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Sequential cross-metathesis/cyclopropanation: short syntheses of (+/−)-cascarillic acid and (+/−)-grenadamide

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Dedicated to the memory of Professor G. Ourisson

Abstract—The total synthesis of (+/−)-cascarillic acid has been achieved by a sequential cross-metathesis/Simmons–Smith cyclopropanation between, respectively, 1-octene with an appropriate unsaturated carboxylic acid. In parallel, a direct access to grenadamide was developed from 1-nonene with a readily available unsaturated amide. In both cases, the chemical yields were high (up to 98%) and the *E*/*Z* ratio was near 80/20. The synthesis of a dibromocyclopropane analogue has also been considered.
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Numerous natural products possess as subunit a cyclopropane framework.[1,2] This three-membered ring can be found on linear compounds like for cascarillic acid **1** or grenadamide **2**, metabolites, respectively, isolated as a major constituent of cascarilla essential oil[3] and the marine cyanobacterium *Lyngbia majuscula*.[4] Interestingly, a rare trans relationship of the two substituents can be observed in these two compounds. In some cases, the cyclopropane can be fused to a larger ring like in africanol **3** and its naturally occurring epimer **4** (Fig. 1).[5] A large number of processes have been disclosed to allow an access to these small rings. Among them, Simmons–Smith cyclopropanation of alkenes has been widely used while the reaction is smoothly performed with diiodomethane in the presence of zinc derivatives.[6,7] In parallel, since the discovery of suitable catalysts like Grubbs types I and II reagents **5** and **6**, ring-closing metathesis (RCM) has emerged as one of the most powerful reactions to prepare medium and large unsaturated heterocyclic and carbocyclic structures.[8,9] Cross-metathesis is also a suitable reaction to deliver in good yields functionalized alkenes.[10–12] The *E*/*Z* ratio is sometimes difficult to control but usually it is in favour of the *E* isomer reflecting the reversibility of the reaction and the formation of the thermodynamic product.[13] In this context, the synthesis of **4** has been realized by Paquette et al. by using an RCM leading to the seven-membered ring structure which was isolated in very good yields and later engaged in a cyclopropanation step.[5,14]

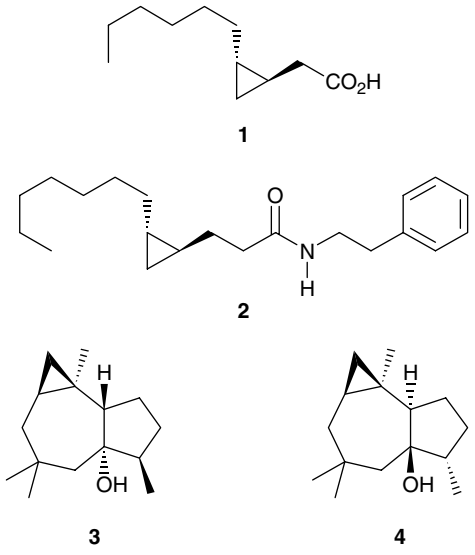

Figure 1.

Keywords: Metathesis; Cyclopropanes; Marine natural products.
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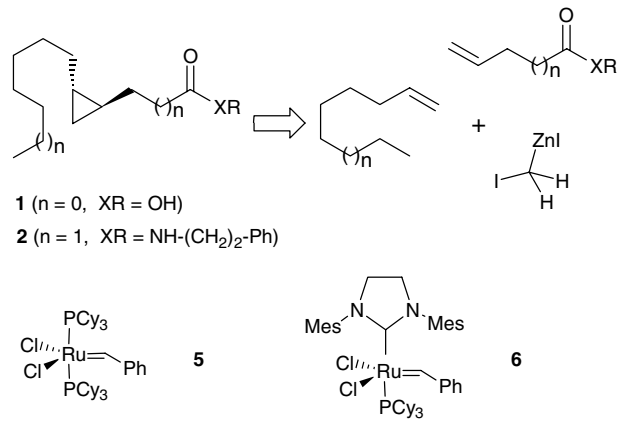
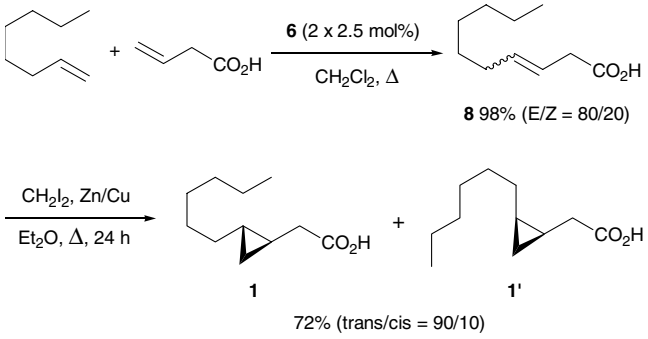


Scheme 1.

In connection with our interest in sequential and tandem reactions including at least one metathesis process and their application in total synthesis,[15,16] we have investigated the possibility to combine in the same vessel the formation of disubstituted alkenes by CM with a subsequently Simmons–Smith reaction (Scheme 1). By this way, purification and one isolation step could be avoided with a significant gain of time and yields.[17–20] To our knowledge, cyclopropanation associated to a metathesis step has been scarcely described in the literature and required diazo species in domino processes.[21,22]

First attempts were performed to realize the synthesis of cascarillic acid **1** from commercially available vinylacetic acid and 1-octene. Compound **1** was first prepared by a two-step procedure. Cross-metathesis of 1-octene with vinylacetic acid **7** was easily performed by heating for 24 h a dichloromethane solution of the two alkenes in the presence of catalyst **6** (2×2.5 mol%). After flash-chromatography on silica, the corresponding acid **8** was obtained in nearly quantitative yield with a significant 80/20 *E*/*Z* ratio. The two unseparable diastereoisomers were next submitted to Simmons–Smith cyclopropanation conditions in diethyl ether (Scheme 2). In that case, the reaction took place smoothly and delivered cascarillic acid and its cis-stereoisomer **1′** in 72% combined yield and a 90:10 trans:cis ratio. This value was determined by comparison of the spectra of the crude product with data already reported in the literature.[3b]



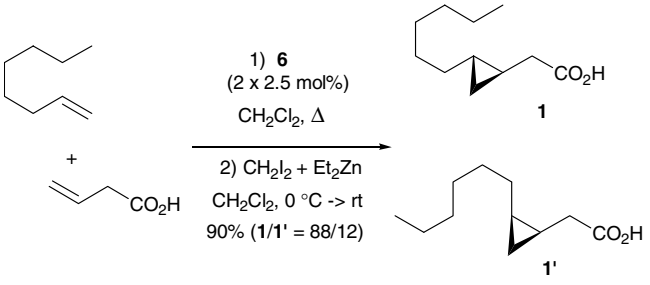
Scheme 2.

The expected sequential reaction necessitates the same solvent for the two different transformations. Therefore, the cross-metathesis was performed as above while the cyclopropanation was promoted by reaction of diiodomethane in the presence of diethylzinc. After cooling of the reaction mixture to 0 °C, diiodomethane and a large excess of diethylzinc (10 equiv) were directly added (Scheme 3). After stirring for an additional 5 h at this temperature, the solvent was concentrated and the reaction mixture was chromatographed to give a mixture of compounds **1** and **1′** in a very high chemical yield (90%).[23,24]

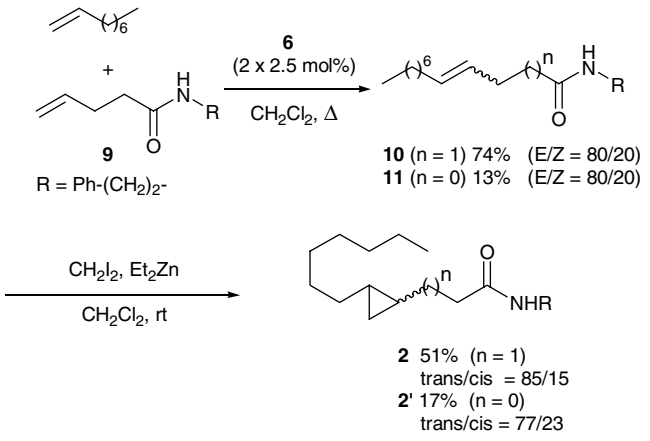
We next decided to develop a similar strategy for the synthesis of (+/−)-grenadamide **2** starting from commercially available reagents. Amidation of 4-pentenoic acid was performed in 74% via formation of a transient anhydride with 2,4,6-trichlorobenzoyl chloride and reaction with 2-phenylethylamine.[13a,25] Cross-metathesis of **9** with 1-nonene delivered an inseparable 85/15 mixture of unsaturated amides **10** and **11**. Each of them was present as a 8:2 mixture of *E*:*Z* isomers. Formation of **11** resulted from an in situ isomerization of the terminal double bond of the pentenoic acid subunit in the presence of ruthenium catalyst **6**. We already noticed a similar side reaction during the synthesis of lyngbic acid and analogues.[13] Attempts to avoid this isomerization by addition of 1,4-benzoquinone according to Grubbs recommendation[26] were however unsuccessful. Cyclopropanation of the mixture of **10** and **11** afforded grenadamide **2** and the nor-methylene structure **2′** in a cumulative 68% yield (Scheme 4). A carefully made flash-chromatography on silica allowed the separation of the two compounds still as a mixture of trans/cis isomers.

Similarly, the one-pot procedure furnished a mixture of the cyclopropane natural product **2** and its nor-isomer **2′** (75:25 ratio) in 98% yield (Scheme 5).

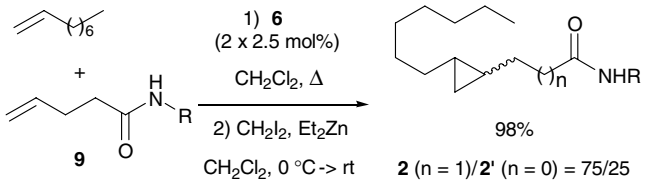
Dibromo analogue **12** was synthetized from amide **9** by reaction with a dibromocarbene, which can be usually generated from bromoform under phase transfer conditions (Scheme 6).[27,28] It was first expected that the cross-metathesis of amide **9** could be made with bromoform as the solvent in the presence of **6** but at lower temperature ($T > 30$ °C) to avoid the homolytic cleavage of a C-halogen bond promoted by a ruthenium species.[29–31] Unfortunately, the process conducted under these experimental conditions delivered dibromocyclopropane **12**



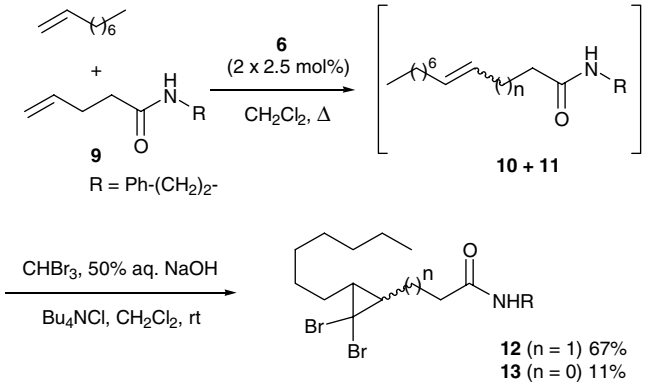
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

in a miserable yield. Therefore, the sequential reaction was performed in dichloromethane as the solvent. After the first step, bromoform and an aqueous solution of sodium hydroxide were added at once with also a few amount of *n*-Bu_4NCl as a phase transfer agent. According to this sequence, (+/−)-dibromogrenadamide **12** ($n = 1$) was isolated in 67% yield with its parent structure **13** ($n = 0$) in 11%.

In conclusion, we report here a straightforward synthesis of two natural cyclopropane compounds and one dibromo-analogue. Interestingly the smooth conditions required for both the cross-metathesis and the cyclopropanation allow the combination of the two processes in one single pot. Compared to other racemic syntheses, this high yielding and shorter procedure is expected to be generalized to other naturally occurring *trans*-cyclopropane derivatives. Work is in progress to combine other metathetical reactions with Simmons–Smith cyclopropanation toward the synthesis of polycyclic structures.

Acknowledgment

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23. Typical procedure for the tandem reaction:
A solution of vinyl acetic acid (0.086 g, 1 mmol) and octene (0.561 g, 5 mmol) in dichloromethane (20 mL) was bubbled with a stream of dry nitrogen. Grubbs type II catalyst (21.2 mg, 0.025 mmol) was next added and the resulting solution was heated for 12 h. After a second addition of the same amount of catalyst, the reaction was heated for an additional 12 h. Diethylzinc (1.23 g, 10 mmol) was introduced at 0 °C by canula. After stirring for 5 min at this temperature, diiodomethane (4.28 g, 16 mmol) was added. After stirring 5 h at rt, the mixture was treated with a 10% HCl aqueous solution, washed successively with a saturated $NaHCO_3$ solution and brine. The organic layers were dried over $MgSO_4$, filtered off and concentrated under vacuum. Cyclopropane **1** and **1′** were obtained in a 88/12 trans/cis ratio and 90% cumulative yield.
24. All new compounds were characterized by ^1H, ^{13}C NMR and mass spectroscopy.
Grenadamide **2** and its cis-isomer (mixture of isomers): ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.11$–0.23 (m, 1.7H, trans-isomer), 0.30–0.47 (m, 1.7H, trans-isomer), 0.50–0.63 (m, 0.6H, cis-isomer), 0.87 (t, $J = 7.0$ Hz, 3H), 1.05–1.70 (m, 14H), 2.19 (t, $J = 7.5$ Hz, 2H), 2.82 (t, $J = 7.0$ Hz, 2H), 3.53 (dt, $J = 6.5$ and 7.0 Hz, 2H), 5.35–5.50 (m, N–H), 7.18–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): *trans*-**2**: $\delta = 12.06$, 14.4, 18.5, 19.2, 22.9, 29.6, 29.7, 29.9, 30.7, 32.2, 34.4, 36.0, 37.1, 40.8, 126.7, 128.9, 129.0, 139.2, 173.3.
Compound **2′** (mixture of cis and trans-isomers): ^1H NMR ($CDCl_3$, 300 MHz): $\delta = -0.05$–0.06 (m, 0.45H cis-isomer), 0.15–0.25 (m, 1.55H, trans-isomer), 0.30–0.55 (m, 2H), 0.81 (t, $J = 6.2$ Hz, 3H), 1.97 (dd, $J = 7.3$ and 16.2 Hz, 1H), 2.09 (dd, $J = 6.8$ and 16.2 Hz, 1H), 2.75 (t, $J = 6.8$ Hz, 2H), 3.48 (dt, $J = 6.6$ and 6.4 Hz, 2H), 5.48–5.60 (N–H, 0.22H cis-isomer), 5.80–6.00 (N–H, 0.78H trans-isomer), 7.10–7.35 (m, 5H). MS: 302 ($M^{+\cdot}$), 288, 232.
Compound **12**: ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.88$ (t, $J = 6.8$ Hz, 3H), 1.10–1.15 (m, 2H), 1.20–1.50 (m, 12H), 1.60–1.77 (m, 1H), 1.90–2.07 (m, 1H), 2.19–2.40 (m, 2H), 2.83 (t, $J = 7.0$ Hz, 2H), 3.53 (dt, $J = 6.0$ and 6.8 Hz, 2H), 5.40–5.55 (N–H), 7.10–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): *trans*-**12**: $\delta = 14.4$, 22.9, 28.5, 29.5, 29.6, 32.1, 32.8, 35.2, 35.9, 36.2, 37.4, 38.6, 40.9, 126.8, 129.1, 131.9, 172.1. MS = 476, 474, 472 ($M^{+\cdot}$), 394, 316, 274.
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