Total Synthesis

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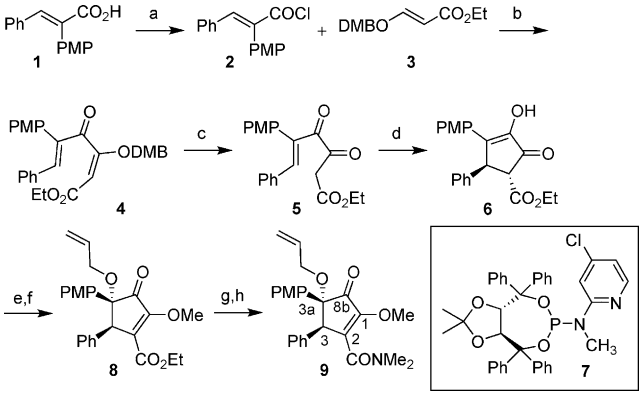
Synthesis of Each Enantiomer of Rocaglamide by Means of a Palladium(0)-Catalyzed Nazarov-Type Cyclization**

*Zhe Zhou and Marcus A. Tius**

Abstract: *A recently reported Pd^0-catalyzed asymmetric Nazarov-type cyclization has been successfully applied in the key step of the first catalytic asymmetric total synthesis of (−)-rocaglamide (natural) and (+)-rocaglamide. The stereochemistry at the C3 position that controls the stereochemistry of all other stereocenters is determined in the cyclization step. This versatile and modular synthesis proceeds from simple reagents.*

Rocaglamide was isolated in 1982 by King and co-workers from *Aglaia elliptifolia*, a tree native to south-east Asia, the extracts from which are used in traditional medicine.[1] More than 100 related compounds have been isolated from related *Aglaia* species.[2] Pharmacological interest in this class of compounds derives from their potent cytostatic and anti-inflammatory activities,[3–5] which are the result of rocaglamide impairing multiple targets. Rocaglamide targets protein translation initiation by targeting the eukaryotic initiation factor eIF4A and thereby inactivates heat shock factor 1 (HSF1), which is a transcriptional regulator that controls the heat shock response and processes essential for anabolic metabolism. As such these compounds can deprive cancer cells of energy and impair the proliferation of malignant and premalignant cells.[6] Rocaglamide has also been reported to impair transcription factor NFkB signaling (which contributes to its anti-inflammatory activity) and the kinase pathway cRAF–MEK–ERK.[7,8] Significant progress toward clinical development has only taken place during approximately the last three years, in large part because of problems with supply of materials. There are barriers in scaling up the isolation of rocaglamide from the natural source because it occurs as a mixture with structurally related compounds which are difficult to separate. Trost et al. published the first chiral-pool total synthesis of rocaglamide in 1990.[9] Since then several syntheses of racemic rocaglamide have been described.[10] The biogenetically inspired enantioselective synthesis by Porco and co-workers provides the ponapensin–thapsakon family of compounds as well as rocaglamide and is the current state-of-the-art procedure.[10a] We describe an efficient and scalable synthesis[11] of both enantiomeric forms of rocaglamide that makes use of a Nazarov-type cyclization that we have recently described in the key step.[12]

The core of rocaglamide is a fully substituted cyclopentane ring containing adjacent quaternary centers at the C3a and C8b positions. Stereochemical control, especially at the C3 position, has been a challenge for many of the previously published syntheses. Embedded within the rocaglamide we perceived a structure that we could access enantioselectively through a Pd^0-catalyzed Nazarov-type cyclization that we have recently developed.[12] Although Frontier and co-workers[10o] and Magnus et al.[10p] have prepared racemic rocaglamide by means of Nazarov cyclizations, our strategy disconnects the molecule differently. The first steps of our synthesis are summarized in Scheme 1. Known cinnamic acid (**1**)[13] was converted into acid chloride **2** by conventional means. Exposure of ethyl propiolate to 3,4-dimethoxybenzyl alcohol in dichloromethane at RT in the presence to DABCO (1,4-diazabicyclo[2.2.2]octane) produced vinylogous carbonate **3** in 82% yield.[14] Compound **3** was reacted with TMPMgCl·LiCl (TMP = 2,2,6,6-tetra-



Scheme 1. Synthesis of **9**. a) $(COCl)_2$, CH_2Cl_2, cat. DMF, RT, 12 h. b) TMPMgCl·LiCl, THF, RT, 30 min; CuCN·2 LiCl, −30 °C, 30 min; addition of **2**; 0 °C, 2 h (70%). c) $NaBrO_3$, $Na_2S_2O_4$, EtOAc, H_2O, 0 °C; Na_2SO_3 (72%). d) $[Pd_2(dba)_3]$ (5 mol%), **7** (12 mol%), MeCN, RT 20 h; after 20 h, $[Pd_2(dba)_3]$ (2.5 mol%) and **7** (7.5 mol%) were added (70%, 89:11 e.r.). e) PIFA, allyl alcohol:HFIP 2:1, −10 °C to RT, 2 h (4:1 d.r.). f) $Me_3O{\cdot}BF_4$, iPr_2NEt, CH_2Cl_2, RT, 30 min (55% yield of the major diastereomer for two steps). g) $LiOH{\cdot}H_2O$, THF:EtOH:H_2O 4:1:1, RT, 4 h. h) Me_2NH, HATU, iPr_2NEt, CH_2Cl_2, RT, 12 h (73% for two steps). PMP = 4-methoxyphenyl; DMB = 3,4-dimethoxybenzyl; TMP = 2,2,6,6-tetramethylpiperidyl; dba = dibenzylidene acetone; PIFA = phenyliodine bistrifluoroacetate; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate.

[*] Z. Zhou, Prof. Dr. M. A. Tius
Chemistry Department, University of Hawaii at Manoa
2545 The Mall, Honolulu, HI 96822 (USA)
E-mail: tius@hawaii.edu
Prof. Dr. M. A. Tius
University of Hawaii Cancer Center
701 Ilalo Street, Honolulu, HI 96813 (USA)

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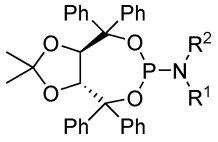
methylpiperidyl) according to the method of Bresser and Knochel,[15] followed by transmetalation with CuCN·2 LiCl and exposure to acid chloride **2** to form dienone **4** in 70% yield. Oxidative removal of the 3,4-dimethoxybenzyl (DMB) protecting group was accomplished in 72% yield (Scheme 1, step c).[16] As a result of the ease with which acid-catalyzed Nazarov cyclization of **4** takes place, the deprotection had to be performed under almost neutral conditions. Diketoester **5** was treated with Pd^0 and TADDOL-derived phosphoramidite **7** (TADDOL = α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol).[17] After 40 h at RT, cyclic product **6** was isolated in 70% yield in 89:11 e.r. The stereochemistry at the C3 position (rocaglamide numbering) controlled all subsequently introduced stereocenters.

In our earlier study of the asymmetric Pd^0-catalyzed Nazarov-type cyclizations, we had not examined substrates bearing aryl substitution at the α-enone carbon atom, nor any that lacked substitution at positions α to the ester.[12b] We predicted that these unique features in **5** might alter the stereochemical outcome of the reaction by enabling alternative modes of interaction of the substrate with the catalyst, either sterically or through π stacking. Our prediction was correct, and the conversion of **5** into **6** differed from our earlier work in that the absolute stereochemical course of the cyclization was reversed in the case of **5**. This was revealed when, based on precedence from our earlier work, we initiated the synthesis using the enantiomer of **7**, assuming that the stereochemical outcome would lead to natural (−)-rocaglamide. Instead, when we recorded the optical rotation of the final product we found that we had prepared unnatural (+)-rocaglamide. Thus ligand **7**, derived from D-(−)-tartrate was needed for the desired (*S*)-C3 stereochemistry. We then repeated the steps from **5** (Scheme 1) using **7** as the ligand, which led to the formation of (−)-rocaglamide, as detailed below.

A modest number of ligands were prepared from which **7** was selected (Table 1). Our starting point was *N*-methyl-*N*-2-pyridyl phosphoramidite (**10**) that we have described in earlier work[12b] and which led to *ent*-**6** in 85:15 e.r. but in a slow reaction. Ligand *ent*-**7** accelerated the cyclization and improved the e.r. value to 89:11. Varying the size of the aliphatic group on the phosphoramidite nitrogen atom while maintaining the 2-pyridyl (entries 4–7, **12**–**15**) led to inferior results. Ligand **11** (entry 3) was comparable to **10**, whereas **16**–**18** (entries 8–10) were inferior. Varying the phenyl groups on the TADDOL fragment decreased the product e.r. and led to a slower reaction. Accordingly, ligand **7** was chosen for further reactions.[18]

The introduction of the oxygen atom at the C3a position was challenging. In the presence of base, oxidation invariably took place at the C2 position so a procedure for regio- and stereospecific oxidation at C3a was developed that proceeded under mildly acidic conditions. We combined the oxidation with the protection of the hydroxy group at the C3a position. The protecting group must be small enough to not suppress later addition of the aryl nucleophile at C8b, precluding the use of trialkylsilyl ethers. Protection as the methyl ether did not suppress the nucleophilic addition, but its subsequent removal could not be achieved. We postulated that the readily cleaved allyl ether might be small enough to permit nucleophilic addition at C8b. Accordingly, treatment of **6** with PIFA in a 2:1 mixture of allyl alcohol and HFIP (Scheme 1) resulted in the introduction of an allyloxy group at the C3a position in a stereoselective reaction (4:1 d.r.).[19,20] Exposure of the product to Meerwein's salt ($Me_3O·BF_4$) led to formation of the enol ether **8** in 55% overall yield for the two steps. Ester hydrolysis followed by conversion of the carboxylate into the dimethyl amide gave **9** in 73% yield.

Table 1: Phosphoramidite ligands for the cyclization of **5** to form **6**.[a]



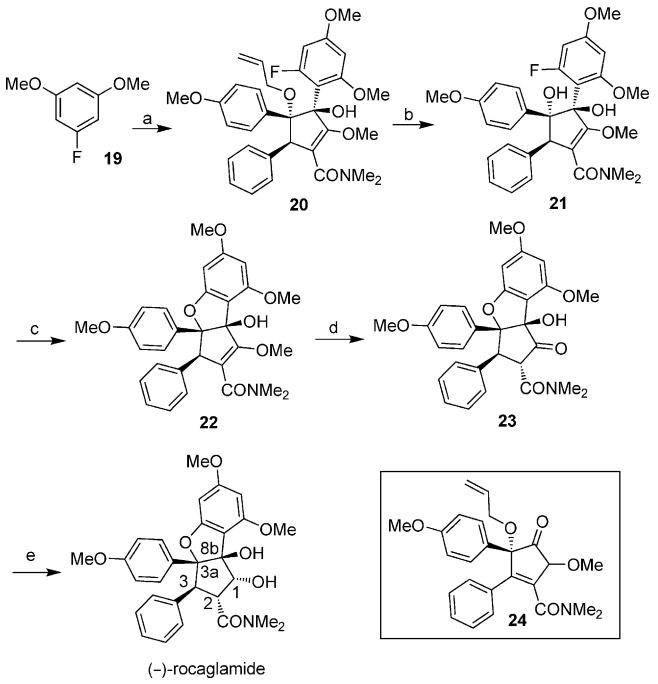
Entry	ligand	R^1	R^2	e.r. of *ent*-**6**[b]
1	**10**	Me	2-pyridyl	85:15
2	*ent*-**7**	Me	2-(4-chloro)pyridyl	89:11
3	**11**	Et	2-(6-phenyl)pyridyl	85.5:14.5
4	**12**	*n*Bu	2-pyridyl	75:25
5	**13**	Ph	2-pyridyl	72:28
6	**14**	2-pyridyl	2-pyridyl	71.5:28.5
7	**15**	H	2-pyridyl	60:40
8	**16**	Me	2-quinolyl	71.5:28.5
9	**17**	$(CH_2)_2O(CH_2)_2$		27:73[c]
10	**18**	Me	(2-furyl)methyl	25:75[c]

[a] All reactions were performed with $[Pd_2(dba)_3]$ (10 mol%) and ligand (25 mol%) in MeCN at RT. [b] e.r. values were determined by HPLC analysis on a chiral stationary phase using Chiralpak AD-H, OD-H, or OD columns. [c] The ligand was derived from (*4S*,*5S*)-TADDOL.

The concluding steps of the synthesis are summarized in Scheme 2. Commercially available 3,5-dimethoxyfluorobenzene (**19**) was lithiated and then transmetallated with $LaCl_3·2$ LiCl prior to exposure to **9**,[21,22] producing tertiary alcohol **20** in 87% yield as a single isomer. The two adjacent *cis* aryl groups in **9** direct the nucleophilic addition. Transmetallation to lanthanum is essential to the success of the reaction. If this step is omitted, the yield of **20** is 38% and substantial amounts of **24** are formed from competitive deprotonation at the C3 position. Recrystallization of the scalemic mixture from dichloromethane/hexanes led to the recovery of highly optically enriched **20** (98.5:1.5 e.r.) in 75% yield from the mother liquor. This material was carried forward to the end of the synthesis.

Cleavage of the allyl protecting group in **20** was challenging. Palladium-catalyzed reductive cleavage of the allyl protecting group[23] failed under a number of conditions, possibly because of steric inhibition to forming the initial complex. However, SeO_2-mediated oxidative cleavage of the allyl group in refluxing dioxane[24] took place in 78% yield leading to the formation of diol **21**.

Exposing **21** to potassium *tert*-butoxide in THF at RT for a few minutes led to the formation of the dihydrobenzofuran ring, leading to **22** in 89% yield.[25] This process likely takes place by means of nucleophilic aromatic substitution, as these conditions do not generate the benzyne. For the cleavage of the methyl ether at the C1 position in **22**, MgI_2 was freshly prepared in ether, the solution was diluted with toluene, **22** was added, and the solution heated to 90 °C for 15 min leading



Scheme 2. Conversion of **9** into (−)-rocaglamide. a) *n*BuLi, THF, −78 °C, 1 h; $LaCl_3$·2 LiCl, −78 °C, 1 h; addition of **9**; −30 °C, 1.5 h (87%, 89:11 e.r.); recrystallized from CH_2Cl_2:hexanes to 98.5:1.5 e.r. (75% recovery). b) SeO_2, HOAc, dioxane, reflux, 30 min (78%). c) *t*BuOK, THF, RT, 15 min (89%). d) MgI_2, PhMe, 90 °C, 15 min (92%). e) $NaBH(OAc)_3$, HOAc, MeCN, RT, 16 h (73%, 99:1 e.r.).

to **23** in 92% yield.[26] Reduction of the keto group in the last step was accomplished according to a published procedure,[10n] furnishing (−)-rocaglamide in 73% yield (99:1 e.r.). (+)-Rocaglamide was prepared in the same way, except using *ent*-**7** as the ligand for the catalytic asymmetric cyclization.

There are several noteworthy features of this synthesis. We have reported the first application of the catalytic asymmetric Nazarov-type cyclization in total synthesis for the preparation of natural (−)-rocaglamide and for the first preparation of (+)-rocaglamide. The stereochemistry at the C3 position that is established during the cyclization controls the stereochemistry at all subsequent stereocenters. We have followed a unique strategy in which the benzofuran ring is formed at a late stage. This feature is significant because our synthesis provides easy access from **9** to rocaglamide analogues differing in the dimethoxyaryl ring, an important pharmacophoric region of the molecule. Additionally, the highly stereoselective oxidative etherification of **6** by means of PIFA provides a new example of this useful process and the use of novel reagents such as TMPMgCl and $LaCl_3$·2 LiCl demonstrates their utility in synthesis.

Keywords: cyclization · enantiomers · natural products · palladium · total synthesis

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