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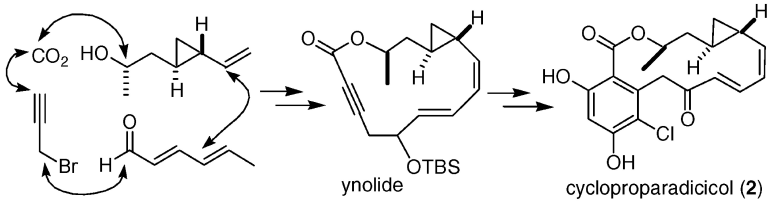
J. Am. Chem. Soc., **2003**, 125 (32), 9602-9603• DOI: 10.1021/ja036192q • Publication Date (Web): 17 July 2003



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A Concise Route to Benzofused Macrolactones via Ynolides: Cycloproparadicicol

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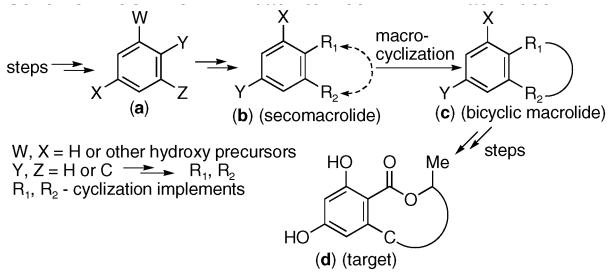
Nature produces a variety of biologically active products (presumably of polyketide genesis), which are comprised of a resorcinylic moiety fused to a macrolactone (cf., **d**).[1] Two early examples of such systems are zearelenone[2] and lasodiplodin.[3] The general approaches to building such compounds in a chemical laboratory have followed, broadly, the sequence format shown in Scheme 1: (i) assembly of an aromatic core, with an actual or virtual resorcinylic functionality bearing minimal benzyl-like handles (cf., **a**); (ii) chain extension of these minimal implements to reach a macrocyclization candidate structure (see **b**); (iii) macrocyclization, followed by (iv) late stage deprotection and other functional group adjustments (see **1**) to reach the target.[1]

Recently, a 14-membered resorcinylic macrolide, radicicol[4] (**1**, Scheme 2), attracted our attention due to its novel antitumor properties. Originally isolated form *M. bonorden*,[4] radicicol shows a high affinity binding to (K_d = 20 nM) and inhibition of the Hsp90 molecular chaperone.[5] Our interest in radicicol arose from a larger program directed to Hsp90 as a potential target in cancer chemotherapy.[6] Other inhibitors of the action of Hsp90 on key cancer related client proteins are based on geldanamycin (**3**) scaffolds.[7] Radicicol, which is also a nanomolar inhibitor of Hsp90, avoids the potential liabilities of the quinone moiety of the geldanamycins. Not surprisingly, in view of our experiences in the epothilone area,[8] we were concerned that the epoxide linkage of **1** might serve as a locus of nondiscriminating cell toxicity. As recently described, we "edited out" the oxido function of **1** through total chemical synthesis, replacing it with a cyclopropane group (see cycloproparadicicol **2**, Figure 1).[9] Following early assessments, **2** is a candidate for drug development, or minimally, a promising lead structure warranting optimization.[9] However, for these goals to be pursuable, it would be necessary to devise a far more efficient and concise total synthesis of precursors to **2** and **2** itself, than had hitherto been accomplished. The chances for achieving major progress through fine-tuning and optimization of our previous synthesis seemed none too promising.

Below, we report a new approach to the broad family of resorcinylic fused macrolides. The underlying concept is captured graphically in Scheme 2, which is directed to our focusing target, cycloproparadicicol (**2**). However, as is suggested by the very facile synthesis of model compound **13** (vide infra), and has been further established in ongoing work,[10] the method is quite general. The central element of our plan is the building of an "ynolide" intermediate and its advancement to the benzomacrolide by a Diels−Alder cycloaddition. The ynolide is constructed through olefin metathesis, enabled only by presentation of the acetylene linakge as its dicobalt hexacarbonyl cluster (see **9** → **10** and **14** → **15**).[11]

Scheme 1. Common Approach to Resorcinylic Macrolides



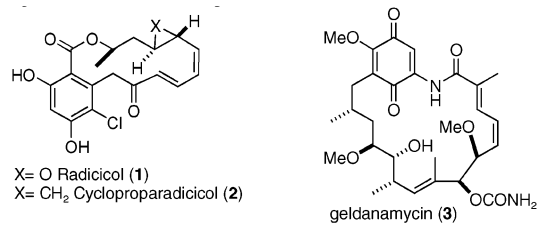
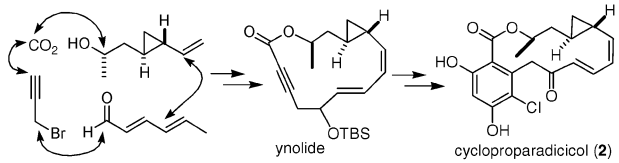
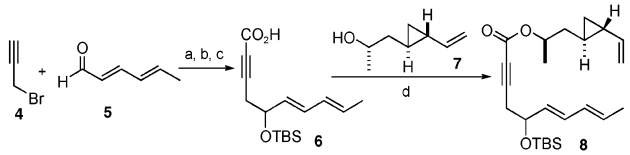


Figure 1. Structures of Hsp90 inhibitors.

Scheme 2. New Synthetic Strategy



Scheme 3. Synthesis of the Acyclic Alkynoic Ester[a]



[a] Reagents and conditions: (a) (i) Zn, THF, 66%; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, 100%; (c) BuLi, −78 °C; then CO_2; (d) DIAD, Ph_3P, THF, −20 °C, 47% (two steps).

Our synthesis commenced with commercial 2,4-hexadienal (sorbaldehyde, **5**, Scheme 3). Reformatsky-like condensation of propargyl bromide (**4**) with **5**, followed by TBS ether protection and subsequent reaction of the lithium alkynide ion with CO_2, provided acid **6**. Following reaction of racemic **6** and the known optically pure and defined alcohol **7**[9] under Mitsonobu conditions, ester **8** was obtained.

Projected ring-closing metathesis (RCM) reactions were conducted with a cyclic alkyne. Unfortunately, triene **8** failed to cyclize under a variety of RCM conditions. We took this negative finding to reflect impediments to cyclization arising from the linear

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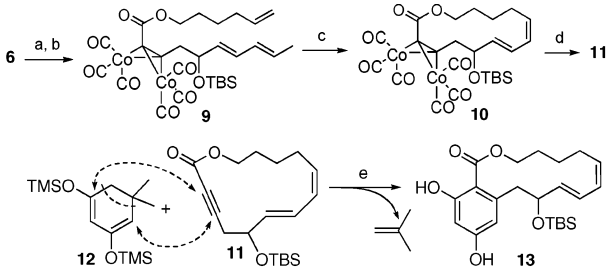
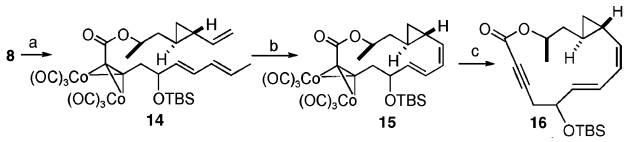
10.1021/ja036192q CCC: $25.00

Scheme 4. Synthesis of the Model Resorcinylic Macrolactone[a]



[a] Reagents and conditions: (a) 5-hexen-1-ol, EDC/DMAP, CH_2Cl_2, 59%; (b) $Co_2(CO)_8$, PhMe, 86%; (c) second generation Grubbs catalyst (25 mol %), CH_2Cl_2 (0.2 mM), 45 °C, 71%; (d) CAN, acetone, −10 °C, 92%; (e) 140 °C, neat; then SiO_2, 60%.

Scheme 5. Synthesis of the Ynolide[a]



[a] Reagents and conditions: (a) $Co_2(CO)_8$, PhMe, 100%; (b) second generation Grubbs catalyst (25 mol %), CH_2Cl_2 (0.2 mM), 45 °C, 57%; (c) I_2, THF, 0 °C, 69%.

character of the acetylene, possibly aggravated by rigidities associated with the trans-disubstituted cyclopropane. A more flexible model compound was prepared from acid **6** and 5-hexen-1-ol and was subjected to RCM reactions (Scheme 4). Again, only starting material was recovered. Aside from the constraint to cyclization imposed by linear alkyne, the cyclization could further be complicated by nonproductive coordination of the acetylene to the RCM catalytic machinery. It is well known that reaction of dicobalt carbonyl with acetylenes can lead to stable complexes,[12] wherein the geometry of cobalt-complexed alkynes is distorted to approximately 140°.[13]

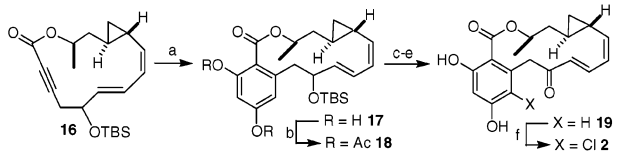
In the event, cyclization of **9** proceeded smoothly under the conditions shown. Following oxidative removal of the cobalt using ammonium cerium(IV) nitrate (CAN), the desired cyclic alkynoic ester **11** was generated in high yield (Scheme 4).

Construction of the resorcinylic skeleton called for a Diels−Alder reaction of **11** with a 1,3-bis-oxygenated diene. We found that the known dimedone-derived diene, 5,5-dimethyl-1,3-bis-trimethylsilyloxycyclohexa-1,3-diene[14] (**12**, Scheme 4), served our purpose best. Indeed, Diels−Alder reaction of cyclic alkyne **11** with **12** proceeded smoothly at 140 °C, providing the desired aromatic product **13** in 60% yield, after concomitant retro-Diels−Alder loss of isobutene from the initial adduct and hydrolysis of the trimethylsilyl ether groups during chromatography.

We applied this strategy to the targeted system (**8**). Gratifyingly, under the same RCM conditions, cyclopropane-containing cobalt complex **14** cyclized to give **15** in 57% yield, as a 2:1 mixture of two diastereomers (Scheme 5).[15] In this case, removal of cobalt on **15**, however, proved to be challenging, presumably due to the presence of the sensitive vinyl cyclopropane functionality. After screening a variety of conditions, we found that I_2−THF worked best.[16] The key cyclic alkyne dienophile **16** was thus obtained in 69% yield.

Diels−Alder reaction of **16** with diene **12** furnished the desired product **17** in 75% yield (Scheme 6). Transformation of **17** to the desired ketone by direct oxidation turned out to be a nontrivial

Scheme 6. Completion of the Synthesis[a]



[a] Reagents and conditions: (a) **12**, 140 °C, neat, 75%; (b) Ac_2O, DMAP, DMF, 87%; (c) HF/Pyr. THF; (d) Dess−Martin periodinane, CH_2Cl_2, 68% (two steps); (e) 5% $NaHCO_3$/MeOH, 92%; (f) SO_2Cl_2, CH_2Cl_2, 0 °C, 61%.

matter. In the end, it was accomplished following protection of the two phenolic functions, as shown, by straightforward transformations to afford dechlorinated analogue **19** (Scheme 6). Finally, regioselective chlorination of **19** using SO_2Cl_2 in CH_2Cl_2[9,17] converted **19** into cycloproparadicicol (**2**).

In summary, a new efficient synthetic route has been developed for a preclinical candidate, cycloproparadicicol (**2**), and, by extension,[10] to a broad range of benzofused macrolactones.

Acknowledgment. Support for this research was provided by the National Institute of Health (CA28824). Dr. Geoge Sukenic and Anna Dudkina are acknowledged for NMR and mass spectrometric analysis. We thank Drs. Kana Yamamoto and William Berkowitz for helpful discussions.

Supporting Information Available: Experimental procedure and physical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA036192Q