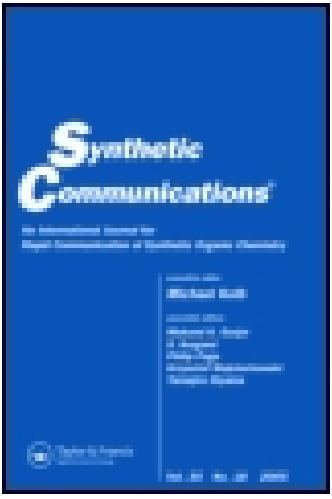

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# Synthesis of (E)-1-Bromo-3-ethyl-3-pentene

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# SYNTHESIS OF (*E*)-1-BROMO-3-ETHYL-3-PENTENE

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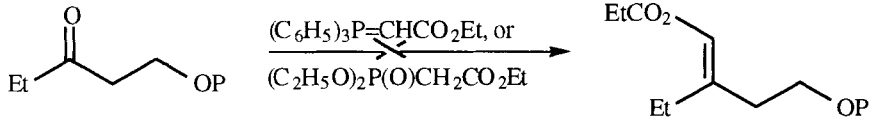
**Abstract:** The synthesis of (*E*)-1-bromo-3-ethyl-3-pentene **1** is described in which the (E)-stereochemistry of the alkene is set up *via* a diastereoselective glyoxylate ene reaction.

As part of our synthetic program directed towards the synthesis of the polyether antibiotic salinomycin[1] we required a stereoselective synthesis of (*E*)-1-bromo-3-ethyl-3-pentene **1** derived from (*E*)-3-ethyl-3-penten-1-ol **2**. Alcohol **2** has been prepared previously[2] by reduction of methyl 3-ethyl-3-hydroxypentanoate which in turn was prepared *via* the Reformatsky reaction of methyl bromoacetate and diethyl ketone. This procedure, however, only provided a 6:5 *E:Z* isomeric mixture. A method was therefore sought to provide predominantly the (*E*)-isomer.

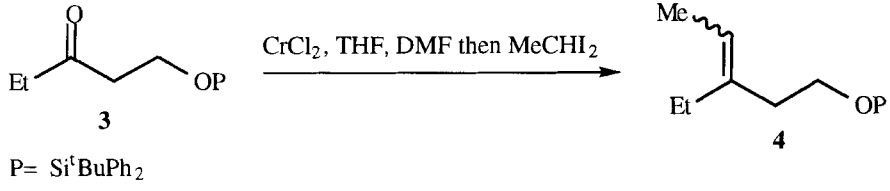
The most obvious way to prepare (*E*)-alkene **2** involved the use of a Wittig reaction on a hydroxyl protected derivative of 1-hydroxy-3-pentanone. Formation

of the desired (*E*)-alkene required the use of an α-stabilized ylide. Attempts to effect this Wittig reaction using methyl (triphenylphosphoranylidene)acetate and ethyl triethylphosphonoacetate met with little success due to competition from β-elimination of the protected β-alkoxy group (Scheme 1).




**Scheme 1**

At this point the use of organochromium methodology, whereby gem-dichromium reagents have been reported[3] to react with aldehydes and ketones to form (*E*)-alkenes, was applied to the synthesis of alkene **2**. Thus, *gem*-dichromioethane, prepared *in situ* from chromium (II) chloride and 1,1-diiodoethane was reacted with 1-(*tert*-butyldiphenylsilyloxy)-3-pentanone **3** to afford an unsatisfactory 2:3 *E*:*Z* mixture of the alkene **4** (Scheme 2).




**3**

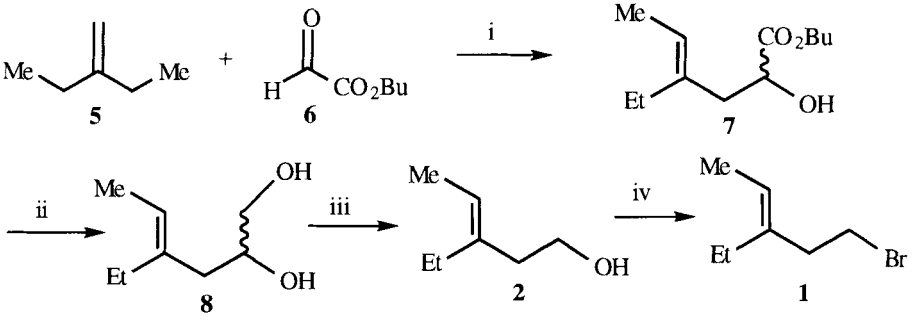
P= $Si^tBuPh_2$

**4**

**Scheme 2**

Our final successful approach to alkene **1** made use of a glyoxylate ene reaction to construct the desired *E*-stereochemistry (Scheme 3). Mikami *et al.*[4,5] have prepared (*E*)-4-ethyl-2-hydroxy-4-hexenoate enantioselectively *via* reaction of 2-ethyl-1-butene **5** with methyl glyoxylate mediated by a chiral titanium catalyst derived from (*R*)-(+)-binaphthol and $Ti(O^iPr)_2Cl_2$. In the present work butyl

glyoxylate was used for the ene reaction due to its ease of preparation and lower water solubility which aided work-up. Thus, addition of 2-ethyl-1-butene **5** to butyl glyoxylate **6** complexed to the titanium catalyst derived from racemic binaphthol and $Ti(O^iPr)_2Cl_2$ provided α-hydroxyester **7** as a 5:1 *E*:*Z* mixture in 54% yield after 24h. at room temperature. A higher reaction temperature was required than that used for methyl glyoxylate presumably due to the greater steric hindrance between the butyl glyoxylate and the titanium catalyst.




*Reagents and conditions* : (i) (+)-binaphthol, $Ti(O^iPr)_2Cl_2$, 4A mol sieves, $CH_2Cl_2$, 1h., -70°C to room temp., 24h., 57%; (ii) $LiAlH_4$, $Et_2O$, 94%; (iii) $Pb(OAc)_4$, $Na_2CO_3$, $CH_2Cl_2$, 16h., then $LiAlH_4$, $Et_2O$, 63% over 2 steps; (iv) MsCl, $Et_3N$, $CH_2Cl_2$ then LiBr, acetone, Δ, 71%.

## Scheme 3

Conversion of ester **7** to the target bromide **1** could be achieved by hydrolysis of ester **7** to an acid followed by periodate cleavage to the aldehyde which after reduction to an alcohol could be converted to a bromide. Whilst hydrolysis of ester **7** occurred in high yield (93%) the subsequent periodate cleavage was low yielding (10-18%). Hence it was decided that reduction of the α-hydroxyester **7** to the diol **8** prior to periodate cleavage might prove to be more effective. Thus, reduction of ester **7** with lithium aluminium hydride afforded diol

**8** in 94% yield, however, cleavage with periodate proved to be low yielding. Use of lead tetraacetate provided the aldehyde which was then reduced to the alcohol **2** using lithium aluminium hydride in 63% yield over the two steps.

Having successfully synthesized alcohol **2** all that remained was conversion to the corresponding bromide **1**. Use of carbon tetrabromide / triphenyl phosphine[6] led to difficulties associated with the removal of the bromoform by-product by column chromatography or distillation. Following several unsuccesssful attempts to perform a one pot synthesis of the bromide using chlorotrimethylsilane and lithium bromide[7], a clean and efficient conversion of the alcohol **2** to the bromide **1** was achieved in two steps in 71% yield *via* the mesylate.

In summary the use of an asymmetric ene reaction has been used to synthesize (*E*)-alkene **1**. It is envisaged that this procedure could provide a general method for the synthesis of (*E*)-homoallylic alcohols and bromides by varying the nature of the olefin in the glyoxylate reaction.



## EXPERIMENTAL

### Dibutyl (+)-tartrate[8]

A mixture of (+)-tartaric acid (75 g, 0.50 mol), Zerolit 225/$H^+$ resin (15 g) and 1-butanol (135 ml, 1.48 mol) in AR benzene (150 ml) was heated under reflux for 8 h, in a 500 ml flask equipped with an overhead stirrer and Dean and Stark apparatus. The organic layer was decanted off and the resin was washed with hot benzene (2 × 30 ml). The combined organic layer was then washed with saturated aqueous sodium bicarbonate

(3 × 70 ml) and distilled water (70 ml) then dried over magnesium sulphate. The benzene was then removed under reduced pressure and the residual oil was distilled under reduced pressure to afford dibutyl tartrate as a colourless solid (89 g, 68%), b.p. 135°C/0.3 mm Hg (lit.[8], b.p. 150°C/1.5 mm Hg).

**Butyl glyoxylate 6**

Dibutyl (+)-tartrate (4.33 g, 16.5 mmol) was stirred vigorously with a 0.486 mol/L sodium periodate solution (34 ml, 16.5 mmol) for 40 h. After filtration to remove the white precipitate which had formed, the filtrate was extracted with diethyl ether (3 × 30 ml) and the combined organic layers were dried over magnesium sulphate. The solvent was removed under reduced pressure to afford a pale pink liquid which was distilled under reduced pressure from phosphorus pentoxide to afford butyl glyoxylate **6** as a colourless oil (2.18 g, 50%), b.p. 68-69°C/5 mm Hg (lit.[8], b.p. 66-69°C/5 mm Hg).

**Diisopropoxytitanium(IV) dichloride[5]**

To a solution of titanium(IV) isopropoxide (2.98 ml, 10 mmol) in hexane (10 ml) was added titanium(IV) chloride (1.10 ml, 10 mmol) slowly at room temperature. After stirring for 10 min. the reaction was allowed to stand for 6 h. at room temperature. The precipitate was then collected, washed with hexane (2 × 5 ml) and dried under high vacuum for 12 h. to give diisopropoxytitanium(IV) dichloride as a white solid (958 mg, 20%)

**Butyl (*E*)-4-ethyl-2-hydroxy-4-hexenoate 7**

To a suspension of activated powdered 4A molecular sieves (6.0 g) in dry dichloromethane (60 ml) were added diisopropoxytitanium(IV) dichloride (264 mg, 1.11 mmol) and (±)-1,1'-bi-2-naphthol (318 mg, 1.11 mmol) at room temperature under a nitrogen atmosphere. After stirring for 1 h. at room temperature the mixture was cooled to -70°C. To the mixture was added 2-ethyl-1-butene **5** (2.96 g, 35.2 mmol) followed by

freshly distilled butyl glyoxylate **6** (2.29 g, 17.6 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. The molecular sieves were removed by filtering the reaction mixture through a plug of celite and the resulting deep red solution was poured into a saturated aqueous solution of sodium bicarbonate (120 ml), stirred for 5 min., then extracted with ethyl acetate (3 × 60 ml). The combined organic layer was dried over magnesium sulphate then reduced to an orange oil. Purification of the oil by flash chromatography, using hexane/ethyl acetate (9:1) as eluant, afforded *butyl (E)-4-ethyl-2-hydroxy-4-hexenoate* **7** as an oil and as a 5:1 mixture of *E/Z* isomers (2.16 g, 57%) (Found: $M^+$, 214.1570. $C_{12}H_{22}O_3$ requires M, 214.1569.); $\upsilon_{max}/cm^{-1}$ (film) 3485 (br, s, OH) 2878, 2937, 2969 (s, C-H) and 1739 (s, C=O); $\delta_H$ (270 MHz; $CDCl_3$) 0.92-1.02 (6H, m, 2 × $CH_3$), 1.35-1.44 (2H, m, $CH_2$), 1.59-1.67 (2H, m, $CH_2$), 1.62 (3H, d, $J_{6,5}$ 6.7, $CH_3C$=), 2.04-2.11 (2H, m, $CH_2$), 2.28 (1H, dd, $J_{3A,3B}$ 14.2 and $J_{3A,2}$ 8.4, $C\underline{H}_AH_BCHOH$), 2.53 (1H, dd, $J_{3B,3A}$ 14.2 and $J_{3B,2}$ 4.5, $CH_A\underline{H}_BCHOH$), 2.84 (1H, m, OH), 4.17 (2H, t, $J_{1",2"}$ 6.7, $CO_2CH_2$), 4.25 (1H, m, C<u>H</u>OH) and 5.31 (1H, q, $J_{5,6}$ 6.7, =CH); $\delta_C$ (67.8 MHz; $CDCl_3$) 12.7 ($CH_3$, C-2'), 13.2 ($CH_3$, C-6), 13.7 ($CH_3$, C-4"), 19.1 ($CH_2$, C-3"), 22.6 ($CH_2$, C-1'), 30.6 ($CH_2$, C-2"), 41.7 ($CH_2$, C-3), 65.3 ($CH_2$, C-1"), 69.4 (CHO), 122.5 (=CH), 136.9 (quat., C-4) and 175.0 (C=O, C-1); *m/z* 214 ($M^+$, 3%), 196 (M - $H_2O$, 33), 140 (M - $C_4H_9O$, 59), 95 ($C_6H_{11}$, 64), 83 ($C_6H_{11}$, 63) and 55 (100).

The *Z* isomer gave an additional $^1H$ NMR resonance at δ 5.43 (1/5H, q, $J_{5,6}$ 6.7, =CH).

**(*E*)-4-Penten-1,2-diol 8**

To a solution of butyl (*E*)-4-ethyl-2-hydroxy-4-hexenoate **7** (1.68 g, 7.84 mmol) in dry diethyl ether (80 ml) was added lithium aluminium hydride (167 mg, 4.40 mmol). After stirring for 1 h. the reaction was quenched carefully with 3M hydrochloric acid until residual lithium/aluminium salts formed solid clumps. These were then washed with diethyl ether (3 × 20 ml) and the ether was decanted off. Additional 3M hydrochloric acid (20 ml) was added to the solid and the resulting aqueous solution was extracted with

diethyl ether (3 × 30 ml). The combined organic layers were dried over magnesium sulphate. The solvent was removed under reduced pressure and the resultant oil was purified by flash chromatography, using hexane/ethyl acetate (1:1) as eluant, to afford *(E)-4-penten-1,2-diol* **8** (1.06 g, 94%) as a colourless oil; (Found: $M^+$, 114.1151. $C_8H_{16}O_2$ requires M, 144.1150.); $\upsilon_{max}/cm^{-1}$ (film) 3384 (br, vs, OH), 2965, 2934, 2875 (m, $CH_2$), 1031 (s, C-O primary) and 1067 (s, C-O secondary); $\delta_H$ (270 MHz; $CDCl_3$) 0.98 (3H, t, $J_{2',1'}$7.5, $CH_2C\underline{H}_3$), 1.63 (3H, d, $J_{6,5}$ 6.6, $CH_3C$=), 1.95-2.24 (4H, m, $CH_2$), 2.37 (1H, s, OH), 2.52 (1H, s, OH), 3.46 (1H, dd, $J_{1A,1B}$ 11.0, $J_{1A,2}$ 6.8, $C\underline{H}_AH_BOH$), 3.67 (1H, dd, $J_{1B,1A}$ 11.0, $J_{1B,2}$ 2.9, $CH_A\underline{H}_BOH$), 3.75-3.83 (1H, m, C<u>H</u>OH) and 5.30 (1H, q, $J_{5,6}$ 6.6, =CH); $\delta_C$ (67.8 MHz; $CDCl_3$) 12.6 ($CH_3$, C-2'), 13.0 ($CH_3$, C-6), 22.6 ($CH_2$, C-1'), 40.4 ($CH_2$, C-3), 66.4 ($CH_2O$), 69.9 (CHO), 121.8 (=CH) and 137.7 (quat., C-4); *m/z* 144 ($M^+$, 3%), 126 (M - $H_2O$, 10), 113 (M - $CH_2OH$, 11), 95 (M - $CH_5O_2$), 84 (77), 69 (100), 61 (55), 55 (65), 43 (52) and 41 (60).

**(*E*)-3-Ethyl-3-penten-1-ol 2**[2,9]

To a solution of (*E*)-4-penten-1,2-diol **8** (1.06 g, 7.35 mmol) in dry dichloromethane (70 ml) at 0°C under argon was added sodium carbonate (1.63 g, 15.4 mmol) followed by lead tetraacetate (3.91 g, 8.82 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. then filtered and washed with additional dry dichloromethane (3 × 30 ml). The solvent was removed under reduced pressure to afford a pungent pale yellow oil. This oil was dissolved in dry diethyl ether (75 ml) and lithium aluminium hydride (78 mg, 2.06 mmol) was carefully added with stirring. After stirring for 1 h. the reaction was quenched by the slow addition of 3M hydrochloric acid (5 ml) until residual lithium/aluminium salts formed solid clumps. These were then washed with diethyl ether (2 × 30 ml) and the ether was decanted off. Additional 3M hydrochloric acid (15 ml) was added to the solid and the resulting aqueous solution was extracted with diethyl ether (2 × 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to

give a yellow oil which was purified by flash chromatography, using hexane/ethyl acetate (4:1) as eluant, to afford *(E)-3-ethyl-3-penten-1-ol* **2** as a yellow oil (530 mg, 63%) (Found: $M^+$, 114.1043. $C_7H_{14}O$ requires M, 114.1045.); $\upsilon_{max}/cm^{-1}$ (film) 3342, 3325 (br, s, OH), 3017 (m, =CH), 2955, 2924, 2867 (s, C-H), 1041 (s, $CH_2$-OH) and 824 (m, =C-H); $\delta_H$ (270 MHz; $CDCl_3$) 0.98 (3H, t, $J_{2',1'}$ 7.7, $CH_3$), 1.62 (3H, d, $J_{5,4}$ 6.6, $CH_3C$=), 2.05 (2H, q, $J_{1',2'}$ 7.7, $C\underline{H}_2CH_3$), 2.26 (2H, t, $J_{2,1}$ 6.2, 2-$CH_2$), 3.65 (2H, t, $J_{1,2}$ 6.2, $CH_2OH$) and 5.29 (1H, q, $J_{4,5}$ 6.6, =CH); $\delta_C$ (67.8 MHz; $CDCl_3$) 12.5 ($CH_3$, C-2'), 12.8 ($CH_3$, C-5), 22.4 ($CH_2$, C-1'), 39.4 ($CH_2$, C-2), 60.4 ($CH_2O$), 120.6 (=CH, C-4) and 137.9 (quat., C-3); *m/z* 114 ($M^+$, 29%), 96 (M - $H_2O$, 15), 81 (M - $CH_5O$, 53), 67 (45), 55 (100), 41 (45) and 29 ($C_2H_5$, 14).

**(*E*)-1-Bromo-3-ethyl-3-pentene 1**

To a stirred solution of (E)-3-ethyl-3-penten-1-ol **2** (200 mg, 1.75 mmol) in dry dichloromethane (10 ml) under argon was added triethylamine (0.37 ml, 2.65 mmol). The reaction mixture was then cooled to -25° C and methanesulphonyl chloride (0.15 ml, 1.94 mmol) was added. After stirring for 30 min. the reaction mixture was quenched with distilled water (5 ml). The aqueous layer was then extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure to afford a yellow oil. The oil was dissolved in dry acetone (5 ml) and heated under reflux with lithium bromide (456 mg, 5.25 mmol) for 5 h. Distilled water (2 ml) was added and the reaction mixture was extracted with dichloromethane (4 × 10 ml). The combined organic layers were dried over magnesium sulphate, the solvent evaporated under reduced pressure, and the resulting oil was purified by column chromatography, using hexane/ethyl acetate (20:1) as eluant, to afford *(E)-1-bromo-3-ethyl-3-pentene* **1** as a colourless oil (220 mg, 71%) (Found: $M^+$, 176.0203, 178.0181. $C_7H_{13}{}^{79}Br$, $C_7H_{13}{}^{81}Br$ require M, 176.0201, 178.0180.); $\upsilon_{max}/cm^{-1}$ (film) 2956, 2922, 2863 (s, C-H), 1736 (m, C=C), 1455 (m, C-H), 828 (m, =CH) and 567 (m, C-Br); $\delta_H$ (270 MHz; $CDCl_3$) 0.97 (3H, t, $J_{2',1'}$ 7.3,

$C\underline{H}_3CH_2$), 1.60 (3H, d, $J_{5,4}$ 6.8, $CH_3C$=), 2.03 (2H, q, $J_{1',2'}$ 7.3 , $C\underline{H}_2CH_3$), 2.54 (2H, t, $J_{2,1}$ 7.7, $CH_2$), 3.41 (2H, t, $J_{1,2}$ 7.7, $CH_2Br$) and 5.27 (1H, q, $J_{4,5}$ 6.8); $\delta_C$ (67.8 MHz; $CDCl_3$) 12.8 ($CH_3$, C-2'), 13.0 ($CH_3$, C-5), 22.5 ($CH_2$, C-1'), 31.9 ($CH_2$, C-1), 40.2 ($CH_2$, C-2), 121.3 (CH, C-4) and 138.7 (quat., C-3); *m/z* 178 ($M^+$, 20%), 176 ($M^+$, 20), 97 (M - Br, 44), 69 (27), 55 (100) and 21 (32).



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