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Synthesis of resorcinylic macrocycles related to radicicol via ring-closing metathesis

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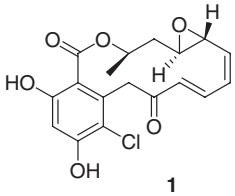
Abstract—Novel resorcinylic macrolides, for example, **17**, **24**, were prepared via ring-closing metathesis as analogues of the HSP90 inhibitor radicicol.

Radicicol **1**, is reported to inhibit the ATPase activity of the chaperone protein HSP90 with $K_D = 19$ nM.[1] Several oncogenic proteins are clients for HSP90 and are down-regulated when HSP90 is blocked.[2] There is therefore much current interest in developing inhibitors of HSP90 as drugs for cancer treatment.[3] Towards that end we have recently reported the discovery[4] by high throughput screening (HTS) of the novel pyrazole inhibitor **2**, and of potent inhibitors[5] based on this structure.



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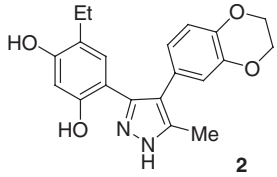

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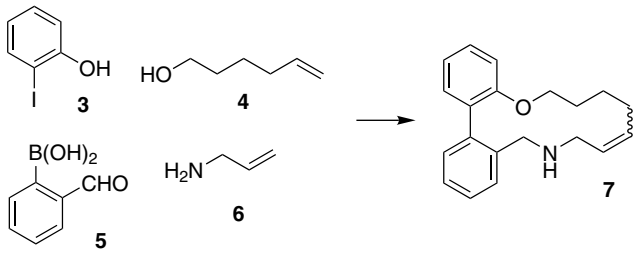
In the preceding letter,[6] we described the development of short modular synthetic routes to macrocyclic compounds related to radicicol, based on lactone formation as the cyclisation step. Because yields were modest we have since explored ring-closing metathesis[7] (RCM) as an alternative strategy for preparing collections of drug-like compounds related to radicicol. One objective is to extend the diversity of our biological screening collection by preparing drug-like compounds related to natural products.

A prototype 14-membered macrocyclic amine **7** was prepared from four fragments as outlined in Scheme 1. There is considerable scope for varying the substitution patterns in both phenyl rings, or replacing these by heterocycles; for varying ring size; and for introducing substituents by starting with appropriate aliphatic fragments. If compounds are found to show activity in biological screening assays the basic nitrogen allows the formation of water-soluble salts and is an additional site for the preparation of analogues.

To effect the synthesis of **7**, phenol **3** and alcohol **4** were converted to ether **8** under Mitsunobu conditions. Suzuki coupling of **8** with boronic acid **5** was followed by reductive amination with **6**. Boc-protection afforded cyclisation precursor **9** and the RCM cyclisation step to **7**



Scheme 1.

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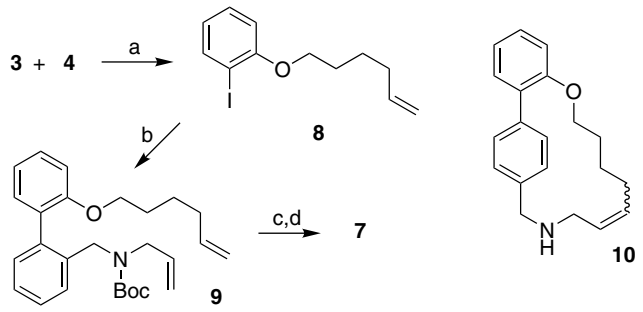
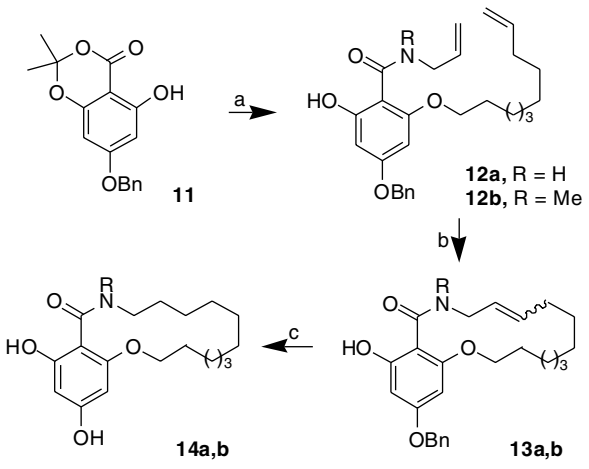


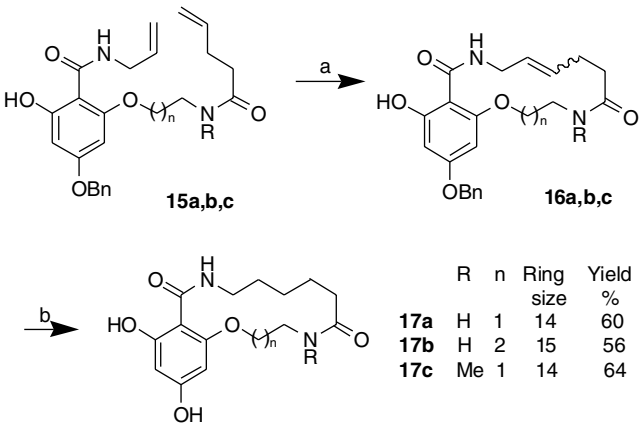
Scheme 2. Reagents and conditions: (a) DEAD, PPh_3, THF, rt (90%); (b) (i) 2-formylbenzene boronic acid **5**, $Pd(PPh_3)_4$, Cs_2CO_3, DMF, 12 h (50%), (ii) allylamine **6**, $NaBH(OAc)_3$, CH_2Cl_2, rt 16 h (65%), (iii) Boc_2O (90%); (c) $Cl_2Ru{=}CHPh(PCy_3)_2$ 0.1 equiv, CH_2Cl_2, reflux, 10 h (90%); (d) 1:1 TFA–CH_2Cl_2, rt, 30 min (90%).

gave an encouragingly high yield of 90%. Impressively, RCM cyclisation of the analogous precursor from 4-formylbenzene boronic acid gave the *para*-cyclophane **10** in 88% yield (Scheme 2).

When our studies on resorcinylic pyrazole inhibitors of HSP90 (discovered by high throughput screening) revealed that protein–phenol interactions contribute strongly to binding and inhibitory activity[4] we turned our attention to the synthesis of radicicol mimetics incorporating a resorcinol functionality. To provide a template suitable for elaboration to resorcinol-fused macrocycles 2,4,6-trihydroxybenzoic acid was reacted with acetone in trifluoroacetic acid/trifluoroacetic anhydride to give the benzodioxinone[8] followed by selective protection of the 4-hydroxy group by Mitsunobu reaction with benzyl alcohol. The free phenolic OH of **11** was converted into an alkene–ether via a second Mitsunobu reaction with dec-l-en-10-ol. Hydrolysis of the lactone protecting group and subsequent reaction with allylamine or *N*-methyl allylamine afforded the amide cyclisation precursors **12a** and **12b** (Scheme 3).



Scheme 3. Reagents and conditions: (a) (i) Dec-1-en-10-ol, DEAD, PPh_3, THF, 90%, (ii) 48% KOH–DMSO 1:1, 65 °C, 1 h, (iii) $RNHCH_2CH{=}CH_2$, EDC, HOBt, CH_2Cl_2, 3 h, 85–90%; (b) $Cl_2Ru{=}CHPh(PCy)_3$ 0.1 equiv, CH_2Cl_2, reflux, 2 h; (c) H_2/Pd–C, EtOH, 24 h, 100%.



Scheme 4. Reagents and conditions: (a) $Cl_2Ru{=}CHPh(PCy)_3$ 0.1 equiv, CH_2Cl_2, reflux, 2 h, 56–64%; (b) H_2/Pd–C, EtOH, 24 h, 100%.

These compounds underwent RCM to give 16-membered ether lactams **13a**,**b** with cyclisation yields of 85% and 62%, respectively. Catalytic hydrogenation effected deprotection and simultaneous alkene reduction to resorcinols **14a**,**b**.

Macrocycles **16a**–**c** and **17a**–**c** incorporating additional polar functionality were prepared from the dienes **15a**–**c** (Scheme 4). Dienes **15** were prepared from **11** by Mitsunobu reaction with an *N*-Boc-protected hydroxyamine, opening of the dioxinone ring, condensation with allylamine, removal of the Boc-protecting group and amide formation with pent-4-enoic acid.

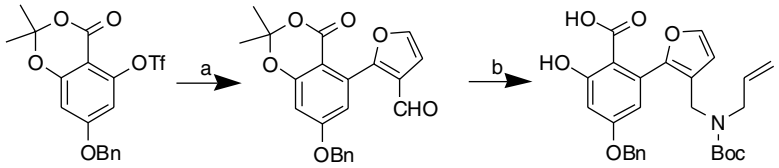
Finally, a small collection of furanyl macrocycles was prepared. These compounds have structural features in common with both radicicol and the resorcinylic pyrazole series of HSP90 inhibitors, for example, **2**, and incorporate a basic nitrogen atom to enhance aqueous solubility via salt formation, and to allow optimisation of properties by N-substitution.

Protected resorcinol **11** was converted to triflate **18** (using triflic anhydride in pyridine–dichloromethane) and palladium-catalysed arylation using 2-tributylstannyl-3-formylfuran gave aldehyde **19**. Reductive amination followed by Boc-protection and alkaline hydrolysis of the dioxinone afforded the phenolic acid **20** (Scheme 5).

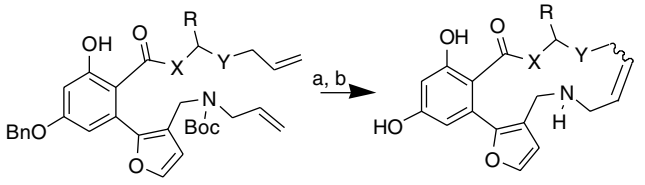
Acid **20** was converted to amide **21** and to the set of esters **22a**–**e**, and each precursor was cyclised by RCM using $Cl_2Ru{=}CHPh(PCy_3)_2$ in CH_2Cl_2 (Scheme 6). Yields are reported in Table 1.

Simultaneous removal of both benzyl and Boc-protecting groups was achieved by treatment with BCl_3 to afford olefinic resorcinols **23** and **24a**–**e**. The corresponding saturated macrocycles were obtained by hydrogenation.

In summary, we have developed short routes to a variety of macrocyclic lactones and lactams with incorporation



Scheme 5. Reagents and conditions: (a) 2-tributylstannyl-3-formylfuran, $Pd(Ph_3P)_2Cl_2$ DMF, 60 °C, 1 h; (b) (i) allylamine, $NaBH(OAc)_3$, 4 Å sieves, CH_2Cl_2, rt, 2 h, (ii) Boc_2O, CH_2Cl_2, 3 h, (iii) 48% KOH/DMSO, 65 °C, 1 h.



Scheme 6. Reagents and conditions: (a) $Cl_2Ru{=}CHPh(PCy)_3$ 0.1 equiv, CH_2Cl_2, reflux, 2 h; (b) BCl_3, CH_2Cl_2 (30–35%).

Table 1.

	X	Y	R	Ring size	Cyclisation yield (%)
21	NH	$(CH_2)_2$	H	15	56
22a	O	Bond	H	13	60
22b	O	CH_2	H	14	64
22c	O	CH_2	Me	14	83
22d	O	$(CH_2)_2$	H	15	62
22e	O	CH_2O	H	15	79

of resorcinol functionality.[9–11] Cyclisation to form 13- to 15-membered rings using ring-closing metathesis generally gave better yields of macrocyclic products than the lactonisation methods described in the previous letter.

The compounds were designed to have a topology resembling radicicol but with replacement of the undesirable epoxide and dienone functionality and introduction of amine and amide functional groups to provide potential sites for molecular recognition and for solubilisation. Six of these compounds are modest inhibitors (IC_{50} range 12–56 μM) of the ATPase activity of HSP90, and offer potential as starting points for the development of anti-cancer drugs. Assay details and structure–activity relationships (SAR) will be discussed in future publications.

Acknowledgements

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