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Development of synthetic routes to macrocyclic compounds based on the HSP90 inhibitor radicicol

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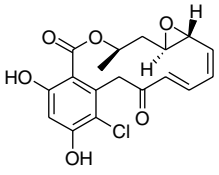
Abstract—Short routes are reported to novel macrolides (e.g., **9**, **12**, **20**) related to the HSP90 inhibitor radicicol.

Radicicol **1**,[1] a fungal natural product from *Monosporium bonorden*, is an inhibitor of the ATPase activity of the heat shock protein HSP90.[2] In cells HSP90 acts as a chaperone ensuring the correct folding of many client proteins including several that are implicated in cancer.[3] Inhibitors of HSP90 bring about depression of cellular levels of several oncogenic proteins and 17-AAG, a derivative of geldanamycin, is currently in Phase II trials for treatment of cancer.[4]



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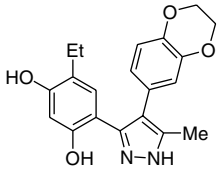

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We therefore initiated research aimed at the identification of small molecule inhibitors of HSP90 that might be developed as totally synthetic drugs. One of these studies resulted in the discovery, by high throughput screening, of a series of resorcinylic pyrazoles,[5] for example, **2** and has led to compounds with high potency both in vitro and in inhibiting the growth of cancer cells.[6] Here we describe an alternative approach to hit generation based on the natural product radicicol.[7]

Radicicol **1** inhibits yeast HSP90[2] with $K_D = 19$ nM: it is active in cells but not in vivo. Radicicol **1** has structural features, which are undesirable in a clinical drug candidate. The epoxide and dienone functionalities have the potential to react with nucleophiles in vivo resulting in rapid reduction of drug levels in tissues and potential toxicity due to modification of essential biopolymers. The phenols are likely to be metabolised by conjugation also leading to high clearance in vivo. We therefore decided to design short synthetic routes that would give access to collections of compounds resembling radicicol. The compounds should be devoid of electrophilic functionality, and the designs should allow preparation of analogues to enhance biological profile and confer drug-like properties including aqueous solubility.

Our initial approach, outlined in Scheme 1, would afford a collection of acetylenic lactone ($X = O$) and lactam ($X = NR^2$) macrocycles **6** with differing ring sizes. Combinatorial variation of the three starting materials would allow replacement of the resorcinol ring by a wide range of substituted phenyl or heteroaryl rings, and the versatile alkyne could be converted to various functional groups including (by hydration) the benzyl ketone of radicicol. The design includes a second ring heteroatom to afford an additional site for the preparation of analogues (NR^1) and for enhancing water solubility. Finally, fragments **4** and **5** could carry substituents, for example, alkyl, aryl on any of their carbon chain atoms.

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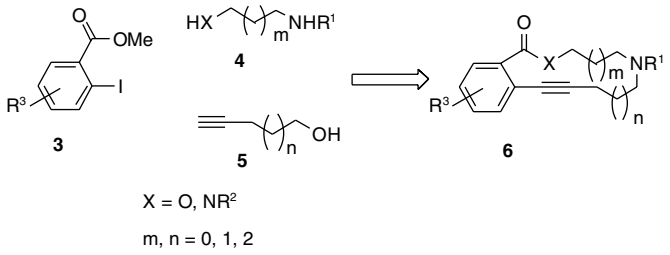
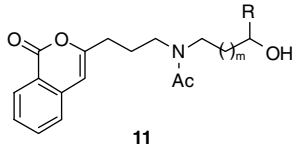


Scheme 1.

Sonogashira[8] coupling of methyl 2-iodo-benzoate (**3**, $R^3 = H$) and pentyn-5-ol (**5**, $n = 1$) in degassed piperidine[9] mediated by tetrakis(triphenylphosphine)palladium(0) and copper iodide gave the desired product **7** in 86% yield. The alcohol function of **7** was converted to either the triflate or the more stable 4-nitrobenzenesulfonate[10] and these activated substrates reacted with a variety of amino-alcohols followed by acetylation of the resultant secondary amine to give the hydroxy-esters **8** in yields of 60–86% (Scheme 2).

Liberation of the hydroxy-acid for cyclisation to the macrolide, through hydrolysis of esters **8**, proved to be problematic due to the formation of isocoumarin **11**.[13] However, careful monitoring of the hydrolysis reaction performed with LiOH in methanol at room temperature gave the desired hydroxy-acid and the isocoumarin as a 2:1 mixture, readily separable by flash chromatography.



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For the crucial step of macrocyclisation, success was achieved only with Yamaguchi's reagent.[11,12] Five prototype lactones were produced with 13–16-membered rings (Table 1).

Cyclisation of a parallel series of amino acids **10** was attempted using a number of reagents.[14] However, only one 13-membered macrolactam **12** was synthesised by closing the ring at a different position according to Scheme 3.

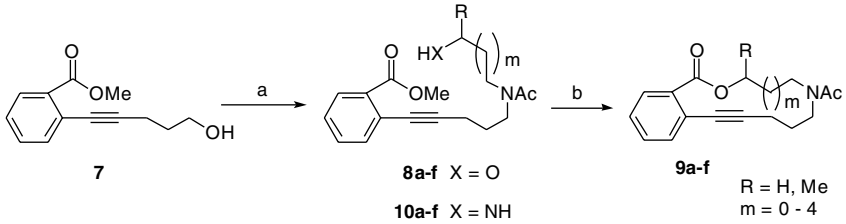
Table 1. Cyclisation yields for conversion hydroxy-esters **8** to lactones **9**

	m	R	Ring size	Yield % of **9**
a	0	Me	12	No product
b	1	H	13	63
c	2	H	14	28
d	3	H	15	32
e	3	Me	15	30
f	4	H	16	32

Modest yields in the foregoing cyclisation steps (0–63% for lactones, zero for lactams) were attributed to ring strain imposed by the linear character of the acetylene bond. The formation of macrolides should be more facile if the acetylene were replaced with a cis double bond but conversion of acetylenic precursors to intermediates with cis double bonds proved difficult.[16] Therefore, attention was switched to a new design (outlined in Scheme 4) incorporating an *ortho*-substituted aryl group in place of the acetylene. These target compounds **13** have an aryl fused macrocyclic structure that is not present in radicicol. However, the biaryl motif is found in the resorcinylic pyrazole series[5,6] of HSP90 inhibitors, for example **2**, and so these hybrid structures were of interest for increasing the diversity of our screening set.

Boronic ester **14** was synthesised by *ortho* lithiation of ethyl benzoate with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) followed by in situ reaction with triisopropyl borate; boronic ester exchange with 2,2-dimethylpropane-1,3-diol[17] then afforded **14** in 84% yield. Palladium mediated cross-coupling of **14** with iodides **15** and **16** afforded the biaryl compounds **17** and **18** in 74% and 54% yield, respectively (Scheme 5).

Aldehyde **17** was reductively aminated with 6-amino-hexan-1-ol and sodium triacetoxyborohydride, while

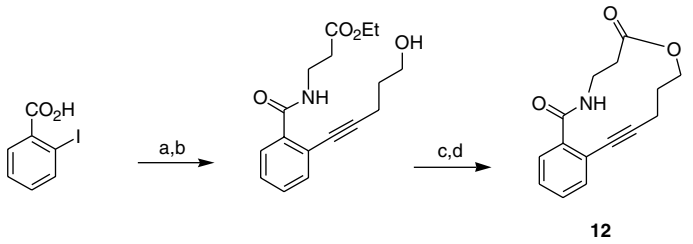


7 **8a-f** X = O **9a-f**

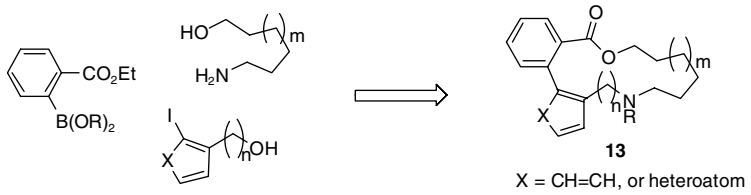
10a-f X = NH

R = H, Me
m = 0 - 4

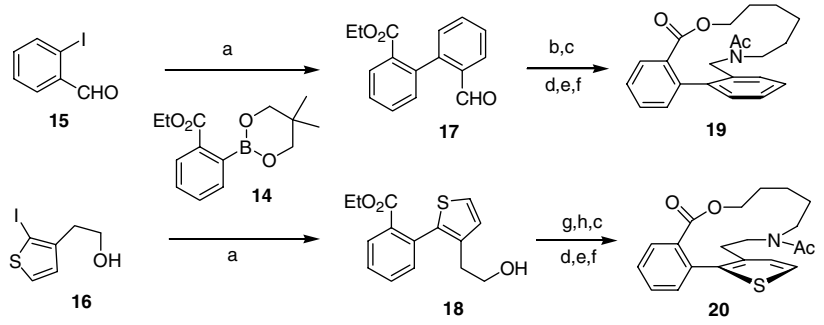
Scheme 2. Reagents and conditions: (a) (i) Tf_2O, Et_3N, CH_2Cl_2, 0 °C, 30 min or 4-$NO_2C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2, rt, 12 h; (ii) $H_2NCH_2(CH_2)_mCH(R)OH$, Et_3N, CH_2Cl_2, 12 h; (iii) Ac_2O, Et_3N, CH_2Cl_2, 12 h; (b) (i) LiOH (2 equiv), MeOH, rt, 4 h; (ii) Yamaguchi's reagent.[11] C_6H_6, DMAP, Et_3N, reflux, 16 h.



Scheme 3. Reagents and conditions: (a) $H_2NCH_2CH_2CO_2Et{\cdot}HCl$, EDC,[15] HOBt (90%); (b) 4-pentyn-1-ol, CuI, $Pd(PPh_3)_4$, piperidine (95%); (c) LiOH, MeOH (78%); (d) Yamaguchi's reagent[11] C_6H_6, DMAP, reflux, 24 h (22%).



Scheme 4. Proposed synthetic route to biaryl macrolides.

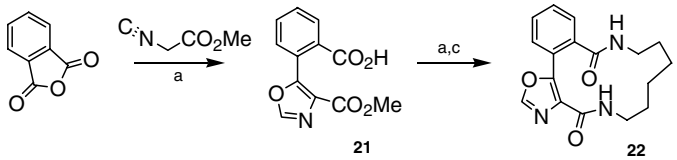


Scheme 5. Reagents and conditions: (a) $Pd(PPh_3)_4$, K_3PO_4, dioxane, 100 °C; (b) $H_2N(CH_2)_6OH$; (c) $NaBH(OAc)_3$; (d) Ac_2O, py, CH_2Cl_2; (e) LiOH, MeOH, rt; (f) Yamaguchi's reagent, C_6H_6, DMAP, Et_3N, reflux; (g) Dess–Martin; (h) $H_2N(CH_2)_5OH$.

alcohol **18** was oxidised (Dess–Martin periodinane) and the aldehyde product was reacted with 5-aminopentan-1-ol/sodium triacetoxyborohydride. The resultant secondary amines were acetylated and the required hydroxy acid precursors were generated by base catalysed hydrolysis of the ethyl esters. Macrolactonisation using the Yamaguchi reagent yielded the corresponding 14-membered lactones **19** and **20** in yields of 60% and 32%, respectively.

One further macrocycle was synthesised as shown in Scheme 6. Reaction of phthalic anhydride with methyl isocyanoacetate in the presence of DBU gave oxazole **21** in moderate yield. This was coupled to $BocNH(CH_2)_6NH_2$ via the acid chloride followed by hydrolysis of the methyl ester with bis(tributyltin)oxide (BBTO) in refluxing toluene.[18,19] Removal of the Boc group with HCl/dioxane gave the required amino acid, which was then cyclised with pentafluorophenyl diphenylphosphinate (FDPP)[20] to give 14-membered macrocycle **22** in 31% yield.

In summary, we have developed short modular syntheses to three classes of macrocycles that are topologically similar to radicicol but do not have the undesirable functionality found in the natural product.[21]



Scheme 6. Reagents and conditions: (a) DBU, THF, rt, 24 h (56%); (b) (i) $(COCl)_2$, Et_3N, (ii) $BocNH(CH_2)_6NH_2$ (76%); (c) (i) BBTO, PhMe, reflux, 24 h, (ii) HCl, dioxane, (iii) FDPP, DMF, rt, 38 h (31%).

Acknowledgements

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