Tetrahedron Vol. 47, No. 7, pp. 1157-1162, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

CHEMICO-ENZYMATIC SYNTHESES OF RACEMIC AND CHIRAL ISOMERS OF 7- METHYL-1,6-DIOXASPIRO[4.5]DECANE

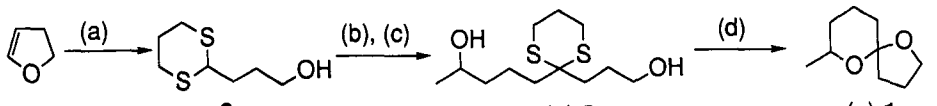
Sowmianarayanan Ramaswamy and Allan C. Oehlschlager
Department of Chemistry
Simon Fraser University
Burnaby, B.C.
Canada V5A 1S6

(*Received in USA* 26 *October* 1990)

Abstract: Porcine pancreatic lipase (PPL) mediated resolution of 6-heptene-2-ol afforded the enantiomers in high optical purities. Alkylation products of the dianion of the 2-4'-hydroxypentyl-1,3-dithiane prepared from the enantiomers, followed by alkylative hydrolysis, afforded 97% optically pure E-7-methyl-1,6-dioxaspiro[4.5]decane.

A number of natural products contain the spiroketal moiety.[1] Francke and coworkers have identified a number of spiroketal-containing insect pheromones.[2] Recently (**E**)-7-methyl-1,6-dioxaspiro[4.5]decane, **1**, was identified as a component of the volatiles produced by the males of jack pine tip beetle, *Conophthorus banksianae* (McPherson), red pine cone beetle, *C. resinosae* (Hopkins) and white pine cone beetle, *C. coniperda* (Schwarz).[3] These beetles infest and destroy cones of pines thus adversely affecting reforestation. The economic havoc these pests cause make development of an effective pheromone based pest management program a worthy endeavour. To establish the chirality of the natural material and provide racemic spiroketal for field tests, we undertook the chemico-enzymatic syntheses which complement the few reported racemic and chiral syntheses of one enantiomer of this spiroketal.[4,5]

Our synthesis of racemic **1** commenced with commercially available 2,3-dihydrofuran (Scheme 1). Thioketalization of the masked aldehyde using 1,3-propanedithiol and BF_3-Et_2O afforded 2-3'–hydroxypropy-1,3-dithiane, **2**. The dianion of **2** was generated by treatment with a slight excess of 2 equivalents of n-butyllithium and alkylation with 1-bromo-4-tetrahydropyranyloxypentane.[6]



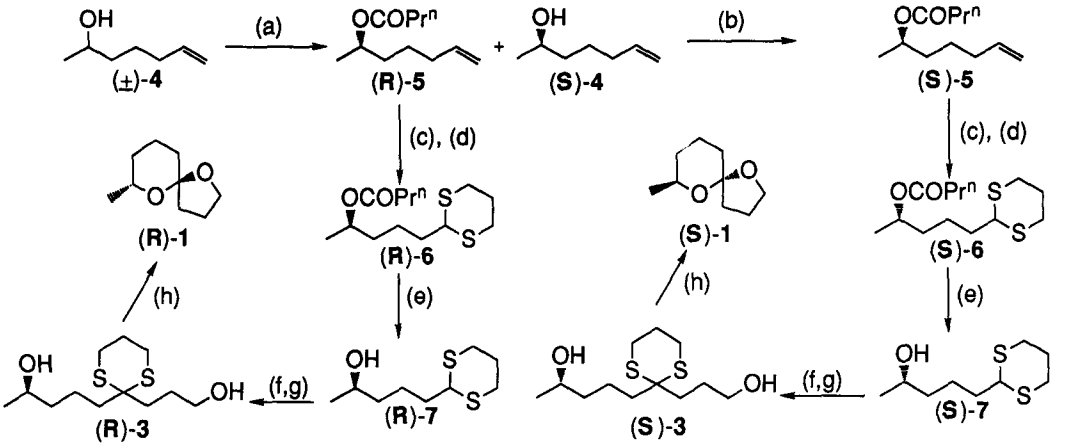
2 (±)-**3** (±)-**1**

(a) $HS(CH_2)_3SH$, $BF_3.Et_2O$; (b) 2 eq. n-BuLi , $THPOCH(Me)(CH_2)_3Br$; (c) MeOH, Amberlyst 15; (d) MeI, CH_3CN-H_2O

Scheme 1

Deprotection of the alcohol was effected by stirring in methanol with catalytic quantities of Amberlyst 15 to afford the diol **3**. Alkylative hydrolysis of the dithiane with iodomethane in aq. acetonitrile[7] gave racemic **1** containing almost entirely one diastereoisomer.[8]

The chiral components required for the fabrication of the enantiomers of **1** were obtained from porcine pancreatic lipase (PPL) mediated resolution of 6-heptene-2-ol, **4**[15-17] (Scheme 2). Use of trifluoroethyl butyrate as the acylating agent gave the (**R**)-butyrate, **5**, in an optical yield of 93%[10] at ~40% conversion.[12] The double bond was then cleaved by ozonolysis and the resulting aldehyde was thioketalized *in situ.* The crude dithiane butyrate, **6**, was hydrolyzed to give (**R-**)**7.**



(a) TFEB / PPL; (b) $(C_3H_7CO)_2O$ / Py; (c) O_3 / DMS; (d)$HS(CH_2)_3SH$, BF_3-Et_2O; (e) NaOH / MeOH-H_2O; (f) 2 eq. n-BuLi, $THPO(CH_2)_3Br$; (g) MeOH, Amberlyst 15; (h) MeI, CH_3CN-H_2O

Scheme 2

The dianion of (**R**)-**7** was generated as above and alkylated with 1-bromo-3-tetrahydropyranyloxypropane. Removal of the THP group followed by spiroketalization was carried out as above to give the (**R**) isomer of **1** (Scheme 2).

The (**S**) alcohol recovered from the PPL transesterification was 82% optically pure. Further transesterification of this alcohol increased the optical purity to ~97% ee.[10] The (**S**) alcohol was converted to the butyrate (**S**)-(**5**) and thence to (**E**)-(**S**)-**1** as described above Gas chromatographic analysis of (**E**)-(**R**)-**1** and (**E**)-(**S**)-**1** on a Chirasil-Dex(8) capillary column revealed both spiroketal enantiomers to be 97% optically pure. Analysis of **1** obtained form *Conophthorus banksianae, C. resinosae* and *C. coniperda* revealed a: three of these beetles produce (**E**)-(**S**)-**1** in essentially optically pure form (95-97%ee).[3] Bioassay of the enantiomers of **1** is in progress.

EXPERIMENTAL

Nmr spectra were recorded on Brucker WM-400 or SY-100 spectrometers in $CDCl_3$ using residual $CHCl_3$ as the internal standard. IR spectra were recorded as neat films between NaCl plates on a Perkin Elmer 599B spectrometer. Gas chromatographic analyses were performed on a Hewlett-

Packard 5880A gas chromatograph operating with a fused silica DB-1 capillary column (15 m x 0.25 mm), a flame ionization detector and a linear oven temperature program initiated at 100°C and increased at 20°C / min to 250°C and held for 5 min at 250°C. Optical rotations were measured on a Rudolph model 70 polarimeter. Elemental analyses were performed at the microanalytical laboratory of the Department of Biological Sciences of Simon Fraser University on a Perkin Elmer Model 240 elemental analyzer. Tetrahydrofuran (THF) was distilled fresh from sodium - benzophenone ketyl. Reagent grade CH_2Cl_2 was distilled from calcium hydride and stored over activated 4A molecular sieves. Porcine pancreatic lipase (PPL, Type II) was purchased from Sigma Chemical Company and had an activity of 16 units per mg solid by olive oil at pH 7.7. All the reagents were purchased from Aldrich Chemical Company and were used without purification. Flash chromatography[14] was conducted on Merck Silica gel 60 (230 - 400 mesh) using specified solvent systems.

Preparation of **2**. To a soln. of 3.50 g (50 mmol) of 2,3-dihydrofuran and 5.04 g (50 mmol) of 1,3-propanedithiol 50 mL of benzene was added ~0.10 mL of BF_3-Et_2O. The reaction was refluxed for ~2 h, cooled to rm. temp. and treated with a drop of Et_3N. Benzene was then removed *in vacuo* and the residue distilled under vacuum. The fraction distilling between 120°C and 135°C (0.1 Torr) was collected and redistilled to afford 3.79 g (43%) of ~90% pure **2**. An analytical sample was obtained by flash chromatography of 0.2 g of the dithiane on 30 g of Silica gel, using 20 - 40% ethyl acetate in hexanes (v/v) as the elution solvent. bp 120°C / 0.1Torr IR: 3420 cm^{-1}; ^1H NMR δ: 1.61 (bs, 1), 1.67 - 1.95 (m, 4), 2.08 - 2.35 (m, 2), 2.78 - 2.92 (m, 4), 3.68 (t, 2, J = 6.0), 4.08 (t, 1, J = 7.0); ^{13}C NMR δ: 62.08, 47.26, 31.82, 30.24 (2C), 29.57, 25.82; Anal. calcd. for $C_7H_{14}OS_2$: C 47.15, H 7.91; found: C 47.33, H 7.81.

Preparation of (**R,S**)- **3**. To a soln. of 3.56 g (20 mmol) of **2** in 40 mL of freshly distilled THF cooled to -10°C was added 17.5 mL of 2.5 M (43.7 mmol) n-BuLi over ~10 min. Stirring was continued for 1 h at -10°C and the reaction was warmed to 0°C over 30 min. A soln. of 5.0 g (20 mmol) of 1-bromo-4-tetrahydropyranyloxypentane in 5 mL THF was added with vigorous stirring which was continued for an additional 0.5 h. The reaction mixture was quenched with 5 mL of water, partitioned between 100 mL of diethyl ether and 20 mL of water. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford ~7.5 g of crude **3**. Volatile impurities were removed by Kugelrohr distillation at 60°C at 0.1 Torr. The residual oil was then dissolved in 50 mL methanol, ~50 mg of Amberlyst 15 was added and the reaction stirred for ~2 h. The soln. was then filtered to remove the catalyst and concentrated *in vacuo*. Chromatography of the residue on 60 g of basic activity I alumina using 50% ethyl acetate in hexanes to 10% methanol in ethyl acetate (v/v) as the elution solvent afforded, in order, 0.82 g (4.6 mmol, 23%) of unreacted starting material, **2** and 3.86 g (14.6 mmol, 73%, 95% yield based on recovered starting material) of (**R,S**)-**3** as an oil. IR: 3410, 920 cm^{-1}; ^1H NMR δ: 1.18 (d, 3, J = 6.0), 1.44 (m, 2), 1.55 (m, 2), 1.64 (m, 2), 1.85 (m, 2) 1.90 - 2.00 (m, 4), 2.11 (bs, 1), 2.80 (m, 4), 3.65 (bt, 2, J = 6.0), 3.80 (bq, 1, J = 6.0); ^{13}C NMR δ: 67.61, 62.51, 53.08, 39.20, 38.31, 34.47, 27.57, 26.01, 25.45, 23.59, 20.24; Anal. calcd. for $C_{12}H_{24}O_2S_2$: C 54.50, H 9.15; found: C 54.42, H 9.16.

Preparation of (E)-(R,S)-1. A mixture of 2.64 g (10 mmol) of (±)-3 and 10 mL of iodomethane was stirred in 50 mL of 20% aq. acetonitrile for 18 h. An additional 25 mL of water was added and the reaction mixture was extracted with 3x50 mL of pentane. The combined pentane extract was filtered through 25 g of basic activity I alumina and concentrated at atmospheric pressure, using a Vigreux column. Residual pentane was removed by quick evaporation *in vacuo* at 0°C. The residue was flash distilled at 6 Torr using a bath temperature of 40 - 50°C (lit.[5b] bp. 166 - 184°C / 740 Torr) and the vapours condensed in a flask cooled to -78°C, to give 0.69 g (44% yield) of racemic **1** as a colorless oil. IR: 1025, 1005 cm^{-1}; ^1H NMR δ: 1.10 (d, 3, J = 6.0), 1.50 - 2.10 (m,10), 3.80 - 3.90 (m, 3); ^{13}C NMR δ: 105.8, 66.6, 66.2, 37.9, 32.7, 32.6, 23.7, 21.8, 20.3.

Porcine Pancreatic Lipase Catalyzed Resolution of (R,S)-(4). A mixture of 8.16 g (71.6 mmol) of (±)-**4**,[15-17] 5.62 g (33.1 mmol) of trifluoroethyl butyrate and 5.0 g PPL in 40 mL dry diethyl ether was stirred at rm. temp. until the starting material to product ratio reached 58 : 42 (~9 d). The enzyme was removed by filtration through a Celite pad and the soln. was concentrated *in vacuo*. The starting material and product were separated using flash chromatography on 50 g of Silica gel using hexanes to 50% ethyl acetate in hexanes (v/v) as the elution solvent to give, respectively, 4.05 g (22.25 mmol) of (**R**)-**5**, ee = 93.5%[10] bp. 60°C / 6 Torr (Kugelrohr), $[\alpha]_D^{22}$ -7.28° (neat); IR: 1745, 1643 cm^{-1}; ^1H NMR δ: 0.95 (t, 3, J = 7.0), 1.20 (d, 3, J = 6.3), 1.32 - 1.65 (m, 6), 2.05 (dt, 2, J = 6.5, 6.5), 2.25 (t, 2, J = 7.5), 4.91 (m, 1), 4.95 (ddt, 1, J = 10.5, 2.0, 1.7), 5.00 (ddt, 1, J = 17.5, 2.0, 1.5), 5.78 (ddt, 1, J = 17.5, 10.5, 6.5); ^{13}C NMR δ: 173.10, 138.27, 114.58, 70.33 , 36.48, 35.28, 33.36, 24.58, 19.89, 18.44, 13.50; Anal. calcd. for $C_{11}H_{20}O_2$: C71.69, H10.94; found: C 71.51, H 10.69, and 5.50 g (48.25 mmol) of (**S**)-(**4**), ee = 81.8%;[10] The unreacted starting material (**S**)-(**4**) was dissolved in 25 mL of dry diethyl ether and stirred with 6.25 g (36.8 mmol) of trifluoroethyl butyrate and 2.5 g PPL until the optical purity of the starting material reached 96.6% (10 d), the reaction mixture was worked up as above to give ~2.75 g (15.1 mmol) of the butyrate and 3.60 g (31.6 mmol) of (**S**)-(**4**), ($[\alpha]_D^{22}$ +6.64° (neat), spectral characteristics were identical with those of racemic starting material.

Preparation of (R)-7: A soln. of 3.68 g (20 mmol) of (**R**)-**5** in 20 mL of CH_2Cl_2 was ozonized at -78°C to the point of appearance of blue color. Excess ozone was removed with a stream of oxygen The ozonide was decomposed with 2 mL of dimethyl sulfide, the cooling bath was removed and the reaction mixture was warmed to rm. temp. (~0.5 h). The reaction mixture was cooled to -10°C, 4 g (40 mmol) of 1,3-propanedithiol and 5 mL (~40 mmol) of BF_3-Et_2O was introduced. The reaction mixture was warmed slowly to rm. temp. and stirred overnight. Solvent and excess dimethyl sulfide were removed *in vacuo* and the residue was dissolved in 100 mL of diethyl ether which was washed with 15 mL of satd. $NaHCO_3$. The ethereal soln. was dried ($MgSO_4$), concentrated *in vacuo*, and the volatile impurities were removed at 60°C under 0.1 Torr. The residue was dissolved in 5 mL of methanol, 5 mL of 10M NaOH was added and the mixture was refluxed for 1 h. The reaction mixture was cooled to rm. temp., methanol was remove *in vacuo*, the residue dissolved in 50 mL of diethyl ether, washed several times with water and the ethereal soln. dried ($MgSO_4$). The soln. was concentrated *in vacuo* to afford 1.45 g product which upon Kugelrohr distillation afforded 1.03 g (5.34 mmol, 27% yield) of (**R**)-**7**, bp 100 - 110°C / 0.2 Torr (Kugelrohr); $[\alpha]_D^{22}$ -8.98° (MeOH,

c 34.2); IR: 3410, 920 cm^{-1}; ^1H NMR δ: 1.16 (d, 3, J = 6.0), 1.31 - 1.87 (m, 6), 2.06 (m, 2), 2.83 (m, 4), 3.77 (m, 2), 4.05 (t, 1, J = 6.0); ^{13}C NMR δ: 67.89, 47.99, 39.43, 36.14, 31.33, 26.98, 24.51, 23.91; Anal. calcd. for $C_9H_{18}OS_2$: C 52.38, H 8.79; found: C 52.46, H 8.88.

Preparation of (**R**)-**3**: A soln. of 1.03 g (5 mmol) of (**R**)-**7** in 5 mL THF cooled to -10°C was reacted with 4.4 mL of 2.5M (11 mmol) of n-BuLi in hexanes. The reaction mixture was stirred at -10°C for 1 h and then warmed to 0°C and stirred for an additional 0.5 h. To this soln. was added 1.20 g (5.38 mmol) of 1-bromo-3-tetrahydropyranyloxypropane in 1 mL of THF. Stirring was continued for an additional hour. and the reaction was worked up as for the preparation of racemic **3**. Chromatography of the crude product on basic alumina as above afforded 0.26 g (1.24 mmol) of recovered starting material and 0.88 g (3.34 mmol, 89% based on recovered (**R**)-**7**) of (**R**)-**3**, ($[\alpha]_D^{22}$ -8.00° (MeOH, c 20.0). Spectral characteristics of the optically pure material were identical with those of racemic **1**.

Preparation of (**E**)-(**R**)-**1** was carried out as for the preparation of (**R,S**)-**1** from (**R,S**)-**3**; $[\alpha]_D^{22}$ +87.8° (neat). Gas chromatographic analysis on a Chirasil-Dex(8) capillary column (V. Schruig, Tubingen, 25 m x 0.25 mm) at 85°C revealed (**E**)-(**R**)-**1** to be 97% optically pure (separation factor, α=1.034).[3]

Preparation of (**S**)-**5**. A mixture of 3.6 g (31.6 mmol) of (**S**)-**4**, 5 mL of butyric anhydride, 5 mL pyridine and ~10 mg DMAP was kept at rm. temp. for 18 h. Methanol (2 mL) was added to destroy the unreacted anhydride.The reaction mixture was diluted with 100 mL of diethyl ether, washed with 3x10 mL of 2M NaOH, dried ($MgSO_4$) and concentrated *in vacuo* to afford 4.58 g (25.16 mmol, 80% yield) of (**S**)-**5**, $[\alpha]_D^{22}$ +8.37° (neat). The spectral characteristics of (**S**)-**5** were identical with those of the enantiomer.

Preparation of (**S**)-**7** from (**S**)-**5** was carried out as for the preparation of (**R**)-**7** from (**R**)-**5**; $[\alpha]_D^{22}$ +10.20° (MeOH, c 29.4). The spectral characteristics of (**S**)-**7** were identical with those of the enantiomer.

Preparation of (**S**)-**3** from (**S**)-**7** was carried out as for the preparation of (**R**)-**3** from (**R**)-**7**; $[\alpha]_D^{22}$ +8.26° (MeOH, c 19.0).

Preparation of (**E**)-(**S**)-**1** from (**S**)-**3** was carried out as for the preparation of (**R,S**)-**1** from (**R,S**)-**3**; $[\alpha]_D^{22}$ -80.36° (neat), lit.[5] $[\alpha]_D^{20}$ -78.2° (neat). Gas chromatographic analysis on a Chirasil-Dex(8) capillary column (V. Schruig, Tubingen, 25 m x 0.25 mm) at 85°C revealed (**E**)-(**S**)-**1** to be 97% optically pure (separation factor, α=1.034).[3]

Acetyl (**S**)-lactyl derivatization of alcohols. To ~ 2 mg of each alcohol in 0.2 mL of dry CH_2Cl_2 were added ~10 μL of pyridine and ~ 50 μL of acetyl (**S**)-lactyl chloride. The reaction mixture was stirred for ~ 1 h, then diluted with 1 mL diethyl ether, washed successively with 0.5 mL of 2M HCl, 0.5 mL water, dried ($MgSO_4$) and 1 - 2 μL of this soln. was analyzed by gas chromatography.

ACKNOWLEDGEMENT

We thank the Natural Sciences and Engineering Research Council of Canada for financial support. in the form of a NSERC Strategic Grant (Biotechnology) to ACO. We wish to thank Dr. H. D. Pierce, Jr. for determination of the optical purity of the spirketal enantiomers prepared in this study.

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8. The diastereoisomeric ratio was ~98.5:1.5.The preferential formation of the **E** diastereoisomer of **1**[8] has its origin in the anomeric effect[5a] which is expressed much more strongly in those 1,6-dioxaspiro[4.5]decanes containing alkyl substituents in the pyran ring. In a synthesis of (**R**,**S**)-**1** *via* a Nef reaction followed by acid catalyzed equilibration, Rosini, *et. al.*[1]. also determined that (**E**)-**1** was formed to the virtual exclusion of (**Z**)-**1**· When the alkyl group is appended to the tetrahydrofuran ring of 1,6-dioxaspiro[4.5]decanes both **E** and **Z** isomers are formed. This reflects a smaller energy difference between axial and equatorial substituents in this system. In an oxidative hydrolysis using mercuric chloride leading to spiroketals, Seebach and coworkers have reported the formation of a 3:2 **E**/**Z** mixture of diastereoisomers for 2-methyl and 2-ethyl-1,6-dioxaspiro[4.5]decane.[9] Rosini *et al* have observed an **E**/**Z** ratio of 2:1 for the 2-methyl derivative when it is derived under Nef reaction conditions from a nitro diol and subjected to acid conditions.

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