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Natural Product Synthesis

The Evolution of the Total Synthesis of Rocaglamide

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Abstract: The complex flavagline, (−)-rocaglamide, possesses a synthetically intriguing tricyclic scaffold with five contiguous stereocenters and also exhibits potent anticancer, anti-inflammatory and insecticidal activity. This full account details distinct approaches to (±)- and (−)-rocaglamide utilizing Brønsted acid catalyzed and asymmetric Pd^0-catalyzed Nazarov chemistry developed in our laboratory, respectively. The successful asymmetric synthesis revealed unforeseen mechanistic complexity that required adjusting our strategy to overcome an unanticipated racemization process, an unusual reversible ring-cleavage step and a very facile trialkylsilyl group migration.

Introduction

In a recent communication, we described the first catalytic asymmetric synthesis of (+)- and (−)-rocaglamide (Figure 1).[1] The key step was a Pd^0-catalyzed Nazarov-type cyclization.[2,3] Herein, we disclose a more detailed description of our work with the goal of illuminating the evolution of our strategy.

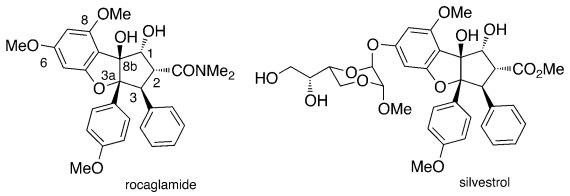

Figure 1. Structures of (−)-rocaglamide and (−)-silvestrol.

Rocaglamide was isolated in 1982 from *Aglaia elliptifolia*, a tree native to SE Asia, by the King group.[4] More than 100 related compounds have been isolated from related *Aglaia* species.[5] Pharmacological interest in this class of compounds derives from their potent cytostatic and anti-inflammatory activities.[6–8] These activities are the result of rocaglamide impairing multiple targets. Rocaglamide inhibits protein translation initiation by engaging 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.[9] The mechanism of the inhibition is by forcing the close association of eIF4A with the polypurine segments of messenger RNA in an ATP-independent process which leads to premature initiation of protein translation.[10] Rocaglamide has also been reported to impair NFkB signaling (that contributes to its anti-inflammatory activity) and the cRAF-MEK-ERK pathway.[11,12] Additionally, rocaglamide and other flavaglines are potent insecticides.[13]

Results and Discussion

The promising pharmacological activity of rocaglamide and also of silvestrol (Figure 1),[14] as well as the challenging, sterically congested structures have led to a great deal of interest from the organic synthesis community.[15] A significant challenge is associated with the control of relative stereochemistry at C3 and C3a. The first total synthesis by Trost and co-workers made use of the [3+2] cycloaddition of a trimethylene methane.[15a] The absolute stereochemistry was successfully controlled by means of a chiral auxiliary, however, the stereochemistry at C3 had to be inverted, thereby adding three steps to the synthesis. Taylor and co-workers' synthesis of racemic rocaglamide achieved around 6:1 diastereoselectivity favoring the desired *cis* C3–C3a stereochemistry through Michael addition to cinnamaldehyde.[15b,c] Both the Frontier[15n] and Magnus[15i,p] groups employed a Nazarov cyclization for the assembly of the five-membered ring. Porco and co-workers developed a unique biosynthetically patterned photochemical synthesis.[15f,j,k,q] A recent review summarizes the recent progress in this area.[16]

We will first discuss our synthesis of racemic rocaglamide that differs from the synthesis of the enantioenriched product in several ways. The known product **1** (PMP = 4-methoxyphenyl), from the Perkin condensation of 4-methoxyphenylacetic acid with benzaldehyde[17] was a convenient starting material for the synthesis of both the racemate as well as the enantio-

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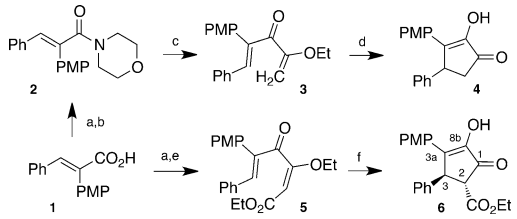


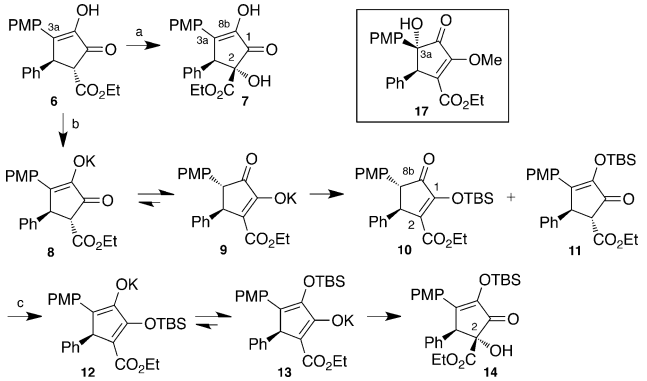
Scheme 1. Preliminary studies of the cyclization. a) $(COCl)_2$, CH_2Cl_2, cat. DMF, RT, 4 h. b) Pyr, morpholine, CH_2Cl_2, RT, 2 h; 82%. c) Ethyl vinyl ether, *t*BuLi, THF, −78 °C to 0 °C to −78 °C; add **2**, −78 °C, 1 h. d) 6 mol% $[PdCl_2(MeCN)_2]$, acetone, 2–2.5 d, RT; 67% from **2**. e) Add TMPMgCl·LiCl to 3-ethoxy ethyl acrylate, THF, RT, 30 min; CuCN·2 LiCl, −30 °C, 30 min; add acid chloride; warm to 0 °C, 2 h; 79%. f) Cat. Tf_2NH, CH_2Cl_2, −78 °C to RT, 2 h; 89%.

merically enriched natural product (Scheme 1). The conversion of **1** to morpholino enamide **2** was straightforward. Deprotonation of ethyl vinyl ether by *tert*-butyllithium,[18] followed by trapping of ethoxyvinyllithium by **2** led to dienone **3**. Exposure of **3** to catalytic $[PdCl_2(MeCN)_2]$ complex in acetone, led to α-hydroxycyclopentenone **4** in 67% yield for the two steps from **2**. This reaction is an application of the method that we described in 2003 which proceeds through an intermediate Pd^{II} enolate.[19] When $[PdCl_2(PPh_3)_2]$ was used in place of the acetonitrile complex no cyclization took place, presumably because of the attenuation of the electrophilicity of the palladium. Consequently, homochiral diphosphine ligands could not be used to induce asymmetry in **4**. Also, whereas hydroxyenone **4** was readily converted to the enol triflate in 94% yield, all attempts to perform cross-coupling reactions with it or with the trimethylstannyl cyclopentenone derived from it, led to disappointing results. Fortunately, a much better approach suggested itself.

The acid chloride derived from the Perkin condensation product **1** was allowed to react with the vinyl copper species prepared from commercially available 3-ethoxy ethyl acrylate according to Knochel's excellent protocol.[20] Dienone **5** was thus formed in 79% overall yield for the two steps from **1**. For the purposes of the racemic series synthesis, exposure of **5** to 5–10 mol% triflimide in dichloromethane at room temperature led to cyclopentenone **6** in 89% yield. Although conrotation of the pentadienyl carbocation derived from protonation of **5** would have led to the *cis* diastereomer of **6**, facile isomerization to the observed *trans* isomer in all likelihood took place under the conditions for the cyclization. Cyclopentenone **6** represents the core structure of rocaglamide in which C1 and C8b (rocaglamide numbering) are oxidized, the phenyl and 4-methoxyphenyl appendages are attached to C3 and to C3a, respectively, with the carboethoxy group of **6** standing in for the C2 *N,N*-dimethylamide of rocaglamide.

At the time of this work we had been developing CBA-(chiral Brønsted acid)[21] and Pd^0-catalyzed[2] Nazarov cyclizations. Cyclopentenone **6** was an attractive starting material because it could be accessed from either reaction. Eventually, the Pd^0-catalyzed process was deployed for the enantioselective synthesis, whereas racemic **6** was prepared from the acid catalyzed cyclization of **5**. Since cross coupling reactions with **6** were expected to be very challenging based on our experience with **4**, we planned to first exploit the enolic function so as to introduce the required hydroxyl function at C3a. The stereochemistry would be controlled by approach of the oxidant from the α-face so as to avoid an unfavorable steric interaction with the C3 phenyl substituent. This would generate C8b ketone **17** that provides two options for further elaboration: either nucleophilic addition to the ketone to form the C–C bond to the dimethoxyaryl group, or alternatively, arylation of the tertiary alcohol to form the C–O bond to the dimethoxyaryl group.

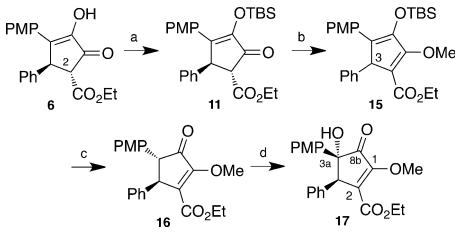
Formation of the C3a C–O bond turned out to be much more challenging than we had anticipated. Exposure of **6** (Scheme 2) to a small excess of NaHMDS followed by 2-[(4-



Scheme 2. Undesired C2 oxidation. a) NaHMDS, THF, −78 °C, 10 min; 2-[(4-methylphenyl)sulfonyl]-3-phenyl-oxaziridine, 10 min; 80%; b) KHMDS, THF, −78 °C; TBSOTf; 50%; c) on **10**; KHMDS, THF, −78 °C, 10 min; 2-[(4-methylphenyl)sulfonyl]-3-phenyl-oxaziridine, 10 min; 80%.

methylphenyl)sulfonyl]-3-phenyl-oxaziridine led exclusively to C2 alcohol **7** in 80% yield as a single diastereomer.[22] To probe this process, **6** was deprotonated with KHMDS and the product immediately trapped with *tert*-butyldimethylsilyl triflate. This led to approximately a 5:1 mixture of enol silanes **10** and **11** in a combined yield of 60% along with some unreacted starting material **6**. These results can be understood in terms of rapid proton transfers that convert the initially formed enolate **8** to the more stable enolate **9** that was then either trapped as the enol ether to give **10**, or that was oxidatively converted to **7**. We next attempted to deprotonate enol ether **10** at C3a and then oxidize the derived enolate. Exposure of **10** to base followed by 2-[(4-methylphenyl)sulfonyl]-3-phenyl-oxaziridine, however, led to **14** through oxidation at C2 rather than at C3a. We surmise that in this case rapid silyl migration converted the initially formed enolate **12** to the more stable **13** that was then trapped by the oxidant.[23,24]

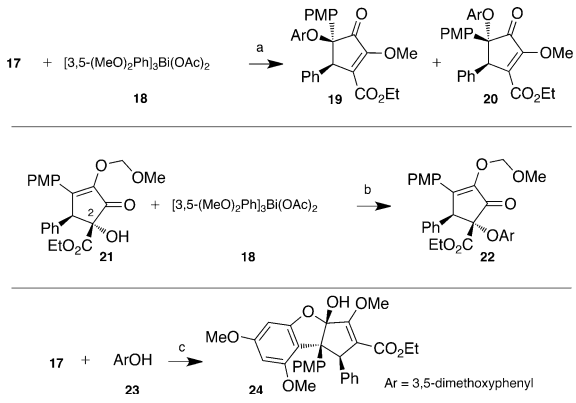
It was clear that this approach would only succeed if a non-migrating protecting group were deployed at the C1 oxygen atom. This led to the circuitous route that has been summarized in Scheme 3. Silyl enol ether **11** was prepared quantitatively from **6**. Exposure of **11** to trimethylsilyldiazomethane and Hünig's base at room temperature led to cyclopentadiene **15** in 76% yield. Selective cleavage of the silyl enol ether was accomplished with triethylamine tris-hydrofluoride (TREAT·HF)



Scheme 3. Oxidation at C3a, racemic series. a) TBSCl, Hünig's base, cat. DMAP, CH_2Cl_2, RT, 2 h; 100%. b) $TMSCHN_2$, Hünig's base, MeCN/MeOH (9:1), RT, 12 h; 76%. c) TREAT·HF, THF, 0 °C to RT, 20 min; 96%; d) NaHMDS, THF, −78 °C, 10 min; 2-[(4-methylphenyl)sulfonyl]-3-phenyl-oxaziridine, 10 min; 81%.

to give enone **16** in 96% yield. The sodium enolate of **16** was generated with NaHMDS and was trapped with oxaziridine leading to the desired C3a alcohol **17** in 81% yield.

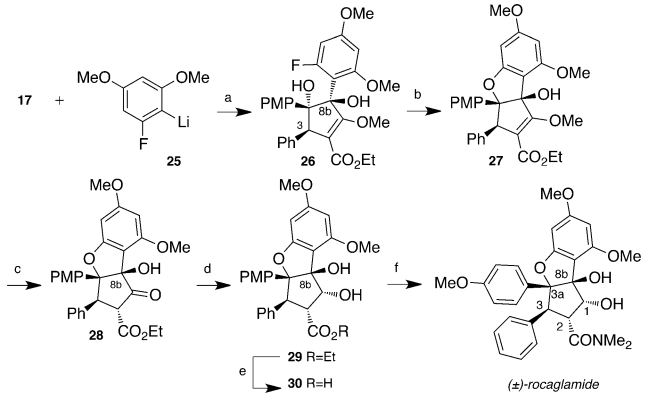
Having defined a serviceable, but somewhat long route to **17**, two alternative strategies to complete the synthesis presented themselves. The first was to form the C3a aryl ether first, followed by closure of the dihydrobenzofuran ring. The alternative was to form the C–C bond of the dihydrobenzofuran ring first, followed by the aryl ether C–O bond. Scheme 4 summarizes our efforts to implement the first strategy through the use of organobismuth chemistry that has been described by Mukaiyama and co-workers.[25,26] Exposure of **17** to tri(3,5-dimethoxyphenyl)bismuth diacetate **18**[27] in dichloromethane at room temperature in the presence of dicyclohexylmethylamine and $Cu(OAc)_2$ led to an inseparable mixture of aryl ethers **20** and **19**, indicating that epimerization at C3a had taken place through a cationic intermediate. The yield of **20**, as judged by integration of the ^1H NMR spectrum of the mixture, was about 30%. Interestingly, tertiary alcohol **21** that is related to **14** upon treatment with **18** underwent arylation without isomerization, indicating that the PMP group was responsible for the isomerization. α-Keto cations are usually highly destabilized, but in the case of **17**, the electron-donating PMP group compensates for the electron-withdrawing keto carbonyl carbon



Scheme 4. Aryl bismuth reactions, racemic series. a) Dicyclohexylmethylamine, $Cu(OAc)_2$, CH_2Cl_2, RT, 12 h; ca. 30% **20**. b) Dicyclohexylmethylamine, cat. $Cu(OAc)_2$, CH_2Cl_2, RT, 16 h; 60%. c) $BiCl_3$, CH_2Cl_2, 40 °C, 16 h; 95%.

atom, thereby stabilizing the cation.[28] This reactivity might have been exploited by trapping the α-keto cation with 3,5-dimethoxyphenol **23**, however, exposure of **17** to **23** and bismuth trichloride in dichloromethane at 40 °C, led to dihydrobenzofuran **24** in 95% yield from Friedel–Crafts alkylation of the activated phenol followed by formation of the hemiacetal.

Although the aryletherification failed, the alternative strategy of forming the C–C bond at C8b led to success (Scheme 5). Exposure of **17** to a three-fold excess of (2-fluoro-4,6-dimethoxyphenyl)lithium **25**[29] led to desired diol **26** in 51% yield as a single diastereomer probably due to the C3 and C3a aryl groups blocking β-face approach of the nucleophile. The assembly of the dihydrobenzofuran ring took place readily upon exposure of **26** to LiTMP (lithium 2,2,6,6-tetramethylpiperidide) leading to tricyclic product **27** in 64% yield. We assume that this reaction proceeds through a benzyne intermediate.[30] Cleavage of the methyl enol ether was accomplished by exposure of **27** to magnesium bromide with illumination by the laboratory's fluorescent lights. Control experiments showed that light played an important role in the success of this reaction.[31] β-Ketoester **28** was formed in 79% yield and was reduced with triacetoxyborohydride that was formed in situ to provide diol **29** in 76% yield. The stereochemical outcome of the reduction follows from intramolecular delivery of hydride directed by the C8b alcohol.[15a] Ester hydrolysis to **30** was followed by amidation to provide racemic rocaglamide in 70% yield for the two steps from **29**.

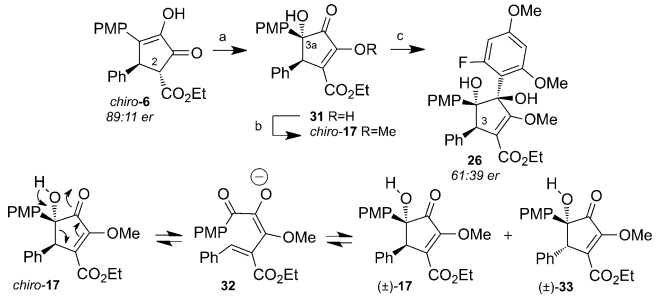


Scheme 5. Synthesis of racemic rocaglamide. a) THF, −78 °C to −40 °C; −40 °C, 1 h; 51%. b) LiTMP, THF, −78 °C to RT; 64%. c) $MgBr_2$, THF, $h\nu$, RT; 79%. d) $NaBH_4$, HOAc, MeCN, RT, 12 h; 76%. e) LiOH·H_2O, THF/MeOH/H_2O, RT, 12 h. f) DCC, DMAP, Me_2NH·HCl, CH_2Cl_2, RT, 12 h; 70% from **29**.

Although Schemes 3–5 define a serviceable synthesis of racemic rocaglamide, the approach was problematic at two points for reasons that only became clear during the execution of the asymmetric series. We prepared enantiomerically enriched **6**[1] (89:11 e.r.) and carried it through the reactions of Scheme 3 to form **17**. When this sample of **17** was combined with **25**, cyclopentene **26** was isolated as a racemate, indicating that the stereochemical integrity of C3 had been compromised. This presumably happened at the stage of cyclopenta-

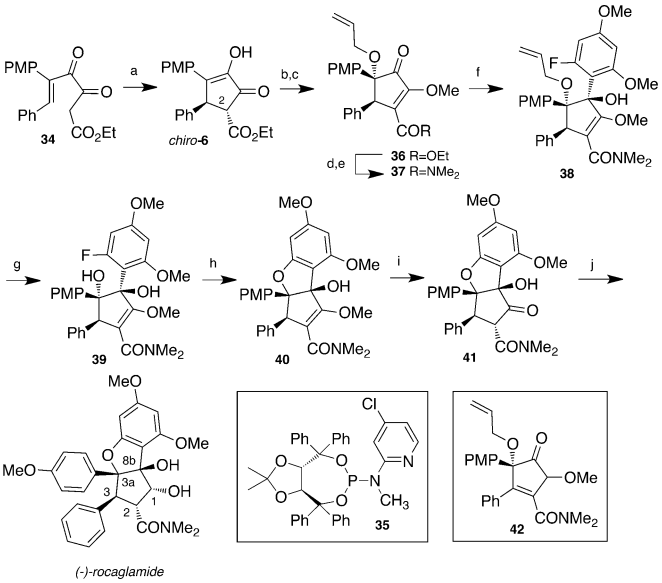
diene **15**, in which facile and reversible deprotonation leads to a planar cyclopentadienide species. It is surprising that reprotonation apparently takes place at C3 rather than in a nonspecific process that would have led to double bond isomers of **15**.

The unanticipated racemization through reversible deprotonation of **15** made it necessary to once again address the issue of oxidation of **6** at C3a. The selective oxidation of **6** is rendered challenging because of the ease with which it is converted to the enolate, suggesting that oxidation under neutral or mildly acidic conditions would be successful. Indeed, exposure of optically enriched **6** to phenyliodine bis(trifluoroacetate) (PIFA) in a 2:1 mixture of water and hexafluoroisopropanol (HFIP) led to diol **31** that was immediately converted to *chiro*-**17** by O-methylation in 55% overall yield for the two steps (Scheme 6). Methyl ether **17** was isolated as a 4:1 mixture of C3a diastereomers. The addition of aryllithium **25** to *chiro*-**17** took place under the conditions that have been described in Scheme 6. Surprisingly, **26** was isolated in 55% yield, but with eroded optical purity (61:39 e.r.). This result is consistent with the reversible vinylogous aldol reaction that is shown in Scheme 6. Deprotonation of the hydroxy group in *chiro*-**17** results in cleavage of the C3–C3a bond with the generation of planar enolate **32** that undergoes ring closure to racemic diastereomeric products (±)-**17** and (±)-**33**.[32] Whereas (±)-**17** was the major product, a small amount (ca. 10–20%) of racemic **33** was isolated and identified. We had overlooked this minor byproduct during the synthesis of racemic rocaglamide. This result left no doubt that the C3a hydroxyl group would have to be protected, and shaped the successful strategy that culminated in the enantioselective rocaglamide synthesis (Scheme 7).



Scheme 6. Racemization through reversible aldol ring opening. a) PIFA, H_2O/HFIP, 2:1, −20 °C to 0 °C, 1 h. b) $Me_3O{\cdot}BF_4$, Hünig's base, CH_2Cl_2, 0 °C to RT; 55% from *chiro*-**6**, 4:1 d.r. c) **25**, THF, −78 °C to −40 °C; −40 °C, 1 h; 55%.

Diketoester **34** was exposed to Pd^0 and phosphoramidite **37** to provide *chiro*-**6** in 70% yield and in 89:11 e.r. as described in earlier work.[1] There were two restrictions placed on the choice of protecting group for the C3a alcohol. First, it had to be small, so that it did not inhibit nucleophilic addition at C8b. This precluded the use of common protecting groups like SEM or TMS. Protection of the C3a hydroxyl group as the TMS ether led to an unreactive ketone in which the addition of **25** took place at the ester carbonyl group. Second, removal of the protecting group had to be accomplished under mild conditions, since the molecule is sensitive to both acid and base. On this basis, the allyl ether group was chosen for protection of the C3a alcohol. Exposure of *chiro*-**6** to PIFA in a mixed solvent of allyl alcohol and HFIP, followed by O-methylation of the resulting β-ketoester, led to the major diastereomer **36** in 55% yield (Scheme 7). Nucleophilic addition might be expected to take place selectively at the keto function of **36**, rather than at the ester group that is a vinylogous carbonate, however, the steric encumbrance about the ketone leads to substantial (10–20%) amounts of phenone derived from addition to the ester. To avoid this undesired process, **36** was converted to dimethylamide **37** in 73% yield prior to the addition of **25**. Even so, it was necessary to transmetallate aryllithium **25** to the organolanthanum species prior to the addition to **37**.[33] Under these conditions, the desired adduct **38** was formed in 87% yield as a single diastereomer. Attempts to add aryllithium **25** to **37** led to **38** in only 38% yield and resulted in the formation of **42** from benzylic deprotonation. Adduct **38** was recrystallized to 98.5:1.5 e.r. with 75% recovery. Enantioenriched **38** was carried through to (−)-rocaglamide. Oxidative deprotection[34] of the allyl ether protecting group led to tertiary alcohol **39** (78% yield) that was treated with potassium *tert*-butoxide at room temperature for 15 min leading to tricyclic **40** in 89% yield. Although LiTMP could also be used for this reaction, higher yields were realized with potassium *tert*-butoxide. This reaction presumably proceeds through a S_NAr mechanism, since dehydrofluorination seems very unlikely under the mild condi-



Scheme 7. Synthesis of (−)-rocaglamide. a) 5 mol% $[Pd_2(dba)_3]$, 12 mol% **35**, MeCN, RT, 20 h; after 20 h, 2.5 mol% $[Pd_2(dba)_3]$, and 7.5 mol% **35** were added; 70%, 89:11 e.r. b) PIFA, allyl alcohol/HFIP, 2:1, −10 °C to RT, 2 h. c) $Me_3O{\cdot}BF_4$, Hünig's base, CH_2Cl_2, RT, 30 min; 55% of major diastereomer from *chiro*-**6**. d) $LiOH{\cdot}H_2O$, THF/EtOH/H_2O, 4:1:1, RT, 4 h. e) Me_2NH, HATU, Hünig's base, CH_2Cl_2, RT, 12 h; 73% from **34**. f) **25**, $LaCl_3{\cdot}2$ LiCl, −78 °C, 1 h; add **35**; −30 °C, 1.5 h; 87%, 89:11 e.r.; recrystallize once from CH_2Cl_2/hexanes; 75% recovery, 98.5:1.5 e.r. g) SeO_2, HOAc, 1,4-dioxane, reflux, 30 min; 78%; h) *tert*-BuOK, THF, RT, 15 min; 89%. i) MgI_2, PhMe, 90 °C, 15 min; 92%. j) $NaBH(OAc)_3$, HOAc, MeCN, RT, 16 h; 73%, 99:1 e.r.

tions.[35] Finally, cleavage of the methyl enol ether to regenerate the β-ketoester (92% yield)[36] and reduction with sodium triacetoxyborohydride[14m] produced (−)-rocaglamide in 73% yield. The spectroscopic data and the melting point of this material matched the published information.[15j] More vigorous conditions were required for the cleavage of the methyl ether in vinylogous carbamate **40** than in vinylogous ester **27** (Scheme 5).

Conclusions

We have disclosed the details that shaped the evolution of the final route of our catalytic asymmetric synthesis of rocaglamide. Noteworthy features of this work are the silatropic rearrangement of enolate **11** to **12** and the unexpectedly facile racemization of cyclopentadiene **15** that did not reveal itself during the synthesis of the racemate. Also noteworthy is the racemization of *chiro*-**17** through reversible aldol ring opening to planar enolate **32**. Although this problem had revealed itself during the synthesis of the racemate, we had overlooked it. The use of the organolanthanum reagent is also an element of novelty of this work and an indication of the value of these highly nucleophilic but less basic organometallic species. This work represents the first catalytic asymmetric synthesis of natural rocaglamide, and is the first synthesis of a natural product making use of a metal catalyzed Nazarov-type cyclization.

Experimental Section

General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova 500 MHz spectrometer at 500 MHz (^{1}H) and 126 MHz (^{13}C) or an Agilent DD2 300 MHz NMR spectrometer 300 MHz (^{1}H) and 75 MHz (^{13}C). Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, that is, 7.26/77.0 for $CDCl_3$. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), hept (heptet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). Infrared spectra were recorded on a Shimadzu IRAffinity spectrophotometer. High resolution mass spectra were obtained on either a VG Scientific VG70SE (EI-MS) or an Agilent 6210 LC/MSD-TOF system (ESI-MS).

Synthesis and characterization

(*E*)-2-(4-Methoxyphenyl)-3-phenylacrylic acid 1: A mixture of 4-methoxylphenylacetic acid (20.0 g, 0.120 mol, 1.0 equiv), benzaldehyde (12.77 g, 0.120 mol, 1.0 equiv), acetic anhydride (22.12 g, 0.216 mol, 1.8 equiv) and triethylamine (8.53 g, 0.084 mol, 0.7 equiv) was heated under argon at 110 °C for 18 h. After cooling to room temperature, the mixture was diluted with 100 mL of water and 100 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The resulting orange solid was recrystallized in a mixed solvent system of ethyl acetate/hexanes to give **1** (15.0 g, 50%) as colorless needle-like crystals.[17] M.p.: 165–167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.92 (s, 1H), 7.25–7.08 (m, 7H), 6.92 (d, J = 8.7 Hz, 2H), 3.84 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 173.2, 159.3, 142.2, 134.5, 131.2, 131.0, 130.8, 129.3, 128.2, 127.3, 114.2, 55.2 ppm; IR $\tilde{\nu}_{max}$ (film): 3426, 2924, 2957, 1670, 1606, 1514, 1269, 1176, 1031, 829, 779, 692 cm^{-1}; EI-MS: m/z calculated for $C_{16}H_{14}O_3$ [M^+]: 254.0943; found 254.0953.

(1*R*,5*S*)-Ethyl 3-hydroxy-4-(4-methoxyphenyl)-2-oxo-5-phenylcyclo-pent-3-enecarboxylate *chiro*-**6**: A solution of **35** (109 mg, 0.17 mmol, 0.12 equiv) and [Pd_2(dba)$_3$] (65 mg, 0.07 mmol, 0.05 equiv) in 20.0 mL dry, degassed acetonitrile was made. The reaction mixture was vigorously stirred for 20 min at room temperature. A solution of **34** (500 mg, 1.42 mmol, 1.0 equiv) in 15.0 mL dry, degassed acetonitrile was added to the solution. After 20 h the reaction was not complete, and an additional portion of catalyst solution prepared with 54 mg **35** and 33 mg [Pd_2(dba)$_3$] in 10.0 mL acetonitrile was added. The reaction was complete after an additional 20 h and was quenched by the addition of 50.0 mL water and filtered through Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified on silica gel (10–20% EtOAc in hexanes) to yield *chiro*-**6** (350 mg, 70%) as pale-yellow solid. Chiral HPLC analysis of *chiro*-**6** on a Chiracel AD-H column: 20% *i*PrOH/hexanes, 1 mL min^{-1}, 254 nm. t = 11.33 min (1*S*,5*R*)-**6**, t = 20.65 min (1*R*,5*S*)-**6**, 89:11 e.r.; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.77 (d, J = 9.0 Hz, 1H), 7.30–7.23 (m, 2H), 7.23–7.15 (m, 3H), 6.83 (d, J = 9.0 Hz, 2H), 6.35 (s, 1H), 4.81 (d, J = 2.1 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.37 (d, J = 2.1 Hz, 1H), 1.32 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 194.7, 168.0, 160.5, 146.5, 142.0, 140.5, 131.1, 130.8, 129.1, 127.3, 127.1, 125.0, 113.9, 62.0, 59.1, 55.2, 45.8, 14.2 ppm; IR $\tilde{\nu}_{max}$ (film): 3350, 2981, 1728, 1682, 1631, 1600, 1514, 1385, 1257, 1180, 1103, 1030, 837, 702 cm^{-1}; EI-MS: m/z calculated for $C_{21}H_{20}O_5$ [M^+]: 352.1311, found 352.1294.

(4*R*,5*R*)-Ethyl 4-(allyloxy)-2-methoxy-4-(4-methoxyphenyl)-3-oxo-5-phenylcyclopent-1-enecarboxylate 36: To a solution of *chiro*-**6** (900 mg, 2.55 mmol, 1.0 equiv) in 8.0 mL allyl alcohol and 8 mL HFIP, was added phenyliodine bis(trifluoroacetate) (1.15 g, 2.68 mmol, 1.05 equiv) in 8.0 mL allyl alcohol at −10 °C with vigorous stirring. The reaction mixture was allowed to warm to room temperature and after 2 h was diluted with 50 mL Et_2O and washed with saturated NaCl (3×25 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in 15.0 mL dry CH_2Cl_2, cooled to 0 °C and treated with trimethyloxonium tetrafluoroborate (560 mg, 3.82 mmol, 1.5 equiv) followed by *N,N*-diisopropylethylamine (820 mg, 6.37 mmol, 2.5 equiv). After 30 min at 0 °C, the reaction mixture was poured into 50 mL of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×25 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Silica gel chromatography (5% EtOAc in hexanes) yielded **36** (600 mg, 55%, 89:11 e.r.) as a greenish-yellow oil (the reaction gives ca. 4:1 of desired and the less polar undesired diastereomer). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.99–6.91 (m, 3H), 6.89 (d, J = 8.8 Hz, 2H), 6.79–6.72 (m, 2H), 6.57 (d, J = 8.8 Hz, 2H), 5.85 (ddt, J = 17.2, 10.5, 5.3 Hz, 1H), 5.28 (dq, J = 17.2, 1.8 Hz, 1H), 5.15 (dq, J = 10.4, 1.4 Hz, 1H), 4.46 (s, 1H), 4.23 (s, 3H), 4.10–4.00 (m, 2H), 3.92 (ddt, J = 13.1, 5.6, 1.6 Hz, 1H), 3.87–3.79 (m, 1H), 3.66 (s, 3H), 1.01 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 201.2, 164.0, 158.7, 155.2, 138.0, 134.5, 132.3, 129.3, 128.8, 128.6, 127.8, 127.3, 126.7, 116.4, 113.0, 84.9, 66.3, 60.9, 59.6, 57.0, 55.1, 13.7 ppm; IR $\tilde{\nu}_{max}$ (film): 3060, 1715, 1713, 1631, 1611, 1514, 1303, 833 cm^{-1}; ESI-MS: m/z calculated for $C_{25}H_{26}NaO_6$ [M+Na^+]: 445.1627, found 445.1605.

(4*R*,5*R*)-4-(Allyloxy)-2-methoxy-4-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-oxo-5-phenylcyclopent-1-enecarboxamide 37: To a solution of **36** (200 mg, 0.47 mmol, 1.0 equiv) in 4.0 mL 4:1:1 THF/EtOH/H_2O

was added LiOH·H_2O (100 mg, 2.73 mmol, 5.8 equiv). After 4 h at room temperature the reaction mixture was acidified with 15.0 mL 1 N HCl and extracted with CH_2Cl_2 (3×20.0 mL). The combined organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to yield 187 mg of carboxylic acid that was used without further purification. To a solution of the carboxylic acid (187 mg, 0.47 mmol, 1.0 equiv) in 10 mL dry CH_2Cl_2 was added HATU (1-[bis-(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate) (215 mg, 0.57 mmol, 1.2 equiv), dimethylamine (0.7 mL, 2.0 M in THF, 1.41 mmol, 3.0 equiv) and triethylamine (0.23 mL, 167 mg, 1.65 mmol, 3.5 equiv). After 12 h at room temperature the reaction mixture was diluted with 30 mL CH_2Cl_2 and washed with brine (3×25 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Silica gel chromatography (25–40% EtOAc in hexanes) gave **37** (145 mg, 73% over 2 steps, 89:11 e.r.) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.01–6.95 (m, 3H), 6.89 (d, J = 8.8 Hz, 2H), 6.81–6.76 (m, 2H), 6.57 (d, J = 8.8 Hz, 2H), 5.84 (ddt, J = 17.1, 10.4, 5.2 Hz, 1H), 5.26 (dq, J = 17.2, 1.8 Hz, 1H), 5.11 (dd, J = 10.5, 1.6 Hz, 1H), 4.48 (s, 1H), 4.04 (s, 3H), 4.03–3.98 (m, 1H), 3.87–3.79 (m, 1H), 3.67 (s, 3H), 3.06 (s, 3H), 2.86 (s, 3H), 2.80 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): 200.4, 165.3, 158.8, 149.8, 138.2, 136.5, 134.7, 129.4, 129.3, 127.8, 127.6, 127.0, 116.0, 113.0, 85.4, 66.0, 58.4, 58.3, 55.1, 38.6, 37.6, 34.4 ppm; IR $\tilde{\nu}_{max}$ (film): 1713, 1680, 1639, 1513, 1336, 1122, 730 cm^{-1}; ESI-MS: m/z calculated for $C_{25}H_{27}NNaO_5$ [M+Na$^+$]: 444.1787, found 444.1781.

(3*S*,4*R*,5*R*)-4-(Allyloxy)-3-(2-fluoro-4,6-dimethoxyphenyl)-3-hydroxy-2-methoxy-4-(4-methoxyphenyl)-*N*,*N*-dimethyl-5-phenylcyclopent-1-enecarboxamide 38: To a solution of 1-fluoro-3,5-dimethoxybenzene (207 mg, 0.17 mL, 1.33 mmol, 4.0 equiv) in 3 mL THF was slowly added *n*BuLi in hexanes (0.48 mL, 2.4 M, 1.16 mmol, 3.5 equiv) at −78 °C. After 1 h at −78 °C, a solution of $LaCl_3$·2 LiCl (1.94 mL, 0.6 M, 1.16 mmol, 3.5 equiv) was added dropwise. The temperature was maintained at −78 °C for 1 h and a solution of **37** (140 mg, 0.33 mmol, 1 equiv) in 2.0 mL THF was added. The reaction mixture was allowed to warm to −30 °C over 45 min before being quenched by the addition of saturated aq. NH_4Cl. The pH was adjusted to 4–5 with 1 N HCl. The mixture was extracted with EtOAc (3×20.0 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. Silica gel chromatography (30–40% EtOAc in hexanes) yielded **38** (167 mg, 87%, 89:11 e.r.) as white solid. Recrystallization: 167 mg of **38** (89:11 e.r.) was dissolved in 1.5 mL CH_2Cl_2 at room temperature 4.5 mL hexanes was slowly added and the resulting solution was left undisturbed at room temperature for 12 h. 125 mg **38** (98.5:1.5 e.r.) was recovered (75% recovery). M.p.: 183.6–185.0 °C (98.5/1.5 e.r.). Chiral HPLC analysis of **38** on a Chiracel OD-H column: 20% *i*PrOH/hexanes, 1 mL min^{-1}, 254 nm. t = 8.15 min (+)-**38**, t = 9.5 min (−)-**38**, 98.5:1.5 e.r.; $[\alpha]_D^{20} = -139^\circ$ (c = 0.75, $CHCl_3$, 98.5:1.5 e.r.); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.50–7.44 (m, 2H), 7.32–7.26 (m, 3H), 6.52–6.46 (m, 2H), 6.41 (d, J = 8.4 Hz, 2H), 6.27 (dd, J = 13.0, 2.5 Hz, 1H), 6.01 (dd, J = 2.5, 1.3 Hz, 1H), 5.85 (ddt, J = 17.2, 10.8, 4.0 Hz, 1H), 5.19 (s, 1H), 5.13–5.03 (m, 2H), 4.54 (s, 1H), 4.37–4.30 (m, 1H), 4.06–4.00 (m, 1H), 3.90 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.27 (s, 3H), 2.99 (s, 3H), 2.91 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 168.0, 163.0, 161.0, 160.1, 160.0, 159.7, 159.6, 158.3, 157.5, 149.4, 139.5, 134.5, 131.3, 131.2, 128.4, 127.6, 127.1, 114.5, 111.7, 108.5, 106.5, 106.4, 94.5, 94.1, 93.9, 89.8, 89.3, 65.1, 58.4, 56.9, 55.4, 55.2, 55.0, 37.8, 34.4 ppm; IR $\tilde{\nu}_{max}$ (film): 3446, 1680, 1624, 1585, 1295, 1217, 1101, 1068 cm^{-1}; ESI-MS: m/z calculated for $C_{33}H_{36}FNNaO_7$ [M+Na$^+$]: 600.2374, found 600.2361.

(3*R*,4*R*,5*R*)-3-(2-Fluoro-4,6-dimethoxyphenyl)-3,4-dihydroxy-2-methoxy-4-(4-methoxyphenyl)-*N*,*N*-dimethyl-5-phenylcyclopent-1-enecarboxamide 39: A solution of **38** (100 mg, 0.17 mmol, 1.0 equiv), selenium dioxide (23 mg, 0.21 mmol, 1.2 equiv) and acetic acid (21 mg, 0.35 mmol, 2.0 equiv) in 10.0 mL dry dioxane was heated to reflux for 30 min. After cooling to room temperature the solvent was removed under reduced pressure. The residue was dissolved in 20.0 mL CH_2Cl_2 and the insoluble salts were removed by filtration. The CH_2Cl_2 solution was washed with brine (2×20.0 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure. Silica gel chromatography (40–50% EtOAc in hexanes) gave **39** (73 mg, 78%) as a white solid. $[\alpha]_D^{20} = -192^\circ$ (c = 0.98, $CHCl_3$, 98.5:1.5 e.r.); m.p.: 120 °C (decomp); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.21–7.09 (m, 5H), 6.97 (d, J = 9.0 Hz, 2H), 6.55 (d, J = 9.0 Hz, 2H), 6.31 (dd, J = 13.5, 2.4 Hz, 1H), 6.13 (dd, J = 2.6, 1.3 Hz, 1H), 5.24 (s, 1H), 4.23 (s, 1H), 3.95 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H), 3.21 (s, 3H), 3.14 (s, 3H), 2.87 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 167.7, 162.2, 160.6, 160.4, 160.3, 159.7, 159.6, 158.2, 156.7, 138.5, 130.9, 130.6, 129.5, 129.4, 127.3, 126.8, 111.7, 109.8, 107.0, 96.2, 94.6, 94.3, 88.9, 88.9, 84.6, 64.0, 58.4, 55.9, 55.5, 55.0, 37.8, 34.6 ppm; IR $\tilde{\nu}_{max}$ (film): 3424, 1721, 1638, 1512, 1496, 1336, 1216, 1097 cm^{-1}; ESI-MS: m/z calculated for $C_{30}H_{32}FNNaO_7$ [M+Na$^+$]: 560.2061, found 560.2070.

(3*R*,3a*R*,8b*S*)-8b-Hydroxy-1,6,8-trimethoxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-3a,8b-dihydro-3*H*-cyclopenta[*b*]benzofuran-2-carboxamide 40: To a solution of **39** (50 mg, 0.093 mmol, 1.0 equiv) in 5.0 mL dry THF was added potassium *tert*-butoxide (52 mg, 0.47 mmol, 5.0 equiv). After 15 min at room temperature the reaction was quenched by addition of saturated aq. NH_4Cl and extracted with EtOAc (3×10.0 mL). The combined organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to yield **40** (43 mg, 89%) as a white solid. $[\alpha]_D^{20} = -206^\circ$ (c = 0.93, $CHCl_3$, 98.5:1.5 e.r.); m.p.: 181.9–183.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.16 (d, J = 8.9 Hz, 2H), 7.08–7.01 (m, 3H), 7.00–6.96 (m, 2H), 6.58 (d, J = 8.9 Hz, 2H), 6.23 (d, J = 2.0 Hz, 1H), 6.07 (d, J = 2.0 Hz, 1H), 4.36 (s, 1H), 3.92 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.08 (s, 3H), 2.84 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 167.0, 163.3, 160.6, 158.5, 157.7, 156.2, 137.4, 129.3, 128.6, 127.6, 127.0, 126.7, 112.3, 107.4, 101.2, 92.5, 89.0, 89.0, 60.2, 59.4, 55.6, 55.5, 55.0, 37.8, 34.5, 29.8 ppm; IR $\tilde{\nu}_{max}$ (film): 3455, 2940, 2840, 1733, 1620, 1498, 1398, 1299, 838, 818 cm^{-1}; ESI-MS: m/z calculated for $C_{30}H_{31}NNaO_7$ [M+Na$^+$]: 540.1998, found 540.1969.

(2*R*,3*S*,3a*R*,8b*R*)-8b-Hydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-1-oxo-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide 41: A solution of MgI_2 (67 mg, 0.24 mmol, 5.0 equiv) in 2.0 mL toluene and 2.0 mL diethyl ether was heated to 90 °C with vigorous stirring. After 15 min a solution of **40** (25 mg, 0.048 mmol, 1.0 equiv) in 1.0 mL toluene and 1.0 mL diethyl ether was added to the MgI_2 solution at 90 °C. The reaction mixture was vigorously stirred for 15 min before being quenched by the addition of 15 mL saturated aq. $Na_2S_2O_3$. The organic layer was separated, diluted with 25 mL diethyl ether and washed with 15 mL saturated aq. NaCl. Aftering drying (Na_2SO_4) the organic layer was concentrated under reduced pressure and the residue was purified on silica gel (30–40% EtOAc in hexanes) to give **41** (22 mg, 92%) as a white solid. $[\alpha]_D^{20} = +62^\circ$ (c = 1.10, $CHCl_3$, 98.5/1.5 e.r.); m.p.: 144.2–146.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.11–7.05 (m, 3H), 6.99 (d, J = 8.8 Hz, 2H), 6.86–6.81 (m, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.33 (d, J = 2.0 Hz, 1H), 6.08 (d, J = 2.0 Hz, 1H), 4.50 (d, J = 13.1 Hz, 1H), 4.33 (d, J = 13.1 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.25 (s, 3H), 2.90 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 205.7, 165.3, 164.8, 161.0, 158.8, 158.5, 136.1, 127.99, 127.96, 127.9, 126.9, 126.0, 113.2, 110.6, 106.0, 99.2, 93.0, 89.8, 88.5, 55.7, 55.1, 53.8, 52.0, 37.7, 36.2 ppm; IR $\tilde{\nu}_{max}$ (film): 3417, 1747, 1651, 1616, 1600, 1516, 1500, 1149, 894 cm^{-1}; ESI-MS: m/z

calculated for $C_{29}H_{29}NNaO_7$ [M+Na$^+$] 526.1842, found 526.1826. These data match those reported in reference [15m].

(1*R*,2*R*,3*S*,3a*R*,8b*S*)-1,8b-Dihydroxy-6,8-dimethoxy-3a-(4-methoxyphenyl)-*N*,*N*-dimethyl-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxamide [(−)-rocaglamide]: $NaBH_4$ (100 mg, 2.62 mg, 60 equiv) was slowly added to 2.0 mL acetic acid at room temperature. After 30 min, a solution of **41** (22 mg, 0.044 mmol, 1.0 equiv) in 1.0 mL acetonitrile was added and the resulting mixture was stirred at room temperature for 20 h. The reaction was quenched with 10 mL saturated aq. NaCl and extracted with EtOAc (3×15 mL). The combined organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Silica gel chromatography (80–100% EtOAc in hexanes) yielded (−)-rocaglamide (16 mg, 73%) as a white solid. Chiral HPLC analysis on a Chiracel OD column: 45% *i*PrOH/hexanes, 1 mL min^{-1}, 210 nm. t=12.93 min (+)-rocaglamide, t=22.05 min (−)-rocaglamide, 99:1 e.r.; $[\alpha]_D^{20}=-102^\circ$ (c=1.0, $CHCl_3$, 98.5:1.5 e.r.);[15j] [$[\alpha]_D^{20}=-99^\circ$ (c=0.13, $CHCl_3$, 94%*ee*); m.p.: 118.4–120.1 °C;[15j] m.p.: 117–118 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.10 (d, J=8.9 Hz, 2H), 7.07–6.98 (m, 3H), 6.89–6.83 (m, 2H), 6.68 (d, J=8.9 Hz, 2H), 6.28 (d, J=2.0 Hz, 1H), 6.10 (d, J=2.0 Hz, 1H), 4.94 (dd, J=6.5, 2.0 Hz, 1H), 4.55 (d, J=13.5 Hz, 1H), 4.06 (s, 1H), 4.05 (dd, J=13.5, 6.5 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 3.31 (s, 3H), 2.94 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ=169.5, 163.9, 161.0, 158.5, 157.2, 137.6, 128.8, 127.7, 127.7, 127.0, 126.3, 112.7, 107.5, 101.6, 94.0, 92.5, 89.2, 78.5, 55.9, 55.7, 55.1, 47.6, 37.0, 35.8 ppm; IR $\tilde{\nu}_{max}$ (film): 3491, 2935, 2841, 1716, 1624, 1514, 1455, 1201, 1149, 1118, 1034, 995 cm^{-1}; ESI-MS: *m/z* calculated for $C_{29}H_{31}NNaO_7$ [*M*+Na$^+$]: 528.1998, found 528.2008.

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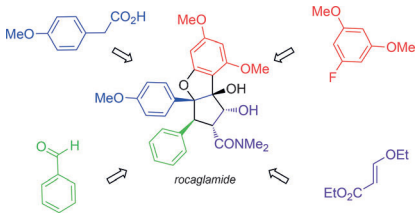
FULL PAPER

Roc(k)ing out! This full account details distinct approaches to (±)- and (−)-rocaglamide, utilizing Brønsted acid catalyzed and asymmetric Pd^0-catalyzed Nazarov chemistry, respectively (see figure). The successful asymmetric synthesis revealed unforeseen mechanistic complexity that required adjustment of the strategy.



Natural Product Synthesis

*Z. Zhou, D. D. Dixon, A. Jolit, M. A. Tius**

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The Evolution of the Total Synthesis of Rocaglamide