Tetrahedron 71 (2015) 5472–5477

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A concise diastereoselective synthesis of 5′-*epi* synargentolide-B

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ARTICLE INFO

Article history:
Received 6 May 2015
Received in revised form 18 June 2015
Accepted 20 June 2015
Available online 26 June 2015

Keywords:
5′-*epi* Synargentolide-B
Asymmetric transfer hydrogenation
Mukaiyama aldol
5,6-Dihydro-α-pyrones
Sharpless' AD reaction

ABSTRACT

A concise linear synthesis of 5′-*epi* synargentolide-B has been accomplished with i) catalytic asymmetric transfer hydrogenation for the genesis of chirality, ii) regioselective Sharpless asymmetric dihydroxylation iii) a vinylogous Mukaiyama aldol reaction to ensure 5,6-dihydro-2H-pyran-2-one reactions as pivotal steps.

1. Introduction

A significant number of natural products with the underlying structural pattern of the 5,6-dihydro-α-pyrones were isolated from various plants.[1] Owing to their privileged 6-substituted α-pyrone scaffold, these natural product molecules exhibit potent inhibitory activities.[2] Among them, the intriguing natural product of three bioactive 5,6-dihydro-α-pyrones, which were isolated initially as minor constituents from *Hyptis oblongifolia* were shown in diverse structural prototypes. Furthermore, their structures were elucidated with the relative stereochemistry of their stereogenic centers as 6′*R*-[5′*R*, 6′*S*-(diacetoxy)-1′*R*-(hydroxy)-2′*R*-(methoxy)-3′*E*-heptenyl]-5,6 dihydro-2H-pyran-2-one **1a**, 6′*R*-[5′*R*, 6′*S*-(diacetoxy)-1′*S*, 2′*R*-(dihydroxy)-3′*E*-heptenyl]-5,6-dihydro-2H-pyran-2-one **1b**, and the respective derivative 6′*R*-[1′*R*,2′*R*,5′*R*,6′*S*-(tetraacetyloxy)-3′*E*-heptenyl]-5,6-dihydro-2H-pyran-2-one **1c** by means of spectral, chiro-optical and chemical evidence.[3]

Later, this generic structural motif was also found in a family of natural product synargentolides A–E, as isolated from *Syncolostemon argenteus* by Rivett's group.[4] Subsequently, total synthesis of synargentolides B (**1b**) ensued and the structure was not only validated as its tetraacetate by X-ray crystallography, but was also assigned absolute stereochemistry unequivocally as 6*R*-[5*R*, 6*S*-(diacetoxy)-1*S*, 2*R*-(dihydroxy)-3*E*-heptenyl]-5,6-dihydro-2H-pyran-2-one.[5] Subsequently, a couple of synthetic routes for 5,6-dihydro-α-pyrone **1b** have been reported[6] (Fig. 1). Thus far, the prevalent approach used for the introduction of 5,6-dihydro-α-pyrone is the ring-closing metathesis protocol, and an alternative dihydroxy stereogenic motif was installed from either the chiral auxiliaries or resident chirality, thereby restricting the potential to introduce stereochemical diversity.

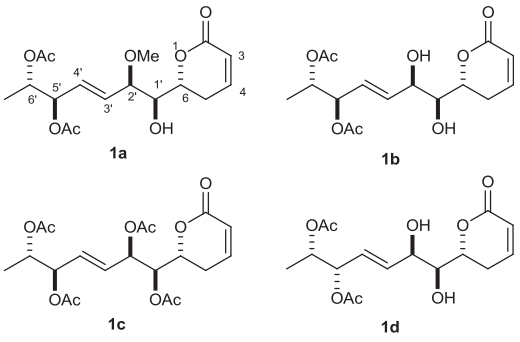

Fig. 1. Diastereomers of synargentolide-B.

2. Results and discussion

The intriguing stereochemical diversity coupled with the promising biological activities of the family of synargentolides led

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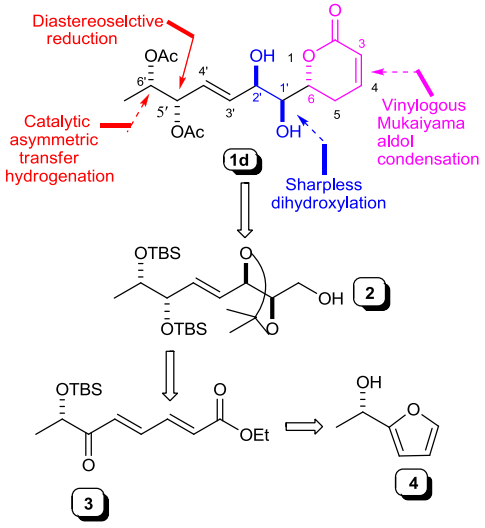
http://dx.doi.org/10.1016/j.tet.2015.06.080
0040-4020/

us to initiate a general synthetic protocol for the family of synargentolides in general and in particular the development of a stereo-divergent route for the synthesis of a diastereoisomer of synargentolide B (1d). In our continuous design of shorter and simpler synthetic routes for bioactive molecules,[7] herein we report a potential stereo-divergent route for the synthesis of a diastereoisomer of synargentolide B (1d) based on the following three catalytic steps: (a) a catalytic asymmetric transfer hydrogenation (CATHy) reaction, (b) catalytic asymmetric dihydroxylation, and (c) catalytic vinylogous Mukaiyama aldol condensation.

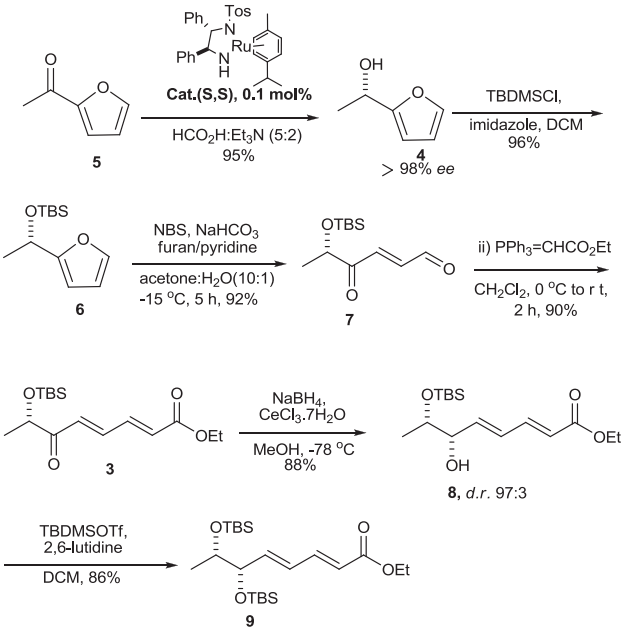
At the outset, we envisioned that the pyrone motif of **1d** could be installed by a catalytic vinylogous Mukaiyama aldol reaction employing precursor aldehyde derived from **2** and silyl dienolate. We choose the enantioenriched hydroxy furyl moiety **4** to generate a five-carbon unit embedded with hydroxy-prochiral keto functionality **3** that in turn will become a logical tool to achieve the intended regioselective catalytic asymmetric dihydroxylation. The stereogenic center in **4** could be derived through catalytic asymmetric transfer hydrogenation, presenting the option of generating both enantiomers with a low level of catalyst loading.[8] The probable corresponding retrosynthesis is exemplified in Scheme 1.



Scheme 1. Retro-synthetic analysis of **1d**.

Our synthesis commenced with a commercially available furyl ketone **5**, which was reduced asymmetrically with the (*S*,*S*)-Noyori catalyst (0.1 mol %) to afford the enantioenriched secondary alcohol **4** at a yield of 95% with >98% ee.[8] Then, protection of secondary alcohol as TBS-ether **6** (TBDMSCl, imidazole, DCM) followed by the NBS-promoted furan oxidation of **6** under basic conditions, resulting in the desired γ-keto α,β-unsaturated aldehyde **7**, at an excellent yield (88%, after two steps).[9] The aldehyde **7** was subjected to Wittig olefination to give the keto conjugated unsaturated ester **3** at a yield of 90% with a 20:1(*E*:*Z*) ratio. The reduction of **3** under Luche conditions[10] delivered the expected *syn* diol **8** with a 97:3 diastereomeric ratio (as judged by the ^{1}H NMR spectra) at a yield of 88%. The relative stereochemistry was assigned by analogy.[7a] Then, subsequent protection of the alcohol of **8** with TBSOTf under basic conditions resulted in bis-TBS dienoate ether **9** at an 86% isolated yield (Scheme 2).

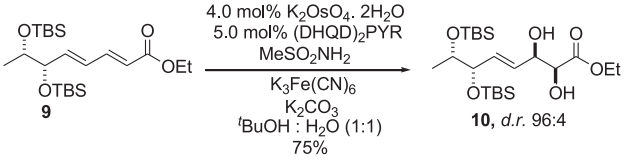
With the requisite di-TBS ether **9** in hand, we considered the application of a typical Sharpless' AD reaction. Initially, we expected that the oxidation of a double bond can occur proximal to the TBS-ether stereogenic center (electron withdrawing-effect)



Scheme 2. Synthesis of bis-TBS ether dienoate **9**.

rather than the α,β-unsaturated double-bond ester.[11] The diene **9** was initially exposed to 1.0 mol % of $(DHQD)_2PHAL$, 1.1 mol % of $K_2OsO_4 \cdot 2H_2O$, 3 equiv of $K_3Fe(CN)_6$—, and K_2CO_3 each, and 1.0 equiv $MeSO_2NH_2$ in 1:1 ^{t}BuOH:H_2O, stirring for 48 h at 0 °C yielded, only a trace amount of the product (Table 1, entry 1).

Table 1
Asymmetric dihydroxylation of ethyl dienoate **9**



Entry	Ligand	Yield, % (10)[a,c]	*dr*[d]
1	$(DHQD)_2PHAL$ (1 mol %)	Trace[b]	ND[e]
2	$(DHQD)_2PHAL$ (1 mol %)	20	90:10
3	$(DHQD)_2PHAL$ (3 mol %)	40	90:10
4	$(DHQD)_2PHAL$ (5 mol %)	87	90:10
5	(DHQD)-9 phen (5 mol %)	35	60:40
6	**$(DHQD)_2PYR$ (5 mol %)**	**75**	**96:4**
7	$(DHQD)_2AQN$ (5 mol %)	40	74:26
8	$(DHD)_2PHAL$ (5 mol %)	5	NR[f]

[a] All reactions were carried out on a scale of 0.5 mmol using 5.0 mol % of ligand, 4.0 mol % of $K_2OsO_4 \cdot 2H_2O$, 3 equiv of $K_3Fe(CN)_6$, and K_2CO_3 each, and 1.0 equiv $MeSO_2NH_2$ at 1:1 ^{t}BuOH:H_2O, while stirring for 48 h at an ambient temperature.
[b] The reaction was carried out at 0 °C.
[c] Isolated yields but not optimized.
[d] Determined by ^{1}H NMR.
[e] ND=not determined.
[f] NR=No reaction.

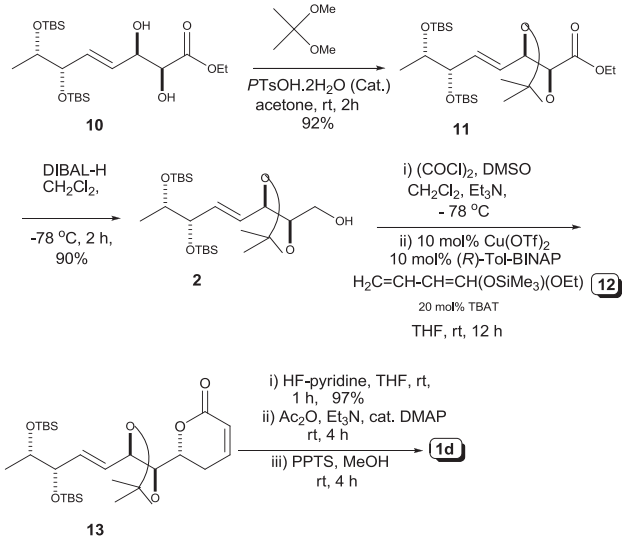
On the other hand, the same reaction at an ambient temperature under otherwise identical conditions resulted in **10** at a 20% isolated yield as an inseparable diastereomeric mixture (Table 1, entry 2). To our surprise, the product was unambiguously characterized as α,β-dihydroxylated product **10**, and no trace of the anticipated γ,δ-dihydroxylated product was observed. The relative stereochemistry was assigned by analogy with the Sharpless model. After considerable experimentation (Table 1, entry 3), it was found that

5.0 mol % of $(DHQD)_2PHAL$, 4.0 mol % of $K_2OsO_4 \cdot 2H_2O$, 3 equiv of $K_3Fe(CN)_6$, and K_2CO_3 each, and 1.0 equiv $MeSO_2NH_2$ at 1:1 ^tBuOH:H_2O under stirring for 48 h at an ambient temperature provided only regio- and diastereomer **10** at an 87% yield (Table 1, entry 4). Remarkably, no regioisomer was detected, and only unreacted starting material **9** was isolated at a 20% yield. In order to enhance the diastereoselectivity of **10**, we also screened common AD ligands for the dihydroxylation of **9** (Table 1, entries 5, 6 and 7). As expected, only the $(DHQD)_2PYR$ ligand under the above typical conditions resulted in **10** with improved diastereoselectivity but compromising the chemical yield (Table 1, entry 6). The significant regioselectivity of **10** can be rationalized on the basis of the steric effect caused by the resident stereogenic TBS-protecting group, wherein the more electron rich olefinic phase is effectively shielding and thereby facilitating the dihydroxylation of the α,β-unsaturated double-bond ester.

Further, we planned to synthesize epimer **10** by employing a pseudo-enantiomeric ligand $(DHQ)_2PHAL$ and **9** under otherwise identical conditions as described in the case of **9**. To our dismay, no trace of ***epi-10*** was formed, and only starting material **9** was recovered[12] (Table 1, entry 8).

Subsequent protection of the resulting diol **10** with 2,2-dimethoxypropane under acidic conditions furnished **11** at a 92% yield. The reduction of the ester using DIBAL-H then gave the primary alcohol **2** at a yield of 90%. Following the Swern oxidation of alcohol **2** produced crude aldehyde that was subjected to a catalytic vinylogous Mukaiyama aldol reaction to ensure 5,6-dihydro-2H-pyran-2-one.[13]

Accordingly, the reaction of the crude aldehyde with silyl dienolate **12** in the presence of 10 mol % (*R*)-Tol-BINAP-CuF_2 at −78 °C led to the α,β-unsaturated δ-lactone **13** as a single diastereomer at a yield of 70%. The configuration of a new stereogenic center was not determined at this point, however, we assumed that (*R*)-Tol-BINAP would induce *R* chirality.[13c] Eventually, **13** was exposed to HF/pyridine followed by the protection of the resulting diol with Ac_2O under basic conditions, after which a treatment with PPTS furnished the target compound **1d** at a 52% isolated yield (over three steps). The spectral and chirooptical data of **1d** were in full agreement with those reported in the literature[5] ($[\alpha]_D^{23}$ +45.6 (*c* 1.2, $CHCl_3$) {lit.[5] $[\alpha]_D^{23}$ +47.3 (*c* 0.7, $CHCl_3$)}) (Scheme 3), which in turn also corroborated the assigned stereochemistry at the 6, 1′, 2′, and 5′ stereogenic centers.



Scheme 3. Synthesis of 5-*epi* synargentolide-B.

3. Conclusion

In conclusion, we achieved a concise diversity-oriented diastereoselective synthesis of 5′-*epi* synargentolide-B in 14 steps (the longest linear sequence) at an overall yield of 12.9%, starting from commercially available 2-acetylfuran **5**. The salient feature of this strategy is all stereogenic centers in the target molecule induced by means of a sub-stoichiometric amount of chiral ligand. This flexible protocol has the potential to generate probable diastereo members of the synargentolide family by switching over to a corresponding complementary ligand. Further optimization and application of this strategy for the synthesis of synargentolide family members and related natural molecules are at present under investigation in our lab.

4. Experimental section

4.1. General procedure

Spectra were recorded at 300, 400 & 500 MHz, and ^{13}C NMR 75 & 125 MHz in $CDCl_3$. The *J* values were recorded in hertz and abbreviations used were as follows: *s*—singlet, *d*—doublet, *t*—triplet, *q*—quartet, *m*—multiplet, br—broad, *dd*—doublet of doublet, *ddd*—doublet of doublet of doublet, *ddt*—doublet of doublet of triplet. Chemical shifts (δ) are reported relative to TMS (δ=0.0) as an internal standard. The IR (FTIR) spectra were measured using KBr pellet or as film. Mass spectral data were compiled using MS (ESI), HRMS mass spectrometers. Column chromatography was carried out using Silica gel 100–200 mesh (commercial suppliers).

*4.1.1. (S)-1-(Furan-2-yl)ethanol (**4**).* To a solution of 1-(furan-2-yl) ethanone (**5**) (5.0 g, 45.5 mmol) in dry EtOAc (50 mL) under argon was added a formic acid–triethylamine azeotropic mixture (5:2, 10 mL) followed by the addition of Ru-catalyst *S,S* (24.0 mg, 0.1 mol %), which was pre-dissolved in DCM (5 mL). The resulting reaction mixture was slowly warmed to 50 °C and allowed to stir until completion (18 h), as indicated by TLC analysis. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3×40 mL). The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash column chromatography eluting with 10% EtOAc:hexanes to furnish the desired alcohol 4 (4.8 g, 95% yield) as colorless oil; R_f 0.20 (hexanes/EtOAc, 9:1); $[\alpha]_D^{24}$ −24.2 (*c* 0.48 in ethanol); [lit. $[\alpha]_D^{23}$ −24.3 (*c* 6.0 in ethanol)]; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (1H, d, *J*=0.9 Hz, ArH), 6.32 (1H, dd, *J*=3.2, 1.8 Hz, ArH), 6.22 (1H, d, *J*=3.2 Hz, ArH), 4.87 (1H, q, *J*=6.6 Hz, C_2HOH), 2.15 (1H, s, OH), 1.54 (3H, d, *J*=6.6 Hz, CC_1H_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5, 141.8, 110.0, 105.0, 63.5, 21.2; IR (neat, cm^{-1}): 3462, 2985, 2935, 1668, 1149, 877, 731.

*4.1.2. (S)-tert-Butyl(1-(furan-2-yl)ethoxy)dimethylsilane) (**6**).* A solution of alcohol (**4**) (4.5 g, 40.2 mmol) in anhydrous dichloromethane (50 mL) was cooled to 0 °C. To this cold solution was added imidazole (3.0 g, 44.2 mmol) followed by *tert*-butyldimethylsilyl chloride (7.3 g, 48.24 mmol). Progress of the reaction was monitored by thin-layer chromatography. After completion (0.5 h) the reaction mixture was quenched by addition of a saturated solution of NH_4Cl (30 mL). The reaction mixture was transferred to a separating funnel and the aqueous layer was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The resulting crude oil was purified by flash column chromatography with 2% EtOAc:hexanes to afford pure TBS ether 6 as colorless liquid; (8.7 g, 96% yield); R_f 0.50 (hexanes/EtOAc, 19:1); $[\alpha]_D^{24}$ −34.6 (*c* 0.8, $CHCl_3$); ^1H

NMR (500 MHz, $CDCl_3$): δ 7.33 (1H, dd, J=1.8, 0.8 Hz, ArH), 6.29 (1H, dd, J=3.2, 1.8 Hz, ArH), 6.16 (1H, d, J=3.2 Hz, ArH), 4.86 (1H, q, J=6.4 Hz, C_2HOH), 1.47 (3H, d, J=6.4 Hz, CC_1H_3), 0.89 (9H, s, t-BuSi), 0.08 (3H, s, Si–CH_3), 0.02 (3H, s, Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 141.2, 109.9, 104.7, 64.5, 25.8, 22.9, 18.2, −4.9, −4.0; IR (neat, cm^{-1}): 3398, 2978, 2922, 1759, 1011, 915, 739; MS (ESI) m/z: 225 $(M-H)^+$; HRMS:calcd for $C_{12}H_{23}O_3Si$ 244.1732; found 244.1735.

*4.1.3. (S,E)-5-(tert-Butyldimethylsilyloxy)-4-oxohex-2-enal (**7**).* To a solution of TBS ether 6 (8.0 g, 35.4 mmol) in acetone–water (50 mL, 10:1 v/v) was added $NaHCO_3$ and cooled to −15 °C. A mixture of *N*-bromosuccinimide (6.9 g, 38.9 mmol) in acetone–-water (50 mL, 10:1 v/v) was added drop wise over a period of 1 h to the cooled reaction mixture. The resulting reaction mixture was stirred at the same temperature for 1 h, and then furan (2 mL, 32.7 mmol) was added to the mixture to quench excess *N*-bromosuccinimide. After 10 min, pyridine (5.7 mL, 70 mmol) was added to the mixture. The resulting reaction mixture was stirred at ambient temperature for 2 h. Then, acetone was removed under reduced pressure at ambient temperature. The residue was diluted with EtOAc and washed with cold 1 N HCl solution (2×30 mL) to remove excess pyridine. The organic layers were washed with an aqueous saturated solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure at room temperature. The crude residue was purified by silicagel flash column chromatography eluting with 15% EtOAc:hexanes to afford aldehyde 7 as a pale yellow liquid; (7.8 g, 92% yield); R_f 0.40 (hexanes/EtOAc, 7:3); $[\alpha]_D^{24}$ −11.7 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (1H, d, J=7.6, C_1HO), 7.43 (1H, d, J=16.0 Hz, C_3H), 6.93 (1H, dd, J=16.0, 7.6 Hz, C_2H), 4.37 (1H, q, J=6.8 Hz, C_5HOH), 1.37 (3H, d, J=6.8 Hz, CH_3), 0.92 (9H, s, t-BuSi), 0.11 (3H, s, Si–CH_3), 0.09 (3H, s, Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1, 192.9, 140.1, 138.5, 74.3, 25.6, 20.6, 18.0, −4.8, −5.1; IR (neat, cm^{-1}): 2931, 2857, 1769, 1739, 1255, 1112, 833, 779; MS (ESI) m/z: 242 $(M)^+$; HRMS:calcd for $C_{12}H_{23}O_3Si$ 243.1411; found 243.1410.

*4.1.4. (S,2E,4E)-Ethyl 7-(tert-butyldimethylsilyloxy)-6-oxoocta-2,4-dienoate (**3**).* The above aldehyde (**7**) (7.0 g, 29 mmol) was dissolved in dichloromethane (60 mL) and cooled to 0 °C. To this, ethyl (triphenylphosphoranylidene)acetate (12.0 g, 34.8 mmol) was added. The resulting reaction mixture warmed to room temperature and stirred for 4 h. Then, dichloromethane was removed under reduced pressure, and the resulting crude residue was purified by silicagel column chromatography using 15% EtOAc:hexanes to give the desired product 3 in 20:1 ratio as light yellow oil; (8.1 g, 90% yield); R_f 0.30 (hexanes/EtOAc, 7:3); $[\alpha]_D^{24}$ −23.4 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.30 (2H, m, C_3H=C_5H), 6.99–6.92 (1H, m, C_4H), 6.29–6.21 (1H, m, C_2H), 4.30–4.22 (2H, m, O–CH_2), 1.34–1.30 (6H, m, CH_3CH, CH_3 of OEt), 0.91 (9H, s, t-BuSi), 0.08 (3H, s, Si–CH_3), 0.07 (3H, s, Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 166.0, 141.4, 139.7, 130, 129.3, 74.5, 60.9, 25.7, 21.0, 18.1, 14.2, −4.8, −5.0; IR (neat, cm^{-1}): 2930, 2857, 1718, 1694, 1594, 1240, 1134, 834, 779; MS (ESI) m/z: 313 $(M+H)^+$. HRMS:calcd for $C_{16}H_{29}O_4Si$ 313.1827; found 313.1826.

*4.1.5. (2E,4E,6S,7S)-Ethyl 7-(tert-butyldimethylsilyloxy)-6-hydroxyocta-2,4-dienoate (**8**).* $CeCl_3{\cdot}7H_2O$ (11.5 g, 30.7 mmol) and keto-TBS ether 3 (8.0 g, 25.6 mmol) were dissolved in methanol at room temperature and stirred for 10 min. Then, $NaBH_4$ (1.1 g, 30.7 mmol) was added at −78 °C to the mixture in four portions over a period of 20 min and was stirred for 2 h at same temperature. After completion of the reaction, the reaction mixture was quenched by addition of a saturated solution of NH_4Cl (5 mL). After removal of MeOH under reduced pressure, the crude residue was filtered with EtOAc (3×80 mL). The combined organic contents were washed with brine solution (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silicagel flash column chromatography eluting with 18% EtOAc:hexanes to afford desired alcohol 8 as viscous liquid; (7.0 g, 88% yield); R_f 0.20 (hexanes/EtOAc, 7:3); $[\alpha]_D^{24}$ −6.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (1H, dd, J=15.3, 11.1 Hz, C_3H), 6.45 (1H, dd, J=15.3, 11.1 Hz, C_4H), 6.08 (1H, dd, J=15.3, 5.5 Hz, C_5H), 5.89 (1H, d, J=15.3 Hz, C_2H), 4.2 (2H, q, J=7.8 Hz, CH_2 of OEt), 3.97 (1H, t, J=5.3 Hz, C_6H), 3.77–3.69 (1H, m, $CHCH_3$), 1.30 (3H, t, J=7.8, Hz, CH_3 of OEt), 1.18 (3H, d, J=6.2 Hz, CH_3), 0.89 (9H, s, t-BuSi), 0.09 (3H, s, Si–CH_3), 0.07 (3H, s, Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 143.7, 141.6, 129.0, 121.5, 76.0, 71.5, 60.3, 25.7, 20.0, 18.0, 14.2, −4.3, −4.8; IR (neat, cm^{-1}): 3489, 2930, 1711, 1253, 1130, 1093, 1001, 833, 754; MS (ESI) m/z: 332 $(M+NH_4)^+$; HRMS:calcd for $C_{16}H_{34}O_4NSi$ 332.2251; found 332.2249.

*4.1.6. (2E,4E,6S,7S)-Ethyl 6,7-bis(tert-butyldimethylsilyloxy)octa-2,4-dienoate (**9**).* To a stirred solution of alcohol 8 (6.0 g, 19.1 mmol) in DCM (70 mL) at 0 °C was added 2,6-lutidine (4.5 mL) and TBSOTf (5.7 mL, 24.83 mmol), respectively. After completion of the reaction (0.5 h) ice cold water was added. Then, the aqueous layer was extracted with dichloromethane (3×80 mL) and the combined organic layers were washed with 1 N HCl (30 mL) to remove the excess 2,6-lutidine. The organic phase was washed with brine solution and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by silicagel flash column chromatography eluting with 5% EtOAc:hexanes to afford di-TBS ether 9 as a clear liquid; (7.0 g, 86% yield); R_f 0.40 (hexanes/EtOAc, 9:1); $[\alpha]_D^{24}$ −29.1 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (1H, m, C_3H), 6.39 (1H, dd, J=15.3, 11.1 Hz, C_4H), 6.25 (1H, dd, J=15.3, 3.9 Hz, C_5H), 5.84 (1H, d, J=15.5 Hz, C_2H), 4.21 (2H, q, J=7.2 Hz, CH_2 of OEt), 3.83–3.75 (1H, m, CH–CH_3), 1.3 (3H, t, J=7.2 Hz, CH_3 of OEt), 0.98 (3H, d, J=6.23 CH_3), 0.91 (9H, s, t-BuSi), 0.89 (9H, s, t-BuSi), 0.06 (6H, s, 2-Si–CH_3), 0.05 (3H, s, Si–CH_3), 0.04 (3H, s, Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 144.3, 142.4, 128.0, 120.3, 75.2, 71.3, 6.2, 25.8, 18.1, 18.0, 17.3, 14.3, −4.6, −4.8, −4.9, −4.9; IR (neat, cm^{-1}): 2930, 2857, 1714, 1255, 1215, 1104, 1003, 833, 749; MS (ESI) m/z: 451 $(M+Na)^+$; HRMS:calcd for $C_{22}H_{48}O_4NSi_2$. 446.3116; found 446.3120.

*4.1.7. (2S,3R,6S,7S,E)-Ethyl 6,7-Bis(tert-butyldimethylsilyloxy)-2,3-dihydroxyoct-4-enoate (**10**).* In an argon fitted round bottom flask *t*-BuOH (10 mL) and water (20 mL) was added. To this K_2CO_3 (2.9 g, 21.1 mmol), $K_3Fe(CN)_6$ (6.9 g, 21.1 mmol), $MeSO_2NH_2$ (665 mg, 7 mmol), $(DHQD)_2PYR$ (248 mg, 0.28 mmol), $K_2OsO_4{\cdot}2H_2O$ (77.2 mg, 0.21 mmol) were added at room temperature in the same order and allowed to stirred for 15 min. To this pale yellow reaction mixture was added pre-dissolved solution of diene 9 (3.0 g, 7 mmol) in *t*-BuOH (10 mL) and allowed to stir at same temperature in a dark place for 48 h. The reaction was quenched by addition of solid Na_2SO_3 and stirred for 0.5 h at 0 °C. Reaction mixture was diluted and extracted EtOAc (3×20 mL). The combined organics contents were washed with brine solution and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified over silicagel flash column chromatography eluting with 20% EtOAc:hexanes to afforded diol 10 as colorless oil in 96:4 dr (inseparable). The dr ratio determined based on NMR spectra. The yield of 10 was 2.4 g (75% yield), based on starting material recovery. Starting material was recovered 0.2 g (20%); R_f 0.20 (hexanes/EtOAc, 8:2); $[\alpha]_D^{24}$ −29.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (1H, dd, J=15.9, 4.5 Hz, C_5H), 5.83 (1H, dd J=15.6, 6.0 Hz, C_4H), 4.49–4.47 (1H, m, C_2H), 4.30 (2H, q, J=6.8 Hz, CH_2 of OEt), 4.16 (2H, m, C_3H,

C_6H), 3.80–3.75 (1H, m, C_7H), 1.33 (3H, t, J=6.8 Hz, CH_3 of OEt), 1.00 (3H, d, J=6.0 Hz, CH_3), 0.90 (9H, s, t-BuSi), 0.89 (9H, s, t-BuSi), 0.06 (6H, s, 2-Si–CH_3), 0.05 (3H, s, Si–CH_3), 0.04 (3H, s, Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 132.1, 129.0, 75.0, 73.7, 73.0, 71.2, 62.0, 25.8, 18.1, 18.1, 17.2, 14.2, −4.7, −4.7, −4.7, −4.9; IR (neat, cm^{-1}): 3451, 2927, 2855, 1737, 1465, 1252, 1100, 833, 774; MS (ESI) m/z: 485 $(M+Na)^+$; HRMS:calcd for $C_{22}H_{50}O_6NSi_2$ 480.3160; found 480.3164.

*4.1.8. (4S,5R)-Ethyl 5-((3S,4S,E)-3,4-bis(tert-butyldimethylsilyloxy) pent-1-enyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**11**).* A solution of diol 10 (2.0 g, 3.98 mmol) in acetone (25 mL) was cooled to 0 °C. To this cooled mixture was added 2,2-dimethoxypropane (0.5 mL, 4.4 mmol) and p-TsOH·H_2O (760 mg, 0.4 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by addition of $NaHCO_3$ (840 mg) at 0 °C and stirred for additional 10 min and then filtered through a pad of Celite. Acetone was removed and the crude residue was purified over silicagel flash column chromatography eluting with 8% EtOAc:hexanes to afford desired acetonide protected diol 11 as colorless oil; (1.8 g, 92% yield); R_f 0.40 (hexanes/EtOAc, 8:2); $[\alpha]_D^{24}$ −17.0 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (1H, dd, J=15.5, 3.7 Hz, C_5H), 5.78 (1H, dd, J=15.4, 8.9 Hz, C_4H), 4.59 (H, t, J=7.4 Hz, C_6H), 4.26 (2H, qdd, J=10.2, 7.2, 3.1 Hz, $C_{3,6}H$), 4.19–4.15 (2H, m, CH_2 of OEt), 3.80–3.75 (1H, m, C_2H), 1.49 (3H, s, CH_3 of acetonide), 1.48 (3H, s, CH_3 of acetonide), 1.28 (3H, t, J=7.2, CH_3 of OEt), 0.99 (3H, d, J=6.2 Hz, CH_3), 0.91 (9H, s, t-BuSi), 0.88 (9H, s, t-BuSi), 0.06 (6H, s, 2-Si–CH_3), 0.05 (6H, s, 2-Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 133.9, 126.9, 111.1, 80.0, 79.4, 74.7, 71.1, 61.3, 27.0, 25.8, 25.8, 18.2, 18.0, 17.0, 14.2, −4.6, −4.7, −4.7, −4.9; IR (neat, cm^{-1}): 2931, 2857, 1756, 1723, 1375, 1253, 1214, 1101, 832, 750; MS (ESI) m/z: 525 $(M+Na)^+$; HRMS:calcd for $C_{26}H_{56}O_6Si_2$ 520.3493; found 520.3493.

*4.1.9. (4R,5R)-5-((3S,4S,E)-3,4-Bis(tert-butyldimethylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**2**).* To a solution of above acetonide 11 (1.5 g, 2.9 mmol) in dry DCM (30 mL) at −78 °C was added DIBAL-H (1 M solution in toluene, 6 mL). After 1 h, excess of DIBAL-H was quenched by addition of 5 drops of methanol followed by saturated solution of sodium potassium tartrate. The mixture was allowed to stir for 2 h at 0 °C. The aqueous layers was extracted with diethyl ether (3×10 mL). The combined organics contents were washed with brine solution and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure at 20 °C. The crude residue was purified over silicagel column eluting with 20% EtOAc:hexanes to afford the desired alcohol 2 as transparent liquid; (2.6 g in 90% yield) R_f 0.50 (hexanes/EtOAc, 1:1); $[\alpha]_D^{24}$ −28.7 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (1H, dd, J=15.5, 3.9 Hz, C_5H), 5.69 (1H, dd, J=15.5, 7.8 Hz, C_4H), 4.37 (1H, t, J=8.0 Hz, C_3H), 4.15–4.12 (1H, m, C_2H), 3.85–3.80 (2H, m, $CH_{6,7}$), 3.78–3.73 (1H, m, CH), 3.62–3.58 (1H, m, CH), 1.44 (3H, s, CH_3 of acetonide), 1.43 (3H, s, CH_3 of acetonide), 0.96 (3H, d, J=6.2 Hz, CH_3), 0.90 (9H, s, t-BuSi), 0.88 (9H, s, t-BuSi), 0.06 (6H, s, 2-Si–CH_3), 0.05 (6H, s, 2-Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 127.5, 109.1, 81.3, 77.8, 74.8, 71.0, 61.0, 27.0, 27.0, 25.8, 18.1, 18.0, 17.2, −4.6, −4.7, −4.8, −4.8; IR (neat, cm^{-1}): 3018, 2931, 1377, 1214, 1105, 834, 744, 667; MS (ESI) m/z: 460 $(M+Na)^+$; HRMS:calcd for $C_{23}H_{48}O_5Si_2Na$ 483.7728; found 583.7731.

Note: This alcohol was oxidized to aldehyde by using dess-martin periodinane and used for next step without purification.

*4.1.10. (R)-6-((4R,5R)-5-((3S,4S,E)-3,4-Bis(tert-butyldimethylsilyloxy)pent-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-2H-pyran-2-one (**13**).* In an argon filled double necked round bottom flask with a magnetic stir bar a solution of $Cu(OTf)_2$ (dried upon P_2O_5 at 100 °C) (72.3 mg, 0.2 mmol), (*R*)-*tol*-binap (148 mg, 0.22 mmol) in anhydrous THF (3 mL) was stirred for 30 min at room temperature to form a pale yellow solution. To this, anhydrous THF (2 mL) solution of TBAT (dried under vacuum for 15 min) (154 mg, 0.4 mmol) was then added via cannula. The resulting bright yellow solution was stirred for an additional 15 min. Then, pre-dissolved solution of silyl dienolate 12 in THF (684 mg, 3 mmol) was added drop wise with cannula and subsequent the crude aldehyde (458 mg, 1 mmol) that was dissolved in 3 mL of THF. The resulting reaction mixture was stirred 8 h at ambient temperature. Then the reaction mixture was quenched by addition of a saturated solution of NH_4Cl (5 mL). The aqueous layers was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine solution (10 mL) and dried over anhydrous Na_2SO_4, transferred and concentrated under reduced pressure. The residue was purified over silicagel flash column chromatography eluting with 25% EtOAc:hexanes to afford desired the lactone 13 as white viscous liquid; (350 mg, 70% yield); R_f 0.40 (hexanes/EtOAc, 1:1); $[\alpha]_D^{24}$ +10.5 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, dd, J=9.6, 6.0 Hz, C_4H), 6.05–6.02 (1H, m, C_3H), 5.97 (1H, dd, J=15.5, 4.0 Hz, C_4H), 5.77 (1H, dd, J=15.5, 6.8C_3H), 4.50–4.44 (2H, m, $CH_{6,2'}$), 4.15–4.12 (1H, m, $C_{1'}H$), 3.98 (1H, dd, J=7.6, 5.0 Hz, $C_{5'}H$), 3.79–3.74 (1H, m, $C_{6'}H$), 2.62 (1H, ddt, J=21.0, 11.8, 2.5 Hz, C_5Ha), 2.47–2.41 (1H, m, C_5H_b), 1.44 (3H, s, CH_3 of acetonide), 1.43 (3H, s, CH_3 of acetonide), 0.98 (3H, d, J=6.2 Hz, CH_3), 0.90 (9H, s, t-BuSi), 0.88 (9H, s, t-BuSi), 0.05 (12H, s, 4-Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 144.7, 133.5, 128.0, 121.4, 110.0, 81.3, 78.8, 77.2, 74.8, 71.1, 27.1, 27.0, 25.8, 25.3, 18.1, 18.0, 17.2, −4.6, −4.7, −4.7, −4.9; IR (neat, cm^{-1}): 2930, 2856, 1739, 1377, 1248, 1105, 1068, 832, 774; MS (ESI) m/z: 549 $(M+Na)^+$; HRMS:calcd for $C_{27}H_{51}O_6Si_2$ 527.3234; found 527.3234.

*4.1.11. (2S,3S,E)-5-((4R,5R)-2,2-Dimethyl-5-((R)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-1,3-dioxolan-4-yl)pent-4-ene-2,3-diyl diacetate (**14**).* TBS ether 13 (200 mg, 0.38 mmol) was dissolved in acetonitrile containing plastic vial with a magnetic stir bar and cooled 0 °C. Hydrogen fluoride–pyridine (0.4 mL) was added in one portion and the reaction mixture warmed to ambient temperature and stirred for 6 h. Then, the reaction mixture was quenched by careful addition of an aqueous saturated solution of $NaHCO_3$ drop wise at 0 °C. Reaction mixture was diluted with EtOAc and the aqueous layer was extracted with same (3×5 mL). The combined organics contents were washed with brine solution and dried over Na_2SO_4 than filtered and concentrated under reduced pressure and applied high vacuum for 15 min. The resulting crude product was directly taken into further step without any purification.

In argon filled round bottom flask with a magnetic stir bar the above crude diol (90 mg, 0.3 mmol), was dissolved in anhydrous DCM. To this solution was added triethylamaine (0.1 mL, 0.9 mmol), and DMAP (4 mg, 0.03 mmol) at 0 °C. After 10 min, acetic anhydride in DCM (75 mg, 0.75 mmol) was added drop wise to the mixture at the same temperature. The resulting reaction mixture was allowed to stir at ambient temperature for 2 h. Then, the solvent was evaporated under reduced pressure. The crude residue was purified over silicagel flash column chromatography eluting with 30% EtOAc:hexanes to afford the desired diacetate as a viscous liquid; (85 mg, 80% yield) R_f 0.30 (hexanes/EtOAc, 1:1); $[\alpha]_D^{24}$ +51.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93–6.87 (1H m, C_4H), 6.05–5.78 (1H, m, C_3H), 5.34 (1H, t, J=6.0 Hz, $C_{1'}H$), 5.06–5.01 (1H, m, $C_{5'}H$), 4.5–4.4 (2H, m, $CH_{6',2'}$), 3.85 (1H, t, J=7.6 Hz, $C_{3'}H$), 2.57–2.51 (2H, m, C_5H), 2.11 (3H, s, CH_3 of acetate), 2.05 (3H, s, CH_3 of acetate), 1.43 (6H, s, CH_3 of acetonide), 1.22 (3H, d, J=6.0 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 170.0, 162.5, 144.5, 132.1, 127.4, 121.4, 110.3, 80.8, 79.2, 78.0, 74.5, 70.5, 29.7, 26.9, 26.2, 21.1, 21.0, 16.1; IR (neat, cm^{-1}): 2932, 2835, 1734, 1374, 1226, 1063, 817, 753; MS (ESI) m/z: 405 $(M+Na)^+$; HRMS:calcd for $C_{19}H_{30}O_8N$ 400.1974; found 405.1973.

*4.1.12. (2S,3S,6R,7S,E)-6,7-Dihydroxy-7-((R)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-4-ene-2,3-diyl diacetate (**1d**).* In an argon fitted round bottom flask with a magnetic stir bar acetonide protected diol (65 mg, 0.22 mmol) was dissolved in anhydrous MeOH. To this solution was added PPTS (160 mg, 0.66 mmol) at ambient temperature and the reaction mixture was slowly warmed until the solvent was being refluxed for 5 h. The reaction mixture was quenched with solid $NaHCO_3$ and stirred for 20 min at ambient temperature, filtered and evaporated the solvent under reduced pressure. The crude residue was diluted with EtOAc and extracted with same (3×8 mL). The combined organic contents were washed with brine solution and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified over silicagel flash column chromatography eluting with 60% EtOAc:hexanes to afforded desired diol **1d** as a clear liquid; (40 mg, 65% yield); R_f 0.10 (hexanes/EtOAc, 1:1); $[\alpha]_D^{24}$ +45.6 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (1H, ddd, *J*=9.8, 5.5, 3.2 Hz, C_4H), 6.04 (1H, ddd, *J*=9.8, 2.3, 1.4 Hz, C_3H), 5.87 (1H, ddd, *J*=15.7, 5.5, 0.9 Hz, C_3H), 5.77 (1H, ddd, *J*=15.7, 6.6, 1.2 Hz, C_4H), 5.34 (1H, t, *J*=6.0 Hz, C_6H), 5.11–5.05 (1H, m, $C_{5'}H$), 4.51 (2H, ddd, *J*=10.2, 7.0, 5.5 Hz, $CH_{2',6'}$), 3.70 (dd, *J*=6.3, 2.8 Hz, 1H, $C_{1'}H$), 2.59–2.53 (2H, m, C_5H_2), 2.11 (3H, s, CH_3 of acetate), 2.06 (3H, s, CH_3 of acetate), 1.22 (3H, d, *J*=6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 170.1, 163.6, 145.6, 133.5, 127.5, 121.0, 76.8, 74.7, 74.2, 70.6, 69.4, 25.6, 21.2, 21.0, 16.2; IR (neat, cm^{-1}): 3394, 3019, 2924, 2854, 1712, 1376, 1247, 1215, 1053, 753, 667; MS (ESI) *m*/*z*: 360 $(M+NH_4)^+$; HRMS:calcd for $C_{16}H_{22}O_4Na$ 365.1214; found 365.1214.

Acknowledgements

We are grateful to Director, IICT, for constant encouragement. Financial support was provided by the DST, New Delhi, India (Grant No: SR/S1/OC-08/2011), and ORGIN (CSC-0108) programme (CSIR) of XII Five year plan. UGC & CSIR (New Delhi) is gratefully acknowledged for awarding the fellowship to N. R, N. J. and K A.

Supplementary data

Supplementary data (copies of ^1H and ^{13}C NMR spectra) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.06.080.

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