Blume, Fabian; Liu, Yu-Chang; Thiel, Daniel; Deska, Jan

Chemoenzymatic Total Synthesis of (+)- & (−)-cis-Osmundalactone

Published in:
Journal of Molecular Catalysis B: Enzymatic

DOI:
10.1016/j.molcatb.2016.11.010

Published: 12/11/2016

Document Version
Peer-reviewed accepted author manuscript, also known as Final accepted manuscript or Post-print

Chemoenzymatic Total Synthesis of (+)- & (–)-*cis*-Osmundalactone

Fabian Blume, Yu-Chang Liu, Daniel Thiel, and Jan Deska*

Department of Chemistry, Aalto-yliopisto, FI-02150 Espoo, Finland

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Biocatalysis
Natural Products
Peroxidase
Dehydrogenase
Oxidative Rearrangement
Chemoenzymatic

ABSTRACT

Both optical antipodes of the *cis*-isomers of osmundalactone, a hydroxypyranone natural product and core structure of the angiopterlactones, have been synthesized from acetylfuran in only three steps through a redox cascade utilizing oxidoreductases and transition metal catalysis in a concerted fashion. The key step in this fully catalytic strategy is the enzyme-mediated Achmatowicz reaction via selective furan oxygenation to furnish the pyran core structure.

1. Introduction

Osmundalactone (**1**), 5-hydroxy-6-methyl-5,6-dihydro-2H-pyran-2-one, is naturally found in various organisms,[1] and it is thought to play a role in e.g. pest control.[2] Moreover, the osmundalactone motif is incorporated into a number of more complex natural products,[3] hence making it a prominent target for total synthetic approaches.[4] While the free osmundalactone and many conjugates thereof commonly found in nature display a *trans*-configuration, some structurally related metabolites such as angiopteroside[5] and the angiopterlactone family (e.g. **4**)[6] feature a *cis*-osmundalactone subunit. So it came to no surprise that soon after the report on the angiopterlactones, in 2010 also the (–)-*cis*-osmundalactone (–)-*epi*-**1** was identified as constituent in *Angiopteris esculenta*.[7]

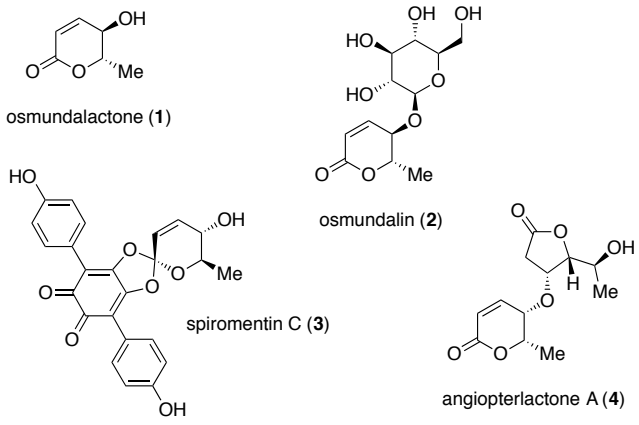
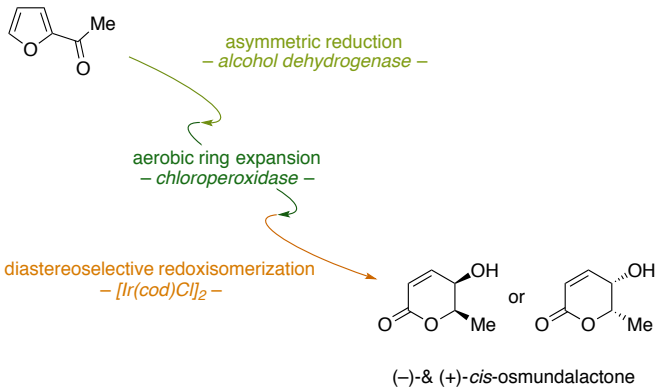


Figure 1. Natural products featuring the osmundalactone motif.

* Corresponding author. E-mail address: jan.deska@aalto.fi (J. Deska)

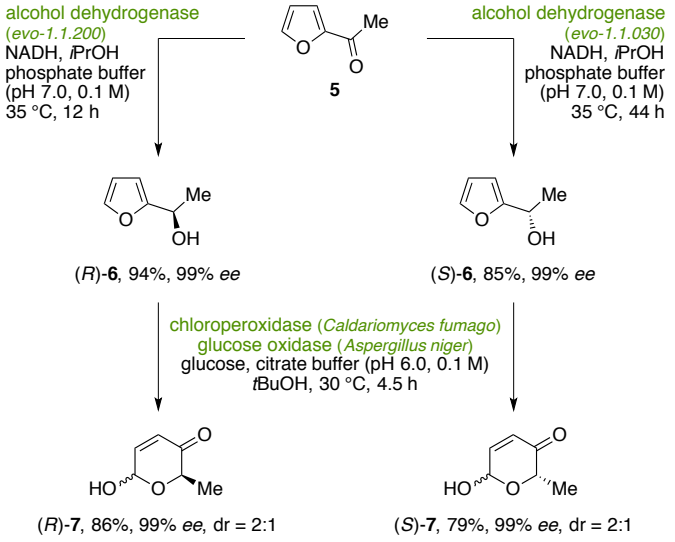
As a result of our recent studies on the enzymatic oxygenative rearrangement of furfuryl alcohols yielding functionalized pyranones,[8] we became interested in small natural product molecules of the δ-lactone type, as targets for the design of synthetic multi-enzyme cascades and their potential (bio)synthetic connections to oligomeric, more complex secondary metabolite relatives. As a first test for our previously reported artificial "Achmatowicz monooxygenase" (using chloroperoxidase from *C. fumago* as oxygenating catalyst for functionalized furans) in a preparative-synthetic context, we constructed a three-step sequence to yield the *cis*-isomer of osmundalactone from simple acetylfuran in a purely catalytic fashion. Here, the choice of a suitable alcohol dehydrogenase for the initial ketone reduction will offer perfect control over the absolute stereochemistry while, after Achmatowicz-type rearrangement [9] of the intermediate alcohol, a metal-catalyzed redoxisomerization ensures high diastereoselectivity in favor of the desired *cis*-configured δ-lactone.



Scheme 1. Triple-catalytic strategy towards stereodefined osmundalactones.

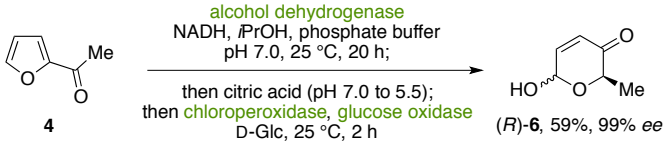
2. Results and Discussion

In order to be able to provide sufficient amounts of enantiomerically pure synthetic starting materials and intermediates en route to the osmundalactones, and eventually to conduct follow-up studies on its more complex dimers, we began our studies with revisiting the previously described biocatalytic scheme accessing pyranone **7** both with regard to scalability as well as to an optimization towards an integrated, yet illusive one-pot protocol. To our delight, the asymmetric reduction protocol employing two commercial alcohol dehydrogenases (evo-1.1.200 and evo-1.1.030, respectively, as known enantiocomplementary reduction biocatalysts) proved to be very robust and reliable. Utilizing isopropanol as solubilizer and terminal reducing agent, both enantiomers of alcohol **6** were obtained on a gram scale in high yields. A simplified workup protocol helped to overcome previously observed limitations and led to excellent yields after extraction (diethyl ether/pentane 2/1) of analytically pure **6**. Due to the low intrinsic enantioselectivity of our recently developed enzymatic Achmatowicz rearrangement, both enantiomers were subsequently converted smoothly to the corresponding six-membered heterocycles (*R*)-**7** and (*S*)-**7**, respectively, without any apparent matched-mismatched effects. Here, the combination of glucose oxidase (GOx, *A. niger*) as oxygen-activating catalyst and chloroperoxidase (CPO, *C. fumago*) as oxygenation mediator exhibited high activity in the desired ring expansion, and a ten-fold upscaling compared to our original protocol was tolerated without any problem, giving rise to the pyranones in around 80% isolated yield. Different other combinations of commercial peroxidases (including horseradish, soybean and lactoperoxidase) and hydrogen peroxide-releasing systems (L-alanin + amino acid oxidase and methanol + alcohol oxidase/formaldehyde dismutase[10]) have been tested, but none of them performed as good as the original GOx/CPO setup.[11]



Scheme 2. Stepwise synthesis of the optically pure pyranones (*R*)- and (*S*)-**7**.

One obvious advantage of biocatalysis lies in the relative ease to construct catalytic cascades. However, as discussed in our previous report, initial attempts to execute the reduction-oxidation sequence from ketone **5** to pyranone **7** in a one-step fashion remained fruitless which was attributed to incompatibilities between the dehydrogenase system and the peroxidase catalyst. Nonetheless, instead of a fully integrated all-at-once approach, we were able to successfully perform the two-step process in one pot in a sequential manner. After asymmetric reduction based on a glucose dehydrogenase/alcohol dehydrogenase couple at pH 7, slight acidification and addition of the Achmatowicz-inducing biocatalysts led to the formation of (*R*)-**7** in 47% yield and perfect enantiopurity. Even better results were obtained when using isopropanol instead of the GDH/D-Glc recycling system with an isolated yield of the heterocyclic product of 59% (Scheme 3).

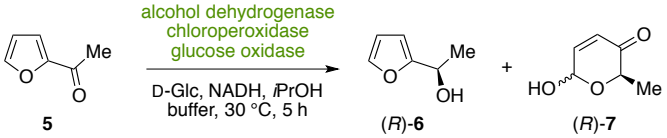


Scheme 3. Sequential reduction/rearrangement cascade with intermediate pH adjustment.

We were however convinced that further fine-tuning of the reaction parameters would allow to identify suitable conditions for all involved enzymes to remain a certain activity as required for a true one-pot reaction. As indicated by GC traces of our initial cascade studies, no alcohol intermediate (**6**) was detected in most cases but in situ analysis revealed the formation of minor amounts of pyranone **7** along with unconverted ketone (**5**). A more in-depth NMR study confirmed these observations. Employing the reduction and oxidation catalyst (dehydrogenase and chloroperoxidase) in a 1:5 ratio (100 U/mmol ADH, 500 U/mmol CPO, 100 U/mmol GOx) only 5% conversion to the enantiomerically pure (*R*)-**7** was detected (Table 1, entry 1). At pH 5.5, the optimal medium for the oxidative rearrangement, apparently the dehydrogenase system, despite not being entirely silent, lacked the necessary activity. Not surprisingly, the increase of the amount of ADH by a factor of five (and doubling the concentration of NADH) resulted in a substantially more productive system providing (*R*)-**7** as major component in the reaction mixture (Table 1, entry 2). A subsequent pH screening revealed an optimal pH of 6.0 giving rise to 90% of the desired pyranone in optically pure form (Table 1, entry 3). With further decrease in acidity, a partial loss of Achmatowicz activity was noted and under neutral conditions, only the intermediate alcohol (*R*)-**6** was accumulated (Table 1, entries 4 & 5). These results

Table 1

Optimization of a one-pot biocatalytic reduction/rearrangement cascade for the synthesis of (*R*)-**7**.

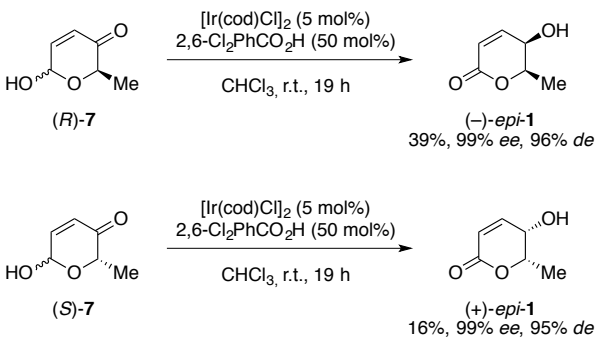


Entry	ADH/GOx/CPO	pH	**5** (%)	**6** (%)	**7** (%)	*ee* (**7**) (%)
1	1 / 1 / 5	5.5	95	0	5	99
2	5 / 1 / 5	5.5	12	2	86	99
3	**5 / 1 / 5**	**6.0**	**0**	**10**	**90**	**99**
4	5 / 1 / 5	6.5	3	17	80	99
5	5 / 1 / 5	7.0	2	98	0	–

[a] Reaction conditions: **5** (100 µmol), D-glucose (125 µmol), NADH (10 - 20 µmol), ADH (10 - 50 U), GOx (10 U), CPO (50 U), citrate or phosphate buffer (9 mL, 100 mM), isopropanol (1 mL), 30 °C, 5 h. Yields were determined by ^{1}H-NMR against N-formylmorpholine as standard; optical purities were determined by GC analysis on chiral phase.

confirm the previously recorded pH optima of the individual transformations. However with the optimized conditions in hand, we are convinced that the triple-enzyme system represents a highly interesting module for the design of more complex synthetic cascades and will therefore be included in much more detail in our future studies.

For the finalization of the fully catalytic total synthesis of the *cis*-osmundalactones (*epi*-**1**), a redoxisomerization was required, providing oxidation of the lactol moiety by concomitant 1,2-reduction of the enone carbonyl. In lack of reports on biocatalytic protocols for this particular transformation,[12] we turned our attention to transition metal catalysis that has shown great potential in various kinds of redox-neutral isomerization processes.[13] Initial attempts employing various Ru- and Rh-complexes previously described in the context of redoxisomerizations remained fruitless. Very recently, however, Guo and Tang reported on precisely the required transformation using a simple commercial iridium dimer in combination with an acidic cocatalyst.[14] Here, the transition metal complex performs a dehydrogenation-reduction sequence via the intermediate γ-keto-δ-lactone while 2,6-dichlorobenzoic acid is described to facilitate epimerization of the stereochemically labile hemiacetal resulting in a dynamic stereoconvergent isomerization. We were pleased to see that the iridium-catalyzed osmundalactone synthesis indeed proceeded with excellent diastereocontrol and provided both enantiomers of the desired *cis*-lactones *epi*-**1** in nearly stereoisomerically pure form after 19 h (Scheme 4). Worth mentioning, however, the reaction proved to be rather unreliable and TLC indicated numerous apolar products as an undesired side effect of the acid cocatalyst. Hence, the reported very high yields were never achieved and the desired target compounds (–)-*epi*-**1** and (+)-*epi*-**1** were obtained in only moderate yields of 39% and 16%, respectively, underlining the necessity for further investigations including the design of a yet elusive enzyme-based alternative of this reaction. In absence of dichlorobenzoic acid, the iridium-catalyzed transformation exhibited much better product selectivity but the stereoselectivity dropped from greater 95% *de* to a mixture of *epi*-osmundalactone (*epi*-**1**) and osmundalactone (**1**) in a ratio of 2:1.



Scheme 4. Synthesis of the *cis*-osmundalactones via iridium-catalyzed redoxisomerization.

3. Conclusion

In summary, a fully catalytic synthetic cascade for the preparation of both enantiomers of *cis*-osmundalactone was developed merging bio- and metal catalysis in a synergistic manner. Herein, we described a novel triple-enzymatic one-pot protocol for the direct transformation of acetylfuran to optically pure 6-hydroxy-2-methyl-2H-pyran-3(6)-one based on a dehydrogenase-mediated asymmetric reduction and a subsequent oxidase/peroxidase-catalyzed Achmatowicz-type ring expansion. An iridium-based redoxisomerization system finally furnished the target lactones with nearly perfect stereocontrol. Based on this work, we will explore the potential synthetic and biosynthetic relationship of *cis*-osmundalactone to the more complex angiopterlactone family. Furthermore, an expansion of the one-pot biotransformation design will include an entirely enzyme-based route towards stereodefined complex lactone natural products.

4. Experimental

4.1 Experimental details

General methods: Reactions carried out under argon atmosphere were performed with dry solvents using anhydrous conditions. Anhydrous solvents were obtained from an MBraun MB-SPS800 drying system. Commercially available reagents were used without further purification. Catalysts and cofactors were obtained from: NADH, Carbolution Chemicals GmbH; Chloroperoxidase from *Caldariomyces fumago* (*CPO*), 9.9 kU/mL, Sigma; Glucose oxidase type II (*GOx*), 17.3 U/mg, Sigma; Alcohol dehydrogenase recombinant (*ADH 200*), 17.6 U/mg evocatal GmbH; Alcohol dehydrogenase, recombinant (*ADH 030*), 18.8 U/mg, evocatal GmbH; Glucose dehydrogenase, recombinant from *Escherichia coli* (*GDH 060*), 214 U/mg, evocatal GmbH; $[Ir(cod)Cl]_2$, TCI Chemicals. All products were purified by column chromatography over silica gel (Macherey-Nagel MN-Kieselgel 60, 40-60 μm, 240-400 mesh). Reactions were monitored by thin layer chromatography (TLC) carried out on precoated silica gel plates (Macherey-Nagel, TLC Silica gel 60 F_{254}) using UV light and $KMnO_4$-solution or Hanessian's stain for visualization. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at room temperature on a Bruker Avance 400 instrument. Chemical shifts are reported in parts per million (ppm) calibrated using residual non-deuterated solvents as internal reference ($CHCl_3$ at 7.26 ppm (^{1}H-NMR) and 77.00 ppm (^{13}C-NMR)). Infrared spectra were recorded on a Bruker Alpha ECO-ATR FT-IR-Spectrometer, absorption bands are reported in wave numbers [cm^{-1}]. Optical rotations were measured on an Atago Polax-2L at 589 nm. High performance liquid chromatography was performed on a Waters system using a Waters 501 pump and a Waters 2487 dual detector. Gas chromatography was performed on a Hewlett Packard HP 6890 Series GC System using a Macherey-Nagel FS-Lipodex A and Macherey-Nagel FS-Lipodex E column (25 m x 0.25 mm), N_2, 1.0 ml/min; method: 50 °C (1 min) / 5 °C·min^{-1} (35 min) / 120 °C (15 min).

(*R*)-1-(2-Furyl)ethanol ((*R*)-6): Acetylfuran (**5**, 550 mg, 5.0 mmol) was dissolved in isopropanol (25 mL) and added to a solution of NADH (0.5 mmol) and alcohol dehydrogenase (evo-1.1.200, 250 U) in phosphate buffer (pH 7.0, 100 mM, 225 mL). The reaction mixture was incubated at 35 °C (125 rpm) for 12 h until TLC indicated full conversion. The solution was saturated with NaCl and afterwards extracted with diethyl ether/pentane (2:1, 4 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to yield the analytically pure alcohol (*R*)-**6** (528 mg, 4.72 mmol, 94%, 99% *ee*) as pale yellow liquid. $[\alpha]^{20}_D$: +21.0 (c 1.00, $CHCl_3$), 99% *ee*. R_f (cyclohexane/ethyl acetate, 2/1): 0.60. ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.39 (d, ^3J = 1.3 Hz, 1H), 6.23 (dd, ^3J = 3.0 Hz, ^3J = 1.7 Hz, 1H), 6.32 (d, ^3J = 3.0 Hz,1H), 4.92-4.84 (m, 1H), 1.99 (d, ^3J = 3.7 Hz, 1H), 1.54 (d, ^3J = 6.5 Hz, 3H). ^{13}C-NMR

(100 MHz, $CDCl_3$): δ [ppm] = 157.7, 141.9, 110.1, 105.9, 63.6, 21.3. FT-IR (neat, ATR): ν [cm^{-1}] = 3344 (br), 2980 (w), 2875 (w), 1450 (w), 1371 (w), 1328 (w), 1228 (w), 1149 (m), 1066 (m), 1008 (m), 991 (m), 927 (m), 877 (m), 810 (m), 734 (s). GC: method A, *Lipodex E*: (*S*)-**6** = 13.3 min, (*R*)-**6** = 13.9 min.

(*S*)-1-(2-Furyl)ethanol ((*S*)-6): Acetylfuran (550 mg, 5.0 mmol) was reduced according to the protocol employed for the preparation of (*R*)-**6**, using the (*S*)-selective dehydrogenase evo-1.1.030 (200 U) instead. Full conversion was achieved after 44 h. Extraction yielded the analytically pure alcohol (*S*)-**6** (474 mg, 4.23 mmol, 85%, 99% *ee*) as pale yellow liquid. $[\alpha]^{20}_D$: –21.1 (c 1.00, $CHCl_3$), 99% *ee*.

(2*R*)-6-Hydroxy-2-methyl-2H-pyran-3(6)-one ((*R*)-7): In a round bottom flask (250 mL), the alcohol (*R*)-**6** (224 mg, 2.0 mmol) was dissolved in a mixture of citrate buffer (pH 6.0, 100 mM, 72 mL) and *tert*-butanol (8 mL). Chloroperoxidase (500 U), glucose oxidase (100 U) and D-glucose (3.0 mmol) were added and the reaction mixture was incubated at 30 °C (150 rpm) under air for 4.5 h until TLC indicated full conversion. L-Methionine (5 mmol) was added and the solution was extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. After removal of all volatiles in vacuo (*R*)-**7** (199 mg, 1.56 mmol, 78%, 99% *ee*, α/β = 67/33)) was obtained as colorless waxy solid. $[\alpha]^{20}_D$: –79.6 (c 0.50, $CHCl_3$), 99% *ee*. M.p.: 61 °C. R_f (cyclohexane/ethyl acetate, 2/1): 0.25. α-**7**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.89 (dd, ^3J = 10.2 Hz, ^3J = 3.2 Hz, 1H), 6.10 (d, ^3J = 10.2 Hz, 1H), 5.63 (m, 1H), 4.71 (q, ^3J = 6.7 Hz, 1H), 3.53 (d, ^3J = 5.0 Hz, 1H), 1.38 (d, ^3J = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 197.0, 144.5, 127.3, 87.7, 70.4, 15.3. β-**7**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 6.94 (d, ^3J = 10.2 Hz, 1H), 6.15 (d, ^3J = 10.2 Hz, 1H), 5.67 (d, ^3J = 7.2 Hz, 1H), 4.23 (1H, m), 3.87 (d, ^3J = 7.2 Hz, 1H), 1.45 (d, ^3J = 6.7 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 196.5, 148.1, 128.6, 91.0, 75.3, 16.2. FT-IR (neat, ATR): ν [cm^{-1}] = 3294 (br), 3051 (w), 2987 (w), 1676 (s), 1435 (m), 1371 (m), 1334 (w), 1273 (w), 1232 (m), 1143 (m), 1109 (m), 1091 (m), 1031 (s), 937 (m), 900 (m), 808 (m), 690 (m). GC: method A, *Lipodex E*: α-(2*R*)-**7** = 37.0 min, α-(2*S*)-**7** = 37.6 min.

(2*S*)-6-Hydroxy-2-methyl-2H-pyran-3(6)-one ((*S*)-7): (*S*)-**7** was obtained under identical conditions as described for (*R*)-**7** as colorless waxy solid (203 mg, 1.59 mmol, 80%, 99% *ee*, α/β = 67/33). $[\alpha]^{20}_D$: +78.5 (c 0.50, $CHCl_3$), 99% *ee*.

ADH/GOx/CPO-mediated one-pot transformation: Alcohol dehydrogenase (evo-1.1.200, 50 U) and D-glucose (22.5 mg, 125 µmol) were added to a solution of acetylfuran (11.0 mg, 100 µmol), NADH (14.4 mg, 20 µmol), chloroperoxidase (50 U), glucose oxidase (5 U) and isopropanol (1 mL) in citrate buffer (9 mL, 100 mM, pH 6.0) and the mixture was incubated for 5 h at 30 °C (200 rpm). Then, the reaction mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, evaporated under reduced pressure and yields/product ratios were determined by NMR with *N*-formylmorpholine as standard.

(5*R*,6*R*)-5-Hydroxy-6-methyl-5,6-dihydro-2H-pyran-2-one ((–)-*epi*-1): Under argon, (*R*)-**7** (64 mg, 0.5 mmol), $[Ir(cod)Cl]_2$ (16.8 mg, 25 µmol), 2,6-dichlorobenzoic acid (47.7 mg, 0.25 mmol) and anhydrous chloroform (5 mL) were added to an oven-dried flask and the pale yellow reaction mixture was stirred at room temperature for 19 h. The reaction was quenched by addition of saturated sodium bicarbonate solution (20 mL), the aqueous phase was extracted with chloroform (3 x 10 mL) and the combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (cyclohexan/ethyl acetate 1/1) to afford the lactone (–)-*epi*-**1** (25 mg, 195 µmol, 39%, 99% *ee*, 96% *de*) was a pale yellow oil. R_f (cyclohexane/ethyl acetate, 2/1): 0.16. $[\alpha]^{23}_D$: –230 (c 0.50, $CHCl_3$). *epi*-**1**: ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.02 (dd, ^3J = 9.7 Hz, ^3J = 5.7 Hz, 1H), 6.12 (d, ^3J = 9.7 Hz, 1H), 4.55 (dd, ^3J = 6.6 Hz, ^3J = 2.8 Hz, 1H), 4.05 (dd, ^3J = 5.7 Hz, ^3J = 2.8 Hz, 1H), 2.49 (br s, 1H), 1.52 (d, ^3J = 6.6 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ [ppm] = 163.9, 144.6, 122.6, 77.2, 62.9, 15.7. **1** (selected signals): ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 4.36 (dd, ^3J = 7.4 Hz, ^3J = 5.4 Hz, 1H), 3.81 (dd, ^3J = 6.1 Hz, ^3J = 5.4 Hz, 1H), 1.68 (d, ^3J = 6.6 Hz, 3H).

(5*S*,6*S*)-5-Hydroxy-6-methyl-5,6-dihydro-2H-pyran-2-one ((+)-*epi*-1): (+)-epi-**1** was obtained under identical conditions as described for (–)-*epi*-**1** from (*S*)-**7** as a pale yellow oil (10 mg, 78 µmol, 16%, 99% *ee*, *de* = 95%). $[\alpha]^{23}_D$: 235 (c 0.50, $CHCl_3$).

Acknowledgments

We gratefully acknowledge support provided by the Suomen Akatemia (298250), the Dr.-Otto-Röhm-Gedächtnisstiftung, and Carbolution Chemicals.

References and notes

1 (a) Hollenbeak, K. H.; Kühne, M. E. *Tetrahedron* **1974**, *30*, 2307; (b) Numata, A.; Hokimoto, K.; Takemura, T.; Fukui, S. *Appl. Ent. Zool.* **1983**, *18*, 129; (c) Holzapfel, M.; Kilpert, C.; Steglich, W. *Liebigs Ann. Chem.* **1989**, 797; (d) Buchanan, M. S.; Hashimoto, T.; Takaoka, S.; Asakawa, Y. *Phytochemistry* **1995**, *40*, 1251.

2 (a) Numata, A.; Hokimoto, K.; Takemura, T.; Katsuno, T.; Yamamoto, K. *Chem. Pharm. Bull.* **1984**, *32*, 2815; (b) Numata, A.; Takahashi, C.; Fujiki, R.; Kitano, E.; Kitajima, A.; Takemura, T. *Chem. Pharm. Bull.* **1990**, *38*, 2862.

3 (a) Dahmén, J.; Gawell, L.; Leander, K. *Acta Chem. Scand. B* **1976**, *30*, 297; (b) Besl, H.; Bresinsky, A.; Geigenmüller, G.; Herrmann, R.; Kilpert, C.; Steglich, W. *Liebigs Ann. Chem.* **1989**; (c) Höller, U.; König, G. M.; Wright, A. D. *J. Nat. Prod.* **1999**, *62*, 114; (d) Zhang, D.; Yang, X.; Kang, J. S.; Choi, H. D.; Son, B. W. *J. Nat. Prod.* **2008**, *71*, 1458; (e) Liu, Y.; Li, X.-M.; Meng, L.-H.; Wang, B.-G. *Phytochem. Lett.* **2015**, *12*, 232.

4 (a) Yamagiwa, S.; Sato, S.; Hoshi, N.; Kosugi, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 570; (b) Hiraoka, H.; Furuta, K.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2777; (c) Murayama, T.; Sugiyama, T.; Yamashita, K. *Agric. Biol. Chem.* **1986**, *50*, 2347; (d) Noshita, T.; Sugiyama, T.; Kitazumi, Y.; Oritani, T. *Tetrahedron Lett.* **1994**, *35*, 8259; (e) Ono, M.; Saotome, C.; Akita, H. *Heterocycles* **1999**, *51*, 1503; (f) Carda, M.; Rodríguez, González, F.; Castillo, E.; Villanueva, A.; Marco, J. A. *Eur. J. Org. Chem.* **2002**, 2649; (g) Zhu, L.; Kedenburg, J. P.; Xian, M.; Wang, P. G. *Tetrahedron Lett.* **2005**, *46*, 811; (h) Matsushima, Y.; Kino, J. *Eur. J. Org. Chem* **2010**, 2206; (i)

Tatsuta, K.; Tokishita, S.; Fukada, T.; Kano, T.; Komiya, T.; Hosokawa, S. *Tetrahedron Lett.* **2011**, *52*, 983; (j) Ono, M.; Kato, K.; Akita, H. *Chem. Pharm. Bull.* **2013**, *61*, 464; (k)

5 Hseu, T. S. *Acta Cryst*. **1981**, *B37*, 2095.

6 Yu, Y.-M.; Yang, J.-S.; Peng, C.-Z.; Caer, V.; Cong, P.-Z.; Zou, Z.-M.; Lu, Y.; Yang, S.-H.; Gu, Y.-C. *J. Nat. Prod.* **2009**, *72*, 921-924.

7 Chen, Y.; Tao, Y.; Lian, X.; Wang, L.; Zhao, Y.; Jiang, J.; Zhang, Y. *Food Chem.* **2010**, *122*, 1173.

8 Thiel, D.; Doknić, D.; Deska, J. *Nat. Commun.* **2014**, *5*, 5278.

9 reviews: (a) Deska, J.; Thiel, D.; Gianolio, E.; *Synthesis* **2015**, *47*, 3435; (b) van der Pijl, F.; van Delft, F. L.; Rutjes, F. P. J. *Eur. J. Org. Chem.* **2015**, 4811.

10 Kara, S.; Schrittwieser, J. H.; Gargiulo, S.; Ni, Y.; Yanase, H.; Opperman, D. J.; van Berkel, W. J. H.; Hollmann, F. *Adv. Synth. Catal.* **2015**, *357*, 1687-1691.

11 similar preference was also observed in enzymatic halocyclizations: Naapuri, J.; Rolfes, J. D.; Keil, J.; Manzuna Sapu, C.; Deska, J. *Green Chem*. **2017**, *19*, doi:10.1039/C6GC01926A.

12 for a related biocatalytic isomerization see: Gargiulo, S.; Opperman, D. J.; Hanefeld, U.; Arends, I. W. C. E.; Hollmann, F. *Chem. Commun.* **2012**, *48*, 6630.

13 (a) Mantilli, L.; Gérard, D.; Torche, S.; Besnard C.; Mazet, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5143; *Angew. Chem.* **2009**, *121*, 5245; (b) Ahlsten, N.; Lundberg, H.; Martín-Matute, B. *Green Chem.* **2010**, *12*, 1628; (c) Manzuna Sapu, C.; Deska, J. *Org. Biomol. Chem.* **2013**, *11*, 1376; (d) Kress, S.; Johnson, T.; Weisshar, F.; Lautens, M. *ACS Catal.* **2016**, *6*, 747; (e) Li, H.; Mazet, C. *Acc. Chem. Res.* **2016**, *49*, 1232.

14 Wang, H.-Y.; Yang, K.; Bennett, S. R.; Guo, S.-R.; Tang, W. *Angew. Chem. Int. Ed.* **2015**, *54*, 8756; *Angew. Chem.* **2015**, *127*, 8880.