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ENANTIOSELECTIVE SYNTHESIS OF SITOPHILATE, THE GRANARY WEEVIL AGGREGATION PHEROMONE

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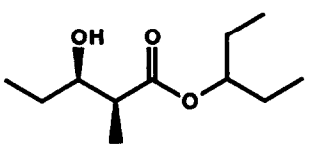
Abstract

Synthesis of each of the enantiomers of sitophilate, the male-produced aggregation pheromone of the granary weevil, is described. Catalytic asymmetric epoxidation of cis-allylic alcohol **2** *[with (+)-DIPT] followed by in situ derivatization with 3,5-dinitrobenzoyl chloride and subsequent recrystallization afforded* **3a** *in high enantiomeric and diastereomeric purity. Conversion to epoxy ester* **6a** *and regioselective C-2 opening with* Me_2CuLi *afforded (2S,3R)-sitophilate (***1a***) in 69% isolated yield (22% overall yield from* **2***) along with β-keto ester* **7**. *(2R,3S)-sitophilate (***1b***) was similarly prepared using (-)-DIPT in the initial step.*

Introduction

The granary weevil *[Sitophilus granarius (L.)]* is a commercially important pest of stored cereal grains. As part of a program to develop methods for the monitoring and control of this insect pest, Burkholder *et al*[1] have recently isolated a male-produced aggregation pheromone. They identified the major component of this pheromone as (R^*,S^*)-1-ethylpropyl 2-methyl-3-hydroxypentanoate (**1**) and proposed the name "sitophilate". While the relative stereochemistry of sitophilate was unambiguously determined to be *syn* (*erythro*), the absolute stereochemistry was not known. To identify the absolute stereochemistry of the natural pheromone and for bioassay studies, samples of both enantiomers of sitophilate with known absolute configurations were required. This paper describes the first enantioselective synthesis of (2R,3S) and (2S,3R)-sitophilate.



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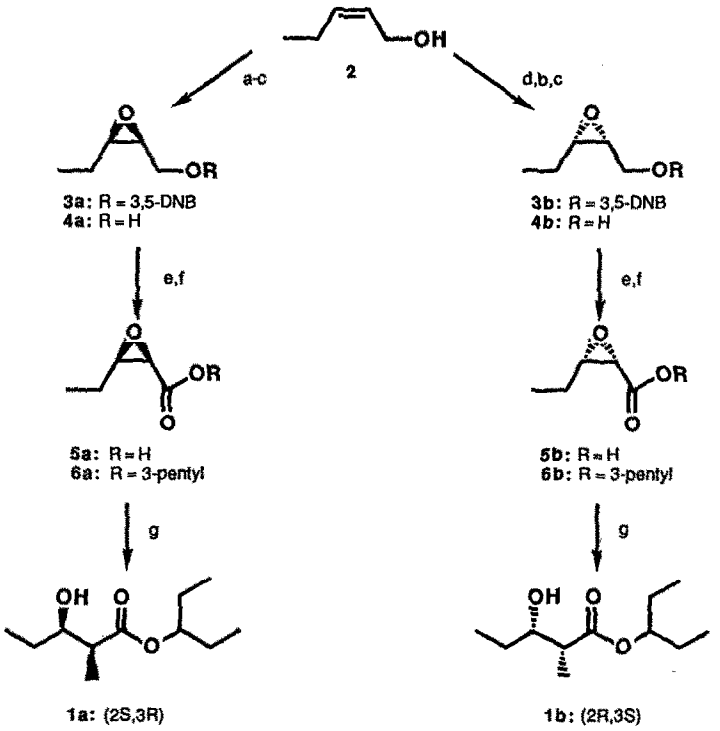
A cursory inspection of the structure of sitophilate suggested that both enantiomers should be readily accessible from either asymmetric aldol chemistry[2] or asymmetric epoxidation chemistry.[3] An interest in the regioselective opening of epoxy alcohol derivatives with organocuprates[4] biased a decision to implement Sharpless asymmetric epoxidation to install the required chiral centres. The proposed (and ultimately used) synthetic pathway is shown in Scheme I. It was anticipated that asymmetric epoxidation of *cis*-2-penten-1-ol (**2**) would proceed with 85-90% ee and that the optical purity of the epoxide could be raised by recrystallization of a suitable derivative. Elaboration to the epoxy ester **6** could then be carried out on optically pure material and methylcuprate opening of **6** would selectively provide each enantiomer of **1** (depending on which tartrate was used in the initial epoxidation).



Scheme I. a. $Ti(OiPr)_4$, L-(+)-DIPT, TBHP then 3,5-DNBCl, Et_3N; b. recrystallization; c. NaOH, THF-H_2O; d. same as a. but with D-(-)-DIPT; e. RuO_4, CCl_4-CH_3CN-H_2O; f. 3-pentanol, DCC, DMAP; g. Me_2CuLi, Et_2O.

Results and Discussion

Using the catalytic asymmetric epoxidation[3b] *cis*-allylic alcohol **2** was epoxidized (10 mol% $Ti(OiPr)_4$, 12 mol% (+)-DIPT, 4Å molecular sieves) and the epoxy alcohol was trapped *in situ* with 3,5-dinitrobenzoyl chloride. The dinitrobenzoate **3a** was readily isolated as a crystalline solid. Since the commercially-obtained *cis*-2-penten-1-ol contained ~10% of the *trans*-isomer[5], it was not surprising that the crude benzoate **3a** was contaminated with ~10% of another epoxide. Recrystallization of the crude material removed the undesired *trans*-isomer and the enantiomeric **3b** (~8%) to afford **3a** (52%) as pale yellow needles, mp 78-79°C. Hydrolysis of **3a** (1N NaOH, THF-H_2O) furnished epoxy alcohol **4a** (88%) which was > 98% enantiomerically pure. [Only signals for one diastereomer were observed in the ^1H NMR spectrum of the ester derived from (+)-MTPA-Cl.[6]]

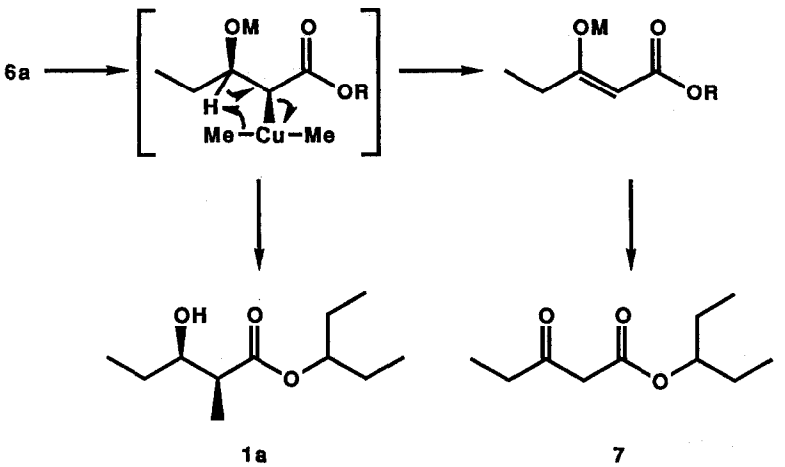
It might be noted that attempts to isolate **4a** directly from the epoxidation reaction were relatively unsuccessful with low (~30%) yields of product of moderate optical purity (~85% ee) being obtained. The low yields may be attributed to the water-solubility and volatility of the product, and appears to be a general problem for low molecular weight epoxy alcohols. The *in situ* derivatization procedure recently described by Sharpless[3b,7] seems to be a viable solution to this problem. These workers showed that *p*-nitrobenzoates (PNBs) of small epoxy alcohols are conveniently isolated (as crystalline materials) and are very useful as homochiral building blocks. Unfortunately, the PNB of **4a** did not readily crystallize from the reaction mixture; it was subsequently found that **4a**-PNB has a mp close to room temperature. In general, 3,5-dinitrobenzoates of alcohols have higher mp's than the corresponding PNBs[8], and this was reflected in the relative ease of isolation of **3a**. In fact, if one wants a crystalline derivative of an epoxy alcohol simply for ease of isolation, 3,5-DNBs may be preferable to PNBs.

Oxidation of **4a** to epoxy acid **5a** proceeded without incident using $NaIO_4$/cat. $RuCl_3$ in CCl_4-CH_3CN-H_2O[9,10]. Coupling of **5a** with 3-pentanol (DCC, cat. DMAP)[11] then furnished **6a** (69% from **4a**) to

set the stage for the final step: regioselective opening of **6a** with a methylcuprate reagent.

While the coupling of epoxides with organocopper reagents is a widely-used synthetic method[12], there are only a few examples of the opening of 2,3-epoxy esters (glycidic esters) with organocuprates.[4a,13-16] The available evidence suggests that reactions of organocuprates with unsubstituted glycidic esters[15] lead to exclusive opening at C-3 to afford α-hydroxyesters while 3-substituted glycidic esters[4a,13,14] afford β-hydroxyesters via ring-opening at C-2. It was thus anticipated that **6a**, being a 3-substituted glycidic ester, would react with Me_2CuLi to afford **1a**, the product of methyl substitution at C-2. In the event, reaction of **6a** with Me_2CuLi (2 equiv., Et_2O, -20°C) gave a mixture of 2 products in a 3:1 ratio. The major product (69% isolated yield) was indeed the expected C-2-opening product **1a** (which exhibited spectral data in good agreement with that published[1] for **1**); surprisingly, the minor product (25% isolated yield) was the β-keto ester **7**.

We are not aware of any reports of the formation of a β-keto ester from the reaction of a glycidic ester with an organocuprate.[17] However, ketones are often by-products of the reaction of epoxides with organocuprates, and, in retrospect, the formation of **7** from **6a** should not have been unexpected. In fact, the formation of both **1a** and **7** from **6a** may be rationalized by formation of a common intermediate[18] which then decomposes via either of two competing pathways (Scheme II). Formation of the putative copper (III) intermediate followed by reductive elimination would afford **1a** while proton transfer as shown (or through the intermediacy of a copper hydride) would give rise to a stable β-keto ester enolate. Thus it is possible that while two products are formed from the 3-substituted glycidic ester **6a**, both arise from attack at C-2.



Scheme II. Formation of **1a** and **7** from **6a**.

Attempts to increase the yield of **1a** by changing the reaction solvent (e.g. THF) or temperature (-78°C → 0°C), the source of MeLi (halide free or LiBr complex), the Cu source (CuBr • SMe_2, or CuI), and the use of various additives (e.g. Me_3SiCl,[19], MeI,[20], BF_3 • OEt_2,[21]) were uniformly unsuccessful, usually affording the same 3:1 product distribution. Nevertheless, a reasonable yield of **1a** could be isolated (69% from **6a**, 22% overall yield from **2**). Moreover, since epoxy alcohol **4a** was isolated in enantiomerically and diastereomerically-pure form, and since no loss of stereochemical integrity was expected in subsequent steps, it was expected that **1a** would be formed as a single isomer. Analysis of the 250 MHz ^1H NMR spectra of **1a** and its (+)-MTPA ester corroborated this expectation: only the signals for one isomer were observed in each case.

The enantiomer of **1a**, (2*R*,3*S*)-sitophilate (**1b**), was prepared from allylic alcohol **2** *via* a series of reactions identical to those described for the preparation of **1a** with the important exception that *D*-(-)-DIPT was used in the initial epoxidation step. As expected, the final product and all intermediates exhibited spectral characteristics identical to those of their enantiomeric counterparts except for the signs of their optical rotations. Also as expected, **1b** was isolated as a single isomer.

In summary, we have described a short route to either enantiomer of sitophilate in high enantiomeric and diastereomeric purity. These compounds are currently being assayed for biological activity with the granary

weevil by Drs. Burkholder and Phillips. The stereochemistry of the natural pheromone and bioassay studies with each of the two synthetic enantiomers will be reported in due course.

Experimental Section

General

All reactions were carried out with dry glassware under an atmosphere of argon unless otherwise noted. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone; CH_2Cl_2 was distilled from CaH_2. Methyllithium was obtained from Aldrich Chemical Co. Inc. and was titrated using the method of Gilman.[22] Other reagents were purchased from Aldrich Chemical Co., Inc. and were used without further purification except as noted below. Dialkyl tartrates were distilled (0.1 torr, Kugelrohr) before use. (+)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride was prepared from the corresponding acid by treatment with oxalyl chloride (3 equiv) and cat. DMF.[23] 3,5-Dinitrobenzoyl chloride was freshly prepared from the acid and excess thionyl chloride (reflux, 24h).[8] Thin layer chromatography was carried out on pre-coated glass plates (Merck 5715) while flash chromatography was performed using Merck 9385 silica gel (230-400 mesh) according to the method of Still.[24] ^1H and ^{13}C NMR spectra were recorded using Bruker AC-200 or AM-250 spectrometers. When $CDCl_3$ was used as solvent, tetramethylsilane (^1H, δ 0.0) or $CDCl_3$ (^{13}C, δ 77.0) were used as internal references ; when C_6D_6 was used, C_6D_5H (^1H,δ 7.15) or C_6D_6 (^{13}C, δ 128.0) were used as references. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer as neat liquids between salts (NaCl) or in $CHCl_3$ soluiton. Optical rotations were measured on a JASCO DIP-360 digital polarimeter. Mass spectra (EI) were obtained on a ZAB-E mass spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

(2*S*-*cis*)-3-Ethyloxiranemethanol 3,5-Dinitrobenzoate (3a).

A 500 mL 3-necked round-bottomed flask was charged with 5 g of powdered, activated 4A molecular sieves and dried with a hot gun while being purged with argon. Dry CH_2Cl_2 (200 mL) was then added and the slurry was cooled to -20°C. $Ti(OiPr)_4$ (2.853 g, 10.0 mmol), *L*-(+)-diisopropyl tartrate (DIPT, 2.987 g, 12.8 mmol), and *t*-butylhydroperoxide (TBHP, 45 mL of a 4.4 M CH_2Cl_2 solution freshly dried over 3A molecular sieves, 198 mmol) were then added sequentially and the mixture was stirred at -20 to -15°C for 1 h. The allylic alcohol **2** (8.60 g, 100 mmol) was then added slowly *via* syringe as a solution in 10 mL of dry CH_2Cl_2. The reaction mixture was allowed to stir at -15°C to -5°C for 10 h and then cooled to -25°C. [TLC on silica gel using petroleum ether-ethyl ether, 1:1 indicated that only traces of **2** (R_f = 0.37) remained after 5 h.] Excess TBHP was destroyed by the cautious dropwise addition of $P(OMe)_3$ (12.4 g, 100 mmol), taking care that the temperature did not rise above -20°C. The mixture was then treated with triethylamine (12.2 g, 120 mmol) and a solution of 3,5-dinitrobenzoyl chloride (23.1 g, 100 mmol) in 30 mL of CH_2Cl_2 and stirred for 1 h at 0°C. After filtration through a pad of Celite, the filtrate was diluted with 500 mL Et_2O and washed with 10% aqueous tartaric acid (2 x 50 mL), saturated $NaHCO_3$ (3 x 50 mL), and brine (2 x 50 mL). Drying ($MgSO_4$) and concentration (15 torr then 0.5 torr at 60°C) afforded a red solid (30.0 g). Analysis of the ^1H NMR spectrum of the solid indicated the presence of both the desired *cis*-epoxide (triplet at δ 1.12, major product) and the *trans*-epoxide (triplet at δ 1.06, ~10%). The solid was recrystallized five times from hexanes - EtOAc to afford 15.3 g (52%, > 98% ee by ^1H NMR analysis of the Mosher ester of the epoxy alcohol hydrolysate) of **3a** as pale-yellow needles. **3a**: mp 78-79°C; $[\alpha]_D^{24}$ -31.3° (c 2.0, $CHCl_3$); IR ($CHCl_3$) 3100, 3015, 1733, 1627, 1544, 1344, 1275 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.27 (t, 1H, J = 1.7 Hz), 9.21 (d, 2H, J = 1.7 Hz), 4.74 (dd, 1H, J = 3.8, 12.1 Hz), 4.41 (dd, 1H, J = 7.5, 12.1 Hz), 3.39 (ddd, 1H, J = 3.8, 4.3, 7.5 Hz), 3.11 (ddd, 1H, J = 4.3, 6.5, 6.5 Hz), 1.75-1.58 (m, 2H), 1.12 (t, 3H, J = 7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.30, 148.53, 133.21, 129.40, 122.48, 65.16, 57.58, 53.30, 21.30, 10.54; m/z 195(100), 179(5), 165(4), 149(12), 75(11). Anal. Calcd for $C_{12}H_{12}N_2O_7$: C, 48.65; H, 4.08; N, 9.46. Found: C, 48.84; H, 4.32; N, 9.53.

(2*R*-*cis*)-3-Ethyloxiranemethanol 3,5-Dinitrobenzoate (3b).

This compound was prepared as described for **3a** except that *D*-(-)-DIPT was used to prepare the epoxidation catalyst. From 8.60 g (100 mmol) of **2** there was obtained 14.8 g (50 mmol) of **3b** which was spectroscopically identical to **3a** with the exception of optical rotation: $[\alpha]_D^{24}$ + 31.2° (c 2.0, $CHCl_3$).

(2*S*-*cis*)-3-Ethyloxiranemethanol (4a).

To a solution of **3a** (5.21 g, 17.6 mmol) in 10 mL of THF at 0°C was added aqueous 1N NaOH (18 mL). The reaction mixture was allowed to warm to room temperature and was stirred for a further 30 min. Solid $NaHCO_3$ was added and the THF was removed *in vacuo* (30 torr). The residue was extracted with Et_2O (4 x 25 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). Drying ($MgSO_4$), concentration, and Kugelrohr distillation (air-bath temperature 85-95°C/30 torr) afforded epoxy alcohol **4a** as a clear colourless liquid (1.574 g, 88%, > 98% ee by ^1H NMR analysis of the ester derived from (+)-MTPA-Cl): $[\alpha]_D^{24}$ - 12.3° (c 2.0, $CHCl_3$); IR (film) 3400(br), 2971, 2935, 2877, 1456, 1042, 894 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.86 (A part of an ABX, 1H, J = 4.1, 12.1 Hz), 3.68 (B part of an ABX, 1H, J = 6.8, 12.1 Hz), 3.17 (ddd, 1H, J = 4.1, 4.3, 6.8 Hz), 3.01 (ddd, 1H, J= 4.3, 6.4, 6.4 Hz), 1.71-1.46 (m, 2H), 1.05 (t, 3H, J = 7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 60.62, 58.36, 57.12, 21.20, 10.53; m/z 103(18), 85(58), 75(100), 67(33). Anal. calcd for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 58.90; H, 9.92.

A small amount of **4a** was converted to the Mosher ester [(+)-MTPA-Cl, Et_3N, cat. DMAP] for analysis of ee by ^1H NMR (200 MHz, $CDCl_3$) spectroscopy. The signals for the CH_2O protons were distinctly different from those of the diasteeomer derived from **4b**. In each case these two protons gave rise to an 8-line pattern characteristic of the AB portion of an ABX system. **4a**: δ_A = 4.47, δ_B = 4.37, J_{AX} = 5.0 Hz, J_{BX} = 6.4 Hz, J_{AB} = 12.0 Hz. **4b**: δ_A = 4.50, δ_B = 4.36, J_{AX} = 4.9 Hz, J_{BX} = 6.6 Hz, J_{AB} = 12.0 Hz. In each case only the signals for a single diastereomer were observed.

(2*R*-*cis*)-3-Ethyloxiranemethanol (4b).

This compound was prepared from **3b** by alkaline hydrolysis as described for **4a**. Thus treatment of ester **3b** (1.387 g, 4.68 mmol) in 5 mL of THF with 5 mL of 1N NaOH followed by the indicated work-up provided alcohol **4b** (0.399 g, 84%) as a clear colourless liquid: $[\alpha]_D^{24}$ + 11.9° (c 2.0, $CHCl_3$).

(2*R*-*cis*)-3-Ethyloxiranecarboxylic acid (5a).

To a well-stirred mixture of **4a** (830 mg, 8.14 mmol) in CCl_4-CH_3CN-H_2O (6:6:9 mL) cooled in a water bath was added $RuCl_3 \cdot 3H_2O$ (64 mg, 0.24 mmol) and $NaIO_4$ (4.05 g, 18.9 mmol). The resulting green mixture was stirred at ambient temperature for 3 h. Extraction with ethanol-free Et_2O (4 x 50 mL) followed by drying ($MgSO_4$) and concentration of the combined ethereal extracts afforded 875 mg of the crude epoxy acid as a purple (traces of ruthenium salts) oil: IR (film) 3600-2400 (br), 2975, 1740, 1435, 1206, 937, 917 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.58 (d, 1H, J = 4.7 Hz), 3.21 (ddd, 1H, J = 4.7, 6.3, 6.3 Hz), 1.88-1.53 (m, 2H), 1.09 (t, 3H, J = 7.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.84, 59.04, 52.63, 20.63, 9.98. This crude acid was converted directly into ester **6a**.

1-Ethylpropyl (2*R*-*cis*)-3-Ethyloxiranecarboxylate (6a).

To a cold (0°C), stirred solution of acid **5a** (875 mg, 7.54 mmol) in 25 mL of dry CH_2Cl_2 was added sequentially 3-pentanol (997 mg, 11.3 mmol), 4-dimethylaminopyridine (DMAP, 92 mg, 0.75 mmol), and 1,3-dicyclohexylcarbodiimide (DCC, 1.711 g, 8.29 mmol). The resulting slurry was stirred at 0°C for 1 h then at room temperature for 3 h. Filtration through a cotton plug followed by concentration of the filtrate afforded a semi-solid. This material was suspended in petroleum ether-ethyl ether (PE-EE) 10:1 (5 mL) and the solid was removed by filtration. The concentrated filtrate was flash chromatographed on silica gel (70 g) using PE-EE, 10:1 as eluant, and the appropriate fractions (R_f = 0.39 using PE-EE, 5:1) were pooled and distilled (Kugelrohr air-bath temperature 70-75°C/0.2 torr) to afford **6a** (1.042 g, 5.60 mol, 69% from alcohol **4a**) as a clear colourless liquid: $[\alpha]_D^{24}$ + 11.1° (c 2.0, $CHCl_3$); IR (film) 2970, 2880, 1748, 1724, 1200 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.89 (quintet, 1H, J = 6.2 Hz), 3.52 (d, 1H, J = 4.6 Hz), 3.13 (dt, 1H, J = 4.6, 6.3 Hz), 1.85-1.51 (m, 6H), 1.04 (t, 3H, J = 7.5 Hz), 0.92 (t, 3H, J = 7.3 Hz), 0.88 (t, 3H, J = 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.94, 78.03, 58.40, 52.86, 26.27, 26.15, 20.62, 10.02, 9.40, 9.33; m/z 117(19), 116(83), 99(51), 71(100), 70(18). Anal. calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.67; H, 9.88.

1-Ethylpropyl (2*S*-*cis*)-3-Ethyloxiranecarboxylate (6b).

This compound was prepared from alcohol **4b** *via* acid **5b** as described above. From 360 mg (3.53 mmol) of **4b** there was obtained 459 mg (2.47 mmol, 70%) of ester **6b**: $[\alpha]_D^{24}$ -11.8° (c 2.1, $CHCl_3$). Other spectroscopic data were identical to that obtained for **6a**.

1-Ethylpropyl (2*S*,3*R*)-2-Methyl-3-hydroxypentanoate (1a)

To a cold (-20°C), stirred solution of Me_2CuLi prepared from CuBr • SMe_2 (989 mg, 4.81 mmol) and MeLi (8.68 mL of 1.11 M MeLi • LiBr in Et_2O, 9.63 mmol) in a total of 25 mL of Et_2O was slowly added a solution of ester **6a** (448 mg, 2.41 mmol) in 5 mL of dry Et_2O. The reaction was allowed to stir at -20°C for 2 h, and was then quenched with aqueous ammoniacal ammonium chloride (5 mL). The mixture was stirred vigorously at room temperature until a clear ethereal layer and a deep-blue aqueous layer formed (15 min.). The ethereal layer was washed with pH8 saturated NH_4Cl (3 x 10 mL), dried ($MgSO_4$), and concentrated to afford a colourless liquid (464 mg). Flash chromatography on silica gel (15 g) using PE-EE, 5:1 as eluant afforded 2 fractions. The less polar component (R_f = 0.29) was isolated as a colourless liquid (114 mg) and identified as the β-keto ester **7**: IR (film) 2970, 1735, 1711, 1310, 1250, 1060 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.81 (quintet, 1H, J = 6.2 Hz), 3.45 (s, 2H) 2.57 (q, 2H, J = 7.3 Hz), 1.63-1.51 (m, 4H), 1.09 (t, 3H, J = 7.3 Hz), 0.89 (t, 6H, J = 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.41, 167.17, 78.07, 49.30, 36.27, 26.34, 9.51, 7.54. This material was identical to a sample prepared by alkylation of the dianion of 1-ethylpropyl 3-oxobutanoate with MeI.[25]

The more polar component (R_f = 0.15) was distilled (Kugelrohr air-bath temperature 70-75°C/0.2 torr) to afford **1a** (336 mg, 69%) as a clear colourless liquid: $[\alpha]_D^{24}$ - 3.1° (c 1.7, $CHCl_3$); IR (film) 3450 (br), 2975, 2945, 1716, 1700, 1460, 1260, 1195, 1110 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.79 (quintet, 1H, J = 6.2 Hz), 3.81 (ddd, 1H, J = 3.5, 5.0, 7.5 Hz), 2.54 (dq, 1H, J = 3.5, 7.2 Hz), 1.65-1.40 (m, 6H), 1.18 (d, 3H, J = 7.2 Hz), 0.97 (t, 3H, J = 7.4 Hz), 0.89 (t, 6H, J = 7.4 Hz); ^1H NMR (200 MHz, C_6D_6) δ 4.82 (tt, 1H, J - 5.8, 6.7 Hz), 3.77 (dt, 1H, J = 8.5, 4.2 Hz), 2.39 (dq, 1H, J = 4.2, 7.2 Hz), 1.52-1.21 (m, 6H), 1.16 (d, 3H, J = 7.3 Hz), 0.89 (t, 3H, J = 7.3 Hz), 0.77 (t, 3H, J = 7.4 Hz), 0.75 (t, 3H, J = 7.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.26, 76.95, 73.18, 44.02, 26.66, 26.42, 26.37, 10.72, 10.38, 9.60, 9.56; ^{13}C NMR (63 MHz, C_6D_6) δ 175.81, 76.54, 73.43, 44.96, 27.47, 26.81, 26.76, 11.36, 10.58, 9.75, 9.71; m/z 144(6), 133(5), 115(56), 103(27), 97(5), 85(11), 74(100). Anal. calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.19; H, 11.12.

The ^1H and ^{13}C NMR spectra of **1a** in C_6D_6 agree very well with the literature data[1] for sitophilate.

Reaction of **1a** with (+)-MTPA-Cl (Et_3N, cat. DMAP, CH_2Cl_2) afforded a single diastereomer by ^1H NMR analysis (200 MHz, $CDCl_3$): δ 7.6-7.3 (m, 5H), 5.36 (q, 1H, J = 6Hz), 4.75 (quintet, 1H, J = 6.2 Hz), 3.55 (q, 3H, J = 1.2 Hz), 2.75 (dq, 1H, J = 5.5, 7.0 Hz), 1.75-1.52 (m, 6H), 1.18 (d, 3H, J = 7.1 Hz), 0.87, 0.86, 0.84 (3xt, 3H each, J = 7.4 Hz).

1-Ethylpropyl (2*R*,3*S*)-2-Methyl-3-hydroxypentanoate (1b)

This compound was prepared by reaction of epoxy ester **6b** with Me_2CuLi as described above. From 402 mg (2.16 mmol) of **6b** there was obtained 285 mg (1.44 mmol, 65%) of (2*R*,3*S*)-sitophilate (**1b**):$[\alpha]_D^{24}$ + 3.0 (c 1.5, $CHCl_3$).

Reaction of **1b** with (+)-MTPA-Cl (Et_3N, cat. DMAP, CH_2Cl_2) afforded a single diastereomer by ^1H NMR analysis (200 MHz, $CDCl_3$): δ 7.6-7.3 (m, 5H), 5.36 (q, 1H, J = 6Hz), 4.72 (quintet, 1H, J = 6 Hz), 3.55 (q, 3H, J = 1.2 Hz), 2.72 (quintet, 1H, J = 7 Hz), 1.81-1.49 (m, 6H), 1.11 (d, 3H, J = 7.1 Hz), 0.94 (t, 3H, J = 7.4 Hz), 0.86 (t, 3H, J = 7.5 Hz), 0.84 (t, 3H, J = 7.5 Hz).

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