Catalytic Activity Studies of Aminocarbonyl Group Containing Hoveyda–Grubbs-Type Complexes for the Syntheses of Herbarumin I and Stagonolide A

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Abstract: The catalytic activity of four aminocarbonyl group containing 'boomerang'-type ring-closing metathesis catalysts have been studied for ten-membered lactone and compared well with the Grubbs I and II as well as the Hoveyda–Grubbs catalysts. The activity was found to be superior to the above three ring-closing metathesis catalysts and suggesting novel stereoselective total syntheses of herbarumin I and stagonolide A.

Key words: decanolides, stagonolides, herbarumin I, Wittig reaction, ring-closing metathesis

The generic name decanolides encompasses a relatively small group of naturally occurring ten-membered lactones of polyketides origin isolated in most cases from various species of fungi.[1] *Stagonospora cirsii* is a pathogen of *Cirsium arvense* and demonstrated development of a mycoherbicide. A new decanolide, named stagonolide A, was isolated and characterized as (8*R*,9*R*)-8-hydroxy-7-oxo-9-propyl-5-nonen-9-olide by spectral and analytical methods.[2] Stagonolide A was shown to be a nonhost-specific but selective phytotoxin. Stagonolide A is structurally related to several known fungal ten-membered lactones, for instance, putaminoxins[3] isolated from *Phoma putaminum*, a pathogen of *Erigeron annuus* (*Asteraceae*), pinolidoxins[4] isolated from *Ascochyta pinodes*, a pathogen of peas (*Fabaceae*), lethaloxins[5] and herbarumins isolated from *Phoma herbarum*, a pathogen of *Zea mays* (*Poaceae*).[6] Among them, herbarumin I[7] is the most related to stagonolide A (Figure 1). Surprisingly, among investigated natural phytotoxic ten-membered lactones, there are no structures with a ketonic carbonyl group in the lactone ring at C7, similar to stagonolide.[8] These naturally occurring ten-membered lactones, isolated from fungal metabolites, commonly known as decanolides, have attracted considerable attention from synthetic organic chemists as well as bioorganic chemists because of their interesting structures and various biological activity like plant-growth inhibition, antifeedant, antifungal, and antibacterial activities.

The construction of lactones through the formation of a C–C bond and particularly by ring-closing metathesis reaction (RCM)[9] is a promising tool for decanolides. In this communication, we found that the catalytic activity of four well defined, air-stable 'boomerang'-type metathesis catalysts[10] compared well with the Grubbs first- and second-generation and Hoveyda–Grubbs catalysts for decanolide suggesting a novel route towards the syntheses of herbarumin I and stagonolide A. Recently, the first stereoselective total synthesis of stagonolide A has been reported.[11]

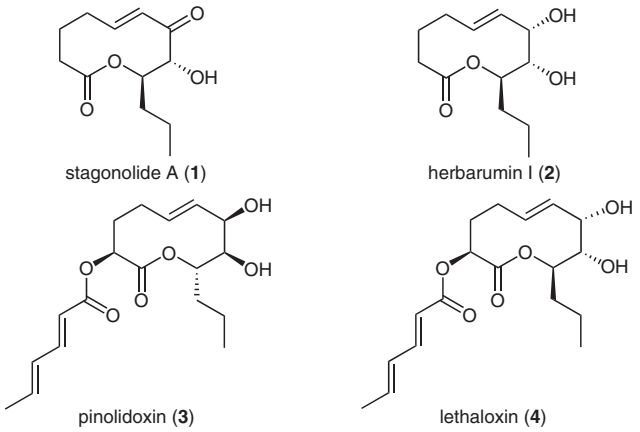
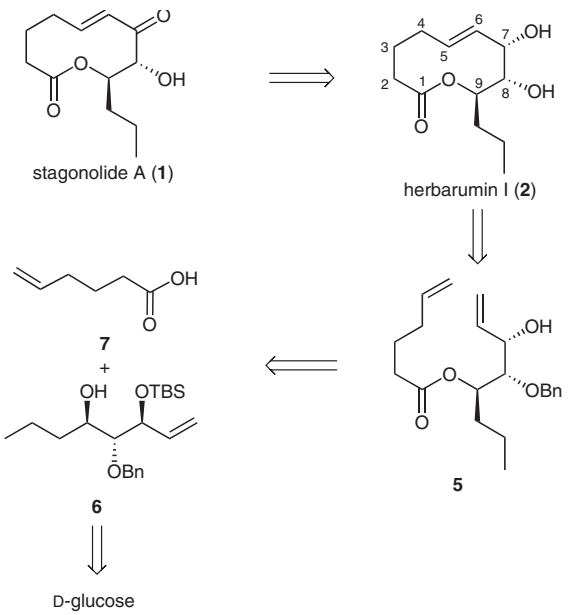


Figure 1 Structures of stagonolide A, herbarumin I, pinolidoxin, and lethaloxin



Scheme 1 Retrosynthetic analysis of herbarumin I and stagonolide A

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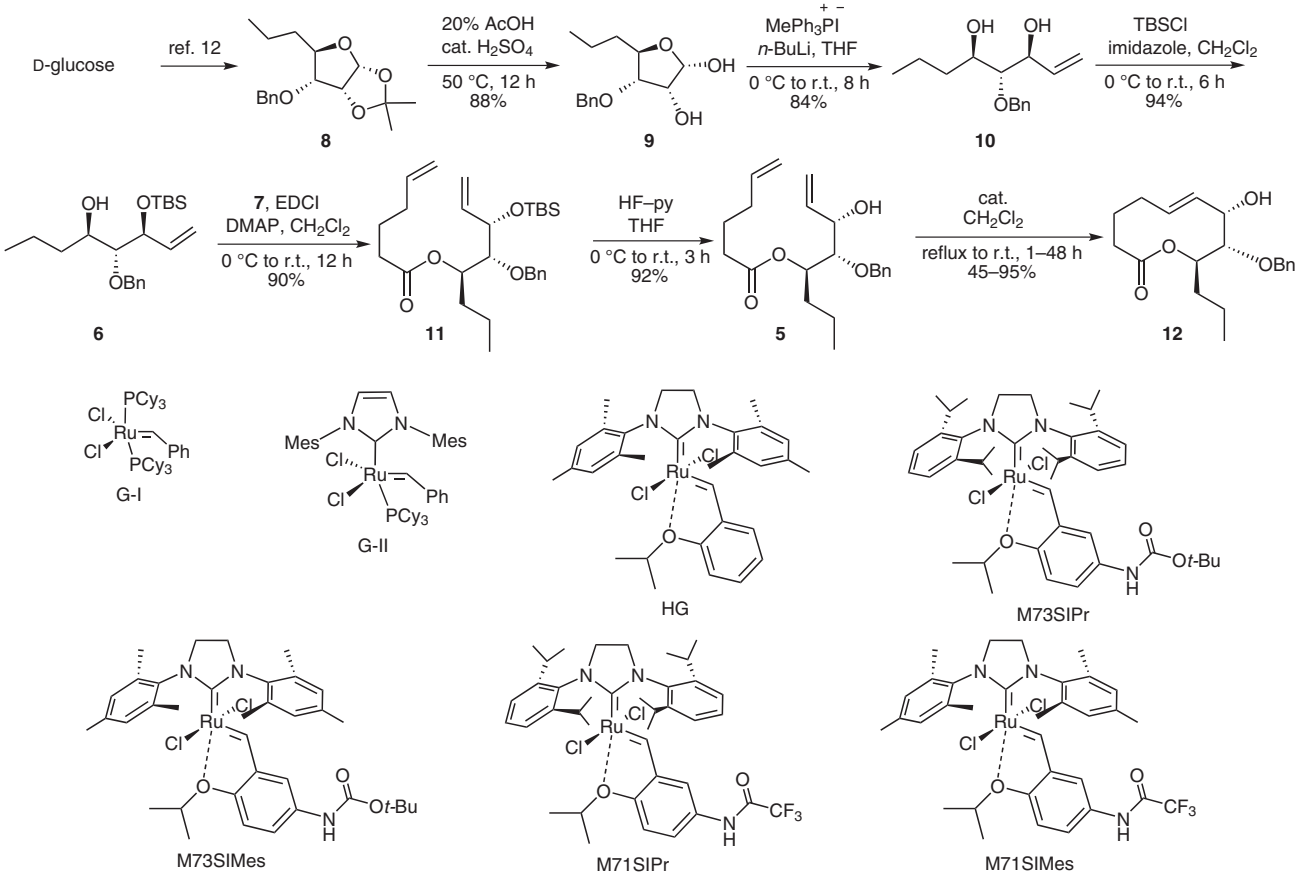
According to our retrosynthetic analysis (Scheme 1), the construction of the ten-membered lactones **1** and **2** would arise from the formation of C5–C6 olefin linkage from bisalkene **5** which in turn would be prepared via the esterification of alcohol **6** and acid **7**. The synthesis of alcohol **6** could be obtained from D-glucose in a concise and high-yielding manner.

The synthesis of the alcohol fragment **6** began with a known intermediate **8** which in turn was obtained from D-glucose.[12] Deprotection of the 1,2-*O*-isopropylidene group of **8** with 20% AcOH in H_2O and a catalytic amount of H_2SO_4 afforded the lactol **9** in 88% yield, which after workup was subjected to one-carbon Wittig homologation[13] with in situ generated methylenetriphenylphosphorane to afford the olefinic intermediate **10**[14] in 84% yield. Selective protection of the allylic hydroxyl group as its TBDMS ether and esterification with 5-hexenoic acid under EDCI and DMAP conditions at room temperature gave the intermediate **11**[15] in 85% yield over two steps (Scheme 2). RCM reaction on substrate **11** did not work with the above metathesis catalysts under different reaction conditions. Deprotection of the TBS ether with HF–pyridine complex afforded the desired RCM precursor **5** in 92% yield.[16]

The RCM reaction was then investigated using Grubbs first- and second-generation catalysts. The reaction of **5** with Grubbs first-generation catalyst (20 mol%) in CH_2Cl_2 with high dilution and under reflux conditions gave the desired lactone **12**[17] in 45% yield as the only product (*E*-isomer) after 48 hours with 42% recovery of the starting material, whereas the second-generation catalyst (10 mol%) afforded the required product in 72% yield in 12 hours. When the Hoveyda–Grubbs catalyst (10 mol%) was used for the same reaction, lactone **12** obtained in 75% yield as the only product. Next, the scope of the metathesis transformation catalyzed by the amino carbonyl group containing Hoveyda–Grubbs-type ('boomerang'-type catalysts) complexes was investigated. The 'boomerang''-type catalysts (Scheme 2) were found to be extremely competent because only 1 mol% catalyst and a reaction time of 1 hours was required to complete the RCM reaction of **5** at room temperature to afford the desired compound **12** in 84–95% yield (Table 1) as the only product.[18]

After having the desired compound **12** in good yield and selectivity, the next task was to deprotect the benzyl group under excess $TiCl_4$[19] (10 equiv) and CH_2Cl_2 at room temperature to afford the herbarumin I (**2**)[20] in 89% yield whose spectral and analytical data were in good agreement with the reported values (Scheme 3).[6a,7b] Finally, selective oxidation of the allylic hydroxyl group with MnO_2 in CH_2Cl_2 gave the stagonolide A (**1**)[21,11] in 84% yield. The spectral and analytical data were in an excellent accord with the natural product which reconfirmed the absolute configuration to be (8*R*,9*R*).[2,11]

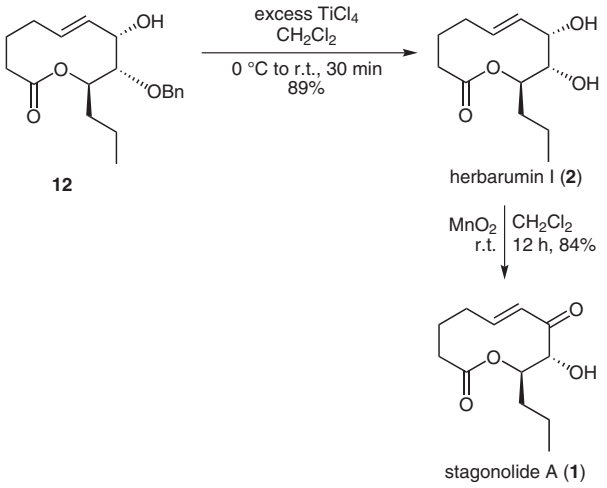


Scheme 2 Catalytic activity studies of 'boomerang' catalysts

Table 1 Results of RCM Reaction

Entry	Catalyst	Conditions	Time (h)	Yield (%)[a]
1	G-I	CH_2Cl_2, reflux	48	45
2	G-II	CH_2Cl_2, reflux	12	72
3	HG	CH_2Cl_2, reflux	12	75
4	M71SIMes	CH_2Cl_2, r.t.	1	84
5	M73SIMes	CH_2Cl_2, r.t.	1	90
6	M71SIPr	CH_2Cl_2, r.t.	1	92
7	M73SIPr	CH_2Cl_2, r.t.	1	95

[a] Isolated yield and only *E*-isomer.



Scheme 3 Syntheses of herbarumin I and stagonolide A

In conclusion, we have shown that well-defined, air-stable, four aminocarbonyl group containing Hoveyda–Grubbs-type complexes are more effective for ten-membered lactones compared to Grubbs and Hoveyda–Grubbs catalysts and en route achieved a convergent synthesis of pharmacologically active herbarumin I and stagonolide A starting from commercially available D-glucose. All these new air-stable catalysts are under investigation for RCM reaction for different substrates leading to lactones of different ring sizes and substituents at the double bond.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Analytical and Spectral Data of 10**
$[\alpha]_D^{25}$ +7.6 (*c* 1.1, $CHCl_3$). IR (neat): 3455, 2924, 2852, 2097, 1461 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.19 (m, 5 H), 6.05 (m, 1 H), 5.34 (dd, *J* = 17.3, 1.5 Hz, 1 H), 5.18 (dd, *J* = 10.6, 1.5 Hz, 1 H), 4.60 (ABq, *J* = 13.6, 11.3 Hz, 2 H), 4.31 (t, *J* = 5.3 Hz, 1 H), 3.74 (m, 1 H), 3.25 (t, *J* = 6.04 Hz, 1 H), 2.90 (br s, 1 H), 2.59 (br s, 1 H), 1.69–1.24 (m, 4 H), 0.92 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.7, 137.9, 137.7, 128.4, 127.8, 128.1, 116.1, 84.2, 73.9, 73.7, 72.6, 35.3, 18.8, 14.0. HRMS: *m/z* calcd for $C_{15}H_{22}O_3Na$: 273.1466; found: 273.1472.

(15) **Analytical and Spectral Data of 11**
$[\alpha]_D^{25}$ +27.0 (*c* 0.7, $CHCl_3$). IR (neat): ν_{max} = 3398, 2963, 2925, 2855, 1723, 1711, 1639, 1461, 1129 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 5 H), 6.02–5.68 (m, 2 H), 5.29–5.12 (m, 2 H), 5.07–4.95 (m, 2 H), 4.66 (ABq, *J* = 17.2, 11.5 Hz, 2 H), 4.21–4.06 (m, 2 H), 3.50 (t, *J* = 4.7 Hz, 1 H), 2.33–2.24 (m, 2 H), 2.14–2.06 (dd, *J* = 7.4, 6.9 Hz, 2 H), 1.78–1.63 (m, 4 H), 1.40–1.22 (m, 2 H), 0.96–0.84 (m, 12 H), 0.07 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 138.5, 138.1, 137.6, 128.2, 127.8, 127.5, 116.5, 115.3, 83.9, 74.6, 74.0, 73.7, 34.9, 33.7, 33.1, 31.5, 25.8, 24.1, 18.7, 14.0, –4.2, –5.0. HRMS: *m/z* calcd for $C_{27}H_{44}O_4NaSi$: 483.2906; found: 483.2914.

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(17) **Analytical and Spectral Data of 12**
$[\alpha]_D^{25}$ +18.2 (*c* 1.0, $CHCl_3$). IR (film): ν_{max} = 4272, 3801, 3471, 2954, 1722, 1641, 1371, 1217, 1091 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.30 (m, 5 H), 5.68–5.57 (m, 1 H), 5.50 (dd, *J* = 15.7, 1.1 Hz, 1 H), 5.21 (dt, *J* = 9.5, 1.1 Hz, 1 H), 4.73–4.53 (m, 3 H), 3.37 (dd, *J* = 9.6, 1.9 Hz, 1 H), 2.34–2.27 (m, 2 H), 2.03–1.78 (m, 4 H), 1.49 (m, 1 H), 1.36–1.22 (m, 4 H), 0.89 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5, 137.3, 133.1, 130.3, 128.5, 128.0, 124.6, 80.9, 72.3, 68.8, 68.8, 34.5, 33.6, 33.5, 24.5, 17.8, 13.9. HRMS: *m/z* calcd for $C_{19}H_{26}O_4Na$: 341.1728; found: 341.1722.

(18) **General Procedure for the Metathesis Reaction**
To a stirred solution of diene (1.0 mmol) in freshly prepared dry CH_2Cl_2 (200 mL) at r.t. was added the metathesis catalyst (0.01 mmol) under argon. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (EtOAc–hexane = 1:6) to afford the *E*-isomer as the sole product.

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(20) **Analytical and Spectral Data of 2**
$[\alpha]_D^{25}$ +10.6 (*c* 1.0, EtOH); lit.:[7b] $[\alpha]_D^{20}$ +10.8 (*c* 0.51, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.61 (d, *J* = 15.9 Hz, 1 H), 5.49 (m, 1 H), 4.95 (td, *J* = 9.4, 2.2 Hz, 1 H), 4.42 (br s, 1 H), 3.51 (d, *J* = 9.8 Hz, 1 H), 2.76 (br s, 1 H), 2.45–2.25 (m, 2 H), 2.06–1.81 (m, 4 H), 1.56 (m, 1 H), 1.43–1.18 (m, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 130.7, 124.6, 73.6, 73.3, 70.1, 34.4, 33.6, 33.3, 24.6, 17.9, 13.8. IR (neat): ν_{max} = 3455, 3038, 2955, 2920, 2867, 1711, 1639, 1219 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{20}O_4Na$: 251.1259; found: 251.1264.

(21) **Analytical and Spectral Data of 1**
Mp 71–72 °C; $[\alpha]_D^{25}$ –59.2 (*c* 0.5, EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.42 (d, *J* = 16.0 Hz, 1 H), 6.32 (m, 1 H), 4.65 (dt, *J* = 9.5, 2.4 Hz, 1 H), 4.05 (dd, *J* = 9.5, 6.2 Hz, 1 H), 3.57 (d, *J* = 6.2 Hz, 1 H), 2.57–2.41 (m, 2 H), 2.20–1.90 (m, 6 H), 1.43–1.18 (m, 3 H), 0.93 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.5, 174.2, 143.1, 131.9, 76.5, 74.4, 34.2, 34.0, 33.5, 24.9, 18.0, 13.7. IR (neat): ν_{max} = 3468, 2925, 1740, 1700, 1638, 1219 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{19}O_4$: 227.1278; found: 227.1274.