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Natural Products

Synthesis of the *seco*-Limonoid BCD Ring System Identifies a Hsp90 Chaperon Machinery (p23) Inhibitor

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Abstract: D-Ring-*seco*-limonoids (tetranortriterpenoids), such as gedunin and xylogranin B display anti-cancer activity, acting via inhibition of Hsp90 and/or associated chaperon machinery (e.g., p23). Despite this, these natural products have received relatively little attention, both in terms of an enabling synthetic approach (which would allow access to derivatives), and as a consequence their structure–activity relationship (SAR). Disclosed herein is a generally applicable synthetic route to the BCD ring system of the *seco*-D-ring double bond containing limonoids. Furthermore, cell based assays revealed the first skeletal fragment that exhibited inhibition of the p23 enzyme at a level which was equipotent to that of gedunin, despite being much less structurally complex.

Heat shock protein 90 (Hsp90),[1] and the Hsp90 co-chaperone machinery,[2] are molecular targets that are currently being clinically evaluated for their effectiveness in cancer therapy.[3] Natural products have been found to inhibit both the N- and C-terminus domains of this suite of enzymes.[4,5] Within this arena various tetranortriterpenoids (limonoids[6]) have been identified as Hsp90 and/or co-chaperone inhibitors. Furthermore, they display significant anti-cancer activity.[7]

Attempting to understand structure–activity relationships amongst the limonoids, however, has been complicated by the wide variety of highly oxidized and rearranged skeletal classes within this group. For example the Hsp90 inhibitor diacetylvilasinin (**1**)[8] maintains an intact ABCD limonoid ring skeleton, whereas Hsp90 inhibition was also observed with the C-ring *seco*-limonoid deacetylsalannin (**2**),[8] the A,D-ring *seco*-limonoid 7α-limonylacetate (**3**),[9] and kotschyin A (**4**) [and D (**5**)],[10] which are members of the B,D-ring *seco* class (Figure 1). Members of this later B,D-*seco* class also include andirolide N (**6**),[11] which inhibits sphingomyelin biosynthesis,[12] and xylogranin B (**7**) that affects Wnt signaling,[13] whereas the A,D-*seco*-limonoid deoxylimonin (**8**) displays anti-tumor activity;[14] however, these three examples (i.e., **6**–**8**) all contain a double bond in the D ring (Figure 1). The most prominent limonoid in the anti-cancer/Hsp90 space is the D-ring *seco* member gedunin (**9**),[15] which has an additional E-ring epoxide moiety also seen in **3** (Figure 1). Interestingly, gedunin was originally identified through a connectivity map to exert antiproliferative activity through Hsp90.[16] Shortly after this disclosure, gedunin was determined to engage Hsp90 through a mechanism unrelated to competitive inhibition of adenosine triphosphate (ATP).[17] Instead, gedunin and close relative 7-oxo-gedunin (**10**) (Figure 1) were found to inactivate the Hsp90 co-chaperone enzyme p23.[18] During this time only gedunin (**9**) has undergone extensive medicinal chemistry development, but these studies have concentrated on the peripheral functional groups in the pursuit of identifying more active inhibitors and understanding the key pharmacophore of the molecule.[19,20]

In terms of accessing skeletal fragments of the limonoid skeleton, the total syntheses of only a few limonoids have been reported [e.g., andirolide N (**6**) by Newhouse,[21] limonin (**11**) by Yamashita,[22] and mexicanolide (**12**) by our group,[23]], along with methodological studies (e.g., Fernández-Mateos,[24] Lhommet,[25] and by our group[26]),[27] but these efforts did not include biological evaluation against cancer cell lines nor Hsp90 machinery. This unfortunate situation has resulted in a lack of general understanding as to the potential active pharmacophore of these molecules. Inspired by this circumstance, we explored the *seco*-limonoid BCD ring system, focusing on developing and understanding a structure activity relationship (SAR) around the Hsp90 co-chaperone enzyme p23, with the aim of unearthing less complex inhibitors.

Before SAR could be performed, a general and flexible synthetic route to the BCD ring system was required. This aspect was achieved, albeit with numerous unforeseen challenges, by drawing on our previous synthetic experiences with mexicanolide (**12**)[23] and gedunin (**9**)[26] (Scheme 1).

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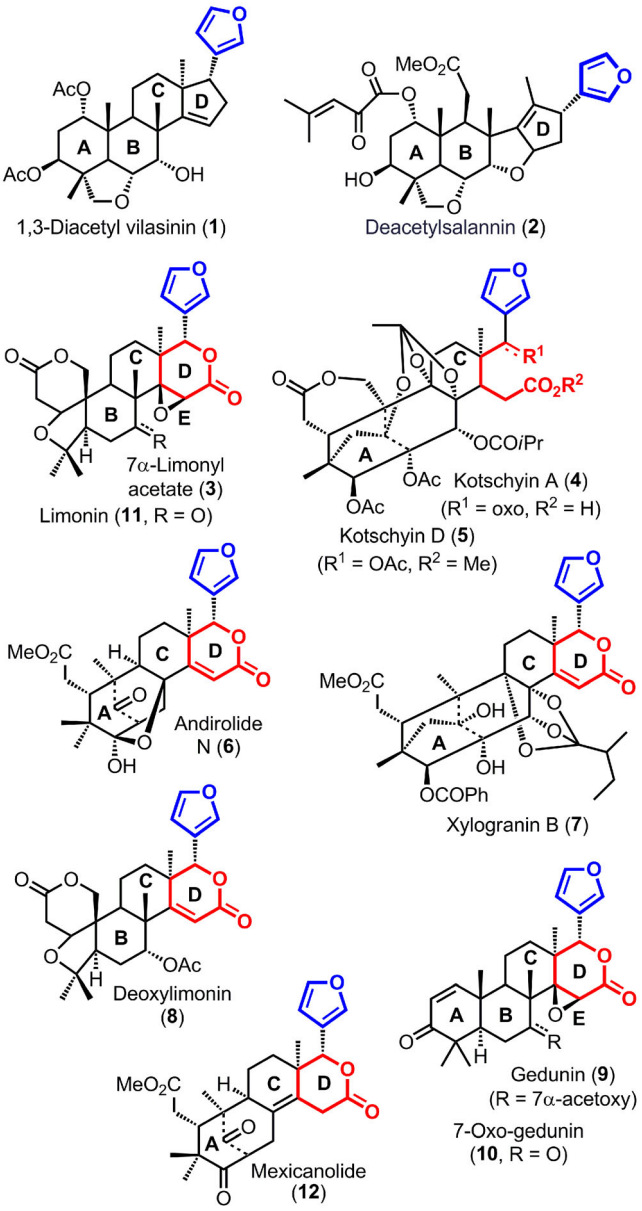
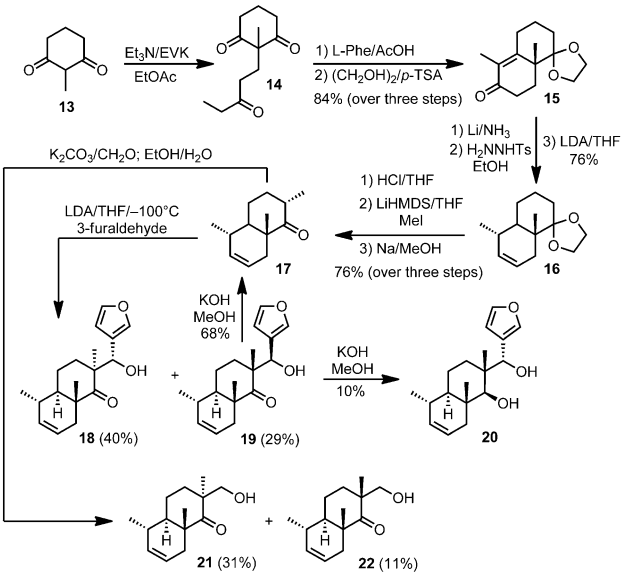


Figure 1. Select limonoids (tetranortriterpenes) that display anti-cancer activity. In the case of **1**–**5**, activity is exerted through inhibition of the enzyme Hsp90, whereas for **9** and **10** through the associated Hsp90 chaperon machinery enzyme p23. The *seco*-D-ring is highlighted in red emphasizing various oxidation modes, with the common 3-furyl ring system highlighted in blue.

Initially, the protocol described by Hanquet[28] was employed, which entailed reaction of dione **13** with ethyl vinyl ketone (EVK) to give trione **14**, which underwent a subsequent Robinson annulation[29] catalyzed by L-phenylalanine. This afforded, after ketal protection, the enantio-enriched (*ee* 59%) methylated Wieland–Miescher ketone, obtained as the monoketal protected surrogate (**15**) (Scheme 1). Dissolving metal reduction, followed by a Shapiro reaction, gave known ketal **16**,[30] which was deprotected and methylated to afford key intermediate **17** in 76% over three steps. With **17** in hand the critical Fernández-Mateos aldol reaction[24] could be performed. Normally, this transformation proceeds in a straightforward manner, providing the temperature is kept below −78 °C;[23]



Scheme 1. Building the functionalized BC ring system (i.e., **18**) and associated SAR derivatives.

however, substantial difficulties were encountered in isolating the products of this reaction. Eventually, it was discovered that lowering the temperature to −100 °C was required along with a rapid quench 1 min after addition of the 3-furaldehyde, so as to prevent the retro-aldol on warm up.

Although this set of conditions was capricious, the desired diastereomer (**18**) was regularly obtained in yields greater than 40% (i.e., setting up the functionalized BC ring system), the undesired diastereomer (**19**) in 29% yield, along with recovered starting material (10% yield). Fortunately, these could be recycled via retro-aldol by treatment with base in 68% yield, although the reduced ketone **20** was obtained as a minor by-product (10%) as a result of a Cannizzaro reaction of a minor diastereomer.[31] In readiness to evaluate the pharmacophore capacity of the furan ring within this system, intermediate **17** was also subjected to an aldol reaction with formaldehyde. Interestingly, unlike the difficulties encountered with 3-furaldehyde, the reaction proceeded with relative ease albeit requiring an elevated temperature of ≈60 °C (Scheme 1). Single-crystal X-ray analysis of compounds **18** and **20** confirmed the proposed stereochemical configurations (Figure 2).

To gain access to the BCD ring system, as well as diversity around this scaffold, advanced intermediate **18** was further ela-

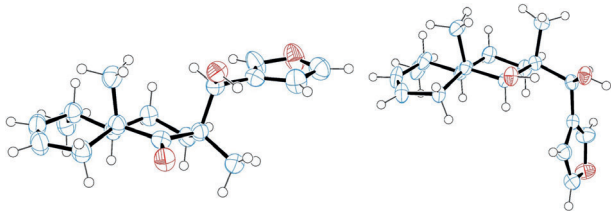
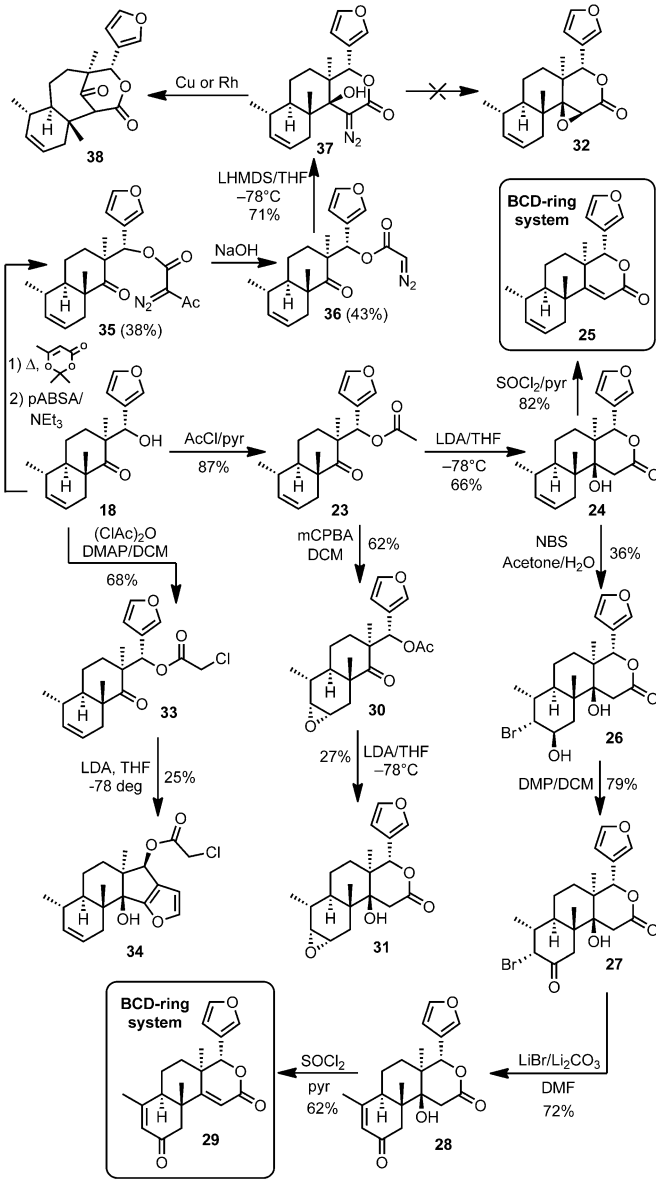


Figure 2. ORTEPs derived from single-crystal X-ray analyses of compounds **18** (left) and **20** (right). Anisotropic displacement ellipsoids show 50% probability levels.

borated in anticipation of building the D-ring and functionalizing the B-ring (Scheme 2). Acylation with acetyl chloride proceeded smoothly giving **23**, which was treated with lithium *N*,*N*-diisopropylamide (LDA) to afford the annulated BCD ring system **24** in 66% yield. Elimination of the tertiary β-hydroxyl to install the double bond seen in limonoids **6**–**8** (Figure 1) was achieved with thionyl chloride affording the target BCD ring system **25** in 82% yield. Focus then turned to derivatization of the B-ring with the aim of increasing oxygenation and electrophilic sites conducive to attack by biological nucleophiles (e.g., thiols).[32] To manipulate the B-ring double bond, however, a return to intermediate **24** was required to avoid side reactions with the D-ring enlactone. Initially, **24** was converted into the bromohydrin **26** with *N*-bromosuccinimide (NBS), which was then readily oxidized to ketone **27** with Dess–Martin periodinane. Stepwise double elimination to give **29** was then put to practice by first using lithium bromide and lithium carbonate followed by treatment of **28** with thionyl chloride under basic conditions (Scheme 2). Installation of an epoxide moiety into the B-ring of the BCD ring system could be achieved by first treating acetate **23** with *meta*-chloroperbenzoic acid (*m*CPBA) (i.e., **30**) followed by annulation with LDA to give **31** (Scheme 2). The final aspects of the synthetic work aimed to access an epoxide in the D-ring (e.g., **32**) to match the functionality seen in the limonin and gedunin family of tetranortriterpenes (i.e., **3**, **9**–**11** in Figure 1). Following the work of Abad,[33] an intramolecular Darzens reaction was attempted. Alcohol **18** was first chloroacetylated using chloroacetic anhydride to afford **33**. The chloroacetate was then exposed to LDA, and other bases, under a range of conditions, but only annulated by-product **34** (i.e., arising from lithiation of the furan ring) was observed (Scheme 2). A second attempt at forming the epoxide was pursued via carbene formation;[34] unfortunately, **35** and **36** failed to produce an epoxide (i.e., **32**). Even after first forming the D-ring diazo **37** followed by treatment with a metal catalyst (e.g., copper and rhodium), the epoxide still resisted formation, resorting instead to undergoing ring expansion to give **38** (Scheme 2).



Scheme 2. Completion of the bifunctionalized BCD ring systems (**25** and **29**), attempts at E-ring epoxide formation, and associated SAR derivatives.

Now having generated a range of enantio-enriched precursors and derivatives of the BCD ring system herein (i.e., **13**–**38**), and having access to a wide range of associated ABC ring system examples from previous studies (**39**–**46**, Figure 3),[26] selected compounds were evaluated for p23 activity with a progesterone receptor reconstitution assay[18] using rabbit reticulocyte lysate (RRL) as a source of molecular chaperones (Figure 4).

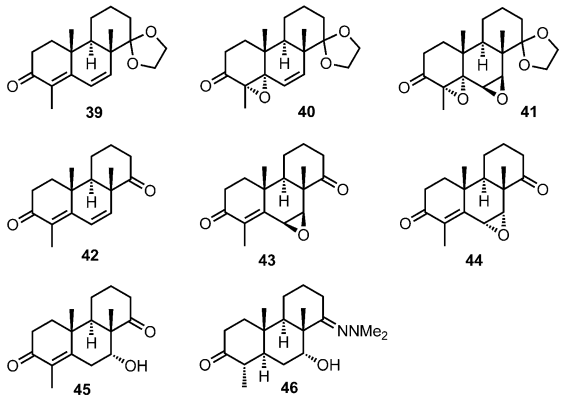


Figure 3. ABC ring system examples from previous studies (**39**–**46**).[26]

Although most compounds were much less inhibitory as compared to the active controls gedunin (**9**) and 17-AAG,[18] chloroacetate **33** showed reasonable activity. However, it was evident from the biological results that the more active compounds (e.g., **18**, **23**, **33**, and **34**) lacked the naturally occurring six-membered D-ring. Secondary analysis of **9** and **33** using the progesterone receptor (PR) reconstitution assay revealed that the activity was equipotent (see Supporting Information, Figure S2A). Similarly to gedunin, Coomassie blue analysis of

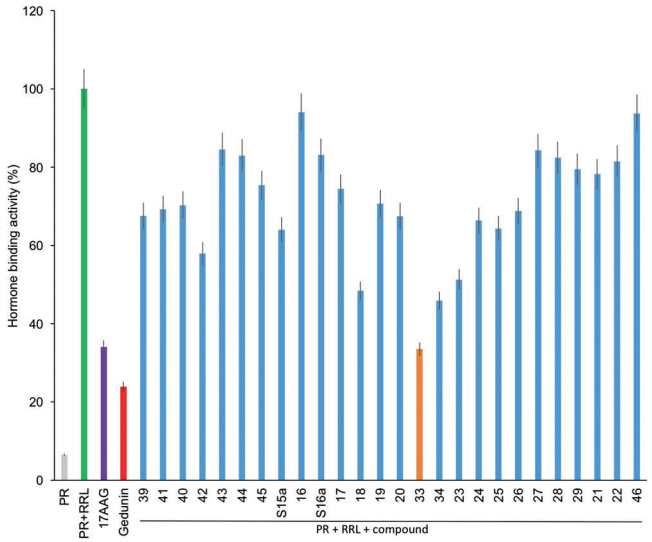


Figure 4. Progesterone receptor (PR) reconstitution assay (96-well plate). Standard protocol using rabbit reticulocyte lysate (RRL) as a source of molecular chaperones. Green: RRL control with DMSO; Purple: RRL with 17AAG; Red: RRL with gedunin (**9**); Gray: negative control with no RRL; Blue: Compounds tested herein except **35**–**38**. All compounds were tested in triplicates. Bars represent the maximum variation between triplicates (10%).

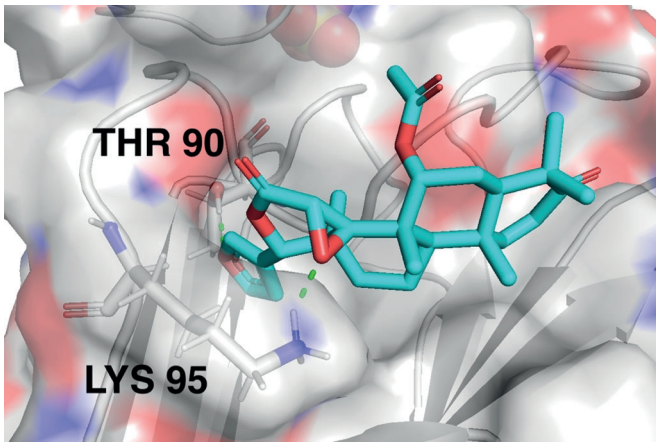


Figure 5. Pose of gedunin in the p23 binding site. Hydrogen bonds with LYS 95 (2.8 Å) and THR 90 (3.0 Å) are shown as green dashed lines.

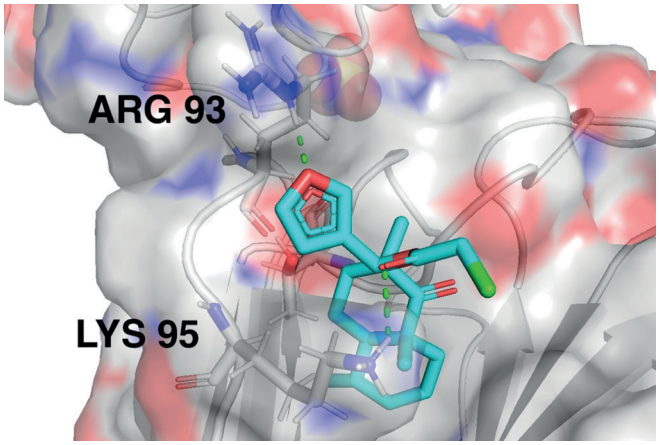


Figure 6. Docked pose of compound **33** into the p23 binding site, with hydrogen bonds to ARG93 (2.8 Å) and LYS95 (3.1 Å).

protein complexes showed that chloroacetate **33** does not induce accumulation of PR complexes rich in Hsp70 and Hop as does 17-AAG (see Supporting Information, Figure S2B). Furthermore, chloroacetate **33** was evaluated against the breast cancer cell lines E0771 and AT-3 giving IC_{50} values of 31 and 65 μM, respectively.

Given chloroacetates have previously found application in the clinic (e.g., lorajmine[35]), and in recent times various chloroacetamides[36] have been found to be potent and site-selective biological probes and covalent enzyme modulators, **33** was mapped onto the gedunin-binding site in p23 for comparison. Further comparison was also made using compounds **18**, **23**, **34**, and **36**.

To understand the likely mode of binding of gedunin (**9**) and 7-oxo-gedunin (**10**) to p23 a docking study was performed, which showed that the furan moiety (not the α,β-unsaturated ketone as suggested in a previous investigation[18]) of these two compounds forms hydrogen bonds with the side chain of THR 90 (i.e., see Figure 5 and Figure S1 in the Supporting Information). This result was obtained in a number of independent docking trials, with poses bound through the enone yielding substantially lower docking scores. The docking study also suggested that LYS 95 hydrogen bonds with the epoxide of gedunin, and is proximal to the epoxide in 7-oxo-gedunin (see Figure 5 and Figure S1). The higher affinity of 7-oxo-gedunin relative to gedunin is replicated in the docking results (docking score of 54 vs. 49); a hydrogen bond is observed between the 7-oxo-substituent of 7-oxo-gedunin and the amide backbone of VAL101 that is not possible for gedunin.

Docking calculations also showed compounds **23**, **33**, and **36** form hydrogen bonds with p23 residues LYS 95 and ARG 93 via their ester carbonyl and furan moieties, respectively (see Figure 6, and Figures S4 and S5 in the Supporting Information), which substantiates the observation from the inhibition data (Figure 4) that **9** and **33** maintain equal potency. In addition, **18** was found to bind consistent with the orientations of gedunin and 7-oxo-gedunin, with THR 90 hydrogen-bonded to the furan oxygen lone pair. It is notable that **18** lacked the ester moiety of the other inhibitors. Interestingly, and in contrast to the other compounds, **34** is predicted to adopt a distinct binding mode whereby the carbocyclic ring makes hydrophobic interactions with the binding pocket, in addition to hydrogen-bonding contacts with LYS 95 and the backbone amides of both LEU99 and VAL101. While the docking results are in agreement with the enzyme inhibition and cell based data (i.e., supporting the essential role of the BCD ring system), the open nature of the binding site and the absence of the C-terminus in the reported crystal structure (which is known to be essential for inhibitor binding[18]), limits firm deductions on whether binding truly occurs through the heterocyclic furan or the enone.

In conclusion, the first synthetic route to the BCD ring system of the unsaturated *seco*-D-ring limonoids has been

achieved. This study has in turn provided a selection of truncated structures to facilitate a structure activity relationship, which revealed the active pharmacophore of this limonoid class, and identified a lead p23 inhibitor, chloroacetate **33**.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: BCD ring · gedunin · Hsp90p23 · limonoids · medicinal chemistry · natural products

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Natural Products

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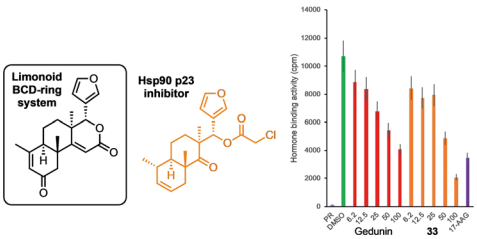
Synthesis of the *seco*-Limonoid BCD Ring System Identifies a Hsp90 Chaperon Machinery (p23) Inhibitor



The first synthetic route to the BCD ring system of the *seco*-D-ring limonoids has been devised. A synthetic intermediate displayed an equipotent p23 enzyme inhibitory effect to that of the more complex gedunin.