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A facile domino metathetic route to a thapsigargin skeleton†‡

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A facile synthesis of a 5,7,5-fused ring system that is present in thapsigargins belonging to a novel family of sesquiterpene lactones, guainanolides, using domino enyne–RCM is reported here.

Guaianolides, characterized by a 5,7,5 fused system **1**, epitomize one of the major groups of sesquiterpene lactones with more than 200 known members (Fig. 1).[1] Recently, thapsigargin **2** along with several closely related guaianolides, altogether called thapsigargins,[2] were isolated from the biologically active components of the Mediterranean species *Thapsia*. Thapsigargins have a densely oxygenated tricyclic scaffold with more than seven stereogenic centers and are functionalized with an array of different acyl groups. Thapsigargins were known to be potent histamine liberators and selective inhibitors of sarcoendoplasmic reticulum Ca^{2+} ATP dependent pumps (SERCAs).[3] Thapsigargins **2–5** also show remarkable specificity for the SERCA isozymes, and so became powerful tools to manipulate and study intracellular Ca^{2+}-dependent signalling pathways.[4] Thapsigargin **2**, in particular, has been reported to restore apoptotic function in cancer cell lines and recently, a prodrug conjugate of **2** has been used in the treatment of prostate cancer.[5] Furthermore, two more guaianolides, Arglabin[6] **6** and Ixerin Y[7] **7**, having the 5,7,5-tricyclic ring system, exhibit strong activities against breast, colon, ovarian, and lung cancer.

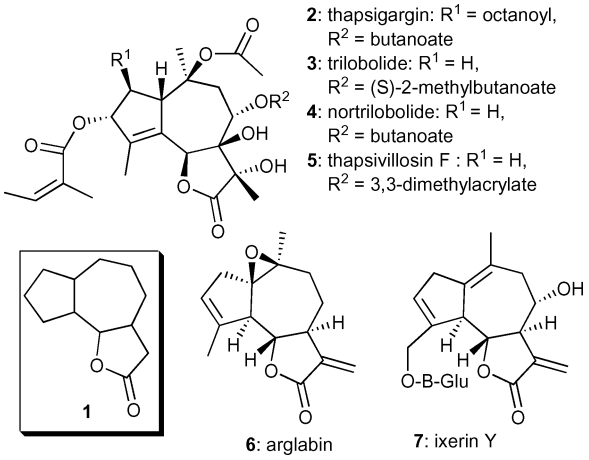
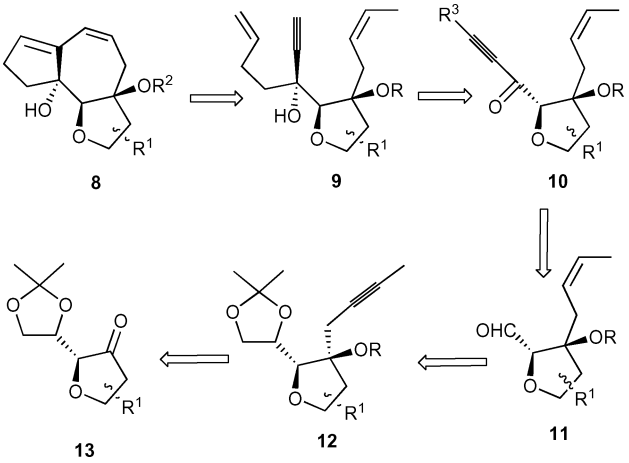


Fig. 1 Biologically active thapsigargins and other guaianolides.

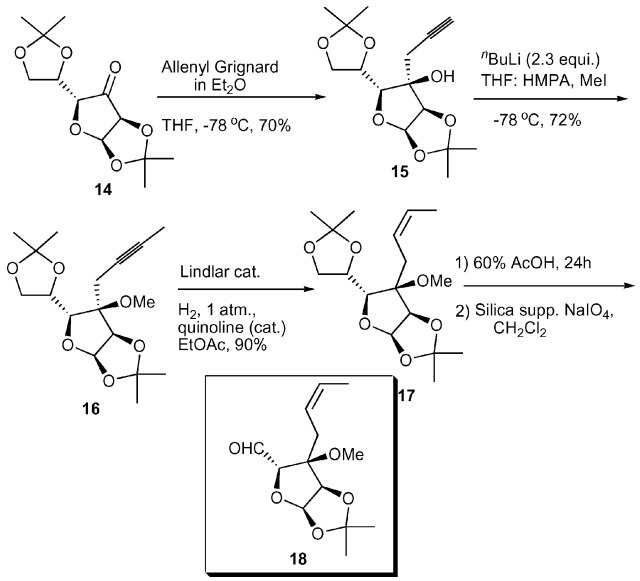
In view of the structural complexity coupled with excellent biological activity and limited availability from natural sources, guaianolides have aroused considerable synthetic interest.[8] As a part of our Chiron approach program,[9] we have begun to explore the possibility of utilizing a domino ring-closing metathesis strategy to prepare the core structure of thapsigargins and related guaianolides.

From a retrosynthetic perspective, we considered the possibility of constructing the 5,7-fused bicycle **8** *via* a tandem enyne–RCM reaction of a dienyne **9** which in turn would be derived from the aldehyde **11** in a couple of steps (Scheme 1). The aldehyde **11** could be traced back to a sugar derived ketone **13**. This strategy should be useful to make several simpler analogues of guaianolides starting from various sugar moieties.



Scheme 1

Our synthesis, as outlined in Scheme 2, began with the readily available ketone **14**. Addition of allenyl Grignard reagent at low temperature afforded the tertiary alcohol **15** in good yield.[10] Protection of this alcohol appeared to be problematic due to the presence of acidic acetylenic hydrogen. After considerable experimentation, protection of the alcohol and methylation of acetylene were achieved simultaneously by treating with *n*-BuLi and quenching with excess MeI to afford **16**. Next, we turned our



Scheme 2

† Electronic supplementary information (ESI) available: spectroscopic data for new compounds. See http://dx.doi.org/10.1039/b510388f

‡ Dedicated to Professor Michael C. Pirrung, University of California, Riverside on the occasion of his 50th birthday.

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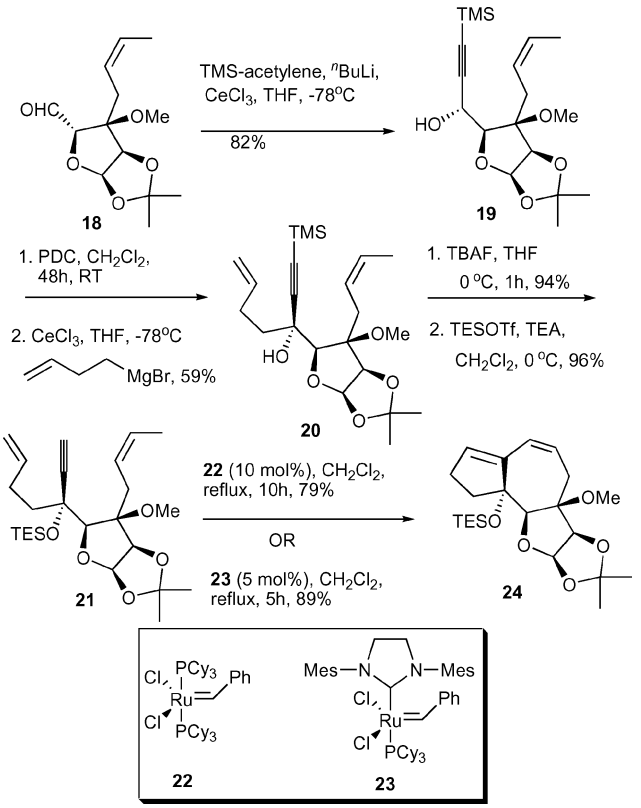
attention to reduce the triple bond to generate one of the double bonds required for the domino metathesis. Attempted reduction of the alkyne **16** with Red-Al provided a complex mixture and thus Lindlar catalyzed reduction was carried out to furnish the *cis*-alkene **17**. Selective removal of the more exposed acetonide group followed by cleavage of the diol with silica gel supported $NaIO_4$ provided the first key intermediate aldehyde **18** in high yield.

To introduce the alkyne moiety, aldehyde **18** was treated with cerium-trimethylsilyl acetylide to furnish the alcohol **19** predominantly as a single diastereoisomer.[11] Subsequent oxidation of **19** with PDC gave an unstable ketone, which was immediately treated with the Grignard reagent derived from 4-bromo-1-butene followed by exchange with $CeCl_3$, which smoothly generated the tertiary alcohol **20**. The stereochemistry of the Grignard reaction was tentatively assigned as shown in Scheme 3 based on the Felkin–Anh model.[11]



Scheme 3

Removal of the TMS group looked straightforward but K_2CO_3 treatment in MeOH often yielded a complex mixture and finally it was successfully accomplished by treating with TBAF. Finally, the key domino enyne–RCM[12] precursor **21** was successfully prepared by protecting the tertiary alcohol as a TES ether.

Having the dienyne **21** in hand, we then attempted the tandem enyne–RCM[12] with Grubbs' first generation catalyst **22**. Gratifyingly, the dienyne **21** underwent a smooth tandem enyne–ring closing metathesis[13,14] to afford the 5,7,5-fused ring system **24** as the only isolable product in high yield. When this reaction was repeated with 5 mol% Grubbs' second generation catalyst, we observed that the reaction[15] was a lot quicker with excellent yield of the formation of the tricyclic system **24**.

In conclusion, we have disclosed here a simple and versatile Chiron approach to a 5,7,5-fused ring system, present in thapsigargins, belonging to a novel class of sesquiterpene lactones. We are currently contemplating the extension of this methodology to the synthesis of various guaianolides in our laboratory.

Acknowledgements

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Notes and references

1 N. H. Fischer, E. J. Olivier and H. D. Fischer, *Fortschr. Chem. Org. Naturst.*, 1979, **38**, 47.
2 S. B. Christensen, A. Andersen and U. W. Smitt, *Fortschr. Chem. Org. Naturst.*, 1997, **71**, 129 and references therein.
3 (*a*) S. A. Patkar, U. Rasmussen and B. Diamant, *Agents Actions*, 1979, **9**, 53; (*b*) J. Lytton, M. Westlin and M. Hanley, *J. Biol. Chem.*, 1991, **266**, 17067; (*c*) C. Caspersen and M. Treiman, *FEBS Lett.*, 1995, **377**, 31.
4 M. Treiman, C. Caspersen and S. B. Christensen, *Trends Pharmacol. Sci.*, 1998, **19**, 131 and references therein.
5 (*a*) Y. Furuya, P. Lundmo, A. D. Short, D. L. Gill and J. T. Isaacs, *Cancer Res.*, 1994, **54**, 6167; (*b*) S. R. Denmeade, C. M. Jakobsen, S. Janssen, S. R. Khan, E. S. Garrett, H. Lilja, S. B. Christensen and J. T. Isaacs, *J. Natl. Cancer Inst.*, 2003, **95**, 990.
6 J.-Y. Ma, Z.-T. Wang, L.-S. Xu and G.-J. Xu, *Phytochemistry*, 1999, **50**, 113.
7 H.-F. Wong and G. D. Brown, *J. Nat. Prod.*, 2002, **65**, 481.
8 (*a*) For selected references: S. V. Ley, A. Antonello, E. P. Balskus, D. T. Booth, S. B. Christensen, E. Cleator, H. Gold, K. Hoegenauer, U. Huenger, R. M. Myers, S. F. Oliver, O. Simic, M. D. Smith, H. Sohoel and A. J. A. Woolford, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 120731; (*b*) S. F. Oliver, K. Hoegenauer, O. Simic, A. Antonello, M. D. Smith and S. V. Ley, *Angew. Chem., Int. Ed.*, 2003, **42**, 5996; (*c*) B. Nosse, R. B. Choor, W. B. Jeong, C. Bohm and O. Reiser, *Org. Lett.*, 2003, **5**, 941.
9 (*a*) K. P. Kaliappan and N. Kumar, *Tetrahedron Lett.*, 2003, **44**, 379; (*b*) K. P. Kaliappan and R. S. Nandurdikar, *Chem. Commun.*, 2004, 2506; (*c*) K. P. Kaliappan and V. Ravikumar, *Org. Biomol. Chem.*, 2005, **3**, 848.
10 K. H. Dotz, O. Neub and M. Nieger, *Synlett*, 1996, 995.
11 (*a*) K. Koto, C. Y. Chen and H. Akita, *Synthesis*, 1988, 1527; (*b*) T. D. Inch, *Carbohydr. Res.*, 1967, **5**, 45.
12 (*a*) For reviews on enyne metathesis, see: M. Mori, in Enyne Metathesis in *Topics in Organometallic Chemistry*, ed. A. Furstner, Springer, Berlin, Heidelberg, 1998, vol. 1, p. 133; (*b*) C. S. Poulsen and R. Madsen, *Synthesis*, 2003, 1; (*c*) S. T. Diver and A. J. Giessert, *Chem. Rev.*, 2004, **104**, 1317; (*d*) For selected reviews on RCM, see: R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413; (*e*) S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 1998, 371; (*f*) A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3012; (*g*) M. E. Maier, *Angew. Chem., Int. Ed.*, 2000, **39**, 2073; (*h*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18.
13 (*a*) S.-H. Kim, N. Bowden and R. H. Grubbs, *J. Am. Chem. Soc.*, 1994, **116**, 10801; (*b*) S.-H. Kim, W. J. Zuercher, N. Bowden and R. H. Grubbs, *J. Org. Chem.*, 1996, **67**, 1073.
14 F.-D. Boyer, I. Hanna and L. Richard, *Org. Lett.*, 2004, **6**, 1817.
15 *Experimental procedure for the domino metathesis reaction. Method A:* To a refluxing solution of dienyne **21** (50 mg, 0.11 mmol) in CH_2Cl_2 (36 mL) was added a solution of Grubbs' catalyst **22** (9.0 mg, 10 mol%) in CH_2Cl_2 (0.5 mL) and the mixture was refluxed for 10 h. The reaction mixture was cooled to room temperature, and DMSO (0.06 mL, 0.56 mmol) was added and the mixture was stirred overnight at room temperature. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography using 49 : 1 hexane–ethyl acetate to afford 36 mg (79%) of **24** as a pale yellow syrup. *Method B:* A solution of Grubbs' catalyst **23** (4.7 mg, 5 mol%) in CH_2Cl_2 (0.5 mL) was added to a refluxing solution of dienyne **21** (50 mg, 0.11 mmol) in CH_2Cl_2 (36 mL) and the mixture was refluxed for 5 h. After cooling to room temperature, DMSO (0.03 mL, 0.28 mmol) was added to the reaction mixture and this was stirred overnight at room temperature. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography using 49 : 1 hexane–ethyl acetate to afford 40 mg (89%) of **24** as a pale yellow syrup.