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Asymmetric synthesis of palitantin by an enzymatic and organocatalytic approach

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ABSTRACT

The natural enantiomer of the fungal metabolite (+)-palitantin has been synthesized by adopting a chemoenzymatic and organocatalytic approach. Lipase catalyzed kinetic resolution, Sharpless asymmetric dihydroxylation and organocatalytic asymmetric hydroxymethylation are the key steps involved in the total synthesis of the target molecule.

1. Introduction

Palitantin and frequentin are highly oxygenated cyclohexane derivatives. They are polyketide-derived fungal metabolites isolated from *Penicillium palitanst* and *Penicillium frequentans*,[1], respectively. Frequentin has been shown to have antifungal and antibiotic activities.[2] Its structural correlation with palitantin has been established through chemical transformation,[3] and it was shown that palitantin is the precursor molecule for frequentin. Till date four asymmetric synthesis of the (+)-enantiomer of palitantin have been reported in the literature. Organocatalytic Robinson annulation of α,β-unsaturated aldehydes,[4] diastereoselective *cis*-hydroxylation of (5*R*)-tert-butyldimethylsiloxy-2-cyclohexenone followed by a selective 1,4-addition of 1,3-heptadienyl cyanocuprate,[5] regioselective dehydration of a homochiral alcohol (1*S*,2*S*,3*R*)-2,3-isopropylideneoxycyclohexanol followed by cuprate addition of 1,3-heptadienyl group[6] and a chiron approach from (−)-quinic acid affords (+)-palitantin.[7]

In our combinatorial biocatalysis project we have designed and synthesized many small multifunctional scaffolds. After biocatalytic and chemical modification the scaffolds will lead us to many natural products and related compounds. Both the enantiomers of 5-hydroxymethyl-cyclohex-2-enone are such scaffolds which can be structurally related to palitantin and frequentin by chemical analogy. In this article we wish to report asymmetric synthesis of the natural enantiomer of palitantin by a chemoenzymatic and organocatalytic approach. The retrosynthetic analysis for (+)-palitantin is shown in Scheme 1 starting from (*R*)-5-hydroxymethyl-cyclohex-2-enone. Whereas the other enantiomer (*S*)-5-hydroxymethyl-cyclohex-2-enone will lead to (−)-palitantin by the same chemical transformation pathway. The main highlights of our synthetic strategy are the enzymatic synthesis of both enantiomers of the small molecular scaffold, for example, 5-hydroxymethyl-cyclohex-2-enone, Sharpless asymmetric dihydroxylation and an organocatalytic asymmetric hydroxymethylation.

2. Results and discussion

The enantiomeric 5-hydroxymethyl-cyclohex-2-enone has been prepared as depicted in the literature.[8] Oxidation of the diol, 5-hydroxymethyl-cyclohex-2-enol **A** with PDC in ethyl acetate as a solvent produced the required ketoalcohol compound **1** in 80% yield.[9] Irreversible enzymatic transesterification with vinylacetate was applied to racemic **1** by using Lipase-PS (*Burkholderia cepacia*) in benzene as a solvent to afford the (*S*)-acetate (ee: 98%) and the (*R*)-alcohol (ee: 99%) with excellent enantioselection.[10] Attempted deacetylation of the (*S*)-acetate with K_2CO_3/MeOH yielded the (*S*)-alcohol in 20% yield. Moreover lipase (*Porcine pancreatic* lipase) catalyzed deacetylation of (*S*)-acetate in phosphate buffer (100 mM, pH 7.0) afforded the (*S*)-alcohol in good yield (75%). The (*S*) alcohol seems not to be useful in our synthetic steps, hence we have decided to develop a racemization method so that we have a steady supply of racemic **1**. The primary hydroxyl group is oxidized with PCC to yield the (*S*)-ketoaldehyde. The racemization of (*S*)-ketoaldehyde to the corresponding racemic mixture is achieved by treatment with catalytic DBU in tetrahydrofuran[11] at room temperature. Chemoselective reduction of the aldehyde functionality is achieved with $NaCNBH_3$ in methanol. So, by a three-step methodology the undesired (*S*)-5-hydroxymethyl-2-cyclohexenone has been racemized to (±)-5-hydroxymethyl-2-cyclohexenone (Scheme 2). This can be used again in the initial kinetic resolution step.

With both enantiomeric 5-hydroxymethyl-cyclohex-2-enones in our hand, we have opted to carry out the total synthesis of (+)-palitantin from (*R*)-5-hydroxymethyl-cyclohex-2-enone. The hydroxymethyl group was protected as its TBDPS ether by treatment with imidazole/TBDPS-Cl in DMF to afford compound **2**.

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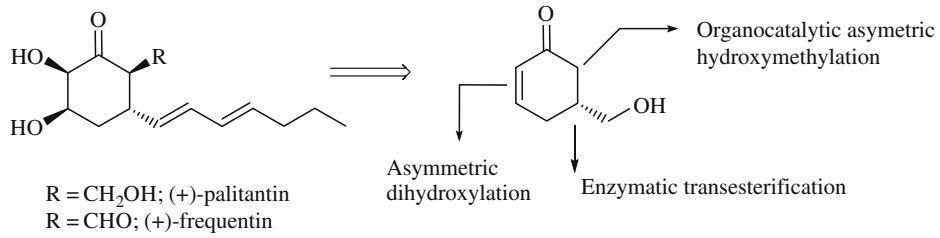
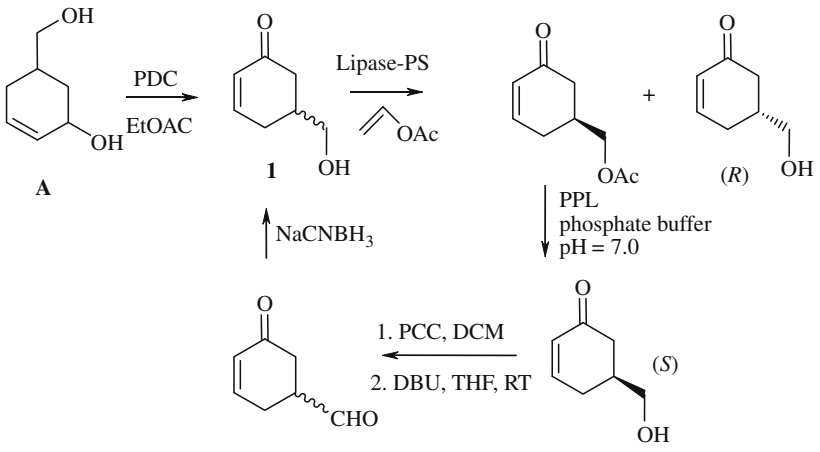
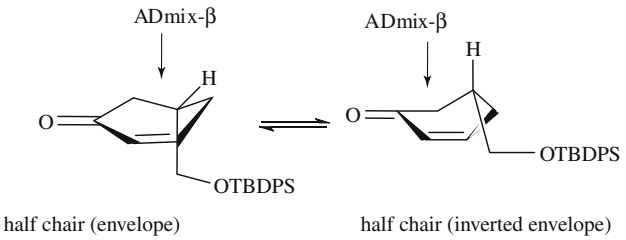


Scheme 1. Retrosynthetic analysis of palitantin and frequentin.



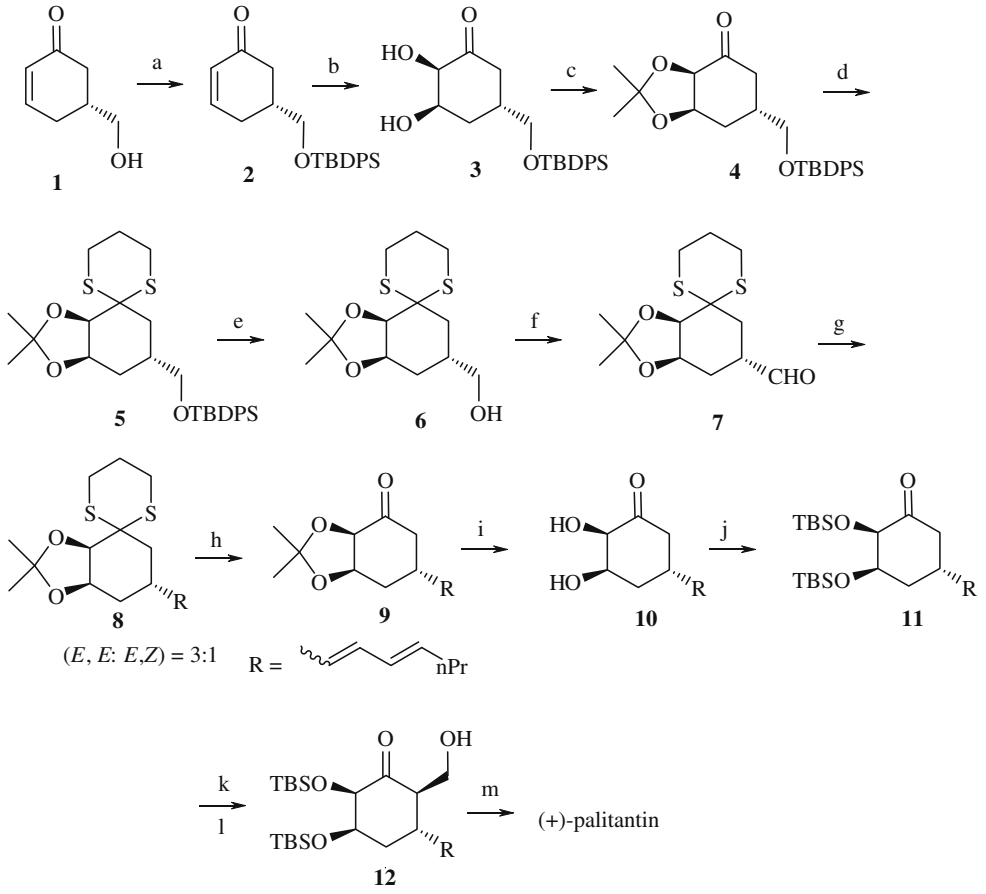
Scheme 2. Enzymatic synthesis of both enantiomers of the ketoalcohol.

Asymmetric dihydroxylation with AD-Mix β of **2** yielded the dihydroxylated compound **3** in 60% yield.[12] The origin of the stereoselectivity in the asymmetric dihydroxylation reaction can be explained assuming a half-chair like conformation[13] for the parent cyclohexenone **2**, in which the bottom face of the ring is blocked by the bulky *tert*-butyl-diphenylsilyl group hence making the α-face inaccessible by the AD-mix reagent system. Thus the attack must take place from the β-face (Scheme 3) of **2** yielding diol **3**.



Scheme 3. Origin of the stereoselectivity in the dihydroxylation reaction.

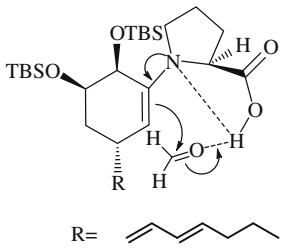
The *syn*-diol **3** is protected as its acetonide by treatment with 2,2-dimethoxypropane (DMP) and PPTS in dichloromethane to afford **4**.[14] The keto functionality in **4** was protected as its dithiane by treatment with 1,3-propanedithiol to yield compound **5**.[15] Deprotection of the silylether (TBDPS) was achieved by treating compound **5** with TBAF/THF at room temperature to afford **6** in 80% yield from **5**.[16] Oxidation of **6** with the SO_3–pyridine complex yielded aldehyde **7** in good yield.[17] Wittig olefination of aldehyde **7** with (*E*)-2-hexenyltriphenylphosphonium bromide at −78 °C[18] afforded compound **8** in 3:1 ratio (*E*,*E*: *E*,*Z*) in 72% yield (by ^{1}H NMR analysis). Separation of the olefin geometrical isomers is not possible at this step. The thioketal group in **8** was deprotected to[19] yield the keto compound **9** (mixture of *E*,*E* and *E*,*Z*) in 60% yield from **8**. The undesired (*E*,*Z*) isomer is converted to (*E*,*E*) **9** by treatment with 0.1 equiv of I_2 and irradiation with 100 W mercury lamp (Scheme 4).[18] The introduction of hydroxymethyl in a regiocontrolled as well as stereocontrolled manner seems to be a challenging and daunting task as depicted by Hanessian et al.[7] Attempted monohydroxymethylation of **9** with several reagents leads to the undesired regioisomer as the major product. The formation of undesired regioisomeric hydroxymethylated compound can be attributed to enhanced kinetic acidity of the α-hydrogen adjacent to the acetonide group hence the enolization always takes place towards the oxygen end. To circumvent this problem we choose a model system **13** (racemic), where the diol functionality is protected as its TBS ether. The presence of a monocyclic *O*,*O*-bis-silyl-protecting group instead of a cyclic acetonide changes the regiochemical outcome of the reaction. When racemic **13** was treated with LTMP (lithium tetramethylpiperidide) and *N*-hydroxymethyl phthalimide (as a formaldehyde equivalent) at −78 °C,[20] the desired regioisomeric product **14** was obtained in 50% yield with the corresponding dihydroxymethylated product in 20% yield. The asymmetric aldol reaction is one of the most significant reactions in modern catalytic synthesis.[21] The possibility of using small chiral organic molecules, for example, amino acids and their derivatives to act like an enzyme for the catalytic intermolecular aldol reaction has been explored by many research groups.[22] It is worth mentioning that, in a similar approach to enzymatic conversion with type-I or II aldolases, a direct asymmetric variant of the aldol reaction was achieved when proline (*R* or *S*) was used as catalyst.[23] Accordingly, the use of enol derivatives of the parent ketone compound is not necessary and the ketone can be used directly without previous modification. This also means that a further reaction step deprotonation or silylation in order to prepare the required enolates and enol ethers, respectively, can be avoided. In the same line of thinking when the substrate **13** was subjected to a proline catalyzed organocatalytic aldol reaction with aq formaldehyde, the de-



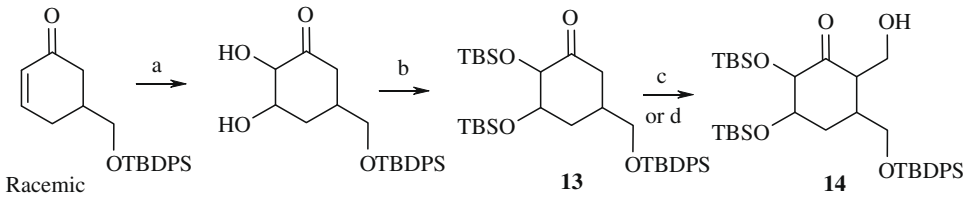
Scheme 4. Reagents and conditions: (a) TBDPS-Cl, imidazole, DMF, rt, 6 h, 90%; (b) AD-Mix-β, *t*-BuOH–H_2O (1:1), $MeSO_2NH_2$, 60%; (c) 2,2-DMP, PPTS, rt, 12 h, 88%; (d) HS–$(CH_2)_3$–SH, $BF_3{\cdot}OEt_2$, 12 h, 80%; (e) TBAF, THF, rt, 2 h, 80%; (f) SO_3–Pyr, Et_3N, DMSO, rt, 3 h, 86%; (g) *n*-BuLi, −78 °C, 1/2 h, (*E*)-2-hexenyltriphenylphosphonium bromide, then add aldehyde **7**, 0 °C, 2 h, 72%; (h) $HgCl_2$, CH_3CN, rt, 2 h, 60%, I_2 (0.1 equiv), 100 W mercury lamp, 1 h; (i) MeOH–HCl, 3 h, rt, 90%; (j) 2,6-lutidine, TBSOTf, 24 h, rt, 80%; (k) (*S*)-proline, HCHO, DMSO, 14 h, rt, 50%; (l) LTMP, *N*-hydroxymethyl phthalimide, −78 °C, 50%; (m) PPTS/MeOH, rt, 6 h, 92%.

sired product was obtained in 50% yield with no other side products (Scheme 5). Hence we have also planned to adopt an organocatalytic approach for installation of the required hydroxymethyl functionality in an asymmetric fashion.

Thus when compound **9** was treated with MeOH–HCl, the acetonide group was removed to afford diol **10**, which was subsequently treated with 2,6-lutidine/TBS-OTf to yield the bis silylated compound **11** in 80% yield from **9**. Compound **11** on treatment with (*S*)-proline (10 mol %), and aq formaldehyde afforded compound **12** in 50% yield (Scheme 4). The origin of diastereoselection of the hydroxymethylation reaction can be explained by *Si*-facial attack of formaldehyde as an electrophile on the proline-derived enamine of compound **11** (Scheme 6). Whereas the *Re*-face of the enamine is blocked by the bulky (1*E*,3*E*)-hepta-1,3dienyl group. Base-induced substrate-directed hydroxymethylation of substrate **11** was also tried with *N*-hydroxymethyl phthalimide (as a formaldehyde equivalent) to afford compound **12** in 50% yield. Deprotection of the silyl ether functionality in **12** with MeOH/PPTS afforded the (+)-palitantin in 16% overall yield from **1** (Scheme 4). The spectral



Scheme 6. Reaction of formaldehyde with the *Si*-face of the proline-derived enamine.



Scheme 5. Reagents and conditions: (a) OsO_4; NMO, Me_2CO–H_2O (9:1); (b) 2,6-lutidine, TBSOTf, 24 h; (c) LTMP, *N*-hydroxymethylphthalimide, −78 °C; (d) proline, HCHO, DMSO, rt.

characteristic values of our synthesized (+)-palitantin are in perfect agreement with those reported in the literature.

3. Conclusion

In conclusion we have developed an efficient asymmetric synthesis of the natural enantiomer of palitantin by adopting a chemoenzymatic and organocatalytic approach.

4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethylether were distilled from sodiumbenzophenone ketyl. Dichloromethane (DCM), dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Benzene was refluxed over P_2O_5 and distilled prior to use. Vinyl acetate was freshly distilled prior to use. Lipase PS (from *B. cepacia*) was obtained from Wako pure chemicals, Japan. Reactions were monitored by thin-layer chromatography(TLC) carried out on 0.25 mm silica gel plates (Merck) 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 Bruker 400 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 spectral analysis was performed in the Central Research Facility (CRF), IIT-Kharagpur. Optical rotations were measured on a JASCO P 1020 digital polarimeter.

4.2. Acetic acid (*S*)-5-oxo-cyclohex-3-enylmethyl ester

Compound **1** (1 g, 7.94 mmol) was taken in 10 ml of anhydrous benzene. Vinylacetate (0.36 ml, 3.97 mmol) was added to the reaction mixture, followed by addition of Lipase-PS (500 mg) and powdered molecular sieves (4 Å, 200 mg). The reaction mixture was kept in an orbital shaker under an argon atmosphere. The progress of the reaction was monitored by TLC measurement. After 50% conversion, it was filtered on a Celite pad, and evaporated to dryness. Purification by flash chromatography (1:1; hexane–EtOAc) afforded the (*S*)-acetate and the (*R*)-alcohol. Attempted deacetylation with K_2CO_3–MeOH yielded the (*S*)-alcohol in 20% yield. Henceforth lipase catalyzed deacetylation was attempted. The (*S*)-acetate (620 mg, 3.69 mmol) was taken in 25 ml of 100 mM phosphate buffer (pH 7.0), followed by addition of PPL (500 mg). The reaction mixture was kept in an orbital shaker (250 rpm) for 8 h. After that time it was extracted twice with EtOAc (2 × 100 ml), and the organic layer was dried (Na_2SO_4) and evaporated to dryness. Flash chromatography (1:1; hexane–EtOAc) afforded the (*S*)-alcohol in 90% yield.

Specific rotation value for (*R*)-**1**, $[\alpha]_D^{29} = -32.85$ (*c* 1.0, MeOH), for (*S*)-acetate, $[\alpha]_D^{29} = +25.7$ (*c* 1.0, MeOH). ^1H NMR of **1** in $CDCl_3$ (400 MHz), δ: 7.0 (m, 1H), 6.0 (d, *J* = 9.6 Hz, 1H), 3.6 (d, *J* = 5.6 Hz, 2H), 2.5–2.2 (m, 5H). ^{13}C NMR of **1** in $CDCl_3$ (100 MHz), δ: 200.11, 150.23, 129.47, 65.58, 40.56, 37.45, 28.48. ^1H NMR of acetate of **1** in $CDCl_3$ (400 MHz), δ: 6.98 (m, 1H), 6.0 (d, *J* = 9.6 Hz, 1H), 4.0 (d, *J* = 5.6 Hz, 2H), 2.57–2.2 (m, 5H), 2.05 (s, 3H). ^{13}C NMR of acetate of **1** in $CDCl_3$ (100 MHz), δ: 198.27, 170.80, 148.73, 129.78, 66.87, 40.65, 34.39, 28.56, 20.72.

4.3. (2*R*,3*R*,5*R*)-5-(*tert*-Butyl-diphenyl-silyloxymethyl)-2,3-dihydroxy-cyclohexanone 3

t-BuOH (41 ml), H_2O (41 ml) and AD-mix β (11.27 g) were mixed and the mixture was stirred for 15 min. Methanesulfonamide (725 mg, 7.6 mmol) was then added and the stirring was continued for a further 15 min. (*R*)-5-(*tert*-Butyl-diphenyl-silanyloxymethyl)-cyclohex-2-enone **2** (2 g, 7.57 mmol) was then added in one portion. The slurry was stirred vigorously at 20 °C for 24 h. After that time, sodium sulfite (15 g) was added and stirring was continued for further 1 h. The reaction mixture was extracted with EtOAc (4 × 100 ml). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The diol was purified by flash chromatography (1:1; hexane–EtOAc) to afford 1.36 g (60%) of the diol. ^1H NMR of **3** in $CDCl_3$ (400 MHz), δ: 7.6–7.5 (m, 4H), 7.45 (m, 6H), 4.42 (br s, 1H), 4.15 (br s, 1H), 3.9 (br s, 1H, –OH), 3.64 (br s, 2H), 2.58–2.46 (m, 4H), 2.2 (m, 1H), 1.9 (t, *J* = 13.2 Hz, 1H). ^{13}C NMR of **3** in $CDCl_3$ (100 MHz), δ: 210.11 (C), 135.63 (CH), 133.28, 129.63 (CH), 127.72 (CH), 76.96 (CH), 72.13 (CH), 65.44 (CH_2), 42.07 (CH_2), 36.14 (CH), 32.18 (CH_2), 26.93 (CH_3), 19.35 (C). $[\alpha]_D^{29} = -18.5$ (*c* 1.0, MeOH).

4.4. (3*R*,6*R*,7*R*)-6-(*tert*-Butyl-diphenyl-silyloxymethyl)-2,2-dimethyl-tetrahydro-benzo[1,3]dioxol-4-one 4

Compound **3** (1.039 g, 3.49 mmol) was taken in 20 ml of dry DCM. 2,2-Dimethoxypropane (DMP, 17.43 mmol, 2.14 ml) was added to it followed by addition of catalytic amount of PPTS (0.35 mmol, 94 mg). The reaction mixture was stirred at rt overnight. The product was purified by flash chromatography (3:1; hexane–EtOAc) to afford 940 mg of compound **4** in 80% yield. ^1H NMR of **4** in $CDCl_3$ (400 MHz), δ: 7.65 (m, 4H), 7.42 (m, 6H), 4.63 (m, 1H), 4.28 (d, *J* = 5.2 Hz, 1H), 3.61 (d, *J* = 3.6 Hz, 2H), 2.53 (m, 1H), 2.37–2.16 (m, 3H), 1.96 (m, 1H), 1.43 (s, 3H), 1.39 (s, 3H), 1.01 (s, 9H). ^{13}C NMR of **4** in $CDCl_3$ (100 MHz), δ: 208.42, 135.50, 133.16, 129.77, 127.71, 109.68, 78.93, 76.39, 66.96, 43.31, 36.00, 31.71, 27.04, 26.82, 25.97, 19.27. $[\alpha]_D^{29} = -5.5$ (*c* 1.0, MeOH).

4.5. Compound 6

Compound **5** (670 mg, 1.56 mmol) was taken in dry THF (10 ml). TBAF (1 M in THF, 1.56 ml) was added to it, and the reaction mixture was stirred for 3 h at room temperature. After that time, THF was evaporated, and water (20 ml) was added to it, the reaction mixture was extracted with EtOAc (2 × 50 ml), the organic layer was washed with $NaHCO_3$ and brine, and dried (Na_2SO_4). It was purified by flash chromatography (1:1; hexane–EtOAc) to afford 350 mg of compound **6** (80%). ^1H NMR of **6** in $CDCl_3$ (400 MHz), δ: 4.62 (m, 1H), 4.53 (m, 1H), 3.54 (d, *J* = 5.2 Hz, 2H), 3.0 (m, 2H), 2.82 (m, 2H), 2.24 (m, 2H), 2.08 (m, 1H), 2.0–1.65 (m, 5H), 1.55 (s, 3H), 1.40 (s, 3H). ^{13}C NMR of **6** in $CDCl_3$ (100 MHz). δ: 108.09 (C), 76.32 (CH), 73.22 (CH), 67.41 (CH_2), 49.48, 35.26 (CH_2), 30.13 (CH), 27.70 (CH_2), 27.04 (CH_2), 26.59 (CH_2), 26.34 (CH_3), 24.55 (CH_2), 24.33 (CH_3). $[\alpha]_D^{29} = -5.9$ (*c* 1.0, MeOH). HRMS (ESIMS) calcd for $C_{13}H_{23}O_3S_2$ $(M+H)^+$ 290.1083, found 291.1076.

4.6. (3*R*,6*R*,7*R*)-6-((1*E*,3*E*)-Hepta-1,3-dienyl)-2,2-dimethyl-tetrahydro-benzo[1,3]dioxol-4-one 9

Compound **8** (180 mg, 0.508 mmol, mixture of *E,E* and *E,Z*) was taken in 80% aq acetonitrile (2 ml). $HgCl_2$ (290 mg, 1.07 mmol) was added to it at once. The reaction mixture was stirred at room temperature for 2 h. after that time water was added and the reaction mixture was extracted with EtOAc, the organic layer was successively washed with $NaHCO_3$, brine and dried (Na_2SO_4). It was puri-

fied by flash chromatography (1:3; hexane–EtOAc) to yield 110 mg of **9** (82% yield, mixture of *E,E* and *E,Z*). The mixture of isomers of **9** (32 mg, 0.12 mmol) was taken in anhydrous DCM (5 mL). Molecular I_2 (0.012 mmol) was added to it followed by the irradiation with a 100 W mercury lamp. The irradiation was continued for 1 h. After that time, the reaction mixture was washed with sodium thiosulfate solution and the organic layer was purified by preparative thin-layer chromatography to yield pure (*E,E*) **9** in 80% yield. ^{1}H NMR of **9** in $CDCl_3$ (400 MHz), δ: 6.06 (dd, J = 14.8, 10.8 Hz, 1H), 5.97 (dd, J = 14.8, 10.8 Hz, 1H), 5.66 (dt, J = 14.8, 7.2 Hz, 1H), 5.46 (dd, J = 14.8, 7.2 Hz, 1H), 4.59 (br s, 1H), 4.28 (d, J = 5.2 Hz, 1H), 2.8 (m, 1H), 2.52 (d, J = 13.6 Hz, 1H), 2.32 (m, 2H), 2.16 (m, 2H), 1.86 (m, 1H), 1.43 (s, 3H), 1.41 (m, 2H), 1.39 (s, 3H), 0.9 (t, J = 7.2 Hz, 3H). ^{13}C NMR of **9** in $CDCl_3$ (100 MHz), δ: 207.54 (C), 134.78 (CH), 132.36 (CH), 130.33 (CH), 129.64 (CH), 109.84 (C), 78.86 (CH), 76.30 (CH), 46.19 (CH_2), 35.55 (CH), 34.71 (CH_2), 29.71 (CH_2), 27.09 (CH_3), 26.04 (CH_3), 22.40 (CH_2), 13.74 (CH_3). $[\alpha]_D^{29} = -7.9$ (*c* 1.0, $CHCl_3$). HRMS (ESIMS) calcd for $C_{16}H_{25}O_3$ $(M+H)^+$ 265.1798, found 265.1792.

4.7. 2,3-Bis-(*tert*-butyl-dimethyl-silyloxy)-5-(*tert*-butyl-diphenyl-silyloxymethyl)-6-hydroxymethyl-cyclohexanone 14

To a stirred solution of *n*-butyllithium (0.14 mL, 0.0855 mmol) in anhydrous THF (2 mL) was added dropwise 2,2,6,6-tetramethylpiperidine (0.013 mL, 0.0855 mmol) at −10 °C. The solution was allowed to stir at 0 °C for 30 min then cooled to −78 °C. Compound **13** (30 mg, 0.057 mmol) in anhydrous THF (1 mL) was added dropwise and stirred for an additional 1 h. *N*-Hydroxymethylphthalimide (20 mg, 0.114 mmol) in anhydrous THF (1 mL) was added dropwise over a 10-min period and kept for 2 h at this temperature. The reaction was quenched with water (5 mL) extracted with diethyl ether (50 mL) then washed successively with 4 M NaOH (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product was purified by flash chromatography (1:5; hexane–EtOAc) to afford 17 mg (50%) of compound **14**. ^{1}H NMR of **14** in $CDCl_3$ (400 MHz), δ: 7.65 (m, 4H), 7.4 (m, 6H), 4.31 (br, 1H), 4.19 (br, 1H), 3.8 (m, 1H), 3.72 (dd, J = 10.6, 4.4 Hz, 1H), 3.66 (dd, J = 10.6, 3.2 Hz, 1H), 3.58 (m, 1H), 2.48 (m, 1H), 2.35 (m, 1H), 2.08 (t, J = 12.8 Hz, 1H), 1.9 (dt, J = 13.6, 4.4 Hz, 1H), 1.08 (s, 9H), 0.91 (s, 9H), 0.86 (s, 9H), 0.15 (s, 3H), 0.069 (s, 3H), 0.053 (s, 3H), 0.020 (s, 3H).^{13}C NMR of **14** in $CDCl_3$ (100 MHz), δ: 210.85, 135.57, 129.90, 127.82, 116.15, 80.09, 74.84, 65.0, 59.52, 51.54, 36.91, 35.29, 26.94, 25.99, 25.69, −4.41, −4.47, −5.05, −5.42.

4.8. (2*R*,3*R*,5*R*)-5-((1*E*,3*E*)-Hepta-1,3-dienyl)-2,3-dihydroxy-cyclohexanone 10

To a solution of **9** (70 mg, 0.265 mmol) in MeOH (6 mL) was added a solution of methanolic HCl (0.25 mL, prepared from 0.05 mL concd HCl in 2 mL of MeOH). The resulting mixture was stirred for 3 h at ambient temperature until the reaction was complete (monitored by TLC). The reaction was quenched by the addition of aqueous saturated $NaHCO_3$ solution (5 mL). The solution was diluted with EtOAc (10 mL), washed with brine (2 mL), dried over Na_2SO_4 and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography (1:1; hexane–EtOAc) to afford diol **10** in 95% yield. ^{1}H NMR of **10** in $CDCl_3$ (400 MHz), δ: 6.06 (dd, J = 14.8, 10.8 Hz, 1H), 5.97 (dd, J = 14.8, 10.8 Hz, 1H), 5.66 (dt, J = 14.8, 7.2 Hz, 1H), 5.46 (dd, J = 14.8, 7.2 Hz, 1H), 4.38 (br s, 1H), 4.18 (d, J = 5.2 Hz, 1H), 3.9 (br, 1H, –OH), 3.0 (m, 1H), 2.75 (br, 1H, –OH), 2.56 (m, 1H), 2.2 (m, 2H), 2.08 (m, 2H), 1.78 (m, 1H), 1.44 (m, 2H), 0.9 (t, J = 7.2 Hz, 3H). ^{13}C NMR of **10** in $CDCl_3$ (100 MHz), δ: 208.69 (C), 134.66 (CH), 132.79 (CH), 130.20 (CH), 129.59 (CH), 76.99 (CH), 71.50 (CH), 44.66 (CH_2), 36.21 (CH), 35.42 (CH_2), 34.70 (CH_2), 22.50 (CH_2), 13.73 (CH_3). $[\alpha]_D^{29} = -6.7$ (*c* 1.0, $CHCl_3$). HRMS (ESIMS) calcd for $C_{13}H_{21}O_3$ $(M+H)^+$ 225.1485, found 225.1481.

4.9. (2*R*,3*R*,5*R*)-2, 3-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5-((1*E*,3*E*)-hepta-1,3-dienyl)-cyclohexanone 11

Diol **10** (35 mg, 0.156 mmol) was taken in dry DCM (2 ml). 2,6-Lutidine was (0.05 ml, 0.312 mmol) added to it at 0 °C and kept for 5 min at the same temperature. TBs-OTf (0.11 ml, 0.468 mmol) was added to the reaction mixture and the solution warmed to attain room temperature. The reaction mixture was kept over night, afterwards it was washed with $NaHCO_3$, brine and dried (Na_2SO_4). It was purified by flash chromatography (10:1; hexane–EtOAc) to afford compound **11** in 78% yield. ^{1}H NMR of **11** in $CDCl_3$ (400 MHz), δ: 6.0 (m, 2H), 5.65 (m, 1H), 5.47 (dd, J = 14.8, 7.2 Hz, 1H), 4.27 (br s, 1H), 4.17 (br s, 1H), 2.98 (m, 1H), 2.44 (m, 1H), 2.1–1.9 (m, 4H), 1.72 (m, 1H), 1.44 (q, J = 7.2 Hz, 2H), 0.9 (21H), 0.06 (s, 3H), 0.0.057 (s, 3H), 0.041 (s, 3H), 0.029 (s, 3H). ^{13}C NMR of **11** in $CDCl_3$ (100 MHz), δ: 206.301 (C), 134.0 (CH), 133.80 (CH), 129.81 (CH), 129.47 (CH), 80.0 (CH), 74.56 (CH), 45.86 (CH_2), 38.70 (CH_2), 35.97 (CH), 34.88 (CH_2), 26.03 (CH_3), 25.75 (CH_3), 22.47 (CH_2), 18.65, 18.05, 13.65 (CH_3), −4.41 (CH_3), −4.48 (CH_3), −5.14 (CH_3), −5.50 (CH_3). $[\alpha]_D^{29} = -13.9$ (*c* 0.7, $CHCl_3$).

4.10. (2*R*,3*R*,5*S*,6*R*)-2,3-Bis-(*tert*-butyl-dimethyl-silyloxy)-5-((1*E*,3*E*)-hepta-1,3-dienyl)-6-hydroxymethyl-cyclohexanone 12

Method k: In a typical hydroxymethylation experiment, formaldehyde (0.055 mmol, 37% in aq solution) was added to a vial containing (*S*)-proline (10 mol %) and compound **11** (50 mg, 0.11 mmol) in DMSO (4.0 mL) at room temperature. After 24 h, the reaction was quenched by the addition of brine and extracted with EtOAc (3 × 15 mL). The combined organic extracts were concentrated and the crude product purified by flash chromatography (hexane–EtOAc; 1:1) affording compound **12** in 50% yield.

Method l: To a stirred solution of *n*-butyllithium (0.14 mL, 0.0855 mmol) in anhydrous THF (2 mL) was added dropwise 2,2,6,6-tetramethylpiperidine (0.013 mL, 0.0855 mmol) at −10 °C. The solution was allowed to stir at 0 °C for 30 min then cooled to −78 °C. Compound **13** (30 mg, 0.057 mmol) in anhydrous THF (1 mL) was added dropwise and stirred for an additional 1 h. *N*-Hydroxymethyl phthalimide (20 mg, 0.114 mmol) in anhydrous THF (1 mL) was added dropwise over a 10-min period and kept for 2 h at this temperature. The reaction was quenched with water (5 mL) extracted with diethyl ether (50 mL) then washed successively with 4 N NaOH (15 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The product was purified by flash chromatography (1:5; hexane–EtOAc) to afford 17 mg (50%) of compound **12**. ^{1}H NMR of **12** in $CDCl_3$ (400 MHz), δ: 6.06–5.95 (m, 2H), 5.65 (m, 1H), 5.38 (dd, J = 14.8, 7.2 Hz, 1H), 4.25 (br s, 1H), 4.21 (br s, 1H), 3.72 (br, 2H), 2.85 (br, 1H, –OH), 2.65 (t, J = 7.2 Hz, 1H), 2.2–2.1 (m, 1H), 2.0 (m, 2H), 1.9–1.8 (m, 2H), 1.5–1.37 (q, J = 7.2 Hz, 2H), 1.0–0.9 (21H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR of **12** in $CDCl_3$ (100 MHz), δ: 209.82 (C), 134.64 (CH), 132.22 (CH), 132.06 (CH), 129.57 (CH), 80.17 (CH), 74.87 (CH), 60.43 (CH2), 54.97 (CH), 38.88 (CH), 38.81 (CH_2), 34.88 (CH_2), 25.95 (CH_3), 25.68 (CH_3), 22.47 (CH_2), 18.66, 18.09, 13.73 (CH_3), −4.47 (CH_3), −4.52 (CH_3), −5.08 (CH_3), −5.46 (CH_3). $[\alpha]_D^{29} = +6.8$ (*c* 0.5, $CHCl_3$).

4.11. (2*R*,3*S*,5*R*,6*R*)-3-((1*E*,3*E*)-Hepta-1,3-dienyl)-5,6-dihydroxy-2-hydroxymethyl-cyclohexanone palitantin

Compound **12** (12 mg, 0.025 mmol) was taken up in 3 ml of MeOH, PPTS (40 mg, 0.15 mmol) was added to it. The reaction mix-

ture was stirred at room temperature overnight. After that time, the MeOH was evaporated, and the residue was taken in DCM. It was washed successively with $NaHCO_3$ and brine. Purification by flash chromatography (1:1; hexane–EtOAc) afforded the title compound as a white solid. ^{1}H NMR of palitantin in $CDCl_3$ (400 MHz), δ: 6.06 (m, 1H), 5.95 (m, 1H), 5.66 (m, 1H), 5.38 (dd, J = 14.8, 7.2 Hz, 1H), 4.38 (br s, 1H), 4.22 (br s, 1H), 3.85 (br s, 1H, –OH), 3.78 (d, J = 4.8 Hz, 2H), 2.86 (m, 1H), 2.56 (br s, 1H, –OH), 2.42 (m, 1H), 2.28 (br s, 1H, –OH), 2.15 (m, 1H), 2.1–2.0 (m, 2H), 1.86 (m, 1H), 1.46–1.4 (q, J = 8.0 Hz, 2H), 0.9 (t, J = 8.0 Hz, 3H).^{13}C NMR of palitantin in $CDCl_3$ (100 MHz), δ: 211.49 (C), 135.26 (CH), 132.79 (CH), 130.99 (CH), 129.36 (CH), 77.12 (CH), 71.76 (CH), 59.76 (CH_2), 54.68 (CH), 39.15 (CH), 35.38 (CH_2), 34.71 (CH_2), 22.38 (CH_2), 13.73 (CH_3). $[\alpha]_D^{29} = +4.4$ (c 0.5, $CHCl_3$); lit. $[\alpha]_D^{22} = +4.3$ (c 2.3, $CHCl_3$);[4] lit. $[\alpha]_D^{23} = +4.5$ (c 0.32, $CHCl_3$);[5] lit. $[\alpha]_D^{23} = +4.4$ (c 0.8, $CHCl_3$).[7] HRMS (ESIMS) calcd for $C_{14}H_{23}O_4$ $(M+H)^+$ 255.1590, found 255.1584.

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