Synthesis of manoalide using a 1,2-metallate rearrangement

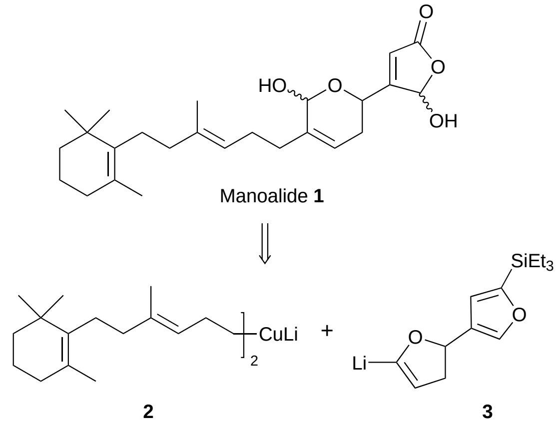
Agnès Pommier and Philip J. Kocieński*

Department of Chemistry, University of Glasgow, Glasgow, UK G12 8QQ

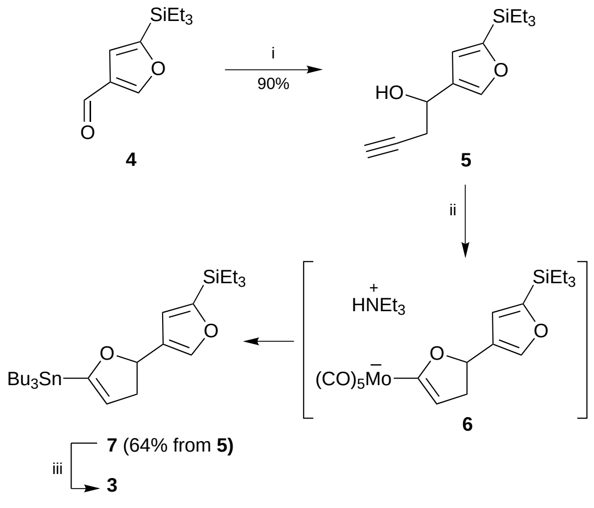
Manoalide, a marine antiinflammatory sesterterpenoid, has been synthesised using a 1,2-metallate rearrangement of a higher order cuprate and a Pd^0-catalysed carbonylation of an iodo alkene to generate the central dihydropyranone ring.

Manoalide **1** is a sesterterpenoid metabolite isolated from the Pacific sponge *Luffariella variablis*.[1] As a potent inhibitor of phospholipase A_2, it has been evaluated in phase II clinical trials for the treatment of psoriasis.[2] We now report a short synthesis of racemic manoalide from the homocuprate **2** and lithiated dihydrofuran **3** (Scheme 1) which features the use of a 1,2-metallate rearrangement of a higher order cuprate and a Pd^0-catalysed carbonylation of an iodo alkene to generate the central dihydropyranone ring.

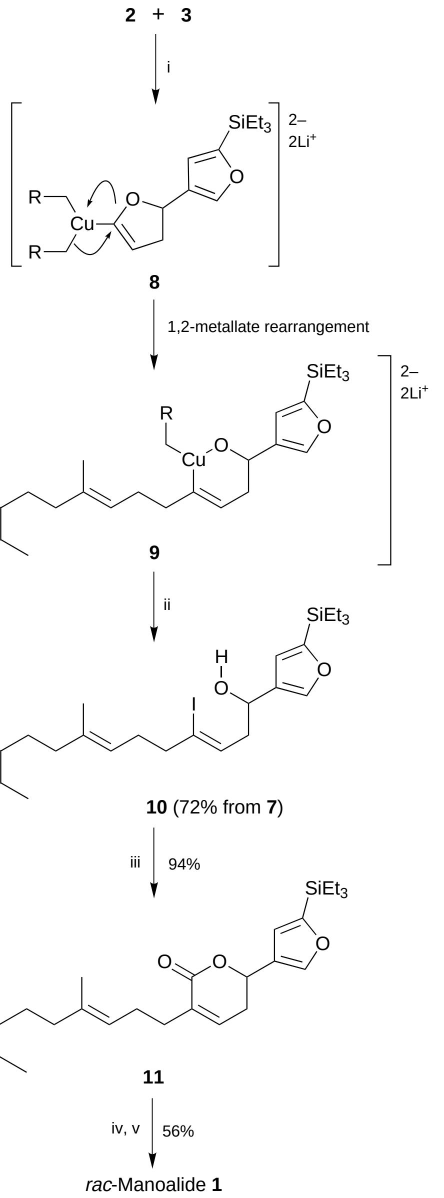
The lithiated dihydrofuran **3** was prepared as shown in Scheme 2. Addition of prop-2-ynylmagnesium bromide to 5-triethylsilyl-3-furaldehyde **4**† gave the homoprop-2-ynylic alcohol **5** in 90% yield. The Fischer carbene complex generated by electrophilic cyclisation of **5** with $(CO)_5Mo{\cdot}NEt_3$‡ was converted *in situ* to the alkenylstannane **7** in the presence of Bu_3SnOTf according to the procedure of McDonald *et al.*[3] (64% overall from **5**). Transmetallation of the alkenylstannane to the desired alkenyllithium **3** was plagued by competing metallation at the 2-position of the furan ring and success was only achieved after a protracted study of the reaction conditions. Clean transmetallation was eventually accomplished with Bu^{s}Li



Scheme 1



Scheme 2 *Reagents and conditions*: i, prop-2-ynylmagnesium bromide, Et_2O, −40 °C → room temp.; ii, $(CO)_5Mo{\cdot}NEt_3$, Bu_3SnOTf, Et_2O–Et_3N, room temp., 48 h; iii, Bu^{s}Li, Et_2O–pentane, −60 °C, 20 min



Scheme 3 *Reagents and conditions*: i, add a solution of **3** in Et_2O–pentane to a solution of **2** in Et_2O–Me_2S (1 : 1) at −40 °C; ii, I_2 (4 equiv.), −30 °C; iii, $Pd(PPh_3)_4$, Pr^i_2NEt, THF–MeOH, CO (2 atm), 60 °C, 24 h; iv, DIBAL-H, CH_2Cl_2, −80 °C; v, O_2, h*ν*, rose bengal, MeOH, −80 °C

in a diethyl ether–pentane mixture at ② 60 °C for 20 min and the lithium reagent **3** used immediately in the next step.

The key step in our synthesis involved a 1,2-metallate rearrangement[4] of the higher order cuprate **8** derived from addition of alkenyllithium **3** to the lower order homocuprate **2**§ which occurred with clean inversion of configuration to give the alkenylcuprate **9** (Scheme 3). Attempts to carboxylate **9** with CO_2 in the presence of triethyl phosphite[5]—a ploy which had been successful in our synthesis of the related terpenoid luffariolide E[6,7]—failed to give any of the desired lactone **11**. We therefore quenched the alkenylcuprate **9** with iodine at ② 30 °C to give iodo alkene **10** in 72% overall yield from **7**, and then introduced the remaining carbon (94% yield) by Pd^0-catalysed carbonylation using a modification of conditions previously described by Heck.[8] Finally, reduction of the lactone to the lactol with DIBAL-H (94%) and photooxidation of the silylfuran (60%)[9] gave manoalide, identical by high field NMR spectroscopy (^1H and ^{13}C) and mass spectrometry with a sample prepared previously and correlated with the natural product.[10]

The synthesis of racemic manoalide reported herein was accomplished in a total of 12 steps (4% overall) from commercially available β-ionone and 3-furaldehyde. The discovery of conditions for transmetallating stannyldihydrofuran **6** without competing metallation of the furan was a crucial advance. Another tactical advance was the iodination of the metallate rearrangement product **10** which provided a clean, efficient and highly stereoselective route to the (*Z*)-iodo alkene **11**, itself a useful precursor to a wide range of trisubstitued alkenes. The overall yield of our synthesis compares favourably with previous syntheses.[10–14]

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Footnotes

* E-mail: p.kocienski@chem.gla.ac.uk

† 5-Triethylsilyl-3-furaldehyde was prepared in one pot from commercial 3-furaldehyde in 73% yield by (i) addition of lithium morpholide to the aldehyde; (ii) metallation of the resultant adduct with Bu^sLi, and (iii) addition of chlorotriethylsilane (ref. 15).

‡ The yellow complex $(CO)_5Mo\cdot NEt_3$ is formed by irradiation of hexacarbonylmolybdenum with intense visible light (Hg lamp) in diethyl ether containing triethylamine at 0 °C.

§ For details of the preparation of cuprate **2** see ref. 6. The homoallylic iodo alkane precursor to cuprate **2** was prepared in four steps (25% overall) from β-ionone by analogy to the procedure described for the corresponding homoallylic bromo alkane (ref. 10).

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