JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

# Formal Synthesis of (±)-Methyl Rocaglate Using an Unprecedented Acetyl Bromide Mediated Nazarov Reaction

Philip Magnus,* Wesley A. Freund, Eric J. Moorhead, and Trevor Rainey

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

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 acetylbromide 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 1*H*-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

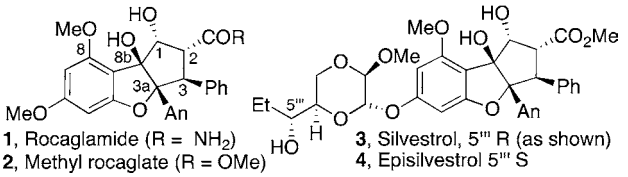



**Figure 1.** Typical 1*H*-cyclopenta[*b*]benzofurans from *Aglaia* (An = $C_6H_4OMe$-*p*).

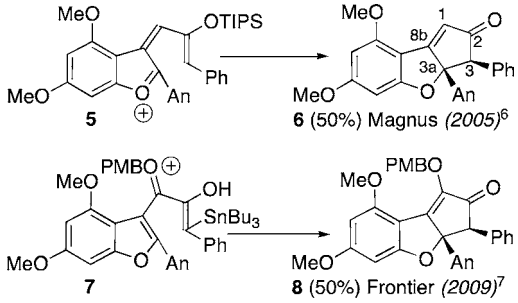
unusual structures, and significant biological properties, has generated considerable interest in the synthesis of this class of natural products.[5a−j]

Our previous work[6] 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 (±)-1,2-anhydro-**1**.

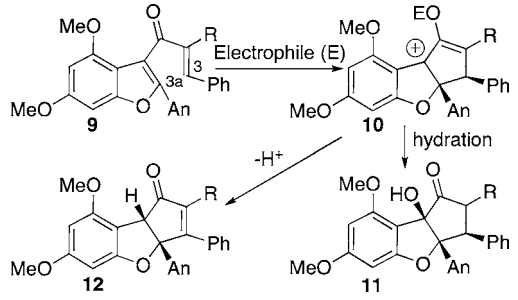
Frontier[7] was able to modify the key Nazarov strategy and convert **7** into **8**, and subsequently elaborate **8** into rocaglamide **1**, and thus validate the original and most direct approach.

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 4π-conrotatory

**Scheme 1. Nazarov-Type Cyclizations for Rocaglates (An = $C_6H_4OMe$-*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]

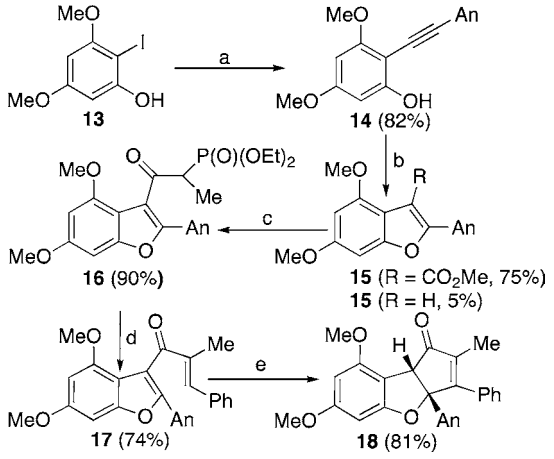
Iodophenol **13** was subjected to Kumada[10] cross-coupling reaction conditions to give **14** (82%) (Scheme 3). Treatment of **14** with $Pd(OAc)_2$/CO in the presence of $CBr_4$/$NaHCO_3$ gave **15** (75%, R = $CO_2Me$) with less than 5% of the protonated byproduct (**15**, R = H).[11,12] Conversion of **15** into **16** (90%), followed by treatment of **16** with benzaldehyde under the Masamune−Roush[13] conditions, provided **17** (74%).

Exposure of **17** to a variety of Lewis acids such as $SnCl_4$, $AlCl_3$, $TiCl_4$, $Sc(OTf)_3$, 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**,

**Received:** February 1, 2012
**Published:** March 24, 2012

   dx.doi.org/10.1021/ja300900p | *J. Am. Chem. Soc.* 2012, 134, 6140−6142

**Scheme 3. Synthesis of the Tricyclic Core of the Rocaglates**[a]

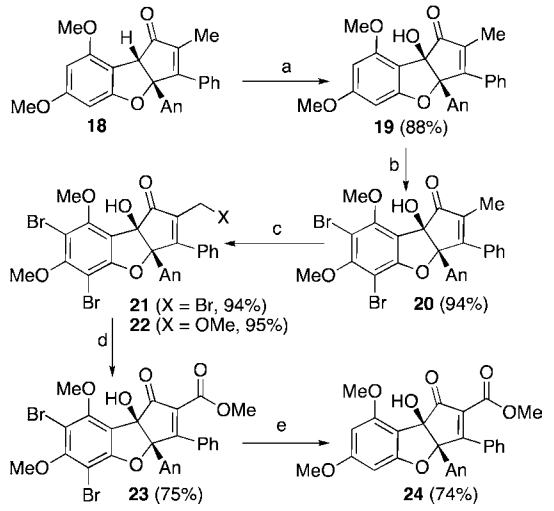



[a]Conditions: (a) AnCCH/EtMgBr/$Pd(PPh_3)_2Cl_2$/THF at 60 °C (99%). (b) $Pd(OAc)_2$/CO atm/$CBr_4$/$NaHCO_3$/MeOH, 25 °C (75%). (c) $EtP(O)(OEt)_2$/*n*-BuLi/THF (90%). (d) PhCHO/LiCl/DBU/MeCN, 82 °C (74%). (e) AcBr/1,2-$ClCH_2CH_2Cl$, 60 °C, 6 h (81%).

and only starting material was recovered. It should also be noted that **9** (R = H) cyclized to give **12** (R = H) in 12% yield when exposed to acetyl bromide, and **12** (R = 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 converted into **23** (75%).[14] Removal of the two bromine atoms in **23** was accomplished by treatment with *t*-BuLi/THF resulting in the known compound **24**.

**Scheme 4. Completion of the Synthesis of 2**[a]



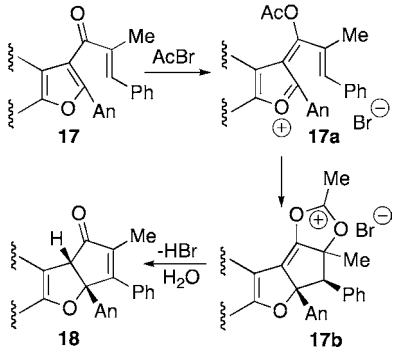

[a]Conditions: (a) CAN/MeCN/$H_2O$ at 23 °C for 20 min (88%). (b) 5,5-Dimethyl-1,3-dibromohydantoin (DBDMH)/dioxane/$H_2O$, 0 °C (94%). (c) DBDMH/PhCl/AIBN, reflux 3 h (94%), followed by NaOMe/MeOH (95%). (d) Trichloroisocyanuric acid/$CCl_4$/$H_2O$/hν (75%). (e) *t*-BuLi/THF at −78 °C (74%).

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.

## ■ AUTHOR INFORMATION

### Corresponding Author

p.magnus@mail.utexas.edu

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The Welch Chair (F-0018) is thanked for their support of this work. Dr. Vince Lynch is thanked for the X-ray structure determinations of **18** and **19**. Professor Alison Frontier is thanked for useful exchanges of information.

## ■ REFERENCES

(1) King, M. L.; Chiang, C.-C.; Ling, H.-C.; Fujita, E.; Ochiai, M.; McPhail, A. T. *J. Chem. Soc., Chem. Commun.* **1982**, 1150−1151.

(2) Ishibashi, F.; Satasook, C.; Isman, M. B.; Towers, G. H. N. *Phytochemistry* **1993**, *32*, 307−310. Cui, B.; Chai, H.; Santisuk, T.; Reutrakul, V.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *Tetrahedron* **1997**, *53*, 17625−17632. Hiort, J.; Chaidir, J. H.; Bohnenstengel, F. I.; Nugroho, B. W.; Schnieder, C.; Wray, V.; Witte., L.; Hung, P. D.; Keit, L. C.; Proksch, P. *J. Nat. Prod.* **1999**, *62*, 1632−1635.

(3) For a review of compounds from *Aglaia* species (Meliaceae), see: Proksch, P.; Edrada, R.; Ebel, R.; Bohnenstengel, F. I.; Nugroho, B. W. *Curr. Org. Chem.* **2001**, *5*, 923−938. For other related natural products, see: Dumontet, V.; Thoison, O.; Omobuwajo, O. R.; Martin, M.-T.; Perromat, G.; Chiaroni, A.; Riche, C.; Païs, M.; Sévenet, T.; Hadi, A. H. A. *Tetrahedron* **1996**, *52*, 6931−6942. Ohse, T.; Ohba, S.; Yamamoto, T.; Koyano, T.; Umezawa, K. *J. Nat. Prod.* **1996**, *59*, 650−652. Nugroho, B. W.; Edrada, R. A.; Güssregen, B.; Wray, V.; Witte., L.; Proksch, P. *Phytochemistry* **1997**, *44*, 1455−1461. Chaidir, J. H.; Nugroho, B. W.; Bohnenstengel, F. I.; Wray, V.; Witte., L.; Hung, P. D.; Keit, L. C.; Sumaryono, W.; Proksch, P.; Proksch, P. *Phytochemistry* **1999**, *52*, 837−842. Bringmann, G.; Mühlbacher, J.; Messer, K.; Dreyer, M.; Ebel, R.; Nugroho, B. W.; Wray, V.; Proksch, P. *J. Nat. Prod.* **2003**, *66*, 80−85.

(4) Hwang, B. Y.; Su, B.-N.; Chai, H.; Mi, Q.; Kardono, L. B. S.; Afriastini, J. J.; Riswan, S.; Santarsiero, B. D.; Mesecar, A. D.; Wild, N. R.; Fairchild, C. R.; Vite, G. D.; Rose, W. C.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Swanson, S. M; Kinghorn, A. D. *J. Org. Chem.* **2004**, *69*, 3350−3358. Correction: *J. Org. Chem.* **2004**, *69*, 6156. The correct taxonomic identity of the plant studied is *Aglaia foveolata* Pannell, not *Aglaia silvestris* (M. Roemer). Merrill. Kim, S.; Salim, A. A.; Swanson, S. M.; Kinghorn, A. D. *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 319−345.

(5) (a) For the synthesis of (±)-**2** before it was known to be a natural product, see: Kraus, G. A.; Sy, J. O. *J. Org. Chem.* **1989**, *54*, 77−83. (b) For synthesis of (−)-**1**, and the C1-OTMS derivative of **2**, see: Trost, B. M.; Greenspan, P. D.; Yang, B. V.; Saulnier, M. G. *J. Am. Chem. Soc.* **1990**, *112*, 9022−9024. (c) For synthesis of (±)-**2**, see: Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2657−2666. (d) For synthesis of (±)-**1**, see: Dobler., M. R.; Bruce, I.; Cederbaum, F.; Cooke, N. G.; Diorazio, L. J.; Hall, R. G.; Irving, E. *Tetrahedron Lett.* **2001**, *42*, 8281−8284. (e) For synthesis of (±)-**1** and **2** via a putative biomimetic route, see: Gerard, B.; Jones, G. II; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2004**, *126*, 13620−13621. (f) For synthesis of (±)-rocaglaol, see: Thede, K.; Diedrichs, N.; Ragot, J. P. *Org. Lett.* **2004**, *6*, 4595−4597. (g) Ragot, J. P.; Thede, K. *Eur. J. Org. Chem.* **2005**, 1731−1735. (h) Gerard, B.; Sangji, S.; O'Leary, D. J.; Porco, J. A. Jr. *J. Am. Chem, Soc.* **2006**, *128*, 7754−7755. (i) For synthesis of (−)-**3**, see: Gerard, B.; Cencic, R.; Pelletier, J.; Porco, J. A. Jr. *Angew. Chem., Int. Ed.* **2007**, *46*, 7831−7834. (j) Synthesis of (−)-**3** and (−)-**4**, see: El Sous, M.; Khoo, M. L.; Holloway, G.; Owen, D.; Scammells, P. J.; Rizzacasa, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7835−7838.

(6) Magnus, P.; Stent, M. A. H. *Org. Lett.* **2005**, *7*, 3853−3855.

(7) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560−7561.

(8) For recent reviews of the numerous reaction conditions that have been used for Nazarov cyclizations, see: Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577−7606. Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193−2206. Denmark, S. E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: 1991; Vol. *5*, pp 751−781. 1-Oxo Nazarov: Tius, M. A.; Astrab, D. P.; Fang, A. H.; Ousset, J. B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438. Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429−442. Carbocations: Sorensen, T. S.; Rauk, A. *Pericyclic reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: 1977; Vol. *II*, pp 1−71. Millar, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919−8930. He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278−14279. Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544−9545. Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 11022−11023.

(9) For recent examples of the so-called interrupted Nazarov reaction, see: Dhoro, F.; Tius, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12472−12473. Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789−3792. White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629−5632.

(10) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268−9269.

(11) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803−11812. Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297−299.

(12) Bokhari, S. A. N. N.; Whalley, W. B. *J. Chem. Soc.* **1963**, 5322−5324.

(13) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(14) Juenge, E. C.; Beal, D. A. *Tetrahedron Lett.* **1968**, *11*, 5819−5820.

(15) Isaacs, N. *Physical Organic Chemistry*, 2nd ed.; Longman Scientific and Technical: U.K., 1995. Briody, J. M.; Satchell, D. P. N. *J. Chem. Soc.* **1964**, 3724−3731.