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A PALLADIUM MEDIATED SPIROKETAL SYNTHESIS

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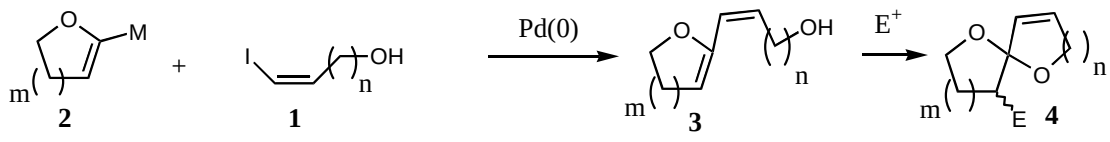
Dedicated to Professor Barry M. Trost on the occasion of his 65th Birthday

Abstract – A Stork-Negishi olefination-coupling sequence has been applied to the synthesis of spiroketals.

INTRODUCTION

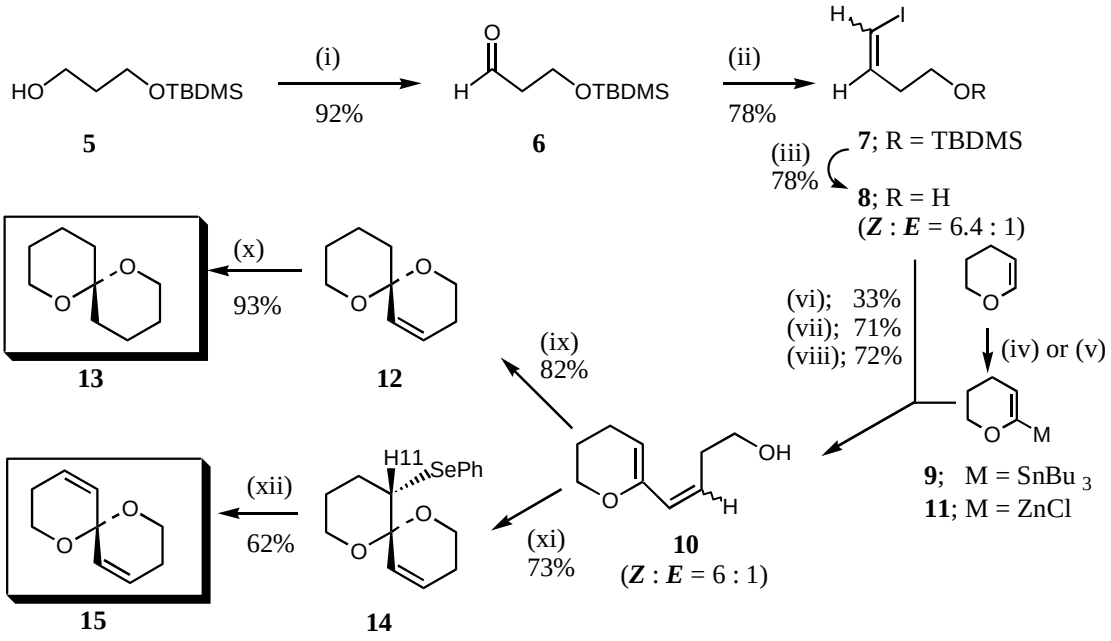
We[1] and others[2] have previously reported on the Stille coupling of tri-n-butylstannyldihydrofuran and -pyran derivatives which provides rapid access to a variety of C-glycosides,[2] heterosubstituted dienes[1] and benzofused spiroketal-containing systems.[3] We now report that extension of this chemistry leads to the rapid synthesis of simple spirocyclic systems which are ubiquitous as pheromones.[4] Our basic strategy centred upon the use of Stork's Wittig methodology[5] for the synthesis of ***Z***-vinyl iodides (**1**) followed by a Stille/Negishi coupling[6] (retention of alkene geometry) with an appropriately metallated enol ether (**2**) to afford a diene (**3**) which would undergo cyclisation to afford the desired spiroketal (**4**), **Scheme 1**.



Scheme 1

RESULTS AND DISCUSSION

Olefination (Ph_3P=CHI, 1.2 eq.; THF; -78 °C) of the readily available aldehyde (**6**) generated **7** which on deproctection (CSA, cat.; MeOH; 25 ºC; 78%) led to the isolation of the vinyl iodide ($\mathbf{8}_{Z,E}$), as a mixture of geometrical isomers (***Z:E*** = 6.4:1). Treatment of the iodide ($\mathbf{8}_{Z,E}$) (1.1 eq.) with the stannane (**9**) (1 eq.) in the presence of $Pd(OAc)_2$ (5 mol%) and tri-*o*-tolylphosphine (10 mol%) at 80 ºC for 1.5 hours in acetonitrile afforded the labile diene alcohol ($\mathbf{10}_{Z,E}$) in moderate yield (33%). As anticipated the coupling reaction proceeds with retention of olefin geometry, generating the dienes ($\mathbf{10}_{Z,E}$) as a 6:1 mixture of geometrical isomers. Substantially higher yields (71% and 72% respectively) of the dienes (**10**) were obtained under milder reaction conditions (0 ºC to 10 ºC; THF; 1 h) from the coupling reaction of the zinc reagent (**11**) with $\mathbf{8}_{Z,E}$ using either "$Pd(PPh_3)_2$"[7] or $Pd(PPh_3)_4$ as catalyst (Negishi coupling).

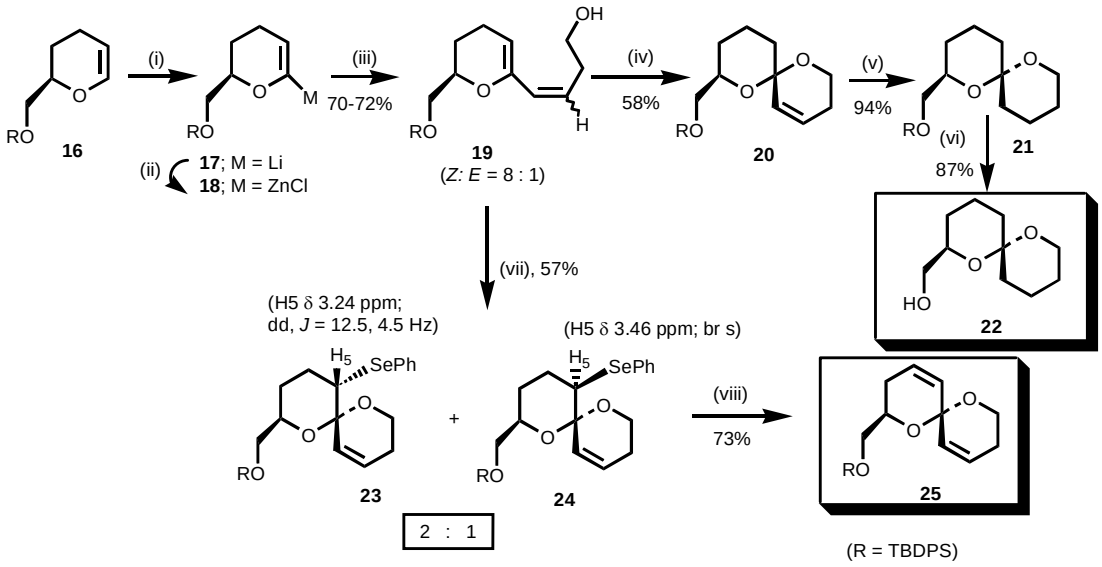


Scheme 2. Reagents and conditions: (i) $(COCl)_2$ (1.1 eq.), DMSO (2.2 eq.), CH_2Cl_2, -78 ^oC; (ii) Ph_3P=CHI (1.2 eq.), THF, -78 ^oC; (iii) CSA (cat.), MeOH, +20 ^oC, 15 h; (iv) a. *t*-BuLi (1 eq.), THF, -78 ^oC to 0 ^oC, b. Bu_3SnCl (0.75 eq.), -78 ^oC; (v) **a**. *t*-BuLi (1 eq.), THF, -78 ^oC to 0 ^oC, **b**. $ZnCl_2$ (1.2 eq.), 0 ^oC to + 20 ^oC, 2 h; (vi) **9** (1 eq.), (*o*-tol)$_3$P (10 mol%), $Pd(OAc)_2$ (5 mol%), Et_3N, CH_3CN, 80^oC, 1.5 h; (vii) **11** (2 eq.), "$(Ph_3P)_2Pd$" (5 mol%), THF, 0 ^oC, 1 hr.; (viii) **11** (2 eq.), $(Ph_3P)_4Pd$ (5 mol%), THF, 0 ^oC, 1 h; (ix) CSA (0.1 eq.), CH_2Cl_2, 20 ^oC; (x) 5% Pd/C, H_2, EtOAc, 1 atm, 6 h; (xi) pyridine (3 eq.), PhSeCl (1 eq.), CH_2Cl_2, -78 ^oC to + 20 ^oC, 1 h; (xii) Davis oxaziridine (1.1 eq.), pyridine (5 eq.), $CHCl_3$, 80 ^oC, 15 h.

Exposure of the diene alcohol ($\mathbf{10}_{Z,E}$), as a 6:1 mixture of diastereoisomers, to a solution of CSA (0.1 eq.) in CH_2Cl_2 at ambient temperature resulted in the isolation of the unsaturated spiroketal (**12**) in 82% yield. Catalytic hydrogenation (H_2, 1 atm; 5% Pd/C; EtOAc; 25 ºC) of (**12**) afforded racemic spiroketal (**13**), the pheromone[8] of *Dacus oleae, D. cacumintus*, in 93% yield. Alternatively, cyclisation of the alcohol ($\mathbf{10}_{Z,E}$)

(as a 6:1 mixture of diastereoisomers) with PhSeCl[9] (1.1 eq.; pyridine, 3 eq.; CH_2Cl_2; -78 °C to +20 ºC) to the diastereoisomerically pure selenide (**14**) (H11 δ 3.21 ppm; dd, *J* = 12.5, 4.5 Hz) in 73% yield followed by oxidation and *in situ* thermolysis[10] (Davis oxaziridine, 1.1 eq.; pyridine; $CHCl_3$; 80 ºC) afforded the doubly unsaturated spiroketal (**15**) in 62% yield, **Scheme 2**.

This basic synthetic strategy was next applied to the TBPDS-protected dihydropyran (**16**). Lithiation[11] of **16** (*t*-BuLi, 2.2 eq.; THF; -78 ºC to 0 ºC), transmetallation[12] ($ZnCl_2$, 1.1 eq.; THF; 2 h) to the organozinc (**18**) and coupling with the vinyl iodides ($\mathbf{8}_{Z,E}$) ("$Pd(PPh_3)_2$", 5 mol%; THF; +5 ºC to +20 ºC, 1 h) afforded the diene-ols ($\mathbf{19}_{Z,E}$) in 72% isolated yield.



Scheme 3. Reagents and conditions: (i) *t*-BuLi (2 eq.), THF, -78 ºC to 0 ºC; (ii) $ZnCl_2$ (1 eq.); THF, 0 ºC, 2 h; (iii) **11** (2 eq.), "$Pd(PPh_3)_2$" (5 mol%); (iv) CSA (0.1 eq.), CH_2Cl_2; (v) 5% Pd/C, H_2, EtOAc, 1 atm; (vi) TBAF ((1 eq.), THF, 20 ºC, 12 h; (vii) pyridine (3 eq.), PhSeCl (1 eq.), CH_2Cl_2, -78 ºC to + 20 ºC, 1 h; (viii) Davis oxaziridine (1.1 eq.), pyridine (5 eq.), $CHCl_3$, 80 ºC, 15 h.

Again, the coupling reaction proceeded with retention of configuration of double bond geometry as $\mathbf{19}_{Z,E}$ was isolated as a 8:1 mixture of diastereoisomers. Dissolution of the alcohols ($\mathbf{19}_{Z,E}$) in CH_2Cl_2 containing camphorsulfonic acid (0.1 eq.) brought about immediate cyclisation to the spiroketal (**20**), which was isolated in 58% yield after chromatography. Catalytic hydrogenation of **20** afforded the spiroketal (**21**), which upon fluoride-induced deprotection afforded the functionalised spiroketal (**22**) in 82% overall yield. Alternatively, reaction of the dienes ($\mathbf{19}_{Z,E}$) with PhSeCl-pyridine, as above, afforded a diastereoisomeric mixture of the selenides (**23**) and (**24**) (57% yield; **23**:**24** = 2:1), in which the major diasteroisomer (**23**) possesses an equatorial phenylseleno-substituent at C5 (H5: δ 3.24 ppm; dd, *J* = 12.5, 4.5 Hz). Removal of the phenylseleno-group was readily accomplished in our standard, two step sequence, affording the unsaturated spiroketal (**25**), as a single diastereoisomer, in 73% yield, **Scheme 3**. In conclusion, this study

illustrates that the 1,7-dioxaspiro[5.5]undec-4-ene system is readily accessible using a Wittig-Negishi route, and that application of this strategy to the synthesis of more elaborate spiroketals of biological interest should be possible. Further studies in this area are in progress, the results of which will be reported at a future date.

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