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Asymmetric total synthesis of (−)-rasfonin

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ABSTRACT

An efficient chemoenzymatic asymmetric synthesis of pyranone containing natural product (−)-rasfonin is presented here. Enantioselective enzymatic desymmetrization (EED) and a unique *Gluconobacter oxydans* mediated oxidative kinetic resolution (OKR) have been successfully employed to install three stereocenters ($C_{6'}$, C_7, and C_9) of the target molecule. Stereoselective Achmatowicz reaction of a properly decorated furyl nucleus led to the core pyranone structure of rasfonin. At the late stage of the synthesis Negishi coupling has been used to complete the synthesis.

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1. Introduction

The protein *ras* functions as a molecular switch for signal transduction pathways that control cell growth and differentiation. Activating mutations in these *ras* proteins result in constitutive signaling, thereby stimulating cell proliferation and inhibiting apoptosis (programmed cell death), and most significantly, as an oncogene that is able to induce tumors in animals or cell cultures. Mutations in the *ras* family of proto-oncogenes (comprising H-ras, N-ras, and K-ras) are very common, being found in 20–30% of all human tumors.[1] Therefore the ras-signaling pathway has attracted considerable attention as a target for anticancer therapy because of its important role in carcinogenesis. Rasfonin, a new apoptosis inducer in *ras* dependent Ba/F3-V12 cells, was isolated by Hayakawa and co-workers from the fermented mycelium of *Talaromyces* species 3656-A1 in 2000.[2] Recent studies have indicated that (−)-rasfonin can selectively destroy *ras*-dependent cells with an IC_{50} of 0.16 μg/mL.[3] Ishibashi and co-workers reported that rasfonin suppressed proliferation of mouse splenic lymphocytes stimulated with the mitogens concanavalin A and lipopolysaccharide with IC_{50} values of 0.7 and 0.5 μg/mL, respectively.[4]

The first asymmetric total synthesis of rasfonin was reported by Ishibashi et al. in 2005.[5] Later on Boeckman Jr. group reported the total synthesis of rasfonin by applying asymmetric alkylation reaction based on a new chiral auxiliary.[6] Whereas our work is in progress another synthesis of rasfonin has been reported by Huang et al. involving asymmetric conjugate addition of MeMgBr and Achmatowicz reaction.[7] Herein we report the asymmetric synthesis of rasfonin by a chemoenzymatic approach. The retrosynthetic analysis of the target molecule rasfonin is presented in Scheme 1. The external double bond (between C_{11} and C_{12}) was introduced by Negishi carbozincation coupling reaction. The crucial ester linkage (between C_5 and $C_{1'}$) was planned to be constructed by Yamaguchi esterification reaction of an appropriately substituted acid (**A**) and alcohol fragment (**B**). The required acid and the alcohol fragments are constructed from the more easily available starting materials. The alcohol fragment is made by the crucial stereospecific Achmatowicz reaction of a properly functionalized furyl system. One stereocenter in the acid fragment ($C_{6'}$) and another stereocenter in the alcohol fragment (C_7) are thought to be constructed by applying EED strategy.[8] Whereas the remaining stereocenter (C_9) in the pyranone alcohol fragment is planned to be constructed by a novel oxidative kinetic resolution (OKR) reaction by *Gluconobacer oxydans*.[9]

2. Results and discussion

2.1. Synthesis of the acid fragment A

For the preparation of acid fragment **A** the synthesis starts from ethane-1,2-diol, selective mono protection of the diol with TBDPS–Cl (*tert*-butylchlorodiphenylsilane) afforded the mono TBDPS protected ether **1** in 80% yield.[10] The primary hydroxyl group in **1** was converted to its corresponding iodo compound **2** by treatment with TPP (triphenylphosphine), imidazole, and iodine in dry THF at −20 °C to room temperature in 94% yield.[11] This iodo compound was then coupled with diethyl malonate using sodium hydride as base at 0 °C to afford mono alkylated compound **3** in 72% yield. Reduction of the diester functionality in compound **3** with LAH in dry ether furnished the diol **4** in 85% yield. The initial EED reaction of compound **4** (enzymatic transesterification)[8] was optimized by employing many lipases, and it was found that lipase-AK (*Pseudomonas fluorescens*) provides the best result in terms of both enantioselectivity (ee=99%) and chemical yield (91%) of the synthesized

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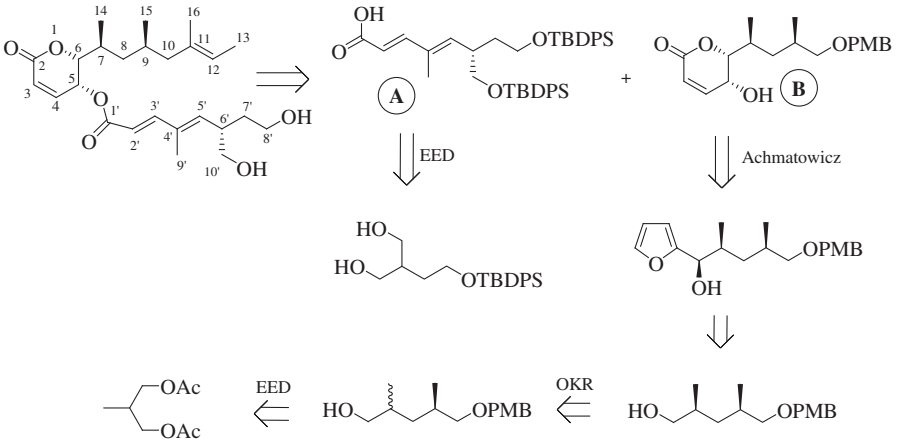


Scheme 1. Retrosynthetic analysis of rasfonin.

monoacetate product **5** (vinyl acetate was used as the acylating agent whereas diisopropyl ether was chosen as solvent). The initial optimization results are summarized in Table 1. The absolute configuration of the acetate **5** is established by chemical analogy, as the stereopreferences for EED reaction of similar 2-substituted 1,3-propane diol are well known in the literature.[8]

Table 1
EED reaction of 2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)propane-1,3-diol (**4**)

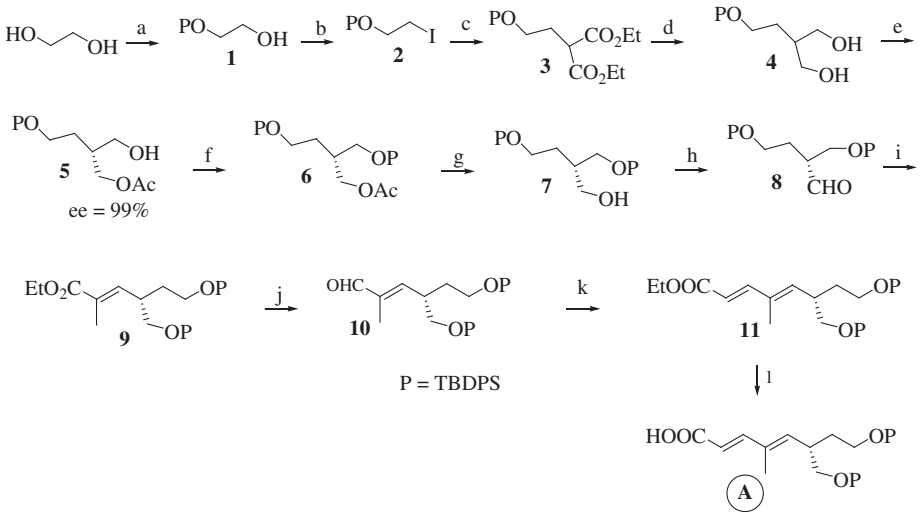
Entry	Lipases	Acyl donor	Yield[a] (%)	ee[b] (%)
1	Lipase AK-Amano	Vinyl acetate	91	99
2	Lipase AK-Amano	Isopropenyl acetate	88	94
3	Lipase PS-Amano	Vinyl acetate	80	82
4	Lipase PS-Amano	Isopropenyl acetate	76	88
5	Lipase A (Amano-6)	Vinyl acetate	56	68
6	Lipase F (AP 15)	Vinyl acetate	62	72
7	Lipase PS-D	Vinyl acetate	90	88
8	Lipase PS-D	Isopropenyl acetate	82	90
9	Novozym-435	Vinyl acetate	40	46
10	Lipozyme	Vinyl acetate	35	30
11	*Rhizopus arrhizus*	Vinyl acetate	22	nd[c]
12	*Candida lipolytica*	Vinyl acetate	20	nd[c]

[a] Isolated yield after purification by chromatography.
[b] Determined by chiral-HPLC (CHIRALCEL AS-H of the corresponding benzoyl derivative of monoacetate compound).
[c] Not determined.

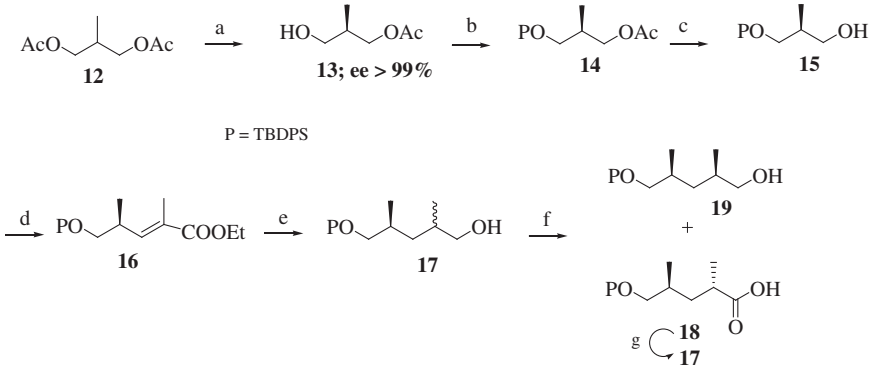
The free hydroxy group in the monoacetate **5** was protected as its TBDPS (*tert*-butyldiphenylsilyl) ether to afford compound **6** in 89% yield. Acetate group was then deprotected with K_2CO_3 in MeOH to yield compound **7** (92%). Oxidation of compound **7** under Swern condition afforded the corresponding aldehyde **8** in 90% yield.[12] Wittig olefination with (1-carbethoxyethylidene)-triphenylphosphorane of aldehyde **8** afforded the unsaturated ester compound **9** in 84% yield. Reduction of carboethoxy group by DIBAL–H (1 equiv) in dry DCM solvent at −78 °C afforded the corresponding unsaturated aldehyde **10** in 84% yield. Horner–Wadsworth–Emmons olefination reaction of aldehyde **10** using triethylphosphonoacetate yielded *E*-ester **11** in 86% yield. Hydrolysis of **11** with LiOH/THF afforded corresponding α, β-unsaturated acid **A** in 84% yield (Scheme 2; overall yield 17% from 1,2-ethane diol).

2.2. Synthesis of the α-pyranone alcohol fragment B

The synthesis starts from prochiral acetic acid 3-acetoxy-2-methyl-propyl ester (compound **12**). Enantioselective enzymatic desymmetrization (EED) of the diacetate **12** was performed by using Lipase PS-D (*Burkholderia cepacia*, immobilized on diatomite) as enzyme in phosphate buffer solution of pH 7.0[13] to yield the monoacetate **13** (yield=86%; ee>99%). The free hydroxy group in alcohol **13** was protected as its TBDPS (*tert*-butyldiphenylsilyl) ether by treatment with imidazole and TBDPS–Cl to afford the TBDPS-protected compound **14** in 89% yield. The acetate functionality was removed by treatment with K_2CO_3 in MeOH to yield enantiomerically pure **15** in 92% yield. Swern oxidation of compound **15** afforded the corresponding aldehyde, which upon Wittig olefination with (1-carbethoxyethylidene)-triphenylphosphorane afforded the unsaturated ester compound **16** in 88% yield in two steps. The olefinic unsaturation in compound **16** was reduced by $NiCl_2/NaBH_4$ followed by reduction of the ester functionality with LAH afforded alcohol **17** (as diastereomeric mixtures; 1:1) in 82% yield (in two steps; Scheme 3). With this alcohol **17** in our hand we have explored an OKR reaction (diastereoselecive enzymatic oxidation) reaction by *G. oxydans* (NCIMB 8035). Thus when a trial reaction (100 mg scale) was run with a 24 h submerged culture of *G. oxydans* in a biphasic solvent (isooctane/water=1:1), (2*S*,4*S*)-acid **18** (the fast reacting diastereomer; yield=48%) and (2*S*,4*R*)-alcohol **19** (slow reacting diastereomer; yield=45%; de=98%; Scheme 3) were obtained after 2 h of incubation in an orbital incubator shaker. Formation of little amount of aldehyde was also detected during the course of the reaction. Similar kind of enantioselective oxidation of racemic 2-phenyl-propan-1-ol with the whole cells of *G. oxydans* is earlier documented in the literature.[14] But to the best of our knowledge this is the first example of a biocatalytic diastereoselective oxidative kinetic resolution by *G. oxydans*. The reaction was next performed in 10 g scale, and similar product distribution was obtained. When the oxidation was kept for longer time (more than 3 h; Table 2), the major product obtained was the acid-**18** (82% yield). For our synthetic exercise we need the (2*S*,4*R*) alcohol-**19**, hence the oxidation was stopped after 2 h interval. The acid **18** can be converted back to alcohol **17** by a two-step epimerization reaction. Thus when acid **18** was refluxed with DBU in THF solvent it afforded the epimerized acid, which was further reduced with LAH to furnish the alcohol **17** (88% in two steps). The alcohol **17** then again can be used in the initial oxidation step. Though alcohol **19** can also be accessed by EED reaction of *meso*-2,4-dimethylpentane-1,5-diol.[15] But it seems that the precursor *meso*-2,4-dimethylglutaric anhydride is difficult to synthesize in large scale.[16] We have initially tried to synthesize the *meso*-anhydride but unable to produce it in a large-scale setup. Actually the fractional crystallization step for separating out the *meso*-anhydride from the (*dl*)-anhydride is extremely tedious and needs careful optimization. As the (*dl*)-anhydride needs to be thrown out, the

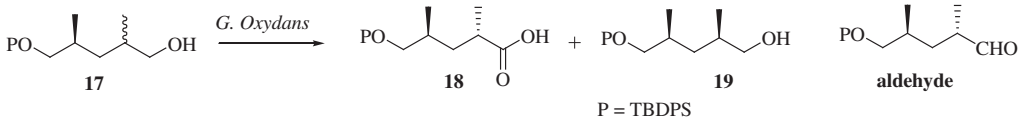


Scheme 2. Preparation of the acid fragment. Reagents and conditions: (a) TBDPS–Cl, imidazole, dry THF (tetrahydrofuran), 0 °C to rt, 80%; (b) I_2, TPP (triphenylphosphine), imidazole, dry THF, 94%; (c) $CH_2(CO_2Et)_2$, NaH, dry THF, 0 °C, 30 min, reflux 12 h, 72%; (d) $LiAlH_4$, dry ether, 0 °C, 85%; (e) vinyl acetate, Lipase-AK, *i*-Pr_2O, 4 Å MS, rt, 91%; (f) TBDPS–Cl, imidazole, DMAP (5 mol %), dry DCM (CH_2Cl_2), 89%; (g) K_2CO_3, MeOH, rt, 92%; (h) $(COCl)_2$, DMSO, Et_3N, dry DCM, −78 °C; (i) $Ph_3P(CHMe)CO_2Et$, dry DCM, 0 °C to rt, 84%; (j) DIBAL–H, dry DCM, −78 °C, 84%; (k) $(EtO)_2POCH_2CO_2Et$, NaH, dry THF, 0 °C to rt, 86%; (l) LiOH, THF/H_2O (5:1), rt, 84%.



Scheme 3. A novel oxidative kinetic resolution by *G. oxydans* and EED reaction for the construction of C_9 and C_7 stereocenters. Reagents and conditions: (a) Lipase PS-D, phosphate buffer (pH=7.0), 86%; (b) TBDPS–Cl, Im, DMAP (5 mol %), dry DCM, 0 °C to rt, 89%; (c) K_2CO_3, MeOH, rt, 92%; (d) (i) $(COCl)_2$, DMSO, Et_3N, dry DCM, −78 °C; (ii) $Ph_3P(CMe)CO_2Et$, dry DCM, 88%; (e) (i) $NiCl_2$, $NaBH_4$, MeOH, 0 °C to rt, (ii) LAH, dry THF, 0 °C, 82%; (f) *G. oxydans*, rt, de=96%, yield=45%; (g) DBU, dry THF, reflux, 2 h; (ii) LAH, dry ether, rt, 88% (over two steps).

Table 2
Product distribution in the oxidative kinetic resolution of alcohol **17** by *G. oxydans*



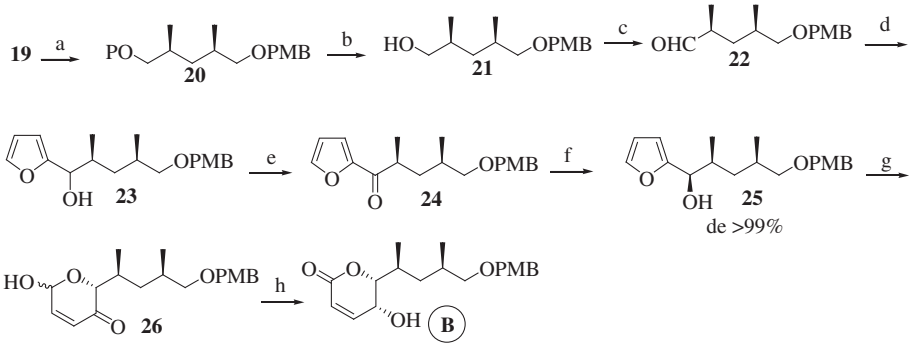
Time (h)	Yield of **18** (%)[a]	Yield of **19** (%)	Yield of aldehyde (%)
1	32	28	10
2	48	45	<5
3	68	20	<5
5	82	15	Nd[b]

[a] The reaction is performed in a biphasic medium (water/isooctane=1:1; subs concentration is 10 g/L) in a rotary shaker. Yields are obtained as isolated yield after purification.
[b] Not detected.

yield of the overall process becomes significantly lower. Whereas in our case we are able to synthesize the required (2*S*,4*R*) alcohol **19** with moderate yield and excellent enantio/diastereo controlled manner though the synthetic steps are little lengthy. Though alcohol oxidases from *Acetobacter* and *Gluconobacter* sp. are well known for their efficiency, but their synthetic utility has not been explored at all.

The alcohol functionality in compound **19** was then protected as its PMB ether by treating with PMB-imidate in the presence of a catalytic amount of CSA (camphor sulfonic acid) furnished PMB and TBDPS protected compound **20** in 86% yield.[17] Deprotection of the TBDPS group was achieved by treating with TBAF/THF[18] at room temperature to afford mono PMB protected compound **21** in 88% yield. Compound **21** is known in the literature,[19] and by comparing its optical rotation value with our synthesized product the absolute configuration of alcohol **19** obtained in the diastereoselective enzymatic oxidation step was confirmed. Swern oxidation of this alcohol **21** afforded the corresponding aldehyde **22** in 90% yield.

Addition of 2-lithiofuran to aldehyde **22** at room temperature gave the compound **23** in 76% yield. Oxidation of the free hydroxy group under several reaction conditions (Swern, Dess–Martin periodinane, TPAP–NMO, IBX) afforded the ketone product **24** with subsequent epimerization at the α-carbon (approximately 1:1 mixture of formation of two epimers have been indicated in ^{13}C NMR analysis). However oxidation with large excess of activated MnO_2[20] afforded the corresponding ketone **24** without any epimerization, which was immediately converted to alcohol **25** by stereoselective reduction with L-Selectride[21] and 35% aqueous H_2O_2 at −78 °C in 85% yield (de >99%). The high diastereoselectivity in the L-Selectride reduction can be explained by invoking Felkin–Ahn type transition state in which the PMB containing appendage act as the largest substituent.[21b] Stereospecific Achmatowicz reaction[22] of **25** with $NaHCO_3$, NaOAc, and NBS (*N*-bromosuccinimide) afforded compound **26** (as a mixture of diastereomers as indicated in ^1H NMR analysis) in 90% yield. Oxidation of the lactol functionality in **26** to the corresponding lactone was achieved by PCC (pyridinium chlorochromate) and the lactone was subsequently reduced stereoselectively, without further purification by Luche reduction[23] to afford the desired alcohol fragment **B** in 74% yield (over two steps, Scheme 4, overall yield=6.7% from compound **12**).



Scheme 4. Reagents and conditions: (a) PMB-imidate, CSA (5 mol %), cyclohexane/DCM (2:1), 86%; (b) TBAF, dry THF, 0 °C, 88%; (c) $(COCl)_2$, DMSO, Et_3N, dry DCM, −78 °C, 90%; (d) furan, *n*-BuLi, dry THF, rt (3 h), 0 °C, 76%; (e) MnO_2, dry DCM, 0 °C-rt, 74%; (f) L-Selectride, dry THF, −78 °C, 85%; (g) $CH_3COONa·3H_2O$, $NaHCO_3$, NBS, THF/H_2O (4:1), 90%; (h) (i) PCC, CH_3COONa, Celite, dry DCM, 0 °C to rt; (ii) $CeCl_3·7H_2O$, $NaBH_4$, dry DCM, anhydrous MeOH, −78 °C, 74% (over two steps).

2.3. Coupling of acid fragment A and alcohol fragment B for the total synthesis of (−)-rasfonin

After successful construction of both the required fragments **A** and **B**, the remaining task was to couple the two fragments followed by functional group manipulation. Yamaguchi coupling[24] of α-pyranone alcohol fragment **B** with diene acid **A** afforded compound **27** in 84% yield. Removal of the PMB group was achieved with DDQ[25] to afford alcohol **27** in 80% yield. In this stage of synthesis we have realized that the remaining task can be accomplished by performing a successful C–C cross coupling reaction (sp^3–sp^2) to attach the 2-butenyl side chain. Therefore the primary hydroxy group in compound **28** was transformed to its corresponding iodo compound **29** by treatment with triphenylphosphine (TPP), imidazole, and iodine. Initially iron-catalyzed [$FeCl_3$ or $Fe(acac)_3$] cross-coupling reaction[26] between iodo compound **29** and vinyl Grignard generated from *E*-2-bromobutene was attempted, but with our dismay we could not detect the formation of product **30**. Later on lithiated species generated from *E*-2-bromobutene and *t*-BuLi was used as the sp^2 coupling partner.[27] Though we were able to isolate compound **30** this time, but the miserably low yield (<10%) forced us to search for other alternatives. Careful optimization was performed to get the best possible result, and it was found that coupling reaction of the iodo compound **29** with *E*-2-bromobutene under Negishi condition[28] afforded compound **30** in 76% yield. Finally deprotection of the TBDPS groups was achieved by treating compound **30** with HF/pyridine[29] in dry THF afforded our target molecule (−)-rasfonin (Scheme 5; overall yield=2.46% from compound **12** and 5.3% from ethane-1,2-diol).

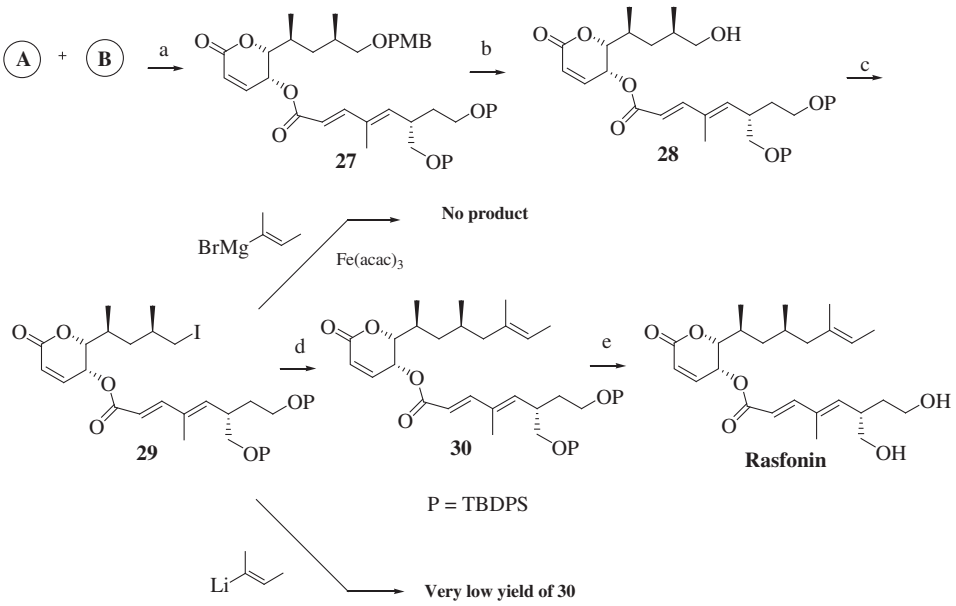
3. Conclusion

In conclusion we have described an efficient asymmetric synthesis of the α-pyranone-containing natural product, (−)-rasfonin in a divergent way. The main highlight of our synthetic strategy is to access two advanced intermediates in a chemoenzymatic way followed by functional group manipulation. A novel oxidative kinetic resolution catalyzed by *G. oxydans* has been employed successfully for the synthesis of one of the intermediate. The other key reactions, which have been successfully applied for the total synthesis of rasfonin are Negishi coupling, Yamaguchi esterification and stereospecific Achmatowicz reaction.

4. Experimental section

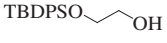
4.1. Materials and methods

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM), dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Diisopropyl ether (DIPE) was refluxed over P_2O_5 and distilled prior to use. Vinyl acetate and isopropenyl acetate were freshly distilled prior to use. Lipase AK (from *P. fluorescens*), lipase PS (from *B. cepacia*), lipase PS-D (immobilized on diatomite), lipase-A (from *Candida antarctica*), lipase-F (from *Rhizopus oryzae*), Novozym-435 (lipase acrylic resin from *C. antarctica*), and lipozyme (immobilized from *Mucor miehei*) were obtained from commercial suppliers and used as obtained. *G. oxydans* (NCIMB 8035) was obtained from NCIMB culture collection and grown as specified in the catalog. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silicagel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 400 and 200 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 ^1H and ^{13}C, respectively. Mass spectroscopic analysis was performed in the IICT, Hyderabad (TOF analyzer). Optical rotations were measured on a digital polarimeter. HPLC analysis was performed with CHIRALPAK AD-H and AS-H (Daicel) columns.



Scheme 5. Synthesis of (−)-rasfonin. Reagents and conditions: (a) **A**, Et_3N, 2,4,6-trichlorobenzoyl chloride, dry toluene, rt, 1 h, then **B**, dry toluene, DMAP, rt, 5 h, 84%; (b) DDQ, DCM/H_2O (19:1), 0 °C, 80%; (c) I_2, Ph_3P, imidazole, dry DCM, 0 °C to rt; 85%; (d) Zn/Cu, dry toluene/dimethylacetamide (19:1), 70 °C, [$Pd(PPh_3)_4$] (5 mol %), *E*-2-bromobutene, 60 °C, 76%; (e) HF/pyridine, dry THF, rt, 48 h, 72%.

4.2. 2-(*tert*-Butyldiphenylsilyloxy)ethanol (1)

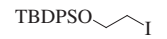


Ethane-1,2-diol (1.52 g, 24.2 mmol) was taken in anhydrous THF (100 mL) and cooled to 0 °C. Imidazole (3.0 g, 44.4 mmol) and DMAP (catalytic) were added to the reaction mixture followed by the addition of TBDPS–Cl (10.5 mL, 40.3 mmol). The reaction mixture was allowed to warm at room temperature, after 24 h water was added to the reaction mixture and it was extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the organic solvent and purification by silica gel chromatography (3:1; hexane/EtOAc) yielded the mono TBDPS-protected diol **1** as a liquid, in 80% yield (5.79 g).

R_f=0.2 (EtOAc/hexane=1:3).

δ_H ($CDCl_3$, 200 MHz): 7.75–7.70 (m, 4H), 7.45–7.42 (m, 6H), 3.82–3.70 (m, 4H), 2.32 (t, *J*=6.0 Hz, 1H), 1.12 (s, 9H).

4.3. *tert*-Butyl(2-iodoethoxy)diphenylsilane (2)



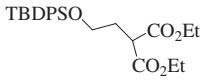
Ph_3P (4.63 g, 17.7 mmol) and imidazole (3.1 g, 45 mmol) were added to a solution of alcohol **1** (4.5 g, 15 mmol) in dry THF (60 mL). The suspension was cooled to −20 °C, and I_2 (4 g, 15.8 mmol) was added to the solution. After being stirred for 30 min, the reaction mixture was warmed to room temperature, and further stirred for 1.5 h. After that the reaction mixture was cooled to 0 °C, and poured into saturated aqueous solution of $NaHCO_3$ (50 mL). The mixture was then extracted with Et_2O (2×60 mL), and the organic extract was washed with saturated aqueous $Na_2S_2O_3$ and brine. The organic extract was dried ($MgSO_4$) and evaporated. The crude iodo compound was then purified by flash chromatography (40:1; hexane/EtOAc) to afford **2** in 94% yield (colorless liquid, 5.77 g).

R_f=0.9 (EtOAc/hexane=1:10).

δ_H ($CDCl_3$, 200 MHz): 7.72–7.68 (m, 4H), 7.46–7.38 (m, 6H), 3.89 (t, *J*=6.8 Hz, 2H), 3.24 (t, *J*=6.6 Hz, 2H), 1.11 (s, 9H).

δ_C ($CDCl_3$, 50 MHz): 135.6, 133.3, 129.9, 127.8, 64.7, 26.8, 19.3, 6.8.

4.4. Diethyl 2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)malonate (3)



Sodium hydride (60% suspension in mineral oil, 640 mg, 16.0 mmol) was taken in 65 mL anhydrous THF, then diethyl malonate (2.56 g, 16 mmol) was added at 0 °C. After 0.5 h, compound **2** (6.54 g, 16 mmol) was added and the reaction mixture was refluxed for 12 h. After that time water was added at 0 °C and the reaction mixture was extracted with EtOAc, the organic layer was successively washed with brine and dried ($MgSO_4$). The organic extract was evaporated in vacuo and purified by silica gel chromatography (10:1; hexane/EtOAc) to afford the diethyl malonate derivative **3** in 72% yield (5.09 g) as a clear liquid.

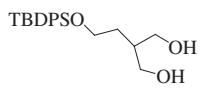
R_f=0.4 (EtOAc/hexane=1:5).

IR (film): 2920, 2855, 1742, 1465, 1427 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.68–7.63 (m, 4H), 7.43–7.35 (m, 6H), 4.25–4.11 (m, 4H), 3.77–3.67 (m, 3H), 2.23–2.13 (m, 2H), 1.26 (t, *J*=7.2 Hz, 6H), 1.05 (s, 9H).

δ_C ($CDCl_3$, 50 MHz): 169.6, 135.5, 133.5, 129.7, 127.7, 61.4, 61.2, 48.7, 31.5, 26.8, 19.2, 14.1.

4.5. 2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)propane-1,3-diol (4)



LAH (750 mg, 19.7 mmol) was taken in 70 mL dry ether followed by addition of the malonate derivative **3** (5.8 g, 13.14 mmol) at 0 °C. After 1 h, saturated solution of Na_2SO_4 was carefully added to quench the reaction mixture. Then the reaction solution was filtered by washing with hot Et_2O for several times and then it was concentrated in vacuo. The crude product was purified by flash chromatography (1:1; hexane/EtOAc) to afford compound **4** as a thick liquid (4.0 g, yield 85%).

R_f=0.2 (EtOAc/hexane=1:1).

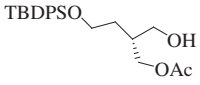
IR (film): 3420, 2925, 2855, 1435 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.73–7.69 (m, 4H), 7.44–7.42 (m, 6H), 3.8–3.72 (m, 6H), 1.95 (m, 1H), 1.65–1.56 (m, 2H), 1.10 (s, 9H).

δ_C ($CDCl_3$, 50 MHz): 135.6, 133.4, 129.8, 127.8, 65.1, 62.4, 40.2, 31.2, 26.9, 19.2.

HRMS (ESI) for $C_{21}H_{30}O_3NaSi$ $[M+Na]^+$, calculated: 381.1862, found: 381.1858.

4.6. (*R*)-4-(*tert*-Butyldiphenylsilyloxy)-2-(hydroxymethyl)butyl acetate (5)



Compound **4** (2.04 g, 5.6 mmol) was taken in 25 mL of anhydrous DIPE (di-isopropyl ether). Lipase-AK (276 mg) was added to the reaction mixture, followed by addition of vinyl acetate (0.52 mL, 5.6 mmol) and powdered molecular sieves (4 Å, 200 m). The reaction mixture was stirred under an argon atmosphere in room temperature. The progress of the reaction was monitored by TLC measurement. After 100% conversion, it was filtered on a Celite pad, washed by ether and evaporated to dryness. The crude product was purified by flash chromatography (5:1; hexane/EtOAc) to afford the (*R*)-mono acetate compound **5** in 91% yield (2.03 g) as a clear liquid.

R_f=0.4 (EtOAc/hexane=1:3).

$[\alpha]_D^{25}$ +20.57 (*c* 1.0, $CHCl_3$).

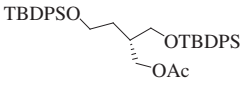
IR (film): 3400, 2955, 2855, 1745, 1427 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.7–7.66 (m, 4H), 7.46–7.38 (m, 6H), 4.21–4.04 (m, 2H), 3.79–3.73 (m, 2H), 3.61 (d, *J*=5.2 Hz, 2H), 2.77 (br, 1H, –OH), 2.1 (m, 1H), 2.07 (s, 3H), 1.67–1.58 (m, 2H), 0.99 (s, 9H).

δ_C ($CDCl_3$, 50 MHz): 171.6, 135.6, 133.3, 129.8, 127.7, 64.8, 62.8, 62.0, 38.3, 31.2, 26.8, 20.9, 19.1.

HRMS (ESI) for $C_{23}H_{32}O_4NaSi$ $[M+Na]^+$, calculated: 423.1968, found: 423.1974.

4.7. (*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)butyl acetate (6)



Mono acetate compound **5** (1.92 g, 4.8 mmol) was taken in anhydrous DCM (25 mL) and cooled to 0 °C. Imidazole (650 mg, 9.5 mmol) and DMAP (catalytic) were added to the reaction mixture followed by the addition of TBDPS–Cl (1.5 mL, 5.7 mmol). The reaction mixture was allowed to warm at room temperature for 3 h, after which water was added to it and extracted with DCM, the organic layer was washed with brine and dried over $MgSO_4$. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (10:1; hexane/EtOAc) to afford compound **6** in 89% yield (2.73 g) as a viscous liquid.

R_f=0.4 (EtOAc/hexane=1:10).

$[\alpha]_D^{25}$ +12.89 (*c* 1.0, $CHCl_3$).

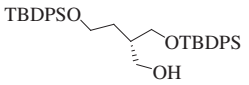
IR (film): 3045, 1750, 1465, 1427 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.74–7.71 (m, 8H), 7.52–7.43 (m, 12H), 4.24 (d, *J*=5.8 Hz, 2H), 3.81–3.64 (m, 4H), 2.26–2.18 (m, 1H), 2.04 (s, 3H), 1.77–1.71 (m, 2H), 1.13 (s, 18H).

δ_C ($CDCl_3$, 50 MHz): 171.1, 135.7, 134.0, 133.7, 129.7, 127.8, 64.8, 63.4, 61.8, 37.2, 31.2, 27.0, 21.0, 19.4, 19.3.

HRMS (ESI) for $C_{39}H_{50}O_4NaSi_2$ $[M+Na]^+$, calculated: 661.3145, found: 661.3149.

4.8. (*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)butan-1-ol (7)



The acetate group in compound **6** (3.84 g, 5.95 mmol) was deprotected by adding K_2CO_3 (410 mg, 2.97 mmol) in MeOH (25 mL) solvent. After completion of the reaction, as indicated by TLC, MeOH was evaporated under reduced pressure. The residue was taken in Et_2O, and washed successively with water and brine. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure to afford the crude product. The crude product was then purified by flash chromatography (3:1; hexane/EtOAc) to afford compound **7** in 92% yield (3.32 g) as a liquid.

R_f=0.3 (EtOAc/hexane=1:5).

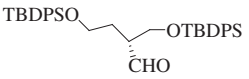
$[\alpha]_D^{25}$ +8.89 (*c* 1.0, $CHCl_3$).

IR (film): 3355, 3069, 2905, 1465, 1427 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.68–7.65 (m, 8H), 7.41–7.34 (m, 12H), 3.79–3.6 (m, 6H), 2.96–2.9 (m, 1H), 1.61–1.52 (m, 2H), 1.06 (s, 9H), 1.04 (s, 9H).

δ_C ($CDCl_3$, 50 MHz): 135.6, 133.6, 133.3, 129.8, 129.7, 127.8, 127.7, 66.7, 65.4, 62.2, 40.2, 31.2, 26.9, 19.2.

4.9. (*R*)-4-(*tert*-Butyldiphenylsilyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)butanal (8)



Oxalyl chloride (0.4 mL, 4.1 mmol) was taken in dry DCM (50 mL). Dry DMSO (0.6 mL, 8.1 mmol) was added to the reaction mixture slowly and the temperature was maintained at −78 °C. After 20 min, alcohol **7** (1.61 g, 2.7 mmol) taken in DCM (10 mL) was added to the reaction mixture. The reaction mixture was kept at −78 °C for 50 min. Then Et_3N (2.3 mL, 16.2 mmol) was added and the mixture is allowed to attain room temperature. After that water was added to it and extracted with DCM, the organic layer was washed with $NaHCO_3$ solution and brine and dried over $MgSO_4$. The reaction mixture was evaporated in vacuo to afford the crude aldehyde **8** as a clear liquid.

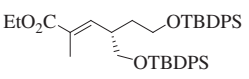
R_f=0.9 (EtOAc/hexane=1:5).

IR (film): 2925, 1730, 1455, 1405 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 9.49 (s, 1H), 7.68–7.63 (m, 8H), 7.51–7.31 (m, 12H), 3.79 (t, *J*=6.6 Hz, 4H), 2.53–2.48 (m, 3H), 1.04 (18H).

δ_C ($CDCl_3$, 50 MHz): 194.4, 135.6, 133.7, 129.6, 127.7, 61.8, 61.6, 51.1, 31.1, 26.8, 19.2.

4.10. (*S*,*E*)-Ethyl-6-(*tert*-butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy)methyl)-2-methylhex-2-enoate (9)



In an argon atmosphere the crude aldehyde **8** (1.62 g, 2.7 mmol) was taken in 16 mL of dry DCM. Then a precooled (0 °C) solution of ylide ((1-carbethoxyethylidene)-triphenylphosphorane) (2.44 g, 6.76 mmol) in DCM was added to the aldehyde solution. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 24 h. After that water was added to it and extracted with DCM, the organic layer was washed with brine and dried over $MgSO_4$. The organic extract was evaporated in vacuo to give the crude product, which was purified by

silica gel chromatography (8:1; hexane/EtOAc) to afford the unsaturated ester compound **9**, in 84% yield (1.53 g) as a liquid.

R_f=0.6 (EtOAc/hexane=1:20).

$[\alpha]_D^{25}$ +4.69 (*c* 1.06, $CHCl_3$).

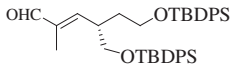
IR (film): 3069, 2925, 2855, 1710, 1465, 1427 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.76–7.62 (m, 8H), 7.39–7.32 (m, 12H), 6.62 (d, *J*=10.2 Hz, 1H), 4.27–4.11 (m, 2H), 3.63–3.57 (m, 4H), 2.99–2.94 (m, 1H), 2.04–1.92 (m, 1H), 1.82 (s, 3H), 1.61–1.46 (m, 1H), 1.25 (t, *J*=6.0 Hz, 3H), 1.04 (s, 18H).

δ_C ($CDCl_3$, 50 MHz): 168.0, 143.3, 135.6, 135.5, 133.8, 133.6, 129.6, 129.2, 127.6, 66.4, 61.7, 60.4, 38.3, 34.2, 26.8, 19.3, 19.2, 14.3, 12.8.

HRMS (ESI) for $C_{42}H_{54}O_4NaSi_2$ $[M+Na]^+$, calculated: 701.3458, found: 701.3462.

4.11. (*S*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)-4-((*tert*-butyldiphenylsilyloxy)methyl)-2-methylhex-2-enal (10)



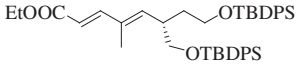
Compound **9** (1.55 g, 2.3 mmol) was taken in dry DCM (15 mL) and cooled to −78 °C. A solution of DIBAL–H (1 M in DCM, 2.3 mL, 2.3 mmol) was added over 15 min. The reaction mixture was stirred for a further 2 h at the same temperature then warmed to room temperature and quenched with dry methanol and stirred for a further 1.5 h. Then the content of the reaction mixture was extracted with DCM, brine and dried over $MgSO_4$. The organic extract was evaporated to dryness to afford the aldehyde **10**, which was directly used for the next step without further purification.

R_f=0.5 (EtOAc/hexane=1:20).

δ_H ($CDCl_3$, 200 MHz): 9.32 (s, 1H), 7.64–7.58 (m, 8H), 7.43–7.31 (m, 12H), 6.25 (dd, *J*=10.0, 1.4 Hz, 1H), 3.75–3.57 (m, 4H), 3.12–3.07 (m, 1H), 2.01–1.92 (m, 1H), 1.7 (s, 3H), 1.62–1.5 (m, 1H), 1.0 (s, 18H).

δ_C ($CDCl_3$, 50 MHz): 195.6, 156.3, 140.5, 135.8, 135.71, 135.67, 133.8, 133.6, 129.96, 129.87, 127.9, 127.86, 66.3, 61.6, 38.7, 27.0, 19.4, 19.3, 9.6.

4.12. (*S*,2*E*,4*E*)-Ethyl-8-(*tert*-butyldiphenylsilyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-4-methylocta-2,4-dienoate (11)



NaH (63 mg, 1.58 mmol) was taken in 5 mL anhydrous THF, then triethylphosphonoacetate (0.32 mL, 1.58 mmol) was added at 0 °C. After 0.5 h, aldehyde (**10**) (1.05 g, 1.58 mmol) was added and the reaction mixture was warmed to room temperature. After that time water was added at 0 °C and the reaction mixture was extracted with Et_2O, the organic layer was successively washed with brine and dried ($MgSO_4$). The crude product was then purified by flash chromatography (30:1; hexane/EtOAc) to afford ester **11** in 86% yield (977 mg) as a clear liquid.

R_f=0.3 (EtOAc/hexane=1:30).

$[\alpha]_D^{25}$ +6.55 (*c* 1.88, $CHCl_3$).

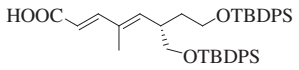
IR (film): 3069, 2931, 2858, 1713, 1624, 1469, 1427, 1300 cm^{-1}.

δ_H ($CDCl_3$, 400 MHz): 7.68–7.64 (m, 8H), 7.45–7.39 (m, 12H), 7.32 (d, *J*=15.6 Hz, 1H), 5.83 (d, *J*=16.0 Hz, 1H), 5.66 (d, *J*=9.6 Hz, 1H), 4.28 (q, *J*=7.2 Hz, 2H), 3.65–3.56 (m, 4H), 3.02–3.0 (m, 1H), 1.98–1.96 (m, 1H), 1.77 (s, 3H), 1.49–1.46 (m, 1H), 1.36 (t, *J*=7.2 Hz, 3H), 1.08 (s, 18H).

δ_C ($CDCl_3$, 50 MHz): 167.6, 149.6, 143.5, 135.73, 135.65, 134.3, 133.9, 133.7, 129.75, 127.7, 116.0, 66.8, 61.7, 60.2, 38.3, 34.5, 26.9, 19.3, 19.2, 14.4, 12.7.

HRMS (ESI) for $C_{44}H_{56}O_4NaSi_2$ $[M+Na]^+$, calculated: 727.3615, found: 727.3611.

4.13. (*S*,2*E*,4*E*)-8-(*tert*-Butyldiphenylsilyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-4-methylocta-2,4-dienoic acid, A



The unsaturated ester **11** (740 mg, 1.03 mmol) was taken in 6 mL of THF/water (5:1). LiOH (50 mg, 2.1 mmol) was added to it and the solution was stirred at room temperature for 48 h. After that time it was extracted several times with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (1:1; hexane/EtOAc) to afford the unsaturated acid **A** in 84% yield (597 mg) as a gummy liquid.

R_f=0.4 (EtOAc/hexane=1:5).

$[\alpha]_D^{25}$ −2.78 (*c* 0.25, $CHCl_3$).

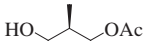
IR (film): 2922, 2852, 1849, 1755, 1655, 1561, 1459 cm^{-1}.

δ_H ($CDCl_3$, 400 MHz): 7.64–7.61 (m, 8H), 7.44–7.34 (m, 13H), 5.79 (d, *J*=15.6 Hz, 1H), 5.67 (d, *J*=9.6 Hz, 1H), 3.64–3.52 (m, 4H), 2.99–2.94 (m, 1H), 1.95–1.90 (m, 1H), 1.74 (s, 3H), 1.49–1.43 (m, 1H), 1.04 (s, 18H).

δ_C ($CDCl_3$, 100 MHz): 172.4, 151.8, 144.8, 135.6, 135.5, 135.48, 135.4, 134.1, 133.7, 133.6, 133.5, 129.62, 129.58, 129.55, 127.60, 127.58, 115.0, 66.6, 61.5, 38.2, 34.3, 26.8, 19.2, 19.1, 12.6.

HRMS (ESI) for $C_{42}H_{52}O_4NaSi_2$ $[M+Na]^+$, calculated: 699.3302, found: 699.3308.

4.14. (*R*)-3-Hydroxy-2-methylpropyl acetate (13)

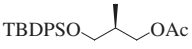


To a stirred suspension of diacetate **12** (9.08 g) in phosphate buffer solution (60 mL) of pH 7.0 at 37 °C was added the enzyme lipase (PSD, 1.3 g). The pH of the suspension was kept constant by the continuous addition of 0.2 M aqueous NaOH using an automatic titrator. The reaction was monitored by TLC (hexane/EtOAc; 3:1). When the desired degree of conversion was reached, the reaction was quenched by the addition of ether (50 mL) and the layers were separated. The aqueous layer was further extracted with ether (3×25 mL) and the combined extracts were washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated. The crude reaction mixture was purified by silica gel chromatography (3:1; hexane/EtOAc) to give the optically active monoester product **13** as yellow oil in 86% yield (5.87 gm).

R_f=0.3 (EtOAc/hexane=1:3).

$[\alpha]_D^{25}$ −10.2 (*c* 1.0, $CHCl_3$), {lit[10] $[\alpha]_D^{25}$ −10.0 (*c* 1.2, $CHCl_3$)}. The optical and spectroscopy data are in good agreement with reported values.

4.15. (*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropyl acetate (14)



Mono acetate compound **13** (8.62 g, 65 mmol) was taken in anhydrous DCM (250 mL) and cooled to 0 °C. Imidazole (8.92 g, 130 mmol) and DMAP (catalytic) were added to the reaction mixture followed by the addition of TBDPS–Cl (20 mL, 78.2 mmol). The reaction mixture was allowed to warm at room temperature for 3 h, after which water was added to it and extracted with DCM, the organic layer was washed with brine and dried over $MgSO_4$. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (10:1; hexane/EtOAc) to afford the TBDPS-protected compound **14** in 89% yield (21.43 g) as a clear liquid.

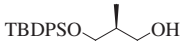
R_f=0.5 (EtOAc/hexane=1:5).

$[\alpha]_D^{25}$ +17.04 (*c* 1.0, $CHCl_3$).

δ_H ($CDCl_3$, 200 MHz): 7.69–7.64 (m, 4H), 7.41–7.38 (m, 6H), 4.18–4.00 (m, 2H), 3.59 (dd, *J*=7.2, 4.0 Hz, 2H), 2.11–2.05 (m, 1H), 2.01 (s, 3H), 1.06 (s, 9H), 0.97 (d, *J*=6.8 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 171.3, 135.8, 133.9, 129.8, 127.8, 66.4, 65.4, 35.4, 27.0, 21.1, 19.5, 13.9.

4.16. (*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-methylpropan-1-ol (15)



The acetate group in compound **14** (24.22 g, 65.2 mmol) was deprotected by adding K_2CO_3 (4.53 g, 33 mmol) in MeOH (100 mL) solvent. After completion of the reaction, as indicated by TLC, MeOH was evaporated under reduced pressure. The residue was taken in Et_2O, and washed successively with water and brine. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The product was purified by flash chromatography (3:1; hexane/EtOAc) to afford compound **15** in 92% yield (19.73 g) as a liquid.

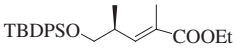
R_f=0.3 (EtOAc/hexane=1:5).

$[\alpha]_D^{25}$ +3.84 (*c* 1.1, $CHCl_3$).

δ_H ($CDCl_3$, 200 MHz): 7.71–7.67 (m, 4H), 7.44–7.38 (m, 6H), 3.78–3.57 (m, 4H), 2.61 (br, 1H, –OH), 2.05–1.96 (m, 1H), 1.08 (s, 9H), 0.85 (d, *J*=7.0 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 135.6, 133.2, 129.8, 127.8, 68.7, 67.6, 37.3, 26.8, 19.2, 13.2.

4.17. (*S,Z*)-Ethyl-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-enoate (16)



Oxalyl chloride (3.6 mL, 41.2 mmol) was taken in dry DCM (160 mL). Dry DMSO (5.9 mL, 82.4 mmol) was added after maintaining the reaction temperature at −78 °C. After 20 min, alcohol **15** (9 g, 27.5 mmol) dissolved in dry DCM was added (40 mL). The reaction mixture was kept at −78 °C for 50 min. Then Et_3N (22.9 mL, 164.9 mmol) was added and the solution was allowed to attain room temperature for a while. After that water was added to it and extracted with DCM, the organic layer was washed with $NaHCO_3$ solution and brine and dried over $MgSO_4$. The organic solvent was evaporated in vacuo to afford the crude aldehyde.

In an argon atmosphere the crude aldehyde was taken with dry DCM (125 mL). Then a precooled (0 °C) solution of ylide ((1-carbethoxyethylidene)-triphenylphosphorane) (24.8 g, 68.7 mmol) in DCM (25 mL) was added to the aldehyde solution. The mixture was stirred at 0 °C for 30 min and then warmed to room temperature and stirred for an additional 24 h. After that time water was added to it and was extracted with DCM, the organic layer was washed with brine and dried over $MgSO_4$. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (20:1; hexane/EtOAc) yielded the unsaturated ester compound **16**, in 88% yield (9.93 g) as a liquid (over two steps).

R_f=0.4 (EtOAc/hexane=1:20).

$[\alpha]_D^{25}$ +6.56 (*c* 1.3, $CHCl_3$).

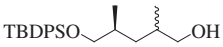
IR (film): 3049, 2855, 1710, 1680, 1465, 1427 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.70–7.66 (m, 4H), 7.42–7.35 (m, 6H), 6.63 (d, *J*=9.8 Hz, 3H), 4.21 (q, *J*=7.0 Hz, 2H), 3.58 (d, *J*=6.2 Hz, 2H), 2.84–2.7 (m, 1H), 1.83 (s, 3H), 1.33 (t, *J*=7.2 Hz, 3H), 1.08 (s, 9H), 1.06 (d, *J*=7.0 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 168.2, 144.5, 135.6, 133.7, 129.7, 128.0, 127.7, 67.8, 60.4, 36.2, 26.8, 19.3, 16.3, 14.3, 12.6.

HRMS (ESI) for $C_{25}H_{34}O_3NaSi$ $[M+Na]^+$, calculated: 433.2175, found: 433.2179.

4.18. (4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylpentan-1-ol (17)



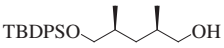
The unsaturated ester **16** (10.52 g, 25.7 mmol) was taken in MeOH (100 mL), $NiCl_2$ (6.21 g, 26.15 mmol) was added to the reaction mixture at 0 °C. The temperature of the reaction was kept at 0 °C, after 0.5 h $NaBH_4$ (5.43 g, 141.0 mmol) was added to the reaction mixture. The reaction mixture was then allowed to warm at room temperature. After completion of the reaction, as indicated by TLC, MeOH was evaporated under reduced pressure. The residue was taken in EtOAc, and washed successively with water and brine. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure.

The crude product was used in the next step without further purification. LAH (1.46 g, 38.5 mmol) was taken in 120 mL dry ether then the ester was added at 0 °C. After 1 h, saturated solution of Na_2SO_4 was added slowly to quench the reaction mixture. Then the reaction solution was filtered by washing with hot Et_2O at several times. The reaction mixture was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (3:1; hexane/EtOAc) yielded compound **17**, in 82% yield (7.77 g) as diastereomeric mixture as a colorless liquid (over two steps).

R_f=0.3 (EtOAc/hexane=1:5).

4.19. Oxidative kinetic resolution of compound 17 by *G. oxydans*

The strains of *G. oxydans* are routinely maintained on GYC solid medium (glucose 50 g/L, yeast extract 10 g/L, $CaCO_3$ 10 g/L, agar 15 g/L, pH=6.8) at 28 °C. Submerged cultures of *G. oxydans* were carried out in a GlyY medium (glycerol 25 g/L, yeast extract 10 g/L, pH 5.0) into 1 l Erlenmeyer flasks containing 500 mL of medium on a reciprocal shaker (100 rpm). After 24 h, isooctane is added to the submerged culture (1:1) to make the required volume. Compound **17** (neat; 10 g/L, 27 mmol) was added directly to the suspension and stirred well in an orbital shaker (100 rpm). The biotransformations were monitored periodically by TLC analysis. After 2 h, the reaction mixture was centrifuged (15,000 rpm) to remove the bacterial cells. The supernatant was extracted several times with large volume of EtOAc and the organic layer was dried with $MgSO_4$. The solvent was evaporated in vacuo and the product was purified through silica gel column chromatography (3:1; hexane/EtOAc). The isolated yield of alcohol **19** is 45% (4.5 g) and that of acid **18** is 48% (4.96 g).



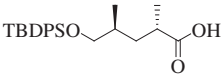
Compound ***19*** (liquid): R_f=0.3 (EtOAc/hexane=1:5).

$[\alpha]_D^{25}$ +2.48 (*c* 1.35, $CHCl_3$).

δ_H ($CDCl_3$, 200 MHz): 7.67–7.62 (m, 4H), 7.44–7.35 (m, 6H), 3.54–3.28 (m, 4H), 1.77–1.57 (m, 2H), 1.50–1.37 (m, 2H), 1.04 (s, 9H), 0.93 (d, *J*=6.6 Hz, 3H), 0.87 (d, *J*=6.4 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 135.6, 134.0, 129.5, 127.6, 68.8, 68.3, 37.2, 33.2, 26.9, 19.3, 17.9, 17.4.

HRMS (ESI) for $C_{23}H_{34}O_2NaSi$ $[M+Na]^+$, calculated: 393.2226, found: 393.2221.



Compound ***18*** (liquid): R_f=0.2 (EtOAc/hexane=1:1).

$[\alpha]_D^{25}$ −8.74 (*c* 1.32, $CHCl_3$).

δ_H ($CDCl_3$, 400 MHz): 7.67–7.65 (m, 4H), 7.42–7.36 (m, 6H), 3.52–3.45 (m, 2H), 2.60–2.51 (m, 1H), 1.54–1.48 (m, 2H), 1.24 (d, J=6.6 Hz, 3H), 1.02 (s, 9H), 0.94 (d, J=6.6 Hz, 3H).

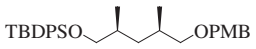
δ_C ($CDCl_3$, 100 MHz): 182.6, 135.6, 129.5, 129.4, 127.5, 68.7, 37.4, 36.9. 33.5, 26.8, 19.2, 17.6, 16.9.

HRMS (ESI) for $C_{23}H_{32}O_3NaSi$ $[M+Na]^+$, calculated: 407.2018, found: 407.2022.

4.20. Preparation of (4*S*)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentan-1-ol (17) from acid 18

DBU (0.21 mL, 1.5 mmol) was added to stirred solution of acid **18** (4.96 g, 12.9 mmol) in THF (73 mL). Stirring was continued at refluxing condition for 1 h and then solvent was evaporated. The crude epimerized acid was then reduced by LAH reduction. LAH (492 mg, 12.9 mmol) was taken in 70 mL dry Et_2O followed by addition of the crude acid at 0 °C. After reaching room temperature the reaction mixture was refluxed for 2 h. After completion of the reaction, as indicated by TLC, saturated solution of Na_2SO_4 was added carefully to quench the reaction mixture. Then the reaction solution was filtered on a Celite pad, by washing with hot Et_2O for several times and then it was concentrated in vacuo. The crude product was purified by flash chromatography (3:1; hexane/EtOAc) to afford compound **17** as colorless liquid (3.92 g, yield 88%, over two steps).

4.21. ((2*S*,4*R*)-4-((4-Methoxybenzyloxy)methyl)-2-methylpentyloxy)(*tert*-butyl)diphenylsilane (20)



A solution of 4-methoxybenzyl alcohol (1.24 g, 9 mmol) in 25 mL of ether was added to a suspension of 60% NaH (0.072 g, 1.8 mmol) in 10 mL of ether at room temperature. The resulting mixture was stirred at room temperature for 30 min and cooled to 0 °C. Trichloroacetonitrile (TCA, 1.1 mL, 18 mmol) was added to it and the reaction mixture was allowed to warm slowly to room temperature over 6 h. The solution was evaporated to orange syrup, which was dissolved in anhydrous hexane (40 mL) containing a few drops of MeOH. This suspension was then shaken vigorously and filtered through Celite, and the filtrate was concentrated to afford the crude imidate. The crude imidate (2.3 g, 8.12 mmol) was taken in cyclohexane (20 mL) and a solution of alcohol **19** (1.5 g, 4.06 mmol) in 10 mL of DCM was added. The resulting solution was cooled to 0 °C and CSA (0.094 g, 0.04 mmol) was added to it. The reaction mixture was stirred overnight at room temperature, and a white precipitate of trichloroacetamide developed slowly. The solution was filtered off, and washed with DCM. The filtrate was washed with $NaHCO_3$ solution, water, and brine. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (20:1; hexane/EtOAc) yielded compound **20** in 86% yield (1.71 g) as a liquid.

R_f=0.5 (EtOAc/hexane=1:10).

$[\alpha]_D^{25}$ −8.46 (c 0.9, $CHCl_3$).

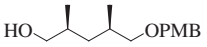
IR (film): 2921, 1700, 1632, 1451, 1355 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.71–7.67 (m, 4H), 7.44–7.34 (m, 6H), 7.26 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.0 Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.6–3.47 (m, 2H), 3.44–3.12 (m, 2H), 1.9–1.7 (m, 2H), 1.52–1.4 (m, 1H), 1.3–1.2 (m, 1H), 1.09 (s, 9H), 0.98 (d, J=6.6 Hz, 3H), 0.93 (d, J=6.6 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 159.0, 135.7, 134.1, 131.0, 129.5, 129.1, 127.6, 113.7, 75.8, 72.6, 68.9, 55.3, 37.8, 33.2, 31.0, 26.9, 19.3, 18.1, 17.9.

HRMS (ESI) for $C_{31}H_{42}O_3NaSi$ $[M+Na]^+$, calculated: 513.2801, found: 513.2806.

4.22. (2*S*,4*R*)-5-(4-methoxybenzyloxy)-2,4-dimethylpentanol (21)



Compound **20** (1.51 g, 3.064 mmol) was taken in dry THF (15 mL). TBAF (1 M in THF, 4.6 mL) was added to it at 0 °C and the reaction mixture was stirred for 3 h at room temperature. After that time, THF was evaporated, and water (7 mL) was added to it, the reaction mixture was extracted with EtOAc (2×30 mL), the organic layer was washed with $NaHCO_3$ and brine, and dried ($MgSO_4$). The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (10:1; hexane/EtOAc) to afford mono PMB protected alcohol **21** (88% yield, 677 mg) as a thick liquid.

R_f=0.4 (EtOAc/hexane=1:5).

$[\alpha]_D^{25}$ −2.4 (c 1.0, $CHCl_3$).

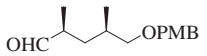
IR (film): 3388, 2924, 1611, 1512, 1460 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.24 (d, J=8.4 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 4.41 (s, 2H), 3.79 (s, 3H), 3.49–3.39 (m, 2H), 3.29–3.2 (m, 2H), 2.03 (br, 1H, −OH), 1.89–1.64 (m, 2H), 1.53–1.4 (m, 1H), 1.28–1.17 (m, 1H), 0.93 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.0 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 159.3, 130.9, 129.4, 113.9, 75.8, 72.9, 68.0, 55.5, 37.9, 33.4, 31.2, 18.4, 17.8.

HRMS (ESI) for $C_{15}H_{24}O_3Na$ $[M+Na]^+$, calculated: 275.1623, found: 275.1626.

4.23. (2*S*,4*R*)-5-(4-Methoxybenzyloxy)-2,4-dimethylpentanal (22)



Oxalyl chloride (0.29 mL, 3.3 mmol) was taken in dry DCM (10 mL). Dry DMSO (0.47 mL, 6.6 mmol) was added to the solution and the reaction mixture was cooled at −78 °C. After 20 min, alcohol **21** (550 mg, 2.2 mmol) was added dissolving in dry DCM (4 mL). The reaction mixture was kept at −78 °C for 50 min. Then Et_3N (1.83 mL, 13.2 mmol) was added to the reaction mixture and it was allowed to attain room temperature. After that time water was added to it and extracted with DCM, the organic layer was washed with $NaHCO_3$ solution and brine and dried over $MgSO_4$. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (8:1; hexane/EtOAc) yielded the aldehyde compound **22**, in 90% yield (491 mg) as a liquid.

R_f=0.7 (EtOAc/hexane=1:5).

$[\alpha]_D^{25}$ −4.89 (c 1.0, $CHCl_3$).

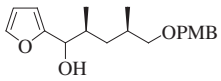
IR (film): 2927, 1705, 1611, 1512, 1461, 1247 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 9.56 (d, J=2.4 Hz, 1H, CHO), 7.25 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.4 Hz, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.3–3.25 (m, 2H), 2.50–2.42 (m, 1H), 1.96–1.75 (m, 2H), 1.6-1.4 (m, 1H), 1.08 (d, J=7.0 Hz, 3H), 0.95 (d, J=6.0 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 205.2, 159.1, 130.6, 129.1, 113.8, 75.1, 72.7, 55.2, 44.2, 35.1, 31.3, 17.6, 14.3.

HRMS (ESI) for $C_{15}H_{22}O_3Na$ $[M+Na]^+$, calculated: 273.1467, found: 273.1462.

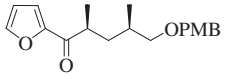
4.24. (2*S*,4*R*)-5-(4-Methoxybenzyloxy)-1-(furan-2-yl)-2,4-dimethylpentan-1-ol (23)



n-Butyllithium (1.34 mL, 2.14 mmol) was added to a solution of furan (0.16 mL, 2.2 mmol) in dry THF (4 mL) solution in an argon

atmosphere at room temperature. The reaction mixture was further stirred at ambient temperature for 3 h, followed by addition of aldehyde **22** (500 mg, 2 mmol) at 0 °C. The reaction mixture allowed to warm room temperature. After that water was added to it and extracted with Et_2O, the organic layer was washed with brine and dried over $MgSO_4$. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (3:1, hexane/EtOAc) afforded compound **23**, in 76% yield (502 mg) as a liquid.

4.25. (2*S*,4*R*)-5-(4-Methoxybenzyloxy)-1-(furan-2-yl)-2,4-dimethylpentan-1-one (24)



To a stirred suspension of MnO_2 (6.32 g, 71.1 mmol), in dry CH_2C1_2 (10 mL) was added a solution of **23** (450 mg, 1.37 mmol) in CH_2Cl_2 (5 mL) at 0 °C. Stirring was continued for 1 h at room temperature. Then the reaction mixture was filtered through a pad of Celite by washing with DCM at several times. The solution was then evaporated to give a crude residue, which was purified by column chromatography on silica gel using hexane/EtOAc (20:1, v/v) as eluent to afford the ketone **24** in 74% yield (331 mg) as a colorless liquid.

R_f=0.4 (EtOAc/hexane=1:10).

$[\alpha]_D^{25}$ +44.8 (*c* 1.0, $CHCl_3$).

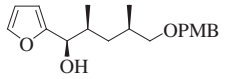
IR (film): 2921, 1715, 1588, 1452, 1365 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.59 (d, *J*=1.8 Hz, 1H), 7.27 (d, *J*=6.8 Hz, 1H), 7.21–7.15 (m, 2H), 6.94 (d, *J*=8.0 Hz, 2H), 6.52 (m, 1H), 4.43 (s, 2H), 3.84 (s, 3H), 3.48–3.24 (m, 3H), 2.03–1.55 (m, 2H), 1.32–1.26 (m, 1H), 1.23 (d, *J*=5.6 Hz, 3H), 0.98 (d, *J*=6.6 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 193.6, 171.3, 159.2, 146.5, 130.9, 129.3, 117.5, 113.9, 112.3, 72.3, 70.6, 55.4, 39.4, 37.9, 31.6, 17.9, 17.3.

HRMS (ESI) for $C_{19}H_{24}O_4Na$ $[M+Na]^+$, calculated: 339.1572, found: 339.1575.

4.26. (1*R*,2*S*,4*R*)-5-(4-Methoxybenzyloxy)-1-(furan-2-yl)-2,4-dimethylpentan-1-ol (25)



To a cooled (−78 °C) stirred solution of ketone **24** (1.32 g, 3.95 mmol) in THF (40 mL) was added L-Selectride (1.0 M solution in THF, 22 mL, 22 mmol). The mixture was stirred at −78 °C for 15 min and 35% aqueous H_2O_2 (10 mL) was added afterward. After being stirred for 1 h, the mixture was quenched with saturated aqueous Na_2SO_3 (20 mL). The resulting mixture was diluted with H_2O and extracted with CH_2Cl_2 (20 mL×5). The combined extracts were dried and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (8:1; hexane/EtOAc) to provide compound **25** (85% yield, 1.12 g) as a colorless liquid.

R_f=0.5 (EtOAc/hexane=1:5).

$[\alpha]_D^{25}$ −6.3 (*c* 1.2, $CHCl_3$).

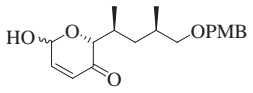
IR (film): 3372, 2921, 1622, 1458, 1375 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.40–7.27 (m, 3H), 6.92 (d, *J*=8.6 Hz, 2H), 6.37–6.24 (m, 2H), 4.56–4.50 (m, 1H), 4.46 (s, 2H), 3.84 (s, 3H), 3.39–3.22 (m, 2H), 2.55–2.44 (br, 1H, −OH), 2.15–2.06 (m, 1H), 1.98–1.85 (m, 1H), 1.76–1.45 (m, 2H), 1.03 (d, *J*=7.2 Hz, 3H), 0.97 (d, *J*=6.5 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 159.2, 156.6, 141.7, 130.8, 129.3, 113.9, 110.2, 106.7, 75.6, 72.9, 71.5, 55.4, 37.5, 35.7, 31.1, 18.6, 16.7.

HRMS (ESI) for $C_{19}H_{26}O_4Na$ $[M+Na]^+$, calculated: 341.1729, found: 341.1724.

4.27. (2*R*)-2-((2*S*,4*R*)-5-(4-Methoxybenzyloxy)-4-methylpentan-2-yl)-6-hydroxy-2*H*-pyran-3(6*H*)-one (26)

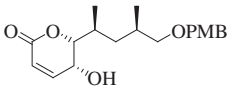


To a mixture of compound **25** (1.32 g, 3.95 mmol) in THF/water (4:1), $NaHCO_3$ (664 mg, 7.9 mmol), NaOAc (324 mg, 3.95 mmol), and NBS (704 mg, 3.95 mmol) were added at 0 °C. The reaction mixture was then allowed to warm at room temperature, after which water was added to it and extracted with Et_2O, the organic layer was washed with brine and dried over $MgSO_4$. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (5:1; hexane/EtOAc) yielded the hemi-acetal compound **26** in 90% yield (1.17 g) as a clear liquid.

R_f=0.6 (EtOAc/hexane=1:10).

δ_H ($CDCl_3$, 200 MHz): 7.31–7.26 (m, 2H), 6.93–6.86 (m, 3H), 6.1 (d, *J*=10.2 Hz, 1H), 5.58 (d, *J*=7.0 Hz, 1H), 4.59–4.47 (m, 1H), 4.44 (s, 2H), 3.82 (s, 3H), 3.48–3.14 (m, 2H), 2.48–2.38 (m, 1H), 1.82–1.73 (m, 2H), 1.38–1.3 (m, 1H), 0.98 (d, *J*=7.0 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H).

4.28. (5*R*,6*R*)-6-((2*S*,4*R*)-5-(4-Methoxybenzyloxy)-4-methylpentan-2-yl)-5,6-dihydro-5-hydroxypyran-2-one (B)



To a stirred suspension of PCC (1.36 g, 6.3 mmol), Celite (971 mg), and anhydrous sodium acetate (516 mg, 6.3 mmol) in CH_2C1_2 (8 mL) was added a solution of **26** in CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was allowed to attain room temperature. Stirring was continued for 24 h, and then the reaction mixture was filtered through Celite-pad by washing with DCM at several times. The solution was evaporated to give the crude lactone.

To a cooled (−78 °C) stirred solution of crude lactone (690 mg, 2.11 mmol) in MeOH (7 mL) was added $CeCl_3 \cdot 7H_2O$ (1.57 g, 4.2 mmol). The mixture was stirred at −78 °C for 20 min, and $NaBH_4$ (80 mg, 2.11 mmol) was added. The reaction mixture was then kept at −78 °C for 3 h. After completion of the reaction, as indicated by TLC, MeOH was evaporated under reduced pressure. The residue was taken in EtOAc, and washed successively with water and brine. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (10:1; hexane/EtOAc) to provide compound **B** (74% yield, 962 mg, over two steps) as a thick clear liquid.

R_f=0.5 (EtOAc/hexane=1:5).

$[\alpha]_D^{25}$ −10.71 (*c* 0.17, $CHCl_3$).

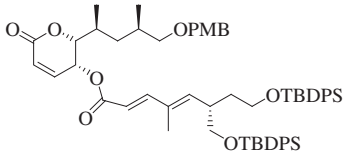
IR (film): 3447, 2924, 1718, 1654, 1543, 1509, 1459 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.15 (d, *J*=6.0 Hz, 2H), 6.84 (dd, *J*=9.4 Hz, 6.0 Hz, 1H), 6.78 (d, *J*=8.6 Hz, 2H), 6.01 (d, *J*=9.6 Hz, 1H), 4.33 (s, 2H), 4.15–4.05 (m, 1H), 3.85–3.76 (m, 1H), 3.71 (s, 3H), 3.21–3.10 (m, 2H), 2.24–1.99 (m, 2H), 1.95–1.78 (m, 2H), 1.05 (d, *J*=7.4 Hz, 3H), 0.82 (d, *J*=6.8 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 164.0, 159.2, 144.3, 129.6, 129.3, 123.1, 113.8, 85.4, 76.1, 72.7, 60.4, 55.3, 35.7, 30.6, 16.3, 15.7.

HRMS (ESI) for $C_{19}H_{26}O_5Na$ $[M+Na]^+$, calculated: 357.1678, found: 357.1681.

4.29. (2*E*,4*E*,6*S*)-(2*R*,3*R*)-2-((2*S*,4*R*)-5-(4-Methoxybenzyloxy)-4-methylpentan-2-yl)-3,6-dihydro-6-oxo-2*H*-pyran-3-yl-8-*tert*-butyldiphenylsilyloxy-6-(*tert*-butyldiphenylsilyloxy-methyl)-4-methylocta-2,4-dienoate (27)



Distilled triethylamine (0.15 mL, 1.095 mmol) was added to a solution of diene acid **A** (378 mg, 0.547 mmol, 1.5 equiv) in anhydrous toluene (20 mL) at room temperature, followed by distilled 2,4,6-trichlorobenzoyl chloride (0.12 mL, 0.73 mmol) was added dropwise, and the resulting clear, colorless solution was stirred at the same temperature. After 1 h, TLC (10% hexanes/EtOAc) showed complete consumption of diene acid **A**. Alcohol **B** (120 mg, 0.365 mmol) in dry toluene (21 mL) was then added, followed by DMAP (156 mg, 1.28 mmol) to give a white suspension. After completion of the reaction (5 h), as indicated by TLC, MeOH was evaporated under reduced pressure and the crude residue was directly loaded into a silica gel column. The compound was purified by column chromatography on silica gel (30:1; hexane/EtOAc) to provide compound **27** (84% yield, 307 mg) as a liquid.

R_f=0.6 (EtOAc/hexane=1:10).

$[\alpha]_D^{25}$ +8.15 (*c* 1.45, $CHCl_3$).

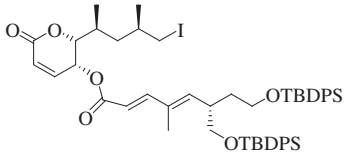
IR (film): 3446, 3069, 2932, 2858, 1962, 1890, 1727, 1618 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.63–7.54 (m, 8H), 7.39–7.19 (m, 13H), 7.09 (d, *J*=6.2 Hz, 2H), 7.04–6.96 (m, 1H), 6.78 (m, 2H), 6.16 (d, *J*=9.6 Hz, 1H), 5.69 (d, *J*=15.8 Hz, 1H), 5.65–5.56 (m, 1H), 5.35–5.32 (m, 1H), 4.35(s, 2H), 4.11–4.03 (m, 1H), 3.71 (s, 3H), 3.58–3.49 (m, 4H), 3.22–3.06 (m, 2H), 2.98–2.84 (m, 1H), 2.19–2.08 (m, 1H), 1.91–1.81 (m, 2H), 1.67 (d, *J*=7.4 Hz, 3H), 1.48–1.32 (m, 2H), 1.02 (d, *J*=5.6 Hz, 3H), 0.96 (s, 19H), 0.91 (d, *J*=5.2 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 166.5, 163.4, 159.1, 151.6, 145.4, 140.8, 140.7, 135.7, 135.6, 134.2, 133.8, 133.7, 130.7, 129.7, 129.3, 129.0, 128.3, 127.74, 125.0, 113.8, 83.1, 74.8, 72.8, 66.7, 61.9, 61.6, 55.3, 38.4, 34.4, 31.75, 31.1, 30.9, 26.9, 19.2, 18.9, 16.1, 12.7.

HRMS (ESI) for $C_{61}H_{76}O_8NaSi_2$ $[M+Na]^+$, calculated: 1015.4976, found: 1015.4972.

4.30. (2*E*,4*E*,6*S*)-(2*R*,3*R*)-3,6-Dihydro-2-((2*S*,4*R*)-5-iodo-4-methylpentan-2-yl)-6-oxo-2*H*-pyran-3-yl-8-*tert*-butyldiphenylsilyloxy-6-(*tert*-butyldiphenylsilyloxy-methyl)-4-methylocta-2,4-dienoate (29)



Compound **27** (320 mg, 0.32 mmol) was taken in 5 mL of DCM/H_2O (19:1). Next, DDQ (109 mg, 0.48 mmol) was added to it in one portion at 0 °C. The reaction mixture was allowed to warm to room temperature and further stirred at same temperature for 3 h. The reaction mixture was then filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, water, and brine. The organic layer was dried ($MgSO_4$) and evaporated. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (3:1, hexane/EtOAc) to afford the pure alcohol **28** in 80% yield (225 mg) as a liquid.

$[\alpha]_D^{25}$ +34.87 (*c* 0.5, $CHCl_3$).

δ_H ($CDCl_3$, 200 MHz): 7.59–7.55 (m, 8H), 7.39–7.18 (m, 13H), 7.01 (dd, *J*=6.2, 3 Hz, 1H), 6.18 (d, *J*=9.6 Hz, 1H), 5.73 (d, *J*=11.6 Hz, 1H), 5.61 (d, *J*=8.8 Hz, 1H), 5.39 (dd, *J*=6.8, 2.6 Hz, 1H), 4.07 (dd, *J*=8.6, 2.8 Hz, 1H), 3.62–3.49 (m, 4H), 3.42–3.31 (m, 2H), 3.01–2.90(m, 1H), 2.65 (br, 1H, –OH), 2.11–2.03 (m, 1H), 1.88–1.85 (m, 1H), 1.77–1.70 (m, 1H), 1.68 (s, 3H), 1.45–1.30 (m, 3H), 1.09 (d, *J*=6.2 Hz, 3H), 1.04 (s, 18H), 0.87 (d, *J*=5.2 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 166.5, 163.4, 151.8, 145.5, 140.7, 135.7, 135.6, 134.2, 133.8, 133.6, 129.7, 128.3, 127.7, 125.0, 114.1, 83.5, 68.7, 66.7, 61.6, 60.5, 38.4, 34.4, 32.7, 31.0, 26.9, 21.1, 19.3, 19.2, 15.2, 14.3, 12.7.

A 0 °C solution of triphenylphosphine (143 mg, 0.55 mmol), imidazole (37 mg, 0.55 mmol), and iodine (138 mg, 0.55 mmol) in CH_2Cl_2 (6 mL) was stirred under argon atmosphere for 15 min. The alcohol **28** (160 mg, 0.18 mmol) was dissolved in CH_2Cl_2 (4 mL) and added dropwise to the reaction mixture. The reaction mixture was stirred for 30 min at this temperature then warmed to room temperature. Stirring was continued for 3 h, and then the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (20:1; hexane/EtOAc) to provide iodo compound **29** (85% yield, 114 mg) as a liquid.

R_f=0.7 (EtOAc/hexane=1:10).

$[\alpha]_D^{25}$ –145.4 (*c* 0.25, $CHCl_3$).

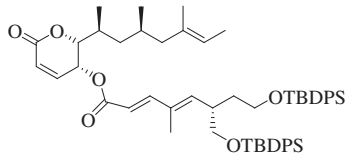
IR (film): 3451, 2924, 1719, 1655, 1459 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.57–7.54 (m, 8H), 7.39–7.25 (m, 13H), 7.05 (dd, *J*=6.4, 3.2 Hz, 1H), 6.16 (d, *J*=9.2 Hz, 1H), 5.73 (d, *J*=13.4 Hz, 1H), 5.63 (d, *J*=9.0 Hz, 1H), 5.29 (dd, *J*=6.2, 2.3 Hz, 1H), 4.06 (dd, *J*=9.0, 2.6 Hz, 1H), 3.59–3.42 (m, 4H), 3.28–3.13 (m, 2H), 3.03–2.92 (m, 1H), 2.11–2.07 (m, 1H), 1.87–1.80 (m, 1H), 1.66 (s, 3H), 1.43–1.33 (m, 3H), 1.11 (d, *J*=6.5 Hz, 3H), 1.02–0.971 (m, 1H), 0.971 (s, 18H), 0.91 (d, *J*=6.5 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 166.5, 163.2, 151.5, 145.2, 141.0, 135.7, 135.6, 134.2, 133.8, 133.7, 129.7, 129.1, 128.3, 127.7, 124.9, 114.7, 83.2, 66.7, 61.6, 61.5, 38.4, 34.4, 31.2, 26.9, 22.3, 19.3, 19.2, 16.4, 15.4, 12.7, 11.6.

HRMS (ESI) for $C_{53}H_{67}O_6NaISi_2$ $[M+Na]^+$, calculated: 1005.3419, found: 1005.3416.

4.31. (2*E*,4*E*,6*S*)-(2*R*,3*R*)-3,6-Dihydro-2-((*E*,2*S*,4*R*)-4,6-dimethyloct-6-en-2-yl)-6-oxo-2*H*-pyran-3-yl-8-*tert*-butyldiphenylsilyloxy-6-(*tert*-butyldiphenylsilyloxy-methyl)-4-methylocta-2,4-dienoate (30)



To a mixture of compound **29** (150 mg, 0.152 mmol) in dry toluene, activated Zn–Cu couple (15 mg, 0.23 mmol) and dimethylacetamide (38 mg, 0.44 mmol) were added at 70 °C. The resulting suspension was vigorously stirred at this temperature for 4 h. The mixture was cooled to 60 °C before $Pd(PPh_3)_4$ (9 mg, 0.007 mmol) and *E*-2-bromobutene (16 μL, 0.152 mmol) were added. After stirring for 1 h at this temperature, the reaction was quenched with water and the aqueous layer extracted with Et_2O. The combined extracts were dried over $MgSO_4$, filtered, and evaporated, and the residue purified by flash chromatography (20:1; hexane/EtOAc) to give compound **30** in 76% yield (106 mg) as a liquid.

R_f=0.6 (EtOAc/hexane=1:10).

$[\alpha]_D^{25}$ –152.6 (*c* 0.25, $CHCl_3$).

IR (film): 3465, 2928, 2857, 1721, 1621, 1463, 1381 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.63–7.59 (m, 8H), 7.42–7.34 (m, 13H), 7.04 (dd, *J*=9.4, 6.2 Hz, 1H), 6.23 (d, *J*=9.2 Hz, 1H), 5.76 (d, *J*=16.0 Hz,

1H), 5.66 (d, *J*=9.6 Hz, 1H), 5.41 (dd, *J*=6.0, 2.2 Hz, 1H), 5.09 (q, *J*=6.7 Hz, 1H), 4.14 (dd, *J*=9.2, 2.4 Hz, 1H), 3.64–3.45(m, 4H), 2.98–2.92 (m, 1H), 2.17–2.10 (m, 1H), 1.98 (m, 1H), 1.83 (s, 3H), 1.75–1.64 (m, 2H), 1.60 (m, 1H), 1.59 (d, *J*=6.5 Hz, 3H), 1.54 (s, 3H), 1.46 (dd, *J*=12.6, 10.2 Hz, 1H), 1.25 (ddd, *J*=13.8, 9.2, 4.4 Hz, 1H), 1.12 (d, *J*=6.5 Hz, 3H), 1.02 (s, 19H), 0.76 (d, *J*=6.5 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 166.5, 163.5, 151.4, 145.4, 140.8, 135.8, 135.7, 134.3, 134.0, 133.8, 129.8, 127.8, 125.2, 120.1, 114.9, 83.7, 66.8, 61.7, 61.5, 43.3, 38.5, 34.5, 31.5, 30.2, 27.0, 24.9, 24.3, 19.3, 15.9, 15.6, 12.7, 11.9.

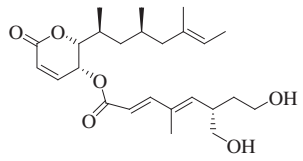
HRMS (ESI) for $C_{57}H_{74}O_6Si_2Na$ $[M+Na]^+$, calculated: 933.4922, found: 933.4927.

4.32. Unsuccessful attempt for the coupling reaction

4.32.1. By tert-BuLi reaction. tert-Butyllithium (0.34 mL, 0.441 mmol) was added to a solution of *E*-2-bromobutene (26 μL, 0.253 mmol) in dry THF (1 mL) solution in an argon atmosphere at −78 °C. The reaction mixture was further stirred at ambient temperature for 1 h, followed by addition of compound **29** (250 mg, 0.253 mmol) in dry THF. The reaction mixture was stirred for 2 h at −78 °C, then allowed to warm to room temperature and stirred for 15 h. After that water was added to it and extracted with Et_2O, the organic layer was washed with saturated ammonium chloride solution then brine and dried over $MgSO_4$. The organic extract was evaporated in vacuo to give the crude product, which was purified by silica gel chromatography (20:1; hexane/EtOAc). Though we were able to isolate compound **30** but the miserably low yield (<10%) forced us to go for other alternatives.

4.32.2. By using $FeCl_3$. To a solution of compound **29** (250 mg, 0.253 mmol) and anhydrous $FeCl_3$ (10 mg, 0.06 mmol) at 0 °C in THF (1 mL) was added a premixed solution of TMEDA (0.17 mL, 1.14 mmol) and (*E*)-1-methyl-1-propenylmagnesium bromide (which was prepared by addition of Mg (32 mg, 1.32 mmol) and *E*-2-bromobutene (0.13 mL, 1.2 mmol) in dry THF (1 mL)) via a syringe pump at a 5 mL/h rate. Once the addition was completed, the reaction mixture was warmed to room temperature. After 30 min, the mixture was quenched by addition of a saturated aqueous solution of NH_4Cl, but with our dismay we could not detect the formation of product **30**.

4.33. (2*E*,4*E*,6*S*)-(2*R*,3*R*)-3,6-Dihydro-2-((*E*,2*S*,4*R*)-4,6-dimethyloct-6-en-2-yl)-6-oxo-2*H*-pyran-3-yl8-hydroxy-6-(hydroxymethyl)-4-methylocta-2,4-dienoate, ((−)rasfonin)



To a cooled (0 °C) stirred solution of compound **30** (70 mg, 0.076 mmol) in dry THF (3 mL), HF/pyridine (110 μL) was added dropwise. The reaction mixture was allowed to warm room temperature and stirring was continued for 72 h. Then the reaction mixture was quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1; hexane/EtOAc) to provide rasfonin (72% yield, 24 mg) as yellow oil.

R_f=0.2 (EtOAc/hexane=1:1).

$[\alpha]_D^{25}$ −166.5 (*c* 1.0, $CHCl_3$), {lit[1] $[\alpha]_D^{25}$ −170 (*c* 0.086, MeOH), lit[3] $[\alpha]_D^{25}$ −162.8 (*c* 0.43, CH_2Cl_2)}.

IR (film): 3365, 2931, 1717, 1622, 1458, 1375 cm^{-1}.

δ_H ($CDCl_3$, 400 MHz): 7.34 (d, *J*=16.0 Hz, 1H), 7.03 (dd, *J*=9.4, 6.2 Hz, 1H), 6.21 (d, *J*=9.2 Hz, 1H), 5.79 (d, *J*=16.0 Hz, 1H), 5.76 (d, *J*=9.8 Hz, 1H), 5.34 (dd, *J*=6.2, 2.2 Hz, 1H), 5.10 (q, *J*=6.7 Hz, 1H), 4.11 (dd, *J*=9.0, 2.2 Hz, 1H), 3.74 (dt, *J*=10.4, 5.2 Hz 1H), 3.61 (m, 3H), 2.9–2.85 (m, 1H), 2.15–2.13 (m, 1H), 2.03 (br d, *J*=12.0 Hz, 1H), 1.83 (s, 3H), 1.77–1.66 (m, 2H), 1.62 (m, 1H), 1.52 (d, *J*=6.5 Hz, 3H), 1.50 (s, 3H), 1.4 (dd, *J*=12.6, 10.2 Hz, 1H), 1.18 (ddd, *J*=13.8, 9.2, 4.4 Hz, 1H), 1.15 (d, *J*=6.5 Hz, 3H), 1.04 (ddd, *J*=13.6, 9.2, 4.0 Hz, 1H), 0.76 (d, *J*=6.5 Hz, 3H).

δ_C ($CDCl_3$, 100 MHz): 166.2, 163.4, 151.1, 143.5, 140.7, 134.8, 134.3, 124.9, 120.1, 115.1, 83.3, 66.0, 61.6, 60.7, 46.4, 39.8, 39.3, 34.8, 31.4, 27.8, 20.5, 15.9, 15.6, 13.2, 12.7.

HRMS (ESI) for $C_{25}H_{38}O_6Na$ $[M+Na]^+$, calculated: 457.2566, found: 457.2561.

The optical and spectroscopy data are in good agreement with reported values.

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Supplementary data

Copies of the ^1H NMR and ^{13}C NMR spectra for all key intermediates and final products with few HPLC chromatograms are available. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.051.

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