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Total synthesis of (±)-acetoxyodontoschismenol using zirconium chemistry†

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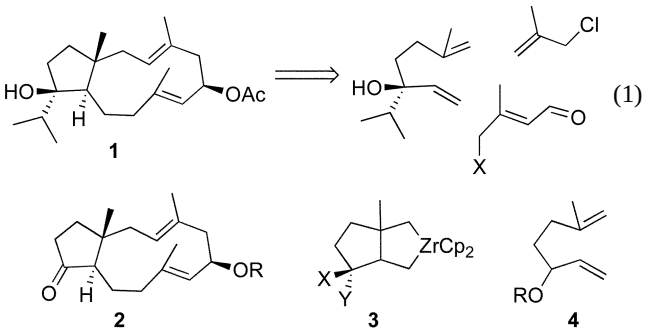
The dolabellane diterpene (±)-acetoxyodontoschismenol has been synthesised for the first time by a short route in which a three component coupling on zirconium is used to assemble all the carbons needed for the skeleton in one-pot.

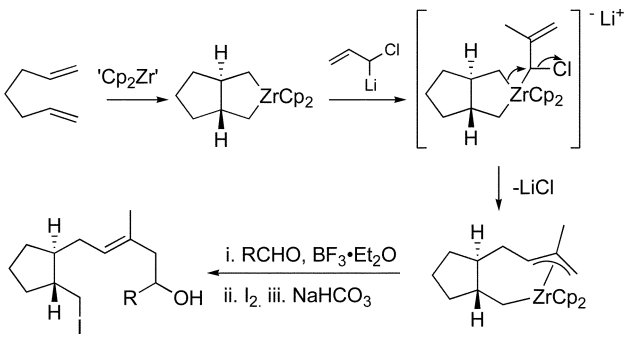
We have described how zirconacyclopentanes, readily derived by co-cyclisation of 1,*n*-dienes,[1] could be elaborated by insertion of metallated allyl chlorides to afford allylzirconocenes followed by addition of electrophiles (Scheme 1).[2] We now report the first total synthesis of the dolabellane diterpene (±)-acetoxyodontoschismenol[3] **1** in which a sequence of zirconium mediated transformations are used to assemble all the carbons required for the basic skeleton in one pot.[4]

The dolabellanes are a widely distributed group of >150 naturally occurring diterpenoids characterised by a *trans*-bicyclo[9.3.0]tetradecane skeleton, many of which exhibit antimicrobial, antitumor and antiviral activities. The family is also important as the likely biogenetic precursors, *via* transannular cyclisations, of several other diterpene classes including the fusicoccanes and dolastanes. The chemistry of the dolabellanes has recently been reviewed.[5] The total synthesis of (±)-δ-araneosene, dolabellatrienone, palominol, claenone, and stolonidiol,[6] and the closely related neodolabellenol and 4,5-deoxyneodolabelline[7] have been reported. Acetoxyodontoschismenol **1** is the major dolabellane of five isolated from the liverwort *Odontoschisma denudatum* and displayed moderate growth-inhibitory activity on a series of plant pathogenic fungi.[3]

Retrosynthetic analysis, based on the transformation shown in Scheme 1, suggested that acetoxyodontoschismenol could be rapidly constructed from the three components shown in Eq 1. Model studies indicated that the ring-junction methyl group in a zirconacycle such as **3** would direct carbenoid insertion to the adjacent C–Zr bond, as required, but also that the ring-junction stereochemistry of **3** was likely to be predominantly *cis*.[8] We thus chose the ketone **2** as an advanced intermediate in our synthesis to allow epimerisation of the adjacent ring junction stereochemistry. Molecular modelling indicated that the desired *trans* fused isomer of **2** was > 12 kJ mol^{-1} more stable than the *cis* and that addition of an isopropyl group should occur from the desired side.[9] The obvious cyclisation precursor to **2** was the alcohol **4** but its zirconocene induced cyclisation failed, presumably due to alkoxide elimination from an intermediate η^2-alkene complex.[10] Allylic silyl groups are compatible with zirconocene induced co-cyclisations and may act as masked hydroxyl groups. We chose the diphenylethoxysilyl substituted diene **6** as our starting material since Tamao oxidation of an alkoxysilane to a hydroxyl occurs under mild conditions.[11] The diene **6** was synthesised from the allylic chloride **5**[12] by S_N2' displacement using the silylcuprate $Ph_2(Et_2N)SiCu(CN)Li$,[11] subsequent ethanolysis furnishing an easily separated 22 : 1 mixture of the desired diene **6** and the regioisomer **7** resulting from S_N2 displacement (Scheme 2). The ratio of regioisomers **6** and **7** was sensitive to the quality and quantity of CuCN used, it being crucial to avoid the presence of any $[Ph_2(Et_2N)Si]_2CuLi$. A suitable equivalent **8** for the aldehyde component required in Eq 1 was synthesised from acetol (Scheme 2).



With all the components now available the key zirconocene induced co-cyclisation, carbenoid insertion and electrophile addition was attempted. Addition of the diene **6** to dibutylzirconocene (generated *in situ* from zirconocene dichloride and 2 equiv. of BuLi) in THF at −78 °C followed by stirring at room temperature for 12 h formed a zirconacyclopentane.[1] After cooling to −78 °C methallyl chloride was added, followed by the dropwise addition of lithium 2,2,6,6-tetramethylpiperidide (LiTMP). The *in situ* generated carbenoid inserted into the zirconacycle to afford an allylzirconium species which was further elaborated by the BCl_3 promoted addition of aldehyde **8**, followed by iodinolytic cleavage of the final carbon–zirconium bond. The resulting unstable iodide **9** was immediately reacted with the sodium salt of benzenesulfinic acid to furnish sulfone **10** as a mixture of 4 diastereoisomers (4 : 4 : 1 : 1) in 51% overall yield based on **6**. The use of BCl_3 rather than the usual $BF_3{\cdot}Et_2O$[2] in the aldehyde addition step avoided by-products probably resulting from cleavage of the C–$SiPh_2$(OEt) bond. As expected, complete relative control was observed between C-11 and C-12, but the remote centre at C-6 was formed as a 1 : 1 mixture (dolabellane numbering).[13] We were surprised and pleased to find that the major isomers of **10** had the desired relative stereochemistry between the carbons C-1 and C-11 implying that the intermediate zirconacycle was formed as a 4 : 1 *trans* : *cis* mixture. Molecular modelling suggests that steric



Scheme 1 Tandem reactions on zirconocene.

† Electronic supplementary information (ESI) available: comparison of reported ^{13}C NMR data of natural **1** and **17** with that observed for synthetic **1** and **17** and their C-6 epimers. See http://www.rsc.org/suppdata/cc/b3/b309848f/

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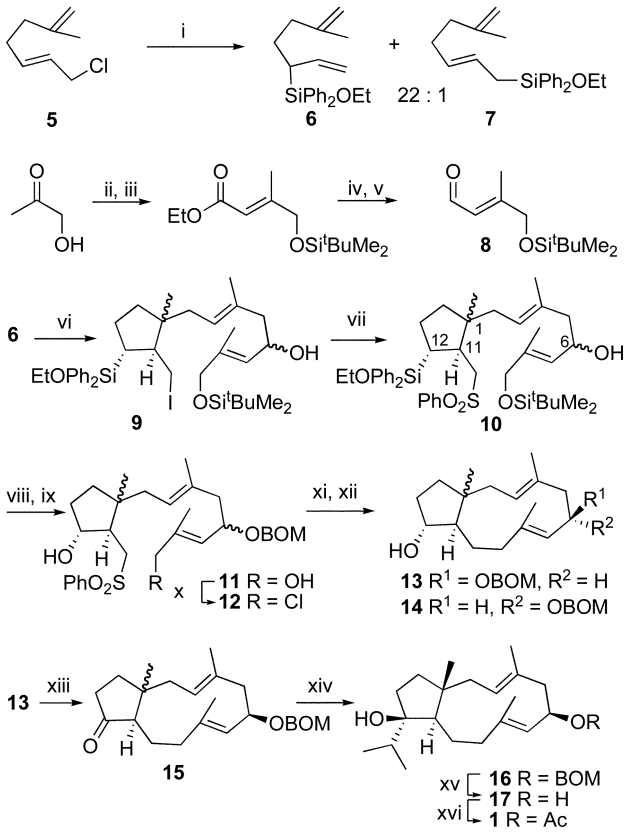

Scheme 2 *Reagents and conditions*: (i) Li dispersion, $Ph_2(Et_2N)SiCl$ (3 equiv.), THF, 0 °C, then CuCN (3 equiv.), then **5** (1 equiv.), −78 °C–rt, 88% of **6**, 4% of **7**; (ii) $Me_2{}^tBuSiCl$, imidazole, DMF, 94%; (iii) NaH, $(EtO)_2P(O)CH_2CO_2C_2H_5$, THF, 0–20 °C, 86% of **9**, 12% of *Z*-isomer; (iv) $^iBu_2AlH$, toluene, 0–20 °C, 80%; (v) $BaMnO_4$, CH_2Cl_2, 20 °C, 81%; (vi) (1) $ZrCp_2Cl_2$, 2 equiv. n-BuLi, THF, −78–20 °C. (2) $CH_2{=}C(CH_3)CH_2Cl$. (3) LiTMP, THF, −78 °C. (4) $Me_2{}^tBuSiOCH_2C(Me){=}CHCHO$, BCl_3, −78–20 °C. (5) I_2, −78–0 °C, 65%; (vii) $C_6H_5SO_2Na$, HMPA/Et_2O, 45 °C, 2 h, 78%; (viii) BOMCl, $^iPrEt_2N$, CH_2Cl_2, 0–20 °C, 83%; (ix) TBAF, THF, 20 °C, 1 h then H_2O_2, $KHCO_3$, MeOH/THF, 12 h, 73%; (x) NCS, Me_2S, CH_2Cl_2, −20–0 °C, 94%; (xi) added to refluxing LiHMDS (0.05 M) in THF over 5 h, 78%; (xii) Mg/MeOH, 50 °C, 3h, 72%; (xiii) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 93%; (xiv) ^iPrMgCl, $CeCl_3$, THF, 0 °C, 0.5h, 76%; (xv) Na, NH_3, THF, EtOH, −70 °C, 86%; (xvi) Ac_2O, pyridine, rt, 81%.

repulsion between the bulky silyl group and the methyl group at C-1 in the intermediate zirconacycle accounts for the reversal in ring junction stereochemistry compared with the model.[8] The secondary allylic alcohol was protected as its benzyloxymethyl ether (BOM) then both cleavage of the *tert*-butyldimethylsilyl ether and Tamao oxidation of the $(EtO)Ph_2Si$–C bond were accomplished with Bu_4NF, KF, H_2O_2, $KHCO_3$ to afford the diol **11** in 71% yield. The macrocyclisation precursor **12** was formed by selective conversion of the primary allylic alcohol to a chloride by reaction with *N*-chlorosuccinimide and Me_2S in CH_2Cl_2.[14] Addition of **12** (0.02 M) to refluxing LiHMDS in THF (0.05 M) over 5 h furnished the desired macrocycle as a mixture of 8 diastereoisomers in an excellent 78% yield. Cyclisation of the analogous allylic iodide occurred in much lower yield. The sulfone moiety was removed with Mg/MeOH[15] to afford the now readily separable epimers at C-6, **13** and **14**, each a 4 : 1 mixture of *trans* : *cis* ring junctions. Dess–Martin oxidation of **13** afforded ketone **15** in good yield. All attempts to alter the ring junction stereochemistry of **15** by epimerisation failed, indeed we could not exchange the C-11 proton with MeOD/MeONa. Fortunately, reaction of ketone **15** with *i*-PrMgCl in the presence of cerium trichloride[16] was selective for the *trans*-isomer giving diastereoisomerically pure **16**. In the *cis*-fused isomer of **15**, both approaches to the ketone are blocked, one by the C-1 methyl group, the other by being on the *endo*-face, so it does not react. Cleavage of the BOM ether in **16** by reaction with Na/NH_3 at −70 °C furnished diol **17**, which is *rac*-(1*R*,6*R*,11*R*,12*R*)-6,12-dihydroxydolabella-3*E*,7*E*-diene, one of the minor dolabellanes isolated from the same source as acetoxyodontoschismenol.[3]

Selective acetylation of the secondary allylic alcohol over the tertiary alcohol in **17** gave (±)-acetoxyodontoschismenol **1**. The NMR data of both **17** and **1** were in good agreement with the literature.[3]† The C-6 epimer **14** was carried through the same sequence as above to afford 6-*epi*-acetoxyodontoschismenol, the NMR data of which was very different to that of the natural product **1**.†

In summary we have accomplished the first total synthesis of the dollabellane diterpene acetoxyodontoschismenol in 12 steps, and 3.5% overall yield from the chloride **5**. The synthesis illustrates the use of tandem reactions on a zirconocene template (cocyclisation, carbenoid insertion, aldehyde addition, iodinolysis) to rapidly assemble complex compounds from simple fragments. Macrocyclisation was achieved in excellent yield *via* an α-lithiosulfone intramolecular displacement of an allylic chloride.

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