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Sharpless Asymmetric Dihydroxylation on α,β-Unsaturated Diazoketones: A New Entry for the Synthesis of Disubstituted Furanones

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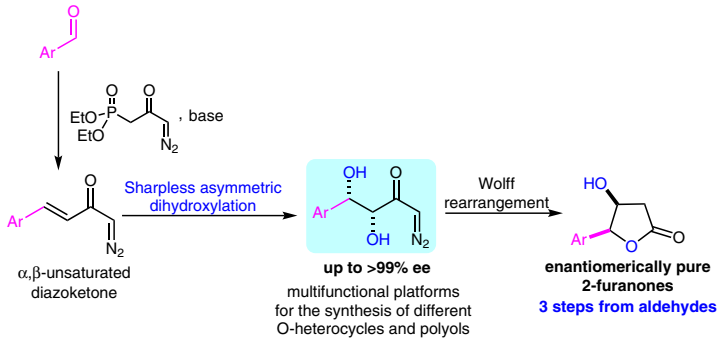

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Abstract The synthesis of enantiomerically pure 4,5-disubstituted 2-furanones is accomplished in three steps from aldehydes. The steps involve a highly enantioselective Sharpless asymmetric dihydroxylation of α,β-unsaturated diazoketones, followed by a photochemical Wolff rearrangement.

Key words unsaturated diazoketones, Sharpless dihydroxylation, furanones, Wolff rearrangement, photochemistry, asymmetric synthesis

α,β-Unsaturated α′-diazoketones[1] have proven to be important building blocks in synthesis. Possessing in the same molecule functions such as a diazo group, a carbonyl group and a double bond, these compounds can furnish the short and direct synthesis of several molecules, including heterocycles. Although very promising, these diazoketones were, for a long period of time, little studied or employed in synthesis, mainly because of the difficulties associated with their preparation. In the last few years our research group developed two new olefination reagents that permitted the selective synthesis of several *E*- and *Z*-α,β-unsaturated α′-diazoketones in one step from aldehydes.[2,3] By employing these building blocks, we could synthesize several nitrogen heterocycles such as pyrrolidines, indolizidines, quinolizidines, and piperidines by means of aza-Michael addition,[4] Wolff rearrangement,[5] and N–H insertion reactions[6] as key steps.

As a continuation of our studies with this class of diazocompounds, we wondered whether a dihydroxylation of the double bond could happen in the presence of the fragile diazo function. This would furnish, for the first time, α,β-dihydroxy α′-diazoketones that could be employed in the direct synthesis of several oxygen heterocycles and polyols as depicted in Figure 1. Herein, we would like to show our preliminary study on how we could accomplish not only the racemic dihydroxylation of α,β-unsaturated diazoketones, but also the enantioselective version. Moreover, application in the short synthesis of enantiomeric pure disubstituted furanones in three steps from aldehydes is demonstrated.

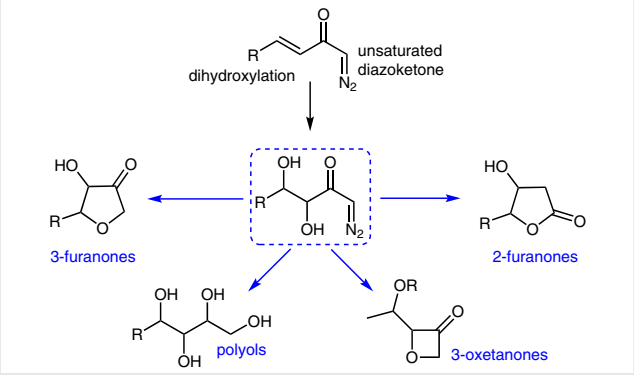
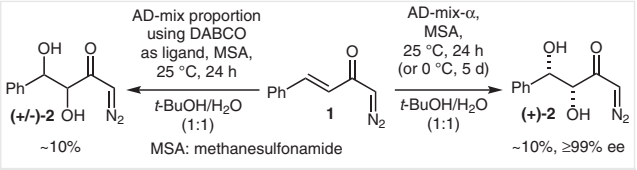


Figure 1 α,β-Dihydroxy α′-diazoketones as useful intermediates in synthesis

We started our work by performing the classical Upjohn dihydroxylation[7] from unsaturated diazoketone **1**, employing catalytic OsO_4 and *N*-methylmorpholine *N*-oxide (NMO), to prepare racemic diol **2** (Scheme 1). These conditions resulted in complete decomposition of **1** to many products, probably via the intermediacy of a reactive osmium carbenoid.[8] No diol was observed after careful analysis. The use of potassium osmate, instead of osmium tetroxide, was also fruitless. We next decided to carry out a Sharpless type racemic dihydroxylation[9–11] employing DABCO as the ligand for the osmium catalyst. This could enhance the steric hindrance around the metal and, perhaps, hinder the formation of the undesired osmium carbenoid. In fact, by using the classical conditions for the Sharpless asymmetric

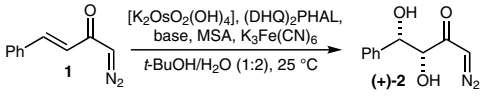


Scheme 1 First and unoptimized results in the dihydroxylation reaction from α,β- unsaturated diazoketone **1**

dihydroxylation (SAD),[9] but replacing the chiral ligand by achiral DABCO, a 5% yield of diol **2** could be obtained after 24 hours, along with a substantial amount of unreacted diazoketone **1**. Increasing the temperature from 0 to 25 °C raised this yield to approximately 10%. Once again, unreacted **1** was recovered, but much less decomposition product was observed. To evaluate the enantioselectivity of the reaction, we also performed this reaction with commercially available AD-mix-α. Although the same low yield was observed, high enantiomeric excess (≥ 99%) could be obtained in this first attempt. This result encouraged us to perform an optimization study for the SAD, aiming to get better yields and reaction conversions.

We started the optimization study by increasing the amount of potassium osmate and chiral ligand $(DHQ)_2PHAL$ found in commercially AD-mix-α, as well as employing the milder base $NaHCO_3$ in place of K_2CO_3 (Table 1, entry 1). These conditions furnished 20% yield of diol **2**, based on the recovery of diazoketone **1** (56% conversion). Raising the amount of ligand provided a better conversion, but gave almost the same yield (entry 2). Increasing the amount of potassium osmate to 5.0 mol% (keeping the amount of ligand or increasing it also to 5.0 mol%) caused faster decomposition of diazoketone **1**, leading to many by-products (entries 3 and 4). From the conditions in entries 1–4, prolonged reaction times (48 to 120 h), as well as higher concentrations of $NaHCO_3$, MSA and $K_3Fe(CN)_6$ did not furnish better yields (data not shown). Returning to commercially AD-mix-α reagent proportions, but enhancing the amount of MSA (entry 5) and of the base/$K_3Fe(CN)_6$ (entry 6) also did not lead to any appreciable change in the yield. Interestingly, reducing the reaction time to 10 hours improved the yield to 48%, keeping the same reaction conversion (entry 7). This suggested that diol **2** was being decomposed with time. In fact, the detection of benzaldehyde in reactions with prolonged times was evidence of the decomposition of **2** by a retro-aldol reaction. When the temperature was increased to 40 °C

Table 1 Optimization Studies on the SAD of Unsaturated Diazoketone **1**[a]



Entry	MSA (equiv) and base (equiv)	$K_3Fe(CN)_6$ (equiv)	$[K_2OsO_2(OH)_4]$ (mol%)	$(DHQ)_2PHAL$ (mol%)	Time (h)	Conv. (%)	Yield (%)[b]	*e.r.*[c]
1	1 and 1 $NaHCO_3$	3	1	2.5	24	56	20	>99:1
2	1 and 1 $NaHCO_3$	3	1	5	24	72	17	–
3	1 and 1 $NaHCO_3$	3	5	1	24	–	trace	–
4	1 and 1 $NaHCO_3$	3	5	5	24	–	trace	–
5	3 and 3 K_2CO_3	3	0.4	1	24	60	18	–
6	3 and 6 K_2CO_3	6	0.4	1	24	72	13	–
7	3 and 6 K_2CO_3	6	0.4	1	10	68	48	>99:1
8[d]	3 and 6 K_2CO_3	6	0.4	1	10	50	75	95:5
9	1 and 3 K_2CO_3	3	0.4	1	10	30	20	>99:1
10	3 and 6 K_2CO_3	6	2.5	5	10	84	49	–
11	3 and 6 K_2CO_3	6	0.4	5	10	72	49	99:1
12	3 and 6 K_2CO_3	6	0.4	10	10	74	55	99:1
13[e]	6 and 12 K_2CO_3	12	0.8	20	20	94	57	99:1
14[e]	6 and 12 K_2CO_3	12	0.8	2	20	84	52	99:1
15[e]	6 and 12 K_2CO_3	12	5	10	20	100	20	–

[a] All reactions were carried out with diazoketone **1** (25.0 mg, 0.145 mmol) in a concentration of 0.1 M.
[b] Isolated yields based on the recovery of starting material.
[c] Measured by HPLC using chiral columns (see the Supporting Information for details). The synthesis of the racemic samples employed the same reaction conditions, but replacing the chiral ligand $(DHQ)_2PHAL$ by achiral DABCO.
[d] Performed at 40 °C.
[e] SAD reagents added in two portions: half at 0 h and the other half after 10 h.

(entry 8), the yield was boosted to 75%, but at a cost to enantioselectivity (95:5) and to diazoketone conversion (50%). It is worth mentioning that when we repeated SAD using AD-mix-α proportions, but with the reduced reaction time (10 h), low yield and conversion was obtained (entry 9), showing that higher concentration of MSA,[12] base and Fe co-oxidant is important. At this point, the conditions shown in entry 7 appeared to be the best option. From these best conditions, increasing the quantity of both osmium salt and ligand raised the conversion of **1** to 16%, but provided basically the same yield (entry 10). Dropping the amount of potassium osmate and keeping the ligand to 5 mol% did not change the yield, but reduced the conversion in 12% (entry 11). Keeping the conditions in entry 11, but increasing the ligand concentration gave a higher yield with the same conversion of **1** (entry 12). Finally, repeating this best conditions (entry 12) and after 10 h adding the same proportions of reagents again, 94% conversion of **1**, together with 57% chemical yield, was obtained (entry 13). The next two studies were done by repeating entries 7 and 10 in the same way described in entry 13 (adding the SAD reagents in two portions). As can be seen in Table 1, after this optimization study, best conditions are described in entries 13 and 14. Entry 13 provided the best yield and conversion, but at the cost of more chiral ligand.[13]

Having established the best conditions[14] to perform SAD from **1**, we turned our attention to other unsaturated diazoketones. Although a high enantiomeric ratio could be obtained for all diazoketones, yields were moderate to good and were substrate dependent (Figure 2). Electron-rich diazoketones, containing a 4-OMe-Ph or an aliphatic group in the β-position furnished the worst yields. On the other hand, diazoketones with 4-Me-Ph and 4-Ph-Ph gave yields more like those observed for **1**. Electron-withdrawing groups such as 4-Cl-Ph and 4-NO_2-Ph provided moderate yields. All these results indicate that electronic effects may not rule too much the reaction yield. Other studies are ongoing to better understand this SAD behavior in unsaturated diazoketones. The *Z* isomer of diazoketone **1** also provided good yield for the SAD, indicating that the double bond geometry has little influence in the chemical yield. This opened the reactional scope for the synthesis of *trans* diols. Finally, employing $(DHQD)_2PHAL$ (found in AD-mix-β), instead of $(DHQ)_2PHAL$, gave the other enantiomer of **2** in good yield (47%, 56% based on recovery of starting material) and in more than 99% enantiomeric excess. The same reaction was also performed in a larger scale (250 mg of **1**, 1.45 mmol; see the Supporting Information), furnishing the same yield. The observed absolute configuration of enantiomeric pure diol **2** is in accordance with Sharpless model and was determined by converting compound **2** into a known furanone, as will be further discussed.

As already noted, chiral dihydroxy diazoketones have not been described before, but can be powerful intermediates for the synthesis of several class of compounds, employing diazo chemistry.[6] One of the many possible applications is the synthesis of disubstituted furanones. Well-known O–H insertion reactions[6] and Wolff rearrangement[5] could provide 3- and 2-furanones, respectively, directly. Furanones[15] are an important class of compounds with several interesting biological activities.[16] Moreover, with appropriate substitution, these compounds can be useful in the synthesis of important tetrahydrofurans, such as the natural compounds jaspine A[17] and B.[18] To demonstrate one of these applications, some of the synthesized dihydroxy diazoketones by SAD were converted into 4,5-disubstituted 2-

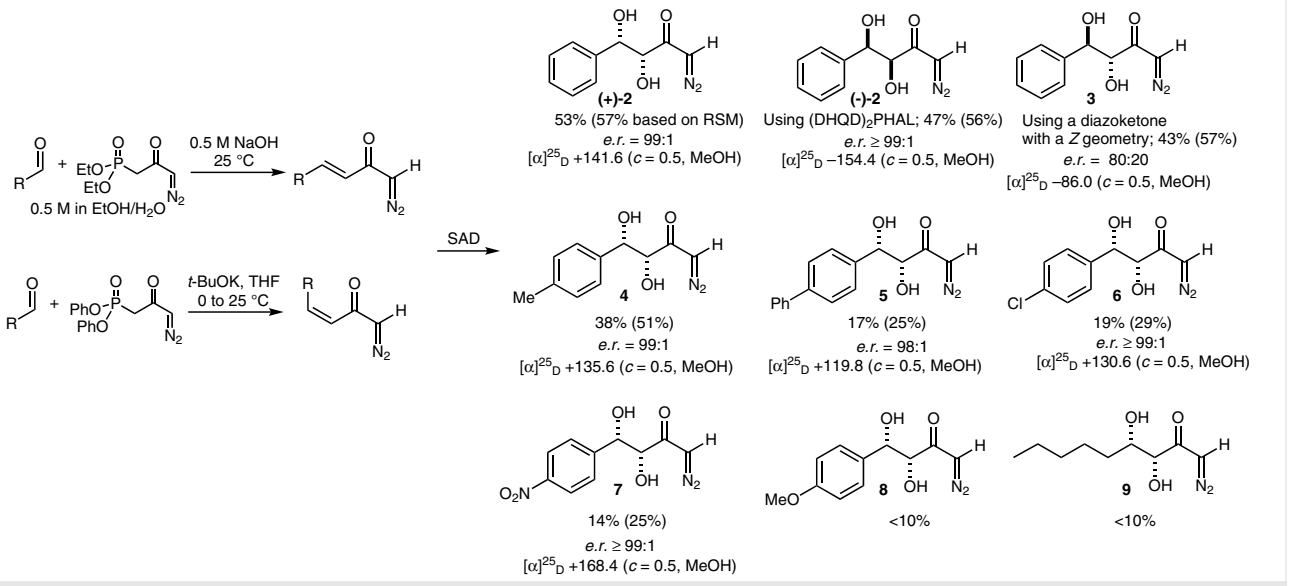


Figure 2 Substrate scope for the SAD on unsaturated diazoketones

furanones[19] in very good yields (70–90%) and high enantiomeric ratios after the exposure to a 300 W xenon lamp for 12 hours (Figure 3). With respect to the stereochemical outcome of the SAD, comparison of the optical rotation values of the cyclized products (+)-**10** and (–)-**10** with the reported values[20] unambiguously confirmed the absolute configuration of diol **2**. This result is in complete accordance with Sharpless model for asymmetric diydroxylation. For the other dihydroxylation products, we assume the same stereochemistry.

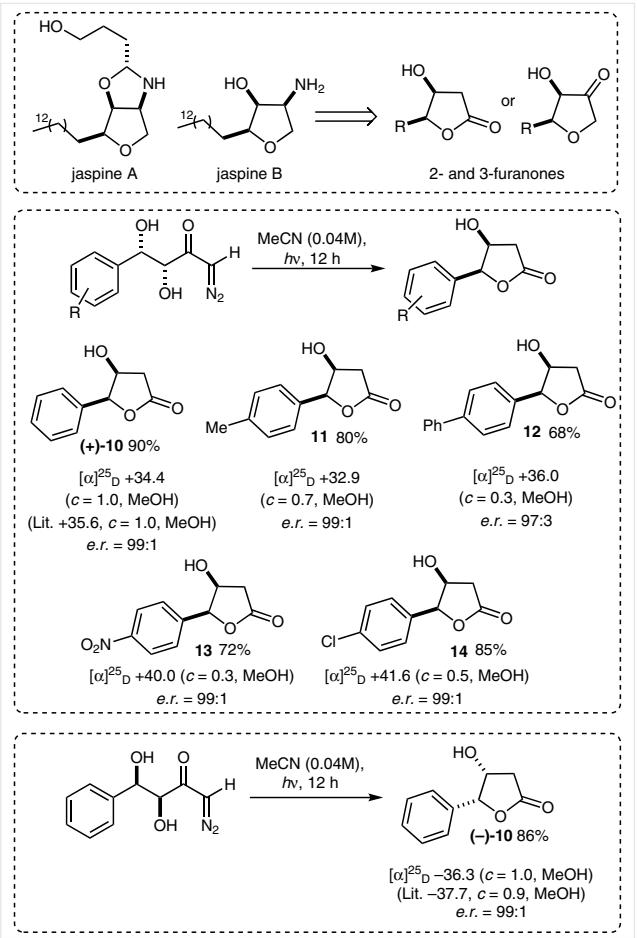


Figure 3 Application of the SAD products in the synthesis of enantiopure 2-furanones

In summary, we have demonstrated our preliminary results in the asymmetric functionalization of α,β-unsaturated diazoketones by means of a Sharpless asymmetric dihydroxylation. Moderate to good yields and excellent enantioselectivities were obtained in the synthesis of a new platform, containing a diazo function: enantiopure α,β-dihydroxy α′-diazoketones. Moreover, application of these intermediates in the direct synthesis of chiral 2-furanones shows one of the many versatilities of these platforms. To our knowledge, this sequence (three steps starting from aldehydes) is among the shortest ways to prepare enantiopure 2-furanones. Additional studies, such as the use of other chiral ligands, will be undertaken to improve the yields of some substrates and to better understand this SAD on unsaturated diazoketones. Finally, other demonstrations, such as the synthesis of 3-furanones and the application in the synthesis of natural jaspines A and B, will be carried out.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590977.

References and Notes

(1) Burtoloso, A. C. B.; Dias, R. M. P.; Bernardim, B. *Acc. Chem. Res.* **2015**, *48*, 921.
(2) Pinho, V. D.; Burtoloso, A. C. B. *J. Org. Chem.* **2011**, *76*, 289.
(3) Rosset, I. G.; Burtoloso, A. C. B. *J. Org. Chem.* **2013**, *78*, 9464.
(4) Rulev, A. Y. *Russ. Chem. Rev.* **2011**, *80*, 197.
(5) (a) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129. (b) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193. (c) Gill, G. B. In *Comprehensive Organic Synthesis*; Fleming, B. M. T., Ed.; Pergamon: Oxford, **1991**, 887.
(6) (a) Gillingham, D.; Fei, N. *Chem. Soc. Rev.* **2013**, *42*, 4918. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; Mckervey, M. A. *Chem. Rev.* **2015**, *115*, 9981. (c) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (d) Doyle, M. P.; Mackervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*; Wiley: New York, **1998**.
(7) Vanrheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973.
(8) (a) Smith, D. A.; Reynolds, D. N.; Woo, L. K. *J. Am. Chem. Soc.* **1993**, *115*, 2511. (b) Demonceau, A.; Lemoine, C. A.; Noels, A. F. *Tetrahedron Lett.* **1996**, *37*, 1025.
(9) (a) Sharpless, K. B.; Amberg, W.; Benani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Kolb, H.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(10) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.
(11) Eames, J.; Mitchell, H. J.; Nelson, A.; O'brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095.
(12) Junttila, M. H.; Hormi, O. O. E. *J. Org. Chem.* **2009**, *74*, 3038.
(13) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(14) **General Procedure for Asymmetric Dihydroxylation of α,β-Unsaturated Diazoketones**: To a 3 mL glass vial containing a magnetic stirrer and fitted with a cap, was added 418 mg of an oxidizing mixture containing $K_3Fe(CN)_6$ (6 equiv, 286.8 mg, 0.87 mmol), K_2CO_3 (6 equiv, 120.4 mg, 0.87 mmol), $(DHQ)_2PHAL$ (11.3 mg, 0.0145 mmol), and $K_2OsO_2(OH)_4$ (0.214 mg, 0.0581 mmol). Then, a *t*-BuOH/H_2O mixture (1:2, 1.5 mL) was added and the mixture was vigorously stirred. $CH_3SO_2NH_2$ (3 equiv, 41.4 mg, 0.435 mmol) and α,β-unsaturated diazoketone (1 equiv, 0.145 mmol) were added and the mixture was allowed to react for 10 hours. After this time, another portion of the oxidizing mixture (418 mg) and $CH_3SO_2NH_2$ (41.4 mg) were added and the mixture was stirred for an additional 10 h (progress of the reaction monitored by TLC). After this time, H_2O (30 mL) was added to the reaction mixture and the aqueous phase was extracted with a mixture of CH_2Cl_2 and 2-propanol (3:1, 2 × 10 mL), followed by another extraction with pure CH_2Cl_2 (3 × 10 mL) (conventional work-up with Na_2SO_3 and base led to degradation of the products). The organic phase was dried over Na_2SO_4, filtered and concentrated. The products were purified by flash chromatography (silica gel, 1:1 hexane/EtOAc) to afford the pure solid diols (Note: all racemic diols were synthesized by using DABCO as the ligand in similar yields; For larger scales, the conditions described in Table 1, entry 14, was preferred).
(3*R*,4*S*)-1-Diazo-3,4-dihydroxy-4-phenylbutan-2-one [(+)-2]: Yield: 16 mg (53% yield; 57% based on recovery of starting material; diazoketone recovered: 1.5 mg); crystalline yellow solid; mp 97–99 °C; R_f = 0.15 (silica gel, 1:1 EtOAc/hexane); IR: 3332, 3268, 3118, 2918, 2115, 1599, 1363, 1300, 1140, 1047, 708 cm^{-1}; ^1H NMR (500 MHz, CD_3CN): δ = 7.40–7.32 (m, 4 H), 7.27 (tt, *J* = 7.2, 1.3, 1.3 Hz, 1 H), 5.88 (s, 1 H), 4.95 (dd, *J* = 5.5, 2.9 Hz, 1 H), 4.16 (d, *J* = 3.3 Hz, 1 H), 3.74 (d, *J* = 6.8 Hz, 1 H), 3.64 (d, *J* = 5.9 Hz, 1 H); ^{13}C NMR (126 MHz, CD_3CN): δ = 196.6, 142.4, 128.9, 128.3, 127.4, 80.2, 74.8, 54.5; $[\alpha]_D^{25}$ +141.6 (*c* = 0.5, MeOH); HRMS (ESI-TOF): *m*/*z* [M$^+$+Na] calcd for $C_{10}H_{10}N_2NaO_3$: 229.05836; found: 229.05801; HPLC conditions: Chiralpak AD-H, 1:1 (*n*-hexane/IPA); flow rate: 1.0 mL/min; λ = 254 nm; t_R = 4.60 (minor), 8.74 (major) min; *e.r.* = 99:1.

(15) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2324.
(16) (a) Shah, N. C.; Pringle, S. D.; Donan, P. T.; Struthers, A. D. *J. Hypertens.* **2007**, *25*, 2345. (b) Raju, R.; Gromyko, O.; Fedorenko, V.; Herrmann, J.; Luzhetskyy, A.; Müller, R. *Tetrahedron Lett.* **2013**, *54*, 900. (c) Yabu, Y.; Yoshida, A.; Suzuki, T.; Nihei, C.; Kawai, K.; Minagawa, N.; Hosokawa, T.; Nagai, K.; Ohta, N. *Parasitol. Int.* **2003**, *52*, 155.
(17) Ledroit, V.; Debitus, C.; Lavaud, C.; Massiot, G. *Tetrahedron Lett.* **2003**, *44*, 225.
(18) (a) Kuroda, I.; Musman, M.; Ohtani, I. I.; Ichiba, T.; Tanaka, J.; Gravalos, D. C.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1505. (b) Martinková, M.; Gonda, J. *Carbohydr. Res.* **2016**, *423*, 1.
(19) **General Procedure for the Synthesis of 4,5-Disubstituted 2-Furanones**: In a quartz cell of 1 cm light path, containing a magnetic stirrer and fitted with a rubber septum, was added the diol (0.1 mmol) and anhydrous acetonitrile (2.5 mL, 0.04 M) under argon atmosphere. The reaction mixture was irradiated with an Osram 150 xenon arc lamp for 10 h under magnetic stirring at room temperature. The solvent was then removed under reduced pressure in a rotatory evaporator and the crude product was purified by flash chromatography with a short pad of silica ($CHCl_3$ as the eluent). Lactones were obtained as solids.
(4*S*,5*S*)-4-Hydroxy-5-phenyldihydrofuran-2(3*H*)-one [(+)-10]: Yield: 16 mg (90% yield); pale-yellow solid; mp 78–80 °C; R_f = 0.2 (silica gel, $CHCl_3$, twice eluted); IR: 3432, 2929, 1773, 1454, 1310, 1154, 1075, 1020, 742, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.43 (m, 2 H), 7.42–7.37 (m, 3 H), 5.52 (d, *J* = 3.5 Hz, 1 H), 4.63 (m, 1 H), 2.90 (dd, *J* = 17.5, 5.1 Hz, 1 H), 2.74 (d, *J* = 17.5 Hz, 1 H), 1.48 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.3, 132.3, 129.1, 129.0, 126.3, 85.0, 70.2, 38.5; $[\alpha]_D^{25}$ +34.4 (*c* = 0.98, MeOH); HPLC conditions: Lux® amilose-2 8:2 (*n*-hexane/IPA); flow rate: 1.1 mL/min; λ = 206 nm; t_R = 18.58 (major), 22.06 (minor) min; *e.r.* = 98:02.
(20) (a) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407. (b) Reddy, G. V.; Sreevani, V.; Iyengar, D. S. *Tetrahedron Lett.* **2001**, *42*, 531. (c) Eissler, S.; Nahrwold, M.; Neumann, B.; Stammler, H.-G.; Sewald, N. *Org. Lett.* **2007**, *9*, 817.