Concise Synthesis of CC-1065/Duocarmycin Pharmacophore Using the Intramolecular Heck Reaction

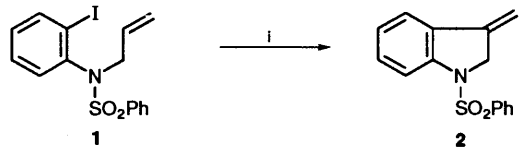
Takao Sakamoto,* Yoshinori Kondo, Masanobu Uchiyama and Hiroshi Yamanaka
Pharmaceutical Institute, Tohoku University, Aobayama, Aoba-ku, Sendai 980, Japan

3-Methyleneindoline derivatives were synthesized by intramolecular Heck reaction of *N*-allyl-2-iodoaniline derivatives in the presence of Ag_2CO_3. This method was successfully applied to the synthesis of the CC-1065/duocarmycin pharmacophore.

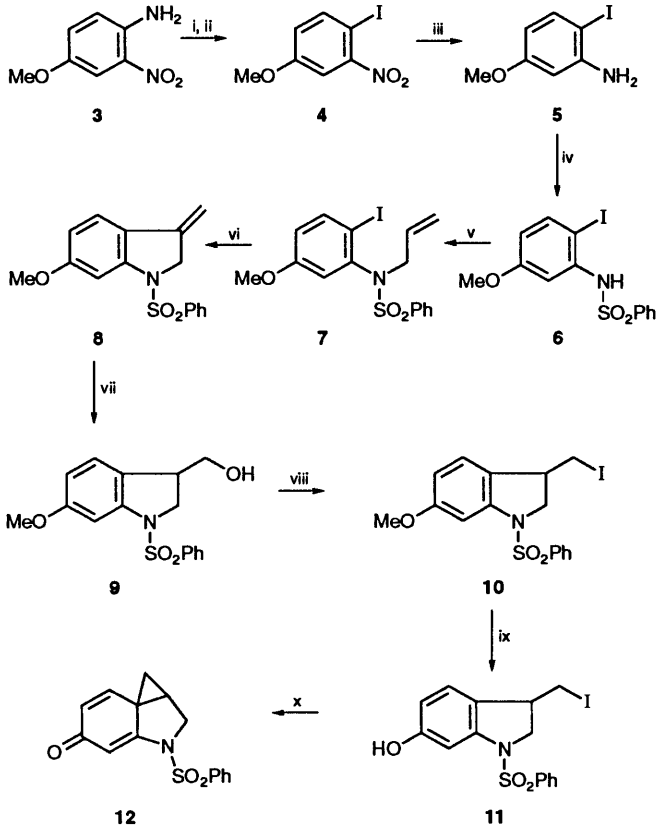
CC-1065[1] and duocarmycin A,[2] have received much attention as potent antitumour antibiotics. They contain a common pharmacophore which consists of a spirocyclic 1,2,7,7a-tetrahydrocyclopropa[*c*]indol-4-one (CI) subunit. The pharmacophore[3] and related analogues[4] have been synthetic targets for chemists in connection with the mechanism of the antitumour activity. 3-Methyleneindoline derivatives have been used as key intermediates for the construction of the cyclopropane ring, and they have been prepared by reductive aryl radical–alkyne cyclization.[5]

On the other hand, Mori[6] and Hegedus[7] reported facile synthesis of 3-substituted alkylindoles using the intramolecular Heck reaction,[8] with 3-alkylideneindoline derivatives considered to be the intermediates. Recently Ag_2CO_3 and other Ag salts have been used in the Heck reaction to avoid the isomerization of the double bond caused by HPdX species.[9]

In order to develop a new preparative method for 3-methyleneindoline derivatives, we investigated the Mori–Hegedus indole synthesis in the presence of Ag_2CO_3 and other bases. *N*-Allyl-2-iodo-*N*-phenylsulfonylaniline **1** was subjected to a palladium-catalysed intramolecular coupling reaction in the presence of Ag_2CO_3 in dimethylformamide (DMF) at room temperature. As shown in Scheme 1, the 3-methyleneindoline derivative **2** was obtained without isomerization to the 3-methylindole derivative. The amount of Ag_2CO_3 and the reaction time slightly influenced the yield of **2**. Employing other bases, such as Et_3N and K_2CO_3, gave a mixture of **2** and the 3-methylindole derivative.



Scheme 1 *Reagents and conditions:* i, $Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, room temp.



Scheme 2 *Reagents and conditions:* i, aq. HCl, $NaNO_2$; ii, KI (89%); iii, NH_2NH_2, $FeCl_3$, MeOH, reflux, 4 h; iv, $PhSO_2Cl$, pyridine, room temp., 6 h (88% from **4**); v, allyl bromide, K_2CO_3, DMF, 80 °C, 48 h (96%); vi, $Pd(OAc)_2$, PPh_3, $AgCO_3$, DMF, room temp., 24 h (73%); vii, 9-BBN, THF, 0 °C, 6 h, then H_2O_2, NaOH, room temp., 6 h (90%); viii, I_2, PPh_3, imidazole, room temp., 30 min (79%); ix, BBr_3, CH_2Cl_2, 20 °C, 75 h (97%); x, NaH, THF, room temp., 1 h (85%)

Table 1 Cyclization of **1** to **2** by palladium-catalysed reaction

Run	Ag_2CO_3 (equiv.)	Reaction time (t/h)	Yield (%)
1	1	24	50
2	1	48	35
3	1.5	24	56
4	1.5	12	57
5	1.5	6	65
6	2	5	80

Our interest was then focussed on the synthesis of the pharmacophore (CI) subunit using this cyclization reaction as the key step. The substrate **7** for the Heck reaction was synthesized from 4-methoxy-2-nitroaniline **3** which was converted into the iodo derivative **4** *via* diazotization followed by reduction of the nitro group to an amino group by hydrazine in the presence of $FeCl_3$. The iodoaniline **5** was treated with benzenesulfonyl chloride to give the sulfonamide **6** which was treated with allyl bromide in the presence of K_2CO_3 in DMF. The desired substrate **7** was obtained in 75% overall yield from compound **3**.

The intramolecular Heck reaction of substrate **7** in the presence of 2 equiv. of Ag_2CO_3 gave the 3-methyleneindoline derivative **8** exclusively in 73% yield. Hydroboration of the alkene **8** followed by oxidation gave the alcohol **9** which was converted into the iodo derivative **10** by treatment with I_2, PPh_3 and imidazole. Demethylation of **10** was carried out with BBr_3 in CH_2Cl_2 at −20 °C. The final cyclization to give the cyclopropa[*c*]indol-5-one subunit **12** was achieved by treatment of the hydroxyiodomethylindoline derivative **11** with NaH in tetrahydrofuran (THF) at room temperature.

Experimental

3-Methylene-1-phenylsulfonylindoline **2**.—A mixture of compound **1** (0.43 g, 1.08 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (8 mg, 0.06 mmol), Ag_2CO_3 (0.6 g, 2.08 mmol) and DMF (2 cm^3) was stirred at room temp. for 5 h. After dilution with Et_2O (60 cm^3), the reaction mixture was filtered, washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual material was purified by silica gel column chromatography using hexane–Et_2O (4:1) as eluent to give a colourless solid which was recrystallised from Et_2O to give colourless needles (237 mg, 80%); m.p. 117–119 °C (Found: C, 66.15; H, 4.9; N, 5.05. $C_{15}H_{13}NO_2S$ requires C, 66.40; H, 5.16; N, 5.16%); ν_{max}(KBr)/cm^{-1} 1360 and 1165; δ_H(300 MHz; $CDCl_3$) 4.55 (2 H, t, *J* 2.9), 4.98 (1 H, t, *J* 2.6), 5.37 (1 H, t, *J* 2.9), 7.01 (1 H, t, *J* 7.7), 7.27–7.21 (1 H, m), 7.34 (1 H, d, *J* 7.7), 7.44 (2 H, t, *J* 7.0), 7.54 (1 H, d, *J* 7.3), 7.73 (1 H, d, *J* 8.4) and 7.79 (2 H, d, *J* 7.0); *m*/*z* 271 (M^+, 11%).

References

1 L. J. Hanka, A. Dietz, S. A. Gerpheide, S. L. Kuentzel and D. G. Martin, *J. Antibiot.*, 1978, **31**, 1211.
2 I. Takahashi, K. Takahashi, M. Ichimura, M. Morimoto, K. Asano, I. Kawamoto, F. Tomita and H. Nakano, *J. Antibiot.*, 1988, **41**, 1915.
3 D. L. Boger, T. Ishizaki, H. Zarrinmayeh, P. A. Kitos and O. Suntornwat, *J. Org. Chem.*, 1990, **55**, 4499.
4 (*a*) J. H. Tidwell and S. L. Buchwald, *J. Org. Chem.*, 1992, **57**, 6380; (*b*) D. L. Boger and M. S. S. Palanski, *J. Am. Chem. Soc.*, 1992, **114**, 9318; (*c*) D. L. Boger, W. Yun and B. R. Teegarden, *J. Org. Chem.*, 1992, **57**, 2873.
5 D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc.*, 1988, **110**, 4796.
6 M. Mori and Y. Ban, *Tetrahedron Lett.*, 1979, 1133.
7 R. Oddle, B. Blevins, M. Ratcliff and L. S. Hegedus, *J. Org. Chem.*, 1980, **45**, 2709.
8 (*a*) R. F. Heck, *Org. React.*, Wiley, New York, 1982, vol. 27, p. 345; (*b*) B. M. Trost and T. R. Verhoeven, *Comprehensive Organometallic Chemistry*, Pergamon Press, Oxford, 1982, vol. 8, p. 854; (*c*) R. F. Heck, *Palladium Reagents in Organic Syntheses*, Academic Press, New York, 1985; (*d*) For recent application of intramolecular Heck reaction in the synthesis of heterocycles see: R. Grigg, V. Sridharan, P. Stevenson, S. Sukirthalingam and T. Worakan, *Tetrahedron*, 1990, **46**, 4003; R. Grigg, V. Sridharan, P. Stevenson and S. Sukirthaligam, *Tetrahedron*, 1989, **45**, 3557 and references cited therein.
9 (*a*) R. C. Larock, *Pure Appl. Chem.*, 1990, **62**, 653; (*b*) M. M. Abelman, T. Oh and L. E. Overman, *J. Org. Chem.*, 1987, **52**, 4130; (*c*) M. M. Abelman and L. E. Overman, *J. Am. Chem. Soc.*, 1988, **110**, 2328; (*d*) K. Karabelas and A. Hallberg, *J. Org. Chem.*, 1986, **51**, 5286; (*e*) K. Karabelas and A. Hallberg, *J. Org. Chem.*, 1989, **54**, 1773.

Paper 3/03515H
Received 18*th June* 1993
Accepted 13*th July* 1993