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RUTHENIUM CATALYZED RECONSTITUTIVE CONDENSATION. APPLICATION TO FUNCTIONALIZED STEROID SIDE CHAINS.

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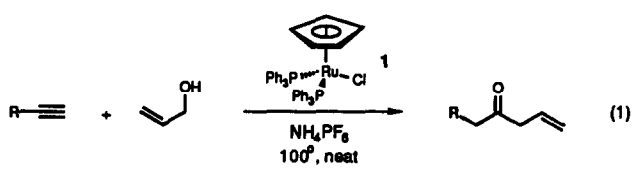
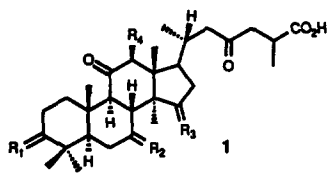
Summary: bis(Triphenylphosphine)cyclopentadienylruthenium chloride catalyzes the addition of steroidal acetylenes with allyl alcohols to introduce functionalized side chains illustrated by the construction of the side chain of ganoderic acid, a novel angiotensin converting enzyme inhibitor.

Construction of steroid side chains constitutes an important continuing challenge.[1] Such structural features frequently play critical roles in determining the biological activity of a steroid. Most recently, attempts to impact discrimination among the myriad of roles played by vitamin D metabolites focussed on side chain modifications.[2] As part of our program to define the scope and limitations of new reactions being developed in our laboratories, we have examined their applicability in the chemoselective construction of steroid side chains.[3] Our invention of a ruthenium catalyzed reconstitutive condensation of allyl alcohols and terminal acetylenes according to eq. 1[4] led us to explore the utility of this process for the construction of steroid chains. This study



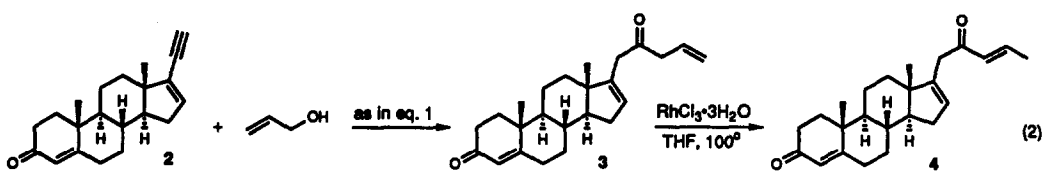
(1)

culminated in a very simple construction of the steroid side chain of a novel class of angiotensin converting enzyme inhibitors, the ganoderic acids 1.[5]



	R_1	R_2	R_3	R_4
B	α-H, β-OH	α-H, β-OH	O	H
(C)D	α-H, β-OH	α-H, β-OH	α-H, β-OH	H
E	O	O	O	H
F	O	O	O	OAc
H	α-H, β-OH	O	O	OAc
K	α-H, β-OH	α-H, β-OH	O	OAc

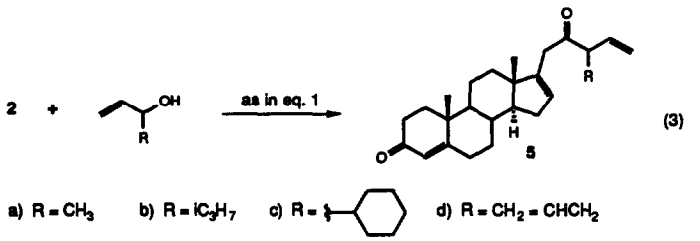
We initially focussed on enyne 2 because of its accessibility from commercially available ethisterone. Heating a neat mixture of enyne 2 and allyl alcohol with 10% of ruthenium complex 1[6] and 20% of ammonium



(2)

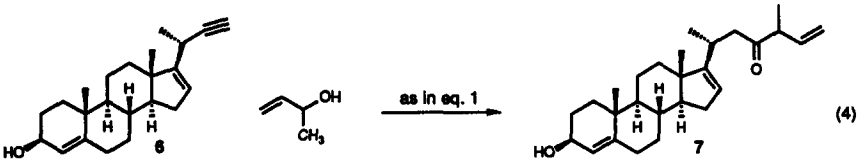
hexafluorophosphate at 100° for 24 h gave a 56% yield of the β,γ-unsaturated ketone 5 admixed with some α,β-unsaturated ketone 4 (eq. 2). To facilitate characterization, the mixture was equilibrated to the thermodynamically more state α,β-unsaturated enone 4.[7]

α-Substituted allyl alcohols 5 condense with equal facility to give the β,γ-enones **5a** (62%),[7] **5b** (41%),[7] and **5c** (47%)[7] *without* the complication of double bond isomerization (eq. 3). Thus, fairly bulky substituents like isopropyl and cyclohexyl at the position α to the OH are accommodated. The example of **5d**

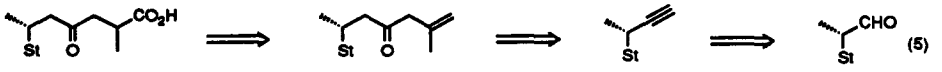


was particularly interesting because of the question of chemoselectivity with respect to the additional monosubstituted double bond. Nevertheless, the reconstitutive addition product showed no evidence that the allyl unit was effected.[8] The somewhat lower yield (33%) led us to explore some modification of reaction conditions. Significantly, switching the catalyst to 10 mol% Cp (COD) RuCl,[9] 20 mol% triphenyl phosphine, and 20 mol % ammonium hexafluorophosphate increased the yield to 50%.

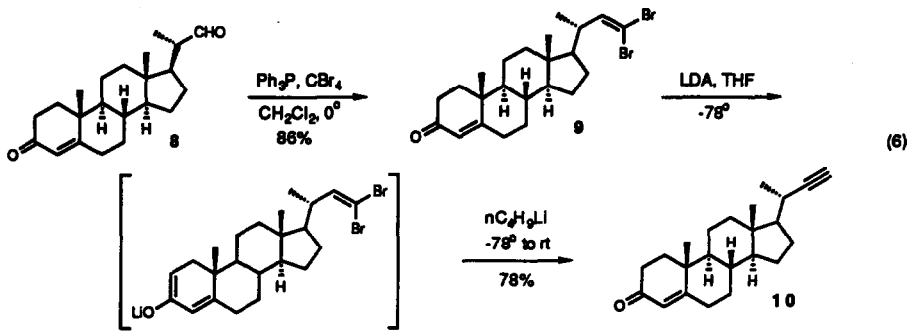
An acetylene attached to a steroid nucleus bearing an allyl alcohol as in **6** condenses smoothly with 3-buten-2-ol to give the β,γ-unsaturated ketone **7** (eq. 4), mp 111-112°C,[7] in 74% yield. It appears that most common oxygen functionality will be tolerated in the steroid nucleus.



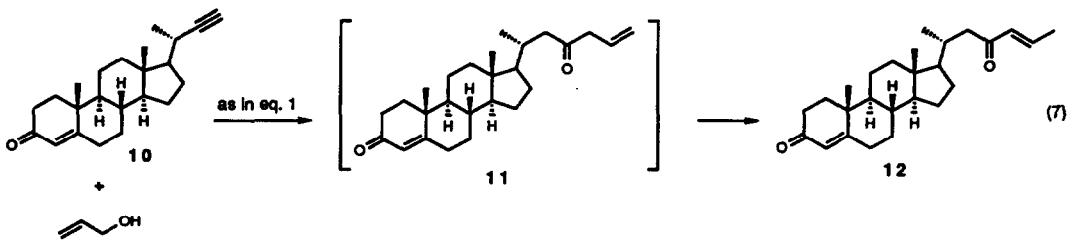
The success of introduction of a side chain onto a functionalized steroid nucleus induced us to consider the retrosynthetic analysis outlined in eq. 5 for creation of the side chain of the ganoderic acids which suggests the readily available bis-nor-cholenaldehyde system as the starting material.



We chose to explore this sequence using the commercially available 3-oxopregn-4-ene-20β-carboxaldehyde **8** as the steroid nucleus. Dibromomethylenation[10] proceeded chemoselectivity at the aldehyde to give dibromoolefin **9**[7] (eq. 6). The presence of the carbonyl group would interfere with conversion to the acetylene by *simple treatment with n-butyllithium. To obviate this problem, the ketone was first converted to its enolate with* LDA. Addition of 4 eq. of n-butyllithium to the enolate then gave the desired acetylene **10**[7] in 78% yield. Using our standard conditions as in eq. 1, reconstitutive condensation occurred in 63% yield to give a mixture of the β,γ-

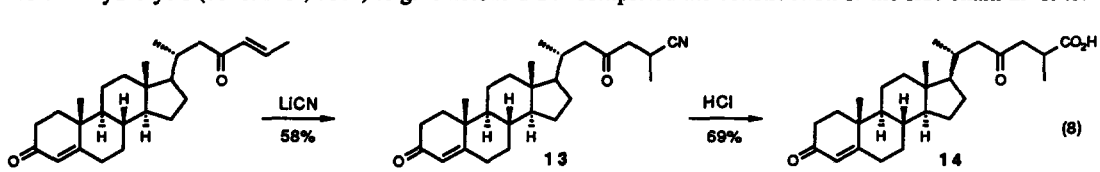


and α,β-unsaturated ketones **11** and **12** in which the latter dominated in 63% yield (eq. 7). The mixture was isomerized to the pure E-α,β-unsaturated ketone **12** with $RhCl_3 \cdot 3H_2O$ in aqueous THF at reflux in 71% yield. Because of the fact that isomerization was occurring during the ruthenium catalyzed reaction, we



explored the reconstitutive condensation directly to the α,β-unsaturated ketone by performing the reaction for a longer time whereby enone **12** was isolated directly from **10** and allyl alcohol in 68% yield. This one step protocol is recommended for formation of the thermodynamically more stable α,β-unsaturated enone in the unsubstituted series.

Completion of the sequence requires only chemoselective conjugate addition of a carboxylic acid function. Chemoselective conjugate addition of cyanide proved difficult under standard conditions - mainly due to lack of reactivity.[11] Even use of ammonium chloride in the presence of KCN proved fruitless.[12] On the other hand, LiCN in DMF-THF[13] added smoothly at room temperature to give the nitrile **13**[7] as a crystalline solid, mp 118-9°. Hydrolysis (conc. HCl, 100°) to give ketoacid **14**[7] completed the construction of the side chain in 69%.



Thus, a simple five step protocol provided the ganoderic acid side chain without the use of any protecting groups.

The excellent chemoselectivity and atom economy of the ruthenium catalyzed reconstitutive condensation coupled with the versatility of the functionality created should make this strategy a useful one for elaborating steroid side chains even in cases of highly functionalized steroid nuclei with minimal need for protecting groups.

*Sample Experimental Procedure: Deaerated 2-propen-1-ol (0.8 mL) was added to a mixture of 24-nor-4-chola-*22-yne-3-one (**10**, 246 mg, 0.758 mmol), $Cp(Ph_3P)_2RuCl$ (55.1 mg, 75.8 μmol), and ammonium hexafluorophosphate (24.7 mg, 152 μmol). The solution was heated at 100° for a total of 48h during which time (0.2-0.3 mL aliquots of 2-propen-1-ol were added after 5h, 23 h and 31 h. The reaction mixture was directly chromatographed (4:1 hexane-ethyl acetate) to give 195.2 mg (68% yield) of enone **12**, R_f = 0.25. Ir ($CDCl_3$): 1694, 1673, 1629, 1616, 1445, 1376, 1353, 1331 cm.$^{-1}$ ^{1}H nmr ($CDCl_3$, 400 MHz): δ 6.83 (1H, dq, J = 15.7, 6.9 Hz), 6.13 (1H, dq, J = 15.7, 1.6 Hz), 5.73 (1H, s), 2.54 (1H, dd, J = 17.5, 1.6 Hz), 2.45-2.20 (5H, m), 2.17-0.82 (15H, m), 1.90 (3H, dd, J = 6.9, 1.6 Hz), 1.18 (3H, s), 0.92 (3H, d, J = 6.4 Hz), 0.76 (3H, s).^{13}C nmr ($CDCl_3$, 100 MHz): δ 200.68, 199.62, 171.53, 142.31, 132.43, 123.72, 56.24, 55.89, 53.67, 47.09, 42.50, 39.46, 38.54, 35.63, 35.53, 33.93, 32.98, 32.86, 31.93, 28.36, 24.09, 20.93, 19.61, 18.20, 17.32, 11.97. Calc'd for $C_{26}H_{36}O_2$: 380.2717. Found: 380.2719.

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