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Transition Metal Promoted Acetylene Isomerisation Reactions:- Application To The Synthesis of (+/-)-Andirolactone.

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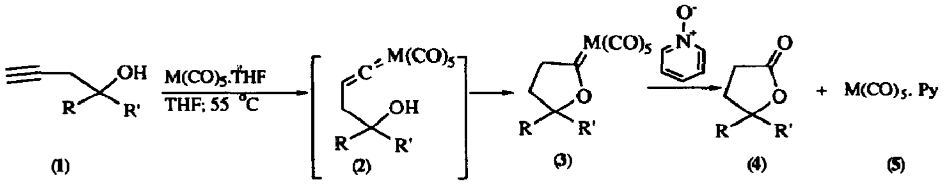
Abstract: *A chromium promoted acetylene-vinylidene rearrangement has been utilised in the synthesis of (+/-)-andirolactone.*

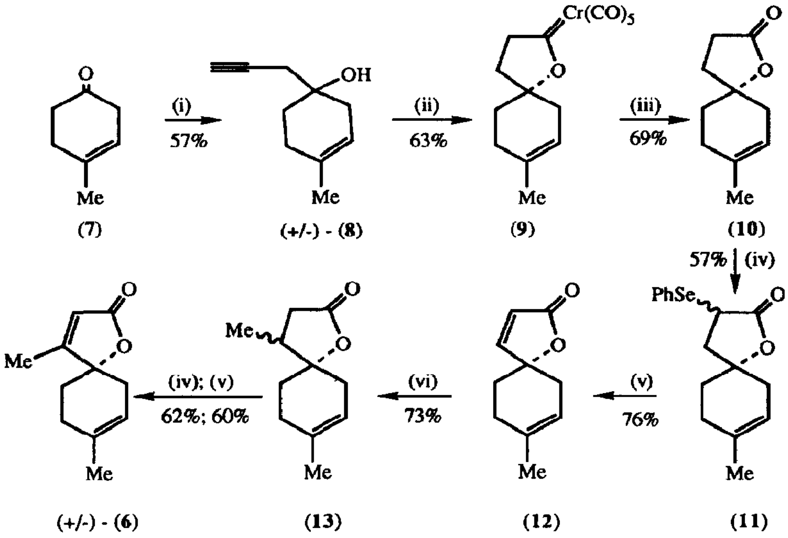
We[1] recently reported a general method for the preparation of γ-butyrolactones from acetylenic alcohols which utilises a group 6 transition metal promoted acetylene rearrangement. Reaction of terminal acetylenic alcohols (1) with $M(CO)_5$.THF (M = Mo, Cr, W) generates vinylidene complexes (2) which undergo rapid intramolecular capture to the stable carbene complexes (3). Mild oxidative decomplexation (*e.g.* pyridine *N*-oxide) of such complexes generates the desired lactones (4) together with the pyridinato complex (5), which is usually readily removed by "flash" chromatography, **Scheme 1**.



Scheme 1

As a continuation of our interest in defining the synthetic utility of this lactone synthesis, we wish to report a synthesis of (+/-)-andirolactone[2] (6), a spirocyclic lactone which has recently been isolated from the wood of the lebanese cedar (*Cedrus libanotica*). Reaction of the readily available enone[3] (7) with propargylmagnesium bromide (1.0 eq.; ether; -20 °C) cleanly afforded the alkynol (8) in 57% isolated yield. Exposure of the alcohol (8) to a freshly prepared solution of $Cr(CO)_5$.THF (1.1 eq.) in THF (0.06 M solution) at 55 °C under an atmosphere of argon resulted in a gradual colour change of the reaction mixture from orange to green. After 16 hours at 55 °C the reaction was complete and purification by "flash" chromatography under nitrogen afforded the carbene complex[4] (9) (63%). Oxidation of the carbene (9) to the lactone (10) was readily accomplished in good yield (69%) upon reaction with cerric ammonium nitrate (CAN; 2.5 eq ; 10 mins.) in acetone at ambient temperature. Elaboration of the lactone (**10**) into (+/-)-andirolactone (**6**) was effected *via* a double selenoxide elimination - cuprate addition sequence, **Scheme 2**. Conversion of the lactone (**10**) into its enolate (LDA, 1.1 eq.; THF; -78 °C) and reaction with phenylselenium chloride (PhSeCl, 1.1 eq.; THF; -78 °C) afforded the selenide (**11**) in 57% yield as a 1:1 mixture of diastereoisomers. Oxidation (Davis oxaziridine[5]) of the selenide (**11**) and mild pyrolysis ($CHCl_3$; Et_3N; 50 °C) afforded the unsaturated lactone (**12**) (76% overall yield), which underwent cuprate addition reaction (Me_2CuLi; 3.5 eq.; Et_2O; 0 °C to 20 °C) to afford a 1:1 mixture of diastereoisomeric lactones (**13**) in 73% isolated yield. Re-introduction of the double bond was accomplished *via* a second selenation (62%) - elimination (60%) sequence generating (+/-)-andirolactone as a colourless oil, whose spectroscopic data was in excellent agreement with that reported by Krause[2b].

In summary we have demonstrated that acetylene-vinylidene isomerisations provide access to γ-butyrolactones which are themselves useful synthetic intermediates. Efforts are currently directed towards the extension of this methodology to the enantiospecific synthesis of lactones of biological interest.



Reagents and conditions:- (i) C_3H_3MgBr; Et_2O; -20 °C to 0 °C; (ii) $Cr(CO)_5$.THF, 1.1 eq.; THF; 55 °C; 16 hrs. (iii) CAN, 2.5 eq.; acetone; 20 °C; 10 mins. (iv) a. LDA, 1.1 eq.; THF; -78 °C; b. PhSeCl, 1.1 eq.; THF; -78 °C; (v) a. CSO, 1.1 eq.; $CHCl_3$; 20 °C; b. $CHCl_3$ - Et_3N (0.5 eq.); 50 °C; 3 hrs. (vi) Me_2CuLi, 3.5 eq.; Et_2O; 0 °C to 20 °C; 16 hrs.

Scheme 2

Acknowledgements

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References and notes

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