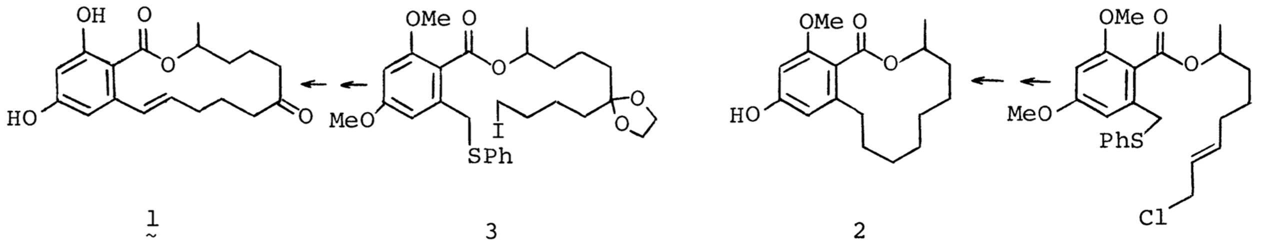
CHEMISTRY LETTERS, pp. 369-372, 1980.

A GENERAL SYNTHETIC METHOD FOR ORSELLINIC ACID MOIETY OF MACROLIDES BY THE PALLADIUM-CATALYZED CARBONYLATION OF ARYL IODIDE AND ITS APPLICATION TO ZEARALENONE SYNTHESIS

Takashi TAKAHASHI, Toshiharu NAGASHIMA, and Jiro TSUJI*
Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152

Palladium-catalyzed carbonylation of 1-iodo-2-phenylthiomethyl-4,6-dimethoxybenzene (9) with 10-iodo-6,2'-[1,3]dioxolane-2-decanol (10) afforded the corresponding ω-iodoalkyl ester of 2-phenylthiomethyl-4,6-dimethoxybenzoate (3) in 70% yield, which is the precursor of Zearalenone (1). 1-Iodo-2-phenylthiomethyl-4,6-dimethoxybenzene (9) was prepared from 3,5-dihydroxybenzoic acid (5a). This method of carbonylation offers a general and convenient synthetic method for an orsellinic acid moiety of orsellinic acid type macrolides.

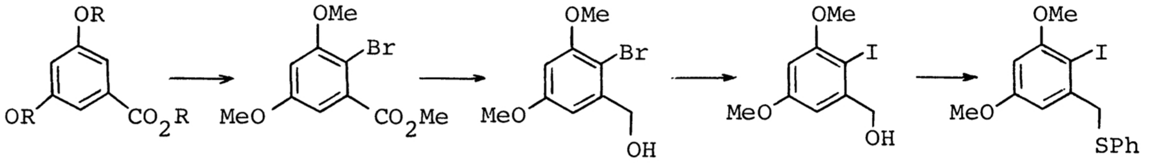
A number of naturally occurring orsellinic acid (2,4-dihydroxy-6-methylbenzoic acid) type macrolides are known. Zearalenone (1),[1)] Lasiodiplodin (2),[2)] and Monorden[3)] are typical examples. We have recently introduced an efficient synthetic method of Zearalenone (1)[4)] and Lasiodiplodin (2)[5)] based on the intramolecular alkylation of ω-haloalkyl 2-phenylthiomethyl-4,6-dimethoxybenzoates 3 and 4, and subsequent oxidative or reductive removal of the phenylthio group from the cyclized products. In these syntheses, the key intermediate esters 3 and 4 were prepared from 2-phenylthiomethyl-4,6-dimethoxybenzoyl chloride and ω-halo alcohols. One problem which needs further elaboration is the somewhat tedious synthetic route of the orsellinic acid moiety, which was prepared from diketene and acetoacetate in six steps.[5)] Therefore we tried to improve the synthetic method for this important aromatic acid moiety, and found a method which is convenient and has general utility.



1 3 2 4

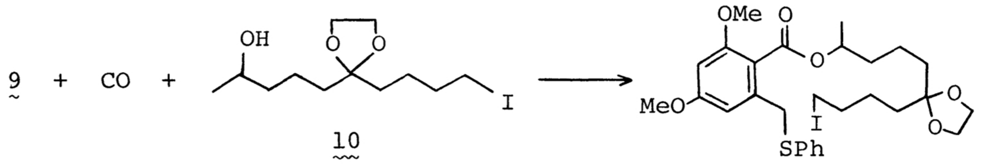
We now wish to report a convenient and general synthetic method for the ω-iodoalkyl ester of orsellinic acid moiety 3 from commercially available 3,5-dihydroxybenzoic acid (α-resorcylic acid) (5a) by applying palladium-catalyzed carbonylation as a key reaction. The palladium-catalyzed carbonylation of aryl and alkenyl iodides and bromides in alcohols or amines affords esters or amides.[6)] However, only few studies on the application of the carbonylation reaction to natural product synthesis have been carried out.[7)] We have successfully synthesized the ester of orsellinic acid moiety 3 by the palladium-catalyzed carbonylation of the aryl iodide 9.

The iodide 9 was prepared from 3,5-dihydroxybenzoic acid (5a) by the following sequence of reactions. Photo-bromination[8)] of methyl dimethoxybenzoate (5b) afforded the bromo ester 6, and reduction of the ester with lithium aluminum hydride in ether at 0°C gave the bromo alcohol 7 in 52% overall yield. The bromo alcohol 7 was metalated with *n*-BuLi at -78°C in THF, and the resulting dianion was warmed to -40°C and quenched with freshly sublimed iodine to give the iodide 8 in 63% yield: NMR ($CDCl_3$): δ 3.77 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.61 (2H, s, CH_2), 6.31 (1H, d, J = 2.8 Hz, aromatic), 6.68 (1H, d, J = 2.8 Hz, aromatic). The benzyl alcohol 8 was converted to benzyl chloride ($SOCl_2$), which was treated with thiophenol in the presence of sodium ethoxide to give 9 in 88% yield: IR (KBr): 1580, 1202, 740 cm^{-1}; NMR (CCl_4): δ 3.55 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.05 (2H, s, CH_2), 6.05 (1H, d, J = 2.4 Hz, aromatic), 6.27 (1H, d, J = 2.4 Hz, aromatic), 7.09 (5H, br. s, aromatic).



5a R=H
b R=Me 6 7 8 9

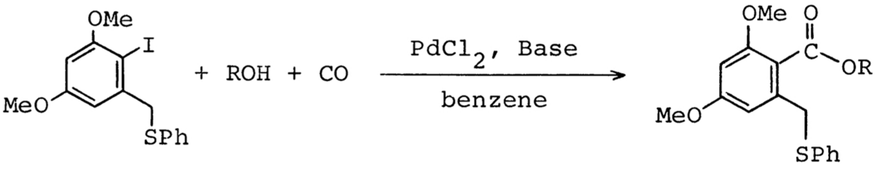
The carbonylation of 9 was carried out in the following way. A mixture of the iodobenzene 9 (0.46 mmol), ω-iodo alcohol 10 (0.83 mmol), K_2CO_3 (1.38 mmol), and $PdCl_2$ (0.04 mmol) in dry benzene (6 ml) was heated at 120°C with stirring in an autoclave under carbon monoxide (12 atm) for 16 h. The reaction mixture was filtered and the ester 3 was isolated by column chromatography in 70% yield, which was identical with an authentic sample prepared in this laboratory.[4)] The conversion of 3 to Zearalenone (1) was done before.[4)]



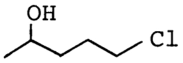
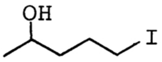
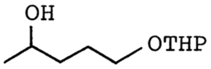
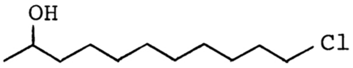
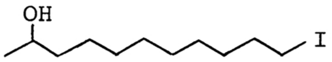
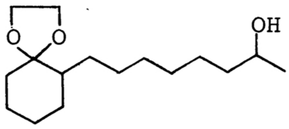
10 3

The carbonylation reaction needs some comments. The palladium-catalyzed carbonylation reaction of various halides was carried out before by other workers usually with a large excess of low-molecular primary alcohols.[6)] We have carried out the reaction successfully in benzene with two equivalents of higher secondary alcohols such as 10. The alcohol 10 contains an alkyl iodide moiety, but this alkyl iodide remained intact, and only the aryl iodide took part in the reaction. Also we have carried out the carbonylation reaction with aliphatic alcohols which have some other functional groups in order to find the scope and limitation of the reaction. As shown in the Table, aliphatic chlorides were inert. Also tetrahydropyranyl ether as a protecting group of alcohols, and ketones protected by acetal formation remained without change. The mild conditions of the carbonylation tolerate the presence of these functional groups. Thus this carbonylation method can be applied to synthesis of complex molecules with various functional groups.

Table



9 11

ROH	ROH/9 Ratio	Base	Reaction Temp (°C)	Reaction Time (h)	Yield of The Ester 11 (%)
	2	NEt_3	80-100	10	69
	2	K_2CO_3	80-100	10	a
	2	NEt_3	80-100	10	68
	2	NEt_3	120	10	67
	2	NEt_3	120	20	72
	2	NEt_3	120	16	a
	2	K_2CO_3	120	10	59
	2	NEt_3	120	10	55
	2	K_2CO_3	120	10	69
	1.5	K_2CO_3	120	10	68

9/$PdCl_2$ = 0.46 mmol/0.046 mmol, Solvent: Benzene (6 ml)
Base: NEt_3 = 0.5 ml, K_2CO_3 = 1.38 mmol, CO: 12 atm

a) The iodide was decomposed.

References

1) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, Tetrahedron Lett., 3109 (1966).

2) D. C. Aldridge, S. Galt, D. Giles, and W. B. Turner, J. Chem. Soc., (C), 1623 (1971).

3a) P. Delmotte and J. Delmotte-Plaquee, Nature, **171**, 344 (1953).

b) R. N. Mirrington, E. Ritchie, C. W. Shoppee, W. C. Taylor, and S. Sternhell, Tetrahedron Lett., 365 (1964).

c) F. McCapra, A. I. Scott, P. Delmotte, J. Delmotte-Plauquee, and N. S. Bhacca, Tetrahedron Lett., 869 (1964).

4) T. Takahashi, K. Kasuga, M. Takahashi, and J. Tsuji, J. Am. Chem. Soc., **101**, 5072 (1979).

5) T. Takahashi, K. Kasuga, and J. Tsuji, Tetrahedron Lett., 4917 (1978).

6a) T. Ito, K. Mori, T. Mizoroki, and A. Ozaki, Bull. Chem. Soc. Jpn., **48**, 2091 (1975).

b) A. Schoenberg, I. Bartoletti, and R. F. Heck, J. Org. Chem., **39**, 3318 (1974).

c) J. K. Stille and P. K. Wong, J. Org. Chem., **40**, 532 (1975).

d) H. Hidai, T. Hikita, Y. Wada, Y. Fujikura, and Y. Uchida, Bull. Chem. Soc. Jpn., **48**, 2075 (1975).

e) A. Schoenberg and R. F. Heck, J. Org. Chem., **39**, 3327 (1974).

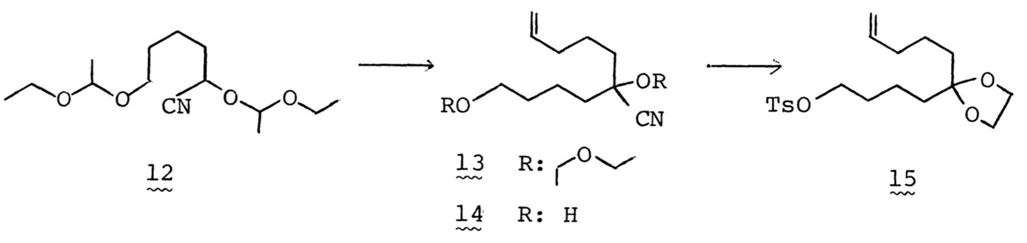
7a) M. Mori, K. Chiba, and Y. Ban, J. Org. Chem., **43**, 1684 (1978).

b) *idem*, Heterocycles, **6**, 184 (1977).

c) Y. Ban, T. Wakamatsu, and M. Mori, Heterocycles, **6**, 1711 (1977).

8) A solution of bromine (35 mmol) in CCl_4 was added dropwise over 6 h under irradiation with a 300 W tungsten lamp at refluxing temperature to a solution of the benzoate **5b** (50 mmol) in CCl_4.

9) The ω-iodo alcohol 10, prepared before from the butadiene telomer,$^{4)}$ was synthesized alternatively by the following sequence of reactions: The alkylation$^{10)}$ (LDA, THF-HMPA, -78°C to -40°C) of the protected cyanohydrin **12**, with 1.2 eq. of 5-iodo-1-pentene gave the cyanohydrin **13** in 90% yield: NMR (CCl_4): δ 0.95-1.40 (12 H, m, CH_3), 1.95-2.30 (2H, m, CH_2-C=C), 3.1-3.9 (6H, m), 4.38-5.25 (4H, m), 5.3-6.09 (1H, m. Olefinic). Removal of the protecting groups of alcohols (3N-HCl/THF, 0°C), the selective tosylation of the primary alcohol (p-TsCl/Py, 0°C), generation of ketone (2% NaOH/Et_2O, 0°C) from the cyanohydrin **14** and the protection of the resulting ketone ($HOCH_2CH_2OH$/p-TsOH) gave the tosylate **15**, which was identical with an authentic sample prepared before in this laboratory. The tosylate was converted to the iodide **10**.



12

13 R:

14 R: H

15

10) G. Stork and L. Maldonado, J. Am. Chem. Soc., **93**, 5286 (1971).

(Received February 9, 1980)