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The Palladium-mediated Cross-coupling of Bromotropolones with Organostannanes; Application to Concise Syntheses of β-Dolabrin, β-Thujaplicin, 7-Methoxy-4-isopropyltropolone, and β-Thujaplicinol

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The bromotropolones (**1**), (**2**), and (**3**) cross-couple with organostannanes in the presence of palladium(0) to produce alkyl, alkenyl, or aryl substituted tropolones; the methodology has been applied to the synthesis of the monoterpenes β-dolabrin (**4**), β-thujaplicin (**5**), 7-methoxy-4-isopropyltropolone (**7**), and β-thujaplicinol (**8**).

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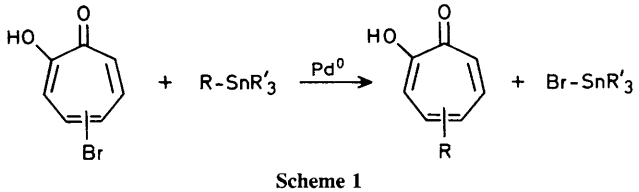
Few methods exist for the creation of new carbon–carbon bonds at the intact α-tropolone nucleus.[1,2] Consequently, we sought to establish whether the readily available bromotropolones (**1**),[3] (**2**),[4] and (**3**)[5] would engage in palladium-mediated cross-coupling reactions with organostannanes[6] as outlined in Scheme 1. We now report that such processes are viable and we describe their use in concise syntheses of the monoterpenes β-dolabrin (**4**),[7–9] β-thujaplicin (**5**),[3,9,10] 7-methoxy-4-isopropyltropolone (**7**)[11] and β-thujaplicinol (**8**).[12] The present work thus provides the first examples of the application of this type of organometallic coupling reaction to the synthesis of tropolonoid natural products.

Reaction of 4-bromotropolone (**1**) with trimethyl(2-propenyl)stannane (1.5 mol. equiv.) and dichlorobis(triphenylphosphine)palladium(II) [10 mole % w.r.t. (**1**)] in refluxing 1,4-dioxane for 1.3 h gave, after an extractive work-up procedure which included an aqueous KF washing step (to remove tin residues), β-dolabrin (**4**) (54% at 95% conversion). The spectral data obtained for tropolone (**4**) and the derived methyl ether (**9**) [prepared by treating (**4**) with diazomethane] compared favourably with the spectra of these compounds kindly provided by Prof. D. A. Evans.[8] Treatment of tropolone (**3**) with trimethyl(2-propenyl)stannane, under the same conditions as used above, gave the expected coupling product (**6**) (89%). Hydrogenation (1 atm. H_2, 5% Pd on C, ethanol) of compounds (**4**) and (**6**) afforded β-thujaplicin (**5**) (98%) and 7-methoxy-4-isopropyltropolone (**7**) (90%, m.p. 81—83 °C), respectively. Demethylation of (**7**), with 45% hydrobromic acid in glacial acetic acid (6 h, 100—110 °C), gave β-thujaplicinol (**8**)[12] (81%). This methodology has thus provided the first chemical syntheses of natural products (**7**) and (**8**).

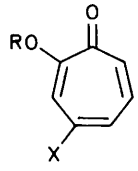
The direct *C*-alkylation of α-tropolones has not been achieved previously. It was therefore interesting to observe that reaction of (**2**) with tetramethylstannane (5 mol. equiv.) and 20 mole % tetrakis(triphenylphosphine)palladium(0) (refluxing dioxane, 48 h) provided 5-methyltropolone (**10**)† (80% yield, m.p. 110 °C, lit.[13] m.p. 110 °C). Under similar conditions, the tri-oxygenated system (**3**) coupled with tetramethylstannane to give the methylated product (**11**) [73%, m.p. 100.5—101 °C].

Reaction of (**2**) with phenyltrimethylstannane (1.5 equiv.) using dichlorobis(triphenylphosphine)palladium(II) (10 mole %) in refluxing dioxane (16 h) gave, after treatment of the crude product mixture with diazomethane [to convert the initial coupling product (**13**) into the corresponding methyl ether and thus allowing chromatographic purification], 2-methoxy-5-phenyltropolone (**14**) [98%, m.p. 141—142 °C, lit.[2] m.p. 141—142°C]. Trace amounts (<2%) of 2-methoxy-5-methyltropolone (**15**) were also isolated from the reaction mixture. The observed ratio of (**14**) to (**15**) reflects the fact that phenyl group transfer from the organostannane to an sp^2-carbon centre is significantly faster than methyl group transfer.[6] Phenylation of bromotropolone (**1**), under the same conditions as employed for isomer (**2**), provided 4-phenyltropolone (**16**) [80%, m.p. 92—95 °C; lit.[15] m.p. 92—94 °C].

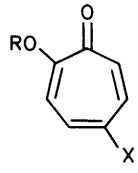
In summary, the palladium-mediated alkylation, alkenylation, and arylation of bromotropolones by organostannanes provides an efficient and flexible route to α-tropolones



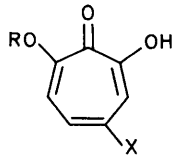
Scheme 1



(**1**); R = H, X = Br
(**4**); R = H, X = —C(CH$_3$)=CH$_2$
(**5**); R = H, X = —CH(CH$_3$)$_2$
(**9**); R = Me, X = —CH(CH$_3$)=CH$_2$
(**16**); R = H, X = Ph



(**2**); R = H, X = Br
(**10**); R = H, X = Me
(**13**); R = H, X = Ph
(**14**); R = Me, X = Ph
(**15**); R = Me, X = Me



(**3**); R = Me, X = Br
(**6**); R = Me, X = —C(CH$_3$)=CH$_2$
(**7**); R = Me, X = —CH(CH$_3$)$_2$
(**8**); R = H, X = —CH(CH$_3$)$_2$
(**11**); R = X = Me
(**12**); R = H, X = Me

† Mexican workers have assigned structure (**10**) to Veracruzalone (m.p. 100 °C), a constituent of *Polyporus tomentosus* (= *Onnia tomentosa*).[14] However, the spectral data reported[14] for Veracruzalone are inconsistent with this assignment and differ substantially from the data we and others[13] have obtained for (**10**). We conclude that the structure of Veracruzalone has been incorrectly assigned.

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containing a new C–C bond at the ring-carbon originally bearing halogen.

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