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A Versatile Approach toward the Ansamycin Antibiotics

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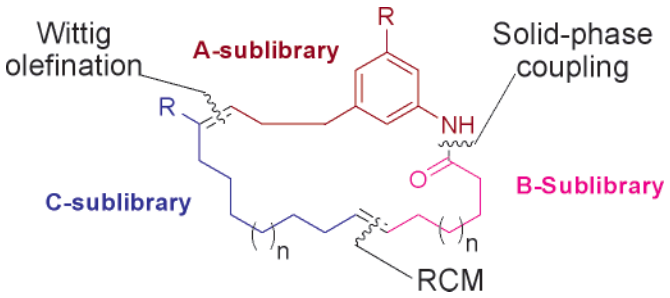
ABSTRACT



The ansamycin antibiotics contain metacyclophanic macrolactams, many of which possess potent antitumor activity. Only a few total syntheses of this family of natural products have been reported, and modifications to increase potency have not been described. Therefore, a method was developed to prepare the trienomycin A core via resin-bound triphenylphosphonium salts, which serve as both a reagent and a traceless linker to afford olefinic products that undergo ring-closing metathesis (RCM) to give macrocyclic scaffolds of varying ring sizes.

The ansamycin family of antibiotics consists of more than 20 members, many of which exhibit potent biological activities such as geldanamycin, from which derivatives are currently in clinical trials for the treatment of cancer (Figure 1).[1,2] Another important member of this family is trienomycin A, which like geldanamycin is also a macrolactam that contains an oxygenated aromatic ring.[3] Similar to geldanamycin, trienomycin A has exceptional activity against several cancer cell lines[4,5] and has been shown to cause a decrease in nitric oxide synthase,[6] suggesting that these molecules may share a common biological target.[7,8] Because the quinone ring of GDA has demonstrated redox-active behavior,[9] it has been proposed that more stable derivatives are likely to serve as important leads for clinical development.[10] Trienomycin A lacks the quinone moiety and instead contains a phenol, which is not subject to the same redox-active behavior. The ancillary ring of trienomycin A contains several functionalities that differ from those of geldanamycin and perhaps can be optimized for increased biological activity. Such attributes make trienomycin A an excellent target for the development of analogues and elucidation of its biological target.

In an effort to provide synthetic access to members of the ansamycin family, we sought to develop a versatile method

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that could enable access to related analogues for elucidation of structure−activity relationships. As a starting point for the development of such a library, the trienomycin A macrocycle was disconnected into three main parts (Figure 1): (1) the A-sublibrary contained the aromatic ring and two additional appendages for connection to other sublibraries; (2) the B-sublibrary contained olefinic acids, which could be coupled directly with the amino group from the A-sublibrary and undergo ring-closing metathesis with a terminal olefin from the C-sublibrary; (3) members of the C-sublibrary contained carbonyls to serve as substrates for Wittig olefination as well as an olefin for ring-closing metathesis (RCM).[11]

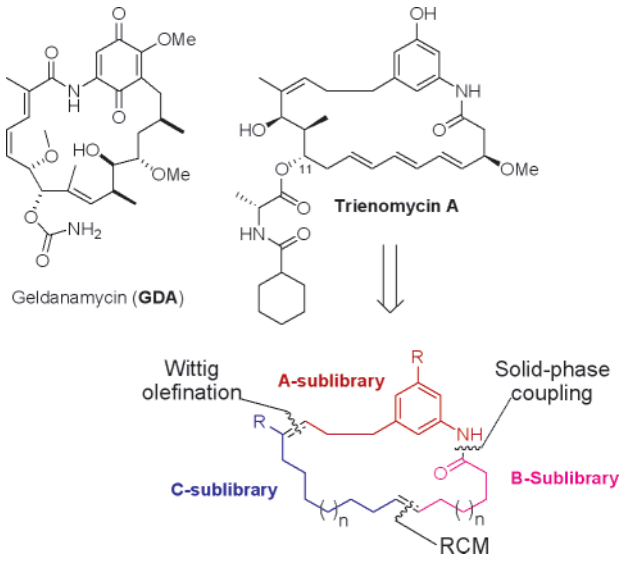
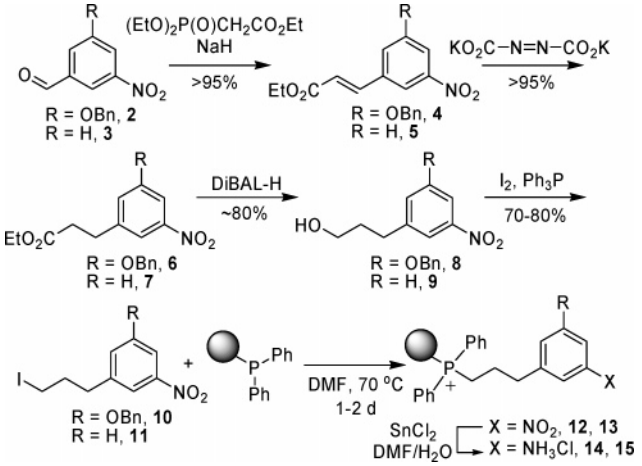


Figure 1. Geldanamycin and trienomycin A are representative members of the ansamycin family of antibiotics.

With this three-component approach toward the trienomycin A core in mind, we began preparation of the A-sublibrary by the synthesis of two members containing a deoxygenated and a benzyloxy-protected aromatic ring. Aldehyde **2** was prepared from 3-hydroxy-5-nitrobenzyl alcohol (**1**)[12] as shown in eq 1, whereas aldehyde **3** was readily available from commercial sources.

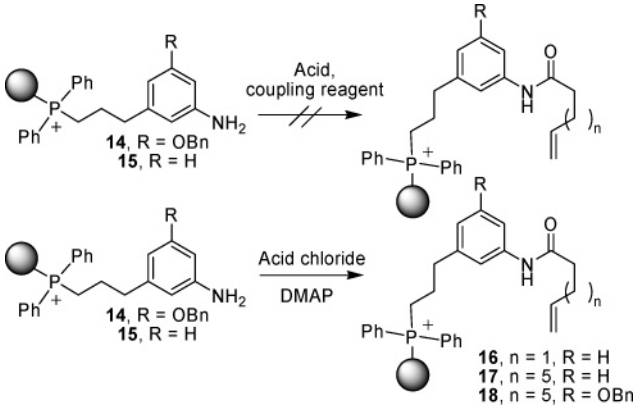
Homologation of the aldehydes with the anion of triethylphosphonoacetate provided the Horner−Wadsworth−Emmons olefination products, **4** and **5** (Scheme 1). Attempts to reduce the α,β-unsaturated esters without affecting the nitro substituent were problematic and eventually led to a two-step process that required reduction of the olefin with potassium diazodicarboxylate[13] to give intermediates **6** and **7**, the esters of which were subsequently reduced with diisobutylaluminum hydride to afford alcohols **8** and **9**. The hydroxyls were converted to the corresponding iodides (**10** and **11**) and then reacted with polymer-bound triphenylphoshine[14] to afford the resin-bound phosphonium salts **12** and **13**. Reduction of the nitro group on solid support was surprisingly difficult as only partial reduction occurred or entrapment of metal ions resulted. After numerous methods were explored, it was found that treatment of the nitrated resin with stannous chloride[15] completely dissolved in *N*,*N*-dimethylformamide gave aniline salts **14** and **15**, which represent members of the A-sublibrary.

Scheme 1. Synthesis of Resin-Bound Phosphonium Salts



Attempts to couple the requisite acids proved burdensome on solid support, as incomplete coupling was commonly observed following product release by Wittig olefination and/or IR spectroscopy. Consequently, acid chlorides were coupled with anilines **14** and **15,** as shown in Scheme 2.

Scheme 2. Synthesis of Resin-Bound Amides



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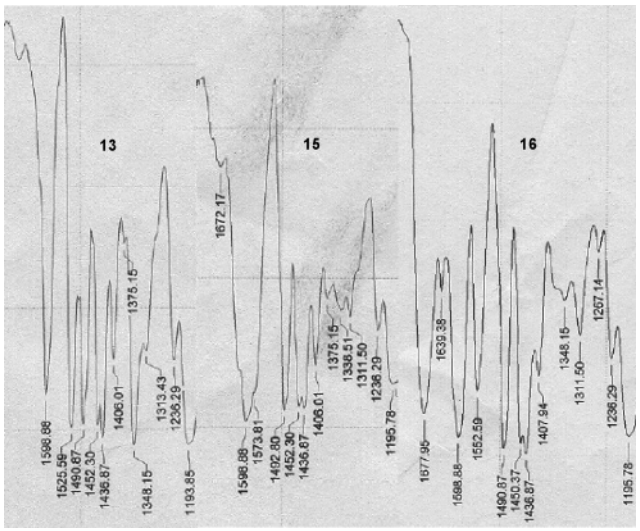


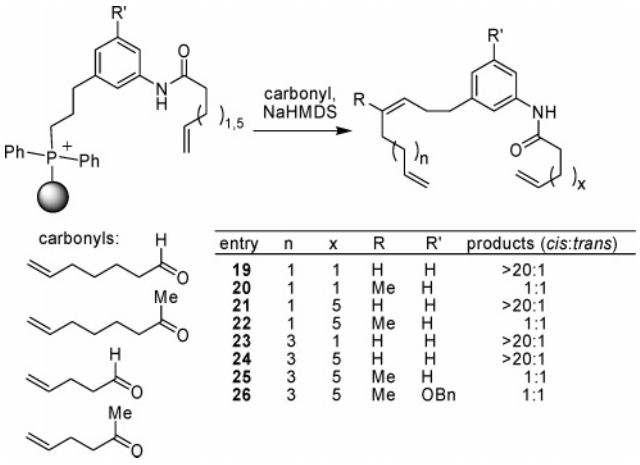
Figure 2. IR spectra for **13**, **15**, and **16**.

Addition of 4-*N*,*N*-(dimethylamino)pyridine to the reaction mixture gave the amide products in good yield as determined by IR spectroscopy.

Figure 2 shows the IR spectra between 1200 and 1700 cm^{-1} for the resin-bound intermediates. The nitrated resin (Figure 2, **13**) produced strong absorption at 1526 and 1348 cm^{-1}, whereas the corresponding region for the aniline-derived resin (Figure 2, **15**) was devoid of these absorptions but produced a broad absorption at ~1600 cm^{-1}. Likewise, the amide resin (Figure 2, **16**) produced a sharpened 1600 cm^{-1} absorption and a strong signal at 1678 cm^{-1}, corresponding to the stretching frequency of the amide carbonyl.

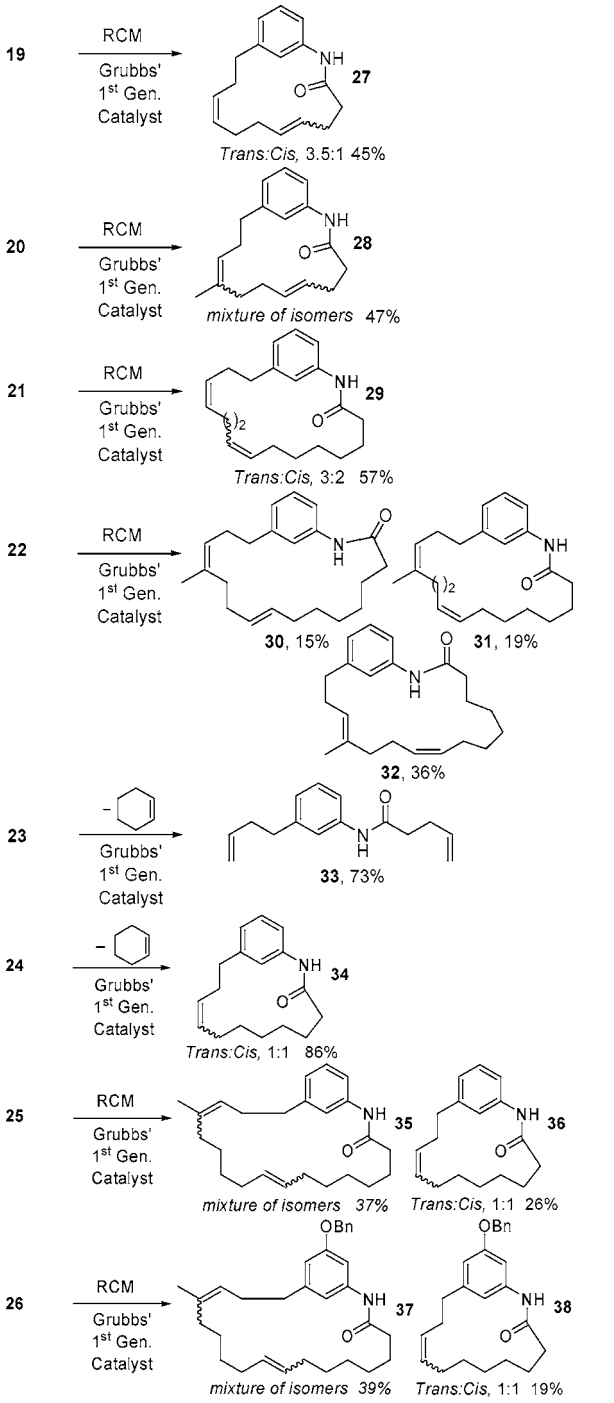
With the amide-containing resin in hand, we next pursued the Wittig reaction with the solid-phase phosphonium salts. The advantage of this method over the solution-phase approach is that the undesired phosphine oxide product produced in this reaction remains attached to the resin and can be easily removed from hydrophobic products by filtration.

Scheme 3. Synthesis of RCM Precursors



entry	n	x	R	R'	products (*cis*:*trans*)
19	1	1	H	H	>20:1
20	1	1	Me	H	1:1
21	1	5	H	H	>20:1
22	1	5	Me	H	1:1
23	3	1	H	H	>20:1
24	3	5	H	H	>20:1
25	3	5	Me	H	1:1
26	3	5	Me	OBn	1:1

Scheme 4. Synthesis of Macrocyclic Products



Four carbonyl substrates were chosen to represent members of the C-sublibrary and consisted of 5- or 7-carbons as well as methyl ketones or aldehydes. After a large number of bases were surveyed, it was found that treatment of a mixture of both the polymer-supported phosphonium salt and the carbonyl substrate with 2.2 equiv of sodium bis-(trimethylsilyl)amide in THF at 0 °C gave the desired

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products. When aldehyde substrates were employed, only cis isomers were obtained. However, ketone substrates gave a 1:1 mixture of cis and trans products. In total, eight Wittig products were prepared as outlined in Scheme 3.

As expected, most of the terminal olefins underwent ring-closing metathesis; however, it was found that Grubbs' first generation catalyst[16] gave the most reproducible RCM results, whereas the second generation catalyst[17] afforded a greater percentage of products resulting from relay metathesis.[18] When these eight molecules were treated with Grubbs' I, the products obtained represented a mixture of cis/trans isomers of the metathesis-derived alkenes as illustrated in Scheme 4. Both cis and trans isomers obtained from the Wittig reaction were substrates for the RCM reaction. However, olefins containing a four-carbon linker devoid of the trisubstituted olefin underwent relay metathesis[18] to give **33** or the ring-contracted macrocylcic product **34** in a trans/cis ratio of 1:1. In contrast, 1,2-substituted alkenes with less than four methylenes between olefins remained substrates for RCM.

These RCM results suggest that incorporation of trisubstituted olefins is sufficient for reducing the amount of relay metathesis products and that various ring sizes are accessible via this approach. In addition, access to smaller metacyclophanic rings through relay metathesis is likely to prove useful in the pursuit of other macrocyclic natural products.

Although Ford[19] and Hughes[20] have shown that resin-bound phosphonium salts provide Wittig products, its application to natural products and library development has not been pursued. In this letter, we have shown that the polymer-supported triphenylphosphonium resin is capable of providing natural product-like analogues of an important class of biologically active natural products. Further elaboration of individual members of each sublibrary will provide structures for biological investigation and may help to explain the antitumor activity manifested by trienomycin A.

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Supporting Information Available: Experimental procedures and characterization for representative compounds in this letter. This material is available free of charge via the Internet at http://pubs.acs.org.

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