Studies Towards the Synthesis of Goniotrionin

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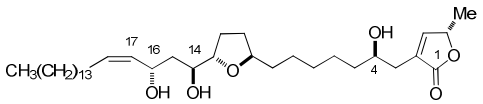
INTRODUCTION

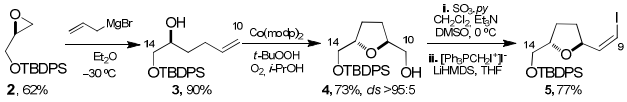
Annonaceous acetogenins are a class of natural polyketides which have promising anticancer, antiinfective, and pesticidal properties. Goniotrionin **1** is a potent antitumor agent which acts in NADH:ubiquinone oxirredutase. It was isolated in small amounts by McLaughlin *et al.* in 1998 from Annonaceae tree native to Thailand.[1] To provide material for further biological studies as well as access to novel analogues, we initiated a study towards the synthesis of Goniotrionin.



Scheme 1. Goniotrionin (**1**)

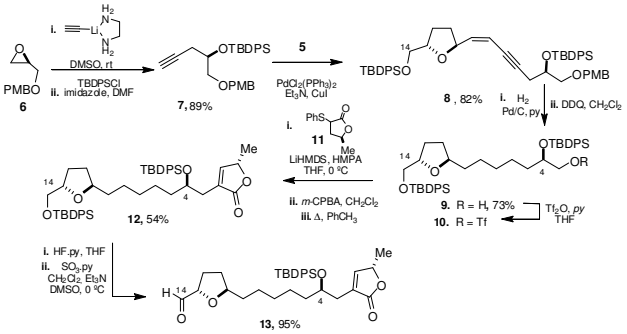
RESULTS AND DISCUSSION

Our approach began with construction of the C9-C14 fragment (**5**). Epoxide ring-opening of **2** by allylmagnesium bromide led to the hydroxyalkene **3** (90% yield). Subsequent oxidative-cyclization of **3** according to Mukaiyama's protocol,[2] provided *trans*-THF **4** (73% yield, ds >95:5). Oxidation of alcohol **4** followed by Wittig olefination provided iodide **5** (77% yield in 2 steps, *Z*:*E* > 95:5).



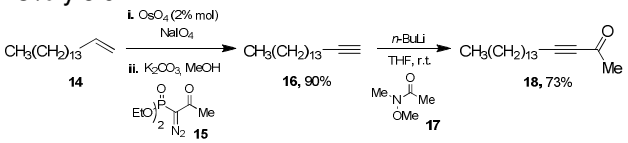
Scheme 2. Synthesis of iodide **5**.

The next step involved epoxide ring-opening of glycidol **6** followed by protection of the hydroxyl group with a TBDPS protecting group leading the alkyne (**7**) (89% yield). Sonogashira cross-coupling between **5** and **7** led to **8** in 82% yield.[3] Reduction of enyne by H_2/Pd-C followed by deprotection of PMB with DDQ led to **9** in 73% yield. Next, treatment of alcohol **9** with Tf_2O provided triflate **10**. The C-C coupling between triflate **10** and lactone **11** followed by oxidation of sulfide to the sulfoxide derivative with m-CPBA followed by thermal elimination led to butenolide **12** (54% yield, 3 steps). Selective deprotection of TBDPS followed by alcohol oxidation provided aldehyde **13** (95% yield, 2 steps).



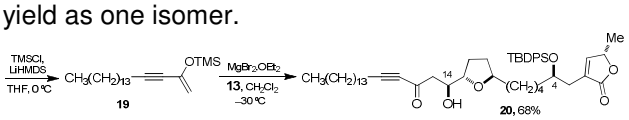
Scheme 3. Synthesis of aldehyde **13**.

The construction of fragment C15-C32 started by oxidative cleavage of terminal alkene **14** in presence of catalytic amounts of OsO_4 and $NaIO_4$ followed by Seyferth-Gilbert homologation providing alkyne **16** (90% yield).[4] Treatment of **16** with *n*-BuLi followed by Weinreb amide **17** provided methyl ketone **18** in 73% yield.



Scheme 4. Synthesis of methylketone **18**.

Chelation controlled Mukaiyama aldol reaction between **13** and enolsilane **19** (obtained from **18**) in the presence of $MgBr_2.OEt_2$ provided **20** in 68% yield as one isomer.



Scheme 5. Mukaiyama aldol reaction.

CONCLUSION

The synthesis of the C1-C32 fragment **20** of Goniotrionin (**1**) was achieved in 13 steps and 11% global yield. Studies aiming to confirmation of C14 stereochemistry are underway.

ACKNOWLEDGEMENTS

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