

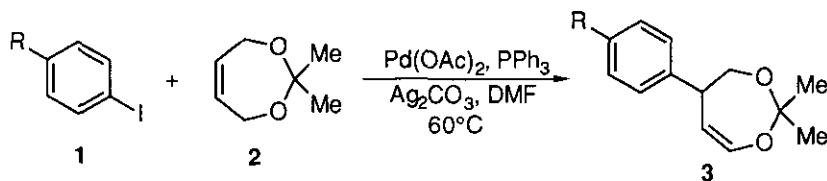
A FACILE SYNTHESIS OF 4-ARYLBUTYROLACTONES VIA THE PALLADIUM-CATALYZED ARYLATION OF 1,3-DIOXEP-5-ENE

Takao Sakamoto^{*a}, Yoshinori Kondo^a, and Hiroshi Yamanaka^b

a) *Pharmaceutical Institute, Tohoku University, Aobayama, Aoba-ku, Sendai 980, Japan*; b) *Department of Education, Yamagata University 1-4-12, Koshirakawa-cho, Yamagata 990, Japan*

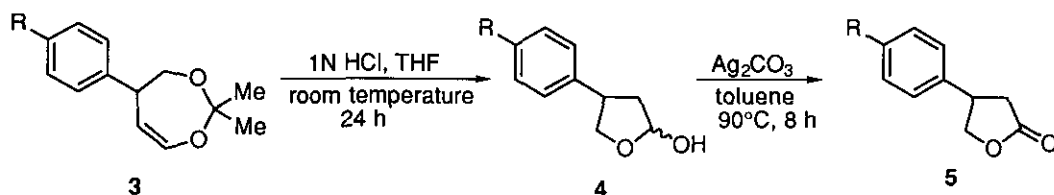
Abstract - 1,3-Dioxep-5-ene was arylated by using Heck reaction, and the arylated 1,3-dioxep-4-ene derivatives were easily converted into 4-arylbutyrolactones, intermediates for the synthesis of natural products and biological active compounds.

Heck reaction is one of the most excellent synthetic procedures for carbon-carbon bond formation.¹ Not only terminal olefins but also cyclic olefins can be arylated by the catalytic action of a palladium complex. As an extension of our work² on the Heck reaction using heterocyclic olefins,³ our interest was focused on the use of the seven-membered heterocyclic olefin, 1,3-dioxep-5-ene.⁴ Among the various conditions for the coupling reaction of cyclic olefins,⁵ the use of Ag_2CO_3 ⁶ as a base gave satisfactory results. As shown below, iodobenzenes (**1a-d**) with various functional groups reacted smoothly with **2** to give 6-aryl-1,3-dioxep-4-ene derivatives (**3a-d**) in good yields. Only 4-nitroiodobenzene (**1e**) gave the product (**3e**) in somewhat low yield.



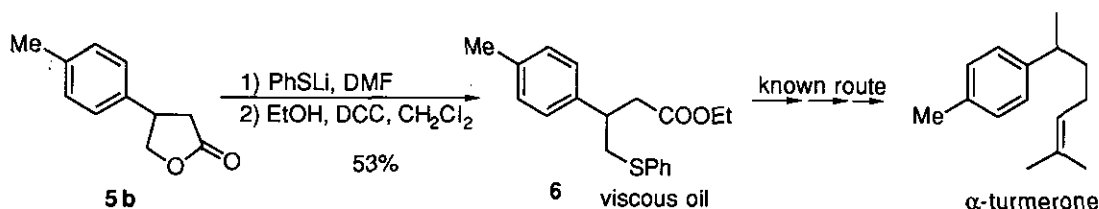
3	R	time (h)	yield (%)
a	H	24	65
b	Me	24	72
c	OMe	24	70
d	COOEt	48	66
e	NO ₂	72	25

Next, the transformation of the cross coupling products (**3**) into butyrolactones (**5**) was investigated. The arylated dioxep-4-ene derivatives (**3**) were hydrolyzed by treating with 1N HCl-THF to form hemiacetals (**4**) which were easily oxidized to the 4-arylbutyrolactone derivatives (**5**) with Ag_2CO_3 in toluene in good yields.



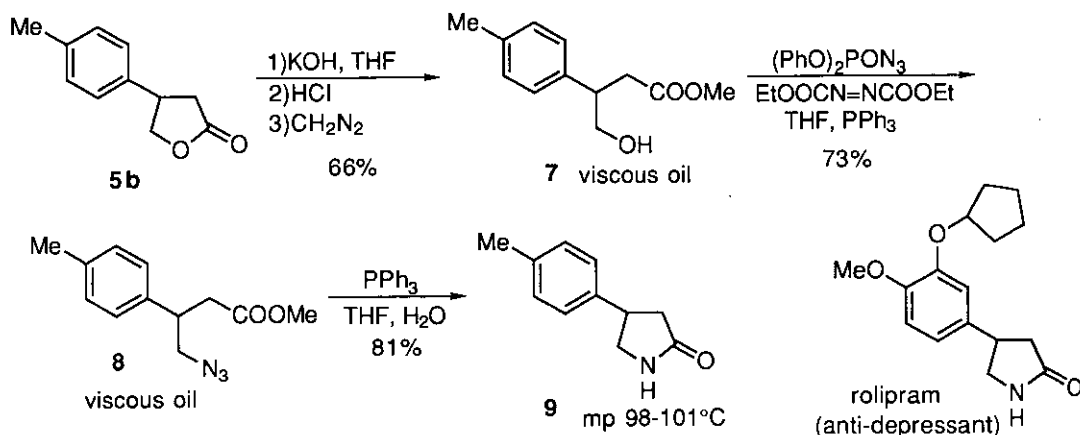
5	R	yield (%)	mp or bp (mmHg)
a	H	55	135-140°C (2)
b	Me	58	43-45°C
c	OMe	61	68-71°C
d	COOEt	56	77-79°C
e	NO_2	53	112-114°C

Some transformations of the 4-arylbutyrolactones (**5**) were examined for the syntheses of natural products and biologically active compounds. Firstly the butyrolactone (**5b**) was treated with lithium phenylmercaptide in DMF, and the obtained acid was esterified to give the sulfide ester (**6**). The conversion of this sulfide ester to α -turmerone has already been reported by Takano *et al.*⁷ The sulfide ester is also a useful intermediate for the other bisabolane sesquiterpenes.



In connection with our interest in the synthesis of anti-depressant rolipram, the transformation of the lactone (**5b**) into the corresponding lactam was examined. Hydrolysis of the butyrolactone (**5b**) with 3N KOH in THF followed by esterification with diazomethane gave hydroxy ester (**7**). The ester (**7**) was converted into the azide (**8**) using Mitsunobu reaction with DPPA. The azide (**8**) was reduced by treating with PPh_3 in aqueous THF and during the reaction the cyclization accompanied to give the five-membered lactam (**9**). The synthesis of rolipram using this manner is under way.

The present study provides a facile method for construction of butyrolactone or butyrolactam moiety on aromatic rings and the method is considered to be widely applicable for the syntheses of other biologically interesting compounds containing such heterocycles.



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- Typical Procedure: **6-p-Tolyl-1,3-dioxep-4-ene(3b)** : A mixture of *p*-iodotoluene (436 mg, 2 mmol), 1,3-dioxep-5-ene (1.28 g, 10 mmol), Pd(OAc)₂ (14 mg, 0.06 mmol), PPh₃ (32 mg, 0.12 mmol), Ag₂CO₃ (1.10 g, 4 mmol), and DMF (1ml) was stirred at 60°C for 24 h. After reaction, the mixture was diluted with ether (30 ml), filtered, and washed with H₂O (10 ml). The aqueous layer was extracted with additional Et₂O (10 ml x2). The combined organic phases were washed with brine (10 ml), dried over anhydrous MgSO₄, and concentrated *in vacuo*. The residual material was subjected to SiO₂ column

chromatography using n-hexane/AcOEt (9:1) as an eluent to give colorless oil (314 mg, 72%). ^1H Nmr (CDCl_3) δ : 7.16 (d, $J=8.6$ Hz, 2H), 7.12 (d, $J=8.6$ Hz, 2H), 6.33 (dd, $J=6.7$, 1.8 Hz, 1H), 4.94-4.91 (m, 1H), 3.95 (dd, $J=11.6$, 9.8 Hz, 1H), 3.83-3.79 (m, 1H), 3.70-3.67 (m, 1H), 2.32 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H).

9 **5b**: ^1H Nmr (CDCl_3) δ : 7.17 (d, $J=7.9$ Hz, 2H), 7.12 (d, $J=7.9$ Hz, 2H), 4.65 (t, $J=8.5$ Hz, 1H), 4.24 (t, $J=8.5$ Hz, 1H), 3.79-3.71 (m, 1H), 2.90 (dd, $J=17.7$, 9.1 Hz, 1H), 2.65 (dd, $J=17.7$, 9.1 Hz, 1H), 2.15 (s, 3H). Ir (CHCl_3) ν : 1780 cm^{-1} .

10 **9**: ^1H Nmr (CDCl_3) δ : 7.15 (s, 4H), 6.29 (br s, 1H), 3.79-3.63 (m, 2H), 3.39 (dd, $J=8.8$, 7.3 Hz, 1H), 2.71 (dd, $J=16.8$, 8.8 Hz, 1H), 2.48 (dd, $J=16.8$, 8.8 Hz, 1H), 2.34 (s, 3H). Ir (CHCl_3) ν : 3440, 1695 cm^{-1} .

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