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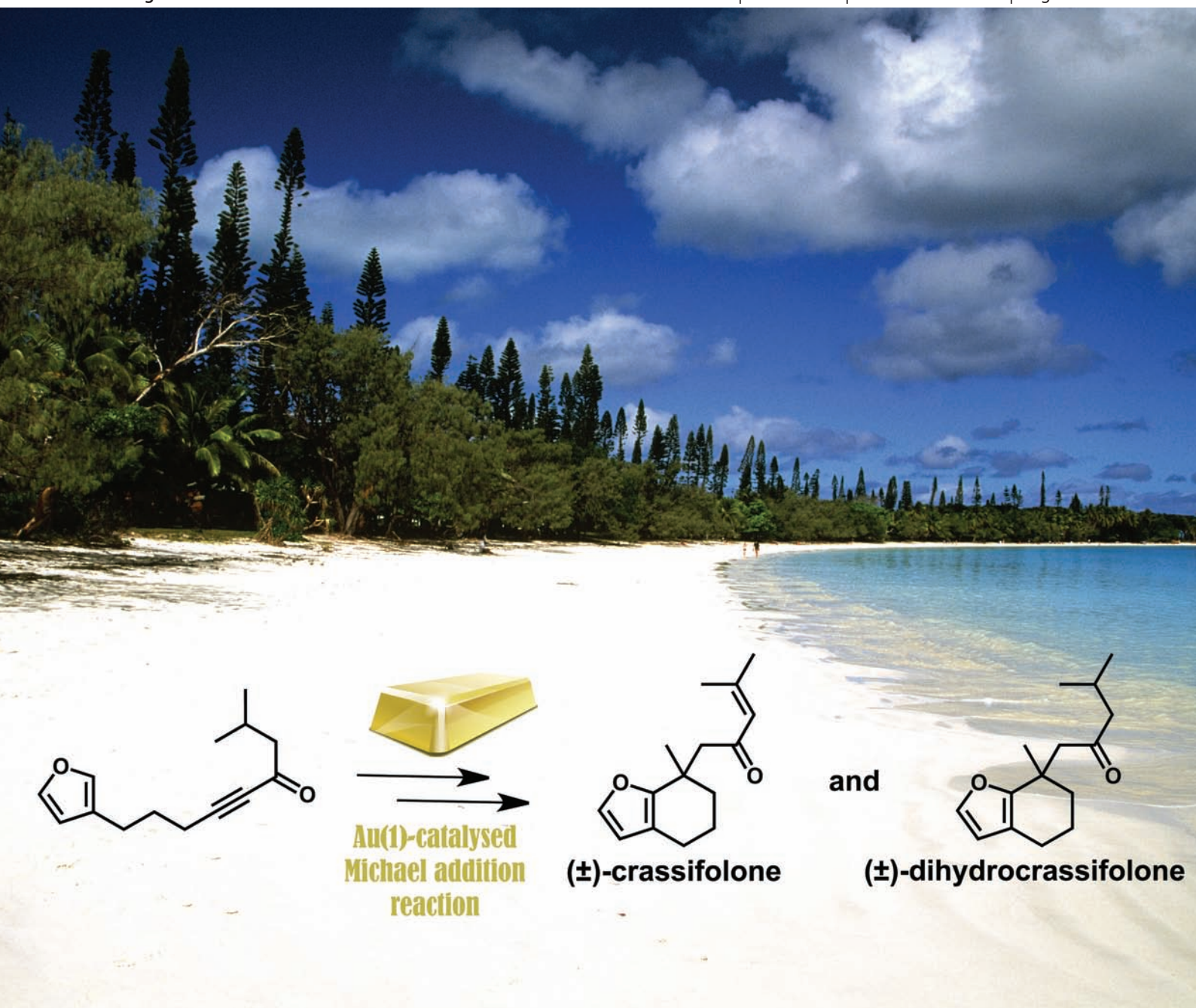

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COMMUNICATION

Rajeev S. Menon and Martin G. Banwell

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Total syntheses of the furanosesquiterpenes crassifolone and dihydrocrassifolone *via* an Au(I)-catalysed intramolecular Michael addition reaction†

Rajeev S. Menon and Martin G. Banwell*

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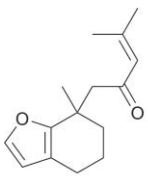
The racemic modifications of title natural products 1 and 2 have been synthesised for the first time. The key step was the Au(I)-catalysed conversion of the furanyl-substituted ynone 13 into the annulated furan 14.

A recent examination of the essential oils derived from the wood of the tree *Myoporum crassifolium* found growing in Noumea, New Caledonia has resulted in the identification of the furanosesquiterpenes crassifolone (**1**) and dihydrocrassifolone (**2**).[1] The basic structures of these optically active natural products were established through detailed ^{1}H and ^{13}C NMR studies but their absolute configurations remain undefined. They bear a strong resemblance to a key part of cyclofurospongin-2, a C_{21}-furanoterpenoid isolated from the sponge *Spongia officinalis* (Spongiidae) collected in the infralitoral zone of La Caleta, Cádiz, Spain.[2] Furthermore, three structurally related C_{15}-hydrocarbons have been found in the leaf and twig extracts of the flowering plant *Eremophila rotundifolia* collected in Kingoonya, South Australia.[3] No significant biological properties have been ascribed to compounds **1** and **2** although they may have some utility as fragrances.[1]



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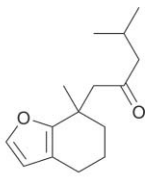


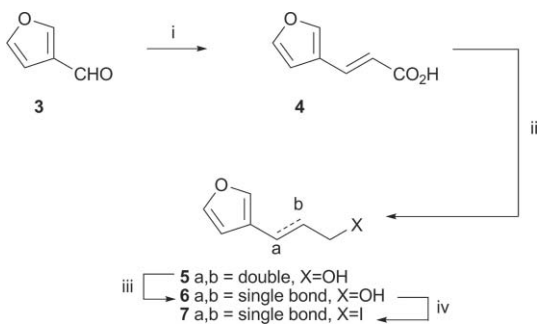
2

Our interest in the synthesis of annulated furan-containing natural products[4] and the possibility of establishing the 4,5,6,7-tetrahydrobenzofuran core of compounds **1** and **2** *via* addition of the nucleophilic furan moiety to a tethered Michael acceptor[5] prompted the studies reported herein. A key feature of these studies, which have resulted in the first total syntheses of the title natural products, is the identification of a novel and highly efficient Au(I)-catalysed intramolecular Michael addition reaction that proceeds rapidly under exceptionally mild conditions. As such, this unprecedented reaction may represent a useful new protocol for the construction of other terpenoids incorporating an annulated furan core.[6]

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia. E-mail: mgb@rsc.anu.edu.au

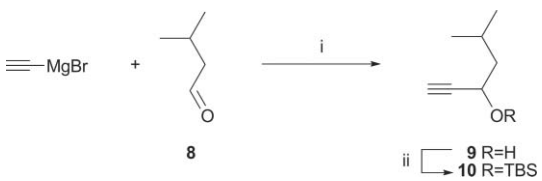
† Electronic supplementary information (ESI) available: Experimental procedures, product characterisation, and ^{1}H or ^{13}C NMR spectra for compounds **4–7**, **9**, **10**, **11–14**, (±)-**2** and (±)-**1** are provided. See DOI: 10.1039/c0ob00487a

The assembly of the substrate required for the pivotal intramolecular Michael addition reaction involved the preparation of two key building blocks, a furanyl-substituted 1-iodopropane and a protected form of an isobutyl-substituted propargyl alcohol. The synthesis of the first of these is shown in Scheme 1 and employed the Doebner modification of the Knoevenagel condensation in which malonic acid was treated with commercially available furan-3-carboxaldehyde (**3**) in the presence of pyridine. The 3-furanacrylic acid **4**[7] (96%) so formed was reduced to the corresponding allylic alcohol **5**[8] (76%) with $LiAlH_4$ and the latter compound then subjected to hydrogenation using Pd on C as catalyst and methanol as solvent. The resulting saturated alcohol **6**[9] (82%) was treated with molecular iodine in the presence of triethylamine and imidazole and thereby affording the required and previously reported primary iodide **7**[10] (75%).



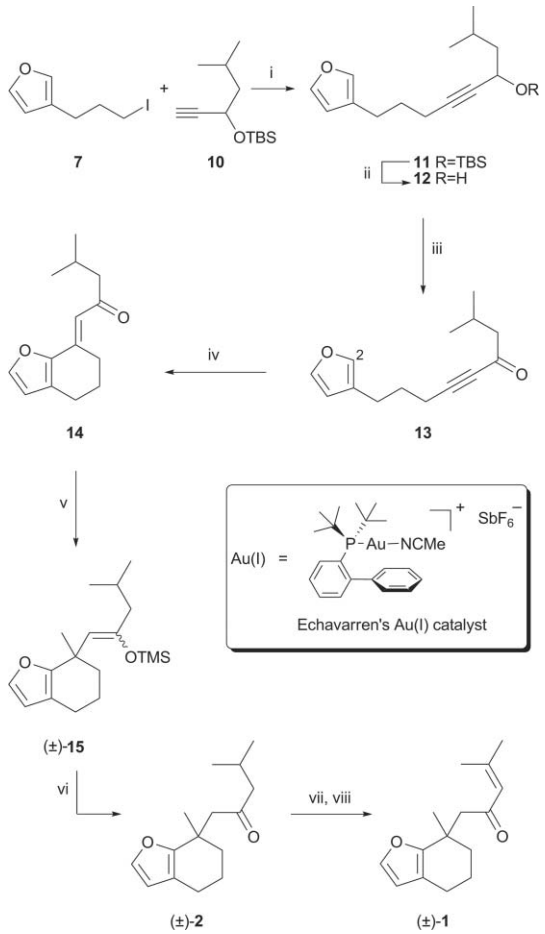
Scheme 1 *Reagents and conditions*: (i) malonic acid, pyridine, 90 °C, 2 h; (ii) $LiAlH_4$, THF, 18 °C, 1 h; (iii) H_2, Pd on C, MeOH, 18 °C, 3 h; (iv) I_2, Ph_3P, imidazole, DCM, 0 → 18 °C, 2 h.

The simple, two-step sequence used to obtain the second building block is shown in Scheme 2 and starts with the addition of ethynyl magnesium bromide to 3-methylbutanal (**8**). The resulting propargyl alcohol **9**[11] (63%) was treated with *t*-butyldimethylsilyl chloride (TBS-Cl) in the presence of imidazole and thus producing the required silyl ether **10** in 67% yield.



Scheme 2 *Reagents and conditions*: (i) Et_2O, 0 → 18 °C, 1 h; (ii) TBS-Cl, imidazole, THF, 0 → 18 °C, 6 h.

The coupling of building blocks **7** and **10** in the appropriate fashion was readily achieved (Scheme 3) by deprotonating the



Scheme 3 *Reagents and conditions*: (i) *n*-BuLi, THF/DMPU, −78 → 18 °C, 3 h; (ii) TBAF, THF, 18 °C, 1 h; (iii) PCC, DCM, 18 °C, 2.5 h; (iv) Au(I), DCM, 18 °C, 5 min; (v) MeMgBr, cat. CuBr·Me_2S, TMS-Cl, HMPA, THF, −78 → 18 °C, 3 h; (vi) TBAF, THF, 18 °C, 0.5 h; (vii) TMSOTf, Et_3N, DCM, 0 → 18 °C, 3 h; (viii) IBX, MPO, DMSO, 18 °C, 24 h.

latter with *n*-BuLi in THF/DMPU then alkylating the resulting acetylide anion with iodide **7**. Product **11** (77%) thus obtained was treated with tetra-*n*-butylammonium fluoride (TBAF) in THF at 18 °C for 1 h and the resulting alcohol **12** (97%) oxidised to the corresponding ketone **13** (90%) using pyridinium chlorochromate (PCC) in dichloromethane at 18 °C.

Compound **13** represents the substrate required for the pivotal intramolecular Michael addition reaction which it was anticipated would proceed *via* attack of C2[12] of the pendant furan ring to the proximate sp-hybridised carbon of the ynone and thereby resulting in the formation of the isomeric tetrahydrobenzofuran **14**. Various Au(III) and Au(I) species have been used to effect the intermolecular Michael addition of furan (*via* C2) to electron-deficient alkenes, most notably, methyl vinyl ketone.[13] However, the reactions normally require high temperatures and/or co-catalysts. Furthermore, no examples of intramolecular variants of such processes appear to have been reported. Our recent observations[14] that Echavarren's Au(I) catalyst[15] (see Scheme 3) can effect the intramolecular hydroarylation of terminal alkynes under exceptionally mild conditions prompted us to examine the capacity of this species to bring about the desired conversion **13** → **14**. In the event, treatment of compound **13** with 1 mole % of the Echavarren's catalyst in DCM at 18 °C for 5 min resulted in the formation of isomer **14** in quantitative yield. We speculate that this remarkable transformation involves initial auration at C2 of the substrate.[16] This is followed by intramolecular Michael addition of the now highly nucleophilic C2 to the sterically uncongested β-terminus of the tethered ynone.[17] Protio-deauration would then give compound **14** that is obtained as a single geometric isomer (and tentatively assigned as possessing the illustrated *E*-configuration).

The completion of the synthesis of the target natural products **1** and **2** required the construction of the associated quaternary carbon centre and, in the former case, introduction of the ketone-conjugated carbon–carbon double bond. Various methods were investigated in an effort to engage compound **14** in a conjugate addition reaction with a methyl-based nucleophile. Treatment of this substrate with the Gilman reagent (Me_2CuLi)[18,19] resulted in a 1 : 3 mixture (80% combined yield) of dihydrocrassifolone (**2**) and the corresponding 1,2-addition product. Reaction of compound **14** with trimethylaluminium in the presence of $Ni(acac)_2$[20] gave, as the only characterisable component of a complex reaction mixture, the undesired 1,2-addition product. A much more satisfactory outcome was observed when enone **14** was treated with excess methylmagnesium bromide in the presence of catalytic quantities of copper(I) bromide dimethyl sulfide complex and stoichiometric quantities of trimethylsilyl chloride (TMS-Cl).[21] Under such conditions the silyl enol ether **15** (61%) was obtained as the exclusive product of reaction and when this was treated with TBAF in THF at 18 °C then dihydrocrassifolone (**2**) was obtained in 66% yield. Effecting the conversion **2** → **1** proved rather problematic. After considerable experimentation, and following a protocol defined by Lalic and Corey,[22] we found that treatment of compound **2** with TMSOTf and Et_3N then IBX in presence of 4-methoxypyridine *N*-oxide (MPO)[23] afforded a chromatographically separable mixture of crassifolone (**1**) (83% at 73% conversion) and dihydrocrassifolone (**2**) (27% recovery).

The ^1H and ^{13}C NMR spectroscopic as well as the mass spectrometric data derived from the synthetic samples of compounds **1** and **2** matched those reported for the corresponding natural products.[1] A detailed comparison of the relevant data sets is presented in the Electronic Supplementary Information associated with this paper.

Efforts to apply the novel Michael addition process disclosed above to the synthesis of other natural products will be reported in due course.

Acknowledgements

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