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Asymmetric synthesis of (*E*)- and (*Z*)-3,7-dimethyl-2-octene-1,8-diol and callosobruchusic acid

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Abstract—Both enantiomers and regioisomers of (*E*)- and (*Z*)-3,7-dimethyl-2-octene-1,8-diol and callosobruchusic acid, which have important biological activity were synthesized by enzymatic transesterification of primary alcohols (*E*)- and (*Z*)-**10**.

1. Introduction

(*E*)-3,7-Dimethyl-2-octene-1,8-diol **1** has been identified as a major component in the secretion products of the monarch butterfly, *Danaus chrysippus*, which is an old world member of the subfamily Danaine.[1] The low availability of the diol in butterflies, makes it difficult to evaluate its biological activity. However the structurally similar (*E*)-3,7-dimethyl-2-octene-1,8-dioic acid (callosobruchusic acid, **2**) acts as a pheromone of the azuki bean weevil, *Callosbruchus chinensis* SL[2] and was found to display specific activity as a sex pheromone in both enantiomeric forms, therefore attracting much attention for bioassay applications in pest control. There are already some reports regarding the total synthesis of the two title compounds, which involve both a chemical and biochemical approach.[3] In our study of diterpene cyclases (mainly taxadiene synthase)[4] we are in constant need of several structurally modified geranyl-geraniols (GGOH), for example, the enantiomers of 7,8-dihydro GGOH. A logical disconnection of 7,8-dihydro GGOH leads to diol (*E*)-**1** and (*Z*)-**1** in both enantiomeric forms. Herein we report the asymmetric total synthesis of compounds **1** and **2** in both regioisomeric forms.

2. Results and discussion

We planned to bring the (*E*)-double bond geometry in **1** and **2** starting from prenol, whereas the (*Z*) geometry in **1** and **2** could be constructed from nerol (Scheme 1). To fix the methyl stereocenter we adopted an enzymatic transesterification reaction with an active ester.

Our synthesis for the (*E*)-isomer started from prenol. The hydroxy group was protected as its *p*-methoxybenzyl ether to give **3** in 95% yield. Selective allylic oxidation with SeO_2/TBHP followed by reduction with $NaBH_4$ afforded compound **4** in 65% yield. The hydroxyl group in **4** was converted to bromide by PBr_3, and the crude bromide then coupled with the copper enolate of ethyl acetate[5] at −110 °C to yield ester **5**. Reduction of the ester with LAH, conversion of the alcohol functionality to a bromide, and successive coupling with an enolate generated previously from ethyl propionate at −110 °C, yielded ester **7**. The yield for the coupling reaction of copper enolate generated from ethyl propionate was low (15%). Changing the base from LDA to LHMDS or KHMDS or altering the solvent (DMF, ether) and temperature proved to have little effect on improving the yield. At this stage we have decided to reach the propionate ester moiety via an alternative method through diethyl methylmalonate coupling. Alcohol **6** was converted to the iodo compound **8** by treatment with I_2/triphenylphosphine/imidazole.[6] Coupling of **8** with diethyl methylmalonate in DMF at 100 °C afforded the dialkylated malonate derivative **9** in 95% yield.[7] Selective hydrolysis and decarboxylation of **9** was achieved by treatment with NaCN/DMSO and H_2O to yield **7** in 60% yield.[8] Reduction with LAH afforded alcohol **10** in 90% yield (Scheme 2).

The (*Z*)-isomer of **10** was prepared by following the above reaction sequences starting from (*Z*)-**6**, which was prepared in high yield from nerol as reported earlier.[9]

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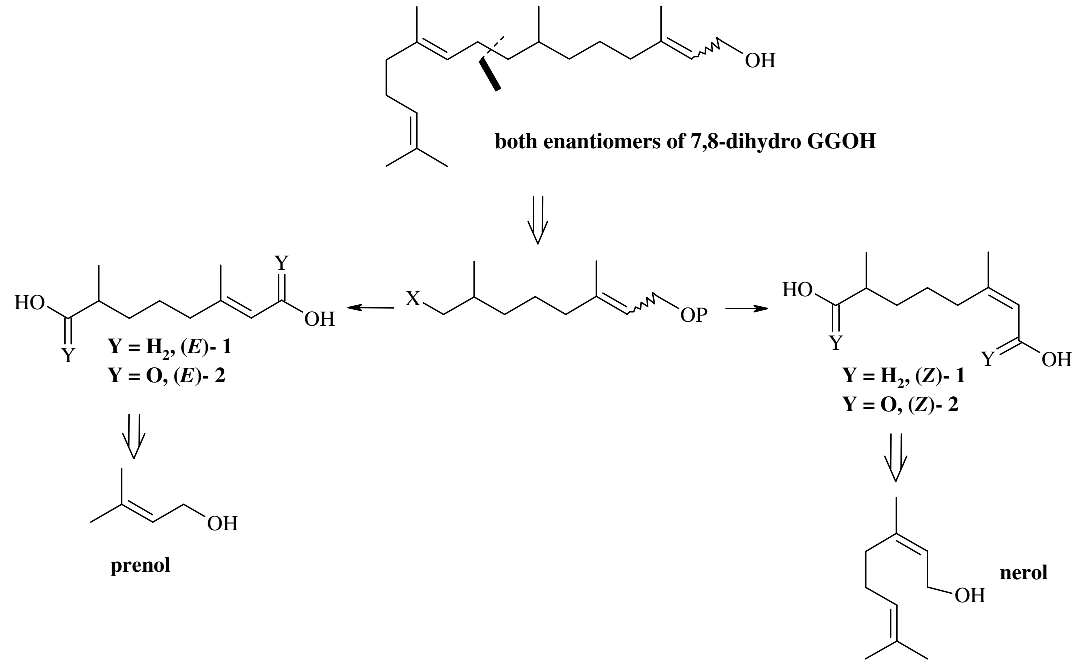
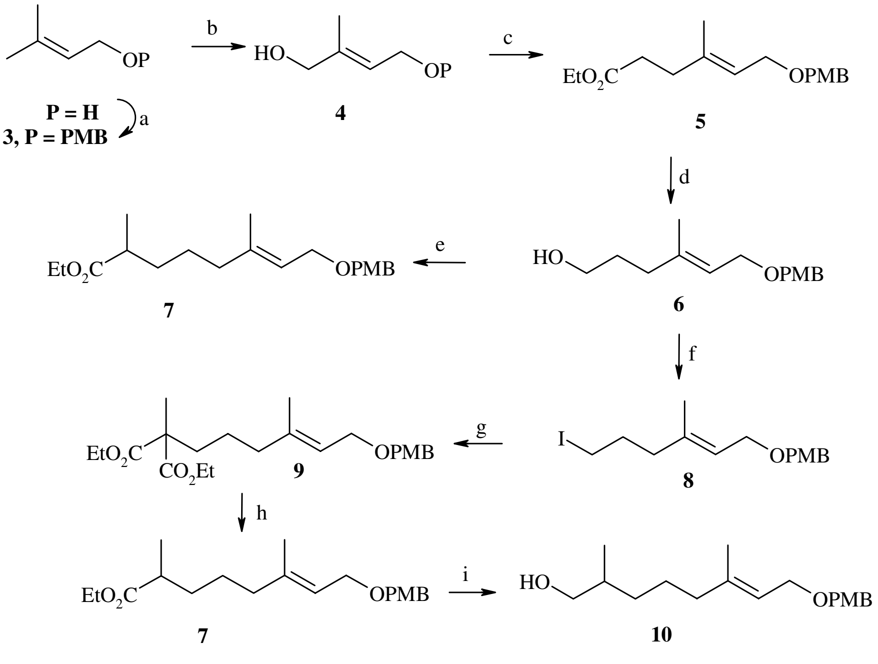


Scheme 1. Synthesis plan for 7,8-dihydro GGOH.



Scheme 2. Reagents and conditions: (a) NaH, PMB-Cl; (b) SeO_2, TBHP, DCM, $NaBH_4$/MeOH; (c) PBr_3, EtOAc, LDA, CuI; (d) $LiAlH_4$; (e) PBr_3, $EtCO_2Et$, LDA, CuI; (f) I_2/triphenylphosphine/imidazole, CH_3CN/ether (1:3); (g) NaH, $MeCH(CO_2Et)_2$, DMF; (h) NaCN, DMSO/H_2O; (i) LAH.

With both regioisomers of **10** in hand, the next step was to install the methyl stereocenter adjacent to the hydroxymethyl group. For this purpose we decided to employ lipase catalyzed transesterification of alcohol **10** with active esters, as acyl donors. For the above studies, a set of lipases [*Pseudomonas fluorescencs* (PFL), *Candida antarctica* (CAL-B), *Candida rugosa* (CRL), *Porcine pancreas* (PPL), wheat germ (WGL), and *Rhizopus niveus* (RNL)] was chosen. Vinyl acetate, isopropenyl acetate, ethyl acetate, and 3,5-dioxomethylhexanoate[10] were selected for the active ester. In all the transesterification experiments, *tert*-butylmethyl ether (containing 0.1% water) was used as the solvent (except in case of 3,5-dioxomethylhexanoate). We have also carried out the transesterification at two different temperatures (25 and 0 °C) to observe any temperature dependence on chemical yield and enantiomeric excess. A careful screening of all the lipases revealed that CRL, WGL, and RNL showed little activity (both optical and chemical yields were low) toward the transesterification

Table 1. Lipase catalyzed transesterification of (*E*)-**10**[a]

Entry	Lipase[a]	Acyl donor[b]	Temp (0 °C)	Time (h)	(*S*)-Ester[c]		(*R*)-Alcohol[c]		Conversion (*c*)[d]	*E*[d]
					Yield (%)	Ee_p	Yield(%)	Ee_s		
1	PPL	Ethyl acetate	25	12	40	88	39	82	48.2	40
2	PPL	Ethyl acetate	0	18	32	91	30	90	49.7	64
3	PFL	Isopropenyl acetate	25	10	46	89	43	88	49.6	49.4
4	PFL	Isopropenyl acetate	0	14	45	92	42	90	49.4	74.2
5	PFL	Ethyl acetate	25	12	42	82	44	88	51.7	29
6	PFL	Ethyl acetate	0	16	44	86	40	80	48.2	32.4
7	CAL-B	Ethyl acetate	25	4	40	88	32	90	50.5	45.1
8	CAL-B	Ethyl acetate	0	9	38	92	44	91	49.7	77.5
9	CAL-B	3,5-Dioxomethyl hexanoate	25	8	46	95	45	93	49.4	132

[a] Weight equivalent (1:1.2, with alcohol **10**) of lipase was used.

[b] Alcohol **10** (1 equiv) and acylating agent (2 equiv) were used.

[c] Ee's were determined by NMR and the $[\alpha]_D^{25}$ value.

[d] $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$, where ee_p = pdt. Ee; $c = ee_s/(ee_s + ee_p)$.[16]

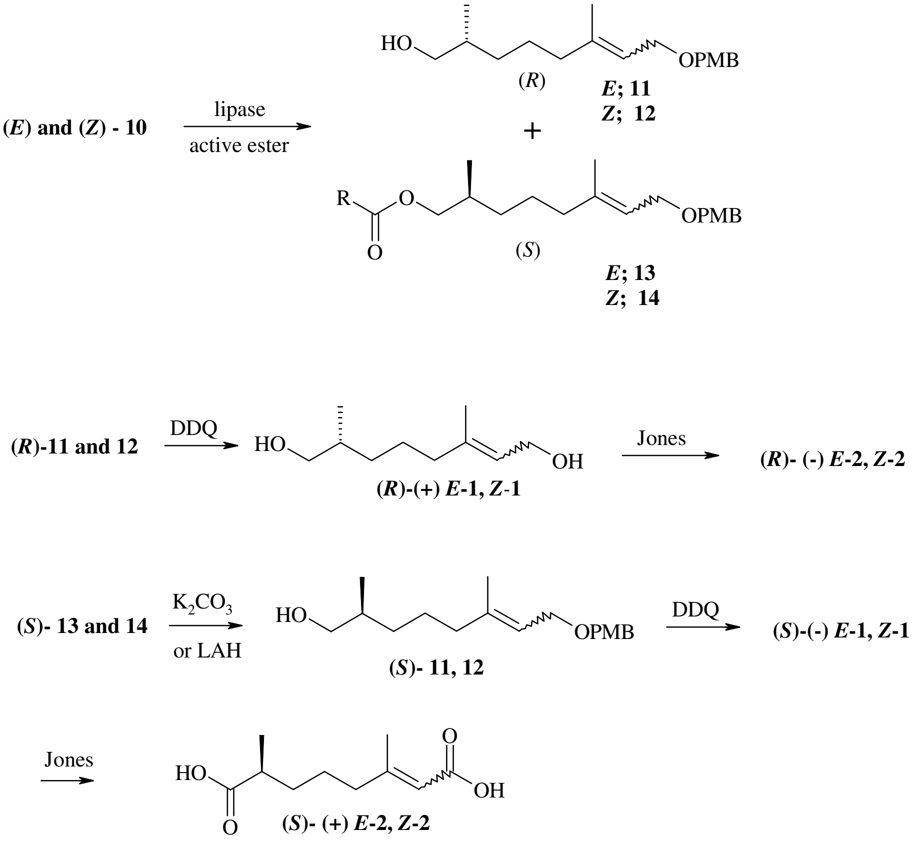
reaction with all the acylating agents employed, whereas other sets, for example, PPL/vinyl acetate, isopropenyl acetate, and 3,5-dioxomethylhexanoate (25 and 0 °C); PFL/vinylacetate, 3,5-dioxomethylhexanoate (25 and 0 °C); CAL-B/vinyl acetate, isopropenyl acetate (25 and 0 °C) also showed disappointing results. The remaining sets showed good to excellent chemical and optical yield as listed in Table 1. From Table 1 it can be seen that the CAL-B/3,5-dioxomethylhexanoate combination provided the optimal result. High chemical yield (46% for the ester and 45% for the alcohol) and excellent optical yield ($E = 132$) was observed, whereas the other systems also provided good yields. Reactions carried out at low temperature (0 °C) took a little longer reaction time but showed more enantioselectivity (entries 2, 4, and 6). For the corresponding (*Z*)-isomers of **10** we applied the same conditions and observed almost similar results both in terms of enantiomeric excess and chemical yield. The only noticeable difference was that the (*Z*)-isomer took a longer reaction time (3–4 h) when compared to its (*E*)-counterpart. For the enantiopreference of lipases toward transesterification of primary alcohols (not containing O at the stereocenter), it was reported that the (*S*)-enantiomer was acylated in most of the cases.[11] We observed the same trend in case of (*E*)- and (*Z*)-**10**. The absolute configuration was determined by removal of *para*-methoxybenzyl group and determining the specific rotation value of the obtained diol.[3] The enantioselectivity of the enzymatic process was determined with the help of NMR by making the chiral derivatized agent with *ortho*-fluoroaryl lactic acid (FAC).[12] In that process the slow reacting (*R*)-enantiomer and fast reacting (*S*)-enantiomer, (released from (*S*)-ester) were derivatized with (*R*)-FAC (EDCI·HCl/DMAP), with their ^{1}H NMR spectra was recorded at room temperature. The methyl signal (doublet, adjacent to hydroxymethyl group) showed different chemical shift values (δ, near 0.9 ppm) in the diastereomeric pairs. By measuring their integral ratio, ee's were measured. With the exception of the methyl signal, other protons did not exhibit visible separation in the diastereomeric pair, hence the determination of the absolute configuration could not be assigned by this analysis. Finally the *para*-methoxybenzyl group was deprotected from (*R*)-**11**, **12** by using DDQ[13] to afford (*R*)-(*E*)-**1** and (*Z*)-**1**. This on Jones' oxidation yielded (*R*)-callosobruchusic acid in both regioisomeric forms. (*S*)-**13** and **14** were deacylated by hydrolytic removal with K_2CO_3 or reduction with LAH, followed by removal of *para*-methoxybenzyl group to give (*S*)-(*E*)-**1** and (*Z*)-**1**. Finally Jones' oxidation of (*S*)-(*E*)-**1** and (*Z*)-**1** furnished (*S*)-callosobruchusic [(*E*)-**2** and (*Z*)-**2**] acid in both regioisomeric forms (Scheme 3).

3. Conclusion

An efficient chemo-enzymatic asymmetric synthesis of 3,7-dimethyl-2-octene-1,8-diol and callosobruchusic acid has been achieved in 9% overall yield starting from easily available building blocks. Both enantiomers of diol (*E*)-**1** and (*Z*)-**1** were further employed for the total synthesis of 7,8-dihydro GGOH, needed for our study on diterpene cyclase pathway evaluation.

4. Experimental

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethylether were distilled from sodium benzophenone ketyl. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Lipase (from *C. rugosa*, type VII, 1440 µg of protein), lipase (from *P. pancreas*, type II, 6 µg of protein), lipase AK (from *P. fluorescens*), lipase (from *C. antarctica* immobilized on acrylic resin), lipase (from *R. niveus*), lipase (from wheat germ, type I, 8.2 µg of protein) were obtained from Sigma and used as obtained. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic vanillin and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on Bruker 500 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^{1}H and ^{13}C, respectively. CHN analysis



Scheme 3. Asymmetric total synthesis of the two title compounds.

was performed in the elemental analysis laboratory at the Department of Chemistry, TAMU. Optical rotations were measured on a JASCO Dip 360 digital polarimeter.

4.1. 1-Methoxy-4-(3-methyl-but-2-enyloxymethyl)-benzene 3

3-Methyl-but-2-en-1-ol (5 g, 58 mmol) was taken in THF (60 mL) at 0 °C, NaH (2.8 g, 69 mmol, 60% in mineral oil) was added portionwise to it followed by the addition of tetra-*n*-butyl ammonium iodide (catalytic). The solution was allowed to attain room temperature for 1 h. 4-Methoxybenzyl chloride (10.8 g, 69 mmol) was added to the solution and heated to reflux for 6 h. Afterwards, cold water was added to it and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the organic layer yielded 11.3 g of product (95%). ^1H and ^{13}C NMR spectra of this material were compared closely with those of the literature[14] and found similar. The product was used for the next step without further purification.

4.2. (*E*)-4-(4-Methoxy-benzyloxy)-2-methyl-but-2-en-1-ol 4

A solution of TBHP (35 mL, 70% aq), salicylic acid (1 g, 7.25 mmol), and SeO_2 (0.22 g, 2 mmol) in dichloromethane (60 mL) was prepared. To this solution was added slowly 1-methoxy-4-(3-methyl-but-2-enyloxymethyl)-benzene (11 g, 53 mmol). The reaction mixture was then stirred for 2 days at room temperature, after which it was diluted with ether (200 mL), washed with aq NaOH, aq sodium bisulfite, and brine. The organic layer was dried over Na_2SO_4 and evaporated to afford the crude product containing the allylic alcohol as well as the aldehyde. The crude was then dissolved in 95% EtOH (150 mL), and $NaBH_4$ (2 g) added to it at 0 °C with the reaction mixture stirred overnight. Removal of ethanol afforded a solid residue, which was partitioned between water and ether. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation and purification through flash chromatography (3:1, hexane/EtOAc) yielded compound **4** (7.1 g, 65%). ^1H and ^{13}C NMR spectra of this material was compared closely with that of literature[15] and found similar.

4.3. (*E*)-6-(4-Methoxy-benzyloxy)-4-methyl-hex-4-enoic acid ethyl ester 5

To a solution of EtOAc (2.6 mL, 29.5 mmol) and cuprous iodide (11.2 g, 59 mmol) in THF (100 mL) at −110 °C (dry ice/ether bath) was added a solution of LDA [made by the addition of ^{n}BuLi (15 mL, 2.0 M in hexane, 29.6 mmol) to a solution of diisopropylamine (4.3 mL, 29.6 mmol) in THF (30 mL) at 0 °C and stirred for 30 min] via cannula. The reaction mixture was allowed to warm to −30 °C over 2 h, followed by the addition of 1-((*E*)-4-bromo-3-methyl-but-2-enyloxy-methyl)-4-methoxy-benzene (generated from **4**, 4.25 g, 15 mmol) in THF (20 mL). Afterwards, the reaction mixture was stirred for 1 h at −30 °C. The mixture was then quenched by the addition of saturated NH_4Cl and allowed to warm to room temperature at which point it was extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Purification by flash chromatography (19:1, hexane/EtOAc) afforded ester **5** as a clear oil (3 g, 70%). δ_H: 7.3 (d, $J = 8.7$ Hz, 2H), 6.9 (d, $J = 8.7$ Hz, 2H), 5.4 (m, 1H), 4.45 (s, 2H), 4.15 (q, $J = 7.0$ Hz, 2H), 4.05 (d, $J = 7.2$ Hz, 2H), 3.8 (s, 3H), 2.48 (m, 2H), 2.4 (m, 2H), 1.7 (s, 3H), 1.28 (t, $J = 7.0$ Hz, 3H). δ_C: 173.4, 159.1, 138.8, 130.7, 129.4, 121.2, 113.7, 72.3, 66.6, 60.6, 55.3, 34.6, 32.9, 16.7, 14.5. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.72; H, 8.39.

4.4. (*E*)-6-(4-Methoxy-benzyloxy)-4-methyl-hex-4-en-1-ol 6

Ester **5** (1.1 g, 3.7 mmol) was taken in ether (20 mL) at 0 °C. Lithium aluminium hydride (140 mg, 3.7 mmol) was then added. The reaction mixture was allowed to return to room temperature and stirred for a further 2 h. Excess LAH was quenched with the addition of saturated Na_2SO_4. The solution was filtered through a Celite pad and the pad washed with hot EtOAc. The organic solvent was then evaporated to afford product **6**, which was pure enough for the next step (847 mg, 90%). δ_H: 7.28 (d, $J = 8.7$ Hz, 2H), 6.9 (d, $J = 8.7$ Hz, 2H), 5.45 (m, 1H), 4.46 (s, 2H), 4.05 (d, $J = 7.2$ Hz, 2H), 3.82 (s, 3H), 3.68 (t, $J = 7.0$ Hz, 2H), 2.16 (t, $J = 7.0$ Hz, 2H), 1.75 (m, 2H), 1.7 (s, 3H). δ_C: 159.3, 140.1, 130.8, 129.7, 121.4, 113.9, 71.9, 66.4, 62.8, 55.5, 36.0, 30.7, 16.6. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.85; H, 8.63.

4.5. (*Z*)-6-(4-Methoxy-benzyloxy)-4-methyl-hex-4-en-1-ol

It was prepared from nerol–PMB ether as described in Ref. 9 for benzyloxygeraniol. δ_H: 7.25 (d, $J = 8.7$ Hz, 2H), 6.9 (d, $J = 8.7$ Hz, 2H), 5.55 (m, 1H), 4.5 (s, 2H), 4.0 (d, $J = 7.4$ Hz, 2H), 3.75 (s, 3H), 3.6 (t, $J = 7.0$ Hz, 2H), 2.26 (t, $J = 7.0$ Hz, 2H), 1.78 (s, 3H), 1.70 (m, 2H). δ_C: 159.4, 141.9, 130.2, 129.8, 122.0, 114.2, 72.3, 65.6, 61.2, 55.4, 30.1, 27.8, 23.2.

4.6. 1-((*E*)-6-Iodo-3-methyl-hex-2-enyloxymethyl)-4-methoxy-benzene 8

Alcohol **6** (2.5 g, 10 mmol) was dissolved in 40 mL (3:1) ether/CH_3CN solution at 0 °C. Imidazole (1.02 g, 15 mmol) was added, followed by I_2 (3.8 g, 15 mmol), and triphenyl phosphine (3.93 g, 15 mmol). The solution was stirred at room temperature for an additional hour after which it was filtered, the filtrate evaporated, and the crude iodide was purified by flash chromatography (19:1, hexane/EtOAc) to afford 2.88 g of **8** (80% yield). δ_H: 7.32 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.45 (m, 1H), 4.47 (s, 2H), 4.06 (d, $J = 7.2$ Hz, 2H), 3.8 (s, 3H), 3.2 (t, $J = 7.0$ Hz, 2H), 2.18 (t, $J = 7.0$ Hz, 2H), 2.0 (m, 2H), 1.7 (s, 3H). δ_C: 159.3, 138.3, 130.7, 129.7, 122.4, 113.9, 72.0, 66.3, 55.4, 40.1, 31.5, 16.6, 6.6. Anal. Calcd for $C_{15}H_{21}IO_2$: C, 50.01; H, 5.88. Found: C, 50.15; H, 5.77%.

4.7. 1-((*Z*)-6-Iodo-3-methyl-hex-2-enyloxymethyl)-4-methoxy-benzene

δ_H: 7.3 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.5 (m, 1H), 4.5 (s, 2H), 4.0 (d, $J = 7.2$ Hz, 2H), 3.82 (s, 3H), 3.18 (t, $J = 7.0$ Hz, 2H), 2.2 (t, $J = 7.0$ Hz, 2H), 2.0 (m, 2H), 1.68 (s, 3H). δ_C: 159.4, 139.6, 130.7, 129.8, 122.9, 113.6, 72.5, 65.93 55.3, 39.9, 31.4, 15.5, 7.2.

4.8. 2-[(*E*)-6-(4-Methoxy-benzyloxy)-4-methyl-hex-4-enyl]-2-methyl-malonicacid diethyl ester 9

Diethylmethylmalonate (1.4 g, 8 mmol) was taken in DMF (20 mL) at 0 °C at which point NaH (0.32 g, 8 mmol) was added. The solution was stirred at the same temperature until hydrogen evolution ceased at which point iodide **8** (2.9 g, 8.1 mmol) was added dropwise to it. The reaction mixture was heated at 100 °C for 2 h and then cooled to room temperature at which point water was added and extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation and purification through flash chromatography (9:1, hexane/EtOAc) yielded diester **9** (3.2 g, 95%). δ_H: 7.3 (d, $J = 8.7$ Hz, 2H), 6.9 (d, $J = 8.7$ Hz, 2H), 5.4 (m, 1H), 4.47 (s, 2H), 4.2 (q, $J = 7.0$ Hz, 4H), 4.0 (d, $J = 7.2$ Hz, 2H), 3.8 (9s, 3H), 2.2 (t, $J = 7.0$ Hz, 2H), 1.85 (m, 2H), 1.65 (s, 3H), 1.4 (s, 3H), 1.28 (t, $J = 7.0$ Hz, 6H). δ_C: 172.6, 159.3, 139.8, 129.6, 121.5, 113.9, 71.9, 66.4, 61.3, 55.4, 39.8, 35.2, 22.4, 20.1, 16.3, 14.2, 14.3. Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.96; H, 8.43. Found: C, 67.88; H, 8.56.

4.9. 2-[(*Z*)-6-(4-Methoxy-benzyloxy)-4-methyl-hex-4-enyl]-2-methyl-malonicacid diethyl ester

δ_H: 7.29 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.46 (m, 1H), 4.45 (s, 2H), 4.16 (q, $J = 7.0$ Hz, 4H), 3.98 (d, $J = 7.4$ Hz, 2H), 3.85 (s, 3H), 2.1 (t, $J = 7.0$ Hz, 2H), 1.86 (m, 2H), 1.72 (s, 3H), 1.4 (s, 3H), 1.4 (s, 3H), 1.25 (t, $J = 7.0$ Hz, 6H). δ_C: 172.5, 159.3, 140.1, 130.7, 129.7, 122.5, 113.9, 70.4, 66.1, 61.3, 55.4, 35.3, 35.2, 23.4, 22.8, 20.1, 19.6, 14.2.

4.10. (*E*)-8-(4-Methoxy-benzyloxy)-2,6-dimethyl-oct-6-enoic acid ethyl ester 7

A sample of 1.72 g (4.2 mmol) of **9** was taken in 20 mL DMSO. NaCN (0.41 g, 8.4 mmol) was added followed by water (0.75 mL, 4.2 mmol). The solution was heated at 145 °C for 6 h. After that time, water was added to it and extracted with ether. The organic layer was dried over Na_2SO_4 and evaporated. Purification by flash chromatography (19:1, hexane/EtOAc) yielded ester **7** in 60% yield (0.84 g). δ_H: 7.3 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.4 (m, 1H), 4.46 (s, 2H), 4.18 (q, $J = 7.0$ Hz, 2H), 4.0 (d, $J = 7.2$ Hz, 2H), 3.86 (s, 3H), 2.45 (m, 1H), 2.08 (t, $J = 7.0$ Hz, 2H), 1.68 (s, 3H), 1.4–1.5 (m, 4H), 1.27 (t, $J = 7.0$ Hz, 3H), 1.14 (d, $J = 7.2$ Hz, 3H). δ_C: 177.0, 159.3, 140.2, 130.8, 129.6, 121.2, 113.9, 71.9, 66.4, 60.3, 55.4, 39.6, 39.5, 33.5, 25.3, 17.3, 16.3, 14.4. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.66; H, 9.11%.

4.11. (*Z*)-8-(4-Methoxy-benzyloxy)-2, 6-dimethyl-oct-6-enoic acid ethyl ester

δ_H: 7.28 (d, $J = 8.7$ Hz, 2H), 6.9 (d, $J = 8.7$ Hz, 2H), 5.42 (m, 1H), 4.43 (s, 2H), 4.16 (q, $J = 7.0$ Hz, 2H), 3.96 (d, $J = 7.4$ Hz, 2H), 3.82 (s, 3H), 2.46 (m, 1H), 2.06 (t, $J = 7.0$ Hz, 2H), 1.72 (s, 3H), 1.35–1.55 (m, 4H), 1.28 (t, $J = 7.0$ Hz, 3H), 1.15 (d, $J = 7.0$ Hz, 3H). δ_C: 176.9, 159.3, 140.6, 130.8, 129.6, 122.1, 113.8, 71.9, 66.1, 60.4, 55.4, 39.6, 33.7, 32.0, 25.8, 23.5, 17.3, 14.4.

4.12. (*E*)-8-(4-Methoxy-benzyloxy)-2,6-dimethyl-oct-6-en-1-ol 10

LAH reduction of ester **9** as described above furnished alcohol **10** in 90% yield. δ_H: 7.32 (d, $J = 8.7$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 5.4 (m, 1H), 4.45 (s, 2H), 4.04 (d, $J = 7.2$ Hz, 2H), 3.85 (s, 3H), 3.5 (dd, $J = 7.4$ Hz, 1.8 Hz, 2H), 2.04 (m, 2H), 1.68 (s, 3H), 1.55–1.4 (m, 4H), 1.1 (m, 1H), 0.92 (d, $J = 7.0$ Hz, 3H). δ_C: 159.3, 140.6, 130.8, 129.6, 121.0, 113.9, 71.9, 68.5, 66.4, 55.4, 39.9, 35.8, 32.9, 25.1, 16.7, 16.6. Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.77; H, 9.42%.

4.13. (*Z*)-8-(4-Methoxy-benzyloxy)-2,6-dimethyl-oct-6-en-1-ol

δ_H: 7.34 (d, $J = 8.7$ Hz, 2H), 6.94 (d, $J = 8.7$ Hz, 2H), 5.46 (m, 1H), 4.46 (m, 1H), 4.0 (d, $J = 7.2$ Hz, 2H), 3.85 (s, 3H), 3.45 (dd, $J = 7.4$ Hz, 1.8 Hz, 2H), 2.08 (t, $J = 7.0$ Hz, 2H), 1.8 (s, 3H), 1.6–1.4 (m, 1H), 1.1 (m, 1H), 0.92 (d, $J = 7.0$ Hz, 3H). δ_C: 159.4, 141.1, 130.8, 129.6, 121.8, 113.9, 72.0, 68.4, 66.1, 55.5, 35.7, 32.9, 32.3, 25.5, 23.6, 16.7.

4.14. Acetic acid (*E*)-(*S*)-8-(4-methoxy-benzyloxy)-2,6-dimethyl-oct-6-enyl ester

Commercially available anhydrous *tert*-butylmethyl ether 5 mL was taken and 0.1% of water added. After vigorous stirring at room temperature for 30 min the mixture was allowed to settle. The upper layer (3 mL) was placed in a resealable sample vial, to which (*E*)-alcohol (50 mg, 0.17 mmol), acylating agent (vinyl acetate/isopropenyl acetate/ethyl acetate, 0.35 mmol), and lipase (60 mg) were successively added. The vial was sealed, and the reaction mixture stirred for the time listed in Table 1. Afterwards it was filtered and the filtrate concentrated and purified by preparative TLC on silica (3:1, hexane/EtOAc). $[\alpha]_D^{25} = -3.1$ (c 0.98, $CHCl_3$); δ_H: 7.3 (d, $J = 8.7$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.40 (m, 1H), 4.46 (s, 2H), 4.05 (d, $J = 7.2$ Hz, 2H), 3.9 (dd, $J = 7.4$ Hz, 1.8 Hz, 2H), 3.82 (s, 3H), 2.1 (s, 3H), 2.05 (t, $J = 7.0$ Hz, 2H), 1.67 (s, 3H), 1.5–1.3 (m, 4H), 1.15 (m, 1H), 0.96 (d, $J = 7.0$ Hz, 3H). δ_C: 171.5, 159.3, 140.3, 130.8, 129.6, 121.1, 113.9, 71.9, 69.5, 66.4, 55.4, 39.8, 33.1, 32.6, 25.0, 21.8, 17.0, 16.5. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.71; H, 8.97.

4.15. Acetic acid (*Z*)-(*S*)-8-(4-methoxy-benzyloxy)-2,6-dimethyl-oct-6-enyl ester

δ_H: 7.28 (d, $J = 8.7$ Hz, 2H), 6.9 (d, $J = 8.7$ Hz, 2H), 5.5 (m, 1H), 4.48 (s, 2H), 4.1 (d, $J = 7.2$ Hz, 2H), 3.95 (dd, $J = 7.4$ Hz, 1.8 Hz, 1H), 3.88 (dd, $J = 7.4$ Hz, 1.8 Hz, 1H), 3.85 (s, 3H), 2.06 (s, 3H), 2.0 (t, $J = 7.0$ Hz, 2H), 1.8 (m, 1H), 1.75 (s, 3H), 1.5–1.3 (m, 3H), 1.16 (m, 1H), 0.94 (d, $J = 7.0$ Hz, 3H). δ_C: 172.5, 159.3, 141.2, 130.8, 129.7, 122.4, 114.0, 72.0, 69.5, 66.6, 55.8, 39.7, 33.4, 32.7, 25.0, 21.8, 17.6, 16.8.

4.16. 3,5-Dioxo-hexanoic acid (*E*)-(*S*)-8-(4-methoxy-benzyloxy)-2,6-dimethyl-oct-6-enyl ester

Alcohol (50 mg, 0.17 mmol), lipase (CAL-B, 60 mg), and acylating agent (3,5-dioxomethylhexanoate, 100 mg) were put into a small round bottomed flask. The flask was put into a rotary evaporator (room temperature, 10 Torr) under argon atmosphere. After the reaction time, DCM was added to it, and filtered with the filtrate then concentrated. The product ester and the unreacted (*R*) alcohol were separated by preparative TLC on silica (4:1, hexane/EtOAc). δ_H: 7.3 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.62 (s, 1H), 5.4 (m, 1H), 4.44 (s, 2H), 4.1 (d, $J = 7.2$ Hz, 2H), 3.98 (m, 2H), 3.82 (s, 3H), 3.35 (s, 2H), 2.1 (s, 3H), 2.06 (t, $J = 7.0$ Hz, 2H), 1.64 (s, 3H), 1.5–1.35 (m, 4H), 1.18 (m, 1H), 0.96 (d, $J = 7.0$ Hz, 3H). δ_C: 190.3, 187.4, 167.9, 159.3, 140.3, 130.7, 129.6, 121.1, 113.9, 100.7, 71.9, 70.4, 66.4, 55.4, 45.3, 39.8, 33.0, 32.5, 24.9, 24.6, 16.9, 16.6. Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.88; H, 8.19. Found: C, 68.76; H, 8.13.

4.17. 3,5-Dioxo-hexanoic acid (*Z*)-(*S*)-8-(4-methoxy-benzyloxy)-2,6-dimethyl-oct-6-enyl ester

δ_H: 7.32 (d, $J = 8.7$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 5.68 (s, 1H), 5.45 (m, 1H), 4.45 (s, 2H), 4.05 (dd, $J = 7.4$ Hz, 1.8 Hz, 1H), 4.0 (d, $J = 7.2$ Hz, 2H), 3.9 (dd, $J = 7.4$ Hz, 1.8 Hz, 1H), 3.8 (s, 3H), 3.35 (s, 2H), 2.1 (s, 3H), 2.04 (t, $J = 7.0$ Hz, 2H), 1.75 (s, 3H), 1.5–1.3 (m, 4H), 1.15 (m, 1H), 0.95 (d, $J = 7.0$ Hz, 2H). δ_C: 190.3, 187.4, 167.8, 159.3, 140.8, 130.8, 129.6, 122.0, 114.1, 100.7, 71.9, 70.4, 67.2, 55.4, 45.3, 33.1, 32.5, 32.3, 31.0, 25.4, 24.5, 16.9.

4.18. Release of (*S*)-alcohols from (*S*)-esters

Method A: Esters were taken in MeOH followed by the addition of solid K_2CO_3 (1.5 equiv). The solution was stirred at room temperature for 1 h. The solution was filtered and the filtrate evaporated. Water was added to the residue and extracted with DCM. The final product was purified by preparative TLC on silica (3:1, hexane/EtOAc).

Method B: Reduction with powdered LAH in ether as described previously yielded the (*S*)-alcohol.

4.19. (*R*)- and (*S*)-(*E*)-1 and (*Z*)-1

(*R*)- and (*S*)-**11** and **12** (100 mg, 0.34 mmol) were taken in 10 mL DCM/H_2O (19:1). DDQ (116 mg, 0.52 mmol) was added to it and the reaction mixture stirred for 1 h at room temperature. Afterwards it was filtered, the filtrate washed with 5% $NaHCO_3$, brine, and dried over Na_2SO_4. Evaporation and purification by flash chromatography (1:1, hexane/EtOAc) yielded the diols in 75% yield.

(*S*)-(*E*)-**1**, $[\alpha]_D^{25} = -6.1$ (*c* 3.0, $CHCl_3$). δ_H: 5.38 (m, 1H), 4.14 (d, $J = 7.4$ Hz, 2H), 3.45 (m, 2H), 2.0 (t, $J = 7.0$ Hz, 2H), 1.68 (s, 3H), 1.65–1.4 (m, 4H), 1.1 (m, 1H), 0.9 (d, $J = 7.0$ Hz, 3H). δ_C: 139.6, 123.6, 68.3, 59.3, 39.7, 35.7, 32.6, 24.9, 16.6, 16.2. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.56; H, 11.57. (*R*)-(*E*)-**1**, $[\alpha]_D^{25} = +6.7$ (*c* 2.8, $CHCl_3$) {lit.[2b] $[\alpha]_D^{20} = +6.9$ (*c* 3.9, $CHCl_3$)}. (*S*)-(*Z*)-**1**, $[\alpha]_D^{25} = -7.8$ (*c* 2.0, $CHCl_3$) δ_H: 5.46 (m, 1H), 4.18 (m, 2H), 3.45 (d, $J = 7.0$ Hz, 2H), 2.1 (m, 2H), 1.8 (s, 3H), 1.7–1.4 (m, 4H), 1.1 (m, 1H), 0.94 (d, $J = 7.0$ Hz, 3H). δ_C: 140.2, 124.4, 68.4, 59.1, 35.5, 32.6, 31.8, 25.2, 23.5, 16.6. (*R*)-(*Z*)-**1**, $[\alpha]_D^{25} = +8.0$ (*c* 1.8, $CHCl_3$) {lit.[2b] $[\alpha]_D^{20} = +8.1$ (*c* 1.6, $CHCl_3$)}.

4.20. Jones' oxidation of diols for the synthesis of 2 and 2a

Jones' reagent was prepared as follows: CrO_3 (1.65 g, 0.017 mol) was dissolved in water (2.5 mL). The solution was cooled at 0 °C and then concentrated H_2SO_4 (1.45 mL) was added. The water was added up to 7 mL. Diols (86 mg, 0.5 mmol) were dissolved in 10 mL of acetone at 0 °C, and freshly prepared Jones' reagent was added to it until the orange brown color persisted. The mixture was stirred at room temperature for 30 min. After that time, water (10 mL) was added to it and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over Na_2SO_4. Evaporation and purification by flash chromatography yielded 80 mg of the diacid as a white solid (80% yield).

4.21. (*S*)-(*E*)-Callosobruchusic acid

$[\alpha]_D^{25} = +10.1$ (*c* 0.9, $CHCl_3$) {lit.[2b] $[\alpha]_D^{20} = +10.5$ (*c* 1.0, $CHCl_3$)}. δ_H: 5.7 (br s, 1H), 2.5 (m, 1H), 2.26 (t, $J = 7.0$ Hz, 2H), 2.2 (d, $J = 1.2$ Hz, 3H), 1.8–1.55 (m, 3H), 1.49 (m, 1H), 1.23 (d, $J = 7.0$ Hz, 3H). δ_C: 191.6, 182.8, 128.9, 115.3, 43.6, 39.3, 32.9, 30.1, 21.5, 17.1. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.85; H, 8.19.

4.22. (*R*)-(*E*)-Callosobruchusic acid

$[\alpha]_D^{25} = -10.5$ (*c* 4.2, $CHCl_3$) {lit.[2b] $[\alpha]_D^{20} = -10.9$ (*c* 7.6, $CHCl_3$)}.

4.23. (*S*)-(*Z*)-Callosobruchusic acid

$[\alpha]_D^{25} = +11.2$ (*c* 1.5, $CHCl_3$). δ_H: 5.75 (br s, 1H), 2.55 (m, 1H), 2.25 (t, $J = 7.0$ Hz, 2H), 2.18 (d, $J = 1.2$ Hz, 3H), 1.75–1.5 (m, 3H), 1.48 (m, 1H), 1.23 (d, $J = 7.0$ Hz, 3H). δ_C: 191.7, 183.0, 128.8, 115.4, 43.6, 39.3, 32.9, 30.1, 21.4, 17.0.

4.24. (*R*)-(*Z*)-Callosobruchusic acid

$[\alpha]_D^{25} = -11.5$ (*c* 2.0, $CHCl_3$) {lit.[2b] $[\alpha]_D^{20} = -11.0$ (*c* 2.0, $CHCl_3$)}.

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