OL Organic Letters

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Total Synthesis of (±)-Leonuketal

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03364 Read Online

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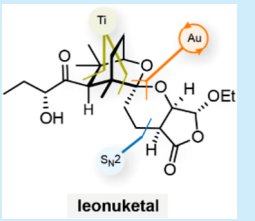
ABSTRACT: Leonuketal is an 8,9-*seco*-labdane terpenoid with a unique tetracyclic structure, owing to a diversity-generating biosynthetic C−C bond cleavage event. The first total synthesis of leonuketal is reported, featuring a Ti(III)-mediated reductive cyclization of an epoxy nitrile ether, an unusual ring-opening alkyne formation as part of an auxiliary ring strategy, and the previously undescribed Au(I)-catalyzed cyclization of a β-keto(enol)lactone to assemble the core spiroketal motif.



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).[10] 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 ketalization 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).[11] Peng and co-workers isolated **1** from Chinese liverwort (*Leonurus japonicus*) in 2015 and reported significant vasorelaxant activity (EC_{50} = 2.32 μM) against KCl-induced contraction of rat aorta.[11] 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).[12,13] This characteristic—alongside important bioactivities—has rendered *seco*-labdanes attractive synthetic targets and useful platforms for the development of synthetic methods.[14−33]

Previously, we reported the synthesis of the bridged oxabicyclic core of leonuketal (**1**), as lactone **5**, by an efficient Diels−Alder reductive-cyclization sequence (Figure 1C).[34] 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 toward 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 cyclization of alkyne **8**, which could be accessed from iodide **9** through appendage of the lactone moiety by alkylation.[35]

Efficient synthesis of the alkyne-substituted cyclohexanol ring of **9** appeared to pose a challenge. While related cyclohexanols have been assembled from geraniol derivatives, we aimed to identify a method to efficiently incorporate the requisite alkynyl moiety.[36−44] 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** (Figures 1D and 2A). Bicyclic ketone **11** could, in turn, be disconnected to epoxide **12**, a derivative of geraniol, by a Ti(III)-mediated radical cyclization.

Our synthesis thus began with treatment of epoxide **12** with *in situ* generated Cp_2TiCl_2, efficiently affording bicyclic ketone **13** after acidic hydrolysis (Scheme 1).[45−49] This transformation, while proceeding in modest yield (32%), scaled up easily (6.5 g) and afforded reliable access to diastereomerically pure ketone **13**.[50] 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).[51]

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 the SI for details).

Received: October 8, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03364
Org. Lett. XXXX, XXX, XXX−XXX

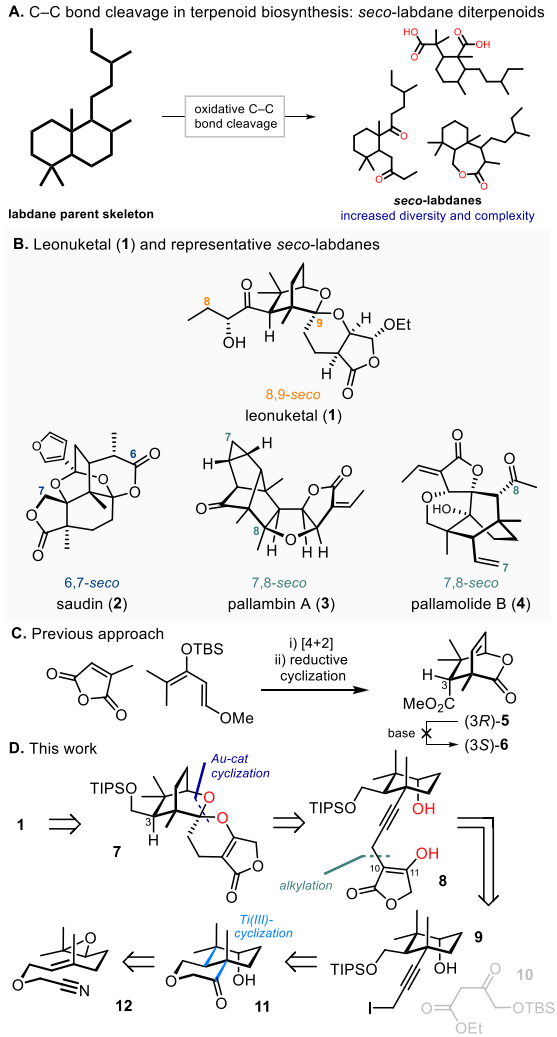


Figure 1. Background and retrosynthetic analysis; NB: numbering in 1B based on parent labdane skeleton.

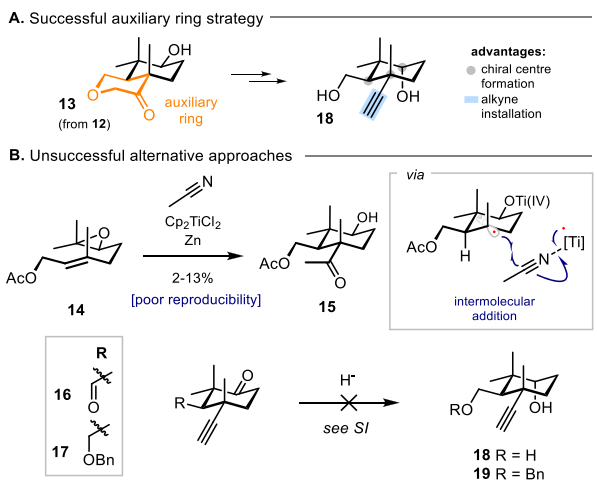


Figure 2. Discussion of auxiliary ring strategy for synthesis of **18**.

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.[52] 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.[53] 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. The value of this sequence is underscored by an abundance terpenoids sharing the dimethylcyclohexanol substructure of **18**; indeed, a structure search revealed >14 000 natural products containing this motif.[54]

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.[55,56] 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 stereocenters of leonuketal (**1**). Typically, dihydroxy alkynes are employed in Au-catalyzed 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-catalyzed 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.

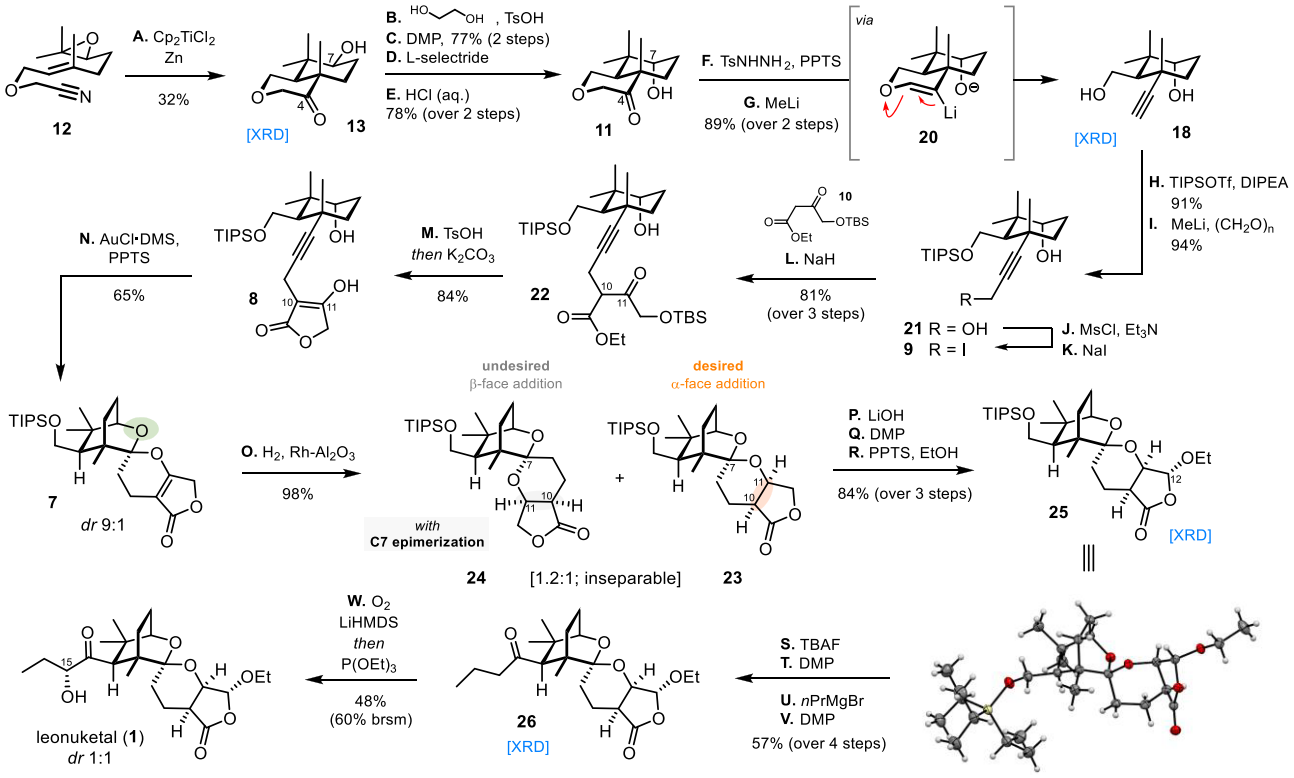
Initial investigations yielded the desired spiroketal product upon treatment of **22** with Au(I)-complexes; however, these results had poor reproducibility, and this process often resulted in decomposition of the substrate. We therefore sought an alternative spiroketal precursor.

TBS deprotection and lactonization 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 with an excellent 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

https://dx.doi.org/10.1021/acs.orglett.0c03364
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 1. Total Synthesis of (±)-Leonuketal (1)[a]



[a]Reagents and conditions: (a) Cp_2TiCl_2 (2.2 equiv), Zn (4.6 equiv), THF, 60 °C, 1 h *then* aq. KH_2PO_4, rt, 30 min, 32%; (b) ethylene glycol (15 equiv), TsOH (5 mol %), benzene, reflux, 4 h; (c) DMP (1.2 equiv), pyridine (2.5 equiv), CH_2Cl_2, rt, 1 h, 77% over 2 steps; (d) L-selectride (2.2 equiv), 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 equiv), PPTS (5 mol %), THF, rt, 16 h; (g) MeLi (9 equiv), THF-Et_2O (1:1, v/v), 0 °C, 3 h, 89% over 2 steps; (h) TIPSOTf (1.2 equiv), DIPEA (3 equiv), 50 min, 91%; (i) paraformaldehyde (12 equiv), MeLi (9 equiv), Et_2O, −78 to 0 °C, 1.5 h, 94%; (j) MsCl (1.1 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 40 min; (k) NaI (2.2 equiv), acetone, rt, 16 h; (l) **10** (3 equiv), NaH (2.9 equiv), 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; (q) DMP (4 equiv), CH_2Cl_2, rt, 30 min; (r) PPTS (10 mol %), EtOH, 45 °C, 24 h, 84% over 3 steps from **23** (39% from **23**−**24** combined); (s) TBAF (5 equiv), THF, 40 °C, 2 h; (t) DMP (4 equiv), K_2CO_3 (7 equiv), CH_2Cl_2, rt, 30 min; (u) *n*PrMgBr (1.85 equiv), Et_2O, 0 °C, 1 h, (v) DMP (4 equiv), K_2CO_3 (7 equiv), CH_2Cl_2, rt, 30 min, 57% over 4 steps; (w) O_2, LiHMDS (34 equiv), THF, −78 °C, 3.3 h *then* $P(OEt)_3$ 0.5 h, 48% combined (60% brsm), *dr* 1:1; thermal ellipsoids set at the 50% probability level.

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.[57] After some experimentation, rhodium on alumina was revealed to be a competent catalyst for hydrogenation of **7** at elevated pressure (65 psi); however, the desired α-face addition product **23** was accompanied by diastereomer **24** as an inseparable 1:1.2 mixture.[58,59] Interestingly, **24** bore inverted stereogenic centers at C10, C11, and the spiroketal carbon C7.

The observed mixture of **23** and **24** appears most likely to arise from nonselective hydrogenation of **7** from either face of the alkene, to initially give a mixture of the desired hydrogenation product **23** and 7-*epi*-**24**, respectively. Subsequent thermodynamically driven spiroketal epimerization of 7-*epi*-**24** to **24** would then afford the observed product mixture. Calculations suggested that C7 epimerization should be favorable for β-face addition product 7-*epi*-**24** but not for the desired product **23** (see the Supporting Information (SI)), indicating that nonselective hydrogenation would result in the observed mixture of **23** and **24**, as was observed experimentally.

The diastereomeric mixture **23** and **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 over three steps. This sequence required only one chromatographic separation after acetalization, at which point, the desired diastereomer **25** could be separated from the product derived from **24** (*not shown*). Completion of **25** secured the unique tetracyclic core of leonuketal (**1**) and all but one chiral center 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%

https://dx.doi.org/10.1021/acs.orglett.0c03364
Org. Lett. XXXX, XXX, XXX−XXX

yield over four steps with only two chromatographic separations. α-Hydroxylation of the newly formed ketone **26** was the final step in completion of the total synthesis and required some investigation (see Tables S4 and S5, SI). Deprotonation of **26** with LiHMDS followed by treatment with (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine effected the desired oxidation, but favored 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 consumption of starting material. 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 (Tables S6 and S7, SI).[11]

In summary, we report the first total synthesis of complex *seco*-labdane leonuketal (**1**) over 23 steps from **12**.[60] Successful completion of the synthesis was enabled by development of three key transformations: the Ti(III)-mediated cyclization of **12**, the unusual Shapiro-type fragmentation of **11** as part of an auxiliary ring strategy, and the previously undescribed Au-catalyzed spirocyclization of a β-keto(enol)lactone (**7**) . We anticipate that these extensions to the synthetic toolkit will find wider application in the preparation of complex structures and that ongoing investigations into the chemistry and biology of natural product frameworks exemplified by **1**, and more particularly **18**, will prove to be fruitful fields of research.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03364.

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

Accession Codes

CCDC 2017573−2017575 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the University of Auckland for the Doctoral Scholarship Award (PSG) and Dr. Tania Groutso (UoA) for assistance with crystallography.

■ REFERENCES

(1) Boronat, A.; Rodríguez-Concepción, M. Terpenoid Biosynthesis in Prokaryotes. In *Biotechnology of Isoprenoids*; Schrader, J., Bohlmann, J., Eds.; Advances in Biochemical Engineering/Biotechnology; Springer International Publishing: Cham, 2015; pp 3−18.

(2) Chen, K.; Baran, P. S. Total Synthesis of Eudesmane Terpenes by Site-Selective C−H Oxidations. *Nature* **2009**, *459* (7248), 824−828.

(3) Christianson, D. W. Structural Biology and Chemistry of the Terpenoid Cyclases. *Chem. Rev.* **2006**, *106* (8), 3412−3442.

(4) Davis, E. M.; Croteau, R. Cyclization Enzymes in the Biosynthesis of Monoterpenes, Sesquiterpenes, and Diterpenes. In *Biosynthesis: Aromatic Polyketides, Isoprenoids, Alkaloids*; Leeper, F. J., Vederas, J. C., Eds.; Topics in Current Chemistry; Springer: Berlin, Heidelberg, 2000; pp 53−95.

(5) Janocha, S.; Schmitz, D.; Bernhardt, R. Terpene Hydroxylation with Microbial Cytochrome P450 Monooxygenases. In *Biotechnology of Isoprenoids*; Schrader, J., Bohlmann, J., Eds.; Advances in Biochemical Engineering/Biotechnology; Springer International Publishing: Cham, 2015; pp 215−250.

(6) Pateraki, I.; Heskes, A. M.; Hamberger, B. Cytochromes P450 for Terpene Functionalisation and Metabolic Engineering. In *Biotechnology of Isoprenoids*; Schrader, J., Bohlmann, J., Eds.; Advances in Biochemical Engineering/Biotechnology; Springer International Publishing: Cham, 2015; pp 107−139.

(7) Schmidt-Dannert, C. Biosynthesis of Terpenoid Natural Products in Fungi. In *Biotechnology of Isoprenoids*; Schrader, J., Bohlmann, J., Eds.; Advances in Biochemical Engineering/Biotechnology; Springer International Publishing: Cham, 2015; pp 19−61.

(8) Shul'ts, E. E.; Mironov, M. E.; Kharitonov, Y. V. Furanoditerpenoids of the Labdane Series: Occurrence in Plants, Total Synthesis, Several Transformations, and Biological Activity. *Chem. Nat. Compd.* **2014**, *50* (1), 2−21.

(9) Ishihara, Y.; Baran, P. S. Two-Phase Terpene Total Synthesis: Historical Perspective and Application to the Taxol Problem. *Synlett* **2010**, *2010* (12), 1773−1745.

(10) Almeida, A.; Dong, L.; Appendino, G.; Bak, S. Plant Triterpenoids with Bond-Missing Skeletons: Biogenesis, Distribution and Bioactivity. *Nat. Prod. Rep.* **2020**, *37*, 1207.

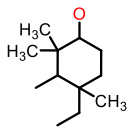
(11) Xiong, L.; Zhou, Q.-M.; Zou, Y.; Chen, M.-H.; Guo, L.; Hu, G.-Y.; Liu, Z.-H.; Peng, C. Leonuketal, a Spiroketal Diterpenoid from Leonurus Japonicus. *Org. Lett.* **2015**, *17* (24), 6238−6241.

(12) Mossa, J. S.; Cassady, J. M.; Antoun, M. D.; Byrn, S. R.; McKenzie, A. T.; Kozlowski, J. F.; Main, P. Saudin, a Hypoglycemic Diterpenoid, with a Novel 6,7-Seco-Labdane Carbon Skeleton, from Cluytia Richardiana. *J. Org. Chem.* **1985**, *50* (6), 916−918.

(13) Li, Y.; Xu, Z.; Zhu, R.; Zhou, J.; Zong, Y.; Zhang, J.; Zhu, M.; Jin, X.; Qiao, Y.; Zheng, H.; Lou, H. Probing the Interconversion of Labdane Lactones from the Chinese Liverwort Pallavicinia Ambigua. *Org. Lett.* **2020**, *22* (2), 510−514.

(14) Boeckman, R. K.; del Rosario Rico Ferreira, M.; Mitchell, L. H.; Shao, P. An Enantioselective Total Synthesis of (+)- and (−)-Saudin. Determination of the Absolute Configuration. *J. Am. Chem. Soc.* **2002**, *124* (2), 190−191.

(15) Dong, J.-Q.; Wong, H. N. C. Biomimetic Total Synthesis of (±)-Pallavicinolide A. *Angew. Chem., Int. Ed.* **2009**, *48* (13), 2351−2354.
(16) Zhang, X.; Cai, X.; Huang, B.; Guo, L.; Gao, Z.; Jia, Y. Enantioselective Total Syntheses of Pallambins A−D. *Angew. Chem., Int. Ed.* **2019**, *58* (38), 13380−13384.
(17) Ebner, C.; Carreira, E. M. Pentafulvene for the Synthesis of Complex Natural Products: Total Syntheses of (±)-Pallambins A and B. *Angew. Chem., Int. Ed.* **2015**, *54* (38), 11227−11230.
(18) Huang, B.; Guo, L.; Jia, Y. Protecting-Group-Free Enantioselective Synthesis of (−)-Pallavicinin and (+)-Neopallavicinin. *Angew. Chem., Int. Ed.* **2015**, *54* (46), 13599−13603.
(19) Winkler, J. D.; Doherty, E. M. The First Total Synthesis of (±)-Saudin. *J. Am. Chem. Soc.* **1999**, *121* (32), 7425−7426.
(20) Peng, X.-S.; Wong, H. N. C. Total Synthesis of (±)-Pallavicinin and (±)-Neopallavicinin. *Chem. - Asian J.* **2006**, *1* (1−2), 111−120.
(21) Martinez, L. P.; Umemiya, S.; Wengryniuk, S. E.; Baran, P. S. 11-Step Total Synthesis of Pallambins C and D. *J. Am. Chem. Soc.* **2016**, *138* (24), 7536−7539.
(22) Bian, Y.-C.; Peng, X.-S.; Wong, H. N. C. Total Synthesis of Pallavicinia Diterpenoids: An Overview. *Tetrahedron Lett.* **2016**, *57* (50), 5560−5569.
(23) Hagiwara, H.; Takeuchi, F.; Hoshi, T.; Suzuki, T.; Ando, M. First Total Synthesis of Chapecoderin A: Absolute Configuration of the Natural Product. *Tetrahedron Lett.* **2001**, *42* (43), 7629−7631.
(24) Hagiwara, H.; Takeuchi, F.; Nozawa, M.; Hoshi, T.; Suzuki, T. The First Total Synthesis and Determination of the Absolute Configuration of Chapecoderin A, B and C. *Tetrahedron* **2004**, *60* (9), 1983−1989.
(25) Tambar, U. K.; Kano, T.; Zepernick, J. F.; Stoltz, B. M. Convergent and Diastereoselective Synthesis of the Polycyclic Pyran Core of Saudin. *J. Org. Chem.* **2006**, *71* (22), 8357−8364.
(26) Tambar, U. K.; Kano, T.; Stoltz, B. M. Progress toward the Total Synthesis of Saudin: Development of a Tandem Stille-Oxa-Electrocyclization Reaction. *Org. Lett.* **2005**, *7* (12), 2413−2416.
(27) Bos, M. E.; Loncaric, C.; Wu, C.; Wulff, W. D. Studies on the Synthesis of Richardianidin-1 via the Tautomer-Arrested Annulation of Fischer Carbene Complexes. *Synthesis* **2006**, *2006* (21), 3679−3705.
(28) Sanchez, M.; Bermejo, F. Stereoselective Approach to the BCD Framework of Richardianidins via Intramolecular Reformatsky-Type Reaction Promoted by Diethylaluminum Chloride. *Tetrahedron Lett.* **1997**, *38* (28), 5057−5060.
(29) Cravero, R. M.; González-Sierra, M.; Labadie, G. R. Convergent Approaches to Saudin Intermediates. *Helv. Chim. Acta* **2003**, *86* (8), 2741−2753.
(30) Labadie, G. R.; Cravero, R. M.; Sierra, M. G. A Short Synthesis of the Main Lactone Ketal Backbone Present in Saudin. *Molecules* **2000**, *5* (3), 321−322.
(31) Labadie, G. R.; Luna, L. E.; Cravero, R. M.; González-Sierra, M. A Simple Synthesis of a Model of the Tetracyclic Bisketal Lactone Mainframe of Saudin. *Helv. Chim. Acta* **2006**, *89* (11), 2732−2737.
(32) Labadie, G. R.; Cravero, R. M.; González-Sierra, M. Studies Toward the Total Synthesis of Saudine: Simple and Stereoselective Synthesis of a Model Caged Ketal Backbone. *Synth. Commun.* **1996**, *26* (24), 4671−4684.
(33) Labadie, G. R.; Luna, L. E.; Gonzalez-Sierra, M.; Cravero, R. M. Synthesis of the Tetracyclic Bis(Acetal) Lactone Portion of Saudin. *Eur. J. Org. Chem.* **2003**, *2003* (17), 3429−3434.
(34) Grant, P. S.; Brimble, M. A.; Furkert, D. P. Synthesis of the Bicyclic Lactone Core of Leonuketal, Enabled by a Telescoped Diels−Alder Reaction Sequence. *Chem. - Asian J.* **2019**, *14* (8), 1128−1135.
(35) Quach, R.; Furkert, D. P.; Brimble, M. A. Gold Catalysis: Synthesis of Spiro, Bridged, and Fused Ketal Natural Products. *Org. Biomol. Chem.* **2017**, *15* (15), 3098−3104.
(36) Goldsmith, D. J. The Cyclization of Epoxyolefins: The Reaction of Geraniolene Monoepoxide with Boron Fluoride Etherate. *J. Am. Chem. Soc.* **1962**, *84* (20), 3913−3918.
(37) Van Tamelen, E. E. Bioorganic Chemistry. Total Synthesis of Tetra- and Pentacyclic Triterpenoids. *Acc. Chem. Res.* **1975**, *8* (5), 152−158.
(38) Marson, C. M. Oxygen-Directed Carbocyclizations of Epoxides. *Tetrahedron* **2000**, *56* (45), 8779−8794.
(39) Huang, A. X.; Xiong, Z.; Corey, E. J. An Exceptionally Short and Simple Enantioselective Total Synthesis of Pentacyclic Triterpenes of the β-Amyrin Family. *J. Am. Chem. Soc.* **1999**, *121* (43), 9999−10003.
(40) Zhang, J.; Corey, E. J. A Simple Enantioselective Synthesis of Serratenediol. *Org. Lett.* **2001**, *3* (20), 3215−3216.
(41) Mi, Y.; Schreiber, J. V.; Corey, E. J. Total Synthesis of (+)-α-Onocerin in Four Steps via Four-Component Coupling and Tetracyclization Steps. *J. Am. Chem. Soc.* **2002**, *124* (38), 11290−11291.
(42) Shenvi, R. A.; Corey, E. J. Synthetic Access to Bent Polycycles by Cation-π Cyclization. *Org. Lett.* **2010**, *12* (15), 3548−3551.
(43) Suzuki, K.; Yamakoshi, H.; Nakamura, S. Construction of Bridged Polycyclic Systems by Polyene Cyclization. *Chem. - Eur. J.* **2015**, *21* (49), 17605−17609.
(44) Feilner, J. M.; Wurst, K.; Magauer, T. A Transannular Polyene Tetracyclization for Rapid Construction of the Pimarane Framework. *Angew. Chem., Int. Ed.* **2020**, *59*, 12436.
(45) Gansäuer, A.; Piestert, F.; Huth, I.; Lauterbach, T. Nitriles and Carbonyl Groups as Acceptors in Titanocene-Catalyzed Radical Cyclizations. *Synthesis* **2008**, *2008* (21), 3509−3515.
(46) Fernández-Mateos, A.; Burón, L. M.; Clemente, R. R.; Silvo, A. I. R.; González, R. R. Radical Cyclization of Epoxynitriles Mediated by Titanocene Chloride. *Synlett* **2004**, No. 06, 1011−1014.
(47) Fernández-Mateos, A.; Teijón, P. H.; Clemente, R. R.; González, R. R.; González, F. S. Stereoselective Radical Cascade Cyclizations of Unsaturated Epoxynitriles: Quadruple Radical Cyclization Terminated by a 4-Exo Process onto Nitrile. *Synlett* **2007**, *2007* (17), 2718−2722.
(48) Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. Annulative Methods Enable a Total Synthesis of the Complex Meroterpene Berkeleyone A. *J. Am. Chem. Soc.* **2016**, *138* (45), 14868−14871.
(49) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. Titanocene-Catalyzed Cascade Cyclization of Epoxypolyprenes: Straightforward Synthesis of Terpenoids by Free-Radical Chemistry. *Chem. - Eur. J.* **2004**, *10* (7), 1778−1788.
(50) The *dr* of the reaction could not be determined due to byproducts in the crude NMR; no alternative diastereomer was isolated.
(51) Fernández-Mateos, A.; Madrazo, S. E.; Teijón, P. H.; González, R. R. Titanocene-Promoted Intermolecular Couplings of Epoxides with Nitriles. An Easy Access to β-Hydroxyketones. *J. Org. Chem.* **2009**, *74* (10), 3913−3918.
(52) Adlington, R. M.; Barrett, A. G. M. Recent Applications of the Shapiro Reaction. *Acc. Chem. Res.* **1983**, *16* (2), 55−59.
(53) Hecker, S. J.; Heathcock, C. H. Total Synthesis of (+)-Dihydromevinolin. *J. Am. Chem. Soc.* **1986**, *108* (15), 4586−4594.
(54) Dictionary of Natural Products; Structure Search. Methyl groups specified as completely saturated



(55) Seebach, D.; Wasmuth, D. Herstellung von Erythro-2-Hydroxybernsteinsäure-Derivaten Aus Äpfelsäureester. Vorläufige Mitteilung. *Helv. Chim. Acta* **1980**, *63* (1), 197−200.
(56) Fráter, G.; Müller, U.; Günther, W. The Stereoselective α-Alkylation of Chiral β-Hydroxy Esters and Some Applications Thereof. *Tetrahedron* **1984**, *40* (8), 1269−1277.

https://dx.doi.org/10.1021/acs.orglett.0c03364
Org. Lett. XXXX, XXX, XXX−XXX

(57) Thompson, H. W. Haptophilic Control of Hydrogenation Stereochemistry*. *Ann. N. Y. Acad. Sci.* **1973**, *214* (1), 195−203.
(58) Lee, Y. Y.; Kim, B. H. Total Synthesis of Nonactin. *Tetrahedron* **1996**, *52* (2), 571−588.
(59) Lygo, B. Stereoselective Synthesis of (±)-Methyl Homononactate and (±)-Methyl 8-Epi-Homononactate. *Tetrahedron* **1988**, *44* (22), 6889−6896.
(60) Grant, P. S.; Furkert, D. P.; Brimble, M. A. Total Synthesis of (±)-Leonuketal. *ChemRxiv.org* **2020**, DOI: 10.26434/chemrxiv.12673757.v1.

https://dx.doi.org/10.1021/acs.orglett.0c03364
Org. Lett. XXXX, XXX, XXX−XXX