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NEW SYNTHESIS OF TWO OPTICALLY ACTIVE STEROID CD RING SYNTHONS BY MICROBIAL ASYMMETRIC REDUCTION

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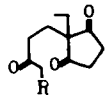
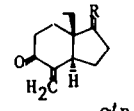
Abstract ——— Two optically active steroid CD ring synthons **4** and **19** were synthesized from **11** obtained by the microbial asymmetric reduction of a pro-chiral trione **10** which could be efficiently prepared by the reaction of a new annelating reagent **9** with 2-ethyl-cyclopentane-1, 3-dione.

The optically active α-methyleneketone **1a**[1] and sulfone **3**[2] have been reported as steroid CD ring synthons. **1a** was obtained from indanone t-butyl ether **2a**,which was derived from **2b** prepared by the amino acid mediated asymmetric aldol condensation of a pro-chiral trione compound **I**(R=H)[3], via carboxylation with magnesium methyl carbonate followed by hydrogenation and decarboxylative Mannich reaction[1]. **3** was obtained from endione **2b** by reaction with paraformaldehyde and benzenesulfinic acid followed by hydrogenation[2].In our previous work[4], the optically active α-methyleneketone **4** has been synthesized from a trione compound **I**(R=$-CH_2OTHP$) obtained from an annelating reagent, γ-keto-sulfoxide **5** by microbial asymmetric reduction. We now wish to report herein a new synthesis of two optically active steroid CD ring synthons **4** and **19**(Scheme 1), starting from a pro-chiral trione compound **10** obtained from a new annelating reagent, γ-keto-alkyl mesylate **9**(Scheme 1) by microbial asymmetric reduction[7].

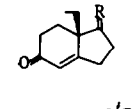


I



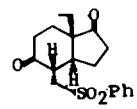
1a. R=$\overset{O^tBu}{H}$

b. R=$\overset{OAc}{H}$



2a. R=$\overset{O^tBu}{H}$

b. R=O



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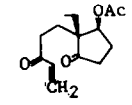

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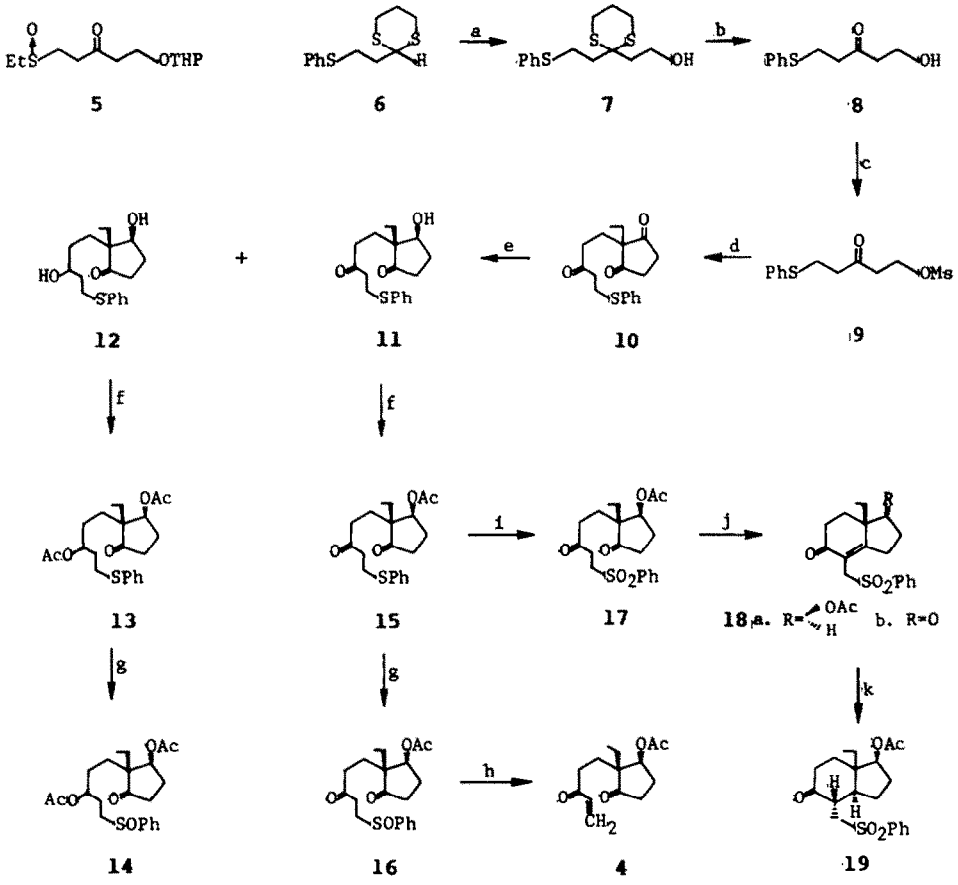

Scheme 1

a). n-BuLi/ethylene oxide, -75°C to r.t., b). $HgCl_2/CaCO_3$, 80% aq. CH_3CN, reflux 9h, c). $CH_3SO_2Cl/Py.$, CH_2Cl_2, 0°C, 2h, d). 2-ethylcyclopentane-1, 3-dione/1.5 eq. Et_3N/THF, reflux 14h, e). Saccharomyces cerevisiae (2.346), 30°C, 25h, f). $Ac_2O/Py.$, 100°C, 1h, g). $NaIO_4/CH_3OH-H_2O$, 0°C, 2h, h). CCl_4, 70°C, 9h, i). 2 equivalent MCPBA, CH_2Cl_2, 15°C, 1.5h, j). PTS/PhH, 90-100°C, 40h, k). H_2/ 10% Pd-C, acidic EtOH, r.t..

The hydroxy compound **7** was prepared by the reaction of **6**[5] with ethylene oxide in 74% yield. Hydrolysis of **7** with $HgCl_2/CaCO_3$ in 80% aqueous CH_3CN afforded **8** in 65% yield. Mesylation of **8** gave the corresponding mesylate **9** in 85% yield, which reacted with 2-ethyl-cyclopentane-1,3-dione in the presence of Et_3N to give the trione sulfide **10** in 75% yield. The major side reaction was found to be an intramolecular cyclization of the product, which could be minimized by reducing the reaction time and the amount of Et_3N used. The trione sulfide **10** was fermented with Saccharomyces cerevisiae(2.346) to give (2R,3S)-dione sulfide **11** $[\alpha]_D^{15}$+7.23° (c,15,$CHCl_3$)in 53% yield and a by-product in 13% yield, $[\alpha]_D^{15}$+37.8° (c,0.79, $CHCl_3$), which was deduced as the dihydroxy compound **12** from its spectral data. **12** was also obtained from the further fermentation of the monohydroxy compound **11** with S.cerevisiae (2.346). Acetylation of **12** with Ac_2O/Py yielded **13** quantitatively, $[\alpha]_D^{15}$ +36.3°(c, 0.76,$CHCl_3$). Oxidation of **13** with $NaIO_4$ gave the corresponding sulfoxide **14** in quantitative yield, which was heated in CCl_4 at 70°C for 20h and no elimination of phenyl sulfenic acid was found. It is obvious that one of these two hydroxy groups might exist in the side chain, otherwise the eliminated product, α-methyleneketone compound could be obtained under pyrolysis. Acetylation of **11** with Ac_2O/Py. yielded **15** quantitatively. Oxidation of **15** with $NaIO_4$ gave the dione sulfoxide **16**, which underwent pyrolysis in CCl_4 at 70°C for 9h to give the known synthon **4** in 76% overall yield from **15**, $[\alpha]_D^{15}$+61.3°(c,1.68, $CHCl_3$), Lit.[4], $[\alpha]_D^{14}$+61.2°(c,2.02, $CHCl_3$). While oxidation of **15** with 2 equivalent of m-chloroperbenzoic acid provided the sulfone **17** in quantitative yield, which was cyclized in benzene containing catalytic amount of p-toluenesulfonic acid at 90-100°C for 40h to give the unsaturated ketone sulfone **18a** in 63% yield, $[\alpha]_D^{10}$+31.4°(c,4.0,$CHCl_3$),m.p.99-100°C (ethyl acetate/iso-propyl ether). Hydrolysis of the acetate group in **18a** under various basic conditions failed. Fortunately, the reduction of **18a** with lithium aluminum hydride selectively gave the deacetylated product, which could be converted to the unsaturated ketone sulfone **18b**[3] after Jones oxidation in 68% overall yield from **18a**. Catalytic hydrogenation of **18a** in acidic EtOH solution over 10% Pd-C gave the γ-keto-sulfone **19** in 70% yield, $[\alpha]_D^{10}$+32.4°(c,1.44,$CHCl_3$), m.p.147-9°C (ethyl acetate/iso-propyl ether), which could be regarded as a precursor of **1b**.

Experimental

Eluates used for the flash chromatography or preparative thin layer chromatography are ethyl acetate/petroleum ether(60-90°)(systems: A 3:7; B 4:6) and acetone/petroleum ether (60-90°)(system: C 2:8). Usual work-up is dealing with the following operations: wash with brine, dry over anhydrous sodium sulfate and remove solvent under reduced pressure. All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 683 or a Shimadzu 440 spectrometer. UV spectra were performed on a 730 spectrometer made by Shanghai Factory of Analytic Instrument. ^1H NMR spectra were determined on a Varian EM 360A or EM 360L (60MHz) spectrometer, using TMS as an internal standard. MS spectra were run on a Finnigan 4021 GC-MS instrument. The optical rotations were measured on a Autopol® III automatic polarimeter.

2-(2'-Hydroxyethyl)-2-(2'-phenylthioethyl)-1,3-dithiane 7

To a solution of freshly distilled acrolein (7.1ml,0.1mole) and triethylamine(2.1ml, 0.015mole) in chloroform(50ml) cooled in an ice-water bath, thiophenol(10.5ml,0.1mole) was added dropwise,maintaining the internal temperature below 50°C and the reaction mixture was stirred for 3h at 12°C. To the mixture cooled in an ice-water bath, freshly distilled

boron trifluoride etherate(5.5ml,0.045mole) was injected and then 1,3-propanedithiol(10.2ml, 0.1mole) was added dropwise,maintaining the internal temperature below 50°C, followed by stirring for 4h at 12°C. Water(25ml) was added into the reaction mixture and the organic layer was separated, washed with 7% aqueous solution of potassium hydroxide, followed by usual work-up to afford 25.65g of a colourless oil **6**[5] (92%), which could be used for the following experiment without further purification. IR(Film): 1583,1470,740 and 690 (monosubstituted benzene)cm^{-1}.^{1}H NMR(CCl_4): 1.66-2.21(4H,m,-$SCH_2\underline{CH_2}CH_2S$-,-$\underline{CH_2}CH_2SPh$), 2.72-3.20(6H,m,-$SC\underline{H_2}$), 4.15(1H,t,J=6Hz, $\rightarrow C\underline{H}$), 7.36(5H,m,Ar-H).

To a tetrahydrofuran(100ml) solution of **6**(22.6g) cooled in a dry ice-acetone bath(-78°C) under nitrogen,n-butyllithium(0.95M in hexane,120ml) was added dropwise and the mixture was warmed to -35°C within 1.5h with stirring. The resulting red-brown solution was cooled to -70°C and to which ethylene oxide(12ml) was added. The temperature was allowed to rise slowly to 10°C and the reaction mixture was allowed to stand in a refrigerator for two days. Tetrahydrofuran was removed under reduced pressure followed by addition of water(50ml), neutralization with 10% aqueous solution of hydrochloric acid, extraction with ethyl acetate and usual work-up to furnish an orange-red oil(26.92g). Column chromatography of 18.25g over silica gel H(250g) eluted with methylene chloride(800ml) and then ethyl acetate/ petroleum ether (60-90°)(2:8, 500ml; 4:6, 500ml; 1:1,500ml) afforded 13.29g of a pale yellow oil **7**(68% from acrolein). UV(CH_3OH): λ_{max} 207nm (ε 12,290,), 254nm (ε 8,180). IR (Film): 3410(-OH), 1583,1471,740,690(monosubstituted benzene) and 1025(C-O)cm^{-1}.^{1}H NMR($CDCl_3$): 1.93-2.41(6H,m,-$SCH_2\underline{CH_2}CH_2S$-,-$CH_2\underline{CH_2}$-),2.66-3.27 (6H,m,-$SC\underline{H_2}$-), 3.86(2H,t,J=6Hz,-$C\underline{H_2}OH$), 7.43(5H,m,Ar-H).

Phenyl 3-oxo-5-hydroxy-amyl sulfide **8**

To a stirred suspension of 6.48g of mercury(II) chloride(23.8mmole) and 2.38g of powdered calcium carbonate(23.8mmole) in 80% aqueous acetonitrile(60ml), **7**(3.24g, 10.8 mmole) in 80% aqueous acetonitrile(20ml) was added and the mixture was refluxed for 9h under nitrogen. The precipitate was filtered and the filtrate was extracted with ethyl acetate. The combined organic layer was washed with 5 M aqueous solution of ammonium acetate until no precipitate formed. Usual work-up and cloumn chromatography(silica gel H, eluate B) afforded a pale yellow oil **8**(1.47g) in 65% yield. UV(CH_3OH): λ_{max}207nm(ε10,010), 254nm (ε7,890). IR(Film):3420(-OH), 1710(C=O), 1583,1482,740,690(monosubstituted benzene) and 1025(C-O)cm^{-1}. ^{1}H NMR($CDCl_3$+CCl_4): 2.56(2H,t,J=6Hz,-$COC\underline{H_2}CH_2OH$), 2.70-3.22(4H,A_2B_2, -$SC\underline{H_2}C\underline{H_2}CO$-), 3.20-3.40(1H,-O$\underline{H}$,exchanged by D_2O), 3.77(2H,t,J=6Hz,-$C\underline{H_2}OH$), 7.10-7.40(5H,m, Ar-H). MS: m/e 210(M^+, 19%), 193(M^+-17, 18.5%), 137($CH_2CH_2S^+Ph$,16%), 123(CH_2S^+Ph,46%), 109 (S^+Ph,28%),45(100%).

3-Oxo-5-phenylthio-amyl mesylate **9**

To a mixed solution of **8**(0.87g, 4.14mmole) and pyridine(2ml) in methylene chloride(20 ml)cooled in an ice-water bath, methanesulfonyl chloride(1ml,12.9mmole) was added dropwise. After stirring for 2h at 20°C, the reaction mixture was washed with precooled 10% aqueous solution of hydrochloric acid, followed by usual work-up to give a crude product which was crystallized from isopropyl ether/ethyl acetate/n-hexane to afford a white solid **9**(1.01g) in 85% yield. m.p. 51.5-53.5°C. UV(CH_3OH): λ_{max} 206nm (ε10,970), 254nm (ε7,670). IR(Film): 1715(C=O), 1582,1479,740,690(monosubstituted benzene),1352 and 1171(SO_2)cm^{-1}.^{1}H NMR($CDCl_3$+ CCl_4): 2.43-3.10(6H,m,-$SC\underline{H_2}C\underline{H_2}COC\underline{H_2}$-), 2.84(3H,S,-$SO_3C\underline{H_3}$), 4.23(2H,t,J=6Hz,-$C\underline{H_2}OMs$), 7.10-7.27(5H,m,Ar-H). MS: m/e 288 (M^+, 10.5%), 55(CH_2=CHC$\equiv$O$^+$,100%)[8].

2-Ethyl-2-(3'-oxo-5'-phenylthio-amyl)-cyclopentane-1,3-dione **10**

A mixture of **9**(1g, 3.47,mmole), 2-ethyl-cyclopentane-1,3-dione(0.68g,5.4mmole), triethylamine(0.68ml, 4.9mmole) and hydroquinone(20mg) in tetrahydrofuran(14ml) was refluxed for 14h with stitting under nitrogen. Solvent was removed under reduced pressure and the residue was submitted to column chromatography(silica gel H, eluate C) to afford a pale yellow oil **10** (0.83g) in 75% yield. UV(CH_3OH):λ_{max} 207nm (ε 11,400), 254nm (ε 8,140). IR(Film): 1760(5-ring C=O), 1720(C=O), 1583,1481, 740 and 690(monosubstituted benzene) cm^{-1}.^{1}H NMR($CDCl_3$): 0.73(3H, t,J=7Hz, $-CH_2\underline{CH_3}$), 2.65(4H,S, $-COC\underline{H_2}C\underline{H_2}CO-$), 7.23(5H,m,Ar-H). MS: m/e 318(M^+, 29.5%), 165(14.0%), 139(56.4%), 137($CH_2CH_2S^+Ph$, 39.0%), 127(37.7%), 123(CH_2S^+Ph, 63.1%), 109(S^+Ph, 30.0%), 55(CH_2=CH-C≡O^+, 100%).

(2R,3S)-(+)-2-Ethyl-2-(3'-oxo-5'-phenylthio-amyl)-3-hydroxy-cyclopentanone **11** and (2R,3S)-(+)-2-ethyl-2-(3' -hydroxy-5'-phenylthio-amyl)-3-hydroxy-cyclopentanone **12**

To a solution of 1000ml of culture medium containing 3% glucose, 2% corn stach, 0.2% K_2HPO_4, 0.2% $NaNO_3$, 0.1% KH_2PO_4,0.05% $MgSO_4$,0.02% KCl and 0.02% $FeSO_4$ in 5L of Erlenmeyer flask, 25ml of Saccharomyces cerevisiae 2.346 medium which had been cultured for 24h was added. After shaking at 30°C for 24h, the pH of the solution was adjusted with 6 **N** aqueous solution of sodium hydroxide to 6.7-7.0 and **10**(0.75g,2.36mmole) dissolved in ethanol(20ml) containing 6 drops of Toween 80 was added. The mixture was shaken continuously for 25h at 30°C. The mycelia were removed and the solution was extracted with ethyl acetate, followed by usual work-up and column chromatography(silica gel H, eluate A) to give a yellow oil **11**(0.40g) in 53% yield and a yellow oil **12**(100mg) in 13% yield.**11**:$[\alpha]_D^{15}$+7.23°(c,15,$CHCl_3$)[9]. UV(95%EtOH):λ_{max} 205nm(ε 10,360),254.5nm(ε 5,900).IR(Film),3440(-OH),1738,1720(C=O),1585, 1480,755,695(monosubstituted benzene),1090(PhS-C) and 1065(C-O)cm^{-1}. ^{1}H NMR(CCl_4):0.78(3H, t, J=7.5Hz, $-CH_2\underline{CH_3}$), 2.48-3.16(4H,A_2B_2, $-COC\underline{H_2}C\underline{H_2}CO-$), 2.92(1H,S,$-O\underline{H}$), 3.96(1H,t,J=3Hz, $C\underline{H}OH$), 7.2(5H,m,Ar-H). MS: m/e 320(M^+, 15%),193(M^+-127, 15%),181(M^+-30-109, 37%),137(CH_2-CH_2S^+Ph, 50%),123(CH_2S^+Ph, 100%),109(S^+Ph, 46%),55(CH_2=CHC≡O^+,66%). **12**:$[\alpha]_D^{15}$+37.8°(c,0.79, $CHCl_3$). UV(95%EtOH):λ_{max} 204nm(ε 10,570), 254.5nm(ε 6,720). IR(Film): 3370(-OH),1738,1720 (C=O),1580,1480,740,690(monosubstituted benzene),1090(PhS-C) and 1065(C-O)cm^{-1}.^{1}H NMR($CDCl_3$ CCl_4):0.79(3H,t,J=7Hz,$-CH_2\underline{CH_3}$),2.73(2H,S,$-O\underline{H}$),3.00(2H,t,J=7Hz,$-C\underline{H_2}SPh$),3.40-3.90(1H,$W_{1/2}$= 16Hz,$-C\underline{H}OH$), 4.17(1H,t,J=5Hz,$-C\underline{H}OH$),7.37(5H,m,Ar-H). MS: m/e 322(M^+,69%),305(M^+-17, 100%), 287(M^+-35, 12%), 195(M^+-127, 19%), 123(CH_2S^+Ph, 38%), 109(S^+Ph, 18%).

(2R,3S)-(+)-2-Ethyl-2-(3' -acetoxy-5'-phenylthio-amyl)-3-acetoxy-cyclopentanone **13**

A solution of **12**(16mg) and acetic anhydride(0.05ml) in pyridine(0.5ml) was heated at 100°C for 1h. The mixture was poured into ice-water and extracted with ethyl acetate. The combined organic layer was washed successively with 20% aqueous solution of hydrochloric acic and saturated solution of sodium bicarbonate. Usual work-up and preparative thin layer chromatography(silica gel GF_{254},developing agent C) afforded a colourless oil **13**(20mg) in quantitative yield. $[\alpha]_D^{15}$+36.3°(c,0.76,$CHCl_3$). UV(95%EtOH):λ_{max} 204nm(ε 7,980), 254.5nm (ε 12,600). IR(Film): 1745, 1378,1240(acetate), 1730(5-ring C=O), 1590,1485,745 and 698 (monosubstituted benzene)cm^{-1}. ^{1}H NMR($CDCl_3$+CCl_4): 0.81(3H,t,J=7.5Hz,$-CH_2\underline{CH_3}$), 2.11(6H,S, $-OCOC\underline{H_3}$), 2.93(2H,t, J=6.5Hz,$-C\underline{H_2}SPh$), 4.80-5.13(1H,$W_{1/2}$=14Hz,$-C\underline{H}OAc$), 5.29(1H,t,J=5Hz, $-C\underline{H}OAc$), 7.42(5H,m,Ar-H). MS: m/e 406(M^+, 62%), 347(M^+-59,36%), 287(M^+-59-60, 13%), 123 (CH_2S^+Ph, 38%), 43(100%).

(2R,3S)-2-Ethyl-2-(3' -acetoxy-5'-phenylsulfinyl-amyl)-3-acetoxy-cyclopentanone **14**

To a stirred solution of **13**(20mg) in methanol(0.3ml), sodium periodate (11mg) in w (0.3ml) was added and the mixture was stirred for 1h at 15°C. The precipitate was filt and the filtrate was extracted with methylene chloride, followed by usual work-up to gi 20mg of pale yellow oil **14** in quantitative yield. IR(CCl_4): 1740(5-ring C=O and acetate 1380,1245(acetate), 1050 and 1030(SO)cm^{-1}.^{1}H NMR(CCl_4):0.74(3H,t,J=7Hz,-$CH_2\underline{CH}_3$), 1.98(6. -OCOC$\underline{H}_3$), 4.54-4.94(1H, $W_{1/2}$=18Hz,C$\underline{H}$OAc), 5.14(1H,t,J=5Hz,-C$\underline{H}$OAc), 7.51(5H,m,Ar-H).

After being heated in tetrahydrofuran for 20h, **14** remained unchanged.

(2R,3S)-(+)-2-Ethyl-2-(3'-oxo-5'-phenylthio-amyl)-3-acetoxy-cyclopentanone **15**

A solution of **11**(50mg) and acetic anhydride(0.05ml) in pyridine(0.5ml) was heated 100°C for 1h. The mixture was poured into ice-water and extracted with ethyl acetate. combined organic layer was washed with precooled 20% aqueous solution of hydrochloric a and saturated solution of sodium bicarbonate, followed by usual work-up to give 55mg of pale yellow oil **15** in quantitative yield. $[\alpha]_D^{15}$+41.4°(c,3.67,$CHCl_3$). IR(Film):1740(5-ri C=O and acetate), 1720(C=O),1375,1245(acetate),1590,1485,745,695(monosubstituted benzen and 1090(PhS-C)cm^{-1}.^{1}H NMR(CCl_4): 0.75(3H,t,J=7.5Hz,-$CH_2\underline{CH}_3$),1.98(3H,S,-OCOC$\underline{H}_3$), 2.46-3 (4H,A_2B_2,-COC$\underline{H}_2$C$\underline{H}_2$S-), 5.08(1H,t,J=4Hz,-C$\underline{H}$OAc), 7.19(5H,m,Ar-H).

(2R,3S)-(+)-2-Ethyl-2-(3'-oxo-5'-phenylsulfinyl-amyl)-3-acetoxy-cyclopentanone **16**

To a stirred solution of **15**(55mg) in methanol(0.5ml) coold in an ice-water bath, s periodate(33mg) in water(0.5ml) was added and the mixture was stirred at 15°C for 1h. T precipitate was filtered and the filtrate was extracted with methylene chloride, follow usual work-up to give 60mg of a yellow oil **16** in quantitative yield.$[\alpha]_D^{15}$+30°(c,3.67,CH IR(Film):1740,1370,1240(acetate),1725,1715(C=O), 1582,1480,760,692(monosubstituted benz and 1040(SO)cm^{-1}.^{1}H MNR(CCl_4):0.70(3H,t,J=7.5Hz,$CH_2\underline{CH}_3$),1.96(3H,S,-OCOC$\underline{H}_3$),5.04(1H,t,J= -C$\underline{H}$OAc), 7.42(5H,m,Ar-H).

(2R,3S)-(+)-2-Ethyl-2-(3'-oxo-4'-ene-amyl)-3-acetoxy-cyclopentanone **4**

16(55mg) in tetrachloromethane(0.5ml) was heated at 70°C under nitrogen for 9h, mo by ^{1}H NMR. Removal of solvent and preparative thin layer chromatography(silica gel GF developing agent C) gave 30mg of a pale yellow oil **4** in 76% yield.$[\alpha]_D^{15}$+61.3°(c,1.68,CH UV(EtOH):λ_{max} 211nm(ε11,970). IR(Film):1740(5-ring C=O and acetate), 1708,1688(trans-a cis-α,β-unsaturated C=O), 1622(C=C),1380 and 1245(acetate)cm^{-1}. ^{1}H NMR(CCl_4): 0.76(3H,t 7.5Hz,-$CH_2\underline{CH}_3$),1.97(3H,S,-OCOC$\underline{H}_3$),5.11(1H,t,J=4Hz,-C$\underline{H}$OAc), 5.56-6.23(3H,ABX,-COC$\underline{H}$=C$\underline{H}_2$). m/e 253(M^++1, 35%), 193(M^+-59, 100%), 55(CH_2=CHC≡O^+, 82%).

(2R,3S)-(+)-2-Ethyl-2-(3'-oxo-5'-phenylsulfonyl-amyl)-3-acetoxy-cyclopentanone **17**

To a solution of **15**(100mg) in methylene chloride(1ml) cooled in an ice-water bath, 85% of m-chloroperbenzoic acid(120mg) was added in portions and the mixture was stirred 15°C for 2h. m-Chlorobenzoic acid was filtered and the filtrate was diluted with methyl chloride and then washed with saturated solution of sodium bicarbonate followed by usua work-up to give 110mg of a yellow oil **17** in quantitative yield.$[\alpha]_D^{15}$+32.5°(c,6.70,$CHCl_3$ IR(Film):1740,1378, 1245(acetate), 1730(5-ring C=O),1720(C=O),1590,1455,758,695(monosub tituted benzene), 1320,1310 and 1156(SO_2)cm^{-1}. ^{1}H NMR(CCl_4): 0.70(3H,t,J=7.5Hz,-$CH_2\underline{CH}_3$) 1.95(3H,S,-OCOC$\underline{H}_3$),2.54-3.33(4H,A_2B_2,-COC$\underline{H}_2$C$\underline{H}_2SO_2$),5.14(1H,t,J=4Hz,-C$\underline{H}$OAc), 7.33-7.65(3 Ar-H), 7.82(2H,dd,J=6Hz,J=3Hz,Ar-H).

(1S,7aS)-(+)-1-Acetoxy-5,6,7,7a-tetrahydro-7a-ethyl-4-phenylsulfonylmethyl-indan-5-one

A solution of **17**(110mg) in benzene(2ml) containing p-toluenesulfonic acid monohydr

(50mg) was heated at 90-100°C for 40h. After removal of solvent, the residue was dissolved in methylene chloride, washed with saturated soltuion of sodium bicarbonate followed by usual work-up and preparative thin layer chromatography(silica gel GF_{254}, developing agent B, developed for two times) to afford 65mg of white solid **18a** in 63% yield. m.p. 99-101°C (isopropyl ether/ethyl acetate). $[\alpha]_D^{10}$+31.4°(c,4.0,$CHCl_3$). UV(EtOH):λ_{max}218nm(ε10,330),249nm (ε 10,400).IR(KCl):1752,1380,1240(acetate), 1678, 1650(α,β-unsaturated C=O and C=C), 1590, 1455,768,705(monosubstituted benzene), 1322,1310,1290 and 1145(SO_2)cm^{-1}.^{1}H NMR(CD_3COCD_3+ CCl_4): 0.98(3H,t,J=7Hz,-$CH_2C\underline{H}_3$), 2.03(3H,S,-OCO$C\underline{H}_3$), 3.97 and 4.25(2H,AB,J=14Hz,-$C\underline{H}_2SO_2Ph$), 4.85(1H,t,J=9Hz,-C$\underline{H}$-OAc),7.58-7.98(5H,m,Ar-H). MS: m/e 377(M^++1,45%), 316(M^+-60, 18%), 235(M^+-141,30%), 193(M^++1-141-43, 53%), 175(M^+-60-141, 54%),43(100%). Anal.: $C_{20}H_{24}O_5S$. Calcd.: C 63.81; H 6.43 Found: C 63.79; H 6.43.

(1S,3aS,4S,7aS)-(+)-1-Acetoxy-7a-ethyl-3a,4,5,6,7,7a-hexahydro-4-phenylsulfonylmethyl-indan-5-one **19**

A solution of **18a**(220mg) in acidic ethanol (25ml, 0.25ml of 1N HCl) was hydrogenated over 10% Pd-C under atmospheric pressure at ordinary temperature until hydrogen uptake ceased. The catalyst was filtered and the solvent was removed under reduced pressure to give a residue which was dissolved in chloroform and filtered again. Usual work-up gave colourless crystals(150mg) **19** in 70% yield. m.p. 147-9°C(ethyl acetate/isopropyl ether). $[\alpha]_D^{11}$+32.4°(c,1.44, $CHCl_3$). IR(KCl):1738,1368,1255(acetate), 1715(C=O), 1590,1455,760,690 (monosubstituted benzene), 1310,1295 and 1140(SO_2)cm^{-1}.^{1}H NMR(CD_3COCD_3): 0.98(3H,t,J=7Hz, $CH_2C\underline{H}_3$),1.90(3H,S,OCO$C\underline{H}_3$),2.82(1H,m,$W_{1/2}$=6Hz,$C\underline{H}_2SO_2Ph$),3.13(1H,m,$W_{1/2}$=12Hz,-$C\underline{H}CH_2SO_2Ph$), 3.90(1H,ABX,J=16Hz,J=6Hz,-$C\underline{H}_2SO_2Ph$), 4.62(1H,t,J=8Hz,-C$\underline{H}$OAc), 7.55-7.80(3H,m,Ar-H), 7.91 (2H,dd,J=7.5Hz,J=3Hz,Ar-H). MS: m/e 379(M^++1,96%), 237(M^+-141,39%),195(M^++1-141-43, 100%), 43(89%). Anal: $C_{20}H_{26}O_5S$. Calcd.: C 63.47; H 6.92. Found: C 63.12; H 6.81.

(7aS)-(+)-5,6,7,7a-Tetrahydro-7a-ethyl-4-phenylsulfonylmethyl-indan-1,5-dione **18b**

To a stirred solution of **18a**(100mg) in tetrahydrofuran(2ml) cooled in an ice-water bath, a suspension of lithium aluminum hydride(40mg) in tetrahydrofuran(1ml) was added dropwise. The mixture was stirred for 10 min, then neutralized with 10% solution of hydrochloric acid. After filtration, solvent was removed to give a residue which was submitted to the following Jones oxidation.

The crude product was dissolved in acetone(2ml) cooled in an ice-water bath. To which Jones reagent(excess) was added dropwise and the mixture was stirred for 45 min. 2-propanol was added to destroy the excess Jones reagent and the mixture was diluted with ethyl acetate. After filtration, the filtrate was washed with saturated solution of sodium bicarbonate,followed by usual work-up and preparative thin layer chromatography(silica gel GF_{254}, developing agent C, developed for two times) to afford a white solid **18b**[3] (60mg) in 68% yield from **18a**. m.p 124-6°C(ethyl acetate/isopropyl ether). $[\alpha]_D^{20}$+198°(c,1.0,$CHCl_3$). UV (CH_3OH):λ_{max} 218nm(ε 11,630),251.5nm(ε10,460). IR(KCl): 1748(5-ring C=O), 1674,1638(α,β-unsaturated C=O and C=C),1586,1462,745,690(monosubstituted benzene). 1305,1298 and 1139 (SO_2)cm^{-1}.^{1}H NMR($CDCl_3$): 0.97(3H,t,J=7Hz,$CH_2C\underline{H}_3$). 4.07 and 4.38(2H,AB,J=13Hz,-$SO_2C\underline{H}_2C$=C), 7.47-7.70(3H,m,Ar-H), 7.87(2H,dd, J=8Hz, J=3Hz,Ar-H). MS: m/e 333(M^++1, 30%), 77(Ph^+,100%).

Fermentation of **11** with S.cerevisiae(2.346)

11(70mg) in 50ml of culture medium containing S.cerevisiae(2.346) was shaken continuously for 47h at 30°C.The mycellia were removed and the solution was extracted with ethyl acetate, followed by usual work-up and preparative thin layer chromatography(silica gel GF_{254},

developing agent B) to give 5mg of **12**. 35mg of **11** was recovered. It is proved that the absolute configuration of C2 and C3 in **12** is 2R, 3S, the same as those in **11**.

References and notes:

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8. Combustion analysis: **9** $C_{12}H_{16}O_4S_2$. Calcd.: C 49.98; H 5.59; S 22.23. Found: C 49.56; H 5.56; S 22.17.
9. The enantiomeric excess(e.e.)of **11** was estimated as ca. 100% by conversion of **11** to the known compounds **4** and **18**b.