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Letter

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Hydroxylamine-Mediated Anthrapyranone Formation, Solving 5-exo/6-endo Issue toward Synthesis of Pluramycin-Class Antibiotics

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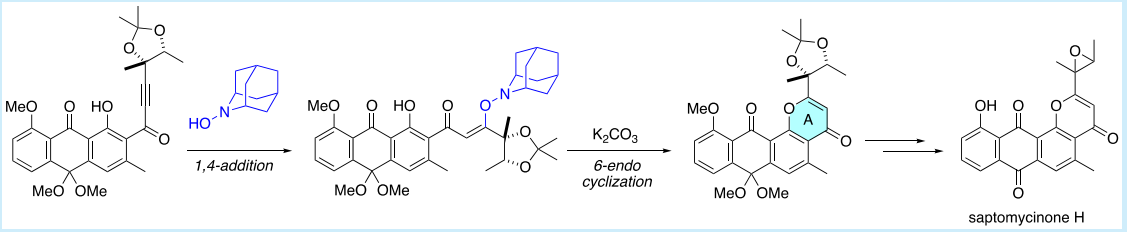
Supporting Information



ABSTRACT: In our synthetic study on pluramycin-class antibiotics, an unexpected issue arose, i.e., unfavorable regioselectivity of 5-*exo* rather than 6-*endo* cyclization to form the pyranone ring. The issue was solved by an addition–elimination process of a phenol–ynone substrate. AZADOL was specifically effective, enabling the first synthesis of saptomycinone H.

The pluramycins constitute a class of antitumor antibiotics, as represented by pluramycin A (**1**; Figure 1).[1] By

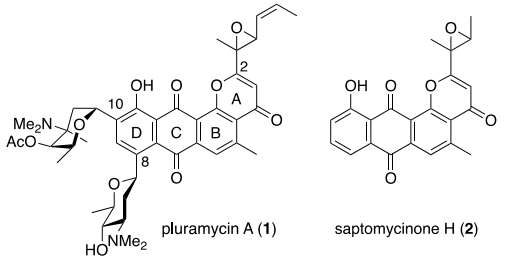


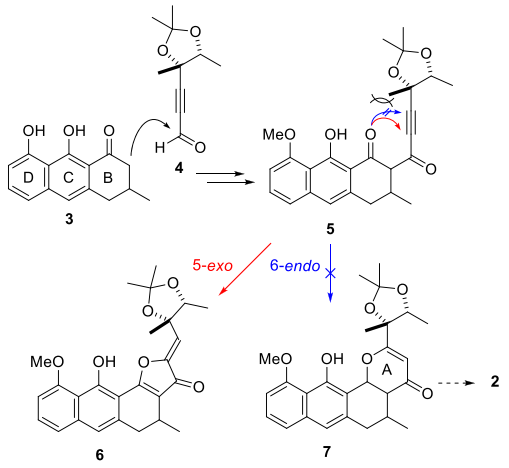
Figure 1. Pluramycins.

Nature's ingenuity, they share a composite structure of several well-aligned motifs for targeting/cleaving DNA: amino sugar(s) for the sequence specificity, a tetracyclic core for the major-groove binding, and a side chain epoxide for the strand scission via *N*-alkylation.[2,3]

Potent bioactivities of these compounds have attracted sizable interest in their synthesis,[4] which is not easy due to the structure complexity and chemical sensitivity. Only two total syntheses of *C*-glycosylated structures have been achieved to date,[5,6] which, however, dealt with the targets without an epoxide function at the side chain. Note the synthesis of the epoxide-bearing congeners would suffer from complication by potential issues for installing this sensitive functionality.[7]

We set out to address this issue by setting saptomycinone H (**2**) as a model target.[8,9] Scheme 1 shows our original synthetic plan. Anthrone **3** was set as the starting material, to be envisioned for future application to the *C*-glycosylated structures.[10] Ynal **4** has a protected 1,2-diol as a latent epoxide, assuming the late-stage formation of the stereodefined oxirane ring.

Scheme 1. Synthetic Plan of 2 and 5-*exo*/6-*endo* Issue



Along these lines, we began the synthetic study of **2**, which encountered an unexpected difficulty in the A-ring cyclization of 1,3-diketone **5** (Scheme 1): the 5-*exo* cyclization prevailed over the electronically favored 6-*endo* cyclization to give furanone **6**.

In this letter, we wish to describe a unique solution to this issue via the discovery of a hydroxylamine-mediated addition–elimination process, achieving the synthesis of **2** (see abstract graphic).

Scheme 2 shows the preparation of ynal **4**. Dihydroxylation of methyl angellate (**8**) and acetalization of the resulting diol gave acetonide **9**. Reduction of **9** with DIBAL-H gave alcohol **10**, which was converted to aldehyde **11** by Swern oxidation,[11]

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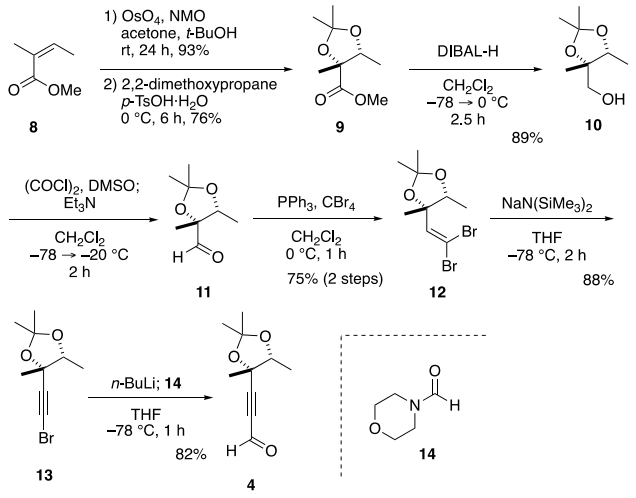
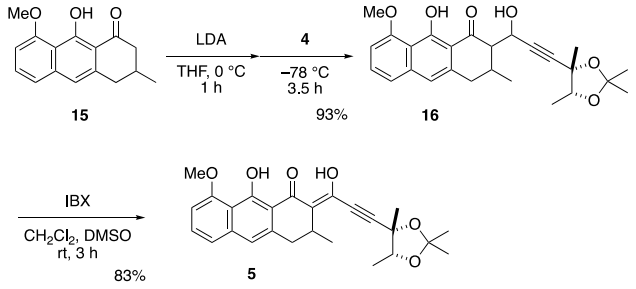
Scheme 2. Synthesis of Side Chain 4



and further to dibromoolefin **12**. Treatment of **12** with $NaN(SiMe_3)_2$ at −78 °C gave bromoacetylene **13**, which was converted into ynal **4** by treatment with *n*-BuLi followed by the reaction with 4-formylmorpholine (**14**).[12] We noted that the direct conversion of **12** into the corresponding lithium acetylide (*n*-BuLi, THF, −78 °C) followed by addition of **14** was low-yielding.

For the assembly of the entire carbon skeleton, anthrone **15**[6b,13] was enolized with LDA (2.8 equiv, 0 °C, THF) and treated with ynal **4** at −78 °C, giving aldol **16** as a mixture of four diastereomers in 93% yield (Scheme 3). Oxidation of **16** with IBX[14] gave 1,3-diketone **5** in 83% yield.[15]

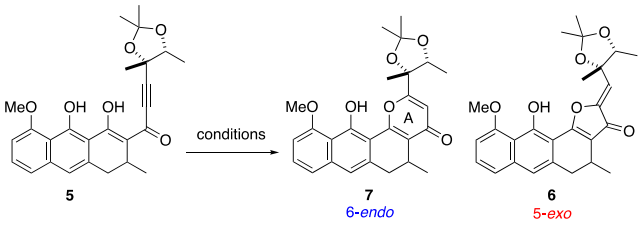
Scheme 3. Conversion to Diketone 5



With ynone **5** in hand, the projected A-ring cyclization was examined. As the first attempt, ynone **5** was treated with K_2CO_3 (entry 1, Table 1). The starting material **5** was slowly consumed (MeOH, 0 °C → room temperature, 52 h). Surprisingly, the single product, thus obtained, was not the expected pyranone **7**, but furanone **6** in quantitative yield.[16] Further efforts using various other bases or nucleophilic catalysts failed to give the desired pyranone **7**, resulting invariably in the exclusive 5-*exo* cyclizations (entries 2−6).[17]

The result was totally unexpected, since the electronic consideration naturally pointed to the conjugate addition to the ynone, producing pyranone **7** as the expected product. In contrast, our previous total synthesis of saptomycin B exploited diketone **17** as a viable substrate for the key A-ring cyclization (Scheme 4),[18] giving only the six-membered product **18**. The structural difference of **17** and **5** is the steric bulk around the C2 reaction site: the C14 center in **5** is quaternary, while it is tertiary in **17**. Since Baldwin's rule predicts that the *dig*

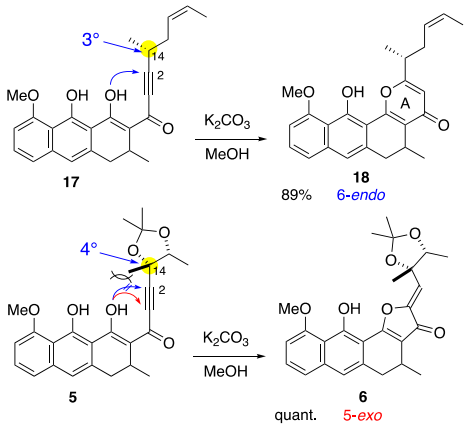
Table 1. Cyclization of 5



entry	base	solvent	temp.	time/h	7/%	6/%
1	K_2CO_3[a]	MeOH[b]	0 °C → rt	52	–	quant.
2	DMAP[c]	MeOH[d]	rt	55	–	71
3	NaOH[e]	MeOH[d]	rt	20	–	quant.
4[f]	Et_2NH	EtOH	0 °C → rt	9	–	76
5	Et_3N[a]	CH_2Cl_2[b]	0 °C	48	–	quant.
6	PMe_3[c]	DMSO[d]	rt	15	–	74

[a]3.0 equiv. [b]0.01 M. [c]1.0 equiv. [d]0.02 M. [e]2.0 equiv. [f]Et_2NH, EtOH = 1/1vol (0.01 M).

Scheme 4. 6-*endo* vs 5-*exo* Cyclizations

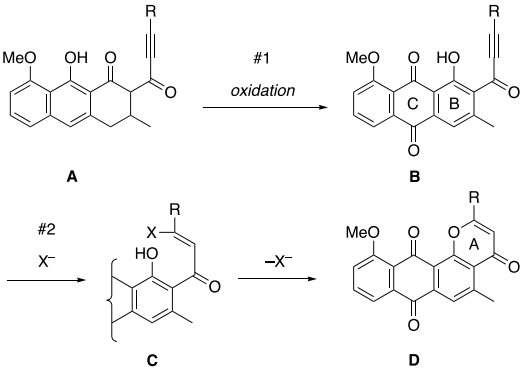


processes are durable for the 6-*endo* and 5-*exo* cyclizations,[19] we ascribed the prevalence of the 5-*exo* cyclization to the steric factor that overrides the electronic factor.

Hoping to enable the desired 6-*endo* cyclization, we decided to make two substrate structure modifications (Scheme 5).

(1) Conversion of 1,3-diketone **A** into the corresponding phenol **B**: The basis was that all successful precedents of the 6-*endo* cyclizations of ynones exploited phenols, rather than a 1,3-diketone, as the internal nucleophile. A

Scheme 5. Two Substrate Modifications



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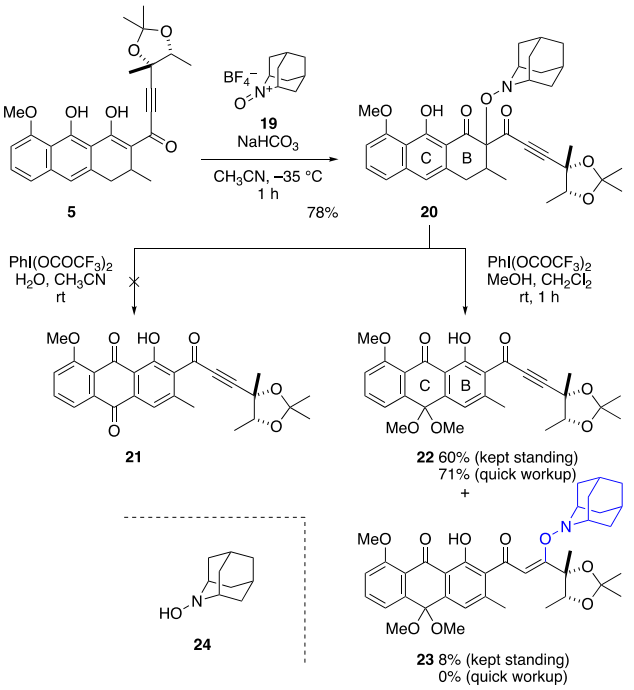
promising aspect was that some examples included substrates with a C14-quaternary center.[20]

(2) Conversion of ynone **B** to β-substituted enone **C**: Inspired by our previous experience,[20a,21] we envisioned that the intermediacy of **C** may enable the 6-*endo* cyclization via an addition−elimination process.

With these scenarios in mind, we examined the conversion of 1,3-diketone **5** into phenol−quinone **21** (Scheme 6).

Scheme 6. Oxidation of 5



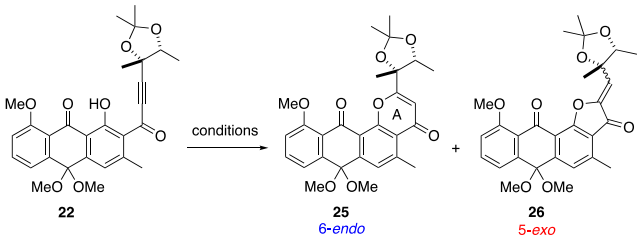
Treatment of 1,3-diketone **5** with oxoammonium salt **19**[22] (CH_3CN, −35 °C) gave α-oxy-adduct **20** in 78% yield.[23,24] For further conversion into quinone **21**, α-oxy-adduct **20** was treated with $PhI(OCOCF_3)_2$[25] in H_2O and CH_3CN. However, none of the desired product **21** was obtained, only giving an intractable mixture of unidentified products. By contrast, the same reaction in MeOH and CH_2Cl_2 (v/v = 1/2) gave the corresponding acetal **22** in 60% yield, and thus, we decided to use **22** as a substrate to address the viability of the cyclization, **B** → **C** → **D**.

It would be appropriate to note here that the reaction of **20** → **22** gave small, varying amounts of enone **23** as a side product, which was not seen during the reaction, but formed if the crude products were kept standing. Indeed, the formation of **23** was suppressed by quick workup, where the yield of **22** was improved to 71%. We ascribed it to the 1,4-addition of 2-hydroxy-2-azaadamantane, AZADOL (**24**) to ynone **22**, which later guided us to a breakthrough.

Having ynone **22** in hand, we tested its conversion to the planned intermediate, β-X-substituted enone **C**, which would hopefully cyclize in a 6-*endo* fashion. To this end, ynone **22** was treated with various nucleophiles, and the results are summarized in Table 2.

When Et_2NH was used as a nucleophile, the major product was furanone **26**[26] via the 5-*exo* cyclization, and pyranone **25** was obtained only in low yield (entry 1).[20a,21] Treatment of **22** with K_2CO_3 in MeOH[18] also led to a preferential 5-*exo*

Table 2. A-Ring Formation from 22



entry	reagent	solvent[a]	temp.	time/h	**25**/%	**26**/%
1[b]	Et_2NH	EtOH	rt	0.5	8	21
2	K_2CO_3[c]	MeOH	0 °C	3	12	47
3		CH_2Cl_2	rt	24	—	68
4	PMe_3[d]	CH_2Cl_2	rt	4	—	32
5	PhSH,[e] Et_3N[e]	CH_2Cl_2	rt	42	—	—[e]

[a]Solvent (0.02 M). [b]Et_2NH, EtOH = 1/2 vol. [c]3.0 equiv. [d]2.0 equiv. [e]No reaction.

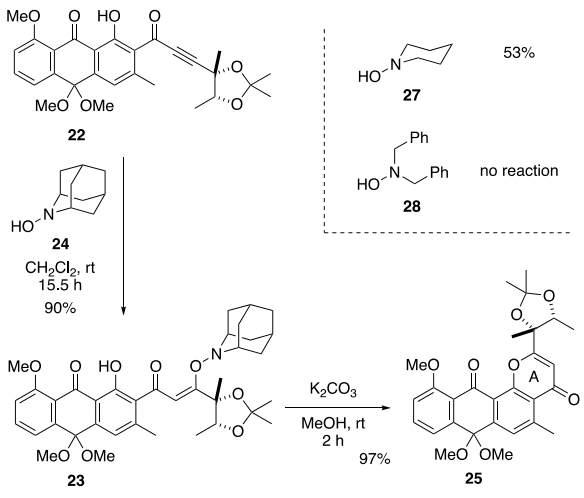
cyclization (entry 2). The expectation was a minute amount of methoxide in equilibrium acting as a nucleophile. With the idea of using nucleophilic catalysis, DABCO[27] and Me_3P[28] were used, which, contrary to our expectation, resulted in the exclusive 5-*exo* cyclization (entries 3 and 4). Use of a thiolate anion was not effective, resulting in no reaction (entry 5).

Implications from these experiments include the following: (1) the planned 1,4-addition of X^- (or X:) to alkynone **22** is not easy, and (2) it seems that a direct cyclization of phenol **22** to the internal triple bond is competing even under slightly basic conditions, where the 5-*exo* cyclization is favored.

At this juncture, we noticed that the side product **23** obtained in the previous experiment has the required β-X-substituted enone structure (X = aminoxy) and may serve as a viable cyclization precursor. Despite uncertainty, a perfect solution to the problem was provided (Scheme 7).

β-Aminoxyenone **23** underwent clean A-ring formation, upon treatment with K_2CO_3 in MeOH, giving pyranone **25** in

Scheme 7. A-Ring Formation from AZADOL-Adduct 23



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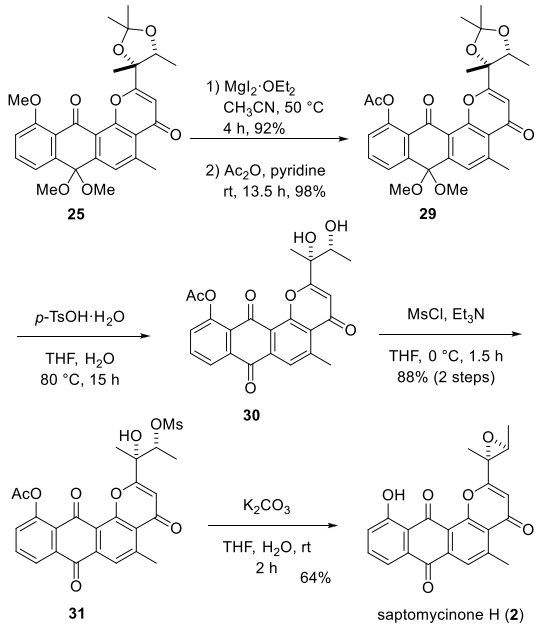
virtually quantitative yield. Importantly, an exclusive 6-*endo* cyclization occurred.

Pleasingly, we further learned that enone **23** is available in excellent yield from ynone **22** by the reaction with AZADOL (**24**). The efficacy of this hydroxylamine in this context is ascribable to high nucleophilicity by the α-effect,[29] enabling the 1,4-addition under neutral conditions. An additional feature in **24** is a conformationally locked adamantane-like structure. In contrast, two other hydroxylamines **27** and **28** proved less effective.[30] Furthermore, the $-ONR_2$ moiety is significantly less donating than an OR or an NR_2 moiety (the inverse α-effect),[29b] thereby not deactivating the β-carbon in enone **23** toward the nucleophilic attack.

After a long quest, the 6-*endo* cyclization became realized via an addition−elimination process by using AZADOL (**24**) as a nucleophile and a nucleofuge.

Scheme 8 shows the synthesis of **2**. To remove the methyl ether, tetracycle **25** was treated with $MgI_2{\cdot}OEt_2$ (CH_3CN, 50 °C),[31] and acetylation of the resulting phenol gave acetate **29**.[32] Acid hydrolysis of two acetals in **29** gave the corresponding quinone diol **30**, in which the secondary alcohol was selectively mesylated,[33] giving *mono*-mesylate **31**. Treatment of **31** with K_2CO_3 in THF and H_2O enabled the oxirane ring formation and removal of the acetyl group, giving **2** in 64% yield.[34]

Scheme 8. Synthesis of Saptomycinone H (2)



In summary, the synthesis of saptomycinone H (**2**) has been achieved by exploiting the unique reactivity of AZADOL (**24**), opening a general path to the pluramycins. Further studies are in progress. The synthetic utility of hydroxylamine-mediated reactions will also be studied.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04127.

Full experimental procedure, characterization data, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Takenori Kusumi on the occasion of his 77th birthday (*Kiju*).

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(15) Extensive NMR analyses showed that the major tautomer of 1,3-diketone **5** is an enol form shown in Scheme 3 (see the Supporting Information). Other schemes and a table depict a conventional structure of **5**.
(16) Extensive spectroscopic analyses showed that furanone **6** was solely composed of the (*Z*) isomer. See Supporting Information.
(17) In entry 6, the geometry of the olefin was a mixture (*Z*/*E* = 1.7:1).
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