PERKIN 1

Regulation of diastereoselectivity through the epimerisation of a cyclic intermediate in the reaction of cyclic ketene ortho ester with aldehydes

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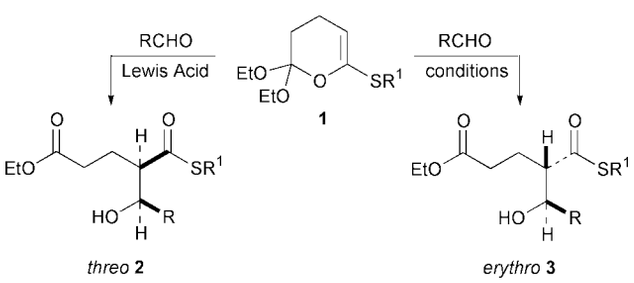
A highly stereocontrolled synthesis of **3** was accomplished. This involves the conversion of the cyclic intermediate **5** (from the reaction of dihydropyran **1** with aldehyde promoted by Lewis acid catalyst) to **6** in the presence of bases and introduction of an ester functionality from hydrolysis of the ortho ester intermediate. The method described herein is successful with a variety of aldehydes and affords products in high yields (55–89%) with useful levels of diastereoselectivity (10–30 : 1). Experiments are described which unambiguously established the stereochemistry for the coupling products. Synthetic manipulations of products by functional group transformations to useful compounds are also reported.

The availability of efficient synthetic methods for achieving stereocontrol *via* catalytic processes in the construction of acyclic systems is of considerable current interest in synthetic chemistry.[1] During the past decades, substantial progress has been made, and as a result, many diastereoselective synthetic routes have been extensively explored.[2] Nonetheless, only a few methods exist which establish both diastereomers in a stereoselective manner, despite their plentiful synthetic potential.[3] For example, significant advances in diastereocontrol have been made in the formation of β-hydroxy esters through the aldol reaction.[4] We recently reported our discovery of a broadly useful method for assembling **2** containing a *threo*-stereochemical relationship from the reaction of dihydro-2*H*-pyran derivatives **1** with aldehydes in the presence of a Lewis acid catalyst as depicted in Scheme 1.[5]

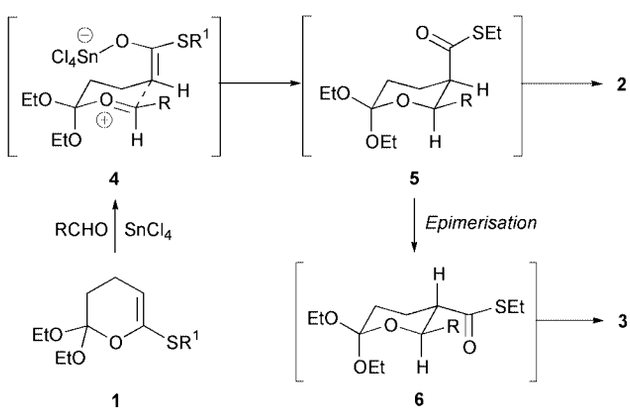


Scheme 1

The characteristic of this chemical transformation regarding catalytic diastereocontrolled processes has encouraged us to carry out further investigations concerning a reversal of diastereoselection. This research led to the discovery of an efficient synthetic route in the formation of *erythro*-adduct **3** with high levels of diastereoselectivity. In the course of this study, the practical chemoselective manipulations of multifunctional products to structurally useful substances have also been investigated.

Results and discussion

In an effort to expand the scope of chemical transformations in the synthesis of *threo*-**2**, we have designed a new reaction pathway to give *erythro*-**3** a reverse diastereoselectivity as depicted in Scheme 1. From the mechanistic perspective, the stereoselectivity in the catalytic process plays a crucial role. Although the exact mechanistic aspects of this transformation have not been rigorously elucidated, Scheme 2 could illustrate a



Scheme 2

probable stereochemical route on the basis of product population. We reasoned that if a cyclic ortho ester **5**, was an intermediate *via* **4** in the reaction pathway, then epimerisation might be possible *in situ* to produce *erythro*-**6** under appropriate reaction conditions in a predictable fashion.[6] The key to this prediction is the thermodynamic stability of *erythro*-**6** in comparison with *threo*-**5**.

To investigate the sequence outlined in Scheme 2, the conversion of **5** to **6** could be accomplished in two ways using acidic or basic conditions. The starting compound **1** was prepared in quantity by a two step sequence, purified by distillation, and stable to storage.[7] The reaction of **1** with aldehyde is carried out in acidic media, therefore the use of an additional Lewis acid was evaluated first in the formation of the intermediate **5** and subsequent reaction to **6**. Compound **5** (R = $PhCH_2CH_2$) was obtained from the reaction of **1** with hydrocinnamaldehyde in the presence of $SnCl_4$ (10 mol%) at −78 °C, by the addition of Lewis acid. Preliminary investigations for the transformation of **5** indicated that the conversion to the corresponding **6**

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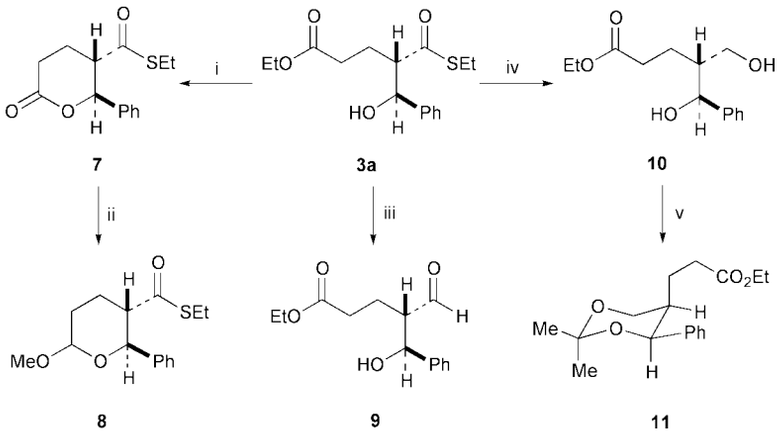

Scheme 3 *Reagents and conditions*: i) Et_2AlCl, Pr^i_2NEt, −20–20 °C, CH_2Cl_2; ii) a. DIBAL-H, −78 °C toluene; b. $CH(OMe)_3$, Amberlyst-15; iii) Et_3SiH, Pd/C, 0 °C, CH_2Cl_2; iv) $NaBH_4$, $Hg(OAc)_2$, 0–20 °C, EtOH; v) 2-methoxypropene, PTSA, 4 Å MS, CH_2Cl_2.

Table 1 *erythro*-Selective reaction of **1** (R^1 = Et) with aldehydes[a]

Entry	RCHO	Product	Dr (**3**:**2**)[b]	Yield (%)[c]
1	Ph	**a**	97:3	89
2	$PhCH_2CH_2$	**b**	93:7	83
3	C_6H_{13}	**c**	91:9	77
4	Me_2CHCH_2	**d**	92:8	86
5	Me_2CH	**e**	94:6	55
6	PhCH=CH	**f**	93:7	67

[a] Reactions were carried out in toluene at −78 °C to ~50 °C for 7 h. [b] Diastereomeric ratio was determined by the analysis of 500 MHz ^{1}H NMR spectra of crude products (all entries) and by GC analysis using HP-1 (Hewlett-Packard, cross linked methyl siloxane, 25 m × 0.32 mm × 0.52 μm, entries 3, 4, 5). [c] Yields refer to isolated and purified products.

was not satisfactory with a variety of additional Lewis acids such as $SnCl_4$, $Ti(OPr^i)_4$, and $BF_3{\cdot}OEt_2$ and resulted in low chemical yields and stereoselectivities; we observed less than 2:1 diastereomeric ratio with 41% yield when 1.1 equiv. of $BF_3{\cdot}OEt_2$ was employed for 20 h. We next turned our attention to examining the feasibility of bases. Initial attempts to convert **5** to **6** with bases such as Et_3N, DMAP, 1,1,3,3-tetramethylguanidine, and imidazole were met with limited success, providing moderate diastereoselectivities up to 4:1. After surveying numerous conditions, the remarkable observation has been made that the use of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in the presence of pyridine led to the best results in terms of chemical yields and diastereoselectivities (83% yield, **2**:**3** = 7:93). a) The addition of base at −78 °C and maintaining this temperature for 30 min was crucial to obtain the best results; b) reaction at 50 °C for 7 h in toluene proved to be optimal, while with longer reaction times diminished chemical yields were observed; c) R^1 = Et in **1** was generally superior to other substituents such as Me and Pr^i in terms of chemical availability and efficacy, and was chosen for systematic studies.

With the notion that this protocol might lead to a general and efficient method for the synthesis of multifunctional substances, we set out to determine the scope of the reaction with various aldehydes. Indeed, the method is successful with a variety of aldehydes and affords products of high diastereomeric purity as can be seen in Table 1. Under optimal conditions, the reaction was performed by addition of $SnCl_4$ (10 mol%) to a solution of **1** (R^1 = Et) and benzaldehyde in toluene at −78 °C. After 2 h at −78 °C, freshly distilled pyridine (15 equiv.) and DBU (7 equiv.) were added and a white precipitate was formed. After stirring for 30 min at −78 °C, the cooling bath was removed and the temperature was allowed to rise to ambient temperature and stirring was continued at 50 °C for 7 h. After cooling to 0 °C, the reaction mixture was quenched with 2 M aqueous HCl in EtOH followed by work up and silica gel chromatography to afford *erythro*-**3a** with *threo*-**2a** in a ratio of 97:3 as judged by 500 MHz ^{1}H NMR of the crude products. The diastereoselectivity and stereochemistry of the major component **3** in each case was determined by comparison with authentic *threo*-components **2** which proved their stereochemical relationship unambiguously based on the vicinal coupling patterns of the 1,3-dioxane derivatives in the ^{1}H NMR spectra.[5]

The coupling products **3** are readily amenable for further conversion to useful synthetic intermediates by functional group transformations in a chemoselective manner of the thioester and ester functionalities as demonstrated in Scheme 3. For example, the reaction of **3a** with Et_2AlCl in the presence of Pr^i_2NEt in CH_2Cl_2 at −20 °C for 2 h and then 20 °C for 4 h resulted in the formation of **7** (84% yield). Chemoselective reduction of the ester group in **7** by DIBAL-H at −78 °C in toluene for 3 h and then acetalization of crude product with $CH(OMe)_3$ in the presence of Amberlyst-15 gave **8** in 77% overall yield (α:β = 65:35). Compound **3a** was allowed to stand for 3 h at 0 °C with Et_3SiH in the presence of Pd/C in CH_2Cl_2 to give **9** in 81% yield.[8] This aldehyde was readily reduced to the diol **10** by $NaBH_4$. The diol **10** was obtained exclusively from **3a** by the chemoselective reduction of the thioester functionality in 77% isolated yield ($NaBH_4$, $Hg(OAc)_2$, EtOH, 0–20 °C, 4 h). Treatment of **10** with 2-methoxypropene in the presence of catalytic amounts of *p*-TsOH and 4 Å molecular sieves in CH_2Cl_2 at 0 °C afforded the dioxane **11** in 88% yield. The dioxane **11** has an *erythro*-stereochemical relationship on the basis of the ^{1}H NMR analysis of vicinal protons as demonstrated by coupling constant of 2.74 Hz at δ 5.20.

In summary, this paper describes a new methodology for the synthesis of *erythro*-**3** to realize a reverse diastereoselection in a general and efficient way which promises to be synthetically useful. This highly stereocontrolled transformation involves the epimerisation of cyclic intermediate **5** to **6** using DBU and pyridine followed by hydrolysis of the ortho ester functionality to introduce an ester moiety during acidic work up. With the synthetic methods for construction of each of the diastereomers in hand, studies are in progress to incorporate chiral catalysts into the catalytic asymmetric synthesis to establish all four stereoisomers in a selective manner.

Experimental

General

All reactions were run in flame-dried glassware under an atmosphere of nitrogen. Tetrahydrofuran (THF) was dried by

refluxing over sodium and benzophenone until a permanent purple coloration was presented, and distilled prior to use. Diethyl ether was also distilled from Na–benzophenone ketyl prior to use. Dichloromethane was distilled from CaH_2 prior to use. Pentane was distilled from P_2O_5 prior to use. All liquid reagents purchased from Aldrich were distilled properly prior to use, unless otherwise indicated. Compound **1** was prepared by a previously described procedure.[5a] Purification was conducted by flash column chromatography on silica gel (230–400 mesh), eluting with a mixture of hexane and ethyl acetate, unless otherwise stated. Proton NMR spectra were recorded at 500 MHz in $CDCl_3$ as solvent, with TMS or residual chloroform as the internal standard. *J* values are given in Hz. Diastereomeric ratios of *erythro*-products **3** were determined by analysis of 500 MHz ^{1}H NMR spectra in comparison with that of authentic *threo*-**2** and/or by GC analysis of products using HP-1 (Hewlett-Packard, cross linked methyl siloxane, 25 m × 0.32 mm × 0.52 μm) column with FID detector.

Ethyl (4*S,5*S**)-4-ethylthiocarbonyl-5-hydroxy-5-phenylpentanoate 3a: typical procedure**

A flame-dried flask containing 2,2-diethoxy-6-ethylthio-3,4-dihydro-2*H*-pyran (**1**, 0.83 g, 3.57 mmol) was evacuated and purged with nitrogen three times and then charged with freshly distilled toluene (12 mL). The solution was cooled to −78 °C in a dry ice–acetone bath, and benzaldehyde (0.35 g, 3.25 mmol) was added. To the resulting solution was added dropwise a solution of $SnCl_4$ in toluene (0.5 M, 0.65 mL, 0.325 mmol) with a gas-tight syringe. The reaction progress was monitored by TLC. After stirring for 2 h at −78 °C, distilled pyridine (3.86 g, 48.75 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.46 g, 22.75 mmol) was added dropwise at this temperature. After 30 min at −78 °C, the resulting mixture was allowed to warm to room temperature and then 50 °C in an oil bath. After 7 h, the mixture was cooled to 0 °C and the reaction was quenched by addition of a solution of 1:1 aqueous 20% HCl–EtOH. The aqueous layer was extracted with ether (3×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1×), water (1×), brine (1×), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Final purification was effected by column chromatography (SiO_2, 25% EtOAc in hexane) to afford **3a** along with an inseparable minor diastereomer **2a** (0.90 g, 2.90 mmol, 89%) as a colourless liquid; diastereomeric ratio was 97:3 as judged by the analysis of 500 MHz ^{1}H NMR of crude products (Found: C, 61.06; H, 7.22; S, 10.30. $C_{16}H_{22}O_4S$ requires C, 61.91; H, 7.14; S, 10.33%); TLC, R_f 0.29 (3:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3487 (br), 2962, 2931, 1732, 1677, 1452, 1164 and 1028; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.15 (3 H, t, *J* 7.37, SCH_2CH_3), 1.22 (3 H, t, *J* 7.11, OCH_2CH_3), 1.96–2.03 (1 H, m, $CHHCH_2CO_2Et$), 2.07–2.15 (1 H, m, $CHHCH_2CO_2Et$), 2.24 (1 H, ddd, *J* 7.37, 8.51 and 16.44, CH_2CHHCO_2Et), 2.37 (1 H, ddd, *J* 5.67, 9.09 and 16.44, CH_2CHHCO_2Et), 2.71–2.90 (2 H, m, SCH_2CH_3), 2.84 (1 H, d, *J* 2.55, OH), 2.95 (1 H, ddd, *J* 3.97, 5.39 and 9.79, CHCOSEt), 4.08 (2 H, q, *J* 7.11, OCH_2CH_3), 4.99 (1 H, dd, *J* 2.55 and 5.39, PhCHOH) and 7.24–7.38 (5 H, m, Ph); δ_C(50 MHz; $CDCl_3$; Me_4Si) 14.1, 14.4, 22.4, 23.4, 31.7, 60.3, 60.4, 74.1, 126.2, 127.8, 128.3, 141.1, 172.9 and 202.2; *m*/*z* (EI) 310 (M^+, 2.7 × 10^{-1}), 231 (28.8), 204 (49.0), 185 (32.0), 143 (83.1), 115 (71.5) and 79 (100%).

Ethyl (4*S,5*R**)-4-ethylthiocarbonyl-5-hydroxy-7-phenylheptanoate 3b**

This compound was obtained in 83% yield according to the above procedure for **3a** as a colourless oil (Found: C, 63.71; H, 7.80; S, 9.38. $C_{18}H_{26}O_4S$ requires C, 63.87; H, 7.74; S, 9.47%); TLC, R_f 0.28 (3:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3460 (br), 3011, 2962, 2931, 1739, 1675, 1452 and 1258; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.25 (3 H, t, *J* 7.35, SCH_2CH_3), 1.27 (3 H, t, *J* 7.21, OCH_2CH_3), 1.73–1.86 (2 H, m, CH_2CH_2Ph), 1.97–2.14 (2 H, m, $CH_2CH_2CO_2Et$), 2.30 (1 H, ddd, *J* 7.97, 7.97 and 15.59, CH_2CHHCO_2Et), 2.44 (1 H, ddd, *J* 5.95, 8.22 and 15.59, CH_2CHHCO_2Et), 2.53 (1 H, d, *J* 3.97, OH), 2.63–2.75 (2 H, m, CH_2Ph), 2.83–2.94 (3 H, m, SCH_2CH_3 and CHCOSEt), 3.85 (1 H, m, $HOCHCH_2$), 4.13 (2 H, q, *J* 7.21, OCH_2CH_3) and 7.17–7.30 (5 H m, Ph); δ_C(50 MHz; $CDCl_3$; Me_4Si) 14.2, 14.5, 22.4, 23.5, 31.6, 32.2, 36.2, 58.6, 60.5, 71.4, 125.9, 128.4, 128.4, 141.6, 173.1 and 202.4; *m*/*z* (EI) 277 (M^+ − SEt, 9.0), 231 (14.6), 185 (14.9), 143 (24.5), 117 (27.2), 104 (22.1), 97 (22.7), 91 (100) and 55 (94.9%).

Ethyl (4*S,5*R**)-4-ethylthiocarbonyl-5-hydroxyundecanoate 3c**

This compound was obtained in 77% yield according to the above procedure for **3a** as a colourless oil (Found: C, 60.61; H, 9.29; S, 10.10. $C_{16}H_{30}O_4S$ requires C, 60.34; H, 9.50; S, 10.07%); TLC, R_f 0.41 (3:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3453 (br), 2955, 2859, 1735, 1680, 1455 and 1169; δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.88 (3 H, t, *J* 7.09, CH_2CH_3), 1.25–1.52 (16 H, m, $CHCH_2CH_2CH_2CH_2CH_2CH_3$, SCH_2CH_3 and OCH_2CH_3), 1.96–2.13 (2 H, m, $CH_2CH_2CO_2Et$), 2.28–2.47 (3 H, m, CH_2CO_2Et and OH), 2.65–2.69 (1 H, m, CHCOSEt), 2.90 (2 H, q, *J* 7.37, SCH_2CH_3), 3.80–3.84 (1 H, m, $HOCHCH_2$) and 4.14 (2 H, q, *J* 7.09, OCH_2CH_3); δ_C(50 MHz; $CDCl_3$; Me_4Si) 14.0, 14.2, 14.6, 22.3, 22.6, 23.5, 25.8, 29.1, 31.7, 34.6, 52.6, 58.6, 60.5, 72.1, 173.1, 202.6; *m*/*z* (EI) 257 (M^+, 85.1), 239 (82.9), 211 (74.1), 165 (48.6), 143 (62.4), 115 (55.9), 87 (34.4), 55 (100) and 43 (51.1%).

Ethyl (4*S,5*R**)-4-ethylthiocarbonyl-5-hydroxy-7-methyloctanoate 3d**

This compound was obtained in 86% yield according to the above procedure for **3a** as a colourless oil (Found: C, 57.79; H, 9.22; S, 11.14. $C_{14}H_{26}O_4S$ requires C, 57.90; H, 9.02; S, 11.04%); TLC, R_f 0.33 (3:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3462 (br), 2958, 2874, 1735, 1679, 1459, 1382, 1171 and 1031; δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.90 (3 H, d, *J* 6.80, CH_3CHCH_3), 0.93 (3 H, d, *J* 6.80, CH_3CHCH_3), 1.19 (1 H, ddd, *J* 5.53, 9.11 and 13.89, $CHHCHMe_2$), 1.25 (3 H, t, *J* 7.09, SCH_2CH_3), 1.26 (3 H, t, *J* 7.37, OCH_2CH_3), 1.46 (1 H, ddd, *J* 4.82, 9.64 and 13.89, $CHHCHMe_2$), 1.77 (1 H, m, CH_2CHMe_2), 2.01 (1 H, m, $CHHCH_2CO_2Et$), 2.17 (1 H, m, $CHHCH_2CO_2Et$), 2.32 (1 H, m, $CHHCO_2Et$), 2.35 (1 H, d, *J* 4.26, OH), 2.43 (1 H, ddd, *J* 5.95, 8.51 and 16.44, $CHHCO_2Et$), 2.63 (1 H, ddd, *J* 4.38, 4.38, 9.64, CHCOSEt), 2.87–2.95 (2 H, m, SCH_2CH_3), 3.89 (1 H, m, $HOCHCH_2$) and 4.14 (2 H, q, *J* 7.37, OCH_2CH_3); δ_C(50 MHz; $CDCl_3$; Me_4Si) 14.2, 14.5, 21.7, 22.3, 23.4, 24.7, 31.7, 43.6, 59.0, 60.5, 70.1, 173.1, 202.5; *m*/*z* (EI) 229 (M^+ − SEt, 7.3), 183 (22.0), 137 (27.7), 115 (24.4), 97 (27.7), 87 (38.7), 71 (25.4), 69 (35.3), 55 (95.0) and 41 (100%).

Ethyl (4*S,5*R**)-4-ethylthiocarbonyl-5-hydroxy-6-methylheptanoate 3e**

This compound was obtained in 55% yield according to the above procedure for **3a** as a colourless oil (Found: C, 56.33; H, 8.59; S, 11.60. $C_{13}H_{24}O_4S$ requires C, 56.49; H, 8.75; S, 11.60%); TLC, R_f 0.32 (3:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3454 (br), 2958, 2874, 1735, 1679, 1462, 1171 and 1021; δ_H(500 MHz; $CDCl_3$; Me_4Si) 0.93 (3 H, d, *J* 7.27, CH_3CHCH_3), 0.99 (3 H, d, *J* 7.07, CH_3CHCH_3), 1.26 (3 H, t, *J* 7.11, SCH_2CH_3), 1.27 (3 H, t, *J* 7.35, OCH_2CH_3), 1.75 (1 H, m, $CHCHMe_2$), 1.97–2.12 (2 H, m, $CH_2CH_2CO_2Et$), 2.28–2.52 (3 H, m, CH_2CO_2Et and OH), 2.83–2.97 (3 H, m, CHCOSEt and SCH_2CH_3), 3.53 (1 H, m, $HOCHCH_2$) and 4.14 (2 H, q, *J* 7.37, OCH_2CH_3); δ_C(50 MHz; $CDCl_3$; Me_4Si) 14.2, 14.5, 17.6, 19.5, 22.1, 23.5, 30.8, 31.6, 55.9, 60.5, 77.0, 173.1 and 202.9; *m*/*z* (EI) 215 (M^+ − SEt, 54.0), 169 (88.7), 141 (40.0), 115 (37.3), 97 (94.4) and 55 (100%).

Ethyl (4*S,5*R**)-4-ethylthiocarbonyl-5-hydroxy-7-phenylhept-6-enoate 3f**

This compound was obtained in 67% yield according to the above procedure for **3a** as a colourless oil (Found: C, 66.11; H, 7.13; S, 9.61. $C_{18}H_{24}O_4S$ requires C, 64.26; H, 7.19; S, 9.53%); TLC, R_f 0.24 (3:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3445 (br), 3012, 2977, 2933, 1729, 1676, 1438, 1166 and 1028; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.22 (3 H, t, *J* 7.35, SCH_2CH_3), 1.24 (3 H, t, *J* 7.37, OCH_2CH_3), 2.03–2.14 (2 H, m, $CH_2CH_2CO_2Et$), 2.36 (1 H, ddd, *J* 7.24, 7.93 and 16.24, $CHHCO_2Et$), 2.45 (1 H, ddd, *J* 6.24, 8.22 and 16.24, $CHHCO_2Et$), 2.53 (1 H, br s, OH), 2.83–2.94 (3 H, m, CHCOSEt and SCH_2CH_3), 4.13 (2 H, q, *J* 7.37, OCH_2CH_3), 4.53 (1 H, dd, *J* 4.50 and 6.24, HOCHCH=CH), 6.19 (1 H, dd, *J* 6.24 and 15.87, PhCH=CHCHOH), 6.64 (1 H, d, *J* 15.87, PhCH=CH) and 7.23–7.39 (5 H, m, Ph); δ_C(50 MHz; $CDCl_3$; Me_4Si) 14.1, 14.5, 22.9, 23.5, 31.7, 58.8, 60.4, 73.1, 126.6, 127.8, 128.5, 128.5, 131.9, 136.4, 172.9 and 201.6; *m*/*z* (EI) 275 (M^+ − SEt, 24.5), 229 (22.5), 200 (29.3), 142 (27.0), 133 (83.7), 115 (52.4), 114 (65.0), 103 (21.4), 91 (32.4), 77 (32.0) and 55 (100%).

(5*S,6*R**)-5-Ethylthiocarbonyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one 7**

To a solution of **3a** (97:3 diastereomeric mixture, 0.23 g, 0.74 mmol) and diisopropylamine (0.11 g, 0.88 mmol) in CH_2Cl_2 (10 mL) was added diethylaluminium chloride (1.8 M in toluene, 0.42 mL, 0.74 mmol). The reaction mixture was stirred at −20 °C for 3 h and allowed to warm slowly to room temperature. After 3 h, the mixture was poured into a separating funnel and extracted with ether (2×). The combined organic extracts were washed with cold saturated aqueous $NaHCO_3$ (1×), water (1×), brine (1×), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of crude products by flash column chromatography (SiO_2, 25% EtOAc in hexane) provided **7** (0.164 g, 0.62 mmol, 84%) as a colourless oil (Found: C, 63.48; H, 6.2; S, 11.87. $C_{14}H_{16}O_3S$ requires C, 63.61; H, 6.10, S, 12.13%); TLC, R_f 0.48 (2:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 1740 and 1676; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.10 (3 H, t, *J* 7.37, SCH_2CH_3), 2.19 (1 H, m, CHHCHCOSEt), 2.28 (1 H, m, CHHCHCOSEt), 2.63–2.88 (4 H, m, CH_2CO_2 and SCH_2CH_3), 3.11 (1 H, ddd, *J* 2.81, 6.24 and 9.64, CHCOSEt), 5.52 (1 H, d, *J* 9.64, OCHPh) and 7.28–7.39 (5 H, m, Ph); δ_C(50 MHz; $CDCl_3$; Me_4Si) 14.3, 23.5, 23.5, 28.4, 54.5, 81.9, 126.8, 128.6, 128.9, 137.2, 170.1 and 198.8; *m*/*z* (EI) 264 (M^+, 6.6), 208 (52.5), 203 (1.1), 174 (65.1), 147 (73.7), 130 (23.5) 115 (15.8), 105 (47.4), 97 (48.7), 91 (30.0), 88 (35.3), 77 (39.3) and 55 (100%).

(5*S,6*R**)-5-Ethylthiocarbonyl-2-methoxy-6-phenyl-3,4,5,6-tetrahydro-2*H*-pyran 8**

To a solution of **7** (0.107 mg, 4.0 mmol) in toluene (7 mL) at −78 °C was added DIBAL-H (1 M in hexane, 0.5 mL, 5.0 mmol) over a period of 10 min. After 3 h, the reaction mixture was sequentially treated with 10% HCl (0.5 mL) and extracted with ether (3×). The combined organic extracts were dried over anhydrous $MgSO_4$ and then filtered through a sintered glass funnel containing silica gel (*ca*. 3 cm). Removal of the solvents under reduced pressure gave the product, which was used without further purification. This product was immediately dissolved in $CH(OMe)_3$ (5 mL). To this solution Amberlyst-15 (20 mg) was added. The resulting solution was stirred for 3 h and then filtered through a sintered glass funnel. After concentration under reduced pressure, purification of crude product by flash column chromatography (SiO_2, 20% EtOAc in hexane) provided **8** (0.087 g, 3.1 mmol, 77%) as a colourless oil; anomeric ratio was 65:35 (α:β) as judged by the analysis of 500 MHz ^{1}H NMR of crude products (Found: C, 63.98; H, 7.11; S, 11.63. $C_{15}H_{20}O_3S$ requires C, 64.26; H, 7.19, S, 11.44%); TLC, R_f 0.58 (3:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3011, 1681, 1373 and 1267; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.03 (0.65 × 3 H, t, *J* 7.33, SCH_2CH_3), 1.04 (0.35 × 3 H, t, *J* 7.33, SCH_2CH_3), 1.61–1.92 (3 H, m, CHHCH$_2$CHCOSEt), 2.17–2.28 (1 H, m, CHHCH$_2$CHCOSEt), 2.60–2.74 (2 H, m, SCH_2CH_3), 2.89 (0.65 × 1 H, ddd, *J* 2.75, 10.07 and 12.91, CHCOSEt), 3.39 (0.65 × 3 H, s, OCH_3), 3.48 (0.35 × 3 H, s, OCH_3), 4.54 (0.35 × 1 H, dd, *J* 2.14 and 9.77, MeOCHO), 4.64 (0.35 × 1 H, d, *J* 9.77, OCHPh), 4.85 (0.65 × 1 H, d, *J* 2.75, MeOCHO), 4.91 (0.65 × 1 H, d, *J* 10.07, OCHPh) and 7.28–7.36 (5 H, m, Ph); *m*/*z* (EI) 280 (M^+, 5.64), 249 (24.7), 219 (100), 203 (31.8), 178 (19.4), 128 (32.4), 99 (28.0) and 77 (48.4%).

Ethyl (4*R,5*S**)-4-formyl-5-hydroxy-5-phenylpentanoate 9**

To a stirred suspension of **3a** (0.093 g, 0.30 mmol) and Pd/C (10 wt%, 16 mg, 0.015 mmol) in CH_2Cl_2 (3 mL) was added Et_3SiH (0.1 mL, 0.072 g, 0.63 mmol) at 0 °C. The resulting solution was stirred for 3 h at 0 °C and then filtered through a sintered glass funnel containing Celite with additional EtOAc. Concentration under reduced pressure and removal of volatile materials under high vacuum (10^{-2} mmHg) gave **9** (0.058 g, 0.23 mmol, 77%) in fairly pure form based on ^{1}H NMR analysis; TLC, R_f 0.19 (2:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3464 (br), 2825, 2724, 1728 and 1376; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.21 (3 H, t, *J* 7.33, OCH_2CH_3), 1.93 (1 H, m, CHHCHCHO), 2.00–2.08 (1 H, m, CHHCHCHO), 2.22–2.36 (2 H, m, CH_2CO_2Et), 2.42–2.45 (1 H, br s, OH), 2.76–2.86 (1 H, m, CHCHO), 4.08 (2 H, q, *J* 7.33, OCH_2CH_3), 5.14 (1 H, dd, *J* 1.83 and 4.60, HOCHPh), 7.24–7.42 (5 H, m, Ph) and 9.74 (1 H, d, *J* 1.48, CHO); *m*/*z* (EI) 250 (M^+, 3.1 × 10^{-1}), 232 (1.1), 205 (77), 177 (11.4), 146 (16.1), 128 (100), 107 (22.5), 105 (36.8), 100 (21.2), 91 (28.0) and 73 (48.4%). Purification of product by flash column chromatography (deactivated SiO_2) turned out to be unpromising mainly due to decomposition of product. However, the crude product was cleanly reduced to the diol **10** by using $NaBH_4$.

Ethyl (4*R,5*S**)-4-hydroxymethyl-5-hydroxy-5-phenylpentanoate 10**

A grey suspension of **3a** (0.24 g, 0.77 mmol) and mercury acetate (0.25 g, 0.77 mmol) in distilled ethanol (10 mL) was cooled to 0 °C, and sodium borohydride (0.12 g, 3.1 mmol) was added in small portions. After 30 min, the resulting pale yellow solution was warmed to 20 °C. After 3 h, the mixture was cooled to room temperature and then poured into a separating funnel and extracted with ether (3 × 20 mL). The combined organic extracts were washed with 10% aqueous HCl (1×), saturated aqueous $NaHCO_3$ (1×), water (1×), brine (1×), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of crude product by flash column chromatography (SiO_2, 50% EtOAc in hexane) provided **10** (0.157 g, 0.62 mmol, 81%) as a colourless oil (Found: C, 66.74; H, 7.65. $C_{14}H_{20}O_4$ requires C, 66.65; H, 7.99%); TLC, R_f 0.33 (1:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 3404 (br) and 1735; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.22 (3 H, t, *J* 7.08, OCH_2CH_3), 1.68–1.79 (3 H, m, CH_2CHCH_2OH), 2.29 (2 H, t, *J* 7.09, CH_2CO_2Et), 2.84 (1 H, br s, OH), 3.25 (1 H, br s, OH), 3.68–3.74 (2 H, m, $CHCH_2OH$), 4.08 (2 H, q, *J* 7.08, OCH_2CH_3), 5.00 (1 H, d, *J* 3.68, HOCHPh) and 7.25–7.35 (5 H, m, Ph); δ_C(125 MHz; $CDCl_3$; Me_4Si) 14.1, 19.7, 32.1, 46.3, 60.5, 63.8, 76.7, 126.0, 127.3, 128.3, 142.6 and 174.3; *m*/*z* (EI) 252 (M^+, 1.8 × 10^{-1}), 177 (11.4), 146 (16.1), 128 (100), 117 (16.8), 107 (44.6), 105 (36.8), 91 (28.0), 79 (48.4) and 55 (73.6%).

(4*S,5*R**)-2,2-Dimethyl-5-(2′-ethoxycarbonylethyl)-4-phenyl-1,3-dioxane 11**

To a solution of **9** (0.101 mg, 0.4 mmol) along with 2-methoxy-

propene (0.11 g, 1.05 mmol) in CH_2Cl_2 (4 mL) in the presence of 4 Å molecular sieves at 0 °C was added toluene-*p*-sulfonic acid (3 mg, 0.016 mmol). After being stirred for 3 at 0 °C, anhydrous K_2CO_3 (20 mg) was added to the reaction mixture which was stirred at room temperature for 30 min, filtered, and concentrated under reduced pressure. Purification of crude product by flash column chromatography (SiO_2, 25% EtOAc in hexane) provided **11** (0.103 g, 0.35 mmol, 88%) as a colourless oil (Found: C, 70.04; H, 8.11. $C_{17}H_{24}O_4$ requires C, 69.84; H, 8.27%); TLC, R_f 0.52 (3:1 hexane–EtOAc); ν_{max} (neat)/cm^{-1} 2989, 1731 and 1255; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.17 (3 H, t, *J* 7.17, OCH_2CH_3), 1.43 (1 H, m, $CHCHHCH_2$), 1.52 (3 H, s, CH_3CCH_3), 1.54 (3 H, s, CH_3CCH_3), 1.67 (1 H, m, $CHCHH$-CH_2), 1.87 (1 H, m, OCH_2CH), 2.06 (1 H, ddd, *J* 7.94, 7.94 and 15.87, $CHHCO_2Et$), 2.16 (1 H, ddd, *J* 5.80, 8.55 and 15.87, $CHHCO_2Et$), 3.85 (1 H, dd, *J* 1.83 and 11.90, $OCHHCH$), 4.03 (2 H, q, *J* 7.17, OCH_2CH_3), 4.21 (1 H, dd, *J* 1.53, 11.90, $OCHHCH$), 5.20 (1 H, d, *J* 2.74, $OCHPh$) and 7.23–7.36 (5 H, m, Ph); δ_C(125 MHz; $CDCl_3$; Me_4Si) 14.8, 19.7, 20.1, 30.4, 32.8, 39.0, 60.8, 63.7, 73.9, 99.8, 126.1, 127.7, 128.9, 141.2 and 174.1; *m*/*z* (EI) 292 (M^+, 7.9), 277 (10.8), 247 (37), 234 (10.1), 191 (82.6), 173 (72.0), 128 (100), 79 (41.1) and 45 (38.6%).

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