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Gaining Synthetic Appreciation for the Gedunin ABC ring system

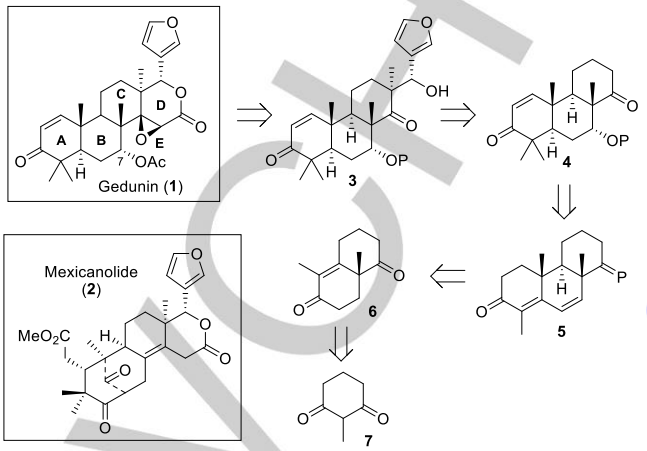
David M. Pinkerton, Timothy J. Vanden Berg, Paul V. Bernhardt and Craig M. Williams*[a]

Abstract: Gedunin, first isolated in 1960, displays a remarkable range of biological activity, but has yet to receive dedicated synthetic attention from a ground up construction perspective. Presented herein is a successfully executed approach to the fully-functionalized ABC ring system of this challengingly complex natural product.

The tetranortriterpenoid gedunin (**1**), which was first isolated from the West African timber *Entandrophragma angolense* by Taylor in 1960,[1-3] has been reported to exhibit antimalarial,[4] antifungal,[5] allergic response,[6] peptic ulcer,[7] anti-cancer,[8] eryptosis,[9] antifilarial,[10] and insecticidal[11] activity.[12] In terms of anticancer activity, however, gedunin (**1**) was explored through the use of a connectivity map, and found to exert antiproliferative activity through the heat shock protein Hsp90.[13] Gedunin (**1**) was later determined to interact with Hsp90 *via* a mechanism that does not involve competitive inhibition of ATP,[14] and therefore, the interaction of gedunin (**1**) with Hsp90 was viewed as structurally and mechanistically distinct from that of other Hsp90 active inhibitors.[15] More recent work has indicated that **1** binds directly to the co-chaperone protein, p23, leading to inactivation of the Hsp90 machinery.[16] Therefore, it is no surprise that gedunin (**1**) has attracted attention from medicinal chemists to potentially access unique Hsp90 modulatory ability for the treatment of cancer.[17]

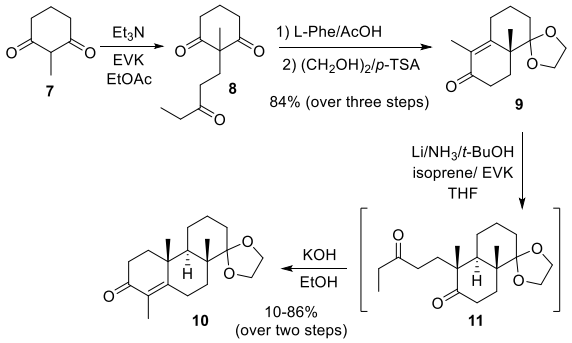
From a synthetic perspective, however, the majority of work in this area has been based on the derivitization of gedunin (**1**) itself, isolated from natural sources,[17,18] although Fernández-Mateos[19] and Lhommet[20] have used model systems to elegantly devise methods for the synthesis of the CDE ring system.[21]

In the view that in-depth medicinal chemistry, tackling all points of skeletal change, will be required in the near future, and that no laboratory synthesis is currently available, we initiated an ambitious investigation into the total synthesis of **1**. Retrosynthetically, we had initially hoped to incorporate aspects of our synthesis of mexicanolide (**2**),[22] but it was soon realized these were not applicable and a new approach was required. Such steroidal systems usually invoke deployment of intramolecular Diels-Alder (IMDA)[23] or polyene[24] type cyclisations, but the C-7 acetate burdens these approaches. Thus, it was hard to avoid entertaining the multifaceted Robinson annulation,[25] although incorporation of C-7 functionality onto the B ring has not previously been explored in this context. On this premise, further retrosynthetic analysis would see opening of the D and E rings to give an advanced intermediate akin to alcohol **3**, which would be derived from the key intermediate enone **4** (Scheme 1). Functionalisation of the B ring would most likely eventuate from tricycle **5**, ultimately obtained from a methylated Wieland–Miescher ketone (i.e. **6**), accessed *via* Robinson annulation of 2-methylcyclohexan-1,3-dione (**7**).



Scheme 1. Retrosynthetic analysis of gedunin (**1**) [P = protecting group].

Utilising the procedure described by Hanquet,[26] reaction of dione **7** with ethyl vinyl ketone (EVK) gave trione **8**, which underwent a Robinson annulation catalyzed by L-phenylalanine. This afforded after ketal protection, the enantio-enriched (ee 59%) methylated Wieland–Miescher ketone, obtained as the mono ketal protected surrogate (**9**) (Scheme 2). [Note: Although it was possible to procure enantiopure **9** via recrystallisation,[26,27] we chose to focus on developing a route towards the ABC ring system of gedunin without incurring losses associated with enantio-enrichment.] Annulation of **9** using a dissolving metal reduction, followed by conjugate addition and a Claisen condensation produced the target (**10**), *via* intermediate **11**. This sequence, however, was both delicate and capricious, giving yields in the range of 10-86%, with most reaction yields matching that reported for related systems (i.e. ~30%).[28] Nevertheless, this process was tolerated, because alternatives would substantially elongate the synthesis.



Scheme 2. Second ring annulation giving the initial ABC ring system framework **10**.

Manipulation of the B ring was the pivotal challenge to our endeavour, as the majority of work on closely related systems have not required oxygenation on the B ring.[21] Only in the case of Corey's polyene derived azadiradione synthesis[29] was a C-7 hydroxyl group required and this was laboriously achieved through a Barton type C-H functionalisation strategy. With this in

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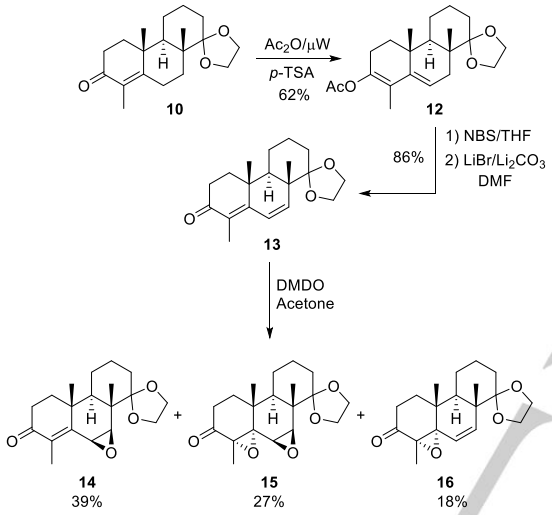
mind, we adopted from steroid chemistry the well-known two-step method for installing a B ring 6,7-double bond.[30]

Treatment of **10** with acetic anhydride in the presence of acid gave the dienol (**12**) in 40% yield. Subsequent exposure of this compound to *N*-bromosuccinimide (NBS) and base smoothly converted it into the desired dienone **13** in 76% (Scheme 3). However, the newly formed γ,δ-double bond was surprisingly unreactive towards standard double bond functional group manipulation protocols. Finally, the powerful and compact oxidant dimethyl dioxirane (DMDO) was found to induce epoxidation. This level of forcing conditions lead to the formation of multiple oxidation products,[31] which included, as the major product, the undesired 6β,7β-epoxide **14** in 39% yield (Scheme 3).



Scheme 3. Functionalisation of the B ring.

Epoxide **15** and the diepoxide **16**, obtained as minor products from the oxidation of dienone **13** with DMDO, provided crystals that were suitable for single-crystal X-ray analyses (Figure 1). Presumably, epoxidation of the A-ring was directed to the less-encumbered α-face by the axial methyl group at C-10. However, epoxidation on the B-ring proceeded *syn* with respect to the axial B-ring methyl groups as evinced by the single-crystal X-ray structure of compound **15**, and revealed by spectroscopic analysis of epoxide **14**. This indicated that another structural feature may be overriding the normal mode of reactivity expected for compound **13**.

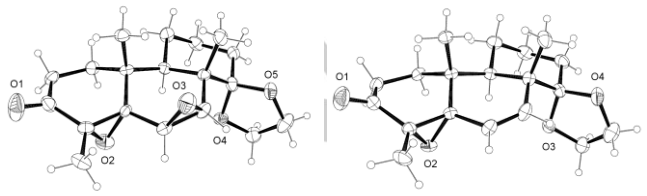
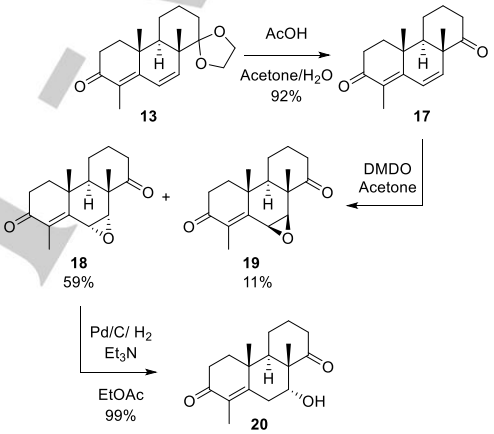


Figure 1 ORTEPs derived from single-crystal X-ray analyses of compounds **15** (left) and **16** (right). Anisotropic displacement ellipsoids show 30% probability levels.

Conformational assessment of **13** clearly showed that the dioxolane protecting group was substantially encumbering the α-face, thereby impeding reagent approach from that direction. To overcome this problem, the ketal was hydrolyzed to afford diketone **17**, which on subsequent epoxidation with DMDO gave the desired epoxide **18** as the major isomer in addition to a minor amount of the β-epoxide, **19** (Scheme 4). Cornered, with respect to working with an epoxide, it was thought advantageous to retain both ketones while enacting selective epoxide reduction. This requirement dramatically limited the range of suitable reductants. However, after extensively evaluating the reactivity of numerous systems (e.g. Al-Hg[22c,32] and NaI/Na_2SO_3[33]), only catalytic hydrogenation provided alcohol **20**. This remarkable reduction, which will not proceed in the absence of triethylamine, is quantitative and occurs almost instantaneously (Scheme 4).[34] Extending the duration of the reduction, however, led to the hydrogenation of the alkene in a process that was found to favour formation of the undesired isomer exhibiting *cis*-fusion at the AB ring junction.



Scheme 4. Stereoselective epoxidation and reductive ring opening.

Epoxides **18** and **19** were amenable to single-crystal X-ray analysis (Figure 2). The ORTEP diagrams were in accord with our stereochemical assignment of the epoxides and supported our hypothesis that removal of the dioxolane ring would restore conventional facial selectivity to reactions with the B-ring alkene.

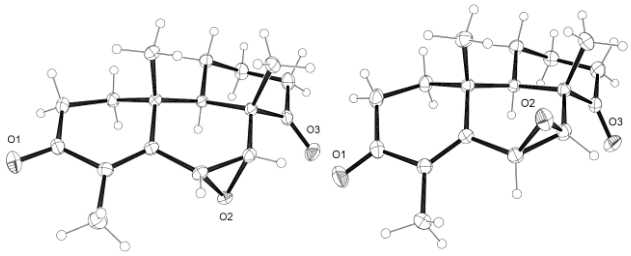
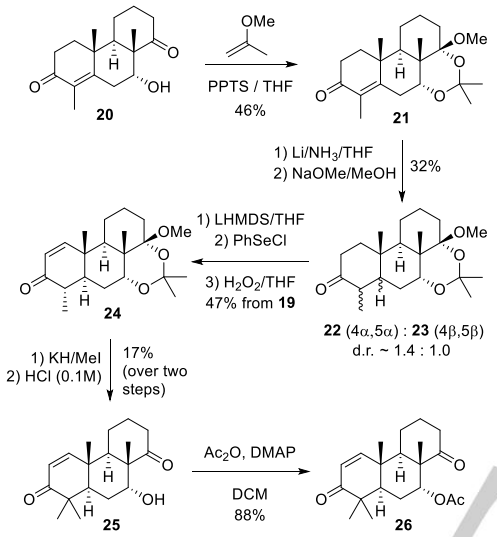


Figure 2 ORTEPs derived from single-crystal X-ray analyses of compounds **18** (left) and **19** (right). Anisotropic displacement ellipsoids show 30% probability levels.

Poised for completion of the fully decorated ABC ring system of gedunin (**1**), several significant hurdles remained, specifically distinguishing between the two keto functions. Ultimately, success was achieved by engaging the C-7 hydroxyl in the formation of bis-ketal **21**. Subjecting **21** to reduction by lithium in ammonia, followed by epimerisation with sodium methoxide, gave a slightly favourable ratio of desired ketone **22**, which underwent smooth two-step A-ring oxidation to enone **24**. The final stages of methylation and deprotection were unexpectedly difficult, but were finally overcome using potassium hydride and weakly acidic conditions, respectively. Subsequent acetylation of alcohol **25** proceeded efficiently and afforded the advanced intermediate (i.e. acetate **26**) (Scheme 5).



Scheme 5. Conversion of alcohol **20** into the fully decorated ABC ring system of gedunin (**1**), as embodied by acetate **26**.

In conclusion, an arduous synthetic campaign has secured the first route to the ABC ring system of gedunin (i.e. **26**) and exposed some of the difficulties associated with assembling this motif. Accordingly, these challenges may well have contributed to the deficiency of published synthetic studies directed towards gedunin. It is expected that this work will strategically inform subsequent approaches towards a total synthesis of gedunin (**1**) and related limonoid natural products. Lastly, it is our hope that lessons learned in this campaign will assist future medicinal chemistry surrounding this biologically important molecule.

Acknowledgements

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Keywords: gedunin • limonoid • epoxidation • catalytic hydrogenation • ATP

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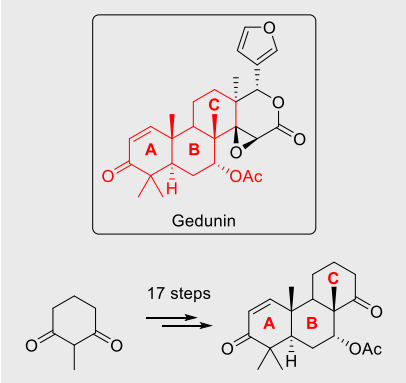
The complex limonoid natural product gedunin displays a remarkable range of biological activity, inspiring herein the first synthetic attention from a ground up perspective. The fully-functionalised ABC ring system of this challengingly complex molecule was obtained.



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