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Synthesis of *E*- and *Z*-substituted methylene-3,4-dihydro-2*H*-1-benzopyrans by regio- and stereocontrolled palladium-catalyzed intramolecular cyclization

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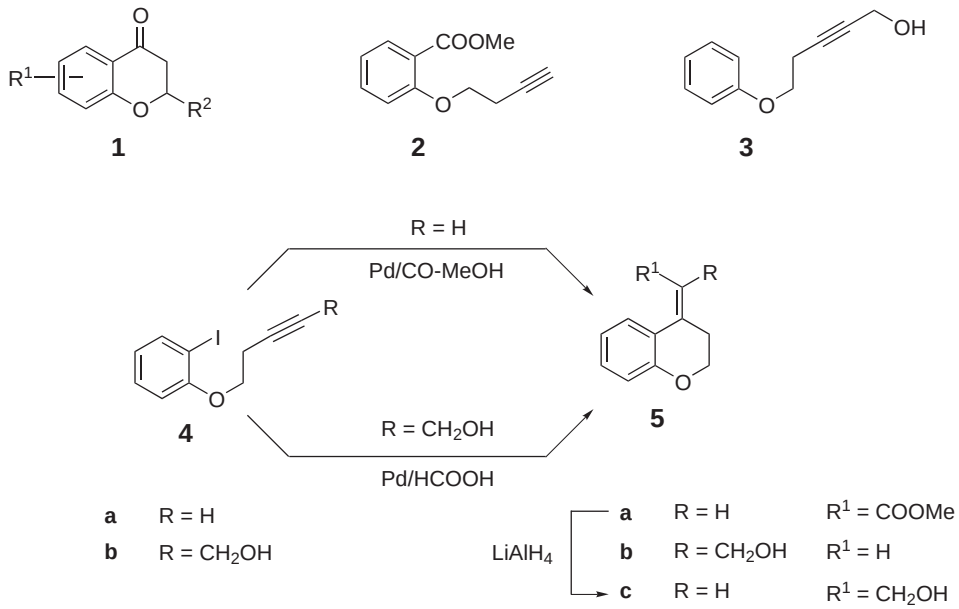
Abstract—A stereocontrolled synthetic approach to *E*- and *Z*-substituted methylene-3,4-dihydro-2*H*-1-benzopyrans **5** is described from acyclic derivatives using as a key step the palladium-catalyzed intramolecular cyclic carbopalladation of iodoalkynes **4** followed by a carbonylation or a hydride ion capture process.

The preparation of heterocyclic steroid derivatives has been an area of great interest due to their biological activities.[1] Besides their well-known hormonal activity, some of them are already described as antineoplasic agents (for instance, 2-methoxyestradiol and analogs which display cytotoxicity and inhibition of tubulin[2]…) and/or antiangiogenic agents (medroxyprogesterone acetate,[3] U42129[4]…). In order to increase these therapeutic activities, we were interested in the synthesis and evaluation of 6-oxasteroids for biological activity.

4-Substituted methylene-3,4-dihydro-2*H*-1-benzopyrans **5** have been shown to be suitable key intermediates for



Scheme 1.

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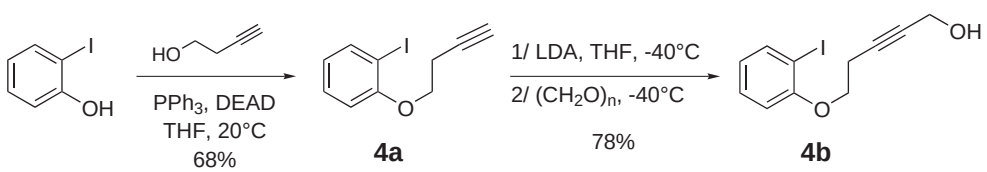

Scheme 2.

the synthesis of 6-oxasteroid derivatives. Several approaches to **5** from substituted chroman-4-ones **1** have been disclosed in the literature by using a Peterson,[5] a Wittig,[6] a Reformatsky[7] or a Torgov[8] type reaction. Except in the last case, these methods display little stereoselectivity and give a mixture of isomers. Palladium-catalyzed bond forming processes, which have evolved as powerful tools for the construction of complex natural compounds, should in principle open an attractive stereoselective alternative route to both *Z*- and *E*-isomers. To our knowledge, approaches to **5** based on transition metal-catalyzed cyclization of acyclic compounds have scarcely been reported.[9,10] The latter offer potent possibilities to obtain various derivatives **5**, since acyclic compounds are easily accessible. In this communication, we wish to report a simple and stereoselective approach to *Z* and *E* compounds **5** using as a key step the palladium-catalyzed intramolecular cyclic carbopalladation of iodoalkynes **4a**–**b**. The resulting vinyl–palladium(II) intermediates may undergo either carbonylation reaction in the presence of MeOH to give (from **4a**) the ester **5a** precursor of the *Z*-alcohol **5c** or hydride ion capture to afford the *E*-alcohol **5b** (from **4b**) (Scheme 1).

The required alkyne **4a** was readily prepared in 68% yield by a Mitsunobu coupling reaction between *ortho*-iodophenol and but-3-yn-1-ol. Subsequent deprotonation of alkyne **4a** with LDA followed by reaction with paraformaldehyde led to aromatic alkyne **4b** (Scheme 2).

Initial attempts to perform the cyclic carbopalladation–carbonylation cascade of iodoalkyne **4a** with $PdCl_2(PPh_3)_2$ (5%), CO (1 atm)[11] and Et_3N (4 equiv.) in MeOH at 100°C following the procedure of Negishi[12] were encouraging. The desired cyclic product **5a** was formed (49%) together with the acyclic derivative **2** (12%), due to a competitive carbonylation before carbopalladation, in a 80:20 ratio. Changing the solvent to DMF–MeOH (1/1: v/v) resulted in better selectivity (**5a**/**2**: 90/10). This one was enhanced (**5a**/**2**: 97/3) by adding water[12] to the reaction mixture (DMF/MeOH/H_2O: 1/1/0.2, v/v/v). Under these conditions, **5a** was isolated in a 59% yield within 24 h. Palladium sources including $Pd(OAc)_2$, $Pd(dba)_2$ and $Pd(PPh_3)_4$ were examined either with or without added triphenylphosphine ligand. The effect of the addition of various additives[13] (Et_4NCl, Tl_2CO_3, TlOAc and AgOAc) on selectivity were also studied. Suitable conditions were found which employed $Pd(PPh_3)_4$ (10%), CO (1 atm), Et_3N (4 equiv.), AgOAc (3 equiv.) in a medium consisting of 1:1:0.2 MeOH–DMF–H_2O at 100°C. The presence of AgOAc accelerated the rate of the reaction and completed the carbopalladation–carbonylation sequence within 10 h at 100°C. Under these conditions,[14] the desired cyclic compound **5a**[15] was obtained selectively in a 79% isolated yield and less than 2% of acyclic methyl benzoate **2** was formed (**5a**/**2** >98/2). Further reduction of **5a** using lithium aluminium hydride in THF afforded stereoselectively the *Z*-alcohol **5c**.

We next turned our attention to the stereoselective synthesis of the *E*-alcohol **5b** from iodoalkyne **4b** by the palladium catalyzed tandem cyclization-anion capture reported by Grigg.[16] Thus, when using the catalyst system[16] $Pd(OAc)_2$ (10%), PPh_3 (20%), piperidine (4 equiv.), HCOOH (3 equiv.) in acetonitrile at 80°C, the iodoalkyne **4b** cyclized regio- and stereoselectively via a 6-*exo*-dig process to **5b** over 18 h in 51% yield. Under these conditions, a minor quantity (6%) of compound **3** was formed arising from direct anion capture by the initial aryl–palladium species (**5b**/**3**: 90/10). Interestingly, the use of sodium formate (2 equiv.) in DMF instead of formic acid and piperidine in acetonitrile resulted in better yield of **5b** (64% instead of 51%) but in similar selectivity (**5b**/**3**: 90/10). Finally, the addition of Bu_4NCl (2 equiv.) selectively suppresses the formation of **3** via direct anion capture process and provides only the desired cyclic compounds **5b**[17] in a 79% isolated yield.

In summary, we have succeeded in developing an efficient and flexible synthetic route to *E*- and *Z*-substituted methylene-3,4-dihydro-2*H*-1-benzopyran compounds starting from readily accessible acyclic derivatives. The use of these latter as intermediates for the synthesis of novel highly functionalized 6-oxasteroids is currently in progress and will be reported in due course.

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14. *A typical procedure for the preparation of **5a** is as follows*: In an argon flushed stainless steel autoclave were placed iodoalkyne **4a** (200 mg, 0.73 mmol), Et_3N (0.4 mL, 2.94 mmol), $Pd(PPh_3)_4$ (85 mg, 0.073 mmol), AgOAc (365 mg, 2.19 mmol) in a medium consisting of 1:1:0.2 MeOH–DMF–H_2O (2 mL of MeOH, 2 mL of DMF and 0.4 mL of H_2O). The mixture was stirred under CO (1 atm) at 100°C for 10 h. Solvents were removed in vacuo and the crude material was purified by filtration through silica gel (eluent: petroleum ether/ether 90/10) and gave 178 mg (79%) of pure **5a** as a colorless oil; ^1H NMR (400 MHz): 7.80 (1H, dd, $J=8.0$ and 1.5 Hz), 7.25 (1H, ddd, $J=8.5$, 7.3 and 1.5 Hz), 6.86 (1H, ddd, $J=8.0$, 7.3 and 1.4 Hz), 6.81 (1H, dd, $J=8.5$ and 1.4 Hz), 5.70 (1H, t, $J=1.2$ Hz), 4.37 (2H, t, $J=6.2$ Hz), 3.75 (3H, s), 2.65 (2H, td, $J=6.2$ and 1.2 Hz); ^{13}C NMR (100 MHz): 167.0, 155.2, 145.6, 131.9, 129.9, 119.5, 119.0, 116.9, 113.7, 66.4, 51.4, 33.7.
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17. *A typical procedure for the preparation of **5b** is as follows*: To a stirred solution of iodoalkyne **4b** (250 mg, 0.83 mmol), sodium formate (170 mg, 2.49 mmol) and tetrabutylammonium chloride (460 mg, 1.66 mmol) in anhydrous DMF (5 mL), under an inert atmosphere, was added $Pd(OAc)_2$ (19 mg, 0.083 mmol) and PPh_3 (44 mg, 0.166 mmol). After stirring at 80°C for 12 h, the mixture was hydrolyzed with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic extract was dried over $MgSO_4$ and the solvent was removed in vacuo. Purification through silica gel (eluent: petroleum ether/ether 80/20) gave 116 mg (79%) of pure alcohol **5b** as a colorless oil ^1H NMR (400 MHz): 7.40 (1H, dd, $J=8.2$ and 1.2 Hz), 7.10 (1H, t, $J=7.9$ Hz), 6.79 (2H, m), 5.75 (1H, t, $J=8.1$ Hz), 4.51 2H, d, $J=8.1$ Hz), 4.11 (2H, t, $J=5.9$ Hz), 2.50 (2H, t, $J=5.9$ Hz); ^{13}C NMR (100 MHz): 149.1, 141.2, 128.3, 126.4, 120.4, 119.4, 118.3, 114.6, 69.8, 59.7, 37.6.