Concise Synthesis of (±)-γ-Indomycinone

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The first total synthesis of (±)-γ-indomycinone (**2**) has been accomplished starting from juglone (**5**) in nine steps, including Diels–Alder reaction of **5** and diene **6** and the formal 6-endo-dig cyclization of alkynone **3** as the key steps.

The pluramycin-class antibiotics, such as **1a** and **1b**, contain an anthra[1,2-*b*]pyran nucleus, to which amino sugars are typically attached at C-8 and C-10 positions (Figure 1).[1] These molecules exhibit a variety of interesting biological activities, including antimicrobial and anticancer activity and also show significant DNA sequence selectivity.[2] In our long-standing interest in the synthesis of aryl *C*-glycoside antibiotics,[3] we have been recently centering attention to the synthesis of the pluramycins, where two basic problems must be addressed, (1) bis-*C*-glycosylation,[4] and (2) the selective construction of the anthra[1,2-*b*]pyran chromophore. This letter deals with the latter aspect by describing a short synthesis of (±)-γ-indomycinone (**2**) based on the construction of an anthraquinone core by exploiting Diels–Alder reaction and the formal 6-endo-dig cyclization.

γ-Indomycinone (**2**) was isolated from the culture broth of a *Streptomyces* sp. collected from a deep-sea sediment core,[5] which possesses an anthra[1,2-*b*]pyran skeleton and a 1-hydroxy-1-methylpropyl side chain at the C-2 position. Retrosynthetically, we envisaged the cyclization of *o*-hydroxy alkynoylanthraquinone **3** to be a potential access to the requisite tetracycle **2** (Scheme 1). The γ-pyrone precursor **3** could be derived from anthraquinone ester **4**, which, in turn, could be obtained from juglone (**5**) and diene **6** via Diels–Alder cycloaddition.

The Diels–Alder reaction of juglone (**5**) with diene **6**[6] in the presence of $B(OAc)_3$[7] gave cycloadduct **7**. After evaporation of CH_2Cl_2, the crude mixture was then dissolved in THF and treated with Bu_4NF followed by bubbling air into the solution for 1 h to afford anthraquinone **4** in 62% yield as a single isomer (Scheme 2). The high regioselectivity was achieved when

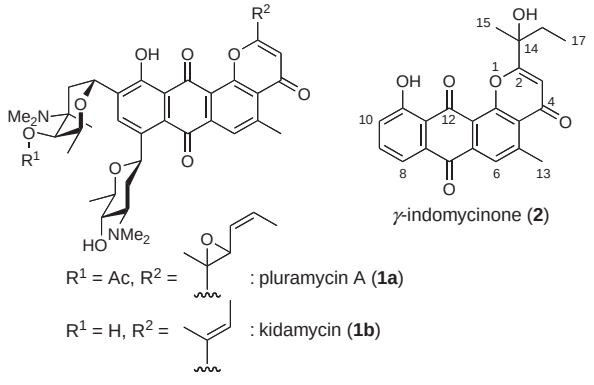
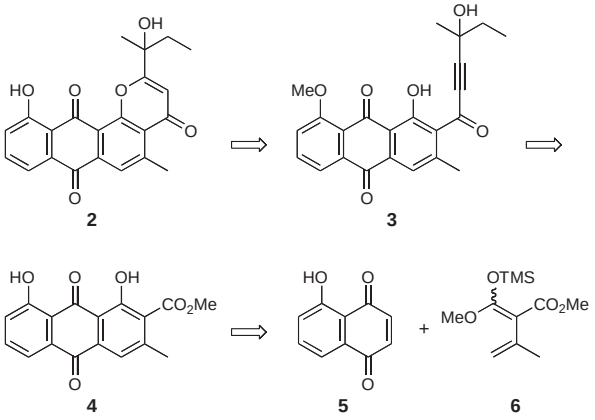
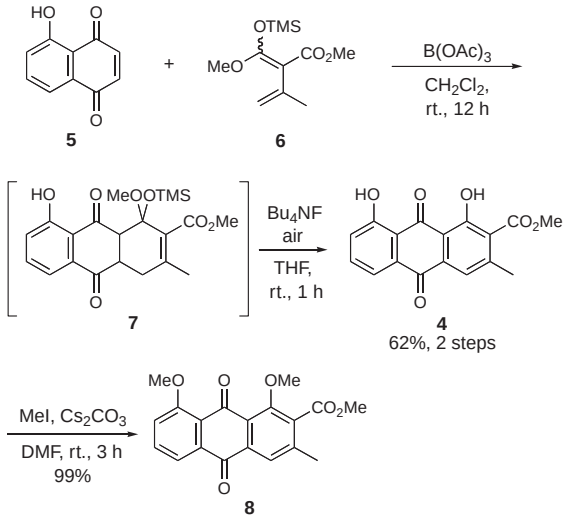


Figure 1.



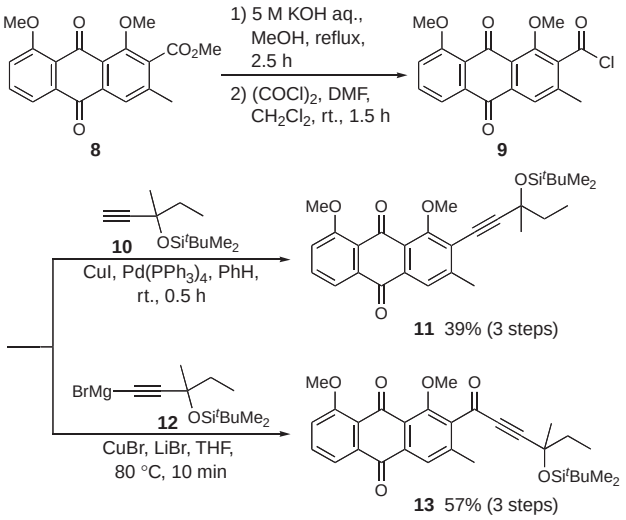
Scheme 1.



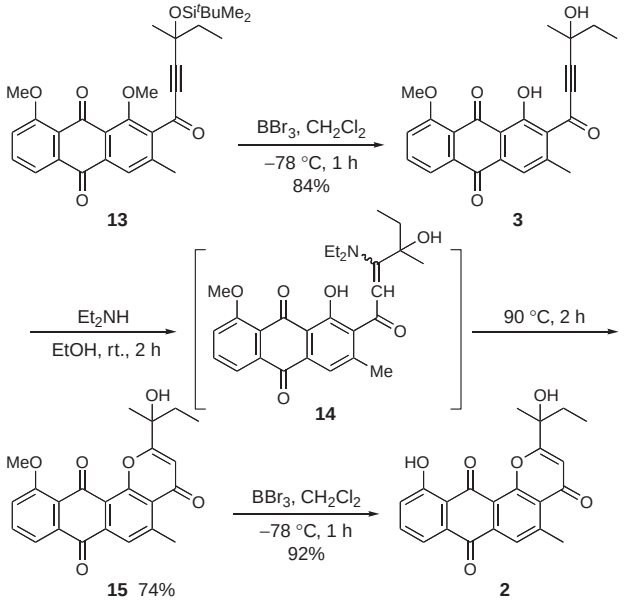
Scheme 2.

$B(OAc)_3$ was used as a Lewis acid.[8] The phenolic hydroxys were then protected as methyl ethers by using methyl iodide and Cs_2CO_3 in DMF to give quinone **8**.[9]

Having secured the anthraquinone core, the stage was set for the introduction of an α,β-acetylenic ketone. Toward this end, methyl ester **8** was hydrolyzed with aqueous KOH in refluxing methanol, and, without purification, the resulting acid was treated with oxalyl chloride and a catalytic amount of DMF in CH_2Cl_2 to produce acid chloride **9** (Scheme 3). Initial attempts to form the α,β-acetylenic ketone were in failure by the reactions of acid chloride **9** with terminal alkyne **10** under Sonogashira[10] or other modified conditions,[11] only resulting in the decarbonylation product **11** or recovery of the starting



Scheme 3.



Scheme 4.

material. Fortunately, however, this issue could be solved by the reaction of acid chloride **9** with Grignard reagent **12** in the presence of CuBr and LiBr[12] to give the desired product **13**.

Having alkynone **13** in hand, the C-1-methyl[13] and the *tert*-butyldimethylsilyl protecting groups were selectively detached by using BBr_3 at $-78\,^{\circ}C$ to give γ-pyrone precursor **3** in 84% yield (Scheme 4). The question at the next stage was whether or not the free phenol in **3** can undergo 6-endo-dig cyclization without accompanied by the 5-exo-dig counterpart.[14] This goal was nicely achieved by employing the Mzhel'skaya's method.[15] Thus, treatment of alkynone **3** with diethylamine[16] in ethanol at room temperarure followed by heating at $90\,^{\circ}C$ produced γ-pyrone **15** in 74% yield. Having achieved the *formal* 6-endo-dig cyclization, final deprotection of methyl ether in **15** with BBr_3 provided (±)-γ-indomycinone (**2**). The spectroscopic data of the synthetic material were fully consistent with the literature data.[5]

In conclusion, we described a short synthesis of (±)-γ-indomycinone in nine steps from juglone, which has paved an efficient way to the chromophore of the pluramycin-class antibiotics.

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