



Rapid Access to Tricyclic Compounds Using Zirconium Chemistry and Intramolecular Diels-Alder Reactions: Synthesis of the Pisiferanol and Dolastane Skeletons

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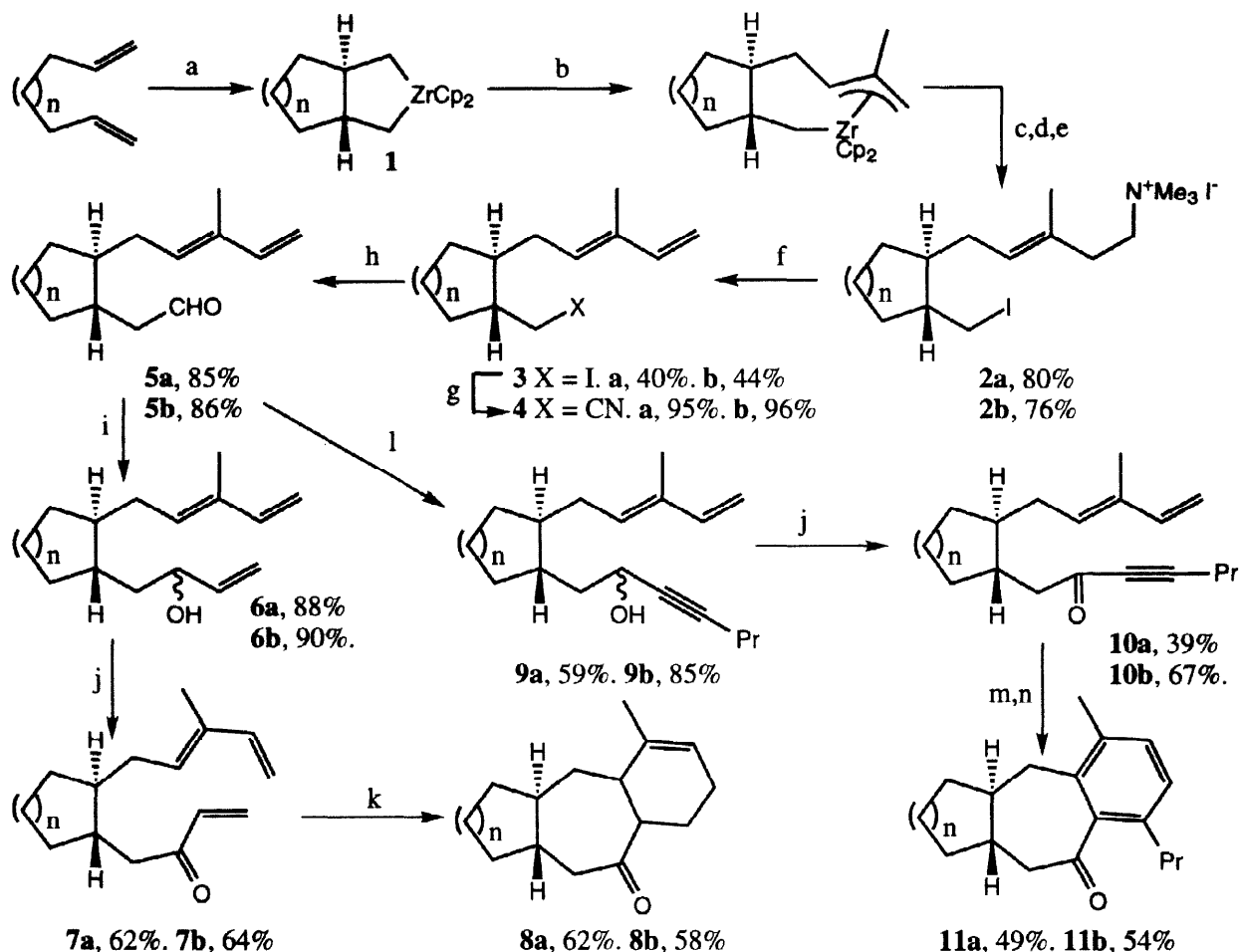
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Abstract: Zirconium mediated cocyclisation of α,ω -dienes to give zirconabicycles, followed by allylcarbenoid insertion, electrophile addition, and iodine quench gave highly functionalised organic structures. Further elaboration including an intramolecular Diels-Alder reaction gave a variety of fused tricyclic compounds including the 5,7,6 skeleton of the dolastane diterpenes and the 6,7,6 (aromatic) rearranged 9(10 \rightarrow 20)-abeo-abietane skeleton of pisiferanol. © 1997 Elsevier Science Ltd. All rights reserved.

The wide variety of zirconabicycles available from simple organic precursors make them attractive as intermediates in organic synthesis.¹ Many methods have been developed by which such zirconabicycles can be elaborated including carbonylation, tandem insertion of isocyanides and further π -components, and copper catalysed reactions.² Recently we have developed the tandem insertion of carbenoids and electrophiles as a versatile route to a wide range of highly functionalised compounds.³ Herein we report how the products from this sequence may be readily elaborated into a variety of fused tricyclic systems *via* intramolecular Diels-Alder (IMDA) reactions.⁴

Intramolecular co-cyclisation of 1,6-heptadiene and 1,7-octadiene using zirconocene(1-butene) (generated *in situ* from dibutylzirconocene - the Negishi reagent⁵) gave the *trans*-fused zirconabicycles **1a** and **1b** (Scheme 1).⁶ Insertion of a carbenoid generated *in situ* from methallylchloride and lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was followed by addition of Eschenmoser's salt ($H_2C=N^+Me_2I^-$) and iodinolysis. After a brief aqueous work-up addition of methyl iodide to the organic extract precipitated the quaternary ammonium salts **2a** and **2b** in excellent overall yield from the starting dienes (Scheme 1).⁷ Selective elimination of the quaternary ammonium moiety of **2** in the presence of the iodide proved difficult. Addition of 1 equivalent of LiTMP to a THF solution of **2a** and **2b**, at $-5^\circ C$ proved to be the most effective route to the required dienes **3a** and **3b**. Nucleophilic displacement of the iodide was hampered by a tendency to eliminate, but pure potassium cyanide with 1 equivalent of 18-crown-6 in acetonitrile gave good yields of the nitriles **4a** and **4b**. Reduction with diisobutylaluminium hydride (DIBAL-H) followed by hydrolysis gave the aldehydes **5a** and **5b** putting us in a position to synthesize a range of potential precursors for IMDA reactions. Addition of vinylmagnesium bromide to the aldehydes **5a** and **5b** gave the allylic alcohols **6a** and **6b** as mixtures of diastereoisomers. Oxidation with pyridinium chlorochromate (PCC) (MnO_2 and $BaMnO_4$ both failed) gave the ketones **7a** and **7b** together with small amounts of the Diels-Alder adducts **8a** and **8b** (PCC acted as a catalyst for the IMDA reaction). Heating at $100^\circ C$ in toluene for 12 h for **7a**, and 16 h at room temperature for **7b** completed the process giving excellent yields of the tricyclic adducts **8a** and **8b**, unfortunately in each case as approximately a 3 : 2 : 2 : 1 mixture of diastereoisomers. Catalysis of the Diels-Alder reactions of **7a** and **7b** with 20 mol% of titanium tetrachloride at $-78^\circ C$ slightly enhanced the selectivity to approximately 5:2:2:1.⁸

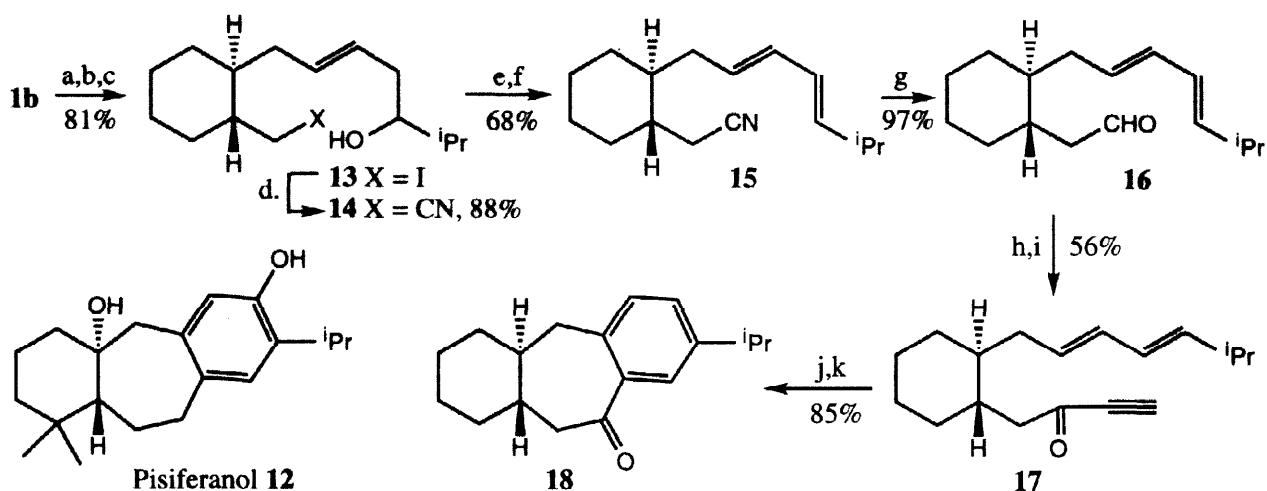
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Scheme 1. **a** $n = 1$; **b** $n = 2$. a) Cp_2ZrBu_2 , THF, -78°C - r.t. (+ 2h at 60°C for $n = 2$); b) $\text{CH}_2=\text{CMeCH}_2\text{Cl}$, LiTMP, -78°C ; c) $\text{CH}_2=\text{N}^+\text{Me}_3 \text{I}^-$, r.t.; d) I_2 , -78°C - 0°C then $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ aq; e) MeI; f) LiTMP, THF, -78°C ; g) KCN, CH_3CN , 18-crown-6, r.t., 16h; h) DIBAL-H, -78°C - r.t. then aqueous work-up; i) $\text{CH}_2=\text{CHMgBr}$; j) PCC, CH_2Cl_2 , r.t. 3h; k) $n = 1$, r.t., 16h. $n = 2$, 100°C , 12h, toluene; l) $\text{PrC}\equiv\text{CLi}$, THF, r.t.; m) Toluene, 110°C , 48 h; n) DDQ, 1h, 110°C .

Treatment of the aldehydes **5a** and **5b** with 1-lithio-1-pentyne gave the propargyl alcohols **9a** and **9b** which were oxidised to the ketones **10a** and **10b** respectively using PCC. Heating the ketones to 110°C for 48 hours gave a mixture of Diels-Alder cyclised products, which were aromatised on heating for 1 hour with dichlorodicyanobenzoquinone (DDQ), to give the aromatic compounds **11a** and **11b**.

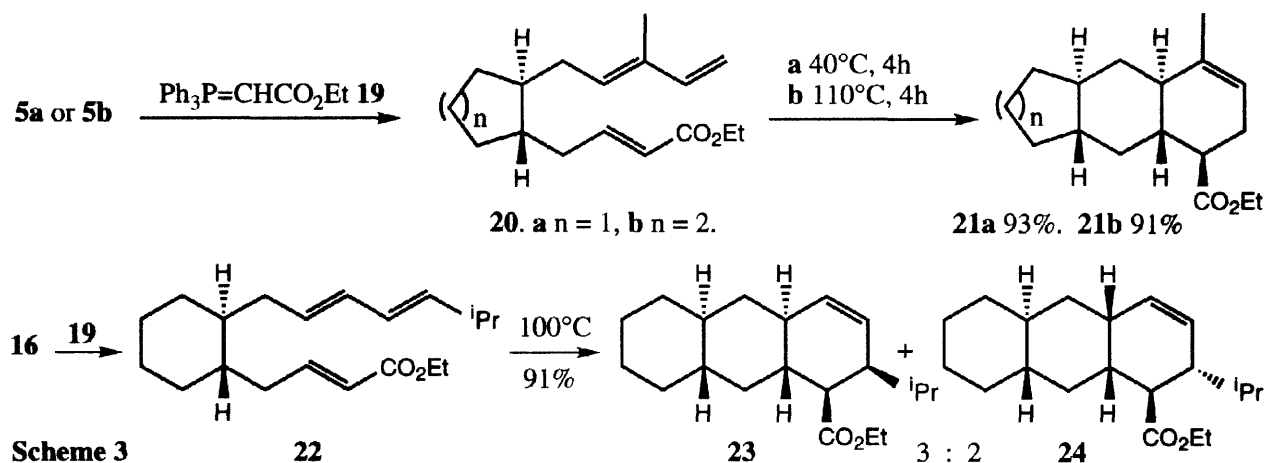
The 5,7,6 tricyclic skeleton present in **8a** is characteristic of the clavularane/dolastane diterpenes.⁹ The 6,7,6(aromatic) system present in **11b** is found in a range of diterpenes with the rearranged 9(10 \rightarrow 20)-*abeo*-abietane skeleton such as piferanol **12**.¹⁰ To extend our method to the synthesis of natural products such as **12** we required a route to dienes with a terminal substituent. Since iminium salts carrying β -hydrogens are difficult to access we modified the synthetic sequence as illustrated by the synthesis of the model **18** for piferanol (Scheme 2). Sequential insertion of lithium chlorallylide (generated *in situ* from allylchloride and LiTMP) and isobutanal into the zirconacycle **1b** obtained from 1,7-octadiene, followed by iodolysis gave the alcohol **13** in excellent yield (Scheme 2). Displacement of the iodide with cyanide followed by mesylation of the alcohol and elimination with potassium *tert*-butoxide gave the conjugated diene **15**. Reduction of the nitrile to afford an aldehyde on aqueous work-up followed by addition of ethynyl magnesium bromide and PCC oxidation gave the IMDA precursor, ketone **17**. Heating **17** at reflux in toluene for 14 h gave a mixture of adducts which afforded the single desired aromatic compound **18** when treated with DDQ.



Scheme 2. a) $\text{CH}_2=\text{CHCH}_2\text{Cl}$, LiTMP, THF, -78°C ; b) $i\text{PrCHO}$, $\text{BF}_3\cdot\text{Et}_2\text{O}$, -78°C - r.t.; c) I_2 , -78°C - 0°C then $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ aq; d) KCN, DMSO, 40°C , 16h; e) MsCl , Et_3N , CH_2Cl_2 -20°C ; f) KO^tBu , THF, 2h, r.t.; g) DIBAL-H, -78°C - r.t. then aqueous work-up; h) $\text{HC}\equiv\text{CMgBr}$, THF, r.t.; i) PCC, CH_2Cl_2 , r.t., 4h; j) Toluene, 110°C , 14h. k) DDQ, 3h, 110°C .

The key intermediate aldehydes **5a**, **b** and **16** prepared above also allowed us to examine the formation of 5,6,6 and 6,6,6 ring systems by IMDA processes. Reaction of the aldehydes **5a** and **5b** with carboethoxymethylene triphenylphosphorane **19** gave the IMDA precursors **20a** and **b**, contaminated with the cycloadducts **21a** and **b**. Heating at 40°C for 4 h in the case of **20a**, and 110°C for 4h in the case **20b** completed the IMDA reactions to yield the tricyclic adducts **21a** and **21b** in excellent yields as single isomers. In the case of **21a** the cycloaddition was so fast that pure **20a** could not be isolated. Consideration of transition states, and literature precedent, very strongly support the shown stereochemistry, but it has not been proven.¹¹

The aldehyde **16** was also treated with carboethoxymethylene triphenylphosphorane to give the IMDA precursor **22**. Heating at 110°C for 16 hours gave a 3:2 mixture of the adducts **23** and **24** (out of the four possible). **23** is a crystalline compound and its relative stereochemistry has been proven by X-ray structure determination.¹² The stereochemistry of the oil **24** was proven by NMR studies.¹³



In conclusion we have demonstrated a method giving rapid access to a variety of tricyclic ring systems combining an efficient zirconium based method for assembling organic fragments, with the intramolecular Diels-Alder reaction.

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service at Daresbury.¹⁴

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