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An Approach to Oxasteroids

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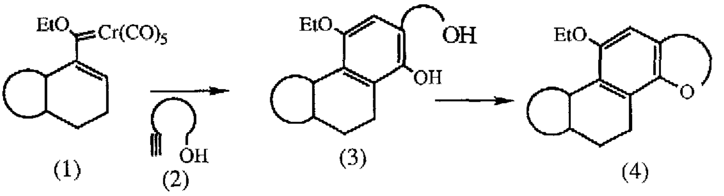
Abstract: *A tandem Dotz-Mitsunobu sequence has been used to prepare the oxasteroid skeleton*

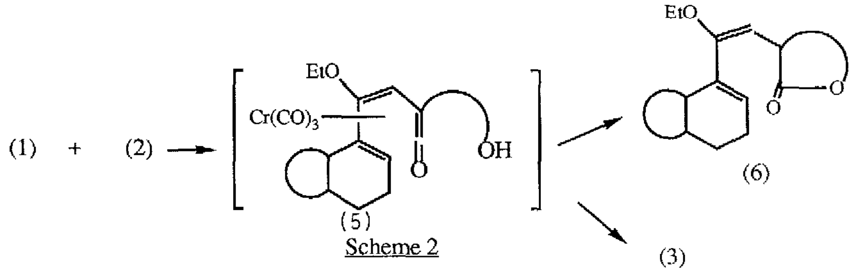
The development of semisynthetic/synthetic approaches to both natural and novel steroidal systems continues to be an active area of interest[1], although, to date, relatively few approaches to hetero-steroidal systems, e.g. oxasteroids[2] exist. As a continuation of our interest into the use of chromium carbene complexes in organic synthesis[3], we have developed a relatively rapid entry into this interesting structural type.

It was envisaged that a Dotz benzannulation[4] reaction of a vinylchromium carbene complex (**1**) with a suitably functionalised acetylenic alcohol (**2**), would afford, after decomplexation, the phenolic alcohol (**3**). Cyclisation using the intramolecular variant of the Mitsunobu reaction[5] would then give rise to the desired heterocyclic system (**4**), Scheme 1.



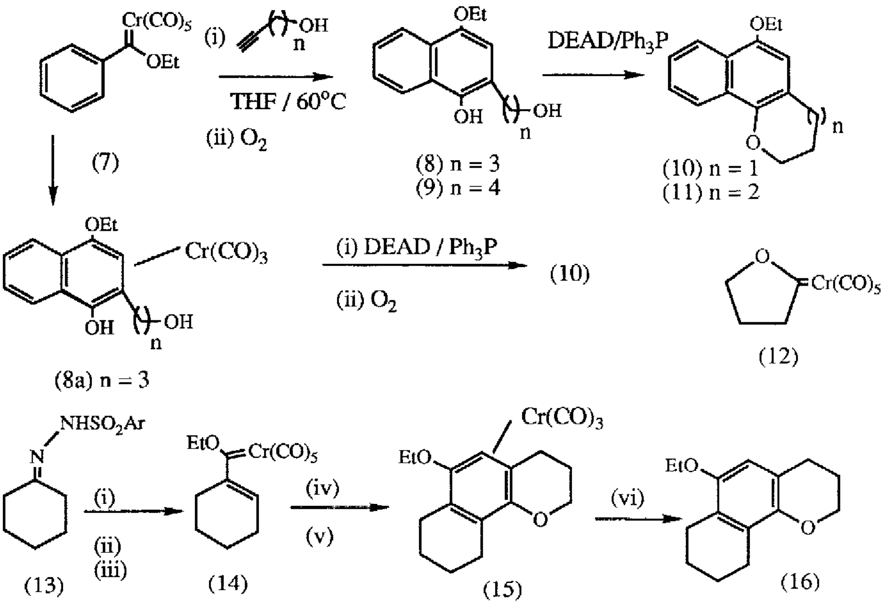
Scheme 1

The utilisation of hydroxy acetylenes, such as (**2**), in the Dotz reaction has received scant attention[6], presumably due to the possibility of processes other than benzannulation occuring after the initial formation of the complexed vinyl ketene[7] (**5**), Scheme 2.



Scheme 2

To our surprise[8], in a model study, reaction of the Fischer carbene complex[8a] (7) with 4-pentynol or 5-hexynol (3 eq., 15 hrs., THF, 60°C), followed by aerial decomplexation, afforded the desired alcohols (**8**) and (**9**), as the sole non-polar products in moderate overall yields (50% and 40% respectively). Finally, subjection of the alcohols (**8**) and (**9**) to Mitsunobu cyclisation conditions (Ph_3P/DEAD, 1 eq.; THF; 20°C; 16 hrs.) afforded the heterocycles (**10**) and (**11**) in acceptable isolated yields (62% and 51% respectively). In agreement with literature precedent[6], reaction of the carbene complex (7) with 3-butynol (3 eq.; THF; reflux 16 hrs.) afforded the cyclic carbene complex (**12**) as a yellow crystalline solid[9] (38% yield). Of interest was the observation that Mitsunobu cyclisation (Ph_3P/DEAD, 1 eq.; THF; 20°C) of the complex (**8a**), which was prepared *in situ* from the carbene (**7**), was complete within 5 minutes (compared with 16 hrs. for the uncomplexed alcohol), Scheme 3.

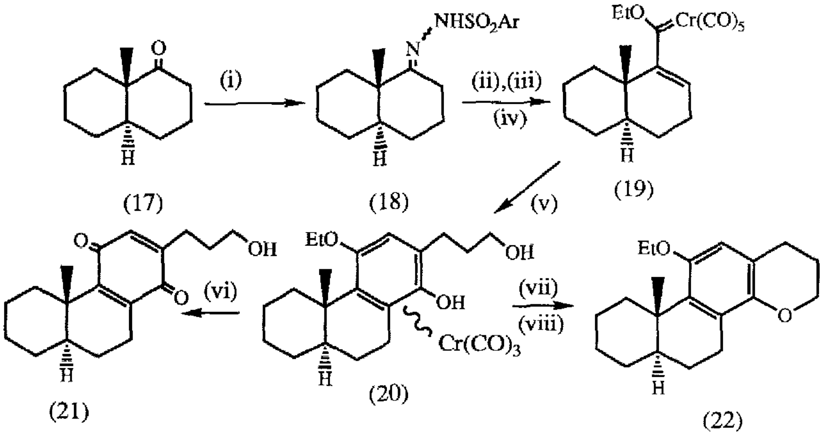


Reagents:- (i) ^{n}BuLi (2.2 eq.; THF; -78°C to 0°C); (ii) $Cr(CO)_6$,-78 °C; (iii) Et_3OBF_4;
(iv) 4-pentynol (3 eq.), THF, reflux; (v) Ph_3P/DEAD, 1.1 eq., THF; 20°C
(vi) hv, PhH; 20°C.

Scheme 3

In a similar manner, conversion of cyclohexanone tri-isopropylsulphonylhydrazone (**13**) to the carbene complex(**14**) ((i) ^{n}BuLi, 2.2 eq., THF-TMEDA; -78°C to 0°C; (ii) $Cr(CO)_6$, 1 eq., (iii) Et_3OBF_4, 1 eq.), benzannulation (4-pentynol, 3 eq.; THF; 60°C) and *in-situ* cyclisation (Ph_3P/DEAD, 1.1 eq.; THF; 20°C) afforded the chromium tricarbonyl complex (**15**) in 41% isolated yield. For substrates similar to (**15**), photolytic removal[10] of the chromium tricarbonyl moiety appeared to be superior to chemical methods of decomplexation. Hence, the complex (**15**) was dissolved in benzene and photolysed (500 W mercury lamp) under a slow stream of nitrogen. After one hour the benzene solution was purged with oxygen and the inorganic material removed by filtration to afford, after chromatography, the pyran (**16**) in 78% yield.

Having developed a basic strategy for the synthesis of polycyclic ethers of the type (**16**), we next turned our attention to the functionalisation of the decalin-derived carbene complex (**19**). The vinyl carbene complex (**19**) was readily obtained from the decalone (**17**) using a modification of the previously described procedure. Hence conversion of the ketone[11] (**17**) to the hydrazone (18) (TPSH, 1 eq; THF; 24 hrs.), vinyl lithium generation (^{n}BuLi, 2.2 eq.; DME; -78°C to 0°C) and subsequent capture ((i) $Cr(CO)_6$, 1 eq.; (ii) Et_3OBF_4, 1.1 eq.) afforded the vinyl carbene complex (**19**) as a deep red oil. Benzannulation of the crude carbene complex (**19**) with 4-pentynol (3 eq.; THF; reflux) afforded the arene complex (**20**), which proved relatively resistant towards decomplexation. Decomplexation with powerful chemical oxidants, led to the isolation of over-oxidized products (e.g. decomplexation with Ce^{IV} afforded the quinone (**21**) in 34% overall yield from the hydrazone (**18**)). However, conversion of the hydrazone (**18**) to the carbene complex (**19**) as above, benzannulation (4-pentynol, 3 eq.; THF; reflux), cyclisation (Ph_3P/DEAD, 1 eq.) and then photolytic decomplexation afforded the tetracyclic system (**22**) in 11% overall yield in an essentially "one-pot" reaction, Scheme 4.

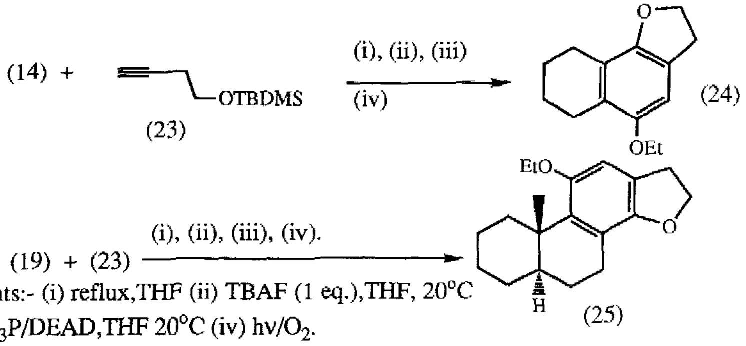


Reagents:- (i) TPSH; THF (ii) ^{n}BuLi (2.2 eq.), -78°C to 0°C (iii) Cr(CO)6, -78°C (iv) Et_3OBF_4 (v) 4-pentynol (vi) Ce^{IV} (vii) Ph_3P/DEAD (viii) hv/O_2

Scheme 4

As noted previously (*vide supra*), attempted benzannulation with 3-butynol leads to the isolation of rearranged products. This unusual reaction may be suppressed however by prior protection of the hydroxy group. Hence, benzannulation of the protected alcohol (**23**) with the carbene complex (**14**), (prepared *in situ* from the hydrazone (**13**)), deprotection (TBAF, 1 eq.; THF; 20°C), cyclisation (Ph_3P/DEAD, 1.1 eq.; THF; 20°C) and finally photolytic decomplexation afforded the benzofuran (**24**) in 9% overall yield. In a similar fashion, *in situ* generation of the carbene (19) from the hydrazone (**18**), benzannulation with the protected alcohol (**23**), deprotection (TBAF, 1.1 eq.; THF; 20°C), cyclisation (Ph_3P/DEAD; THF; 20°C) and decomplexation ((i) hv, PhH; 20°C; (ii) O_2) afforded the 6,6,6,5-ring system (**25**) in 7% overall yield in a "one-pot" operation (*c.a.* 65% yield per step), Scheme 5.

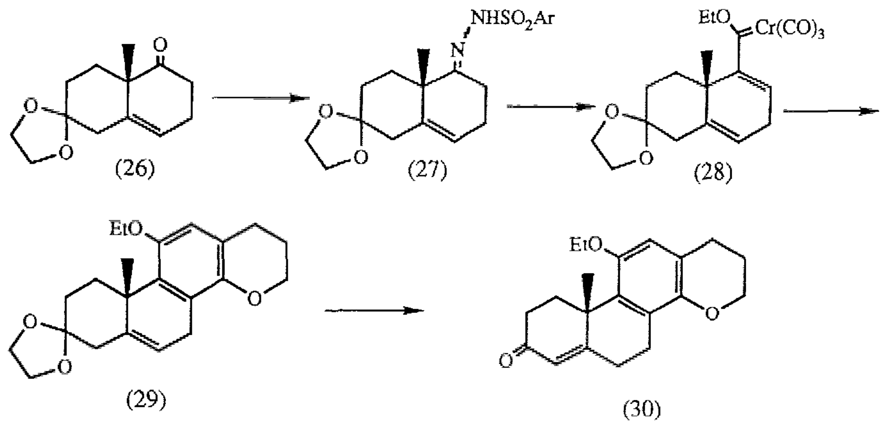
In an attempt to generate more highly functionalised systems, the benzannulation chemistry of the readily available carbene complex (**28**) was next investigated. Conversion of the protected diketone (**26**)[12], as before, led to the isolation of hydrazone (**27**) in 66% yield as a single geometrical isomer (presumably the *E*-isomer based upon steric considerations). Shapiro fragmentation and subsequent reaction with chromium hexacarbonyl, followed by triethyloxonium tetrafluoroborate afforded the rather unstable carbene complex (**28**), which was used without additional purification in the benzannulation step. Benzannulation (4-pentynol, 3eq.; THF; reflux), cyclisation (Ph_3P/DEAD, 1 eq.; THF) and decomplexation (hv, PhH) afforded the benzopyran (**29**) in 31% yield.



Reagents:- (i) reflux,THF (ii) TBAF (1 eq.),THF, 20°C (iii) Ph_3P/DEAD,THF 20°C (iv) hv/O_2.

Scheme 5

Hydrolysis of the ketal (**29**) (70% aqueous acetic acid; reflux, 3hrs.) and concommitant double bond migration afforded the unsaturated ketone (**30**) in 55% isolated yield, Scheme 6.



Scheme 6

In conclusion, these model studies have demonstrated that a tandem Dotz-Mitsunobu sequence can be employed to good effect in the construction of oxasteroidal systems. Further investigations into this area are currently underway and the results of these studies will be reported elsewhere.

Acknowledgement

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References and notes

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