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(S)-(+)-2-(p-TOLYLSULFINYL)-2-BUTEN-4-OLIDE: AN ENANTIOMERICALLY PURE MICHAEL ACCEPTOR FOR ASYMMETRIC SYNTHESIS OF 3-SUBSTITUTED 4-BUTANOLIDES. (—)-PODORHIZON.

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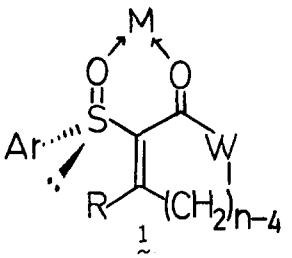
SUMMARY: A short, reliable, and practical synthesis of (S)-(+)-2-(p-tolylsulfinyl)-2-buten-4-olide has been developed, and the utility of this Michael acceptor for highly enantiocontrolled synthesis of 3-substituted 4-butanolides has been demonstrated.

Because of the importance of many 3-substituted cycloalkanones as biologically active natural products and as widely useful synthetic intermediates, we have developed a program for asymmetric synthesis of these chiral molecules in high enantiomeric purity.[1] Our methodology is based on faithful 1,3-transfer of chirality from the sulfur atom of a temporarily attached, chiral, auxiliary sulfoxide group to the β-vinyl carbon atom of a conjugated enone system during organometallic conjugate addition to enantiomerically pure 2-(arylsulfinyl)-2-cycloalkenones 1 (Ar = p-tolyl or p-anisyl[1f]; R'=H, Me[1e], or p-tolyl[1e]; n=5 or 6; W=CH_2; M=Mg, Zn, or Ti). Because of the importance of many 3-substituted and 2,3-disubstituted 4-butanolides (γ-butyrolactones) as biologically active (e.g. anticancer[2], anti-glaucoma[3], pheromone[4], and inducer of streptomycin biosynthesis[5]) natural products and as broadly useful synthons, we have now prepared (S)-(+)-2-(p-tolylsulfinyl)-2-buten-4-olide [(+)-1a, W=O, Ar=p-tolyl, R=H, n=5) in virtually complete enantiomeric purity, and we have illustrated its effectiveness as a Michael acceptor for asymmetric synthesis of 3-substituted 4-butanolides by preparation of a vicinally-disubstituted lignan lactone[6] of high enantiomeric purity.

Despite its structural simplicity, relatively small size, and accessibility in racemic form,[7] enantiomerically pure butenolide (+)-1a is indeed an exceptionally challenging synthetic target. For example, although we have been able to prepare cyclic bromovinylic orthoester 2a from 2-bromo-2-buten-4-olide[8] (anhydrous and freshly distilled BF_3, ethylene oxide, 0°C, 4.5 hr),[9] all attempts at bromine → metal exchange[1,10] using n-butyllithium, t-butyllithium, sodium-containing lithium metal, or Rieke magnesium were unsuccessful, as were all attempts at direct lithiation at the 2-position of the corresponding cyclic orthoester 2b. Following thorough retrosynthetic analysis (bonds a-f in structure 1a) and unsuccessful experiments to form bonds b-f in butenolide (+)-1a, we are now very pleased to report a successful, short, reliable, and practical (i.e. gram scale) synthesis of butenolide (furan-2(5H)-one) (+)-1a in virtually complete enantiomeric purity via the accompanying scheme.



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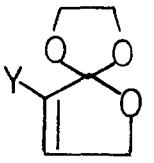
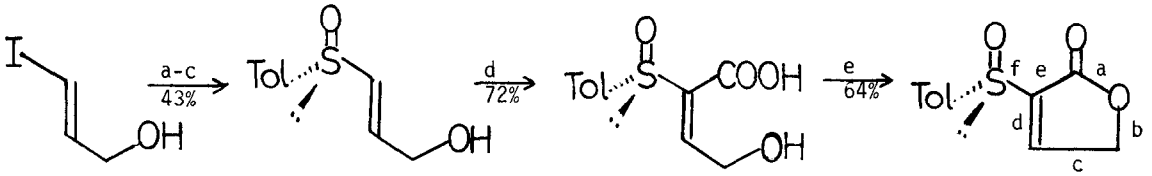


2a, Y = Br
2b, Y = H



3 (+)-4 5 (+)-1a

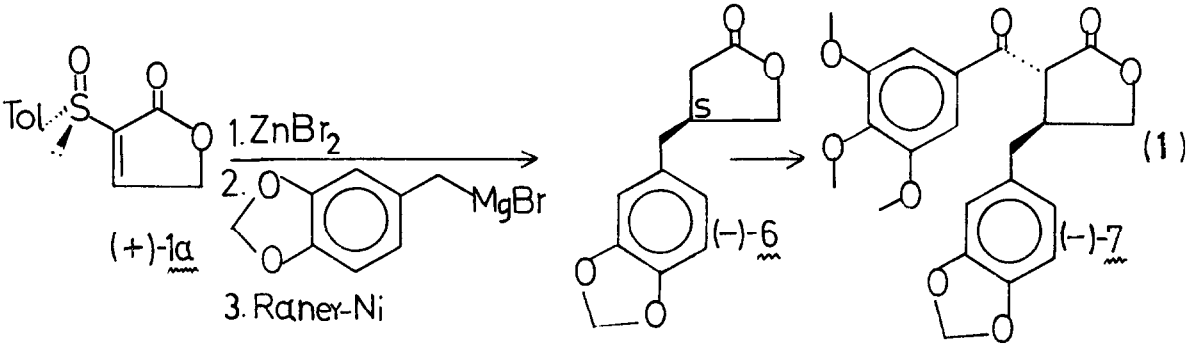
[a] t-Bu(Me$_2$)SiCl, [b] t-BuLi then (–)-p-TolSO$_2$Menthyl [c] n-Bu$_4$NF [d] MeLi, then CO$_2$ [e] CHCl$_3$, 9 days

Propargyl alcohol underwent hydrostannylation (n-Bu$_3$SnH, catalytic azobisisobutyronitrile, 80°C, 2 hr) and then iodination (I_2, CH_2Cl_2, 25°C, 4 hr) according to the literature procedure[12] to afford E-vinylic iodide 3. O-Silylation [t-Bu(Me$_2$)SiCl, imidazole, DMF, 25°, 18 hr] of 4 g of alcohol 3 was followed by iodine → lithium exchange (t-BuLi, 4:1:1 THF:Et$_2$O:pentane, -120°C, 1 hr),[13] sulfinylation [(-)-menthyl p-toluenesulfinate in the same solvent system cannulated at -78°C during 15 minutes into the vinylic lithium solution, 0.5 hr at -120°C then 1 hr at -30°)],[14] and finally O-desilylation (n-Bu$_4$NF, THF, 0°C, 5 min, then 25°C, 40 min) to produce, in 43% overall yield from vinylic iodide 3, crystalline, stable, vinylic sulfoxide (+)-4 [mp. 77-78°C (CH_2Cl_2, Et$_2$O, hexane); $[\alpha]_D^{25}$ + 242.6°, $[\alpha]_{365}^{25}$ + 1065° (c, 0.94 $CHCl_3$); NMR ($CDCl_3$): δ 6.66 (1 H, dt, J_d=14.8 Hz, J_t=2.8 Hz), 6.56 (1 H, dt, J_d=14.8 Hz, J_t=1.3 Hz), 4.33 (2 H, m), 2.51 (1 H, t, J=6.0 Hz, OH), 2.40 (3 H, s, tolyl CH_3); $C_{10}H_{12}O_2$ requires: C, 61.2; H, 6.2; S, 16.45%. Found C, 61.3; H, 6.25; S, 16.45%.] α-Lithiation of vinylic sulfoxide (+)-4 (2.7 equivs. of MeLi, THF, -78°C, 0.5 hr)[15] was followed by carboxylation (CO_2 bubbled through solution, 5 min, -78°C, then -30°C, 2 hr)[1a]; strongly acidic conditions (20% aqueous HCl in presence of EtOAc) were required to liberate hydroxy carboxylic acid 5 [NMR ($CDCl_3$): δ 2.38 (3 H, s, CH_3), 4.75 (2 H, d, J = 4.72 Hz, CH_2), 7.62 (1 H, bs, =CH), 8.35 (2 H, bs, COOH, OH)]. Simply on standing in chloroform solution at 25°C for at least 7 days, hydroxy acid 5 underwent spontaneous cyclization to form the desired butenolide sulfoxide (+)-1a having mp. 121-125°C, decomp. (EtOAc, Et$_2$O, light petroleum ether), $[\alpha]_D^{25°}$ +244°, $[\alpha]_{365}^{25°}$ +1213° (c, 1.3, $CHCl_3$), and having spectroscopic characteristics [e.g. NMR ($CDCl_3$) δ 8.03 (1 H, t, J = 1.7 Hz, H-3)] corresponding to those of independently prepared racemic 2-arylsulfinyl-2-buten -4-olides.[7]

The enantiomeric purity of butenolide sulfoxide (+)-1a was determined directly using the chiral NMR shift reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato] euro-

pium(III). Complexation with 0.25 equivalents of this europium reagent produced a downfield shift of vinylic H-3 from δ 8.03 to δ11.17 with no detectable splitting of this signal; similar treatment of a racemic 2-arylsulfinyl-2-buten-4-olide produced two new signals of equivalent intensity for H-3 appearing at δ11.30 and δ11.45. Therefore, butenolide sulfoxide (+)-1a has an extremely high (>98%) enantiomeric purity.

Complexation of butenolide sulfoxide (+)-1a with 1 equivalent of zinc dibromide in 2,5-dimethyltetrahydrofuran (DMTHF)[1g] as solvent at -78°C, followed first by conjugate addition[16] of 3,4-methylenedioxybenzylmagnesium chloride (3 equivalents) in DMTHF and then by Raney nickel reductive cleavage of the lactone-sulfoxide carbon-sulfur bond, produced 3-benzylated 4-butanolide (—)-6 which was isolated by preparative tlc in 70% overall yield (eq. 1). The negative optical rotation of benzylated lactone (—)-6 [$[\alpha]_D$ - 4.7 ° (c 2.3 $CHCl_3$), lit[2c,17] $[\alpha]_D$ - 4.8° c, 1.14 ($CHCl_3$)] indicated that this asymmetric carbon-carbon bond formation had occurred on the Si face of the vinylic β-keto sulfoxide system, consistent with our previously proposed chelate model.[1] 2-Acylation of lactone (—)-6 using Koga's procedure[2c] led to trans-2,3-disubstituted lignan lactone (—)-7, (—)-podorhizon, mp. 128-9°C [lit.[17] mp. 129-130°C] $[\alpha]_D^{21}$ = -75.5° c 0.2 ($CHCl_3$) [lit.[17] $[\alpha]_D^{21}$ -79.5° c 0.6 ($CHCl_3$)] with literature-identical[17] spectroscopic characteristics in 95% enantiomeric purity. (—)-Podorhizon is the antipode of natural (+)-podorhizon, a member of the podophyllotoxin anticancer family.[17] Because d-menthol has recently become commercially available, (R)-(—)-2-(p-tolylsulfinyl)-2-buten-4-olide [(—)-1a] and therefore (+)-podorhizon should be prepared easily using the same reactions as shown in eq. 1.



The ready accessibility of (S)-(+)-2-(p-tolylsulfinyl)-2-buten-4-olide [(+)-1a] and its extraordinary effectiveness as a Michael acceptor[7] for highly (and predictably) enantiocontrolled conjugate addition of organometallic reagents, as exemplified in this preliminary report by preparation of (—)-podorhizon, represent a highly significant and widely useful advance in asymmetric synthesis. We are pursuing study of butenolide sulfoxide 1a and of other unsaturated lactone sulfoxides.

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