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Total Synthesis of (−)-Neocosmosin A via Intramolecular Diels−Alder Reaction of 2-Pyrone

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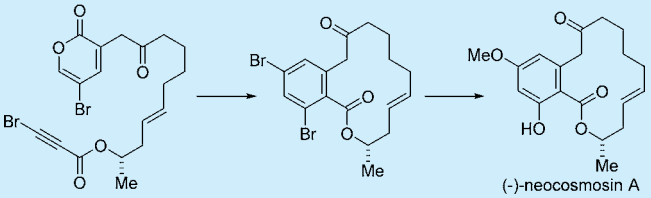
Supporting Information

ABSTRACT: A new synthetic route to (−)-neocosmosin A was devised by elaboration of intramolecular Diels−Alder (IMDA) cycloaddition of 2-pyrone containing a bromopropiolate group as the dienophile. The IMDA reaction was accompanied by cycloreversion of carbon dioxide to give benzannulated macrolide with two bromide groups at C14 and C16. Installation of the pinacolboryl groups and oxidations allowed completion of the total synthesis of (−)-neocosmosin A.



Resorcylic acid lactones (RALs) are polyketide-derived benzannulated macrolides, named for their β-resorcylate core structure fused to a 12- or 14-membered lactone ring (Figure 1).[1] They are synthesized in vivo by a variety of fungi

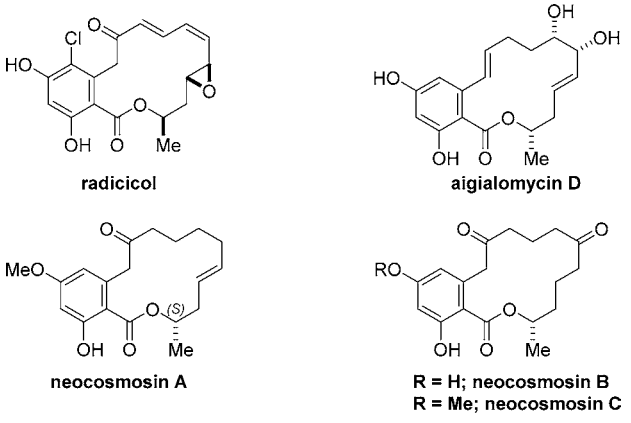


Figure 1. Selected resorcylic acid lactones.

from acetone and malonate units via a series of Claisen condensation reactions.[2] Many of them exhibit intriguing biological activities that include anticarcinogenic, antimalarial, antifungal, and antibiotic properties.[3] Several RAL compounds are, in fact, currently under development for clinical applications. Because of their potential values as new drug candidates, invention of methods and/or routes that allow rapid and divergent synthesis of RALs would be of significant interest. However, literature survey unveils a rather short list in which the strategies based on the ring-closing metathesis (RCM) or macrolactonization reaction prevail.[4,1c]

Neocosmosin A is a recently found RAL, co-isolated with neocosmosins B and C from the fungus *Neocosmospora* sp. (UM-031509) in 2012.[3a,b] It was shown to have a strong binding affinity for human opioid and cannabinoid receptors.[5] The chiral C2 carbinyl center, assigned incorrectly at the isolation,[3a,b] proved to have *S*-configuration as underpinned by two independent total syntheses led by Das[6b] and Banwell.[6a] In both syntheses, ring closing metathesis was employed as a key strategy. The RCM is no doubt an effective method for the formation of a macrocycle but suffers from drawbacks arising from the difficulties in controlling stereochemistry of the double bond and finding proper reaction conditions, high catalyst costs, issues with catalyst recovery/recycling, and necessary high dilution conditions to suppress the undesired intermolecular process.[4]

As a part of our ongoing study of 3,5-dibromo-2-pyrone toward target oriented synthesis,[7] we have devised a new synthetic route that could allow rapid access to (−)-neocosmosin A (Scheme 1). In this elaboration, the key bicyclolactone **2** would be accessed from 2-pyrone **3** containing acrylate linked to the C3 position of the 2-pyrone through intramolecular Diels−Alder cycloaddition (IMDA). Cycloreversion (retro-Diels−Alder) of cycloadduct **2** and subsequent oxidative aromatization affords benzomacrolactone **1**. Introduction of the hydroxyl groups at C14/C16 positions and methylation of the C14 hydroxyl group allows completion of the synthesis.

To prove the concept, a racemic synthesis was first undertaken, starting with the preparation of (±)-homoallylic alcohol **5** from the readily accessible carboxylic acid **4** (Scheme 2).[8] The resulting alkyne **5** was then subjected to the Sonogashira coupling reaction with 3,5-dibromo-2-pyrone **6** to give 3-alkynyl-5-bromo-2-pyrone **7** in 86% yield.[9] Subsequent mercury-mediated hydration of alkyne **7** took place in a highly selective manner at the desired alkyne carbon away from the 2-pyrone to afford ketone **8** in 90% yield, as we expected from the possible

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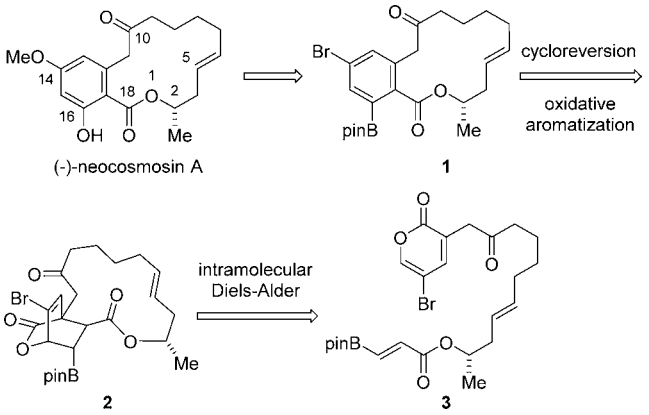
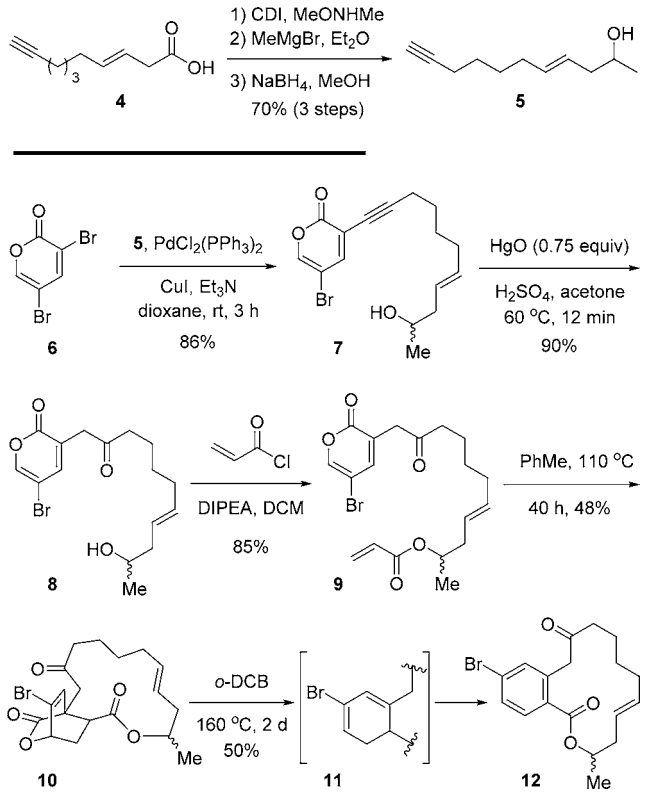
Scheme 1. Retrosynthetic Analysis of Neocosmosin A



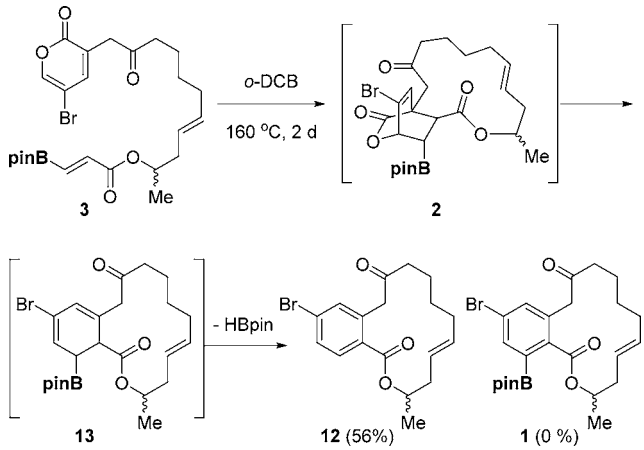
Scheme 2. IMDA of 2-Pyrone Connected with Acrylate as a Model



neighboring group participation of the 2-pyrone carbonyl group.[10] To probe the viability of the 2-pyrone IMDA strategy involving such a long tether,[11] 2-pyrone **9** with a simple acrylate group was prepared for a model study. When heated in refluxing toluene under high dilution conditions (23 mM), the corresponding cycloadduct **10** was obtained in 48% yield. To effect the cycloreversion process, isolated **10** was heated in 1,2-dichlorobenzene under reflux at 160 °C. Under the conditions, the resulting cycloreversion product was found to undergo oxidative aromatization, providing the corresponding benzomacrocyclic lactone **12** in 50% total yield.

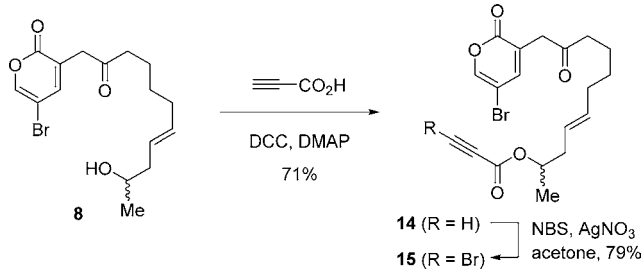
Encouraged by the results, we prepared the IMDA precursor **3** containing a pinacolborane group as a synthetic equivalent of the C16 hydroxyl group. Unfortunately, subjection to the conditions effective for the model system **10** did not bring about the IMDA reaction, presumably due to the steric impediment of the bulky pinacolborane group. The IMDA reaction was eventually effectuated by heating directly at 160 °C. However, the reaction did not give the desired product **1**, but gave **12**, which was identical to the product obtained from cycloadduct **11**. In this reaction, the initially formed cycloreversion product **13** underwent β-elimination instead of oxidative aromatization (Scheme 3).[12]

Scheme 3. IMDA of 2-Pyrone Acrylate with a Pinacolboranyl Group



To unravel the deborylation problem, 2-pyrone IMDA precursor **15** with propiolate as a dienophile partner was elaborated (Scheme 4). The extrusion of CO_2 from the IMDA

Scheme 4. Preparation of 2-Pyrone IMDA Precursor with a Bromopropiolate Group



adduct **15** would directly provid the key benzannulated macrolactone **1** without oxidative aromatization reaction. We opted to use a bromine group, considering the difficulty associated with the installation of a pinacolboryl group in the presence of a base-labile propiolate group[13] as well as an analogous literature precedent on the use of bromopropiolate as the dienophile.[14] Toward this, alcohol **8** was coupled with propiolic acid to give propiolate **14** before the treatment with *N*-bromosuccinimide (NBS) in the presence of $AgNO_3$ to afford IMDA precursor **15**.[15]

In an effort to optimize the reaction, the IMDA reaction of **15** was subjected to both conventional and microwave heating conditions at various temperatures in different solvents (Table 1). The microwave irradiation was conducted in the temperature range from 140 to 200 °C. While the reaction finished very rapidly within 30 min, the reaction yield hardly exceeded 40%, even in the best case (entries 1−3). On the other hand, a product yield of 48% was obtained on conventional heating in toluene at 150 °C (in sealed tube) under high dilution conditions (23 mM)

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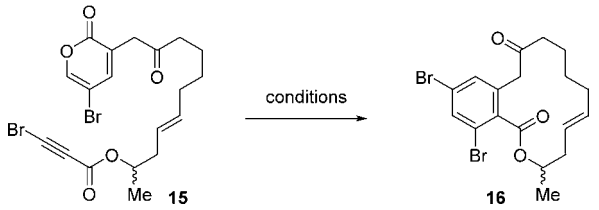
Table 1. IMDA Reaction of Precursor 15



entry	conditions[a]	yield (%)
1	MW, *o*-dichlorobenzene, 140 °C, 10 min	33
2	MW, *o*-dichlorobenzene, 160 °C, 10 min	35
3	MW, *o*-dichlorobenzene, 200 °C, 10 min	15
4	toluene, 150 °C (sealed tube), 3 days	48
5	mesitylene, reflux (165 °C), 2 days	56
6	mesitylene, 0.5 equiv of BHT, reflux (165 °C), 2 days	64

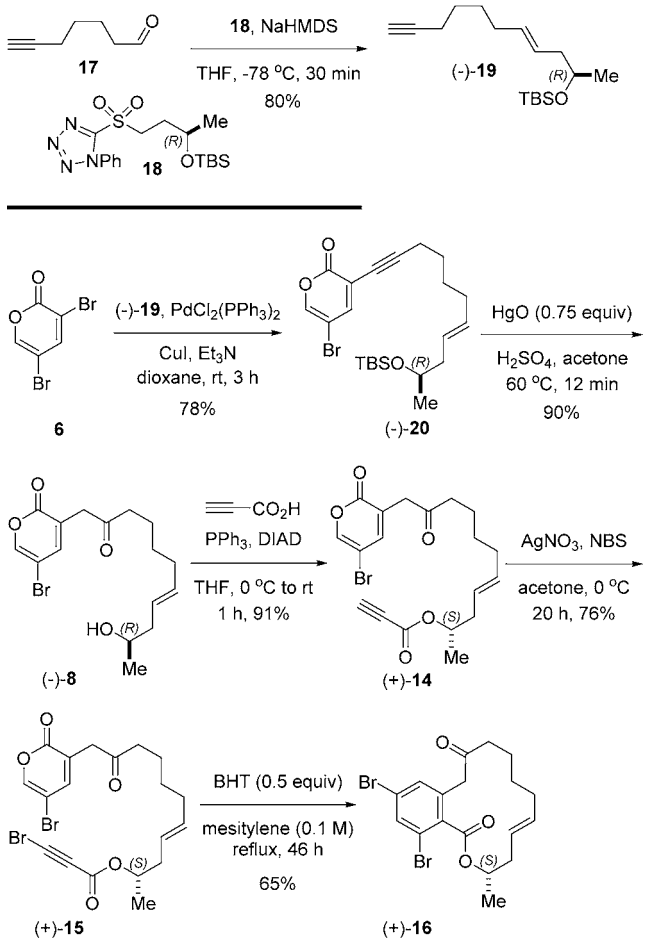
[a]All reactions were conducted at the concentration of 23 mM.

after 3 days (entry 4). The reaction in refluxing mesitylene resulted in a slightly higher yield (56%, entry 5). Meaningful increase in product yield (64%) was observed when the reaction was conducted in the presence of 0.5 equiv of butylated hydroxytoluene (BHT) as the radical scavenger (entry 6).

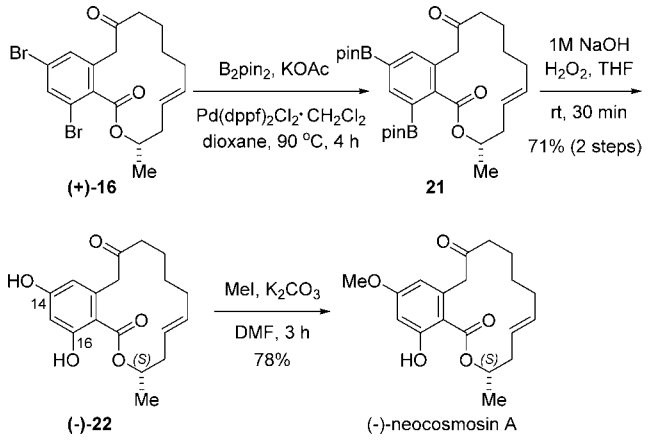
Having proved the effectiveness of our 2-pyrone IMDA strategy, we ushered in the asymmetric synthesis of (−)-neocosmosin A by preparing alkyne (−)-**19** from aldehyde **17**[16] by means of a Julia−Kocienski reaction with sulfone **18** (Scheme 5).[17] Alkyne (−)-**19** with opposite stereochemistry at the carbinyl center was prepared in anticipation of configurational inversion during the installation of the propiolate ester under Mitsunobu conditions (vide infra). Subsequent Sonogashira coupling reaction with 3,5-dibromo-2-pyrone (**6**) and mercury-mediated hydration gave ketone (−)-**8** in good overall yield. The optical purity of (−)-**8** was verified by Mosher ester analysis (see Supporting Information). The same transformation can be mediated by a Au catalyst, albeit in a slightly lower yield (80%; see Supporting Information for details).[18] Coupling reaction with propiolic acid under Mitsunobu conditions gave propiolate (+)-**14** with inversion of configuration at the chiral carbinyl center. Treatment with NBS in the presence of $AgNO_3$ afforded IMDA precursor (+)-**15**. Subsequent IMDA reaction under the optimized conditions (except the concentration, vide infra) afforded the corresponding macrocyclic lactone (+)-**16** in 65% yield. Note the reaction concentration, 0.1 M, is 10 times higher than that of a typical RCM-based reaction, thereby it is more readily adaptable to large-scale synthesis.

With a sufficient amount of dibromobenzo macrocyclic lactone (+)-**16** in hand, we surveyed the ways to convert the aromatic bromides to phenolic hydroxyl groups (Scheme 6). Direct installation of the hydroxyl groups by transition-metal-catalyzed C−O coupling reactions were not compatible with the base-labile macrocyclic lactone moiety. We chose to detour by converting them into pinacolboryl groups. Toward this, dibromide (+)-**16** was subjected to the Miyaura conditions to afford bispinacolborane **21**.[19] Subsequent oxidation of the resulting borane compound **21** provided the resorcinol (−)-**22**[20] in 71% overall yield from (+)-**16**. Treatment with MeI in the presence of K_2CO_3 allowed selective methylation at the sterically less hindered C14 hydroxyl group to deliver (−)-neocosmosin A in 78% yield. The spectroscopic data and optical rotation of our synthetic neocosmosin A are consistent with the literature values (see Supporting Information).[3a,6]

Scheme 5. Synthesis of Dibromobenzomacrolide (−)-16



Scheme 6. End-Game Synthesis of (−)-Neocosmosin A



In summary, a new efficient synthetic route to (−)-neocosmosin A was devised through the elaboration of intramolecular Diels−Alder cycloaddition of 2-pyrone connected to a bromopropiolate group as the dienophile. Subsequent installation of two hydroxyl groups completed the synthesis of (−)-neocosmosin A in a total of eight steps in 17% overall yield from 3,5-dibromo-2-pyrone.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(20) (−)-**22** is the enantiomer of naturally occurring monocillin IV.

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