Short and Practical Syntheses of (*S*)-(+)-3-(*p*-Tolylsulfinyl)furan-2(5*H*)-one and (*S*)-(+)-3-(*p*-Tolylsulfinyl)-5,6-dihydropyran-2-one

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Abstract: (*S*)-(+)-3-(*p*-Tolylsulfinyl)furan-2(5*H*)-one and (*S*)-(+)-3-(*p*-tolylsulfinyl)-5,6-dihydropyran-2-one can be synthesized by a new and significantly improved method consisting of Knoevenagel condensation of benzyl (*R*)-(+)-(*p*-tolylsulfinyl)acetate with the *tert*-butyldimethylsilyl derivatives of 2-hydroxyacetaldehyde or 3-hydroxypropanal, followed by subsequent reactions of the resulting mixtures with hydrogen in the presence of palladium-on-carbon and ethereal hydrogen chloride.

Key words: asymmetric synthesis, chiral auxiliaries, sulfoxides, α,β-unsaturated lactones, butenolides

Enantiomerically pure α,β-unsaturated lactones are versatile building blocks for the construction of a wide range of naturally occurring and/or biologically active molecules. In particular, butenolides constitute the central skeleton of several naturally occurring compounds that show interesting physiological activities. The majority of the applications of these entities in asymmetric synthesis has involved 5-alkoxy- or 5-(hydroxyalkyl)furan-2(5*H*)-ones,[1] where the chiral center at C5, adjacent to the C–C double bond of the lactone ring, efficiently controls the stereoselectivity of intermolecular cycloadditions (1,3-dipolar-,[2] Diels–Alder-,[3] and [2+2] photocycloadditions[4]) and Michael reactions.[5] The incorporation of chiral centers at C3 or C4 has been studied much less, despite the possibility that they might exert a similar degree of control on the stereoselectivity of certain types of reactions. To the best of our knowledge, only the sulfinyl group has been used as chiral auxiliary at the double bond of furan-2(5*H*)-ones. Only two papers concerning the behavior of 4-sulfinylfuran-2(5*H*)-ones in Diels–Alder[6] and 1,3-dipolar reactions with diazoalkanes have appeared.[7] This may well be because of the formation of mixtures in these reactions, where the sulfinyl group, the carbonyl moiety, and the chiral center at C5 compete in controlling the *endo*/*exo* and π-facial selectivities.

In contrast, the incorporation of a sulfinyl group at C3 of the furan-2(5*H*)-one system significantly augments its ability to function as a dienophile, dipolarophile, or Michael acceptor, and therefore such systems have been used in many asymmetric transformations. Thus, (*S*)-(+)-3-(*p*-tolylsulfinyl)furan-2(5*H*)-one (**1a**; Figure 1) is a very good Michael acceptor in the highly and predictably enantiocontrolled conjugate addition of organometallic reagents,[8] a process which has found application in natural product synthesis.[9] The improved dienophilic nature of **1a** compared to that of furan-2(5*H*)-one is also seen in its ready reaction with cyclic and acyclic dienes.[10] The sulfinyl group of **1a** also strongly influences the course of the reaction with diazoalkanes, in terms of reactivity and control of both the *endo*/*exo* and π-facial selectivities (the latter being completely inverted in the presence of Lewis acids).[11] The relative influences on π-facial selectivity of a C3-sulfinyl group and C5 chirality on the course of the reactions with cyclopentadiene (predominant role of C5)[12] and diazoalkanes (predominant role of the sulfinyl group)[13] has been studied with both C5 epimers of 5-ethoxy-3-(*p*-tolylsulfinyl)furan-2(5*H*)-ones.

1a **1b**

Figure 1

The known synthetic utility of 3-(*p*-tolylsulfinyl)furan-2(5*H*)-ones as building blocks (as discussed above) contrasts with the smaller number of publications dealing with the use of butenolide **1a** in asymmetric synthesis. Pentenolide (*S*)-**1b** (Figure 1), has been used even less,[14] although it is expected to exhibit reactivity features similar to those of **1a**. The principal reason for the modest number of applications reported for **1a** and **1b** in asymmetric synthesis is that there have been no efficient synthetic procedures available for these entities. The three known methods for the synthesis of optically pure **1a** have been described by Posner (seven steps, 13% overall yield),[8a] our group (five steps, 27% overall yield),[10] and Holton (four steps, ca. 24% overall yield).[15,16] Only one synthesis of enantiopure **1b** has been described to date (six steps, 17% overall yield).[8b,17]

In our experience, the main problem with the reported syntheses of **1a** is associated with the difficult reproducibility of the yields in the last, and key, step. In this step, enantiopure 3-(*p*-tolylsulfinyl)prop-2-en-1-ol,[8a,10] or its

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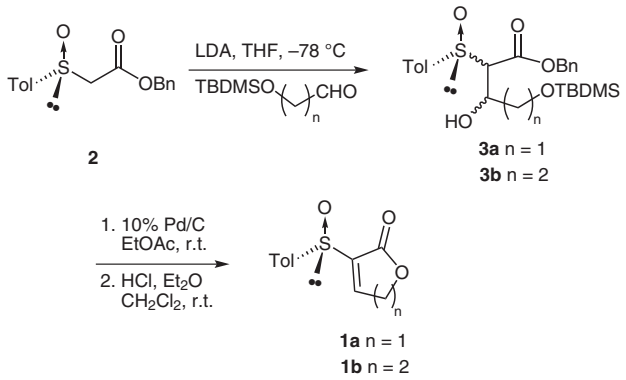
trimethylsiloxy derivative,[15] is carboxylated α to the sulfinyl group, and the mixture thus obtained, containing a mixture of *E*- and *Z*-olefinic isomers, is subjected to the cyclization conditions. We chose to avoid the problem of the olefin stereochemistry by introducing the double bond after the formation of the cyclic system. Our results are described below.

Knoevenagel condensation of benzyl (*R*)-(+)-(*p*-tolylsulfinyl)acetate (**2**)[18] with commercially available 2-(*tert*-butyldimethylsiloxy)acetaldehyde, in the presence of lithium diisopropylamide at –78 °C, gave a mixture of the four possible diastereomers of **3a** (90% combined yield) (Scheme 1). Although these compounds could be separated chromatographically and were fully characterized, this separation is not necessary for synthetic purposes. Hydrogenolysis of this mixture, by use of 10% palladium-on-carbon, and subsequent treatment of the resulting mixture of carboxylic acids with ethereal hydrogen chloride gave the unsaturated lactone **1a** directly in 68% isolated yield (Scheme 1). The hydrogen chloride treatment thus promoted three consecutive steps, namely desilylation, cyclization, and dehydration. It is important to note that **1a** decomposes on attempted purification by chromatography on silica gel.[19] It therefore must be purified by crystallization.



Scheme 1

When this sequence was repeated with 3-(*tert*-butyldimethylsiloxy)propanal, the mixture of the four diastereomers of **3b** was obtained in 82% combined yield. This stereoisomeric mixture, when subjected to the two-step process described above for **3a**, produced compound **1b** in 48% yield (Scheme 1).

Because compounds **1a** and **1b** are mainly useful as starting materials, we then tried to scale up the procedure. The Knoevenagel condensation (step 1) could be performed on a larger scale (up to 10 mmol) with similar or even better yields (90% for **3a** and 85% for **3b**). In contrast, the efficiency of the hydrogenolysis of compounds **3a** and **3b** is highly dependent on the reaction conditions. The yields reported above are obtained for reactions run over four hours at room temperature, under one atmosphere of hydrogen, starting with one millimole of **3a** or **3b**, and with a palladium-on-carbon to substrate ratio of 3:1. When these conditions were used for three millimoles of compounds **3**, the conversions were low. The temperature and the reaction time were increased over several trials, but resulted in no improvement. The use of a 1:1 mixture of palladium-on-carbon and formic acid in methanol resulted only in deprotection of the silyl ether, whereas in the presence of Raney nickel desulfinylation was also observed. Finally, the problem was solved by using the initial conditions but increasing the pressure of hydrogen to three atmospheres. Under these conditions, the complete disappearance of **3a** or **3b** was observed after 20 hours, and the yields were only slightly lower than those obtained on the one-millimole scale. When these conditions were applied to eight millimoles of **3b**, the isolated yield was 42%, whereas five millimoles of **3a** provided a 49% yield, both after 20 hours of reaction.

In conclusion, butenolide **1a** and pentenolide **1b** could be synthesized from benzyl (*R*)-(+)-(*p*-tolylsulfinyl)acetate in procedures that are simpler, shorter, and higher-yielding than those reported previously.[20]

All moisture-sensitive reactions were carried out in flame-dried glassware under argon atmosphere. Reactions were monitored by TLC on silica gel. Flash chromatography was performed on silica gel 60 (230–400 mesh ASTM). Melting points of samples in open capillary tubes were determined with a Culatti melting point apparatus and are uncorrected. The optical rotations were measured at r.t. on a Perkin-Elmer 343 polarimeter (concentration in g/100 mL). The IR spectra were recorded with a FT-IR Bruker Tensor 27 spectrophotometer. The NMR spectra were determined on a Varian Unity 300 or Jeol Eclipse 300 NMR spectrometer. Mass spectra were obtained with a Jeol JMS-SX 102A or JMS-AX 505 HA mass spectrometer.

Benzyl Esters 3; General Procedure

A soln of benzyl (*R*)-(+)-(*p*-tolylsulfinyl)acetate (**2**; 2.88 g, 10 mmol) in THF (20 mL) was added dropwise to a soln of LDA (10 mmol) in THF (20 mL) at –78 °C. The mixture was stirred at –78 °C for 0.5 h. Then a soln of 2-(*tert*-butyldimethylsiloxy)acetaldehyde (for **3a**) or 3-(*tert*-butyldimethylsiloxy)propanal (for **3b**) (30 mmol, 3 equiv) in THF (20 mL) was added, and the resulting mixture was stirred at –78 °C for 2.5 h. The reaction mixture was quenched with sat. aq NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were dried (Na_2SO_4) and concentrated. The residue was analyzed by ^1H NMR spectroscopy and purified by flash chromatography as indicated for each case below.

Benzyl (R_S)-4-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2-(*p*-tolylsulfinyl)butanoate (3a)

Compound **3a** was obtained as a mixture of the four possible diastereomers. The product was purified by flash chromatography (silica gel, hexane–EtOAc, 8:2).

Yield: 4.20 g (90%).

IR (film): 3373, 2930, 2857, 1731, 1256, 839 cm^{-1}.

First Less-Polar Diastereomer

^1H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.03 (s, 3 H), 0.86 (s, 9 H), 2.38 (s, 3 H), 3.68 (dd, *J* = 4.5, 10.5 Hz, 1 H), 3.74 (dd, *J* = 4.5, 10.5 Hz, 1 H), 3.81 (br s, 1 H), 3.92 (d, *J* = 8.7 Hz, 1 H), 4.33–4.39 (m, 1 H), 4.92 (s, 2 H), 7.14–7.37 (m, 7 H), 7.50 (half of an AA′BB′ system, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6, –5.5, 18.3, 21.5, 25.8, 65.0, 67.2, 71.4, 73.3, 125.3, 128.4 (3 C), 129.8, 134.7, 138.0, 142.7, 165.5.

Second Less-Polar Diastereomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.01 (s, 3 H), 0.00 (s, 3 H), 0.82 (s, 9 H), 2.37 (s, 3 H), 3.63 (d, *J* = 7.5 Hz, 1 H), 3.67 (d, *J* = 3.3 Hz, 1 H), 3.74 (dd, *J* = 4.5, 10.5 Hz, 1 H), 3.83 (dd, *J* = 5.7, 10.5 Hz, 1 H), 4.43–4.50 (m, 1 H), 4.96 (s, 2 H), 7.10–7.33 (m, 7 H), 7.50 (half of an AA′BB′ system, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6, –5.5, 18.2, 21.4, 25.7, 64.9, 67.4, 69.2, 73.3, 125.0, 128.3, 128.5, 129.9, 134.5, 138.6, 142.5, 166.8.

Third Less-Polar Diastereomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.04 (s, 3 H), 0.87 (s, 9 H), 2.38 (s, 3 H), 3.76 (dd, *J* = 4.5, 10.8 Hz, 1 H), 3.77 (d, *J* = 6.0 Hz, 1 H), 3.91 (dd, *J* = 4.2, 10.5 Hz, 1 H), 4.14–4.22 (m, 1 H), 5.04 (AB system, 2 H), 7.19–7.33 (m, 7 H), 7.50 (half of an AA′BB′ system, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5 (2 C), 18.2, 21.5, 25.8, 64.4, 67.4, 69.6, 70.7, 124.6, 128.3 (2 C), 128.4, 129.9, 134.8, 138.0, 142.2, 166.3.

More-Polar Diastereomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.01 (s, 3 H), 0.02 (s, 3 H), 0.85 (s, 9 H), 2.36 (s, 3 H), 3.32 (d, *J* = 5.4 Hz, 1 H), 3.62 (dd, *J* = 4.2, 10.8 Hz, 1 H), 3.74 (d, *J* = 8.7 Hz, 1 H), 3.79 (dd, *J* = 3.9, 10.5 Hz, 1 H), 4.44–4.51 (m, 1 H), 4.74 and 4.91 (AB system, 2 H), 7.08–7.13 (m, 2 H), 7.28–7.31 (m, 3 H), 7.23 and 7.43 (AA′BB′ system, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6, –5.5, 18.2, 21.4, 25.8, 64.8, 67.0, 69.0, 70.8, 124.4, 128.4 (2 C), 128.4, 129.7, 134.7, 137.9, 141.7, 164.6.

MS (EI): *m*/*z* (%) = 463 (4) $[M + 1]^+$, 405 (72), 139 (65), 91 (100).

Anal. Calcd for $C_{24}H_{34}O_5SSi$: C, 62.30; H, 7.41; S, 6.93. Found: C, 62.36; H, 7.38; S, 6.85.

Benzyl (R_S)-5-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2-(*p*-tolylsulfinyl)pentanoate (3b)

Compound **3b** was obtained as a mixture of the four possible diastereomers. Purification of the product by flash chromatography (silica gel, hexane–EtOAc, 8:2) gave two mixtures, each containing two inseparable diastereomers.

Yield: 4.05 g (85%).

IR (film): 3382, 2930, 2857, 1730, 1255, 1088, 837 cm^{-1}.

Less-Polar Mixture of Two Diastereomers

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.03 (s, 3 H), 0.07 (s, 3 H), 0.08 (s, 3 H), 0.84 (s, 9 H), 0.89 (s, 9 H), 1.65–2.00 (m, 4 H), 2.37 (s, 3 H), 2.38 (s, 3 H), 3.59 (d, *J* = 6.3 Hz, 1 H), 3.60 (d, *J* = 9.3 Hz, 1 H), 3.72–3.84 (m, 2 H), 3.88 (dd, *J* = 4.8, 6.3 Hz, 2 H), 4.25 (br s, 1 H), 4.36 (br s, 1 H), 4.66 (dt, *J* = 2.4, 8.7 Hz, 2 H), 4.71 and 4.92 (AB system, 2 H), 5.03 and 5.14 (AB system, 2 H), 7.07–7.33 (m, 14 H), 7.42 (half of an AA′BB′ system, 2 H) and 7.53 (half of an AA′BB′ system, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6 (2 C), –5.6 (2 C), 18.1 (2 C), 21.4 (2 C), 25.8 (2 C), 36.1 (2 C), 61.0, 62.1, 67.0, 67.4, 68.8 (2 C), 74.1, 74.8, 124.3, 124.7, 128.3 (2 C) 128.3 (2 C), 128.4 (2 C), 129.7, 129.9, 134.7, 134.9, 138.1 (2 C), 141.6, 142.1, 164.6 (2 C).

More-Polar Mixture of Two Diastereomers

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.87 (s, 9 H), 0.90 (s, 9 H), 1.76–1.81 (m, 2 H), 1.84–1.92 (m, 2 H), 2.38 (s, 6 H), 3.58 (d, *J* = 3.9 Hz, 1 H), 3.77–3.90 (m, 5 H), 4.53 (dt, *J* = 3.0, 7.8 Hz, 1 H), 4.65–4.69 (m, 1 H), 4.96 (s, 2 H), 5.00 (AB system, 2 H), 7.14–7.38 (m, 14 H), 7.51 (half of an AA′BB′ system, 2 H), and 7.51 (half of an AA′BB′ system, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.5 (2 C), –5.4 (2 C), 18.1, 18.2, 21.5, 25.8 (2 C), 36.4, 37.0, 60.9, 61.1, 67.2, 67.3, 68.3, 75.9, 76.1, 125.2 (2 C), 128.4 (2 C), 128.5 (2 C) 128.5 (2 C), 129.8, 129.9, 134.7 (2 C), 138.2, 138.7, 142.5, 142.7, 165.8, 166.6.

MS (EI): *m*/*z* (%) = 477 (5) $[M + 1]^+$, 419 (15), 139 (69), 91 (100), 75 (35).

HRMS–FAB: *m*/*z* $[M + 1]^+$ calcd for $C_{25}H_{37}O_5SSi$: 477.2131; found: 477.2126.

Lactones 1; General Procedure

A mixture of 10% Pd/C (7.16 g for **3a** or 11.5 g for **3b**) was added to a soln of **3** [**3a** (2.31 g, 5 mmol) or **3b** (3.80 g, 8 mmol)] in EtOAc (250 mL for **3a** or 400 mL for **3b**). The reaction mixture was vigorously stirred under H_2 (3 atm) at 25 °C for 20 h, and was then filtered through Celite and washed with EtOH (5 × 100 mL). The combined filtrate and washings were concentrated under vacuum. The residue was diluted with CH_2Cl_2 (25 mL), treated with a sat. soln of HCl in Et_2O (1.7 mL for **3a** or 2.5 mL for **3b**), and stirred at 25 °C for 1 h. The volatiles were removed and the residue was purified as indicated below for each case.

*Alternative with the use of 1 mmol **3a** or **3b***: A mixture of 10% Pd/C (1.5 g) was added to a soln of **3** (1 mmol) in EtOAc (50 mL). The reaction mixture was vigorously stirred under H_2 (1 atm) at 25 °C for 4 h, and then filtered through Celite and washed with EtOH (5 × 20 mL). The combined filtrate and washings were concentrated under vacuum. The residue was diluted with CH_2Cl_2 (5 mL), treated with a sat. soln of HCl in Et_2O (0.5 mL), and stirred at 25 °C for 20 min. The volatiles were removed and the residue was purified as indicated below for each case.

(*S*)-(+)-3-(*p*-Tolylsulfinyl)furan-2(5*H*)-one (1a)

The residual oil was diluted with $CHCl_3$ and stirred at 25 °C for 6 d. Then the solvent was evaporated and the residue was crystallized from Et_2O; yield: 0.543 g (49%).

When **1a** was obtained from 1 mmol of **3a**, it was purified by crystallization from EtOAc–hexane; yield: 0.151 g (68%).

Mp 121–125 °C (Lit.[8a,10] 121–125 °C); $[\alpha]_D^{20}$ +252.9 (*c* 1.3, $CHCl_3$) [Lit.[8a,10] $[\alpha]_D^{20}$ +244 (*c* 1.3, $CHCl_3$)].

IR (film): 3013, 1772, 1340, 1144, 1043, 997 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 4.90 (dd, *J* = 1.7, 18.3 Hz, 1 H), 5.03 (dd, *J* = 1.7, 18.3 Hz, 1 H), 7.33, 7.69 (AA′BB′ system, 4 H), 8.05 (t, *J* = 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 71.3, 125.1, 130.2, 137.7, 141.5, 143.0, 151.2, 167.0.

MS (EI): *m*/*z* (%) = 222 (50) $[M^+]$, 174 (100), 139 (61), 117 (55), 91 (38), 65 (25).

(*S*)-(+)-3-(*p*-Tolylsulfinyl)-5,6-dihydropyran-2-one (1b)

The residual oil was purified by flash chromatography (silica gel, hexane–EtOAc, 2:8); this gave **1b** as white crystals; yield: 0.793 g (42%); ee >98%.[21]

When **1b** was obtained from 1 mmol of **3b**, the crude product was purified by chromatography (silica gel, EtOAc); this gave **1b** as white crystals; yield: 0.113 g (48%).

Mp 81–82 °C (Lit.[8b] 93–94 °C); $[\alpha]_D^{20}$ +254.4 (*c* 0.27, $CHCl_3$) [Lit.[8b] $[\alpha]_D^{20}$ +212.78 (*c* 0.27, $CHCl_3$)].

IR (KBr): 3048, 2966, 2918, 1708, 1086, 1049 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 2.63 (qd, *J* = 4.8, 18.9 Hz, 1 H), 2.73–2.86 (m, 1 H), 4.28 (ddd, *J* = 4.8, 9.9, 11.1 Hz, 1 H), 4.42–4.50 (m, 1 H), 7.28, 7.65 (AA′BB′ system, 4 H), 7.69 (ddd, *J* = 1.5, 3.5, 5.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 24.8, 66.2, 125.5, 129.9, 139.3, 139.7, 142.3, 143.3, 160.1.

MS (EI): *m*/*z* (%) = 236 (100) [M^+], 188 (30), 139 (41), 123 (17), 107 (21), 91 (19).

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(16) One of the starting products is not commercially available and needs to be prepared by ozonolysis of suitable precursors.

(17) The synthesis of (±)-**1b** (three steps and 25% overall yield) has also been reported; see ref. 8b.

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(19) 5-Hydroxyfuran-2(5*H*)-one was the only product we could identify when the crude reaction mixture containing **1a** was purified by column chromatography.

(20) Starting from menthyl *p*-toluenesulfinate (commercially available in the two possible configurations at sulfur), compounds **1a** and **1b** are obtained in 41% (30% on 5 mmol scale) and 26% (24% on 8 mmol scale) overall yield, respectively.

(21) The ee of (+)-**1b** was determined from the well-separated *p*-tolyl signals in the ^{1}H NMR spectrum by use of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]ytterbium(III) as chiral shift reagent.