



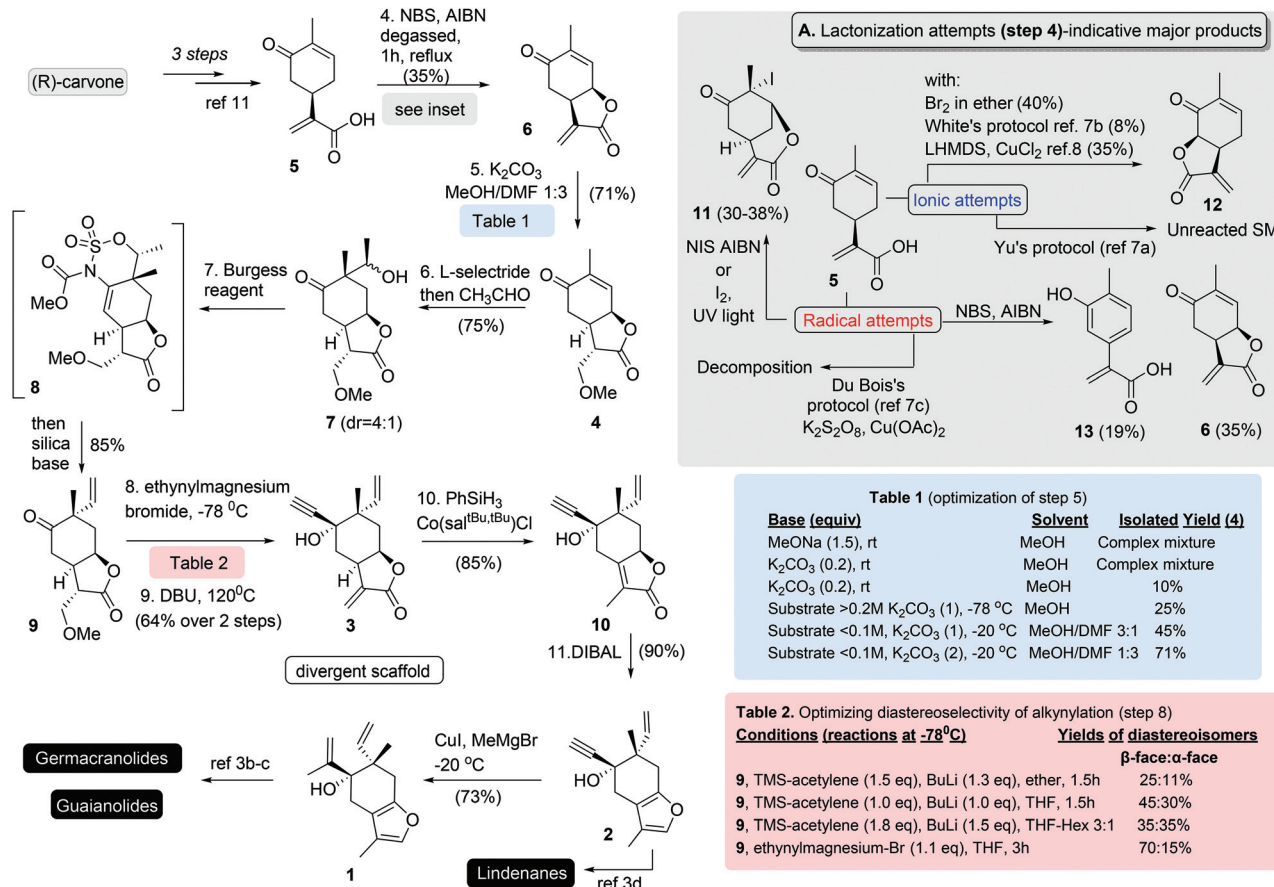
3 was projected to serve not only as a reliable alternative for the synthesis of furo- and  $\alpha,\beta$ -unsaturated sesquiterpenoids that reported earlier by our group,<sup>3b-d</sup> but also as a cornerstone for the future access of  $\alpha$ -methylene- $\gamma$ -butenolide SQLs of both 8,12- and 6,12-complexity. The formal syntheses of natural products bearing the carbocyclic cores of germacranes, guaianes and lindenanes at furan and  $\alpha,\beta$ -unsaturated lactone oxidation states were set as threshold for the developed divergent scaffold.

## Results and discussion

To address the poor scalability of our prior plans, a completely new synthetic strategy was designed for the synthesis of 3. Retrosynthetically, compound 3 (Scheme 1) was projected to derive from protected lactone 4, to allow the consequent successive stereoselective alkylations for the introduction of the two tertiary stereocenters. The necessity for protection of  $\alpha$ -methylene- $\gamma$ -butenolide functionality was expected to be counterbalanced by the selection of a biocompatible cell-cleaved protection.<sup>5</sup> Lastly, a *syn*-direct lactonization was envisioned from the known natural product carvonic acid (5). Early introduction of the lactone moiety would supposedly induce firstly the stereoselective introduction of the vinyl group

through the stereoelectronic effects produced by the *cis*-8,12-junction and secondly the alkylation that follows.

The synthesis began by preparing carvonic acid (5) following reported procedures.<sup>6</sup> Attempts to introduce the *cis*-8,12-lactone functionality was found extremely challenging using various methods (see inset of Scheme 2). Utilization of NCS, NIS and iodine under ionic and radical conditions provided complex mixture of products deriving from the polyhalogenation and halolactonization of alkenes (ex. compound 11), while interestingly the addition of Br<sub>2</sub> produced *cis*-6,12-lactone 12. The same was also evidenced when CH-lactonization was attempted following White's protocol<sup>7</sup> or when LHMDS was used in the presence of CuCl<sub>2</sub> or FeCl<sub>3</sub>,<sup>8</sup> albeit in lower yields. Although product 12 was not the desired, these results show the ability of carvonic acid to selectively access 6,12-lactone, something that is beneficial in cases where 6,12-sesquiterpenoids are targeted. On the other hand, careful addition of NBS under radical conditions with AIBN as initiator allowed the synthesis of *cis*-8,12-lactone 6, in rather low yield (35%) besides the extensive optimization, due to its facile oxidation to aromatic component 13. With lactone 6 in hands, we next set the stage for the introduction of the tertiary vinyl group. As expected, the notorious lability of  $\alpha$ -methylene- $\gamma$ -butenolide in 6 towards nucleophiles prohibited its direct alkylation. Inspired by the concept of pharmacophore-directed



Scheme 2 Synthetic route to furan common scaffolds 1 and 2. Attempted reactions and optimization for crucial steps included.



retrosynthesis,<sup>9</sup> utilization of a biocompatible protection group was selected to allow the biological screening of all prepared precursors. Following literature precedence,<sup>5</sup> reversible protections by amines, alcohols, and thiols were tested. Numerous experiments were run to differentiate the two Michael acceptors in **6** (Scheme 2; Table 1). Typical conditions of a nucleophile employment (MeOH, thiophenol or amines) with or without the presence of K<sub>2</sub>CO<sub>3</sub> and DMAP failed to provide clean protection of methylene group, due to the interference of the conjugated ketone and/or the cleavage of the lactone moiety. Gratifyingly, addition of DMF as a co-solvent with MeOH in the presence of equimolar amount of K<sub>2</sub>CO<sub>3</sub> allowed the introduction of methoxy functionality to provide **4** in 71% yield.

Successful reductive stereoselective alkylation of **4** by L-selectride and acetaldehyde followed.<sup>10</sup> Alkylation provided a 4:1 mixture of alcohols **7** favouring the Felkin-Anh product without witnessing any alkylation from the β-face of the cyclohexane ring. The latter is directly attributed to the incorporation of rigidity from the *syn*-lactone to the cyclohexane ring.<sup>10</sup> Dehydration by Burgess reagent was unencumbered affording compound **9** in 65% yield, along with Burgess-substrate hybrid **8** in 20% yield. The latter was transformed into the desired product by subjection to basic conditions, affording **9** in 85% overall yield.

Alkylation of ketone **9** by lithium TMS-acetylene prepared by TMS-acetylene and *n*-BuLi was found productive but it resulted in poor diastereoselectivities for the desired β-isomer (2:1 ratio over its epimer) (Scheme 2; Table 2). To this end several conditions were tried to find that ethynylmagnesium bromide can allow the synthesis of desired diastereoisomer in a 3.5:1 ratio over its epimer. Subsequent DBU deprotection of methoxy group provided compound **3** in 64% yield over the two steps (Scheme 2). The isomerization of α-methylene-γ-butenolide **3** to α,β-unsaturated-γ-butenolide **10** was found difficult to achieve and was only accomplished by catalytic hydrogen atom transfer to the alkene, a protocol that was developed by Shenvi's group.<sup>11</sup> Finally, the direct reduction of **10** to furan moiety by DIBAL furnishes the known furo-olemane **2**, allowing the formal synthesis of *epi*-lindenene and sarcandalactone **A**.<sup>3d</sup>

Access to the formal syntheses of germacrane: furanoger- menone and methylcurdionolide and to guaiane: zedoarol and gweicurculactone (Scheme 1) and other differentiated scaffolds can be obtained by selective alkylation of acetylene functionality of **2** to unify for the first time all synthetic plans. After extensive experimentation was found that methyl cupration of alkyne can be accomplished with copper iodide followed by slow addition of methylmagnesium bromide<sup>12</sup> allowing the synthesis of 2-propenyl-intermediate **1** as the parent compound for the known oxy-Cope reaction that can build the 10-member macrocycle or the oxy-Cope/ene reaction that serves for obtaining guaiane carbocyclic core. All formal syntheses were accomplished in the same number of steps as in the previously reported plan (11 steps for common scaffold **2** from *R*-carvone) in slightly better yields, nonetheless with the

capacity for current to deliver gram scale quantities for all synthetic intermediates.

## Conclusions

In conclusion, we report a new synthetic route for the synthesis of 8,12-sesquiterpenoids. The synthetic plan employs a highly stereoselective access to both furo-olemanes **2** and **1** for the first time allowing the unified divergent synthesis of germacrane, guaiane and lindenane among other carbocycles by taking advantage of the stereoelectronic effects of an early introduced protected α-methylene-γ-butenolide core for the stereoselective introduction of two tertiary centers. The newly developed divergent scaffold is expected to serve as cornerstone for the synthesis of biologically intriguing α-methylene-γ-butenolide lactone sesquiterpenoids. This work is currently underway and will be reported in due course.

## Author contributions

V. P. D. and A. L. Z. were responsible for the conceptualization of the work in every step of the project. M. K. was responsible for scaling-up some experimental procedures.

## Conflicts of interest

The authors have no conflicts to declare.

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## Notes and references

- 1 A. L. Zografos, in *From Biosynthesis to Total Synthesis: Strategies and Tactics for Natural Products*, Wiley & Sons, Hoboken, 2016.
- 2 Seminar report on divergent synthesis by: (a) C. E. Brotherton and D. L. Boger, Total synthesis of



- azafluoranthene alkaloids: rufescine and imeluteine, *J. Org. Chem.*, 1984, **49**, 4050–4055 For strategies and tactics for the synthesis of divergent scaffolds or common scaffolds can be found on: (b) E. E. Anagnostaki and A. L. Zografos, “Common synthetic scaffolds” in the synthesis of structurally diverse natural products, *Chem. Soc. Rev.*, 2012, **41**, 5613–5625; (c) J. Shimokawa, Divergent strategy in natural product total synthesis, *Tetrahedron Lett.*, 2014, **55**, 6156–6162; (d) L. Li, Z. Chen, X. Zhang and Y. Jia, Divergent Strategy in Natural Product Synthesis, *Chem. Rev.*, 2018, **118**, 3752–3832; (e) A. M. Szpilman and E. M. Carreira, Probing the biology of natural products: molecular editing by diverted total synthesis, *Angew. Chem., Int. Ed.*, 2010, **49**, 9592–9628, (*Angew. Chem.*, 2010, **122**, 9786–9823).
- 3 (a) A. D. Fotiadou and A. L. Zografos, Accessing the Structural Diversity of Pyridone Alkaloids: Concise Total Synthesis of Rac-Citridone A, *Org. Lett.*, 2011, **13**, 4592–4598; (b) E. E. Anagnostaki and A. L. Zografos, Non-natural Elemene as the “Stepping Stone” for the Synthesis of Germacrane and Guaiane Sesquiterpenes, *Org. Lett.*, 2013, **15**, 152–155; (c) E. E. Anagnostaki, V. P. Demertzidou and A. L. Zografos, Divergent pathways to furosesquiterpenes: first total syntheses of (+)-zedoanol and (Rac)-gweicurculactone, *Chem. Commun.*, 2015, **51**, 2364–2367; (d) V. P. Demertzidou and A. L. Zografos, Platinum-catalyzed cycloisomerizations of a common enyne: a divergent entry to cyclopropane sesquiterpenoids. Formal synthesis of sarcandralactone A, *Org. Biomol. Chem.*, 2016, **14**, 6942–6946. For depiction of the synopsis synthetic route leading to diverse furan and  $\alpha,\beta$ -unsaturated lactone sesquiterpenoids please see ESI.†.
- 4 (a) S. Zhang, Y.-K. Won, C.-N. Ong and H.-M. Shen, Anti-Cancer Potential of Sesquiterpene Lactones: Bioactivity and Molecular Mechanisms, *Curr. Med. Chem.: Anti-Cancer Agents*, 2005, **5**, 239–249; (b) S. B. Christensen, D. M. Skytte, S. R. Denmeade, C. Dionne, J. V. Moller, P. Nissen and J. T. Isaacs, A Trojan Horse in Drug Development: Targeting of Thapsigargin Towards Prostate Cancer Cells, *Anti-Cancer Agents Med. Chem.*, 2009, **9**, 276–294; (c) I. Nakase, B. Gallis, T. Takatani-Nakase, S. Oh, E. Lacoste, N. P. Singh, D. R. Goodlett, S. Tanaka, S. Futaki, H. Lai and T. Sasaki, Transferrin receptor-dependent cytotoxicity of artemisinin-transferrin conjugates on prostate cancer cells and induction of apoptosis, *Cancer Lett.*, 2009, **274**, 290–298; (d) A. Ghantous, H. Gali-Muhtasib, H. Vuorela, N. A. Saliba and N. Darwiche, What made sesquiterpene lactones reach cancer clinical trials?, *Drug Discovery Today*, 2010, **15**, 668–678; (e) M. R. Kreuger, S. Grootjans, M. W. Biavatti, P. Vandenabeele and K. D’Herde, Sesquiterpene lactones as drugs with multiple targets in cancer treatment: focus on parthenolide, *Anticancer Drugs*, 2012, **23**, 883–896; (f) M. Chadwick, H. Trewin, F. Gawthrop and C. Wagstaff, Sesquiterpenoid Lactones: Benefits to plants and people, *Int. J. Mol. Sci.*, 2013, **14**, 12780–12805; (g) Y. Ren, J. Yu and A. D. Kinghorn, Development of Anticancer Agents from Plant-derived Sesquiterpene Lactones, *Curr. Med. Chem.*, 2016, **23**, 2397–2420.
- 5 Methoxy-protected butenolides can be readily cleaved in cells, in accordance to similar results for amino-protected sesquiterpenoids: J. R. Woods, H. Mo, A. A. Bieberich, T. Alavanja and D. A. Colby, Amino-derivatives of the sesquiterpene lactone class of natural products as prodrugs, *MedChemComm*, 2013, **4**, 27–33.
- 6 (a) W. Engel, In Vivo Studies on the Metabolism of the Monoterpenes S-(+)- and R-(-)-Carvone in Humans Using the Metabolism of Ingestion-Related Amounts (MICA) Approach, *J. Agric. Food Chem.*, 2001, **49**, 4069–4075; (b) D. W. Lee, C. F. Manful, J. R. Gone, Y. Ma and W. A. Donaldson, Reactivity of acyclic (pentadienyl)iron(1+) cations with phosphonate stabilized nucleophiles: application to the synthesis of oxygenated metabolites of carvone, *Tetrahedron*, 2016, **72**, 753–759.
- 7 For CH-lactonizations please advise: (a) Z. Zhuang and J.-Q. Yu, *Nature*, 2020, **577**, 656–659; (b) K. J. Fraunhoffer, N. Prabakaran, L. E. Sirois and M. C. White, *J. Am. Chem. Soc.*, 2006, **128**, 9032–9033; (c) S. Sathiyamoorthi and J. Du Bois, *Org. Lett.*, 2016, **18**, 6308–6311.
- 8 M. P. DeMartino, K. Chen and P. S. Baran, Intermolecular Enolate Heterocoupling: Scope, Mechanism, and Application, *J. Am. Chem. Soc.*, 2008, **130**, 11546–11560.
- 9 (a) D. Romo, Bioactivity-guided retrosynthesis: “Upping the ante” for natural product synthesis, *Planta Med.*, 2015, **81**; (b) J. R. Hudlicky and G. A. Sulikowski, Simple start for complex products, *Nat. Chem.*, 2019, **11**, 297–298; (c) M. E. Abbasov, R. Alvarino, C. M. Chaheine, E. Alonso, J. A. Sanchez, M. L. Conner, A. Alfonso, M. Jaspars, L. M. Botana and D. Romo, Simplified immunosuppressive and neuroprotective agents based on gracillin A, *Nat. Chem.*, 2019, **11**, 342–350.
- 10 It is known that direct alkylation of R-carvone results sole alkylation from the  $\beta$ -face of the cyclohexane ring. Please see: J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 17938–17954.
- 11 S. W. M. Crossley, F. Barabé and R. A. Shenvi, *J. Am. Chem. Soc.*, 2014, **136**, 16788–16791.
- 12 K. A. Parker and Q. Xie, *Org. Lett.*, 2008, **10**, 1349–1352.

