was started from commercially available 2-amino-5-nitrophenol **8** via the benzylation of the phenolic hydroxyl group (BnBr, K_2CO_3, acetone, reflux, 93%), regioselective iodination (ICl, THF, reflux, 91%), and bis-mesylation (NaH, MsCl, THF, 0 °C to rt), followed by the mono-demesylation reaction [5] (TBAF,

(1) (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Sundberg, R. J. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ress, C. W., Scriven, E. F. V., Bird, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 119.

(2) (a) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126. (b) Hiroya, K.; Itoh, S.; Ozawa, M.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277.

(3) Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111.

(4) (a) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (b) Negishi, E.; Yves, D. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1.

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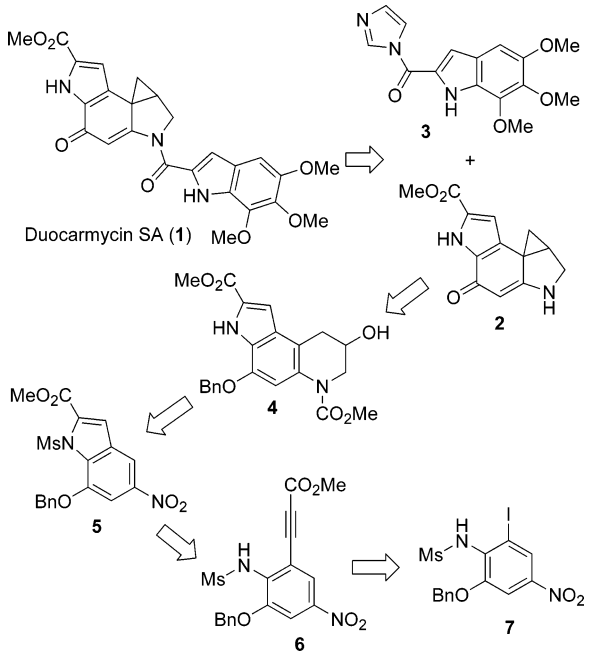
Scheme 1. Synthetic Strategy for Duocarmycin SA (**1**)



THF, rt, 75% from **10**) (Scheme 2). To synthesize the desired **6**, iodide **7** was subjected to Negishi's coupling conditions ($ZnBr_2$, $^iPr_2NEt$, methyl propiolate, $Pd(PPh_3)_4$, THF, reflux).[3] However, the isolated compound was not the cross-coupled product **6**, but methyl indole-2-carboxylate derivative **5** in 56% yield (Scheme 2). The intermediate alkyne **6** cyclized to the indole **5** under the reaction conditions. Unfortunately, the efficiency of both the couplings and the second cyclization reactions highly depends on the character of the substituents on the aromatic ring. Namely, the main products were the coupled acetylenes for the reaction of the compounds having no substituents on the aromatic ring or weak electron-donating group (methyl) in moderate yields (Table 1, entries 1 and 2). Moreover, in the presence of an electron-donating group at the R^2 position on the ring, a remarkable drop in the yield of the coupled product **13c** was observed and the indole **14c** could not obtained at all (Table 1, entry 3).[6]

Scheme 2. Synthesis of Indole **5**

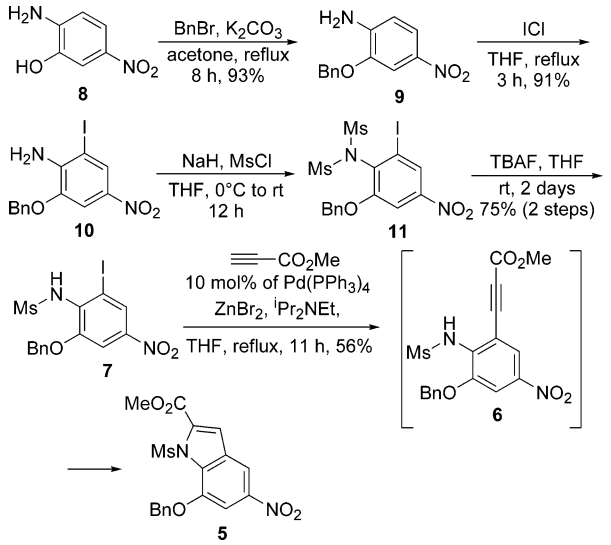
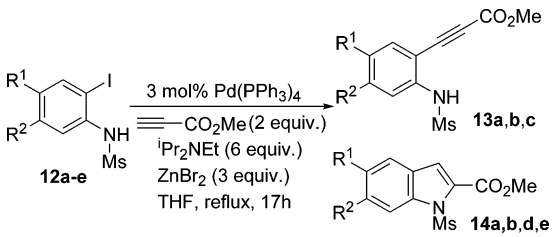


Table 1. Sequential Coupling and Cyclization Reactions



				yield (%)	
entry	substrate	R^1	R^2	**13**	**14**
1[a]	**12a**	H	H	38[b]	10[b]
2	**12b**	Me	H	59	2
3	**12c**	H	OMe	20	0
4	**12d**	H	Cl	0	75[b]
5	**12e**	CN	H	0	69

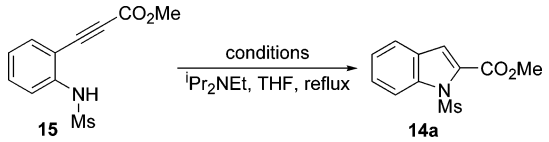
[a] 22% of **12a** was recovered. [b] The yields were calculated by the integration value of ^1H NMR.

On the other hand, the best results could be obtained for the substrates possessing electron-withdrawing groups on the aromatic ring, and all of the coupled products were cyclized from these substrates (Table 1, entries 4 and 5). Although these sequential reactions have limitations regarding the substrates, it is evident that the presence of one electron-withdrawing group is enough to promote the sequential cyclization reaction from the result of **7** which has nitro and benzyloxy groups on the aromatic ring.

We next tried to investigate and identify the true catalyst for this cyclization reaction using the (2-carbomethoxy)-2-ethynlyaniline derivative **15** as the substrate (Table 2). It is apparent that the cyclization reaction is not catalyzed by a Lewis acid ($ZnBr_2$) (Table 2, entry 1). The reactions in the presence of $Pd(PPh_3)_4$ with or without $ZnBr_2$ did not afford any indoles at all, which suggested the formation of other species in the reaction mixture (Table 2, entries 2 and 3). Surprisingly, in the presence of the extra methyl propiolate, the indole **14a** was isolated in 94% yield. Moreover, a palladium complex is required (Table 2, entry 5), but $ZnBr_2$ is not necessary for the cyclization process (Table 2, entry 6). Presumably, $ZnBr_2$ may act as an activator in certain stage(s). $Pd_2(dba)_3$ did not efficiently catalyze the reaction and phenylacetylene did not activate the reaction system (Table 2, entries 7 and 8). These results suggested that the phosphine ligand will be crucial, and acetylene as the additive

(5) Yasuhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998**, *39*, 595.
(6) The reason for the low conversion of the electron rich compounds is not totally clear, but one possibility may be the presence of an undesired deactivation cycle of the catalyst.

Table 2. Requirements for Cyclization Reactions



entry	$ZnBr_2$ (equiv)	Pd complex (mol %)	acetylene[a]	yield (%)
1	3			0
2		$Pd(PPh_3)_4$ (3)		0
3	3	$Pd(PPh_3)_4$ (3)		0
4	3	$Pd(PPh_3)_4$ (3)	A	94
5	3		A	0
6		$Pd(PPh_3)_4$ (3)	A	55
7		$Pd(PPh_3)_4$ (3)	B	trace
8		$Pd_2(dba)_3$ (3)	A	10
9		$Pd(OAc)_2$ (3)		0
10		$PdCl_2(MeCN)_2$ (3)		0

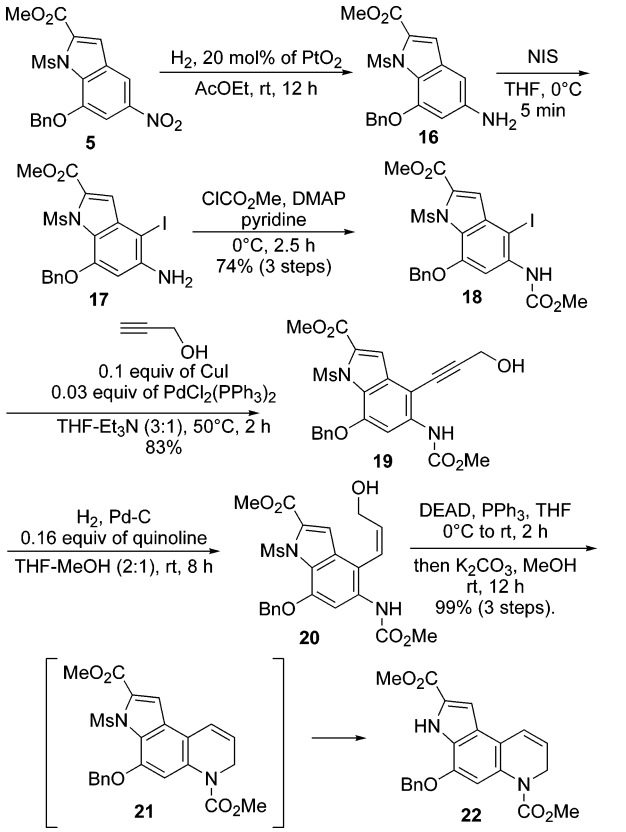
[a] A: methyl propiolate. B: phenylacetylene.

must be electron deficient for the newly formed active catalyst. The most frequently used catalysts for the cyclization of the 2-ethynylaniline derivatives to indoles were the Pd(II) complexes. $Pd(OAc)_2$ and $PdCl_2(MeCN)_2$, which are typical catalysts for this type cyclization reaction,[7] did not promote any reactions (Table 2, entries 9 and 10). Based on the results listed above, we currently speculate that the active catalyst will be formed a combination of $Pd(PPh_3)_4$ and methyl propiolate. Isolation and characterization of the catalyst are now under investigation.

Duocarmycin SA (**1**) is an antitumor antibiotic isolated from *Streptomyces* sp. DO-113 by Ichimura et al. in 1990.[8] The first total synthesis was reported by Boger,[9] and the other three total syntheses were achieved by Natsume's,[10] Terashima's,[11] and Fukuyama's[12] research groups.[13] Quite recently, the interesting bioactivities of the *seco* analogues of duocarmycin have been reported by Tietze's group, and the efficient total synthesis of *seco*-duocarmycin SA was also reported.[14] All of these syntheses were carried out by convergent methodology, and we selected the tetrahydroquinoline derivative **4**, which was synthesized by Natsume et al., as the key intermediate. [10]

The nitro group of **5** was reduced by catalytic hydrogenation in the presence of PtO_2, and the resulting aniline derivative was treated with NIS at 0 °C to afford the 4-iodo derivative (**17**) (indole number) as the sole product. The carbamate **18**, which was derived from **17** under standard reaction conditions ($ClCO_2Me$, DMAP, pyridine, 0 °C, 2.5 h, 75% from **5**), was coupled with propargyl alcohol under Sonogashira conditions ($PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 50 °C, 2 h, 83%), and the acetylene moiety was converted to the *Z*-olefin by catalytic hydrogenation using a poisoned catalyst (Pd−C, quinoline, MeOH−THF, rt, 8 h). Next, the alcohol **20** was subjected to the intramolecular Mitsunobu reaction (DEAD, PPh_3, THF, rt, 2 h) to afford the dihydroquinoline **21**, and the methanesulfonyl group of **21** was eliminated by solvolysis (K_2CO_3, MeOH, rt, 12 h) to afford **22**[10b] in almost quantitative yield from **19** (Scheme 3).

Scheme 3. Synthesis of Tricyclic Intermediate **22**



The epoxide **23** was found to be relatively unstable;[15] thus the epoxide **23** was subjected to a regioselective reductive ring-opening reaction in the same reaction flask to afford the alcohol **4**[10b,c] in 42% yield (*m*-CPBA, CH_2Cl_2, 0 °C, 5 min, then Et_3SiH, $BF_3{\cdot}OEt_2$, 0 °C, 5 min) (Scheme 4). The hydroxyl group of **4** was converted to the corresponding

(7) For examples, see: (a) Esseveldt, B, C, J.; Delft, F. L.; Gelder, R.; Rutjes, F. P. J. T. *Org. Lett.* **2003**, *5*, 1717. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Yu, M. S.; Leon, L. L.; McGguire, M. A.; Botha, G. *Tetrahedron Lett.* **1998**, *39*, 9347.

(8) (a) Ichimura, M.; Ogawa, T.; Takahashi, K.; Kobayashi, E.; Kawamoto, I.; Yasuzawa, T.; Takahashi, I.; Nakano, H. *J. Antibiot.* **1990**, *43*, 1037. (b) Yasuzawa, T.; Saitoh, Y.; Ichimura, M.; Takahashi, I.; Sano, H. *J. Antibiot.* **1991**, *44*, 445. (c) For review, see: Boger, D. L.; Johnson, D. S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1438.

(9) Boger, D. L.; Machiya, K. *J. Am. Chem. Soc.* **1992**, *114*, 10056.

(10) (a) Muratake, H.; Matsumura N. Natsume M. *Chem. Pharm. Bull.* **1995**, *35*, 1064. (b) Muratake, H.; Abe, I.; Natsume, M. *Chem. Pharm. Bull.* **1996**, *44*, 67. (c) Muratake, H.; Tonegawa, M.; Natsume, M. *Chem. Pharm. Bull.* **1998**, *46*, 400.

(11) Fukuda, Y.; Terashima, S. *Tetrahedron Lett.* **1997**, *38*, 7207.

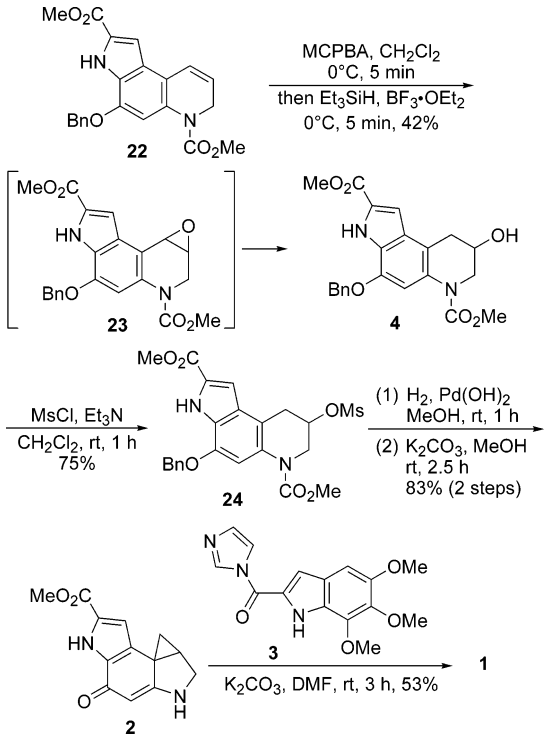
(12) Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am Chem. Soc.* **2003**, *125*, 6630.

(13) For a review, see: Boger,D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787.

(14) Tietze, L. F.; Haunert, F.; Feuerstein, T.; Herzig, T. *Eur. J. Org. Chem.* **2003**, 562 and references therein.

(15) More than half of the epoxide **23** was decomposed during the isolation and the purification. Therefore, **23** could not be characterized.

Scheme 4. Total Synthesis of Duocarmycin SA (**1**)



mesylate **24** under standard conditions (MsCl, Et_3N, CH_2Cl_2, rt, 1 h, 75%), and the benzyl group was eliminated (H_2, $Pd(OH)_2$, MeOH, rt, 1 h). The cyclopropane formation was carried out according to Natsume's procedure[10b] (K_2CO_3, MeOH) to afford the tetracyclic intermediate **2** [10c] in 83% yield from **24**. Finally, the coupling reaction between **2** and **3**[10b,16] were conducted in the presence of excess K_2CO_3 in DMF to furnish total synthesis of duocarmycin SA (**1**). [9−12]

In conclusion, we developed the sequential coupling and cyclization reaction between aryl halides and methyl propiolate employing Negishi's reaction conditions [3] and clarified the scope and limitation of this reaction. Moreover, it was also clarified that some complexes, which may be formed between $Pd(PPh_3)_4$ and methyl propiolate, are minimum requirements for the cyclization step. This reaction was successfully applied to total synthesis of duocarmycin SA (**1**). Although the final product of our synthesis is racemic, but the reaction steps (16 steps from **8**) and total yield (3.0%) are almost comparable those of Fukuyama's recently published elegant asymmetric total synthesis (17 steps, 3.1% yield).[12] In our synthesis, only 11 purifications are necessary through total synthesis (16 steps). This will be the other advantage of our synthesis.

Further applications of the sequential reaction toward the total synthesis of biologically active compounds and the identification of the actual catalyst are now in progress in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, **2**, **4**−**20**, **22**, **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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