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Diastereoselectivity in heterogeneous catalytic hydrogenation of Baylis–Hillman adducts. Total synthesis of (±)-sitophilate

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Abstract—We describe herein a highly diastereoselective total synthesis of racemic sitophilate, based on the results obtained in a diastereoselective heterogeneous catalytic hydrogenation reaction of a set of Baylis–Hillman adducts originating from aliphatic aldehydes.

1. Introduction

In the last few years the Baylis–Hillman reaction[1–4] has attracted the attention of many organic chemists, because it is a simple and straightforward method to generate a new carbon–carbon σ bond. It may be broadly defined as a coupling reaction between the α-position of activated alkenes and electron-deficient sp^2 carbon atom, for instance an aldehyde carbonyl group. The reaction is usually catalyzed by DABCO (1,4-diazabicyclo [2.2.2.] octane) or a phosphine.

In the course of a research directed towards the utilization of the Baylis–Hillman adducts[5–7] in organic synthesis, we decided to explore some of these adducts as starting materials for the preparation of (±)-sitophilate (**1**, Fig. 1), which is the aggregation pheromone produced by the male of the granary weeevil *Sitophilus granarius* (L.).[8,9] This insect, a cosmopolitan pest of stored cereal grains, causes millions of dollars in loses annually.

Sitophilate (**1**) is a β-propionate bearing two chiral centers (2*S*,3*R*). Biological studies made with **1** have demonstrated that the racemic mixture is comparable to the naturally produced pheromone in attracting male and female granary weevils.[9] However, the synthetic *anti* diastereoisomer **2** (Fig. 1, racemic or enantiomerically pure) is significantly less attractive. These biological profiles clearly indicate that control of the absolute configuration is apparently unnecessary, however a *syn* relationship between the methyl and hydroxyl groups is indeed essential for the biological activity of this pheromone.

Sitophilate (**1**) could be employed as a naturally occurring biological attractants, avoiding the utilization of large amount of contact insecticide and fumigants as well as the environmental problem associated with their use.[10,11]

Due to the biological activity of this pheromone, there are several reports in literature concerning to the racemic and asymmetric syntheses of **1**.[9,12–21] Unfortunately the majority of them did not lead to a suitable *syn* isomer, requiring an additional Mitsonobu reaction, in order to cause the configurational inversion of the center which bears the hydroxyl group, or a separation of diastereoisomers followed by a Mitsonobu reaction, in order to recycle the *anti* diastereoisomer.

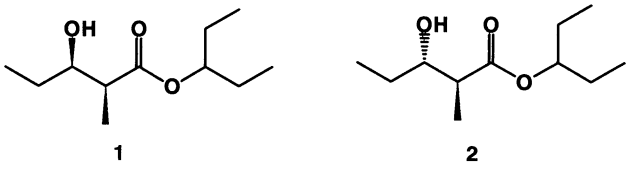
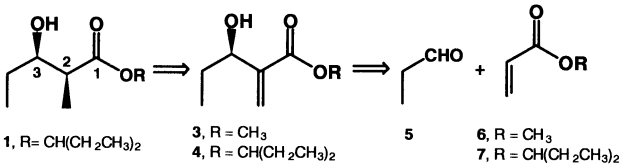


Figure 1. Sitophilate (**1**) and its diastereoisomer (**2**).



Scheme 1. Retrosynthetic analysis to sitophilate.

Keywords: sitophilate; Baylis–Hillman reaction; diastereoselective hydrogenation.
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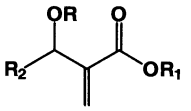


3, R=H; R_1= CH_3; R_2= ethyl
4, R=H; R_1= $CH(CH_2CH_3)_2$; R_2= ethyl
8, R= TBS; R_1= CH_3; R_2= ethyl
9, R= TBS; R_1= $CH(CH_2CH_3)_2$; R_2= ethyl
10, R, R_1= H; R_2= ethyl
11, R= TBS; R_1= H; R_2= ethyl
12, R= H; R_1= CH_3; R_2= propyl
13, R= TBS; R_1= CH_3; R_2= propyl
14, R, R_1= H; R_2= propyl
15, R= H; R_1= CH_3; R_2= butyl
16, R= TBS; R_1=CH_3; R_2= butyl
17, R, R_1= H; R_2= butyl

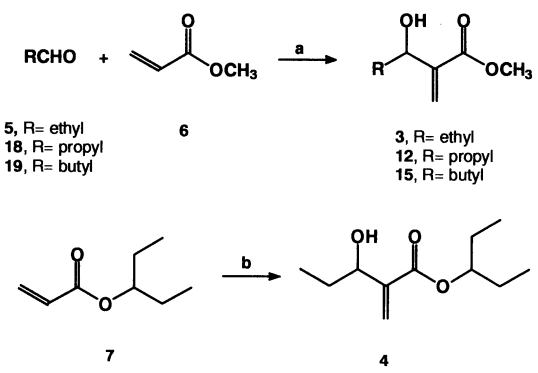
Figure 2. Starting materials chosen for hydrogenation study.

From our point of view (±)-sitophilate could be readily synthesized from Baylis–Hillman adduct as **3** or **4**, by a stereoselective hydrogenation of a double bond (Scheme 1).

To achieve our goal is was necessary to have a highly *syn* diastereoselective hydrogenation reaction. The literature contains several papers[22–28] reporting the utilization of homogeneous catalytic hydrogenation of Baylis–Hillman adducts. Depending on the experimental conditions this hydrogenation reaction provides the *anti* diastereoisomers, with a high degree of diastereoselectivity and the *syn* diastereoisomer with moderate to excellent diastereoselectivity.[28] In contrast there is only one report[29] concerning the use of the hetereogeneous catalyst, where no diastereoselectivity has been observed.

In a study on the heterogeneous catalytic hydrogenation of Baylis–Hillman adducts derived from aromatic aldehydes,[6] we demonstrated that it was possible to obtain the *syn* isomer with a high degree of diastereoselectivity. Based on these prior results we have undertaken an additional study focused on the diastereoselectivity of the heterogeneous catalytic hydrogenation with Baylis–Hillman adducts originating from aliphatic aldehydes. Depending on the ratio of diastereoselectivity observed, this strategy will be used as a key step in the total synthesis of (±)-sitophilate.

To evaluate a possible influence of free or protected hydroxyl groups on the facial preference of hydrogen addition, we selected the investigation of the substrates **3**, **4**, **8**–**17** (Fig. 2). Depending on the degree of diastereoselectivity attained, the compounds **3**, **4**, **8**–**11** should be readily transformed into (±)-sitophilate (**1**) in few steps.



Scheme 2. Baylis–Hillman reaction with aliphatic aldehydes. *Reagents and conditions*: (a) DABCO, room temperature, 5–7 days; (b) CH_3CH_2CHO, DABCO, CH_3CN, ultrasound, 8 days, 43%.

Table 1. Propionaldehyde and 3-pentyl acrylate in Baylis–Hillman reactions

Entry	Conditions[a]	Time (days)[b]	Yield (%)[c]
1	A: rt, CH_2Cl_2	7	20
2	B: Δ, CH_2Cl_2	4[c]	<20[d]
3	C: 0°C, CH_2Cl_2	7	10
4	D: ultrasound, CH_2Cl_2	8	30
5	E: ultrasound, CH_3CN	8	44

[a] DABCO was used as catalyst.
[b] Time after which the reaction mixture no longer evolved.
[c] Isolated yield based on acrylate, after purification by column chromatography.
[d] Analysis by TLC showed a complex mixture of products and the reaction became dark.

At first sight, it was logical to consider adduct **4** (Scheme 1) as the most suitable for our needs, however there are some considerations to be observed. The preparation of adduct **4** is not obvious. Cheskis et al.[14] have described difficult experimental conditions (pressure of 500 MPa at 50°C) to obtain **4**. We were interested in establishing a synthetic strategy which could be easily scaled up, and the Cheskis' conditions were not adequate for our needs.

In this paper we describe our results aiming at a study on the diastereoselectivity of the heterogeneous catalytic hydrogenation of Baylis–Hillman adducts originating from aliphatic aldehydes and their utilization in a simple and highly diastereoselective total synthesis of racemic sitophilate (**1**).

2. Results and discussion

2.1. Preparation of Baylis–Hillman adducts

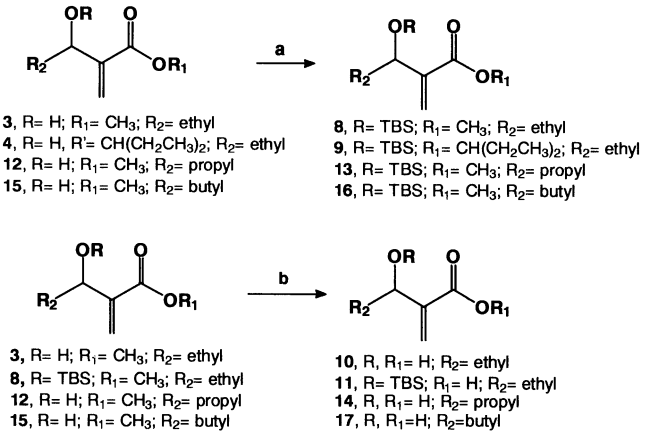
Propionaldehyde (**5**)[27], butyraldehyde (**18**)[30] and valeraldehyde (**19**) were treated with methyl acrylate in presence of DABCO to afford adduct **3**, **12** and **15** in 70, 60 and 74% yield, respectively (Scheme 2).

To prepare **4**, it was first necessary to obtain 3-pentyl acrylate (**7**, Scheme 2), which was easily prepared in 72% yield by the treatment of acryloyl chloride with 3-pentanol in dichloromethane.

In a series of additions of benzaldehyde to alkyl acrylates, Caubère et al.[31] observed that the time required after which no more products are formed increases with steric bulk of the alcohol. Therefore, acrylates derived from secondary alcohols are less reactive than primary ones.

Having in mind our interest to develop an easier way to prepare the adduct **4** and, based on the Caubère observation, we have submitted acrylate **7** to the Baylis–Hillman reaction with propionaldehyde (Scheme 2) under different conditions (A, B, C, D and E). The results obtained are shown in Table 1.

As we can see in Table 1, the use of ultrasound technique with CH_3CN as solvent (condition E, entry 5) provided the best yield of the required product.

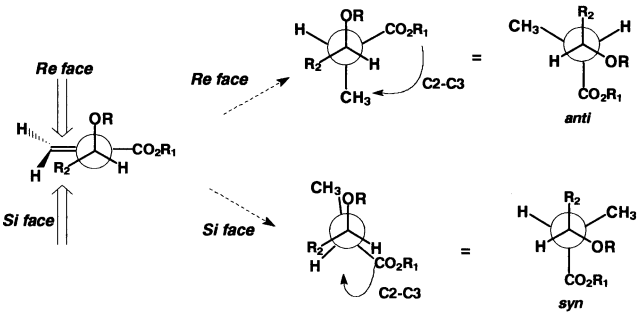


Scheme 3. Hydroxyl group protection and ester hydrolysis of the Baylis–Hillman adducts. *Reagents and conditions*: (a) TBDSCl, DMF, imidazole, rt; **3→8**, 12 h, 78%; **4→9**, 16 h, 78%; **12→13**, 77%; **15→16**, 80%; (b) (i) **3→10**, LiOH–H_2O/THF, 0°C→rt, 18 h, 61%; (ii) **8→11**, LiOH–H_2O/THF, 0°C, then methanol, 0°C→rt, 20 h, 72%; **12→14** 24 h, 95%; **15→17**, 20 h, 70%.

2.2. Preparation of *t*-butyldimethylsilyl derivatives 8, 9, 13, 16 and acids 10, 11, 14, 17

Using a standard procedure[32] the adducts **3**, **4**, **12** and **15** were converted into their *O*-*t*-butyldimethylsilylethers **8**, **9**, **13** and **16**, respectively, in good yields (Scheme 3).

Acids **10**, **14** and **17** were obtained by treatment of ester **3**, **12** and **15** with LiOH in THF–H_2O (Scheme 3). Our first attempts to hydrolyze ester **8** led to acid **11** in only 20% yield. Addition of methanol to the reaction medium increased the chemical yield to 72%.



Scheme 4. Rationalization for the diastereoselectivity observed.

2.3. Catalytic heterogeneous hydrogenation

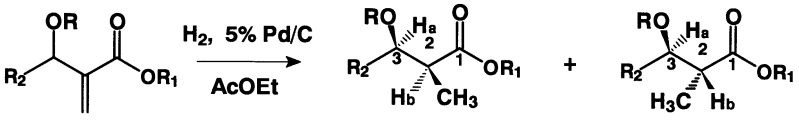
Hydrogenation experiments were carried out in ethyl acetate under atmospheric pressure with the adducts **3**, **4**, **8**–**17**, employing 5% Pd/C as catalyst. The results obtained are summarized in Table 2.

The relative stereochemistry (C2/C3) of the products were determined by using ^{1}H- and ^{13}C NMR spectroscopy. The vicinal constant coupling (*J*) for *syn* diastereoisomer varying between 5.9–6.32 Hz and 7–9 Hz for the *anti* one.[33]

The stereochemical outcome of this hydrogenation reactions can be rationalized based on a conformation in which the alkyl substituent occupies the inside position and the carbon–oxygen bond is perpendicular to the π bond. This reduces any destablizing interaction between the alkyl substituents and the carboxyl group (Scheme 4).[34,35]

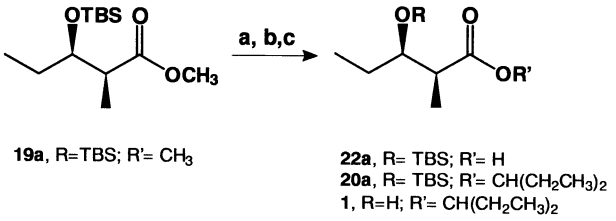
In the case of the free alcohols we have two distinct groups.

Table 2. Heterogeneous catalytic hydrogenation of the Baylis–Hillman adducts



Entry	Adducts	Product	Yield (%)[a]	*syn*/*anti* Ratio[b]
1	**3**, R=H; R_1=CH_3; R_2=ethyl	**18a**,**b**	90	50:50
2	**4**, R=H; R_1=$CH(CH_2CH_3)_2$; R_2=ethyl	**1a**,**b**	81	50:50
3	**8**, R=TBS; R_1=CH_3; R_2=ethyl	**19a**,**b**	82	100:0
4	**9**, R=TBS; R_1=$CH(CH_2CH_3)_2$; R_2=ethyl	**20a**,**b**	80	33:67
5	**10**, R=R_1=H; R_2=ethyl	**21a**,**b**	71	63:37
6	**11**, R=TBS; R_1=H; R_2=ethyl	**22a**,**b**	82	75:25
7	**12**, R=H; R_1=CH_3; R_2=propyl	**23a**,**b**	76	30:70
8	**13**, R=TBS; R_1=CH_3; R_2=propyl	**24a**,**b**	73	95:5
9	**14**, R=R_1=H; R_2=propyl	**25a**,**b**	81	60:40
10	**15**, R=H; R_1=CH_3; R_2=butyl	**26a**,**b**	71	40:60
11	**16**, R=TBS; R_1=CH_3; R_2=butyl	**27a**,**b**	76	95:5
12	**17**, R=R_1=H; R_2=butyl	**28a**,**b**	78	63:37

[a] Yield for isolated products.
[b] Determined by gas chromatography (GC-HP5 column) and ^{1}H- (300 MHz) and ^{13}C NMR (75.4 MHz).



Scheme 5. Synthesis of racemic sitophilate. *Reagents and conditions*: (a) LiOH, MeOH–H_2O (3:1), 20 h, rt, 75%; (b) 3-pentanol, DMAP, DCC, CH_2Cl_2, 4 h, 0°C→rt, 89%; (c) HF, CH_3CN, rt, 1 h, 80%.

In the first one, we have used the Baylis–Hillman adducts itself (Table 2, entries 1, 2, 7 and 10). In the other, the hydrolysed adducts were used as substrates (Table 2, entries 5, 9 and 12). In the first group we have observed no diastereoselectivity (entries 1 and 2) or a poor *anti* diastereoselectivity (entries 7 and 10). In the first examples (entries 1 and 2), the presence of an ethyl group (R_2) or a bulk ester residue apparently has no influence in the face diastereoselection of the double bond. However, when we increase the size of R_2 group the delivery of hydrogen occurs with a moderate preference by the *Re* face, which give the *anti* diastereoisomer as the major product (entries 7 and 10).

For the hydrolysed Baylis–Hillman adducts (entries 5, 9 and 12) we have observed a poor *syn* diastereoselectivity. Probably this result is due to the formation of an internal hydrogen bond between the hydroxyl group and the acid carboxyl group which should contribute to facilitate the delivery of the hydrogen by the *Si* face of the double bond.

To all silylated esters and acids (entries 3, 6, 8 and 11) the presence of the silyl group blocks the *Re* face, directing the delivery of the hydrogen preferentially by the *Si* face to yield the *syn* diastereoisomer (Scheme 4). An exception to this diastereoselectivity was observed with the 3-pentyl ester (entry 4). Probably the presence of a bulk ester residue associated with a large silyl protecting group should lead to an arrangement where there is a preference for the delivery of the hydrogens by the *Re* face to furnish the *anti* diastereoisomer with a poor diastereoselectivity.

The high diastereoselectivity observed for all silylated methyl esters seems to be general to these compounds. These results are similar to that observed by us with aromatic aldehydes.[6]

To demonstrate the synthetic potentiality of this simple methodology the reduced ester **19a** was used as substrate in the total synthesis of racemic sitophilate (**1**). Thus, ester **19a** was treated with LiOH in the presence of a mixture of MeOH–H_2O (3:1) to furnish the silyl-acid **22a** in 75% yield. This acid was then esterified with 3-pentanol in the presence of catalytic DMAP and DCC in dichloromethane to give the ester *syn*-**20a** in 89% yield. Finally, deprotection of the hydroxyl group of **20a** with HF in acetonitrile gave (±)-sitophilate (**1**), as a homogeneous product (Scheme 5).

All the spectral data of this compound were identical to those described in literature for the natural product.

3. Conclusion

In conclusion, this simple and highly diastereoselective heterogeneous hydrogenation methodology of silylated Baylis–Hillman should be considered a simple alternative to the aldolic condensation with propionate derivatives as well as for the homogeneous catalytic hydrogenation reaction of Weinreb amides.[28]

This straightforward strategy has permitted us to synthesize sitophilate in its racemic form, in six steps and with a 22% overall yield. Due to the high degree of diastereoselectivity attained in the heterogeneous hydrogenation step, this strategy avoids the utilization of a Mitsonobu reaction to recycle the *anti* diastereoisomers. It was also possible to demonstrate the synthetic potentiality of the Baylis–Hillman adduct as cheap starting material for the synthesis of natural products. Efforts to extend this simple methodology to the synthesis of natural products structurally related to sitophilate are ongoing in our laboratory.

4. Experimental

4.1. General

The ^1H- and ^{13}C NMR spectra were recorded on a Varian GEMINI BB-300 at 300 and 75.4 MHz, respectively. The ^1H spectra were also recorded on an AW-80 Bruker at 80 MHz and an Inova instrument at 500 MHz. The mass spectra were recorded using a HP model 5988A GC/MS with a High Resolution Autospec-Micromass/EBE. Manipulations and reactions were not performed under dry atmospheres or employing dry solvents, unless otherwise specified. In those cases CH_2Cl_2, DMF and triethylamine were dried over CaH_2 and distilled. Purification and separations by column chromatography were performed on silica gel, using normal or flash chromatography. TLC visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. All the Baylis–Hillman reactions were sonicated in an ultrasonic cleaner (81 W, 40 MHz). Acryloyl chloride was purchased from Aldrich. All the hydrogenation reactions were carried out at atmospheric pressure.

4.2. General procedure for the preparation of Baylis–Hillman adducts 3, 12 and 15

A mixture of freshly distilled aliphatic aldehyde (280 mmol), methyl acrylate (190 mmol) and DABCO (9 mmol), was sonicated for 5–7 days and then diluted with dichloromethane (50 cm^3). The organic solution was washed with 10% aqueous HCl (2×20 cm^3), concentrated under reduced pressure and dried over $MgSO_4$. After filtration and solvent removal, the product was purified by column chromatography on silica gel using hexane–ethyl acetate, 2:1 v/v as eluent.

4.2.1. Methyl 3-hydroxy-2-methylene-pentanoate (3). (19.2 g, 70%). IR (ν_{max}/neat) 3473 (O–H), 2966, 2937, 2879, 1716 (C=O), 1633 (C=C), 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.2 (br s, 1H), 5.7 (br s, 1H), 4.3 (t, J=7 Hz, 1H), 3.8 (s, 3H), 3.4 (br s, 1H), 1.8–1.3 (m, 2H),

0.9 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.6 (C=O), 142.1, 124.6, 72.3, 51.5, 29.0, 9.8; Calcd for $C_7H_{12}O_3$ C 58.34; H 8.33%; Found C 58.30; H 8.32.

4.2.2. Methyl 3-hydroxy-2-methylene-hexanoate (12). (18 g, 60%). IR (ν_{max}/neat) 3600 (O–H), 3500, 2980, 2940, 2850, 2100, 1700 (C=O), 1620 (C=C), 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (t, J= 1 Hz, 1H), 5.80 (t, J=1 Hz, 1H), 4.43 (q, J=7 Hz, 1H), 3.78 (s, 3H), 2.72 (br d, J=6.5 Hz, 1H, OH), 1.75–1.2 (m, 4H), 0.9 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.7 (C=O), 142.4, 124.6, 71.2, 60.3, 38.3, 19.0, 13.8; Calcd for $C_8H_{14}O_3$ C 60.74; H 8.92%; Found C 60.68; H 8.90.

4.2.3. Methyl 3-hydroxy-2-methylene-heptanoate (15). (24.18 g, 74%). IR (ν_{max}/neat) 3600 (O–H), 3500, 2980, 2850, 2100, 1705 (C=O), 1620 (C=C), 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (t, J=1 Hz, 1H), 5.80 (t, J=1 Hz, 1H), 4.43 (t, J=6.5 Hz, 1H), 3.77 (s, 3H), 2.70 (br s, 1H, OH), 1.75–1.2 (m, 4H), 0.9 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.7, 142.4, 124.7, 71.5, 51.8, 35.9, 27.9, 22.5, 14.0; Calcd for $C_9H_{16}O_3$ C 62.77; H 9.36%; Found C 62.72; H 9.35.

4.2.4. 3-Pentyl acrylate (7). To a stirred solution of 3-pentanol (5.0 g, 56.81 mmol) in dry CH_2Cl_2 (25 cm^3), at 0°C, under nitrogen, were added dry triethylamine (8.3 cm^3, 11.52 g, 113.84 mmol), followed by acryloyl chloride (5.13 g, 4.6 cm^3, 57.0 mmol). After 30 min, the mixture and washed with water (20 cm^3). The aqueous layer was back-extracted with dichloromethane (2×20 cm^3) and was warmed to room temperature, diluted with CH_2Cl_2 (20 cm^3) and the combined organic extract washed with brine (3×10 cm^3). After drying over $MgSO_4$ and filtration, the solution was concentrated to furnish 5.82 g (72%) of acrylate **7**, which showed a single spot on TLC and satisfactory NMR data. 3-Pentyl acrylate was employed in the Baylis–Hillman reaction without additional purification. Bp 47°C (15 mmHg) [lit.[14] 46°C (15 mmHg)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.35 (dd, J=17 and 1.5 Hz, 1H), 6.13 (dd, J=17.5 and 6.9 Hz, 1H), 5.81 (dd, J=6.1 and 1.5 Hz, 1H), 4.84 (quintet, J=6.6 Hz, 1H), 1.66–1.56 (m, 4H), 0.97–0.87 (m, 6H); Calcd for $C_8H_{14}O_2$ C 65.75; Found C 65.71; H 9.56.

4.2.5. 1-Ethylpropyl 3-hydroxy-2-methylenepentanoate (4). A solution of 3-pentyl-acrylate (3.11 g, 21.93 mmol), propionaldehyde (1.65 g, 28.51 mmol) and DABCO (1.59 g, 14.25 mmol) in 12 cm^3 of acetonitrile, was sonicated for 8 days, then diluted with ethyl acetate (120 cm^3) and sequentially washed with water (3×30 cm^3), 1% aq. NaOH (4×30 cm^3), water (3×30 cm^3) and brine (2× 30 cm^3). The organic solution was dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish 1.95 g (44%) of **4**, as a slightly yellow oil. The ^{1}H NMR analysis of the crude product revealed that it was at least 95% pure and it was used for the hydrogenation step without any additional purification. Bp 70°C (2 mmHg) [lit.[14] 70°C (2 mmHg)]; IR (ν_{max}/Film): 3440 (O–H), 2970, 2939, 2881, 1709 (C=O), 1628 (C=C), 1462 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (d, J=1.5 Hz, 1H), 5.76 (t, J= 1.4 Hz, 1H), 4.87 (quintet, J=6.6 Hz, 1H), 4.33 (q, J=5.9 Hz, 1H), 2.8 (d, J=5.8 Hz, 1H), 1.75–1.58 (m, 6H), 0.98–0.88 (m, 9H); MS (70 eV, m/z) 200 (M^+), 171, 136, 130, 121, 119, 113, 112, 111, 102, 101, 95, 93; Calcd for $C_{11}H_{20}O_3$ C 65.83; H 10.19%; Found C 65.78; H 10.09.

4.3. General procedure for the protection of Baylis–Hillman adducts as *tert*-butyldimethylsilyl ethers (preparation of 8, 9, 13 and 16)

A mixture of 1 mmol of the adduct (**3**, **4**, **12** and **15**), 1.3 mmol of *tert*-butyldimethylsilyl chloride, 2.5 mmol of imidazole and 0.3 cm^3 of dry *N*,*N*-dimethylformamide was stirred at room temperature, under nitrogen, for 12 (adduct **3**), 16 (adduct **4**) and 24 h (adducts **12** and **16**), then quenched with 10 cm^3 of hexane. After washing with brine (3×5 cm^3), drying over $MgSO_4$ and evaporation, the residue obtained was purified by column chromatography on silica gel (eluent indicated for each adduct).

4.3.1. Methyl 3-*tert*-butyldimethylsilyloxy-2-methylene-pentanoate (8). Eluent: hexane–ethyl acetate, 90:10 v/v. (0.209 g, 78% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.23 (d, J=1.5 Hz, 1H), 5.91 (d, J=1.5 Hz, 1H), 4.56 (t, J= 5.1 Hz, 1H), 3.74 (s, 3H), 1.70–1.79 (m, 1H), 1.52–1.41 (m, 1H), 0.91 (t, J=6.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 143.7, 124.6, 71.0, 51.6, 30.3, 25.8, 25.7, 25.6, 18.1, 9.1, −4.89, −4.83; Calcd for $C_{13}H_{36}O_3Si$ C 58.20; H 13.43%; Found C 58.17; H 13.41.

4.3.2. 1-Ethylpropyl-3-*tert*-butyldimethylsilyloxy-2-methyl-enepentanoate (9). Eluent: hexane–ethyl acetate, 90:10 v/v. (0.289 g, 78% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (d, J=1.8 Hz, 1H), 5.86 (t, J=1.8 Hz, 1H), 4.57 (quintet, J=6.2 Hz, 1H), 4,57 (dd, J=5.9 and 4.8 Hz, 1H), 1.69–1.45 (m, 6H), 0.92–0.83 (m, 18H); 0.06 (s, 3H), −0.01 (s, 3H).

4.3.3. Methyl-3-*tert*-butyldimethylsilyloxy-2-methylene-hexanoate (13). Eluent: hexane–ethyl acetate, 95:5 v/v. (0.209 g, 77% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (br s, 1H), 5.86 (t, J=1.8 Hz, 1H), 4.57 (quintet, J=6.2 Hz, 1H); 4,57 (dd, J=5.9 and 4.8 Hz, 1H), 1.69–1.45 (m, 6H), 0.92–0.83 (m, 18H), 0.06 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.6 (C=O), 144.0, 124.2, 70.1, 51.6, 40.2, 25.9, 18.4, 18.2, 14.1, −4.5, −4.9H.

4.3.4. Methyl-3-*tert*-butyldimethylsilyloxy-2-methylene-heptanoate (16). Eluent: hexane–ethyl acetate, 95:5 v/v. (0.229 g, 80% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (br s, 1H), 5.91 (br s, 1H), 4.49 (m, 1H), 3.76 (s, 3H), 1.64–1.24 (m, 6H), 0.91 (s, 12H, $SiC(CH_3)_3$+CH_3 terminal), 0.06 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 166.6 (C=O), 144.0, 124.2, 70.2, 51.6, 37.6, 27.2, 25.9, 25.7, 22.6, 18.2, 17.1, 14.1, −4.5, −4.9.

4.4. General procedure for the preparation of acids 10, 14 and 17

To a stirred solution of Baylis–Hillman adducts **3**, **12** and **15** (2.0 mmol) was added, at room temperature, a solution of lithium hydroxide (3.1 mmol) in 15 cm^3 of THF. The resulting mixture was stirred at room temperature and then

washed with $CHCl_3$ (2×10 cm^3). The aqueous phase was acidified until pH 1 and extracted with ethyl acetate (5×10 cm^3). The combined organic phase (ethyl acetate) was washed with brine (6×15 cm^3), dried over $MgSO_4$ and evaporated. The residue obtained was filtered through a pad of silica gel (eluent indicated for each adduct).

4.4.1. 3-Hydroxy-2-methylenepentanoic acid (10). Eluent: hexane–ethyl acetate, 1:1 v/v (0.146 g, 61% yield, colorless oil). IR (ν_{max}/Film): 3427, 2623, 1705, 1630, 1427, 1277, 1101, 980 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 6.8 (br, 1H), 5.9 (br, 1H), 5.4 (br, 1H), 4.7 (t, J=7 Hz, 1H), 2.1–1.4 (m, 2H), 0.95 (t, J=7 Hz, 3H).

4.4.2. 3-Hydroxy-2-methylenehexanoic acid (14). Eluent: hexane–ethyl acetate, 1:1 v/v (0.273 g, 95% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.18 (br s, 1H, exchangeable with D_2O), 6.36 (s, 1H), 5.89 (s, 1H), 4.45 (t, J=6.5 Hz, 1H, exchangeable with D_2O), 3.78 (m, 1H), 1.75–1.22 (m, 4H), 0.93 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 170.5 (C=O), 141.7, 126.8, 67.8, 38.2, 19.0, 13.8.

4.4.3. 3-Hydroxy-2-methyleneheptanoic acid (17). Eluent: hexane–ethyl acetate, 1:1 v/v (0.271 g, 86% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.17–6.42 (br s, 1H, exchangeable with D_2O), 6.36 (d, J=1.1 Hz, 1H), 5.89 (br s, 1H), 4.42 (t, J=6.6 Hz, 1H, exchangeable with D_2O), 3.80 (m, 1H), 1.80–1.20 (m, 6H), 0.90 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 170.7 (C=O), 141.7, 127.0, 71.5, 35.8, 27.9, 22.5, 14.0.

4.4.4. 3-*tert*-Butyldimethylsilyloxy-2-methylenepentanoic acid (11). An aqueous solution of lithium hydroxide (3 mol L^{-1}, 4.1 cm^3, 12 mmol) was added dropwise to a stirred and cooled solution of silyl ester **8** (0.65 g, 2.5 mmol) in tetrahydrofuran (10 cm^3) at 0°C. Then methanol (10 cm^3) was added and the mixture was kept under stirring for 20 h at room temperature. The solution was acidified to pH=4 with 3 mol L^{-1} aqueous HCl solution. It was then extracted with ether (5×10 cm^3). The ethereal solution was washed with brine (5×10 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure. The crude acid was used in the hydrogenation step without any additional purification. (0.442 g, 72% yield). IR (ν_{max}/Film): 3430, 1715, 1630, 980 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 6.8 (br, 1H), 5.35 (br, 1H), 4.7 (t, J=7 Hz, 1H), 2.1–1.4 (m, 2H), 0.95 (t, J=7 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); Calcd for $C_{12}H_{34}O_3Si$ C 56.69; H 13.38%; Found C 56.65; H 13.36.

4.5. General procedure for the hydrogenation of Baylis–Hillman adducts

To a suspension of 5% Pd–C (10 mol%) in ethyl acetate (5 cm^3) was added under nitrogen a solution of the adduct (1 mmol) in ethyl acetate (5 cm^3). Then the reaction atmosphere was changed to hydrogen and the reaction mixture was stirred at room temperature. After a period for reaction completion (indicated for each adduct), the suspension was filtered over a pad of celite and the solvent removed under reduced pressure.

4.5.1. 1′Ethylpropyl-3-hydroxy-2-methylpentanoate (1a/b). Reaction time: 90 min; (81% of a 1:1 diastereomeric mixture). Spectral data for *anti* diastereoisomer **1b**: bp 98–100°C (4 mmHg) [lit.[6] 99–100°C (4 mmHg)]; IR (ν_{max}/neat): 3440, 2970, 2933, 2881, 1709, 1628, 1462, 1385, 1273, 1172, 1093, 984, 926, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (quintet, J=6.9 Hz, 1H, C*H*CH_2CH_3), 3.79–3.75 (m, 1H; C*H*OH), 3.49–3.46 (m, 1H), 2.76 (br, 1H), 2.68–2.47 (m, 1H), 1.64–1.44 (m, 6H), 1.23 and 1.19 (d, J=7.3 Hz and d, J=7.3 Hz, respectively, 3H), 0.99 and 0. 89 (t, J=7.3 Hz and t, J=7.3 Hz, respectively, 6H); Calcd for $C_{17}H_{36}O_3Si$ C 64.30, H 11.46; Found C 64.22; H 11.50.

4.5.2. Methyl 2-methyl-3-hydroxypentanoate (18a/b). Reaction time: 16 h; (90% of a 1:1 diastereoisomeric mixture). ^1H NMR (300 MHz, $CDCl_3$) δ 3.98–3.97 (m, 1H, C*H*OH), 3.91 (s, 3H, OC*H*$_3$), 2.82–2.70 (m, 1H, C*H* C=O), 1.41–1.36 (m, 2H, C*H*$_2$CH$_3$), 1.15 (d, J=7.3 Hz, 3H, C*H*$_3$CH).

4.5.3. Methyl 2-methyl-3-*tert*-butyldimethylsilyloxypentanoate (19a). Reaction time: 48 h; (82% of a single diastereomer). ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (dt, J= 5.9 and 5.5 Hz,1H, C*H*OTBS), 3.66 (s, 3H, OC*H*$_3$), 2.56 (dq, J=6.9 and 4.8 Hz, 1H, C*H*C=O), 1.56–1.46 (m, 2H, C*H*$_2$CH$_3$), 1.10 (d, J=6.9 Hz, 3H, C*H*$_3$CH), 0.87 (s, 9H, (C*H*$_3$)$_3$CSi), 0.04 (s, 6H, C*H*$_3$Si×2); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.6 (C=O), 79.2, 51.8, 43.8, 26.7, 10.5, 9.1, −4.93, −4.69.

4.5.4. 1-Ethylpropyl-3-*tert*-butyldimethylsilyloxy-2-methylpentanoate (20a/b). Reaction time:16 h; (80% of a 1:2 *syn*/*anti* diastereoisomeric mixture, *syn* is the minor one, data placed in brackets). ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (quintet, J=6.2 Hz, 1H, OC*H*(CH$_2$CH$_3$)$_2$), 3.87 (*anti*, dq, J=6.6 and 5.9 Hz) and 3.94 [*syn*: dq, J=5.1 and 4.4 Hz], total 1H, C*H*OTBS, 2.63–2.51 (m, 1H, C*H*C=O), 1.67–1.42 (m, 6H, CH$_3$C*H*$_2$ and CH$_3$C*H*$_2$CH×2), *syn*: 1.18 (d, J=7.3 Hz) and *anti*:[1.22, J=7.2 Hz], total 3H, C*H*$_3$CH, 1.00–0.88 (m, 18H, C*H*$_3$CH$_2$×3 and (C*H*$_3$)$_3$CSi); 0.06 (s, 6H, C*H*$_3$Si×2).

4.5.5. 2-Methyl-3-hydroxypentanoic acid (21a/b). Reaction time: 12 h (71% of a 63:47 *syn*/*anti* diastereomeric mixture). ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (br, 1H), *syn*: 3.88 (dq, J=5.5 and 3.3 Hz), *anti*: [3.63, dq, J=6.3 and 4.3 Hz], total 1H, 2.63–2.51 (m, 1H), 1.67–1.42 (m, 2H); *syn*: 1.18 (d, J=7.3 Hz) and *anti*:[1.22, J=7.2 Hz], total 3H, 1.00–0.88 (t, J=7.7 Hz, 3H).

4.5.6. 3-*tert*-Butyldimethylsilyloxy-2-methylpentanoic acid (22a/b). Reaction time: 16 h (82% of a 75:25 *syn*/*anti* diastereomeric mixture). ^1H NMR (300 MHz, $CDCl_3$) δ 11.7 (br, 1H, CO_2H); *syn*, 3.92 (dt, J=5.9 and 5.1 Hz), and [*anti*, 3.83, dt, J=6 and 5.7 Hz], total 1H, CHOTBS), 2.48–2.36 (m, 1H, C*H*C=O), 1.46–1.39 (m, 2H, C*H*$_2$CH$_3$), 1.02 (d, J=6.9 Hz, 3H, C*H*$_3$CH), 0.87 (s, 9H, (CH$_3$)$_3$CSi), 0.05 (s, 6H, CH$_3$Si×2).

4.5.7. Methyl 2-methyl-3-hydroxyhexanoate (23a/b). Reaction time: 24 h; (76% of a 30:70 *syn*/*anti* diastereoisomeric mixture). *syn*-**23a**: ^1H NMR (300 MHz, C_6D_6) δ 3.88 (dq, J=4.0 and 6.0 Hz, C*H*OH)), 3.36 (s, 3H, OC*H*$_3$),

2.82 (br s, 1H, OH), 2.30–2.10 (m, 4H), 1.17 (d, J=7.3 Hz, 3H, 0.9 (t, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 176.4 (C=O), 71.4, 51.8, 44.2, 35.9, 19.2, 14.4, 10.7; HRMS (M^+) Calcd for $C_8H_{16}O_3$ 160.21444; Found 160.21440.

anti-**23b**: ^{1}H NMR (C_6D_6, 300 MHz) δ 3.65 (dq, J=6.2 and 7.7 Hz, 1H, C*H*OH), 3.36 9s, 3H, OCH_3), 2.80 (br s, 1H, OH), 2.52–2.32 (m, 4H), 1.09 (d, J=7.3 Hz, 3H, CH_3CHOH), 0.9, t, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 176.2 (C=O), 73.0, 51.7, 45.2, 36.9, 18.8, 14.4, 14.0.

4.5.8. Methyl 2-methyl-3-*tert*-butyldimethylsilyloxy-hexanoate (24a). Reaction time: 20 h; (73%, only a single diastereoisomer detected ≥ 95%). ^{1}H NMR (C_6D_6, 300 MHz) δ 4.0 (dt, J=4.0 and 6.0 Hz, 1H, C*H*OH), 3.67 (s, 3H), 2.54 (dq, J=4.76 and 6.95 Hz, 1H), 1.5–1.8 (m, 4H), 1.12 (d, J=6.96 Hz, 3H), 0.91 (t, J=7.3 Hz, 3H), 0.86 (s, 9H, SiC(CH_3)$_3$), 0.01 (s, 3H), −0.1 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 175.3 (C=O), 72.9, 51.4, 44.4, 25.8, 18.5, 10,89, −4.1, −4.6. Calcd for $C_{14}H_{30}O_3Si$ C 61.26; H 11.02%; Found C 61.23; H 11.00.

4.5.9. 2-Methyl-3-hydroxyhexanoic acid (25a/b). Reaction time:20 h; (81% of a 60:40 *syn*/*anti* diastereoisomeric mixture, *anti* is the minor one, data placed in brackets). ^{1}H NMR (C_6D_6, 300 MHz) δ 6.4–6.2 (br, s, 1H, OH, exchangeable with D_2O), 3.97 (m, 1H, C*H*OH), [3.71 (m. 1H, C*H*OH)], 1.53–1.32 (m, 4H), 1.24 (d, J=7.3 Hz, 3H), [1.2 (d, J=7.3 Hz, 3H), 0.93 (t, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 170.3 (C=O), 71.6, 44.2, 33.5, 22.3, 14.3, 14.0, 10.6; HRMS (M^+) Calcd for $C_7H_{14}O_3$ 146.0942; Found 146.0941.

4.5.10. Methyl 2-methyl-3-hydroxyheptanoate (26a/b). Reaction time: 24 h; (71% of a 40:60 *syn*/*anti* diastereoisomeric mixture). *syn*-**26a**: ^{1}H NMR (C_6D_6, 300 MHz) δ 3.87 (ddd, J=1.8, 4.4 and 6.0 Hz, 1H, C*H*OH), 3.63 (s, 3H), 2.40–2.12 (m, 6H), 1.18 (d, J=7.3 Hz, 3H), 0.83 (t, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 176.3 (C=O), 71.6, 51.7, 44.2, 33.5, 28.1, 22.3, 14.3, 10.6.

anti-**26b**: ^{1}H NMR (C_6D_6, 300 MHz) δ 3.78 (dt, J=5.9 and 11.9 Hz, 1H, C*H*OH), 3.65 (s, 3H), 2.50–2.38 (m, 6H), 1.10 (t, J=6.9 Hz, 3H), 0.91 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 176.2 (C=O), 73.2, 51.6, 45.2, 34.4, 27.7, 22.3, 14.3, 14.0.

4.5.11. Methyl 2-methyl-3-*tert*-butyldimethylsilyloxy-heptanoate (27a). Reaction time: 20 h; (76%, only a single diastereoisomer detected ≥ 95%). ^{1}H NMR (C_6D_6, 300 MHz) δ 4.14 (ddd, J=1.8, 4.3 and 6.2 Hz, 1H, CHOH), 3.44 (s, 3H), 2.52 (dq, J=4.4 and 6.95 Hz, 1H), 1.59–1.49 (m, 4H), 1.33–1.26 (m, 2H), 1.23 (d, J=7.3 Hz, 3H), 1.02 (s, 9H), 0.90 (t, 3H), 0.11 (s, 6H); ^{13}C NMR (C_6D_6, 75.4 MHz) δ 174.6 (C=O), 73.6, 51.1, 44.6, 35.4, 27.9, 26.2 (3×CH_3), 14.4, 14.4, 11.03, −3.8, −4.3; HRMS (M^+) Calcd for $C_{15}H_{32}O_3Si$ 288.21207; Found 288.21200.

4.5.12. 2-Methyl-3-hydroxyheptanoic acid (28a/b). Reaction time: 20 h; (78% of a 63:37 *syn*/*anti* diastereoisomeric mixture, *anti* is the minor one, data placed in brackets). ^{1}H NMR (C_6D_6, 300 MHz) δ 6.2–5.8 (br s, 1H, OH), 3.95 (m, 1H, C*H*OH), [3.69 (m, 1H, C*H*OH)], 2.64–2.52 (m, 1H), 1.60–1.32 (m, 6H), 1.24 (d, J=7.3 Hz, 3H), [1.20 (d, J=7.3 Hz, 3H), 0.91 (t, 3H); ^{13}C NMR (C_6D_6, 75.4 MHz) δ 170.3 (C=O), 71.6, 44.2, 33.5, 28.1, 22.3, 14.3, 14.0, 10.6; HRMS (M^+) Calcd for $C_8H_{16}O_3$ 160.1099; Found 160.1096.

4.6. Synthesis of (±)-sitophilate

4.6.1. (2*SR*,3*RS*)-3-*tert*-Butyldimethylsilyloxy-2-methyl-pentanoic acid (22a). An aqueous solution of lithium hydroxide (3 mol L^{-1}, 4.1 cm^3, 1.2 mmol) was added dropwise to a stirred and cooled solution of ester **19a** (0.32 g, 1.18 mmol) in methanol (10 cm^3) at 0°C. Then, the mixture was stirred for 20 h at room temperature. The solution was acidified to pH 4 with 3 mol L^{-1} aqueous HCl solution. It was then extracted with ether (5×10 cm^3). The ethereal solutions were combined and washed with brine (5×10 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure to afford 0.439 g, 75%, of acid **22a**. The crude acid was used in next step without any additional purification. IR (ν_{max}/Film); 3500–3430, 1720, 1480, 980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.7 (br s, 1H, CO_2H), 3.92 (dt, J=5.9 and 5.1 Hz, 1H, CHOTBS), 2.48–2.36 (m, 1H, C*H*CH_3), 1.46–1.39 (m, 2H), 1.02 (d, J=6.9 Hz, 3H), 0.87 (s, 9H, Si-*t*-Bu), 0.05 (s, 6H, Si(CH_3)$_2$); Calcd for $C_{12}H_{36}O_3Si$ C 56.25; H 14.06%; Found C 56.20; H 14.01.

4.6.2. 1-Ethylpropyl (2*SR*,3*RS*)-2-methyl-3-*tert*-butyldimethylsilyloxypentanoate (20a). To a cold (0°C), stirred solution of acid **22a** (0.15 g, 0.61 mmol) in 10 mL of dry dichloromethane was added sequentially 3-pentanol (0.08 g, 0.91 mmol), 4-dimethylaminopyridine (DMAP, 7 mg, 0.06 mmol), and 1,3-dicyclohexylcarbodiimide (DCC, 0.138 g, 0.68 mmol). The resulting slurry solution 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 (10:1) (5 cm^3) and the solid was removed by filtration. The concentrated filtrate was flash chromatographed on silica gel (15 g) using petroleum ether–ethyl ether as eluant to furnish 0.171 g (89% yield) of ester **20a** as a colorless oil. IR (ν_{max}/Film): 2950, 1730, 1110, 980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (tt, J=5.4 and 7.4 Hz, 1H, C*H*O(CH_2CH_3)$_2$)), 3.94 (dq, J=5.1 and 4.4 Hz, 1H, CHOTBS), 2.63–2.51 (m, 1H), 1.67–1.42 (m, 6H), 1.18 (d, J=7.3 Hz, 3H), 1.0–0.9 (m, 9H), 0.88 (s, 9H, Si-*t*-Bu), 0.06 (s, 6H, Si(CH_3)$_2$); Calcd for $C_{17}H_{36}O_3Si$ C 64.55; H 11.39%; Found C 54.61; H 11.37.

4.6.3. 1-Ethylpropyl (2*SR*,3*RS*)-2-methyl-3-hydroxy-pentanoate [(±)-sitofilate] (1). To a stirred solution of silyl-ester **20a** (0.1 g, 0.315 mmol) in 10 mL of acetonitrile at room temperature was added a solution of HF (0.2 cm^3, 48% w/v solution of HF in water). The resulting solution was stirred at room temperature for 1 h. After that, ethyl ether (20 cm^3) and distilled water (10 cm^3) were added. The ethereal layer was separated and the aqueous phase was extracted again with ethyl ether (20 cm^3). The organic phases were combined, washed with a saturated solution of $NaHCO_3$ (1×10 cm^3), distilled water (2×10 cm^3) and dried over $MgSO_4$. Evaporation under reduced pressure and purification of the residue by column chromatography (eluant hexane–ethyl acetate 95:5) gave (±)-sitofilate (**1**, 0.049 g,

80% yield) as a clear colorless liquid. IR(ν_{max}/film) 3480, 2970, 2950, 1730, 1455, 1250, 1190, 1100, 1030, 980, 920 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) 4.83 (tt, J=5.4 and 7.4 Hz, 1H), 3.77 (ddt, J=4.4, 8.8 and 4.4 Hz, 1H), 2.39 (dq, J=4.4 and 7.4 Hz, 1H), 2.30 (d, J=4.4 Hz, 1H), 1.24–1.50 (m. 6H0, 1.16 (d, J=7.3 Hz, 3H), 0.89 (t, J=7.5 Hz, 3H), 0.77 (t, J=7.5 Hz, 3H), 0.76 (t, J=7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, C_6D_6) δ 175.8, 76.5, 73.4, 44.9, 27.4, 26.8, 26.7, 11.3, 10.5, 9.75, 9.71; MS (70 eV, *m/z*) (%) 173 (22), 144 (18), 115 (96), 103 (92), 97 (23), 85 (25), 74 (100); Calcd for $C_{11}H_{22}O_3$ C, 65.31; H, 10.96%; Found C 65.30; H 10.93.

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