Zirconium mediated total synthesis of crinitol, 9-hydroxyfarnesoic acid, 9-hydroxyfarnesol, 9-hydroxysargaquinone and the selectively-protected aglycone of moritoside and euplexide A†

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Tandem formation of an unsaturated zirconacycle, insertion of methallyl carbenoid, and addition of an aldehyde provides a rapid synthetic route to several linear terpenoid and terpene–polyketide natural products.

Organotransition metal chemistry provides many novel ways to rapidly assemble organic molecules. The zirconium mediated intramolecular co-cyclisation of α,ω-dienes or -enynes to form zirconacycles has already found several applications in total synthesis.[1] To make efficient use of the metal, we have developed the insertion of carbenoids (R^1R^2CLiX) into intermediate zirconacycles to afford new organozirconium species, which may then be further elaborated.[2] Particularly successful has been the insertion of allyl carbenoids, since the so-formed intermediates add well to carbonyl compounds, as used in our recent total synthesis of the bicyclo[9.3.0]tetradecane (dolabellane) diterpene, acetoxyo-dontoschismenol.[3] Herein, we present a short synthesis of naturally-occurring linear terpenoids and terpene–polyketides using the tandem formation of a monocyclic zirconacyclopentene, allyl carbenoid insertion, and aldehyde addition.

Our targets (Fig. 1) included the sesquiterpene stress metabolites from the sweet potato, 9-hydroxyfarnesoic acid[4] (**1**) and 9-hydroxyfarnesol[4,5] (**2a**) and the diterpene crinitol (**2b**). Crinitol, isolated from marine brown algae, has insect growth inhibition and antimicrobial activity.[6] We also report the synthesis of the mixed biogenetic terpene–polyketide compounds 9-hydroxysargaquinone (**3**) and the selectively-protected aglycone of moritoside **4**[8] and euplexide A **5**.[9] 9-Hydroxysargaquinone was isolated from marine brown algae and shows significant cytotoxicity against cultured P-388 lymphocytic leukaemia cells (ED_{50} = 0.7 μg ml^{-1}).[7] Moritoside **4**[8] and euplexide A **5**[9] were isolated from the gorgonian *Euplexaura* sp. Moritoside inhibits cell division in the fertilized starfish embryo assay at 1μg ml^{-1},[8] and euplexide A is cytotoxic against human leukaemia cells (IC_{50} = 2.6 μg ml^{-1}), inhibits PLA_2 and has significant antioxidant properties.[9]

Reaction of zirconocene(ethylene) (**6**) generated *in situ* from zirconocene dichloride and 2 equivalents of ethylmagnesium chloride,[10] with tributylstannylpropyne gave the α-tributylstannyl substituted zirconacyclopentene **7** (Scheme 1). The regiochemistry is consistent with that reported for the addition to trimethylsilyl-propyne.[11] The carbenoid 1-lithio-1-chloro-2-methylpropene, generated *in situ* by deprotonation of methallyl chloride with lithium tetramethylpiperidide (LiTMP), selectively inserted into the alkyl–zirconium bond[2] of **7** to afford allylzirconocene **8**. Subsequent addition of 3-methyl-2-butenal or geranial gave the alcohols **9a** and **9b** respectively in modest isolated yield, based on 1-tributyl-stannylpropyne. In previous work, similar aldehyde additions occurred in excellent yield in the presence of boron trifluoride etherate.[2] Unfortunately the alkenyl tin moiety in **8** was not stable to $BF_3{\cdot}Et_2O$ or a range of other strong Lewis acids we tried. Relying on the $MgCl_2$ present in the reaction flask to activate the

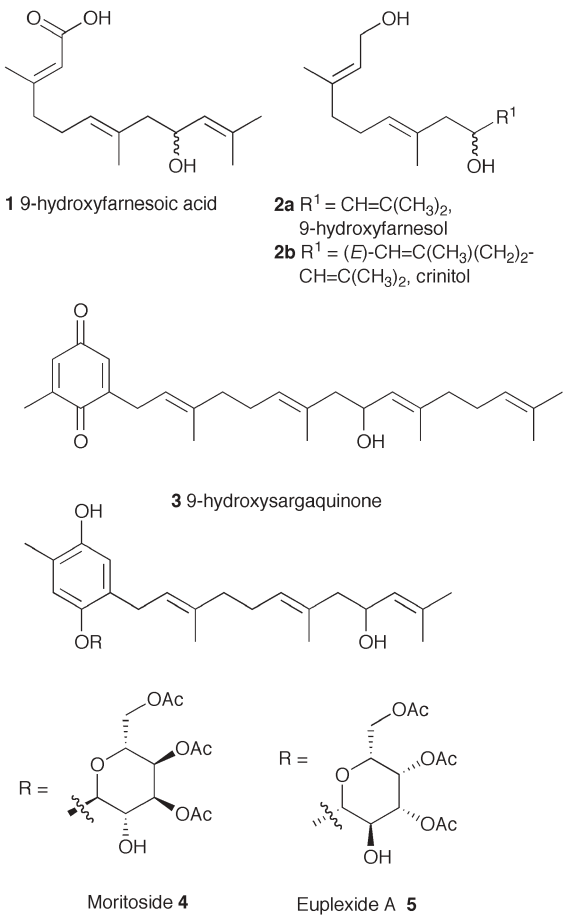

Fig. 1 Natural product targets.

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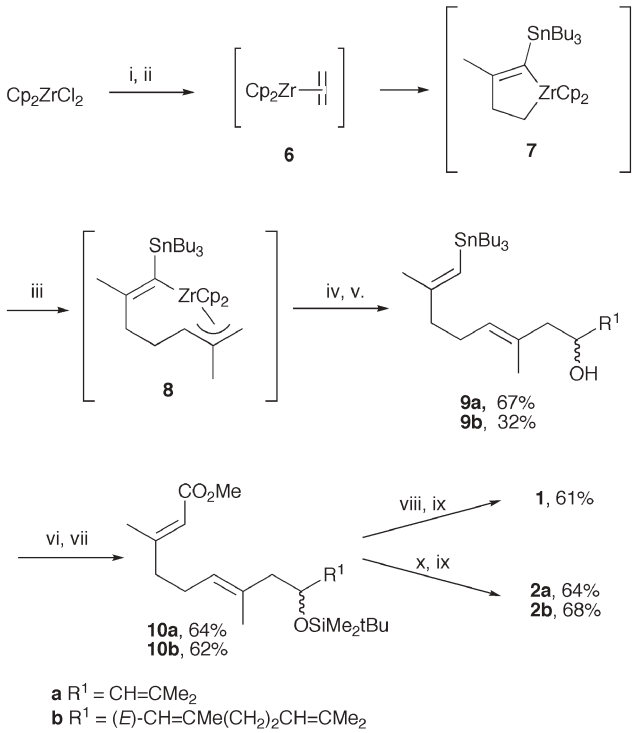
† Electronic Supplementary Information (ESI) available: Tabulation of ^{13}C NMR data for compounds **2a**, **2b**, **3** and **14** against that reported for the natural products. Full data for the synthesis of **1** and its methyl ester. See http://dx.doi.org/10.1039/b508524a

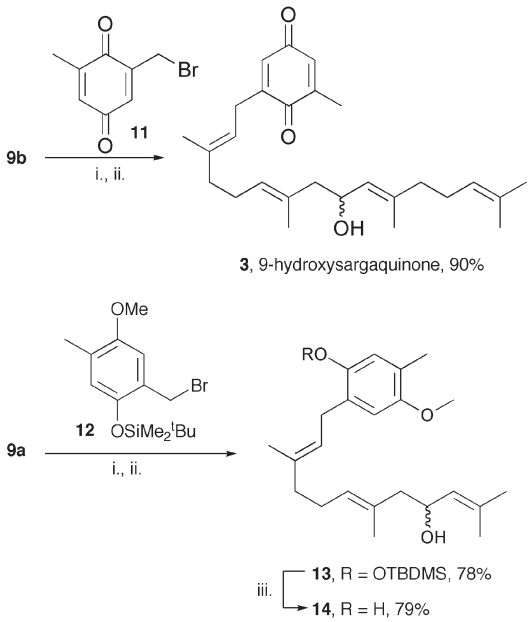


Scheme 1 Reagents and conditions: (i) EtMgCl (2.0 equiv.), −78 °C, 20 min. (ii) 1-tributylstannylpropyne, −78 °C to 0 °C, 1 h, then 0 °C to rt, 2 h. (iii) 3-chloro-2-methylpropene, LiTMP, −78 °C to −70 °C, 40 min. (iv) R^1CHO (2.0 equiv.), −70 °C to rt, 3 h. (v) MeOH, aq. $NaHCO_3$, rt, 12 h. (vi) $^tBuMe_2SiOTf$, DMAP, imidazole, THF, rt, 24 h. (vii) a: Add to $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%) $AsPh_3$ (3.2 mol%) and HMPA (10 mol%) pre-mixed in THF for 15 min at rt, then heat to 65 °C. b: Methyl chloroformate (1.5 equiv.) added over 1 h at 65 °C, then rt, 12 h. c: 10% aq. KF, 2 d. (viii) $^tBuOH/H_2O$ (1 : 1), 1M NaOH, 48 h, rt. (ix) Bu_4NF–THF, rt, 24 h. (x) DIBAL-H, CH_2Cl_2, −78 °C, 2 h.

aldehydes gave the best result. Nevertheless, our key intermediates **9a** and **9b** had been assembled from four components in one reaction sequence with complete control over both double bond geometries.

Alkoxycarbonylation of the alkenylstannanes **9a** and **9b** was accomplished, after *tert*-butyldimethylsilyl protection of the free hydroxyl group, by palladium-catalysed reaction with methyl chloroformate.[12] The use of triphenylarsane as a ligand on palladium to accelerate the rate of transmetallation,[13] and slow addition of the chloroformate to minimise its decomposition, gave good yields of **10a** and **10b**. Cleavage of the silyl ether in **10a** with Bu_4NF gave a product having spectroscopic data consistent with the methyl ester of 9-hydroxyfarnesoic acid, the form in which the natural product was isolated and characterised.[4] 9-Hydroxyfarnesoic acid **1** was obtained *via* saponification of **10a** followed by silyl ether cleavage.

Diisobutylaluminium hydride reduction of the methyl ester **10a** followed by cleavage of the silyl ether gave 9-hydroxyfarnesol **2a**, previously synthesised in 6 steps from geraniol.[5] In the same way, **10b** was converted to the diterpene crinitol **2b**. The only previous synthesis of crinitol took 10 steps from geranyl acetate.[14] Corey synthesised 1-*tert*-butyldimethylsilyl-protected crinitol in 6 steps from geraniol as an intermediate in the synthesis of geranylgeraniol.[15]



Scheme 2 Reagents and conditions: (i) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%), $AsPh_3$ (3.2 mol%), THF, 15 min, rt, then **9** (1.0 equiv.), **11** or **12** (1.0 equiv.), 65 °C, 1.5 h. (ii) 10%, aq. KF, rt, 4 d. (iii) Bu_4NF–THF, rt, 12 h.

We then targeted the mixed terpenoid–polyketide compounds **3–5**. We were delighted to find that Stille coupling of **9b** with quinone **11** gave directly and in excellent yield 9-hydroxysargaquinone (**3**) which has not previously been synthesised (Scheme 2). Compound **11** was made by the oxidation of 1-(bromomethyl)-2,5-dimethoxy-3-methylbenzene[16] with ceric ammonium nitrate (65% yield). To access the desired selectively-protected aglycone **14** of moritoside (**4**) and euplexide A (**5**) the differentially-protected bis-phenol derivative **12** was prepared from 3-methyl-4-methoxyphenol[17] by *ortho*-selective monohydroxymethylation,[18] exhaustive *tert*-butyldimethylsilyl ether formation followed by selective deprotection of the primary alcohol (pyridinium tosylate), and bromination (CBr_4, PPh_3). Palladium catalysed coupling of **12** with the alkenyltin **9a** gave **13** in good yield; removal of the silyl protecting group affording the desired selectively-protected aglycone **14**. The NMR properties of **14**† were consistent with those reported for the aglycone portions of **4** and **5**.[8,9]

Overall, we used tandem reactions on a zirconium template to provide very short synthetic routes to a variety of natural products, several with interesting biological properties.

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