Total Synthesis of (±)-Leonuketal

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ABSTRACT: Cleavage of a C–C bond is a diversifying process in the biogenesis of *seco*-terpenoids that has produced fascinating molecular structures. Leonuketal is an 8,9-*seco*-labdane terpenoid with a unique tetracyclic structure, owing to a C–C bond cleavage event in its biosynthesis. We report the first total synthesis of leonuketal, featuring an unusual Shapiro-type reaction as part of an enabling auxiliary ring strategy, and a novel Au-catalysed spirocyclisation of a β-keto(enol)lactone.

Cyclization and oxidation processes are recognized as the principal drivers of complexity generation in the biosynthesis of terpenoid natural products.[1–9] However, a third mode of complexity generation involving the *cleavage* of a C–C bond is operative in the biogenesis of *seco*-terpenoids (Figure 1A). Such processes lead to increased chemical diversity in a cluster of related secondary metabolites by alteration of the parent carbon skeleton. Moreover, C–C bond cleavage is typically oxidative, and reactions facilitated by the increase in oxidation state—such as ketalisation or aldol processes—lead to further skeletal rearrangement.

Leonuketal (**1**) is a tetracyclic 8,9-*seco*-labdane terpenoid marked by high stereochemical and architectural complexity—chiefly owing to a C–C bond cleavage event in its biosynthesis (Figure 1B).[10] Peng and co-workers isolated **1** from Chinese liverwort (*Leonurus japonicus*) in 2015 and reported significant vasorelaxant activity (EC_{50} = 2.32 mM) against KCl-induced contraction of rat aorta.[10] Leonuketal (**1**), and other *seco*-labdanes such as saudin (**2**), pallambin A (**3**), and pallamolide B (**4**), exemplify the structural complexity enabled by biosynthetic C–C bond cleavage (Figure 1B).[11,12] This characteristic—alongside important bioactivities—has rendered *seco*-labdanes attractive synthetic targets and formidable testing grounds for new methodology.[13–21] We were prompted to investigate the total synthesis of leonuketal (**1**), a previously unmet goal, because of the challenge presented by its daunting molecular structure.

Previously, we reported the synthesis of the bridged oxabicyclic core of leonuketal (**1**), as lactone **5**, by an efficient Diels-Alder reductive-cyclisation sequence (Figure 1C).[22] This strategy relied on a proposed epimerization of the C3 carbon for advancement of **5** to **1**, however, a comprehensive screen of bases failed to identify conditions for the planned transformation.

Our revised retrosynthetic strategy was targeted towards late stage spiroketal **7**, which we recognized would provide access to **1** by incorporation of the C3 hydroxybutanone chain and elaboration of the lactone moiety (Figure 1D). We planned to assemble the spirocyclic core of **7** by Au-mediated cyclisation of alkyne **8**, which could be accessed from halide **9** through appendage of the lactone moiety by alkylation.[23]

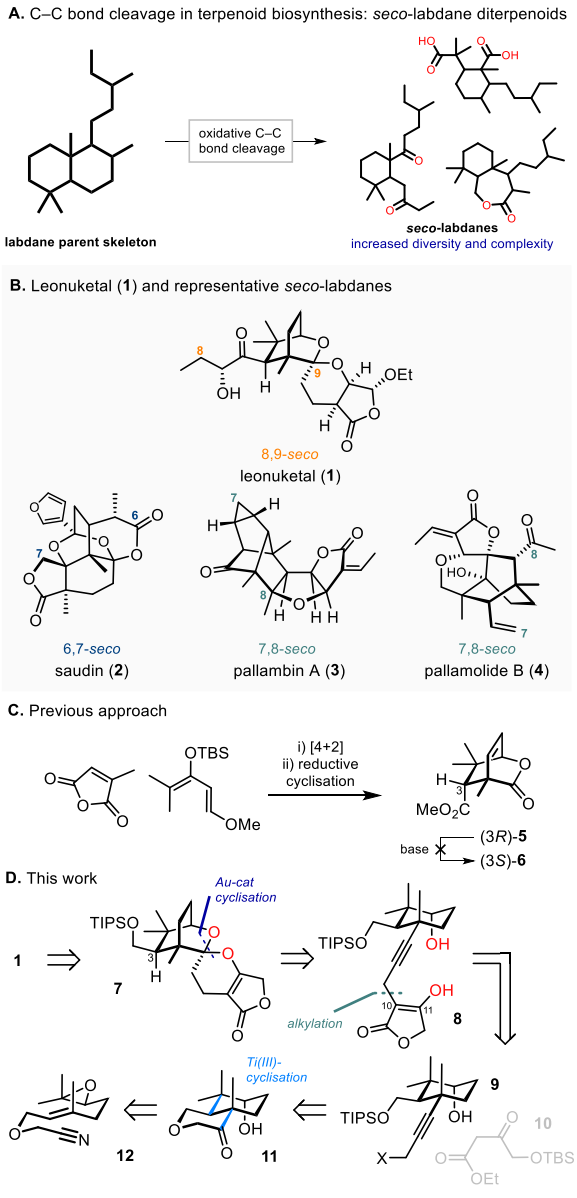
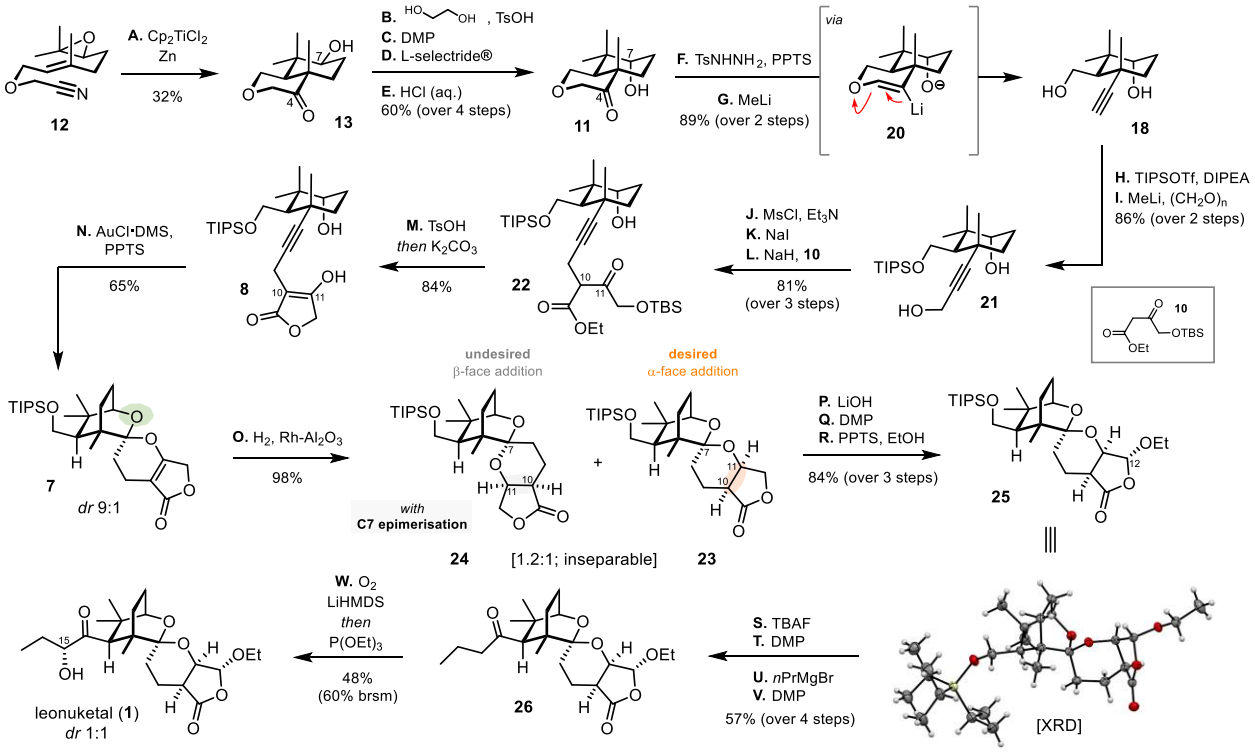


Figure 1. Background and retrosynthetic analysis; NB: numbering in 1B based on parent labdane skeleton.

Scheme 1. Total synthesis of (±)-leonuketal



Reagents and conditions: a) Cp_2TiCl_2 (2.2 eq), Zn (4.6 eq), THF, 60 °C, 1 h *then* aq. KH_2PO_4, rt, 30 min, 32%; b) ethylene glycol (15 eq), TsOH (5 mol %), benzene, reflux, 4 h; c) DMP (1.2 eq), pyridine (2.5 eq), CH_2Cl_2, rt, 1 h, 77% over 2 steps; d) L-Selectride® (2.2 eq), THF, –78 °C to rt, 1.75 h; e) 3 M HCl-THF (1:3, *v/v*), 40 °C, 16 h, 78% over 2 steps; f) NH_2NHTs (1 eq), PPTS (5 mol%), THF, rt, 16 h; g) MeLi (9 eq), THF-Et_2O (1:1, *v/v*), 0 °C, 3 h, 89% over 2 steps; h) TIPSOTf (1.2 eq), DIPEA (3 eq), 50 min, 91%; i) paraformaldehyde (12 eq), MeLi (9 eq), Et_2O, –78 °C to 0 °C, 1.5 h, 94%; j) MsCl (1.1 eq), Et_3N (1.5 eq), CH_2Cl_2, 0 °C, 40 min; k) NaI (2.2 eq), acetone, rt, 16 h; l) **10** (3 eq), NaH (2.9 eq), THF, 0 °C to rt, 16 h, 81% (over 3 steps); m) TsOH (10 mol %), MeOH, rt, 16 h *then* K_2CO_3, rt, 4 h, 84%; n) AuCl·DMS (10 mol %), PPTS (1 mol %), rt, 60 h, 65% combined, *dr* 9:1; o) H_2 (65 psi), Rh-Al_2O_3, MeOH, rt, 60 h, 98%. 1:1.2 **23-24**; p) 1 N LiOH-THF (1:3, *v/v*), rt, 16 h; i) DMP (4 eq), CH_2Cl_2, rt, 30 min; r) PPTS (10 mol %), EtOH, 45 °C, 24 h, 84% over 3 steps; s) TBAF (5 eq), THF, 40 °C, 2 h; t) DMP (4 eq), K_2CO_3 (7 eq), CH_2Cl_2, rt, 30 min; u) *n*PrMgBr (1.85 eq), Et_2O, 0 °C, 1 h, v) DMP (4 eq), K_2CO_3 (7 eq), CH_2Cl_2, rt, 30 min, 57% over 4 steps; w) O_2, LiHMDS (34 eq), THF, –78 °C, 3.3 h *then* $P(OEt)_3$ 0.5 h, 48% combined (60% brsm), *dr* 1:1.

Efficient synthesis of the alkyne-substituted cyclohexanol ring of **9** posed a challenge. While related cyclohexanols have been assembled from geraniol derivatives, we sought an efficient method to incorporate the requisite alkynyl moiety.[24–32] To this end, we developed an auxiliary ring strategy wherein *bicyclic* ketone **11** was used as a synthetic linchpin for the construction of *monocyclic* alkyne **9** (Figure 1D and Figure 2A). Bicyclic ketone **11** could, in turn, be disconnected to epoxide **12**, a derivative of geraniol, by a Ti(III)-mediated radical cyclisation.

Our synthesis thus began with treatment of epoxide **12** with *in situ* generated Cp_2TiCl, efficiently affording bicyclic ketone **13** after acidic hydrolysis (Scheme 1).[33–37] This transformation, while proceeding in modest yield (32%), was found to scale up easily (6.5 g), and afforded reliable access to diastereomerically-pure ketone **13**.[38] Preliminary investigations revealed that the complementary cyclization employing epoxide **14**—terminating with *intermolecular* addition to acetonitrile—was found to be capricious and low yielding (Figure 2B).[39]

Next, epimerization of the C7 alcohol of **13** was achieved by an oxidation-reduction sequence, first requiring protection of the C4 ketone. Following ketal protection, the C7 alcohol was oxidized with DMP, then reduced with L-selectride®—affording desired epimer **11** after ketal deprotection. Attempts to effect alcohol epimerization on more advanced intermediates **16** and **17** in exploratory studies, which would have circumvented the necessary ketone protection-deprotection steps, returned either unreacted starting material or the undesired epimer (Figure 2; see SI for detail).

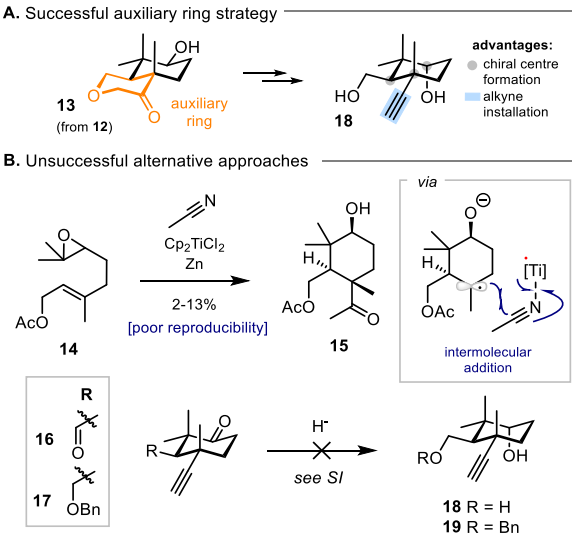


Figure 2. Discussion of the auxiliary ring strategy for synthesis of **20**

Such substrates lacked the rigidifying auxiliary pyran ring of **13**, and as a result, exhibited more conformational freedom. Indeed, the diastereoselectivity observed for formation of **11** may have been enhanced by the rigidity imposed by the auxiliary ring, encouraging equatorial approach of L-selectride® and preventing ring-flipping of the ketone.

With alcohol **11** in hand, attention was turned to cleavage of the auxiliary pyran ring and formation of the requisite alkyne motif. Both transformations were simultaneously achieved by exploitation of an unusual Shapiro-type fragmentation reaction.[40] To this end, **11** was converted to an intermediate tosyl hydrazone, which was subsequently treated with methyl lithium, resulting in formation of alkyne **18** in 89% yield over two steps.[41] This process likely proceeded *via* generation of vinyl lithium **20**, which subsequently underwent β-elimination. This sequence enabled the synthesis of **18** in 7 steps on gram-scale. Our auxiliary ring strategy parallels the synthesis of *seco*-terpenoids in general, wherein ring-deconstruction is leveraged as an enabling (bio)synthetic tool.

With scalable access to alkyne **18** secured, focus was placed on construction of the caged spiroketal core of leonuketal (**1**). To this end, the iodide derived from **21** was synthesized over 3 steps by hydroxymethylation of **18**, followed by mesylation and iodination. The subsequent alkylation of the iodide required some investigation. Initially, we examined the Frater-Seebach alkylation with β-hydroxyesters, which generally resulted in decomposition of the nucleophile, returning starting material.[42,43] Next, we examined β-ketoester nucleophiles. Interestingly, cyclic β-ketoesters afforded exclusively *O*-alkylation products, however, acyclic β-ketoesters, such as **10**, proved to be competent *C*-nucleophiles. Accordingly, known β-ketoester **10** was treated with sodium hydride and the iodide derived from **21**, smoothly affording alkyne **22** in 85% yield.

At this juncture, we identified two possible avenues for construction of the spiroketal and the C7, C10, and C11 stereocentres of leonuketal (**1**). Typically, dihydroxy alkynes are employed in Au-catalysed spiroketalizations. However, **22** was a mixture of C10 epimers and reduction of the C11 ketone would likely have afforded four diastereomers. Instead, we elected to explore the Au-catalysed spiroketalization of β-ketoester **22** *without* first reducing the C11 ketone. This transformation of β-ketoesters had not, to the best of our knowledge, been reported previously.

Initial investigations yielded the desired spiroketal product upon treatment of **22** with Au(I)-complexes, however, these results had poor reproducibility and often resulted in decomposition of the substrate. We therefore sought an alternative spiroketal precursor.

TBS deprotection and lactonisation of **22** afforded cyclic β-keto(enol)lactone **8**, as an alternative spiroketalization substrate. To our delight, treatment of **8** with AuCl·DMS and PPTS reliably delivered spiroketal **7** in 65% yield and 9:1 *dr*, thereby demonstrating this previously unexplored class of substrates to be viable Au-catalyzed spiroketalization precursors.

Investigation of **8** as a spiroketalization substrate was prompted by considering the loss of entropy incurred by formation of the rigid caged spirocycle. Straight-chain β-ketoester **22** had greater conformational freedom than the cyclic congener **8**. Hence, the loss of entropy upon forming **7** from **8**, particularly in preventing rotation of the C10-11 bond, would have been less than for the spiroketalization of straight-chain substrate **22**. This substrate modification proved instrumental to the reliable formation of the caged spiroketal of **1**.

The next challenge in our total synthesis was the diastereoselective reduction of the enol ether of **7**. We posited that hydrogenation at the α-face could be achieved if a haptophilic effect of the posterior spiroketal oxygen (Scheme 1, *green*) directed adsorption of **7** at this face of the molecule.[44] Rhodium on alumina proved to be a competent catalyst for hydrogenation of **7** at elevated pressure (65 psi), however, no diastereoselectivity was observed regardless of solvent choice.[45,46] Hence, the desired α-face addition product **23** and diastereomer **24** were obtained as a 1:1.2 mixture, which unfortunately could not be separated. Interestingly, undesired diastereomer **24** corresponds to β-face hydrogenation followed by epimerization of the spiroketal (C7). This result indicated an interplay between the C7, C10, and C11 stereocentres in which the more stable spiroketal epimer was influenced by the C10-11 configuration.

The diastereomeric mixture **23**-**24** was then advanced to the fully elaborated ketal-γ-lactone portion of leonuketal (**1**). This was achieved by lactone hydrolysis, oxidation of the liberated alcohol, and acid-mediated acetalization to afford **25** as a single C12 epimer in 84% yield over three steps. At this point, the desired diastereomer **25** could be separated from the product derived from **24** (not shown). The securing of **25** completed the unique tetracyclic core of leonuketal (**1**) and all but one chiral centre for the total synthesis. An *X*-ray structure of **25** allowed us to confirm the stereochemical configuration matched that of leonuketal (**1**).

With **25** in hand, the endgame of our total synthesis could be investigated. Deprotection of **25** proceeded smoothly at slightly elevated temperature, and the free alcohol was oxidized with DMP immediately to prevent possible transketalization. The aldehyde was treated with propylmagnesium bromide, then oxidized directly to afford deoxyleonuketal (**26**) in 57% yield over 4 steps. α-Hydroxylation of the newly formed ketone **26** was the final step in completion of the total synthesis and required some investigation (see Table S4 and S5, SI). Deprotonation of **26** with LiHMDS followed by treatment with (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine effected the desired oxidation, but favoured the formation of 15-*epi*-leonuketal (*epi*-**1**) with a 9:1 *dr*. Surprisingly, the use of Davis' oxaziridine under analogous conditions delivered no detectable amount of **1** or *epi*-**1** at either full or partial completion of the reaction. Fortunately, bubbling molecular oxygen through a solution of deprotonated **26** delivered leonuketal (**1**), alongside 15-*epi*-leonuketal (*epi*-**1**), in 48% yield (60% brsm) and 1:1 *dr* after reductive workup. Leonuketal (**1**) was separated from *epi*-**1** by reverse phase HPLC, and to our delight, the NMR data were in good agreement with the isolation report (Table S6 and S7, SI).

In summary, we report the first total synthesis of complex *seco*-labdane leonuketal (**1**) over 23 steps from **12**. Our strategy featured an unusual Shapiro-type fragmentation as part of an enabling auxiliary ring strategy, as well as a novel Au-catalysed spirocyclization of a β-keto(enol)lactone. This work highlights the role of C–C bond cleavage in the biogenesis of complex terpenoids and demonstrates that the total synthesis of these molecules remains an exciting challenge.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge

Experimental procedures, analytical data (^{1}H and ^{13}C NMR, MS, IR) for all compounds (PDF)

Crystallographic information for compound **13** (CIF)

Crystallographic information for compound **18** (CIF)

Crystallographic information for compound **25** (CIF)

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Notes

The authors declare no competing financial interest.

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