

Formal Synthesis of ($\pm$)-Methyl Rocaglate Using an Unprecedented Acetyl Bromide Mediated Nazarov Reaction

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Supporting Information

ABSTRACT: To date the prototype Nazarov cyclization of a cross-conjugated pentadienone to the core structure of the rocaglate natural products has not been successful (**9** into **12**). It has been found that this conversion can be achieved by the use of acetyl bromide in excellent yield and results in a strategically very direct route to these antitumor agents.

Since the isolation and structure determination of rocaglamide in 1982,¹ a number of 1H-cyclopenta[b]-benzofurans, as exemplified by the core structures **1** and **2**,² have been isolated from the plant family *Aglaia* (Meliaceae).³ Recently, the rocaglate derivatives silvestrol **3** and episilvestrol **4**, isolated from the fruits and twigs of *Aglaia foveolata* (Pannell), have been shown to exhibit cytotoxic activity comparable to taxol (Figure 1).⁴ The combination of the

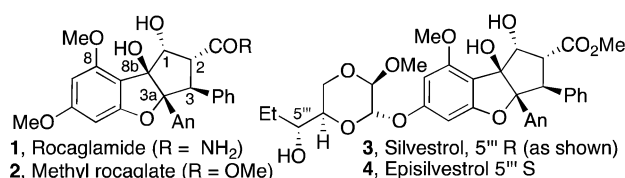


Figure 1. Typical 1H-cyclopenta[b]benzofurans from *Aglaia* (An = C₆H₄OMe-*p*).

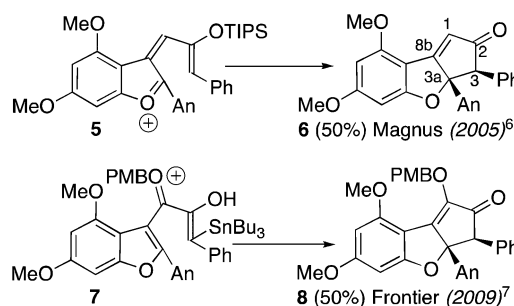
unusual structures, and significant biological properties, has generated considerable interest in the synthesis of this class of natural products.^{5a–j}

Our previous work⁶ demonstrated that conversion of intermediate **5** into **6** was stereospecific and gave only the required *cis*-stereochemical relationship between the 3-phenyl and 3a-anisyl groups (Scheme 1). Unfortunately, subsequent conversion of **6** into **2** was unsuccessful because of cumbersome changes in the oxidation states at C1 and C2, and in particular C8b hydroxylation. As a result we were only able to synthesize ($\pm$)-1,2-anhydro-**1**.

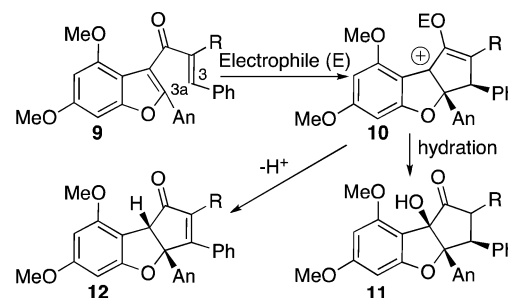
Frontier⁷ was able to modify the key Nazarov strategy and convert **7** into **8**, and subsequently elaborate **8** into rocaglamide **1**, and thus validate the original and most direct approach.

Since we eventually required a carbonyl group at C1, the alternative Nazarov cyclization strategy (Scheme 2)^{8,9} seemed worthy of investigation to construct the crucial C3–C3a carbon–carbon bond. In principle, the cross-conjugated benzofuran **9** is capable of undergoing a 4 π -conrotatory

Scheme 1. Nazarov-Type Cyclizations for Rocaglates (An = C₆H₄OMe-*p*)



Scheme 2. Prototype Nazarov Approach



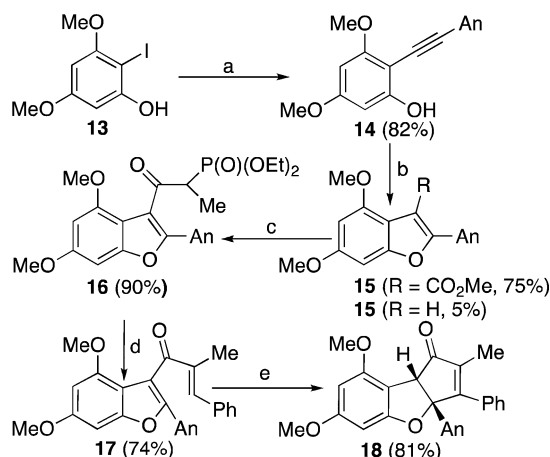
electrocyclization resulting in **10** which can either hydrate to give **11**⁹ or more likely lose a proton resulting in **12**.^{5c}

Iodophenol **13** was subjected to Kumada¹⁰ cross-coupling reaction conditions to give **14** (82%) (Scheme 3). Treatment of **14** with Pd(OAc)₂/CO in the presence of CBr₄/NaHCO₃ gave **15** (75%, R = CO₂Me) with less than 5% of the protonated byproduct (**15**, R = H).^{11,12} Conversion of **15** into **16** (90%), followed by treatment of **16** with benzaldehyde under the Masamune–Roush¹³ conditions, provided **17** (74%).

Exposure of **17** to a variety of Lewis acids such as SnCl₄, AlCl₃, TiCl₄, Sc(OTf)₃, etc. only resulted in a retro-Friedel–Crafts reaction to give **15** (R = H). However, treatment of **17** with HCl (conc) in dioxane at 100 °C for 48 h gave **18** (12%, structure by X-ray). Eventually, it was discovered that treatment of **17** with acetyl bromide in 1,2-dichloroethane at 60 °C for 6 h gave **18** (81%). If **17** is treated with HBr only demethylation of the ethers takes place. In contrast, treatment of **17** with acetyl chloride at 150 °C (sealed tube) did not result in any **18**,

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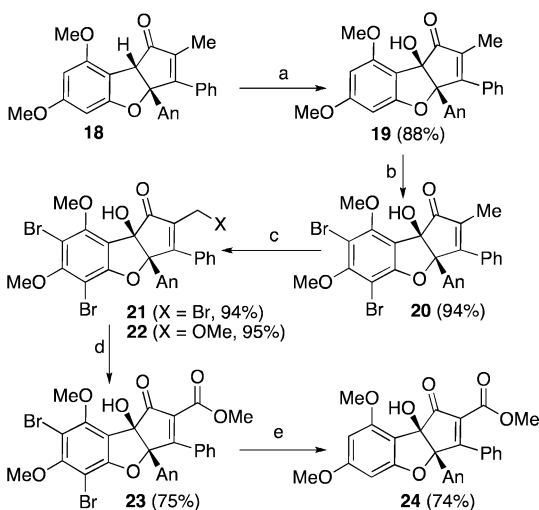
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Scheme 3. Synthesis of the Tricyclic Core of the Rocaglates^a

^aConditions: (a) $\text{AnCCH/EtMgBr/Pd(PPh}_3)_2\text{Cl}_2/\text{THF}$ at 60 °C (99%). (b) $\text{Pd(OAc)}_2/\text{CO atm/CBr}_4/\text{NaHCO}_3/\text{MeOH}$, 25 °C (75%). (c) $\text{EtP(O)(OEt)}_2/n\text{-BuLi/THF}$ (90%). (d) $\text{PhCHO/LiCl/DBU/MeCN}$, 82 °C (74%). (e) $\text{AcBr/1,2-ClCH}_2\text{CH}_2\text{Cl}$, 60 °C, 6 h (81%).

and only starting material was recovered. It should also be noted that **9** ($\text{R} = \text{H}$) cyclized to give **12** ($\text{R} = \text{H}$) in 12% yield when exposed to acetyl bromide, and **12** ($\text{R} = \text{CN}$) did not cyclize at all. As a consequence we examined the conversion of **18** into **24** through oxidation of the allylic methyl group.

All attempts to oxidize the allylic methyl group in **18** failed, and as a result we examined the introduction of the C8b tertiary hydroxyl group into **18**. It was found that treatment of **18** with ceric ammonium nitrate (CAN) in 1:1 acetonitrile and water at 25 °C gave **19** (88%, structure by X-ray) (Scheme 4). Treatment of **19** with dibromohydantoin in dioxane at 0 °C gave **20**, which on further reaction with dibromohydantoin/ PhCl/AIBN reflux resulted in clean conversion into **21**. Exposure of **21** to NaOMe/MeOH gave **22**, which was

Scheme 4. Completion of the Synthesis of **2**^a

^aConditions: (a) $\text{CAN/MeCN/H}_2\text{O}$ at 23 °C for 20 min (88%). (b) 5,5-Dimethyl-1,3-dibromohydantoin (DBDMH)/dioxane/ H_2O , 0 °C (94%). (c) DBDMH/ PhCl/AIBN , reflux 3 h (94%), followed by NaOMe/MeOH (95%). (d) Trichloroisocyanuric acid/ $\text{CCl}_4/\text{H}_2\text{O/h}\nu$ (75%). (e) $t\text{-BuLi/THF}$ at -78 °C (74%).

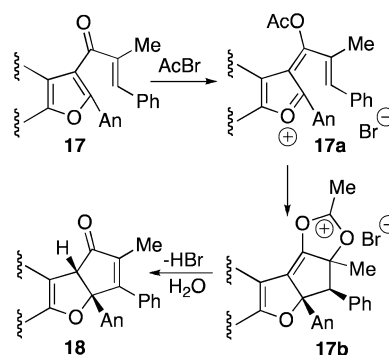
converted into **23** (75%).¹⁴ Removal of the two bromine atoms in **23** was accomplished by treatment with $t\text{-BuLi/THF}$ resulting in the known compound **24**.

Since **24** has been converted into methyl rocaglate **2** by hydrogenation and reduction of the C-1 carbonyl group with NaHB(OAc)_3 , this completes the synthesis.^{5b,7}

The concise route to the core rocaglate structure **18** (6 steps), and the unique acetyl bromide mediated Nazarov cyclization, provides a very direct way of accessing this unusual class of natural products.

The success of the acetyl bromide mediated Nazarov cyclization may be attributed to the fact that acetyl bromide is approximately 200 times more reactive than acetyl chloride.¹⁵ We speculate that acetylation of **17** occurs to give the oxonium ion **17a**, which cyclizes to the acetoxonium ion **17b**. Proton loss from **17b** and aqueous workup provide **18** (Scheme 5).

Scheme 5. Mechanism of AcBr Mediated Nazarov Reaction



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for the synthesis of **13**, **14**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, and **24** are described, along with the X-ray data for **18** and **19** (cif files). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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