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Synthesis of a versatile metacyclophane macrolactam

Mingwen Wang and Brian S. J. Blagg*

Department of Medicinal Chemistry, The University of Kansas, 1251 Wescoe Hall Drive, Malott 4070, Lawrence, KS 66045-7563, United States

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Abstract—As Hsp90 has emerged as a promising target for the development of cancer chemotherapeutics, so has the need for systematic evaluation of structure–activity relationships between natural product inhibitors and this molecular chaperone. Utilizing our chimera approach, which encompasses the quinone moiety of geldanamycin and the resorcinol moiety of radicicol, molecules have been produced that are highly effective inhibitors of the Hsp90 protein folding machinery. These chimeric inhibitors contain metacyclophane macrolactams that are difficult to cyclize and modify for incorporation of functional diversity. To circumvent this problem, a highly diversifiable α-bromo-α,β-unsaturated ester has been prepared, which allows for the introduction of various functionalities that enable elucidation of structure–activity relationships between chimeric compounds and Hsp90. The rationale, synthesis, and optimization for such a molecule is reported herein.

1. Introduction

Recently, the 90 kDa heat shock proteins (Hsp90) have attracted a great deal of interest as targets for the development of cancer chemotherapeutics.[1–3] Likewise, the discovery and synthesis of novel Hsp90 inhibitors have also become increasingly important.[4] The two natural product inhibitors, radicicol and geldanamycin (Fig. 1) have been shown to inhibit the Hsp90-mediated protein folding process at low to mid nanomolar concentrations against various cancer cell lines.[2] However, structure–activity relationships for geldanamycin have been limited by the fact that only one total synthesis of this molecule has been reported to date and it required an excess of 40 synthetic transformations.[5] As a result, derivatives of geldanamycin reported thus far represent only those that are accessible through modification of the natural product. In contrast, the total synthesis of radicicol has been reported and the most recently utilized a [4+2] cycloaddition for installation of the resorcinol ring as reported by Danishefsky and co-workers.[6,7] Unfortunately, radicicol manifests no activity in vivo as it is rapidly converted to inactive species as a result of its highly electrophilic nature (α,β,γ,δ-unsaturated ketone and allylic epoxide).[8] Consequently, there remains a tremendous interest in the development of new inhibitory scaffolds of the Hsp90 protein folding machinery.

To circumvent these issues and to elucidate structure–activity relationships between these natural products and Hsp90, we have proposed the construction of chimeric inhibitors that contain the resorcinol moiety

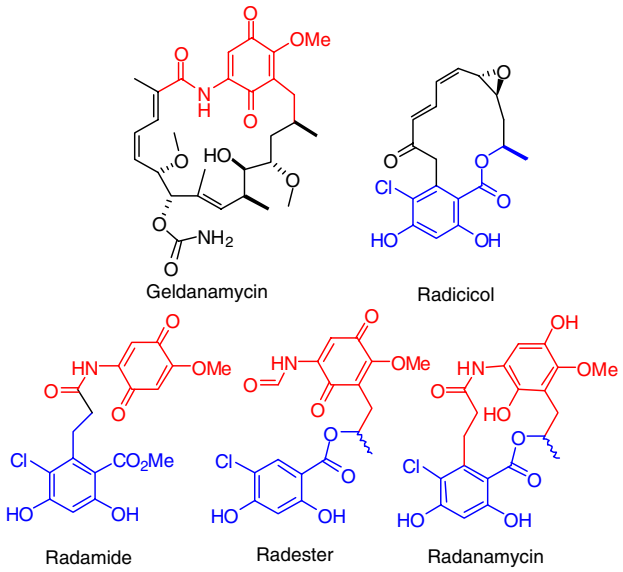

Figure 1. Natural product and chimeric inhibitors of Hsp90.

* Corresponding author. Tel.: +1 785 864 2288; fax: +1 785 864 5326; e-mail: bblagg@ku.edu

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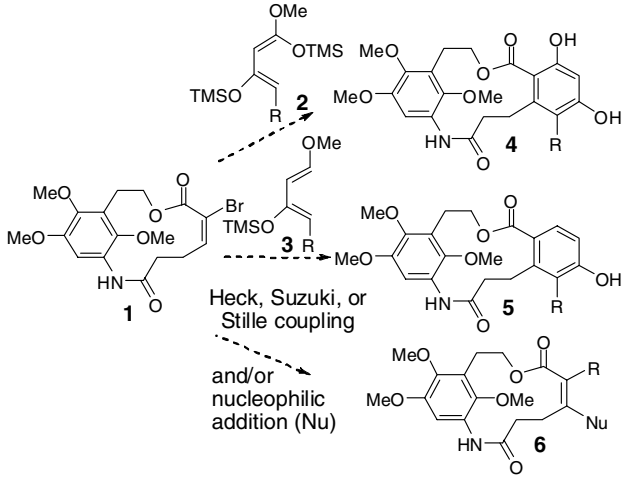
of radicicol and the quinone ring of geldanamycin. Appropriately, the chimeric molecules were named radanamycin[9] for the macrocyclic compound and radamide/radester[10,11] for the *seco*-derivatives as shown in Figure 1.

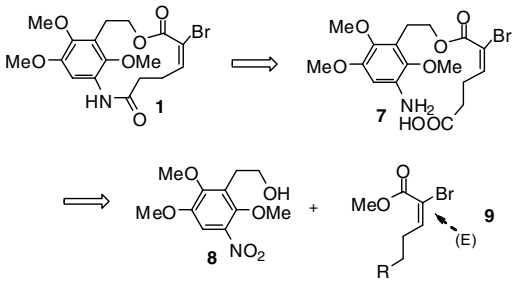
Of the three chimeric species reported thus far, the macrocyclic compound, radanamycin, manifested the most potent activity against several cancer cell lines with an IC_{50} value in the mid to high nanomolar range.[9b] Upon further inspection of the co-crystal structures of radicicol and geldanamycin bound to Hsp90, it was realized that additional functionalities may be tolerated or lead to increased inhibitory activity by modification of the resorcinol moiety of radanamycin.

It was hoped that a macrocyclic inhibitor could be prepared through a mechanism that allowed for modification of the resorcinol moiety, as this functionality appears important for inhibitory activity. Therefore, we chose to prepare a macrocyclic precursor (**1**) to radanamycin, which could then be diversified via a number of chemical transformations (Scheme 1). For example, it was envisioned that **1** could undergo a [4+2] cycloaddition with **2** or **3** to provide the corresponding phenols upon rearomatization of the Diels–Alder cycloadducts. Likewise, it was proposed that the electrophilic nature of the α-bromo-α,β-unsaturated ester could allow for introduction of various functionalities at both the 3- and 4-positions and enable survey of additional structure–activity relationships for this class of inhibitors and the proximal region of the binding site.

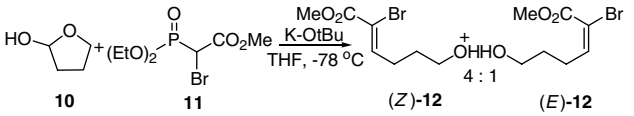


Scheme 1.

Retrosynthetically, **1** was envisioned to be constructed through a macrolactamization, which was aided by the (*E*)-configuration of the α,β-unsaturated ester, allowing for closure of the metacyclophane 14-membered ring. The homobenzylic alcohol was prepared as previously described[9b] with minor modification, however, the α-bromo-α,β-unsaturated ester required ample development before a succinct protocol was produced.

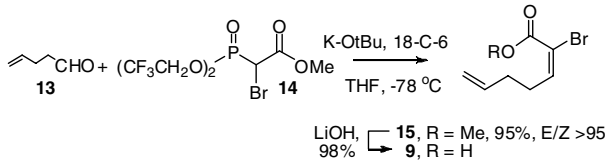


Initial attempts to prepare the α,β-unsaturated ester involved the use of a modified Horner–Wadsworth–Emmons reagent **11**,[12] which gave predominately the (*Z*)-configured bromoacrylate under all conditions investigated. An example of which is given in Eq. 1, wherein treatment of lactol **10** with **11** produced a 4:1 mixture of isomers in favor of (*Z*)-**12** (Eq. 1).



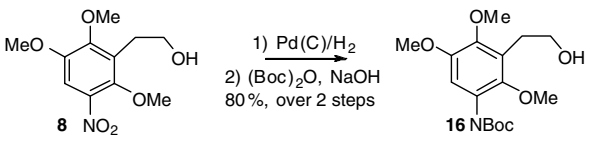
(1)

In contrast, when the bromo substituted bis(trifluoroethoxy)phosphonoacetate (**14**) was prepared as reported by McKenna[13] and reacted with the appropriate aldehyde (**13**) under Still–Genari conditions,[14] the desired (*E*)-α-bromoacrylate, **15**, was afforded in excellent yield following purification by flash chromatography (Scheme 2). The corresponding acid **9** was provided upon treatment of **15** with lithium hydroxide in a heterogeneous solution of tetrahydrofuran and water (3:1). Interestingly, when a homogenous solution of tetrahydrofuran, water, and methanol (3:1:1) was used, isomerization readily occurred to give (*Z*)-acid **9** exclusively.



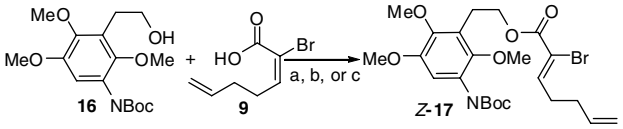
Scheme 2.

With the bromoacrylate in hand, the nitrated trimethoxyphenethanol **8** was prepared as previously described.[9b] However, due to incorporation of the α,β-unsaturated ester into the macrocyclic product, it was necessary to reduce the nitro substituent prior to coupling with the acrylate. Therefore, the nitro group was reduced to the corresponding amine and subsequently masked as the *t*-butyl carbamate **16** as shown in Eq. 2.



(2)

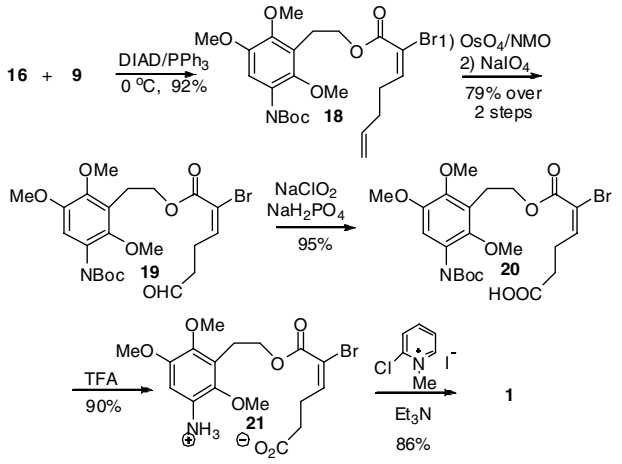
Coupling of acid **9** with homobenzylic alcohol **16** proved difficult as the olefin underwent isomerization under the majority of conditions that produced the ester product. For example, when the more frequently used coupling reagents were employed such as DCC/DMAP, EDCI/DMAP, or oxalyl chloride/triethylamine, only the undesired (*Z*)-α-bromoacrylic ester **17** was obtained as depicted in Eq. 3.



conditions: a) DCC/DMAP; b) EDCI/DMAP; c) $(COCl)_2$/TEA

(3)

Instead of using standard coupling protocols, which utilize the activated carboxylate as the electrophile, we chose to reverse the reactive nature of these partners. Under Mitsunobu conditions,[15] homobenzylic alcohol **16** underwent smooth displacement by carboxylate **9** to afford the corresponding ester (**18**) in high yield and without isomerization of the double bond. Subsequent chemoselective oxidation of the terminal olefin to the requisite aldehyde (**19**) was accomplished via osmium-mediated dihydroxylation,[16] followed by oxidative cleavage with sodium periodate.[9] The aldehyde was then oxidized to acid **20** under relatively neutral conditions,[9,17] before the *t*-butyl carbamate was removed upon exposure to trifluoroacetic acid. The resulting amino acid (**21**) was treated with various coupling reagents that proved to be unproductive, as undesired compounds represented the vast majority of products. However, Mukayama's reagent[18,19] proved especially effective in this transformation and in the presence of triethylamine, the metacyclophane 14-membered macrolactam, **1**,[20] was produced in exceptionally good yield (Scheme 3).



Scheme 3.

2. Conclusion

In this Letter, a highly diversifiable α-bromo-α,β-unsaturated metacyclophane macrolactam has been prepared using a Still–Gennari reaction and a Mukayama reagent-promoted lactamization as pivotal steps. Construction of this 14-membered ring allows for incorporation of multiple functionalities that will enable elucidation of structure–activity relationships between chimeric compounds and Hsp90. Utilization of this scaffold and biological evaluation of new Hsp90 inhibitory scaffolds are now in progress and will be reported in due course.

Acknowledgment

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20. Compound **1** was prepared and fully characterized as described below: to a mixture of **21** (246 mg, 0.57 mmol) and Et_3N in $ClCH_2CH_2Cl$ (300 mL) was slowly added 2-chloro-1-methylpyridinium iodide (220 mg, 0.86 mmol). The mixture was stirred for 20 h at rt. The solvent was

removed under reduced pressure and the residue was purified via chromatography (SiO_2, 60% EtOAc in hexanes) to afford **1** (206 mg, 86%) as a colorless solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (s, 1H), 6.67 (s, 1H), 6.46 (t, $J = 7.4$ Hz, 1H), 4.60 (m, 1H), 4.43 (m, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 3.31 (m, 1H), 3.01 (m, 2H), 2.14 (m, 2H), 1.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.9, 163.8, 150.4, 149.8, 147.6, 142.3, 126.1, 125.7, 114.2, 111.2, 66.8, 61.8, 61.4, 56.4, 34.0, 27.4, 23.8; IR (film) ν_{max} 3380, 2340, 1714, 1668, 1489, 1463, 1344, 1244, 1217, 1172, 1095, 1009 cm^{-1}; HRMS (TOF-ES+) found 414.0579 ($M+H^+$), calcd 414.0552 for $C_{17}H_{21}NO_6Br$.