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SYNTHETIC STUDIES TOWARD CLAVILACTONE A: A CONCISE ACCESS TO α,γ-SUBSTITUTED γ-BUTENOLIDES BY METATHESIS‡

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Abstract – Synthetic studies toward clavilactone A (**1**), using olefin metathesis as key steps, have been described. The ring-opening/ring-closing metathesis of 3-bromo-2-[1-(1-cyclobutenyl)carboxyl-2-propenyl]-1,4-dimethoxybenzene (**9**) constructed a γ-arylated butenolide (**11**). The ring-opening/ring-closing/cross metathesis of 2-[1-(1-cyclobutenyl)carboxyl-2-propenyl-1,4-dimethoxybenzene (**19**) in the presence of methallyl acetate (**20**) provided 2-[4-((*E*)-5-acetoxy-4-methyl-3-pentenyl)-5-oxo-2,5-dihydrofuran-2-yl]-1,4-dimethoxybenzene (**21**). The π-allyl palladium complex-mediated intramolecular cyclization of **21** for construction of the 11-membered lactone moiety in the clavilactones was also explored.

Clavilactones A (**1**), B (**2**) and C (**3**) (Figure 1) were isolated from cultures of the fungus Basidiomycetous *Clitocybe clavipes*.[1] Their relative structures were deduced based on NMR studies and finally determined by a single-crystal X-ray analysis of the dimethyl ether derivative of **1**. These natural products consist of a 1,4-dihydroxybenzene or a 1,4-benzoquinone connected with a 11-membered lactone, which shares with an α,β-epoxy-γ-lactone ring. Later, structurally resembling clavilactones D (**4**) and E (**5**) were isolated from *C. clavipes* by using different culture conditions.[2] Clavilactones A (**1**), B (**2**) and C (**3**) exhibited antifungal and antibacterial activity and inhibited the germination of *Lepidium sativum*.[1] In addition, compounds (**1**), (**2**) and (**4**) exhibited potent inhibitory activity against epidermal growth factor receptor (EGF-R) tyrosine kinase.[2,3] Herein, we describe our synthetic studies toward the clavilactone A (**1**), which are characterized by tandem olefin metathesis.

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‡ This paper is dedicated to Professor Steven M. Weinreb (The Pennsylvania State University), with respect and admiration, on the occasion of his 65th birthday.

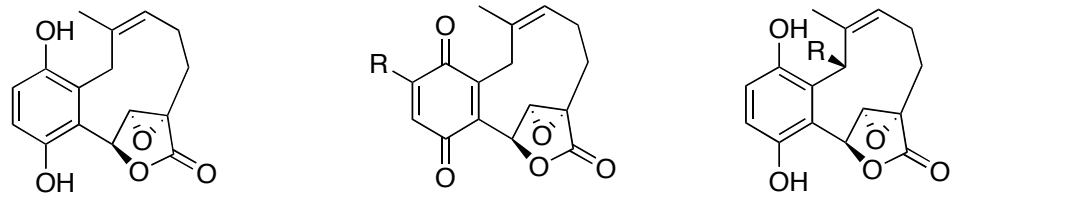
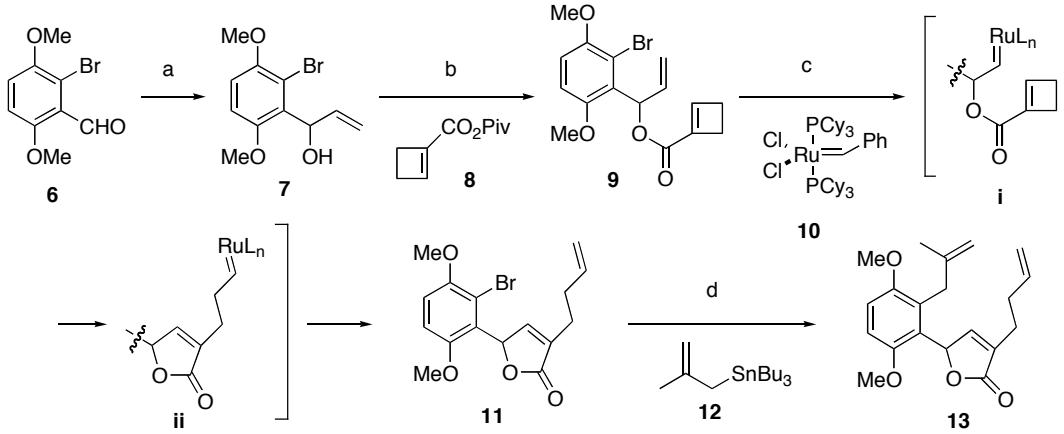


Figure 1. Structures of the clavilactones

During this decade, progress in olefin metathesis has brought significant benefit in the field of natural product synthesis.[4] We have reported some total syntheses of biologically intriguing natural products by using olefin metathesis for the construction of their core skeletons.[5-8] In the first total synthesis of natural (+)-mycoepoxydiene, a structurally unique natural product having a 9-oxabicyclo[4.2.1]nona-2,4-diene core skeleton, we have developed the one-pot ring-opening/cross/ring-closing metathesis of 7-oxanorbornene.[6] For the total synthesis of **1**, we planned the use of two metathesis approaches, i.e., ring-opening/ring-closing metathesis or ring-opening/ring-closing/cross metathesis for concise synthesis of the functionalized butenolides such as **11** and **21** as a clue to the 11-membered lactone formation. The first approach was commenced with known trisubstituted benzaldehyde (**6**)[9] (Scheme 1). Compound (**6**) was converted to allylic alcohol (**7**)[10] by addition of vinylmagnesium bromide. Esterification of the allylic alcohol (**7**) in the presence of lithium hexamethyldisilazide [$LiN(TMS)_2$] with a mixed anhydride (**8**), prepared from cyclobutenecarboxylic acid[11] and pivaloyl chloride, provided ester



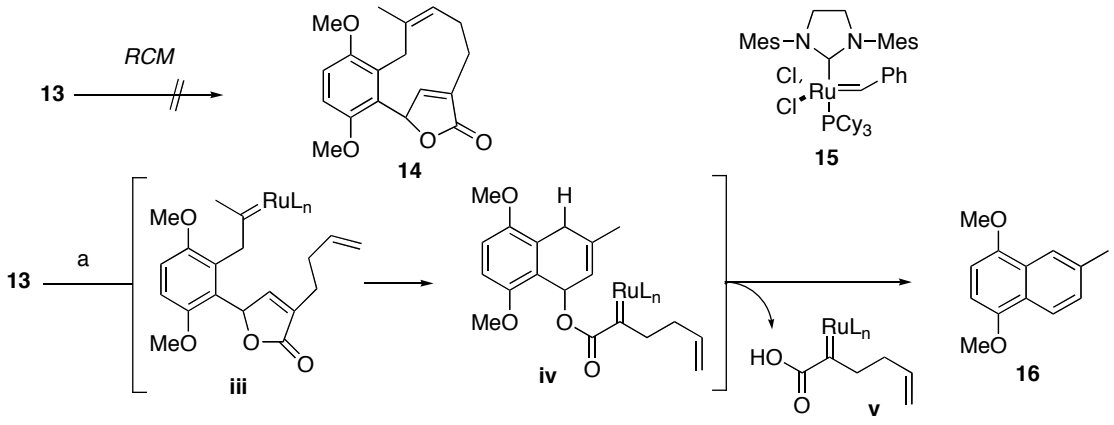
Reagents and conditions: a) CH_2=CHMgBr, THF, 83%; b) $LiN(TMS)_2$, THF, -78 ºC, then **8**, 94%; c) **10** (10 mol%), benzene, reflux, 27% after 4 cycles; d) **12**, $Pd(PPh_3)_4$, CsF, 1,2-dichloroethane, 80 ºC, 58%.

Scheme 1. Preparation of **13** via the ROM/RCM of **9**

(**9**). We explored the one-pot ring-opening/ring-closing metathesis (ROM/RCM) of **9** using 1st generation Grubbs catalyst (**10**).[12] This metathesis reaction was quenched when half amount of **9** was

consumed owing to that prolonged reaction time decreased the yield of **11** significantly. The unreacted **9** was recovered for reuse. As a result, 2-(3-butenyl)-1,4-butenolide (**11**) was obtained in 27% yield after three recycles.[13] As concerns the reaction mechanism for the formation of **11**, we consider that the allylic olefin reacts first with the Grubbs catalyst producing a ruthenium carbene complex (**i**),[14] which is converted to complex (**ii**) by a ring-opening/ring-closing process (Scheme 1). Then, another **9** reacts with **ii**, producing **11** with generation of **i**, which resumes the second catalytic cycle. The Stille coupling of bromobenzene (**11**) and methallyltributylstannane (**12**)[15] in the presence of CsF provided the methallylated product (**13**).[16] The addition of CsF was required for this coupling to maintain good yields.[17]

With substrate (**13**) in hand, we examined the RCM of **13** under a variety of conditions for the formation of the 11-membered lactone part of **1** (Scheme 2). We examined the following reaction conditions: 1) the Grubbs catalyst (**10**) in refluxing CH_2Cl_2 or benzene, 2) the Grubbs 2nd generation catalyst (**15**)[18] in refluxing CH_2Cl_2 or benzene, and 3) the 2nd generation Hoveyda-Grubbs catalyst[19] in refluxing benzene. Unfortunately, none of the conditions employed provided the desired RCM product (**14**). In most cases, an undesired dimerized product and/or a cross metathesis product with styrene were obtained. On the other hand, when **13** was treated with a high loading of the Grubbs catalyst (**15**) in refluxing benzene, 1,4-dimethoxy-6-methylnaphthalene (**16**)[20] was obtained. This conversion can be explained by the mechanism shown in Scheme 2. The ROM/RCM reaction occurred between the carbene derived from the methallyl olefin and the butenolide olefin in **iii**, which followed aromatization of the resulting **iv** accompanied by elimination of the carboxylic acid (**v**).



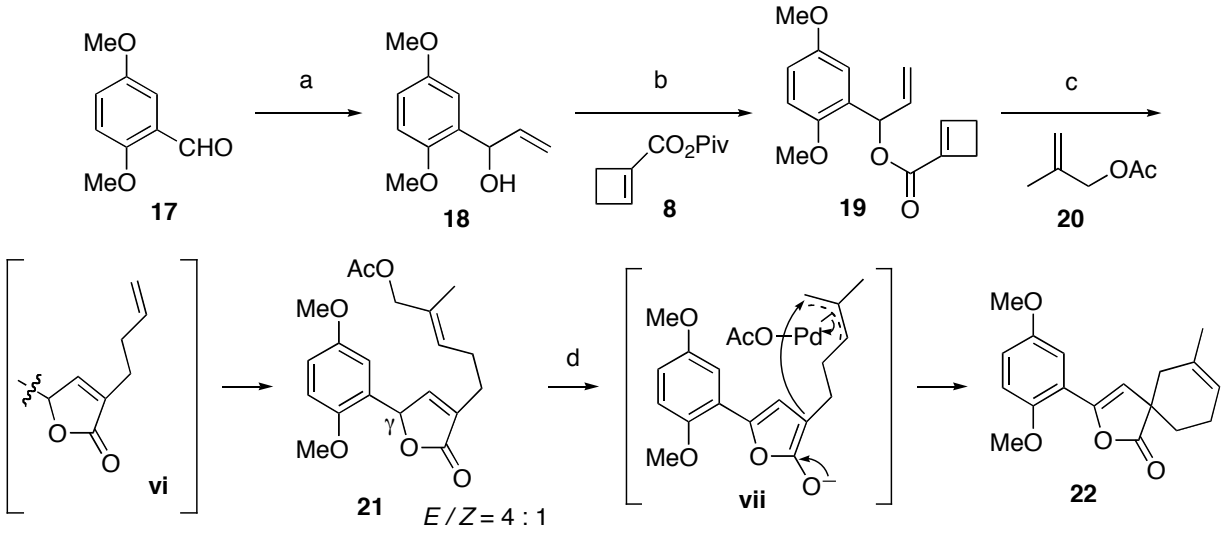
Reagents and conditions: a) **15** (71 mol%), benzene (0.003 M), reflux, 24%.

Scheme 2. The attempted RCM of **13**.

We next investigated another access to the clavilactone core structure by an intramolecular Friedel-Crafts allylation using allylic acetate (**21**) via a π-allyl palladium complex[21] (Scheme 3). For the synthesis of

21, commercially available **17** was converted to **19** via allylic alcohol (**18**) by the reaction sequence analogous to that shown in Scheme 1. The tandem metathesis of **19** was carried out using the Grubbs catalyst (**15**) in the presence of methallyl acetate (**20**), which provided an α,γ-substituted butenolide (**21**) in a yield of 22%.[22] This reaction started with the ROM/RCM reactions of **19** leading to intermadiate (**vi**), followed by the cross metathesis (CM) with **20**. We examined first the use of the Grubbs 1st generation catalyst (**10**) (30 mol%) in benzene for this tandem metathesis. Under these conditions, we observed the formation of the ROM/RCM product (**vi**), which was characterized by comparison with an authentic sample prepared in a separate experiment. However, the CM of **vi** with **20** did not proceed using **10**. On the other hand, treatment of the ROM/RCM product **vi** with **20** in the presence of **15** afforded **21**. Consequently, we used the Grubbs catalyst (**15**) for the tandem metathesis of **19**.

With the substrate (**21**) in hand, we explored the possibility of the attack of the electron-rich aromatic carbon neighboring the methoxy group in **21** to the π-allyl palladium species, generated from the methallyl acetate moiety, to construct the desired 11-membered lactone ring. In contrast to our expectation, brief treatment of **21** with a catalytic amount of $Pd(PPh_3)_4$ in the presence of K_2CO_3 at 80 °C produced a 2-oxospiro[4.5]decane-type compound (**22**)[23] in 59% yield as a sole product.[24] As shown in Scheme 3, oxidative addition of the methallyl acetate moiety to a Pd(0) complex and base-mediated deprotonation of the γ-proton in the butenolide ring provide an intermediary dienolate (**vii**). Then the nucleophilic α-carbon of the dienolate attacks to the π-allyl palladium species regioselectively to produce **22**, accompanying regeneration of the Pd(0) catalyst.[25]



Reagents and conditions: a) CH_2=CHMgBr, THF, 95%; b) $LiN(TMS)_2$, THF, -78 ºC, then **8**, 69%; c) **20**, **15** (10 mol%), benzene, reflux, 22%; d) $Pd(PPh_3)_4$, K_2CO_3, DMF, 80 ºC, 59%.

Scheme 3. Preparation of **21** and formation of **22** by a Pd(0)-catalyzed intramolecular alkylation

In conclusion, we have developed concise syntheses of 1,4-dimethyoxybenzenes (**11**), (**13**) and (**21**), which possess a functionalized butenolide ring at C-2. These synthetic approaches rely on the ROM/RCM or ROM/RCM/CM strategy for the construction of the γ-arylated butenolide moiety. Further synthetic studies toward the total synthesis of clavilactones are in progress in this laboratory.

ACKNOWLEDGEMENTS

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10. All new compounds were fully characterized by spectroscopic means [^{1}H-NMR (270 MHz in $CDCl_3$), ^{13}C-NMR (68 MHz in $CDCl_3$), IR] and gave satisfactory HRMS (EI). Yields referred to homogeneous samples obtained by chromatographic purification on silica gel.
11. Commercially available cyclobutanecarboxylic acid was converted to cyclobutenecarboxylic acid according to a previous report: A. Campbell and H. N. Rydon, *J. Chem. Soc.,* 1953, 3002.
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13. Synthesis of **11**: To a stirred solution of **9** (516 mg, 1.46 mmol) in benzene (150 mL) was added a solution of Grubbs catalyst (**10**) (117 mg, 0.142 mmol) in benzene (0.5 mL). The mixture was refluxed for 2 h, quenched with a few drops of DMSO, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10 to 1:5) to provide 55.7 mg (11%) of **11** and 245 mg of **9** was recovered. The recovered **9** (245 mg) was subjected to the same

reaction conditions using **10** (71.7 mg) to provide 45.6 mg (19%) of **11** and 159 mg of **9** was recovered. The recovered **9** (159 mg) was subjected to the same reaction conditions using **10** (52.8 mg) to provide 24.9 mg (16%) of **11** and 112 mg of **9** was recovered. Again the recovered **9** (112 mg) was subjected to the same reaction conditions using **10** (26.4 mg) to provide 12.8 mg (11%) of **11** and 67.2 mg of **9** was recovered. After the three recycles, totally 139 mg (27%) of **11** was obtained from 516 mg of **9**. Compound (**11**): TLC R_f 0.31 (EtOAc/hexane, 1:2); IR (neat) 2920, 1750 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.32-2.50 (m, 4H), 3.69 (s, 3H), 3.86 (s, 3H), 5.02 (dt, 1H, *J* = 11.4, 1.8 Hz), 5.08 (dt, 1H, *J* = 17.0, 1.8 Hz), 5.85 (ddt, 1H, *J* = 11.4, 17.0, 6.2 Hz), 6.63 (m, 1H), 6.81 (d, 1H, *J* = 9.2 Hz), 6.89 (d, 1H, *J* = 9.2 Hz), 7.02 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.5, 31.3, 56.5, 56.9, 80.4, 111.4, 112.9, 115.1, 115.5, 122.6, 133.6, 137.0, 145.9, 150.4, 153.5, 174.6; HRMS calcd for $C_{16}H_{17}O_4Br$ (M^+) *m/z* 352.0310, found 352.0309.

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16. Compound (**13**) was obtained as a colorless oil: TLC R_f 0.65 (EtOAc/hexane, 1:2); IR 2940, 1750 cm^{-1}; ^1H NMR δ 1.79 (s, 3H), 2.34-2.52 (m, 4H), 3.37 (d, 1H, *J* = 16.9 Hz), 3.55 (d, 1H, *J* = 16.9 Hz), 3.65 (s, 3H), 3.76 (s, 3H), 4.30 (s, 1H), 4.77 (s, 1H), 4.99-5.11 (m, 2H), 5.84 (m, 1H), 6.08 (br s, 1H), 6.72 (d, 1H, *J* = 9.0 Hz), 6.86 (d, 1H, *J* = 9.0 Hz), 6.98 (br s, 1H); ^{13}C NMR δ 17.9, 23.2, 31.5, 33.3, 56.1, 56.5, 78.1, 110.5, 110.7, 112.3, 126.0, 127.0, 128.0, 137.3, 144.8, 147.7, 147.8, 151.9, 153.3, 174.8; HRMS (EI) calcd for $C_{20}H_{24}O_4$ (M^+) *m/z* 328.1675, found 328.1675.
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20. Compound **16** was obtained as amorphous solid: ^1H NMR δ 2.52 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.62 (d, 1H, *J* = 8.1 Hz), 6.67 (d, 1H, *J* = 8.1 Hz), 7.33 (d, 1H, *J* = 8.4 Hz), 7.98 (s, 1H), 8.09 (d, 1H, *J* = 8.4 Hz): ^{13}C NMR δ 21.8, 55.6, 55.7, 102.2, 103.3, 120.8, 121.7, 124.5, 126.4, 127.9, 135.6, 149.0, 149.6. These data were identical with those reported for **16** in the following paper: B. K. Mehta, O. Barun, H. Ila, and H. Junjappa, *Synthesis*, 1998, 1483.
21. An analogous intermolecular Pd(0)-catalyzed allylation of aromatic rings, see: B. Nay, J.-F. Peyrat, and J. Vercauteren, *Eur. J. Org. Chem.* 1999, 2231.
22. Synthesis of **21**: To a stirred solution of **19** (12.6 mg, 45.9 μmol) in benzene (4.6 mL) were added methallyl acetate (56 μL, 460 μmol) and a solution of the Grubbs catalyst (**15**) (11.7 mg, 4.6 μmol)

in benzene (0.5 mL). The mixture was heated under reflux for 22 h, quenched with a few drops of DMSO, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give 3.7 mg (22%) of **21** (*E*/*Z* = *ca*. 4:1, based on ^{1}H NMR analysis) as a colorless oil: TLC R_f 0.31 (EtOAc/hexane, 1:2); IR 2940, 1730 cm^{-1}; ^{1}H NMR for *E*-isomer δ 1.64 (br s, 3H), 2.01 (s, 3H), 2.32-2.39 (m, 4H), 3.74 (s, 3H), 3.85 (s, 3H), 4.43 (br s, 2H), 5.43 (m, 1H), 6.20 (d, 1H, *J* = 1.1 Hz), 6.75-6.84 (m, 3H), 7.20 (d, 1H, *J* = 1.1 Hz), for *Z*-isomer δ 1.73 (br s, 3H), 2.07 (s, 3H), 2.32-2.39 (m, 4H), 3.76 (s, 3H), 3.81 (s, 3H), 4.56 (br s, 2H), 5.38 (m, 1H), 6.20 (d, 1H, *J* = 1.1 Hz), 6.75-6.84 (m, 3H), 7.20 (d, 1H, *J* = 1.1 Hz); ^{13}C NMR for *E*-isomer δ 14.0, 20.9, 24.9, 25.5, 55.8, 55.9, 69.7, 77.8, 111.5, 111.6, 114.1, 124.5, 127.4, 131.6, 132.0, 148.4, 150.4, 153.9, 170.8, 174.0; HRMS calcd for $C_{20}H_{24}O_6$ (M^+) *m*/*z* 360.1573, found 360.1577.

23. To a stirred solution of **21** (30.6 mg, 85.0 μmol) in DMF (17 mL) were added a solution of $Pd(PPh_3)_4$ (4.9 mg, 4.2 μmol) in DMF (0.5 mL) and K_2CO_3 (23.5 mg, 170 μmol). The mixture was stirred for 2 h at 80 °C, diluted with Et_2O (20 mL), and washed with saturated aqueous NaCl (20 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:30) to provide 15.0 mg (59%) of **22** as a colorless oil: TLC R_f 0.67 (EtOAc/hexane, 1:2); IR 2930, 1790, 1500 cm^{-1}; ^{1}H NMR δ 1.72 (s, 3H), 1.75-2.57 (m, 6H), 3.80 (s, 3H), 3.88 (s, 3H), 5.55 (br s, 1H), 6.30 (s, 1H), 6.88 (s, 2H), 7.26 (s, 1H); ^{13}C NMR δ 22.4, 23.6, 29.9, 37.3, 48.3, 55.7, 55.9, 111.9, 112.0, 113.1, 116.0, 117.5, 120.3, 130.7, 147.9, 151.7, 153.4, 181.2; HRMS calcd for $C_{18}H_{20}O_4$ (M^+) *m*/*z* 300.1362, found 300.1374.
24. We examined the conversion of **21** to **22** using the following two conditions; 1) $Pd(PPh_3)_4$, *i*-Pr_2NEt, THF, rt to reflux (decomposition of **21**); 2) $Pd(PPh_3)_4$, *i*-Pr_2NEt, DMF, 80 °C (27% yield of **22**).
25. We consider that the conversion of **21** to **22** seems to be an intramolecular variant of the Tsuji-Trost reaction, see the following seminal papers; 1) J. Tsuji, *Tetrahedron*, 1986, **42**, 4361. 2) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*,1989, **28**, 1173.