ORGANIC LETTERS

2004
Vol. 6, No. 24
4595−4597

Stereoselective Synthesis of (±)-Rocaglaol Analogues

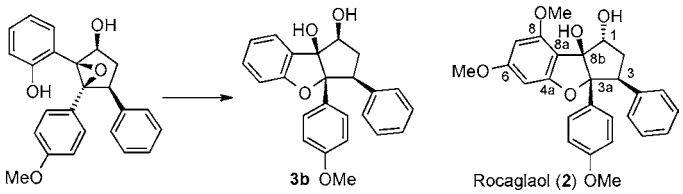
Kai Thede, Nicole Diedrichs, and Jacques P. Ragot*

Medicinal Chemistry, Pharma Research, Bayer HealthCare AG, 42096 Wuppertal, Germany

jacques.ragot@bayerhealthcare.com

Received October 1, 2004

ABSTRACT



An intramolecular hydroxy epoxide opening was used to access the cyclopenta[*b*]benzofuran ring system of the natural product rocaglaol (2). Our route allowed the stereocontrolled preparation of the rocaglaol derivative (±)-(1*S,3*S**,3a*R**,8b*S**)-3b. The synthesis of the (±)-(3*R**)-epimer of 3b was also achieved. Our strategy is well-suited for the production of analogues with variation of the western ring.**

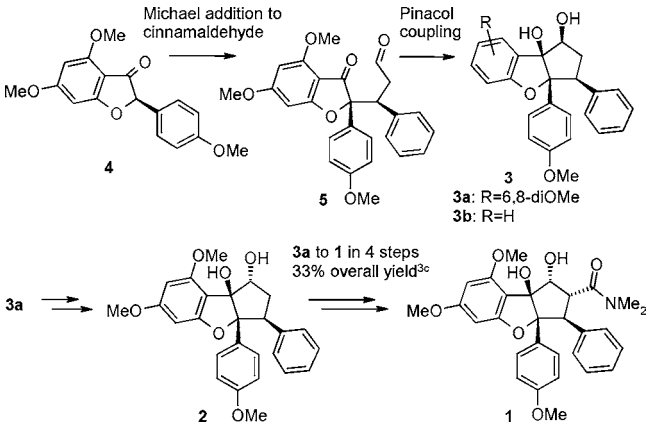
Rocaglamide (**1**), isolated from *Aglaia elliptifolia* in 1982,[1] is the parent compound of a unique family of more than 50 natural products featuring a cyclopenta[*b*]tetrahydrobenzofuran skeleton. The chemistry and biological activity of rocaglamide derivatives have been recently reviewed.[2] Their chemical diversity and biological activity, in particular insecticidal and cytostatic activity, both contribute to make rocaglamide derivatives interesting candidates for therapeutic agents.

Several total syntheses and synthetic studies of rocaglaol (**2**) and rocaglamide (**1**) have been published,[3] the majority of them using **3a** as a common intermediate (Scheme 1).[3b−e]

Compound **3a** was prepared efficiently by Taylor et al.[3c] by a Michael addition of the benzofuranone **4** to cinnamaldehyde and intramolecular pinacol coupling of the aldehyde **5** mediated by samarium iodide (Scheme 1). Unfortunately, access was limited to very electron-rich benzofuranones coming from Hoesch or Friedel−Crafts reactions. Only rocaglaol derivatives bearing a dimethoxy- or diethoxy-substituted western ring could be prepared.

We therefore decided to develop a synthesis of derivatives of type **3** with a (1*S**,3*S**,3a*R**,8b*S**)-core (rocaglaol numbering) that would allow variation of the substituent R on the western ring.

Scheme 1. Synthesis of Rocaglaol/Rocaglamide from Benzufuranone via Intermediate **3a** by Taylor et al.



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

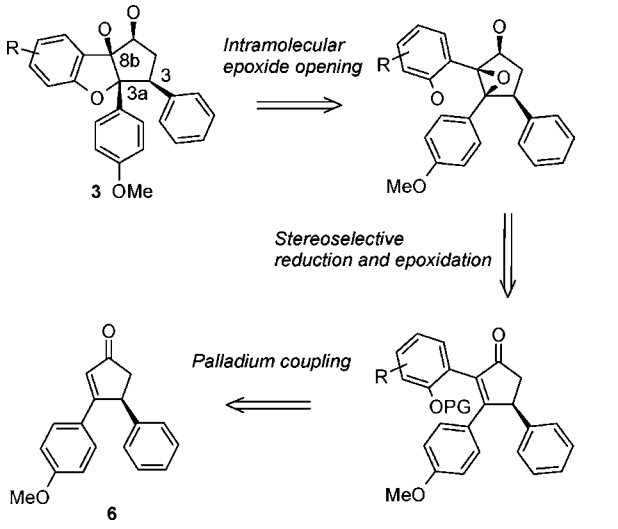
(2) Proksch, P.; Edrada, R.; Ebel, R.; Bohnenstengel, F. I.; Nugroho, B. W. *Curr. Org. Chem.* **2001**, *5*, 923.

(3) (a) Trost, B. M.; Greenspan, P. D.; Yang, B. V.; Saulnier, M. G. *J. Am. Chem. Soc.* **1990**, *112*, 9022. (b) Kraus, G. A.; Sy, J. O. *J. Org. Chem.* **1989**, *54*, 77. (c) Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1991**, 1137. Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2657. (d) Watanabe, T.; Shiraga, Y.; Takeuchi, T.; Otsuka, M.; Umezawa, K. *Heterocycles* **2000**, *53*, 1051. (e) Dobler, M. R.; Brune, I.; Cederbaum, F.; Cooke, N. G.; Diorazio, L. J.; Hall, R. G.; Irving, E. *Tetrahedron Lett.* **2001**, *42*, 8281.

10.1021/ol0479904 CCC: $27.50
Published on Web 11/02/2004

Our retrosynthetic approach was based on the idea of installing the (3a*R**,8b*S**)-stereochemistry using an intramolecular epoxide opening (Scheme 2). The necessary

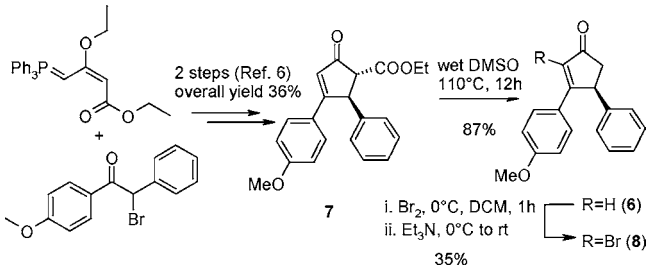
Scheme 2. Retrosynthetic Approach



epoxy-cyclopentanol would be obtained in a stereoselective manner via the corresponding cyclopentenone. This would itself be constructed from the unsymmetrical cyclopentenone **6** using Pd methodology. In a successful implementation of this idea, we were able to prepare (±)-(1*S**,3*S**,3a*R**,8b*S**)-**3b** (R = H).[4]

Symmetrical 3,4-diaryl-cyclopent-2-enones are readily available via cyclization of α,*β*-diketones with acetone followed by elimination of water.[5] Unsymmetrical ones, however, are more troublesome to prepare. An elegant solution was developed at Bayer by Schoop et al.[6] Cyclization of allyldienetriphenylphosphorane with α-bromoketones followed by reaction with HCl provided regioselectively unsymmetrical cyclopentenones (Scheme 3, reaction with 2-bromo-1-(4-methoxyphenyl)-2-phenylethanone).

Scheme 3

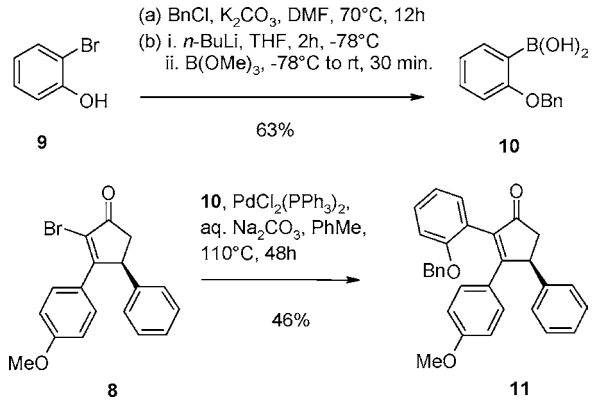


Following Schoop's methodology, cyclopentenone **7** was successfully prepared in multigram quantity and improved yield (80% over two steps) and served as starting material for our synthesis (Scheme 3).

Heating **7** at 110 °C in wet DMSO for 12 h afforded the decarboxylated cyclopentenone **6**. At a more elevated temperature (140 °C), the double bond migrated to produce an inseparable mixture of **6** and its regioisomer 4-(4-methoxyphenyl)-3-phenylcyclopent-2-en-1-one. The α-bromination of **6** proved to be difficult due to the formation of di- and tribrominated side-products. Although different reaction conditions were tried (pyridinium tribromide in pyridine/DCM or oxone followed by treatment with NaBr and triethylamine in CCl_4), addition of Br_2 to the enone **6** followed by elimination of HBr with triethylamine was the preferred method and gave the desired α-bromoenone **8** in 35% yield.

The western side of the molecule was installed using a Pd-mediated Suzuki coupling (Scheme 4). Phenol **9** was

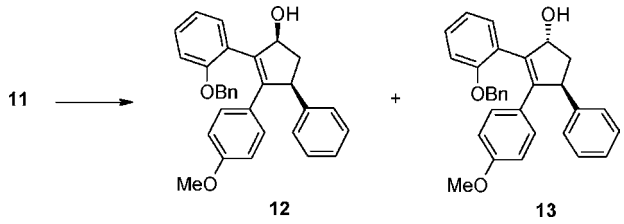
Scheme 4



protected as a benzyl ether which was converted into boronic acid **10** with *n*-BuLi and trimethyl borate. This boronic acid **10** was then reacted with the bromocyclopentenone **8** to give **11**.

Table 1 shows the optimization of the reduction of ketone **11**. $NaBH_4$ and DIBAL-H gave no selectivity. Low selectivity was obtained with the Luche reduction. L-Selectride gave

Table 1. Diastereoselective Reduction of Cyclopentenone **11**



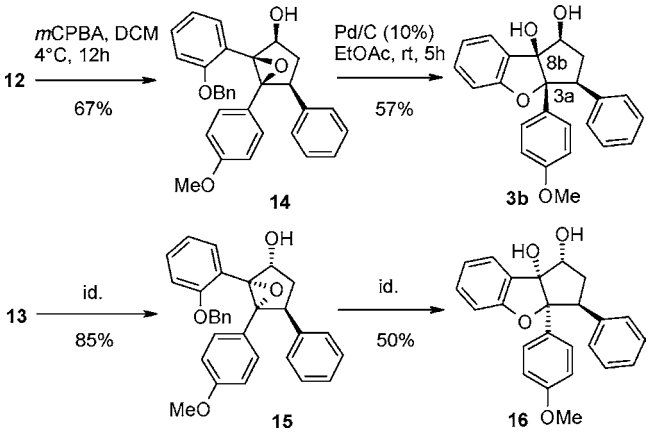
method	**12**:**13**	yield **12** (%)[a]
DIBAL-H (1.1 equiv), DCM, −78 °C	50:50	5
$NaBH_4$ (2 equiv), MeOH, 0 °C	50:50	37
$NaBH_4$ (5 equiv), MeOH, 0 °C−rt	51:49	51
$NaBH_4/CeCl_3$ (2/1), MeOH−DCM, 0 °C	63:37	40
$NaBH_4/CeCl_3$ (1/1), MeOH−DCM, rt	66:33	60
L-Selectride (1.1 equiv), THF, −78 °C	>99:1	70

[a] Isolated yield.

the best results, and the *syn*-alcohol **12** was obtained in 70% yield with complete diastereoselectivity. The stereochemistry of **12** was assigned on the basis of chemical analogy and confirmed with NOESY experiments.[7]

The corresponding anti isomer **13** was isolated in 37% yield with $NaBH_4/CeCl_3$ in MeOH−DCM. With the allylic alcohols **12** and **13** in our hand, we could install the remaining two stereocenters at positions 3a and 8b with a stereoselective epoxidation reaction (Scheme 5). Gratifyingly,

Scheme 5. Stereoselective Formation of the Rocaglaol Core



the use of *m*-chloroperbenzoic acid led to a complete control of the stereochemistry, which was directed by the hydroxy group (Henbest's rule).[8] The structure and stereochemistry of epoxyalcohols **14** and **15** were based on chemical analogy and confirmed with NOESY experiments.[7]

The last step was the cyclization to form the benzofuran ring after the removal of the benzyl group (Scheme 5). We expected that the deprotected phenolic group would react at C-3a and open the epoxide. Because of the fixed geometry of the epoxide, the opening would be stereospecific and lead to the desired stereoisomer (±)-**3b** possessing the rocaglaol core. The deprotection was best achieved using Pd/C (10%) in ethyl acetate (ethanol led to degradation products). We were delighted to see that the cyclization proceeded spontaneously under the deprotection conditions and **3b** was obtained from **14** in 57% yield. The epimer (±)-(3*R*)-**16** was obtained in 50% yield from epoxyalcohol **15** following the same method.

In conclusion, a new methodology for obtaining rocaglaol derivatives in a stereoselective way was successfully developed and exemplified by the preparation of (±)-**3b**. This method also permitted the preparation of 3-epi-rocaglaol derivatives, as was demonstrated for **16**. Simple variation of the boronic acid **10** would allow the preparation of a range of rocaglaol analogues having different substitution patterns on the western ring.

Acknowledgment. We thank Peter Schmitt for the measurement and interpretation of NMR spectra and Stefan Golinski for the preparation of compound **7**.

Supporting Information Available: Full experimental procedures and structural characterization data for all compounds prepared; ^{1}H NMR spectra for compounds **3b** and **16**; NOESY spectra for compounds **12**, **14**, and **15**; and COSY spectra for compounds **12** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0479904

(4) All compounds prepared are racemic. The relative stereochemistry is shown.

(5) Polo, E.; Barbieri, A.; Traverso, O. *Eur. J. Inorg. Chem.* **2003**, *2*, 324.

(6) Schoop, A.; Greiving, A.; Goehrt, A. *Tetrahedron Lett.* **2000**, *41*, 12, 1913.

(7) Spectra of NOESY experiments are included in Supporting Information.

(8) Henbest, H. B.; Wilson, R. A. *J. Chem. Soc.* **1957**, 1958.