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Stereospecific Synthesis of (±)-1,2-Anhydro Methyl Rocaglate

Philip Magnus* and Matthew A. H. Stent

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

p.magnus@mail.utexas.edu

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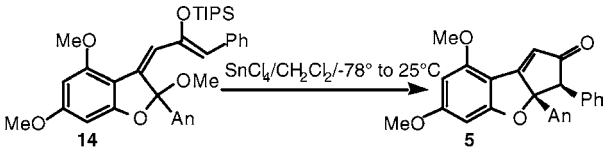
ABSTRACT

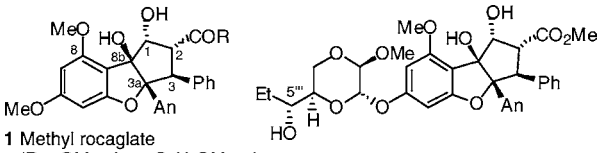


14 5

The rocaglates and analogues thereof have recently become targets for synthesis because of their potent antitumor activity. One of the major difficulties has been the control of stereochemistry of the adjacent –Ph and –An groups. In this letter we show that 14 is converted into 5 as a single stereoisomer and subsequently transformed into 1,2-anhydro methyl rocaglate 20.

The genus *Aglaia* (Meliaceae) is a diverse species that occurs in tropical rain forests (Indo-Malaysian) and produces 1*H*-cyclopenta[*b*]benzofurans as exemplified by the structure of methyl rocaglate **1**[1a] and rocaglamide **2**,[1b] Scheme 1. The

Scheme 1



1 Methyl rocaglate (R = OMe, An = C_6H_4OMe-*p*)
2 Rocaglamide (R = NH_2, An = C_6H_4OMe-*p*)
3 Silvestrol, 5‴ R (as shown)
4 Episilvestrol 5‴ S

rocaglates have insecticidal activity (comparable to azadirachtin),[2] but more importantly, they are very potent cytotoxic compounds when evaluated against human cell lines. More recently, the rocaglate derivatives silvestrol **2** and episilvestrol **3** have been isolated from the fruits and twigs of *Aglaia foveolata* (Pannell) and have cytotoxic activity comparable to that of taxol.[3] The combination of the unusual structures and significant biological properties has generated interest in the synthesis of **2**.[4] The cis stereochemical relationship between C-3 (−Ph) and C-3a

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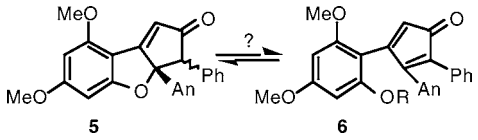
(−An) has proven to be an awkward synthetic problem, and until recently[4h] there was no strategy able to control this stereochemistry without also giving rise to the unnatural trans-3,3a stereoisomer.

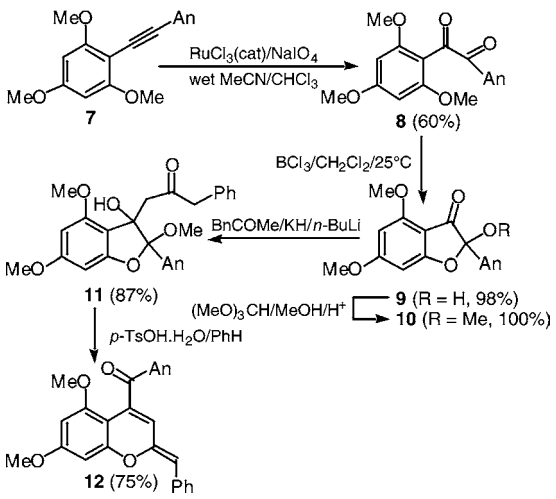
Scheme 2 depicts our initial premise for the synthesis of the enone **5**. If we synthesized the enone **5** and allowed it to equilibrate via β-elimination under both acidic and basic conditions to the triarylcyclone **6** (R = H) or its phenolate anion,[5] would there be a preference for cis-C-3 (−Ph) and C-3a (-An) versus trans stereochemistry?[6]

Scheme 2



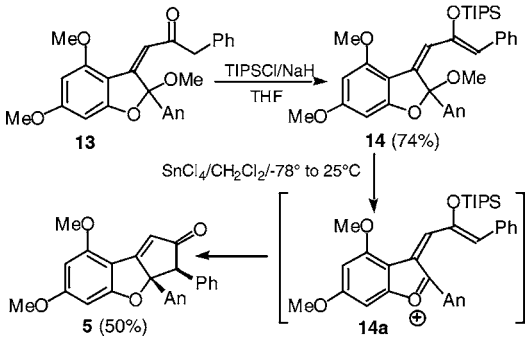
Coupling of 2,4,6-trimethoxyiodobenzene[7] with 4-methoxyphenylacetylene under Sonogashira reaction conditions gave **7** (80%), which was oxidized with $RuCl_3$ (catalyst)/$NaIO_4$/wet $CH_3CN/CHCl_3$ to give **8** (60%), Scheme 3.[8] All attempts to condense **8** with benzyl methyl ketone failed to produce **6** (R = Me) (the characteristic crimson color of a tetra- or triarylcyclone was not observed, see later).[9] Consequently, we adopted an indirect route to achieve the same objective.

Scheme 3



Treatment of **8** with BCl_3/CH_2Cl_2/25 °C gave **9** (98%, R = H), which was exposed to $(MeO)_3CH/MeOH/H_2SO_4$/65 °C to provide **10** (100%, R = Me). To a solution of the dianion of benzyl methyl ketone[10] (benzyl methyl ketone/KH followed by *n*-BuLi/THF/25 °C) was added **10**, and after 16 h the reaction mixture was cooled to −78 °C and quenched with acetic acid to give **11** (87%). Treatment of **11** with *p*-TsOH·H_2O in PhH did not give **5**, but rather **12** (75%, structure by X-ray). To avoid this problem we decided to approach the formation of the crucial C3−C3a bond stepwise.

Scheme 4



Exposure of **11** to Amberlyst 15 acidic ion-exchange resin (50 wt %) in benzene at 23 °C gave **13** (94%), which was converted into the triisopropylsilyl enol ether **14** (TIPSCl/NaH/THF/65 °C) in 74% yield as a single stereoisomer, Scheme 4. Treatment of **14** with $SnCl_4/CH_2Cl_2$/−78 to 25 °C gave **5** (50%, structure by X-ray, Figure 1). We could not detect (^{1}H NMR of crude product) the other stereoisomer of **5**. Interestingly, and somewhat amusingly, when **5** was treated with KOBu^t/HOBu^t, a deep crimson solution formed

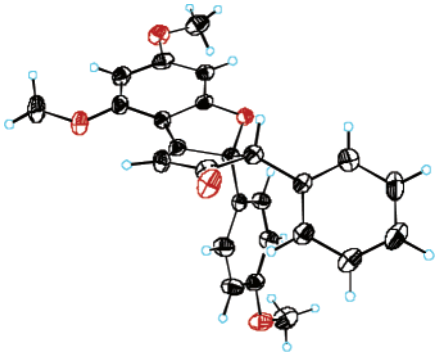


Figure 1. ORTEP drawing of **5** showing the cis arrangement of the 3-phenyl and 3a-anisyl substituents.

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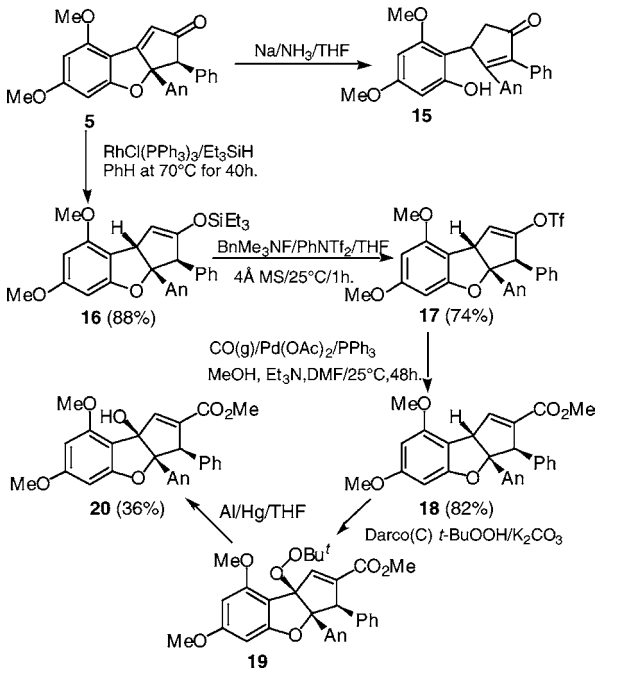
from which **6** (R = H) was isolated, and it could not (under a variety of acidic conditions) be induced to cyclize to **5**! Consequently, while we have arrived at **5** via an Isler−Mukaiyama aldol reaction[11] or conrotatory Nazarov reaction of the cation **14a**,[12] the original premise concerning the reversibility was flawed presumably because of the strongly electron-donating aryl rings in **6** overwhelming the antiaromatic character of the cyclopentadienone ring.

Any attempts to conjugatively reduce **5** without in situ enolate trapping resulted in β-elimination to the enone **15**, Scheme 5. Hydrosilylation of **5** using the Wilkinson's catalyst conditions gave **16**. Desilylation of **16** using a combination of the Corey and Kumajima methodology[13] and trapping of the enolate with *N*-phenyltrifluoromethanesulfonimide[14] resulted in **17**. Carboxymethylation of **16** using the Ortar conditions gave **18**.[15] At this stage we investigated the possibility of benzylic oxidation to convert **18** into **20**.

The substrate **18** proved to be very resistant to most of the standard benzylic/allylic oxidation protocols. Eventually, it was found that exposure of **18** to Darco G-60 activated carbon in the presence of *t*-BuOOH/K_2CO_3[16] in benzene at reflux, followed by reduction of the intermediate *t*-Bu peroxy ether **19** with aluminum amalgam, resulted in clean conversion into the tertiary alcohol **20** (36%) and 22% of recovered **18**.

Scheme 5



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Supporting Information Available: Detailed descriptions of experimental procedures and spectroscopic data for compounds **5**, **7**−**14**, **16**−**18**, and **20**, including crystallographic data (CIF) for **5** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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