Synthesis of Vinyllactones via Allylic Oxidation of Alkenoic Acids

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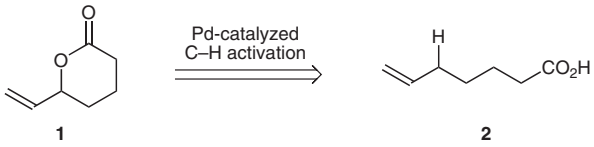
Abstract: A one-step access to vinyllactones is described utilizing the Pd-catalyzed allylic oxidation of alkenoic acids. The influence of ring size as well as the olefin configuration is investigated culminating in the synthesis of goniothalamin analogues.

Key words: allyl complexes, catalysis, lactones, oxidation, palladium

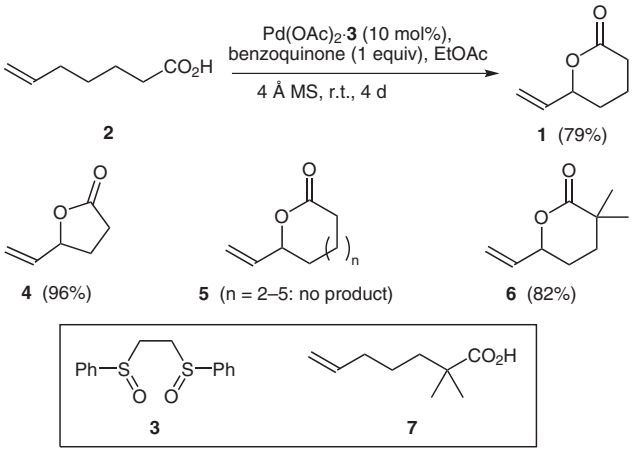
Vinyllactone **1** has regularly attracted considerable interest of organic chemists, both as a key intermediate in synthesis as well as a model compound proving the efficiency of developed synthetic methodology.[1] While enantioselective access is arguably most efficiently achieved via a chemoenzymatic approach,[1d] obviously the shortest route is the one-step Pd-catalyzed allylic C–H activation of alkenoic acids or esters **2** directly leading to the title compound **1** (Scheme 1). Elegant oxidative cyclization processes have been reported to yield five- and six-membered lactones,[1e,f] albeit long reaction times (5–7 d) and byproducts preventing the isolation of pure product **1** need to be considered when utilizing acid **2**.[1f] Tailor-made conditions for the synthesis of macrolactones have more recently been established by the White group.[2] In view of our ongoing efforts towards the syntheses of lactone-containing natural products,[3] we intended to investigate the scope of this alternative catalytic system.



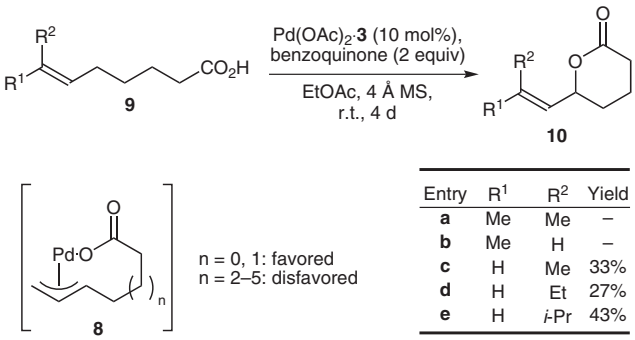
Scheme 1 One-step retrosynthesis of vinyllactone **1**

We were pleased to find that, upon applying the White conditions utilizing catalyst **3** (albeit at room temperature), on heptenoic acid (**2**), formation of lactone **1** was immediately possible in good yield (79%, Scheme 2) not observing any difficulties during purification. While the corresponding butyrolactone **4** could also be readily synthesized (96%), medium-ring lactones **5** could not be isolated. Additional substituents did not hamper the reaction: lactone **6** (from the known[4] acid **7**) was formed in 82% yield. The difficulties observed for the transformation to medium-sized rings can be readily rationalized by the proposed[3c] intermediate **8** (Scheme 3): ring strain will disfavor the formation of compound **8** for n = 2–5. However, the observation would also imply that additional substituents at the ω-position of heptenoic acid **9**[5] should probably slow down the lactonization, but nevertheless give δ-lactones **10**, only. While an acid with two substituents (**9a**: $R^1 = R^2 = Me$) was expected to be a difficult substrate, we were surprised to find that *E*-configured acid **9b** did not react, but all *Z*-substrates **9c–e** resulted in the formation of the expected lactones **10c–e** albeit in poor yield (27–43%). Since the actual coordination sphere on the palladium intermediates is not completely understood in the present transformation, the stereochemical rationalization is still under investigation.

A drawback of the standard conditions is obviously the prolonged reaction time. Microwave-assisted conversions are a common alternative for accelerating reactions.[6] A



Scheme 2 Synthesis of vinyllactones from ω-alkenoic acids



Entry	R^1	R^2	Yield
a	Me	Me	–
b	Me	H	–
c	H	Me	33%
d	H	Et	27%
e	H	*i*-Pr	43%

Scheme 3 Synthesis of substituted vinyllactones **10**

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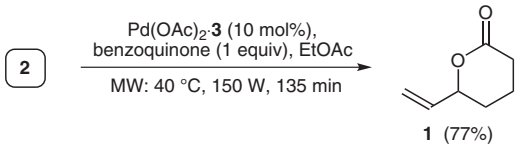
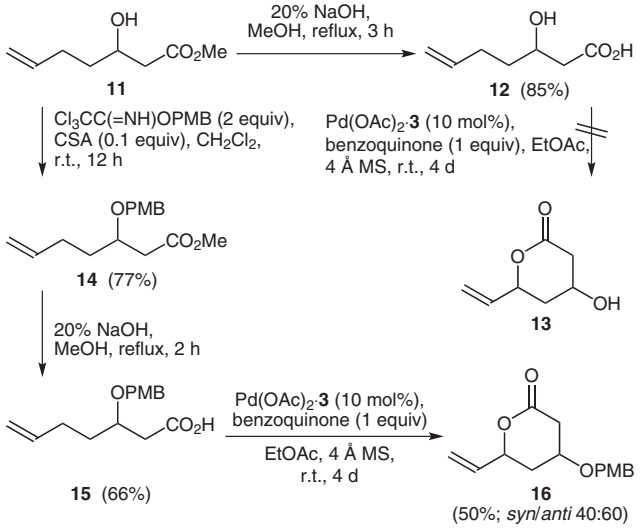
brief survey of different solvents (ethylene glycol, 2-PrOH, EtOH, DMSO, CH_2Cl_2, DCE, EtOAc) indicated that lactone formation was best achieved in EtOAc. Side-product formation was observed at temperatures above 80 °C (at 150 W), and best results were obtained at 40 °C. A yield of 77% of lactone **1** was isolated after 135 minutes representing a dramatic decrease in reaction time. Unfortunately, the conditions do not generally give better results as can been seen for butyrolactone **4** (62%, Scheme 4).



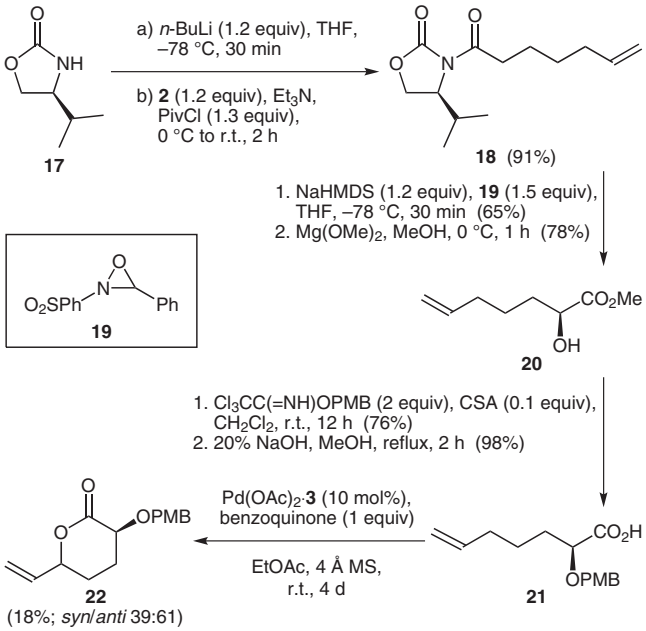
Scheme 4 Microwave-assisted synthesis of lactones **1** and **4**

Next, we investigated stereoselective approaches, but all attempts to apply enantioselective, catalytic variants[7] failed. Furthermore, we noted that, while kinetic enzymatic resolutions worked in principal, the overall efficiency was low since the background (unselective) hydrolysis was too high. Hence we focused on diastereoselectivity: Starting from the known[8] β-hydroxy ester **11**, acid **12** was readily available (85%, Scheme 5). However, allylic oxidation to furnish lactone **13** failed. When introducing a *p*-methoxybenzyl (PMB) protecting group[9] first (yield of ether **14**: 77%), the liberated acid **15** (66%) was shown to be a suitable substrate furnishing the separable δ-lactone **16** in reasonable yield (50%, *syn*/*anti* = 40:60).[10]

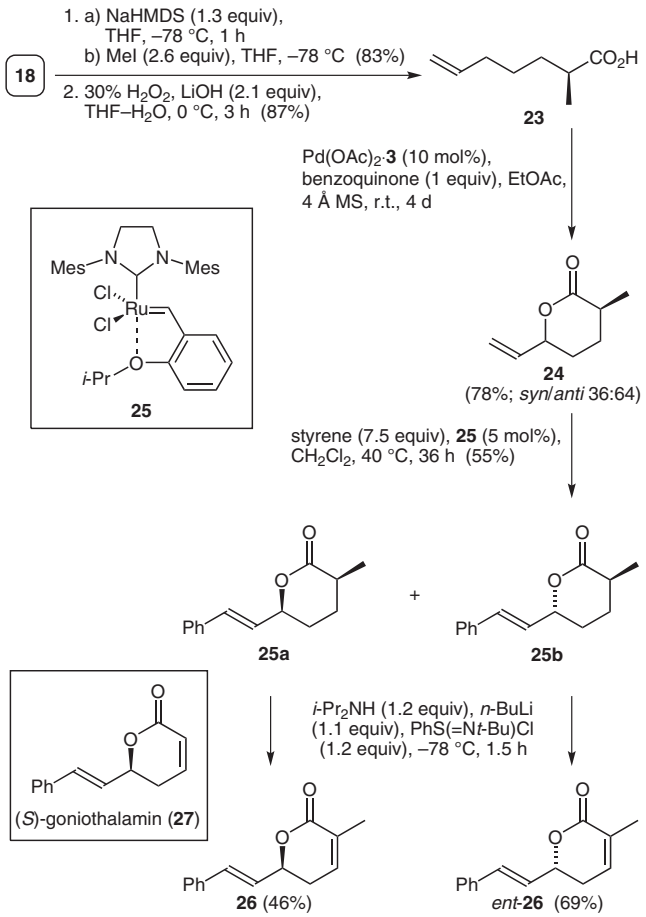


Scheme 5 Simple diastereoselectivity of lactonization

However, the diastereoselectivity was low with the substituent in β-position, and hence we next investigated α-substituted acids.



Scheme 6 Induced diastereoselectivity of lactonization



Scheme 7 Synthesis of goniothalamin analogues **26**

Following a procedure of Guerlavais et al.,[11] Evans auxiliary **17** was acylated yielding amide **18** (91%, Scheme 6); selective oxidation with oxaziridine **19** and solvolysis yielded α-hydroxy ester **20**.[12] Protection[9] and

saponification[4] led to the desired acid **21**. Allylic oxidation provided the separable lactones **22** in low yield and selectivity (18%, *syn*/*anti* = 39:61). Omitting protecting groups that can be cleaved under oxidative conditions, we finally focused on the methyl-substituted acid **23** that was conveniently synthesized from amide **18** (Scheme 7).[11,13] Oxidative cyclization was straightforward (78%); however, the diastereomers were not separable at this stage (*syn*/*anti* = 36:64). Nevertheless, after successful cross metathesis,[14] the lactones **25a** and **25b** were readily isolated (55%). Introduction of the Michael system was achieved utilizing the protocol by Matsuo and Aizawa.[15] The goniothalamin analogues **26** and ent-**26** were obtained, and the assignment of configuration of the stereogenic center formed during allylic oxidation was further confirmed by comparison of the specific rotation with goniothalamin (**27**): while both *S*-enantiomers do have a negative value [(*S*)-**27**: –170 (*c* 1.7, $CHCl_3$); (*S*)-**26**: –153 (*c* 1.5, $CHCl_3$)], the *R*-enantiomers show positive values.[16,17] It is interesting to note that a number of structural features have been included in structure–activity relationship studies,[18] but additional substituents at the Michael system are still elusive in such investigations. On the basis of the present findings, the gap should be closed in due course.

In summary, the present work demonstrates the scope of the White catalyst for the synthesis of γ- and δ-lactones. Substituent effects were investigated and culminated in the first synthesis of new goniothalamin analogues **26** that also allowed the confirmation of the absolute configuration.

Acknowledgment

We gratefully acknowledge the Jürgen Manchot Stiftung (scholarship for M.B.), the Deutsche Forschungsgemeinschaft, the Ministry of Innovation, Science and Research of the German federal state of North Rhine-Westphalia, the Heinrich Heine University Düsseldorf, and the Forschungszentrum Jülich GmbH for the generous support of our projects. Donations from BASF AG, Chemetall GmbH, and Wacker AG were greatly appreciated. We thank Birgit Henßen, Christoph Lorenz, Vera Ophoven, Bea Paschold, and Truc Pham for supporting experiments.

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(17) **Selected Data for Acid 23**
$[\alpha]_D^{20}$ +17.2 (*c* 0.96, $CHCl_3$). IR (film): ν_{max} = 3073, 2977, 2935, 2861, 2648, 1702, 1642, 1465, 1417, 1381, 1290, 1236, 1191, 996, 910, 812, 742 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.19 (d, $^3J_{Me,2}$ = 7.0 Hz, 3 H, CH_3), 1.41–1.49 (m, 3 H, 3-H_a, 4-H), 1.66–1.73 (m, 1 H, 3-H_b), 2.05–2.09 (m, 2 H, 5-H), 2.47 (m_c, 1 H, 2-H), 4.96 (ddt, $^3J_{7E,6}$ = 10.2 Hz, $^2J_{7E,7Z}$ = 2.0 Hz, $^4J_{7E,5}$ = 1.2 Hz, 1 H, 7–H_E), 5.01 (ddd, $^3J_{7Z,6}$ = 17.1 Hz, $^2J_{7Z,7E}$ = 2.0 Hz, $^4J_{7Z,5}$ = 1.6 Hz, 1 H, 7–H_Z), 5.80 (ddt, $^3J_{6,7Z}$ = 17.1 Hz, $^3J_{6,7E}$ = 10.2 Hz, $^3J_{6,5}$ = 6.7 Hz, 1 H, 6-H), 11.5 (br s, 1 H, COOH) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.9 (CH_3), 26.4 (C-4), 32.9 (C-3), 33.6 (C-5), 39.2 (C-2), 114.8 (C-7), 138.4 (C-6), 183.0 (C-1) ppm. MS (EI, 70 eV): *m/z* (%) = 124 (2) $[M - OH]^+$, 101 (3) $[C_5H_8O_2]^+$, 96 (6) $[C_7H_{13}]^+$, 87 (13) $[C_4H_6O_2]^+$, 74 (100) $[C_3H_5O_2]^+$, 69 (90) $[C_4H_6O]^+$, 55 (38) $[C_3H_4O]^+$. Anal. Calcd for $C_8H_{14}O_2$ (142.20): C, 67.57; H, 9.92. Found: C, 67.52; H, 10.02.
Selected Data for Vinyllactone 25[19]
IR (film): ν_{max} = 3027, 2967, 2935, 2875, 1729, 1599, 1578, 1495, 1450, 1376, 1363, 1239, 1184, 1100, 1073, 1011, 969, 933, 749, 694 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 216 (73) $[M]^+$, 187 (5) $[C_{13}H_{16}O]^+$, 160 (7) $[C_{11}H_{12}O]^+$, 146 (37) $[C_{10}H_{10}O]^+$, 129 (77) $[C_{10}H_{10}]^+$, 115 (54) $[C_9H_8]^+$, 104 (100) $[C_8H_7]^+$, 91 (61) $[C_7H_6]^+$, 77 (30) $[C_6H_5]^+$, 56 (80) $[C_4H_8]^+$. Anal. Calcd for $C_{14}H_{16}O_2$ (216.28): C, 77.75; H, 7.46.

Found: C, 77.52; H, 7.35.

Isomer 25a

$[\alpha]_D^{20}$ +18.2 (*c* 0.60, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.35 (d, $^3J_{Me,3}$ = 7.1 Hz, 3 H, CH_3), 1.63–1.70 (m, 1 H, 4-H_a), 1.78–1.85 (m, 1 H, 5-H_a), 2.08–2.12 (m, 2 H, 4-H_b, 5-H_b), 2.53 (ddq, $^3J_{3,4a}$ = 8.8 Hz, $^3J_{3,4b}$ = 7.0 Hz, $^3J_{3,Me}$ = 7.0 Hz, 1 H, 3-H), 4.97 (dddd, $^3J_{6,5a}$ = 10.9 Hz, $^3J_{6,1'}$ = 6.2 Hz, $^3J_{6,5b}$ = 3.4 Hz, $^4J_{6,2'}$ = 1.4 Hz, 1 H, 6-H), 6.21 (dd, $^3J_{1',2'}$ = 16.0 Hz, $^3J_{1',6}$ = 6.2 Hz, 1 H, 1′-H), 6.66 (dd, $^3J_{2',1'}$ = 16.0 Hz, $^4J_{2',6}$ = 1.4 Hz, 1 H, 2′-H), 7.25–7.28 (m, 1 H, arom. 4-CH), 7.31–7.34 (m, 2 H, arom. CH), 7.37–7.39 (m, 2 H, arom. CH) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.3 (CH_3), 28.2 (C-4), 29.5 (C-5), 36.0 (C-3), 81.5 (C-6), 126.6 (arom. CH), 127.5 (C-1′), 128.1 (arom. 4-CH), 128.7 (arom. CH), 131.9 (C-2′), 136.0 (arom. C_{ipso}), 174.0 (C-2) ppm.

Isomer 25b

$[\alpha]_D^{20}$ +29.2 (*c* 1.35, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 1.27 (d, $^3J_{Me,3}$ = 6.8 Hz, 3 H, CH_3), 1.58–1.64 (m, 1 H, 4-H_a), 1.82–1.89 (m, 1 H, 5-H_a), 2.05–2.16 (m, 2 H, 4-H_b, 5-H_b), 2.66 (ddq, $^3J_{3,4a}$ = 10.5 Hz, $^3J_{3,4b}$ = 7.8 Hz, $^3J_{3,Me}$ = 6.8 Hz, 1 H, 3-H), 5.00 (dddd, $^3J_{6,5a}$ = 9.9 Hz, $^3J_{6,1'}$ = 6.0 Hz, $^3J_{6,5b}$ = 4.0 Hz, $^4J_{6,2'}$ = 1.4 Hz, 1 H, 6-H), 6.20 (dd, $^3J_{1',2'}$ = 16.0 Hz, $^3J_{1',6}$ = 6.0 Hz, 1 H, 1′-H), 6.67 (dd, $^3J_{2',1'}$ = 16.0 Hz, $^4J_{2',6}$ = 1.4 Hz, 1 H, 2′-H), 7.25–7.28 (m, 1 H, arom. 4-CH), 7.31–7.34 (m, 2 H, arom. CH), 7.37–7.39 (m, 2 H, arom. CH) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.4 (CH_3), 25.4 (C-4), 27.5 (C-5), 33.7 (C-3), 78.3 (C-6), 126.4 (arom. CH), 126.6 (C-1′), 128.1 (arom. 4-CH), 128.7 (arom. CH), 132.1 (C-2′), 136.0 (arom. C_{ipso}), 175.4 (C-2) ppm.

Selected Data for Goniothalamin Analogue 26

$[\alpha]_D^{20}$ –152.5 (*c* 1.5, $CHCl_3$). IR (film): ν_{max} = 3028, 2926, 1710, 1599, 1578, 1495, 1450, 1362, 1338, 1230, 1144, 1109, 1081, 1042, 1014, 968, 918, 861, 753, 731, 693 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 1.95 (dt, $^4J_{Me,4}$ = 2.2 Hz, $^5J_{Me,5}$ = 1.5 Hz, 3 H, CH_3), 2.48–2.52 (m, 2 H, 5-H), 5.05 (m_c, 1 H, 6-H), 6.27 (dd, $^3J_{1',2'}$ = 15.9 Hz, $^3J_{1',6}$ = 6.3 Hz, 1 H, 1′-H), 6.61 (m_c, 1 H, 4-H), 6.71 (dd, $^3J_{2',1'}$ = 15.9 Hz, $^4J_{2',6}$ = 1.4 Hz, 1 H, 2′-H), 7.26–7.29 (m, 1 H, arom. 4-CH), 7.32–7.34 (m, 2 H, arom. CH), 7.38–7.40 (m, 2 H, arom. CH) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 17.1 (CH_3), 30.3 (C-5), 78.0 (C-6), 126.0 (C-1′), 126.9, 128.3, 128.8 (arom. CH), 128.9 (C-3), 132.8 (C-2′), 135.9 (arom. C_{ipso}), 138.5 (C-4), 165.5 (C-2) ppm. MS (EI, 70 eV): *m/z* (%) = 214 (36) $[M]^+$, 186 (10) $[C_{12}H_{11}O_2]^+$, 171 (4) $[C_{13}H_{14}]^+$, 129 (12) $[C_{10}H_{10}]^+$, 115 (11) $[C_9H_8]^+$, 104 (21) $[C_8H_7]^+$, 89 (29) $[C_7H_6]^+$, 82 (100) $[C_5H_6O]^+$, 54 (24) $[C_4H_6]^+$.

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