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Stereoselective total synthesis of cananginones (D–I) using Ireland–Claisen rearrangement as a key step

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ABSTRACT

A strategy for stereoselective total synthesis of α-substituted γ-hydroxymethyl γ-butyrolactone containing bioactive natural products cananginones (D–I) has been developed using cheap and commercially available D-mannitol as a chiral pool. The Ireland–Claisen rearrangement is utilized as a key step to generate the α-substituted chiral center of the core lactone moiety, while the elongation of aliphatic side chain by different C-8 hydrocarbon groups have been achieved by alkylation, Cadiot–Chodkiewicz, and Sonogashira reactions.

1. Introduction

Functionalized chiral γ-butyrolactone[1] is an important subunit of biologically active compounds. Examples of natural products having such γ-butyrolactone moiety include cananginones (A–I)[2] (**1**–**9**), goniothalamusin[3] (**10**), saccopetrin A[4] (**11**), debilisones (A-F)[5] (**12**–**17**), and oropheolide[6] (**18**), which belong to a family of linear acetogenins[7] (Fig. 1). The common skeleton of these type natural products is most often characterized by α-substituted unbranched unsaturated fatty acid chain terminated with a saturated γ-hydroxymethyl γ-butyrolactone. The substituted γ-butyrolactone groups in this class of natural products remains either in cis- or trans-configuration. Cananginones (A–I) (**1**–**9**) were first discovered by Kanokmedhakul and co-workers[2] from crude hexane extract of the stem bark of traditional Thai medicinal tree *Cananga latifolia*. Stereochemically, the embedded α-substituted long aliphatic side chain and γ-hydroxymethyl group on lactone ring are in trans-orientation (Fig. 1). Most of these compounds show cytotoxicity to human carcinoma cell lines KB, MCF7, and NCI-H187 in micromolar range. In addition some of these members exhibit moderate antimalarial and antifungal activities. Their potential as therapeutic agents as well as the interesting architectural feature (substituted chiral γ-butyrolactone containing polyunsaturated skeleton) of this class of linear acetogenins has rendered them attractive targets for the synthetic organic chemistry community.[8]

A common and very obvious approach[8] to prepare this α-substituted γ-hydroxymethyl γ-butyrolactone skeleton involves stereoselective alkylation at the enolizable α-position of the core γ-lactone moiety by long chain aliphatic halide (Scheme 1). The inherent chirality derived from the substituted parent lactone moiety usually plays a key role for this type diastereoselectivity. Barua and co-workers[8b] adopted this strategy proficiently to prepare debilisone[5] C; a member of the same family (**14**) (Fig. 1). In debilisone C both α- and γ-substituents specifically are in a cis-orientation. However, this synthetic route does not allow synthesis of molecules (**1**–**11**, **18**) where both the α- and γ-substituents on lactone ring are in trans-configuration. The major drawback[8b] of this strategy is that the synthesis of *trans*-α,γ-substituted γ-butyrolactone moiety offers low yield, due to the incomplete consumption or decomposition of starting γ-lactone and the poor diastereoselectivity, due to inefficient chiral induction exerted by remote γ-substituent of parent lactone moiety.

Thus the challenge is in the development of an effective route for the synthesis of *trans*-substituted γ-butyrolactone skeleton. We sought to pursue a very flexible strategy for the stereoselective

Abbreviations: TBAI, tetrabutyl ammonium iodide; TMSI, trimethyl sulphonium iodide; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; LiHMDS, lithium bis(trimethylsilyl)amide; DMPU, *N*,*N*′-dimethylpropylene urea; HMPA, hexamethylphosphoramide; CH_2N_2, diazomethane; CSA, camphorsulfonic acid; NaHMDS, sodium bis(trimethylsilyl)amide; KHMDS, potassium bis(trimethylsilyl)amide; LDA, lithium diisopropylamide; DIBAL-H, diisobutylaluminum hydride; TMS-acetylene, ethynyltrimethylsilane; TBAF, tetrabutyl ammonium fluoride; DMP, Dess–Martin periodinane.

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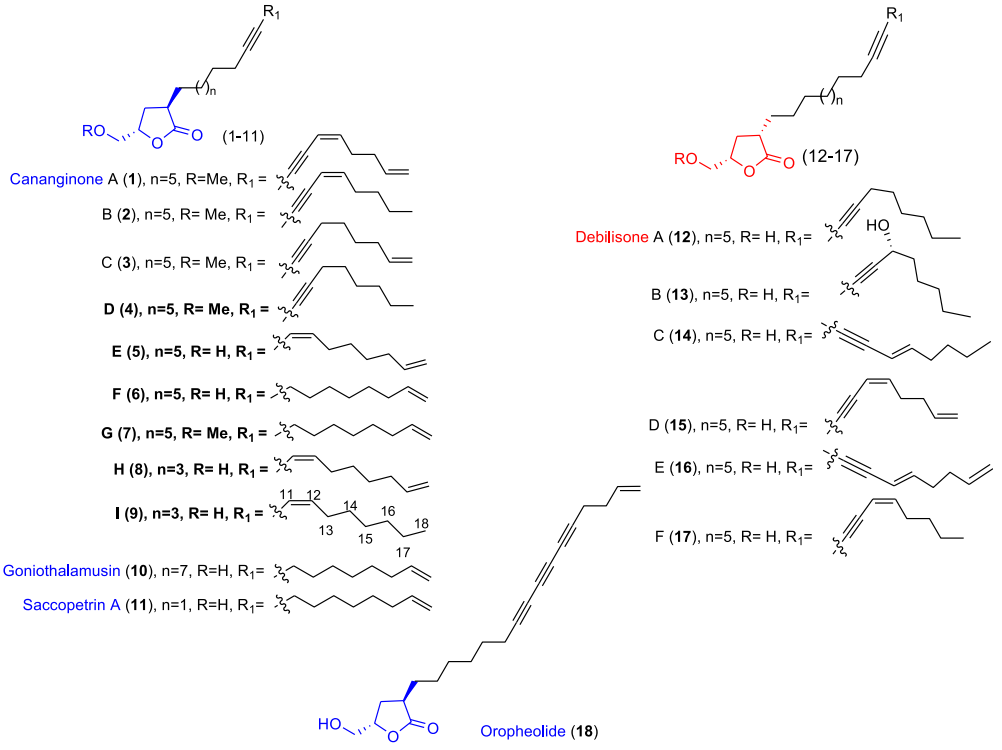
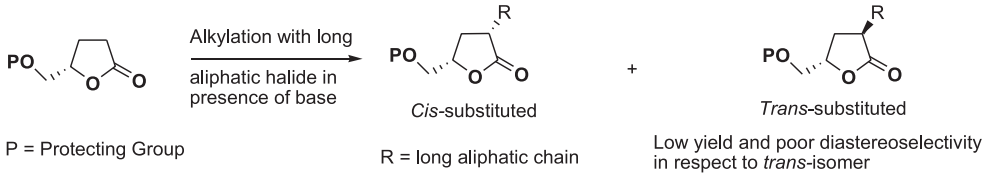


Fig. 1. Natural products with α-substituted γ-hydroxymethyl γ-lactone moiety.



Scheme 1. Known strategy for synthesis of α-substituted γ-hydroxymethyl γ-butyrolactone.

synthesis of γ-butyrolactone containing bioactive natural products using the Ireland–Claisen rearrangement[9] as a key step. The stereochemical outcome of this rearrangement can be ascertained by the predictable relay of chirality of the allylic center (present in the allylester surrogate) in an acyclic system through a well-understood transition state structure.[9,10] Our continual interest[11] in the asymmetric synthesis of bioactive natural products prompted us to embark upon the total synthesis of cananginones. To the best of our knowledge, total synthesis of any member of cananginones has not been reported till the date. Herein we describe the total synthesis of cananginones (D–I) for the first time (**4**–**9**). We believe this strategy can be used for successful stereoselective synthesis of a large number of natural products having the *trans*-α-substituted γ-hydroxymethyl γ-butyrolactone core.

2. Results and discussion

Retrosynthetic analysis of cananginones (D–I) is outlined in Scheme 2. We envisaged that the cananginones (D, E, H, I) (**4**, **5**, **8**, **9**) could be derived from the γ-lactones **22** and **23** by coupling it with the corresponding C-8 hydrocarbon counterparts (**19**–**21**) using Cadiot–Chodkiewicz reaction[12] or Sonogashira reaction.[13] The lactones **22** and **23** could be prepared from the intermediates **24** and **25**, respectively, involving regioselective γ-lactonization as one of the key steps. The construction of the alkynes **24** and **25** could be achieved from the common intermediate **26** utilizing the Ireland–Claisen rearrangement. Compound **26** then could be prepared by esterification of the acid **27** using the allylic alcohol **28**. Both the acid **27** and the allylic alcohol **28** could be synthesized from a single chiral pool; D-mannitol. For the cananginones (F and G) (**6** and **7**), we planned for a little alteration of above reaction sequences to preclude epimerization of the α-alkyl center during installation of the C-8 hydrocarbon part under basic conditions (Scheme 2). Both the cananginone F (**6**) and its methylated analogue cananginone G (**7**) could be prepared from the ester **29** by acid catalyzed γ-lactonization. The ester **29** in turn could be derived from the alkyne **24** by alkylation with the alkyl iodide **30**.

Our synthetic endeavor began with the preparation of known acid **27** and allylic alcohol **28** from commercially available, and cheap, D-mannitol (Scheme 3). The known α,β-unsaturated ester **31**,[14] derived from D-mannitol, was used to synthesize the epoxide **32** in four steps. First, the ester (**31**) was reduced to a saturated alcohol[14b] in the presence of $NaBH_4$/LiCl, which was subsequently benzylated with BnBr/NaH to get the corresponding benzyl ether.[15] Then the resultant benzyl ether was treated with 80% AcOH/H_2O to deprotect the acetonide and finally reacted with tosyl-imidazole in the presence of NaH[16] to afford the known epoxide **32**[15,17a] in good overall yield. The epoxide **32** was then transformed to the known allylic alcohol **28** by Me_3SI/^{n}BuLi following the literature procedure.[17] The required acid **27**[18] was synthesized from the known ester **31** in two steps: hydrogenation followed by saponification in the presence of LiOH.

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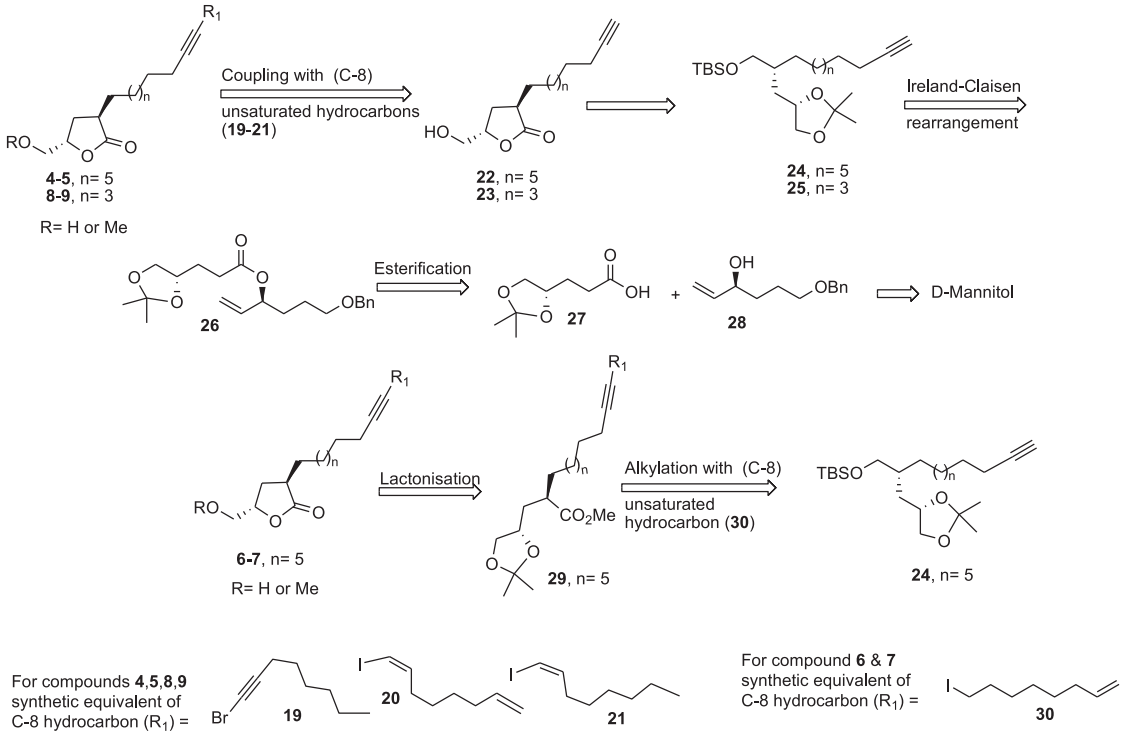
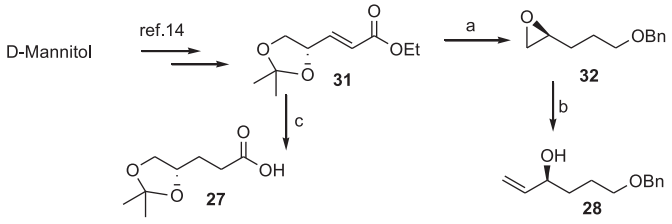


Scheme 2. Retrosynthetic analysis of cananginones (D–I).



Scheme 3. Synthesis of acid **27** and allylic alcohol **28**. Reagents and conditions: (a) (i) $NaBH_4$/LiCl (1:1), THF/MeOH (1:1), 0 °C to rt, 48 h, 78%; (ii) NaH, BnBr, TBAI, 0 °C to rt, 3 h, 87%; (iii) 80% AcOH in H_2O, 12 h, rt, 91%; (iv) tosyl-imidazole, NaH, THF, 0 °C, 45 min, 75%; (b) Me_3SI, ^nBuLi, THF, −40 °C to rt, 2 h, 85%; (c) (i) H_2, Pd/C (10%), EtOAc 3 h, rt, quantitative; (ii) LiOH, MeOH: H_2O (3:1), 0 °C to rt, 14 h, 90%.

The synthesis of crucial α-substituted esters **33** & **33a** is illustrated in Scheme 4. The acid **27** was esterified with the allylic alcohol **28** under Steglich condition[19] (DCC/DMAP) to afford compound **26** in very good yield. The stage was thus set to carry out the Ireland–Claisen rearrangement to install the crucial α-substituent in the lactone domain in a stereoselective manner. The diastereoselectivity of this rearrangement is mainly controlled by either the geometry of silyl ketene acetals (*Z*- or *E*-isomer) or the transition structure (chair or boat).[9,10] The selective formation of the silyl ketene acetals or the adopted preference of the transition geometry are closely dependent on several parameters like solvent polarity, temperature, nature of the base, ester to base ratio, and structure of substrates.[9c,j] Thus several experimental parameters contribute to selectivity and yield of Ireland–Claisen rearrangement reaction. Logically rigorous optimization of conditions is essential to obtain the best yield and diastereoselectivity of the desired product. Our efforts toward standardization of the Ireland–Claisen rearrangement on ester **26** are summarized in Table 1. We had initially kept the ester to base ratio and reaction temperature invariable during the optimization process. A higher base to ester ratio of 4:1 was used to ensure the deprotonation of the enolizable α-proton of the ester functionality. We varied the solvent polarity as well as the nature of amide bases[20] during our optimization process. The rearrangement did not proceed with NaHMDS in THF solvent even after 6 h at −78 °C (Table 1, entry 1). But the same base was effective in the presence of 20% polar aprotic solvents (HMPA or DMPU) dissolved in THF. The use of dipolar HMPA or DMPU solvent assisted the desired rearranged product formation almost in identical diastereoselectivity (~6.6:1) but with different yields (Table 1, entries 2 and 3). The presence of a dipolar solvent seems to be essential for effective enolization.[9c,21] Because the polar solvent helps to disintegrate the base from its original oligomeric form (via solvation) and makes the active ingredient, the amidate anion, more accessible for the enolization process.[9c] Enolization using KHMDS in THF/HMPA (Table 1, entry 4) and THF/DMPU (Table 1, entry 5) was also separately attempted. The changes of metal counter ion from sodium to potassium reduced the yield by a substantial amount in our case. It is necessary to note that the choice of HMPA or DMPU in case of NaHMDS did not result in such a big difference in diastereoselectivity. These differences in results are consistent with the established Ireland cyclic transition state model (Fig. 2).[9b] According to this model, the abstraction of enolizable proton by amide base takes place through a six-member chair like transition state (TS-I or TS-II). TS-I leads to (*E*)-silyl ketene acetal via (*Z*)-enolate formation whereas TS-II facilitates (*Z*)-silyl ketene acetal through (*E*)-enolate formation (Fig. 2).

The metal ion in this transition state is coordinated by both the carbonyl oxygen and the base nitrogen. The changes in size or in degree of solvation of metal ion or both could and possibly would affect the geometry of the transition structure.[22] This would tune the extent of interaction of metal ion with the reacting ester and the base. Consequently this would exert an effect in the kinetics of deprotonation[22] and, subsequently, in the selectivity of TS-I versus TS-II. Consequently the yield and diastereoselectivity of this rearrangement differ with variation in the base used and the polarity of medium. Moreover, the degree of solvation of metal ion by dipolar

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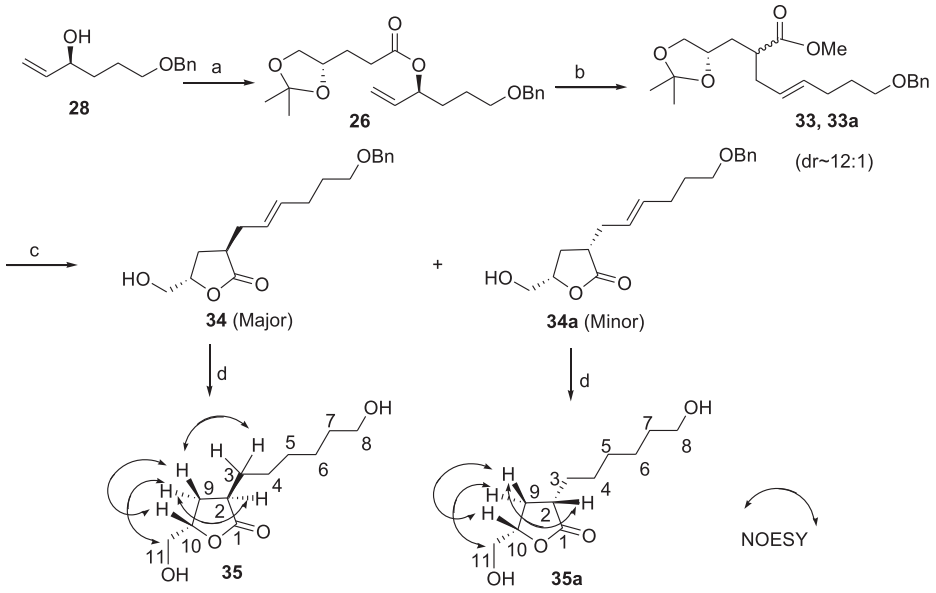

Scheme 4. Synthesis of α-substituted esters **33** and **33a**. Reagents and conditions: (a) **27**, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 20 h, 78%; (b) (i) LiHMDS, TBSCl, THF/DMPU (4:1), −78 °C, 4.5 h; (ii) CH_2N_2, Et_2O, 0 °C, 10 min, overall 85% after two steps [dr ~12:1]; (c) CSA, MeOH, 0 °C to rt, 3 h, 90% (combined); (d) H_2, Pd/C (10%), EtOH, 4 h, rt, (90–92)%.

Table 1
Optimization of reaction conditions for Ireland–Claisen rearrangement of ester **26**

Entry	Base(equiv)/TBSCl (equiv)	Solvents	Temp (°C)	Time (h)	Yield (%)	dr[a]
1	NaHMDS (4.0)/TBSCl (6.0)	THF	−78	6	NR[b]	—
2	NaHMDS (4.0)/TBSCl (6.0)	THF/HMPA (4:1)	−78	4	55	6.7:1
3	NaHMDS (4.0)/TBSCl (6.0)	THF/DMPU (4:1)	−78	5.5	66	6.6:1
4	KHMDS (4.0)/TBSCl (6.0)	THF/HMPA (4:1)	−78	6	18	3.6:1
5	KHMDS (4.0)/TBSCl (6.0)	THF/DMPU (4:1)	−78	5	30	5.5:1
6	LDA (4.0)/TBSCl (6.0)	THF/HMPA (4:1)	−78	10	61	1:2
7	LDA (4.0)/TBSCl (6.0)	THF/HMPA (4:1)	−78 to rt	5	48	1.3:1
8	LDA (4.0)/TBSCl (6.0)	THF/DMPU (4:1)	−78	14	56	3:1
9	LiHMDS (4.0)/TBSCl (6.0)	THF/HMPA (4:1)	−78	9	23	1:1.5
10	LiHMDS (4.0)/TBSCl (6.0)	THF/DMPU (4:1)	−78	4.5	85	12:1
11	LiHMDS (4.0)/TBSCl (6.0)	THF/DMPU (4:1)	−78 to rt	3	70	7:1
12	LiHMDS (4.0)/TBSCl (6.0)	THF/DMPU (11:9)	−78	4	67	7.7:1
13	LiHMDS (1.5)/TBSCl (6.0)	THF/DMPU (4:1)	−78	8	61	5.9:1
14	LiHMDS (3.0)/TBSCl (6.0)	THF/DMPU (4:1)	−78	6	74	7.2:1
15	LiHMDS (6.0)/TBSCl (6.0)	THF/DMPU (4:1)	−78	4	75	8:1

[a] Diastereomeric ratio of inseparable compounds **33** and **33a** was determined from the integration of singlet methyl peaks of ester groups by ^{1}H NMR.
[b] NR=no reaction.

solvents like HMPA or DMPU varies because of their effective abundance in reaction medium at low temperature and also due to the differences in their steric requirements. Bulkier HMPA in THF at −78 °C is heterogeneous due to its higher melting temperature (ca. 7 °C) whereas the relatively smaller DMPU under the same conditions is homogeneous due its low melting temperature (ca. −20 °C).[9c] It is likely that in the case of sodium, due to its smaller size and tight association in transition state, the solvation of metal ion either with HMPA or with DMPU has no substantial effect on the fate of the reaction in our case. This is why we did not observe any noticeable difference in the distribution of the products. But in the case of KHMDS, the effect of polarity of solvent is prominent. Due to the larger size of potassium ion, the chair like transition state may not be very compact, which results an overall drop of diastereoselectivity compared to NaHMDS. The extent of solvation of potassium with DMPU is most likely better than the less abundant (due to insolubility) and bulkier HMPA at low temperatures. As the degree of solvation increases, the interaction of metal ion with base and ester carbonyl decreases. As a result the severe 1,3-*syn* diaxial strain, which exists in the TS-II is diminished whereas the TS-I still suffer from $A_{1,3\text{-strain}}$.[9b,c] Thus the population of TS-II definitely is higher in the case of DMPU when compared with HMPA.

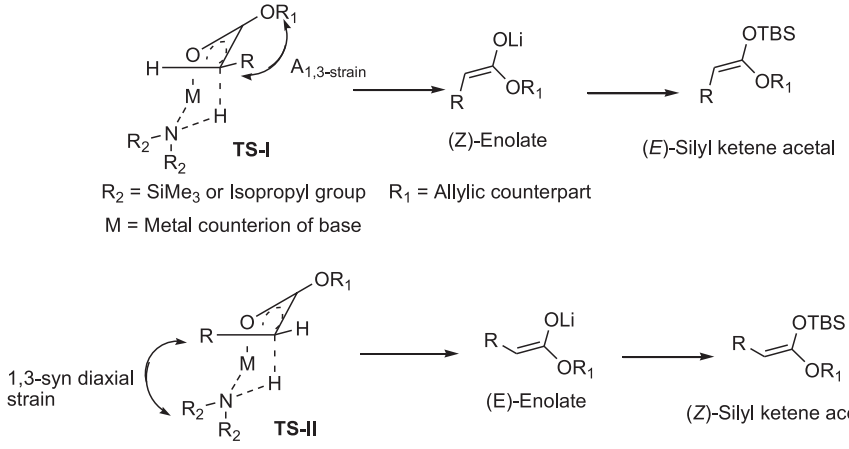

Fig. 2. Cyclic transition model for enolization of carbonyl ester with amide bases.

This provides a plausible mechanism for the observed differences in the diastereoselectivity obtained using KHMDS in THF/DMPU (dr ~5.5:1, Table 1, entry 5) and in THF/HMPA (dr ~3.6:1, Table 1, entry 4) solvent systems.

We were interested to see the effect of smallest metal counter ion containing bases like LDA or LiHMDS in this rearrangement. The ester **26** was treated with LDA in the presence of THF/HMPA (Table 1, enties 6 and 7) or THF/DMPU (Table 1, entry 8) as solvents. The yields were moderate but the diastereoselectivity was very low in both the cases. Although the diastereoselectivity is poor, it is interesting to notice that in the presence of weakly coordinating bulky solvents, HMPA at −78 °C, (Table 1, entry 6) the undesired product is obtained in higher yields than the desired one (dr ~1:2) whereas in the presence of DMPU (Table 1, entry 8) the observed diastereoselectivity favors the formation of the desired isomer (dr ~3:1). According to Ireland model (Fig. 2),[9b] the TS-I is likely to be marginally favored in HPMA whereas TS-II is favored in DMPU. The elevation of temperature from −78 °C to room temperature reduced the selectivity significantly (dr ~1:1) (Table 1, entry 7) as may be expected. The use of LiHMDS in THF/HMPA solvent system provided the rearranged products in very poor yield and diastereoselectivity (Table 1, entry 9) similar to LDA in THF/HMPA (entry 6). Remarkably the variation of diisopropylamide to hexamethyldisilazide bases in THF/DMPU affected both the yield and diastereoselectivity favoring the desired isomer (dr ~12:1, Table 1, entry 10). Li metal ion solvated with DMPU is likely to achieve the optimal size, which is required to bind with the six-member transition state (Fig. 2) most tightly. More importantly as silicon is larger than carbon in size, the N–Si bond in disilazide base is expected to be longer than N–C bond in diisopropylamide base. Consequently the extent of 1,3-*syn* diaxial interaction in TS-II would be less in LiHMDS when compared to LDA in same THF/DMPU solvent system. This probably accounts the differences in observed results. The rise of temperature from −78 °C to room temperature diminished the yield as well as the diastereoselectivity (Table 1, entry 11).

We were next keen to see whether variations[9c] in the concentrations of DMPU used in reaction mixture or the ratio of ester to base (LiHMDS) could improve the yield and diastereoselectivity further. For this purpose, we carried out the rearrangement reaction by LiHMDS in the presence of 45% DMPU in THF (Table 1, entry 12). But both the yield and diastereoselectivity reduced substantially when compared to entry 10. The use of more (Table 1, entry 15) or less amount (Table 1, entries 13 and 14) of base compared to entry 10 was not fruitful to improve either the yield or the diastereoselectivity. In our case LiHMDS in THF/DMPU solvent system at low temperature (Table 1, entry 10) was the optimal condition for the rearrangement to yield the desired isomer.

Exposure of ester **26** to LiHMDS/TBSCl in THF/DMPU (4:1) solvent system at −78 °C affected the expected Ireland–Claisen rearrangement to deliver a pair of inseparable diastereomers **33** and **33a** (dr ~12:1) after methyl ester formation with diazomethane in 85% total yield. To reassure the stereochemical outcome of this rearrangement the mixture of diastereomers **33** and **33a** was further transformed to γ-lactones **34** and **34a** by CSA/MeOH and separated easily by silica gel column chromatography. The stereochemical assignments of both compounds **34** and **34a** by extensive ^{1}H NMR were unsuccessful due to overlapping of $(H\text{-}9)_\beta$ and $(H\text{-}3)_{allyl}$ protons. Both compounds **34** and **34a** were hydrogenated separately to get compounds **35** and **35a**, respectively. The NOESY of both compounds were recorded and the characteristic correlation between $(H\text{-}9)_\beta$/(H-3) (Scheme 4) protons was observed only in the major compound **35**. The speculated correlations among the protons $(H\text{-}9)_\alpha$/$(H\text{-}11)_2$ (1.18% & 0.64%), $(H\text{-}9)_\alpha$/(H-2) (1.47%), $(H\text{-}9)_\beta$/(H-10) (2.63%), and $(H\text{-}9)_\beta$/(H-3) (1.86%) in compound **35** were also seen by NOE experiment. This thereby confirmed the stereochemistry of major product from the Ireland–Claisen rearrangement step.

We used the route outlined in Scheme 5 to construct the key intermediates **22**, **23**, and **24**. The mixture of compounds **33** and **33a** was next reduced by DIBAL-H to get chromatographically separable alcohols **36** as the major and **36a** as the minor isomer. The free alcohol of the required product **36** was masked as a TBS-ether and subsequently hydrogenated to get the alcohol **37** in quantitative yield. The alcohol was iodinated by Ph_3P/I_2 in the presence of imidazole to get an iodide, which was next reacted with TMS-acetylene in the presence of ^{n}BuLi to afford the TMS deprotected alkyne **25** in situ in 74–75% overall yield in two steps. A negligible amount of the terminal alkene, generated from the precursor iodide by elimination process, was also observed as a byproduct in this reaction and was discarded during purification. The alkyne **25** was then converted to **23** in five steps. TBS was first deprotected by TBAF to get an alcohol. Then the corresponding alcohol was oxidized sequential by DMP and Pinnick oxidation[23] conditions to get an acid. The resulting acid was next esterified with diazomethane and finally treated with CSA in MeOH to result in the lactone **23** as a single regioisomer in very good overall yield. On the other hand, we have proceeded from the same alcohol **37** to synthesize **38** in three steps. A one pot Swern oxidation followed by concomitant Wittig olefination using (carbethoxymethylene) triphenylphosphorane to get a α,β-unsaturated ester, which was reduced further by $NaBH_4$/LiCl combination to obtain the higher homologue **38** in 78–80% overall yield (Scheme 5). Utilizing the similar chemistry described above, the alcohol **38** was iodinated and subsequently reacted with TMS-acetylene/^{n}BuLi to produce the alkyne **24**, which was finally converted to the lactone **22** in five steps with very good overall yield (Scheme 5).

Having secured access to the lactone domains, we proceeded to complete the synthesis of cananginones (D, E, H, I) (**4**, **5**, **8**, **9**) as summarized in Scheme 6. The key alkyne **22** was coupled separately with bromo alkyne **19**[24] and vinyl iodide **20**[25] by Cadiot–-Chodkiewicz reaction[12] and Sonogashira reaction[13] to achieve compound **39** and cananginone E (**5**), respectively, in good to moderate yields. Methylation[26] of free primary alcohol of lactone **39** by Me_3OBF_4 in the presence of a proton sponge successfully facilitated the total synthesis of cananginone D (**4**). The physical and spectroscopic data of the synthesized cananginone D were in accordance with the literature data of the isolated natural product.[2] Similarly another key alkyne **23** was subjected separately to Sonogashira coupling with the vinyl iodides **20**[25] and **21**[27] to synthesize successfully proposed cananginones H (**8**) and I (**9**) in good yields, respectively. The spectral data (^{1}H, ^{13}C NMR, HRMS) and optical rotations of synthesized cananginones E (**5**), H (**8**), and I (**9**),[28] measured immediately after their purification (vide infra), are found to be in close agreement with the reported values of these isolated natural products.[2]

It is noteworthy to mention that the *cis*-enyne system of cananginones I (**9**) is susceptible to isomerization and it equilibrates with the *trans*-enyne slowly under ambient conditions.[29] The isomerization of cananginones I (**9**) could be clearly understood from the ^{1}H NMR spectra recorded at different time intervals (Fig. 3). The gradual increase of intensity of the new peaks at δ 6.03 ppm at the expense of peaks at δ 5.78 ppm for cananginone I (**9**), indicates the cis to trans isomerization of the olefin proton (H-12, Fig. 1) β to the alkyne group. The downfield shift[5,30] and large coupling constant (dt, *J=15.8*, 7.0 Hz) of H-12 proton support this isomerization. The observed ratio of *cis*-enyne of cananginone I versus its *trans*-enyne form was around 1.0:0.6 at equilibrium. On the contrary the cananginones E (**5**) and H (**8**), with very similar *cis*-enyne moiety of cananginone I (**9**), did not exhibit any noticeable isomerization within days.[31]

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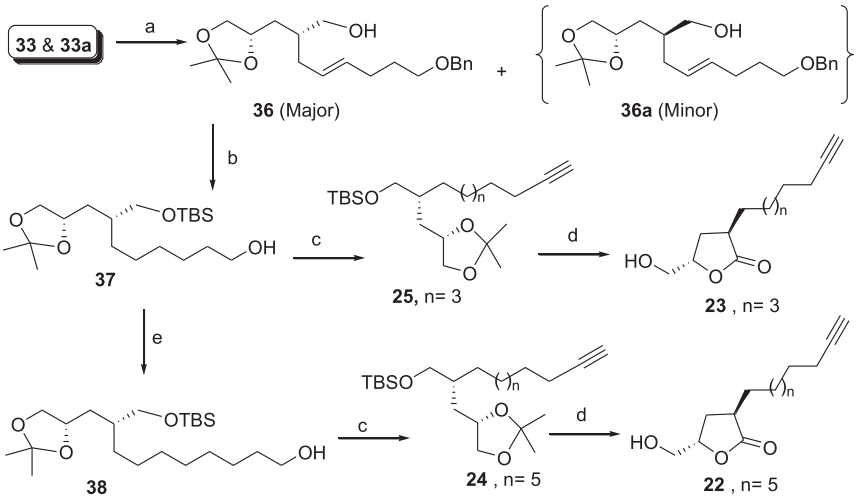
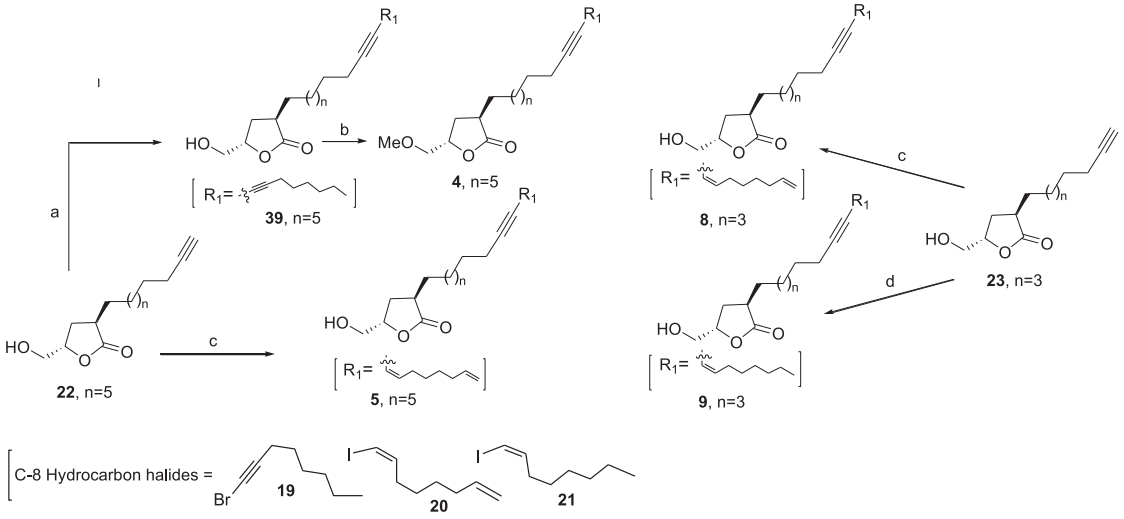


Scheme 5. Synthesis of Alkynes **22**, **23**, and **24**. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, 15 min, 92% (combined); (b) (i) TBSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 1.5 h, quantitative; (ii) H_2, Pd/C (10%), EtOAc, rt, 4.5 h, quantitative; (c) (i) I_2, Ph_3P, imidazole, toluene, 0 °C to rt, 3.5 h; (ii) TMS-acetylene, ^nBuLi, THF: HMPA (5:1), −78 °C to rt, 12 h, (74–75)% in two steps; (d) (i) TBAF, THF, 0 °C to rt, 6 h; (ii) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 2.5 h; (iii) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, *tert*-butanol/2-methyl-2-butene (2:1), 0 °C to rt, 5 h; (iv) CH_2N_2, Et_2O, 0 °C, 10 min; (v) CSA, MeOH, 0 °C to rt, 3 h (78–80)% overall yield in five steps; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 2 h; (ii) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, rt, 36 h; (iii) $NaBH_4$/LiCl (1:1), THF/MeOH (1:1), 0 °C to rt, 48 h, 80% in three steps.



Scheme 6. Completion of cananginones D (**4**), E (**5**), H (**8**), and I (**9**). Reagents and conditions: (a) **19**, CuBr, Et_3N, $NH_2OH{\cdot}HCl$, rt, 12 h, 72%; (b) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 °C to rt, 42 h, 60%; (c) **20**, Pd[$(PPh_3)_2Cl_2$], CuI, Et_3N, rt, 20 h, (65–68)%; (d) **21**, Pd[$(PPh_3)_2Cl_2$], CuI, Et_3N, rt, 20 h, 70%.

For successful construction of cananginones F (**6**) and G (**7**), we followed a slightly modified Scheme 7, because the installation of C-8 hydrocarbon part had to be carried out under basic conditions. The key alkyne **24** was subjected to alkylation with iodide **30**[32] in the presence of ^nBuLi to achieve compound **40** in very good yield. Rest of the steps was similar to the chemistry aforesaid in Schemes 5 and 6. Compound **40** was subjected to a three-step reaction protocol: The alcohol was oxidized sequentially with DMP oxidation followed by Pinnick oxidation[23] to get an acid, which was next treated with diazomethane to afford the methyl ester **29** in 88% overall yield. The ester was then lactonized by CSA in MeOH to get regioselectively cananginone F (**6**) in excellent yield. Methylation[26] of free hydroxyl of cananginone F (**6**) by Me_3OBF_4 in the presence of proton sponge facilitated finally cananginone G (**7**) in 65% yield. The spectral data and optical rotation of synthesized cananginones F (**6**) and G (**7**) are in good agreement with the reported values[2] of natural cananginones F and G.

3. Conclusions

In summary, a very flexible and highly stereoselective strategy has been developed to efficiently access *trans*-α-substituted γ-hydroxymethyl γ-butyrolactone containing bioactive natural products cananginones (D–I) from D-mannitol using Ireland–Claisen as a key step. The various C-8 aliphatic parts have been assembled with the key alkyne intermediates (**22**, **23**, **24**) to construct the full length hydrocarbon side chain of cananginones (D–I) by simple alkylation reaction or by Cadiot–Chodkiewicz or Sonogashira coupling reactions. The cananginones (D, E, F, G) have been synthesized from known intermediates **27** and **28** in 17, 16, 15, 16 steps, respectively, with an overall yields of 11, 17, 17, 11%, respectively, whereas cananginones H and I obtained in 14 steps from same starting materials with overall yields of 21 and 22%, respectively. The general strategy finally developed here can easily be extended to efficiently synthesize a wide range of natural products

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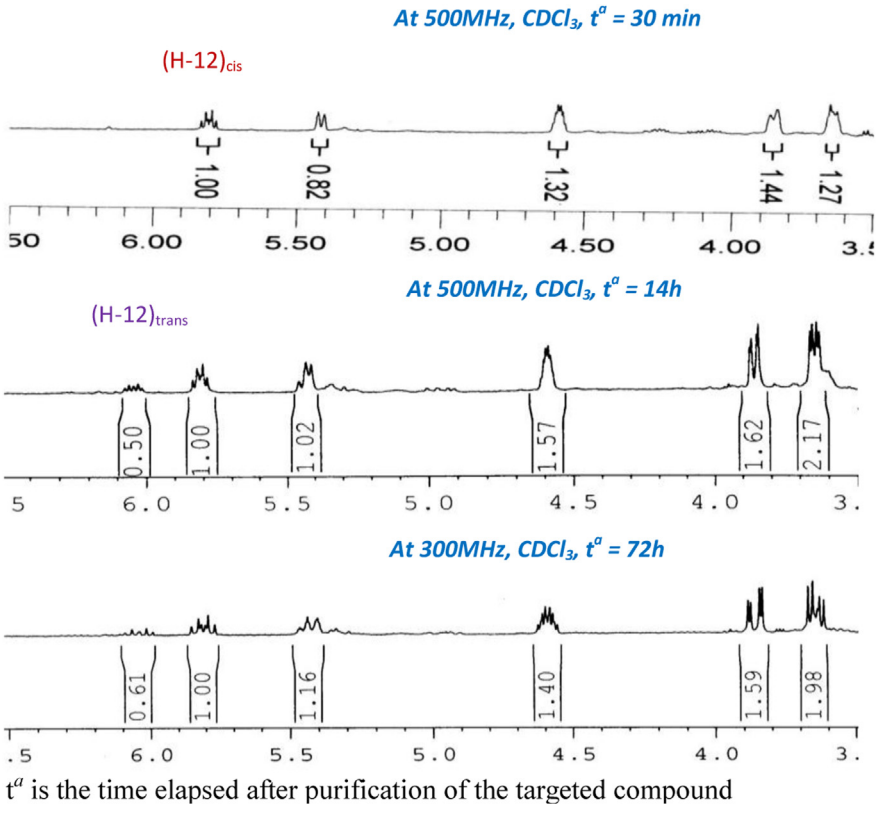
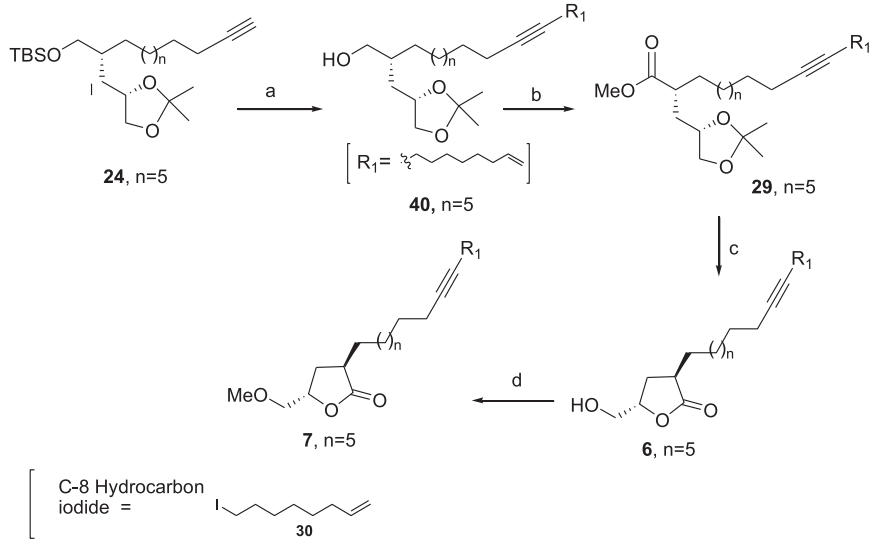


Fig. 3. Stacked ^{1}H NMR (partial) spectra of synthesized cananginones I (**9**) recorded at different time intervals.



Scheme 7. Completion of cananginones F (**6**) and G (**7**). Reagents and conditions: (a) **30**, ^{n}BuLi, THF/HMPA (5:1), 0 °C to rt, 18 h; (ii) TBAF, THF, 0 °C to rt, 2.5 h, 65% in two steps; (b) (i) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 3 h; (iii) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, *tert*-butanol/2-methyl-2-butene (2:1), 0 °C to rt, 3 h; (iv) CH_2N_2, Et_2O, 0 °C, 10 min, 88% in three steps; (c) CSA, MeOH, 0 °C to rt, 3 h, 92%; (d) Me_3OBF_4, proton sponge, CH_2Cl_2, 0 °C to rt, 48 h, 65%.

and their related analogues bearing a functionalized γ-butyrolactone scaffold having α- and γ-substitutions in trans-relationship with judicious selection of allylic ester in initial stage and requisite manipulations to adjust the side chain in later stage.

4. Experimental section

4.1. General

All reactions were carried out in oven or flame-dried glassware with Teflon coated magnetic stirring under argon or nitrogen atmosphere using dry, freshly distilled solvents prior to use unless otherwise noted. Air- and moisture-sensitive liquids were handled through gastight syringe and stainless-steel needle. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid—heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% concd H_2SO_4)—heat as developing agents. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere unless otherwise stated. Flash chromatography was done using silica gel 100–200 unless otherwise stated. Yields mentioned as chromatographically unless

otherwise stated. Optical rotations were measured using sodium (589, D line) lamp and are reported as follows: $[\alpha]_D^{25}$ (c=mg/100 mL, solvent). IR spectra were recorded as neat liquids. High resolution mass spectra were taken using Q-Tof-micro MS system using electron spray ionization (ESI) techniques. CHN analyses were carried out by frontal chromatographic techniques (thermal conducting measurement). ^{1}H NMR spectra were recorded on 300, 400, and 500 MHz spectrometers in suitable solvents and calibrated using residual undeuterated solvent as an internal reference, and the chemical shifts are shown in δ ppm scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C and 2D NMR spectra were recorded on 75, 100, and 125 MHz spectrometers.

4.2. (*S*)-2-(3-(Benzyloxy)propyl)oxirane (32)

To a solution of $NaBH_4$ (26.92 g, 0.71 mol) in anhydrous EtOH (450 mL) and THF (450 mL) at 0 °C under argon atmosphere, dry LiCl (30.18 g, 0.71 mol) was added, and stirred for 10 min. The α,β-unsaturated ester **31**[14] (19.0 g, 94.89 mmol) dissolved in anhydrous THF (100 mL) was then cannulated to the reaction mixture and stirring was continued further for 48 h at ambient temperature. The reaction mixture was cooled again to 0 °C and quenched cautiously with slow addition of saturated aqueous solution of NH_4Cl. The organic solvent was evaporated in vacuo and extracted with EtOAc (3×200 mL). The combined EtOAc extract was washed sequentially with water, brine and dried over Na_2SO_4. The organic extract was concentrated in vacuo and finally subjected to chromatographic purification (SiO_2, 30–35% EtOAc/hexane) to provide corresponding acetonide protected triol (11.85 g, 78%) as a colorless oil: R_f=0.30 (30% EtOAc/hexane); $[\alpha]_D^{28}$ +8.0 (c 4.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.12 (m, 1H), 4.06 (m, 1H), 3.67 (m, 2H), 3.53 (t, J=7.6 Hz, 1H), 1.67 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.1, 76.1, 69.5, 62.7, 30.3, 29.3, 27.0, 25.8 ppm; HRMS (ESI) m/z calcd for $C_8H_{16}O_3Na$ $[M+Na]^+$ 183.0997, found 183.0996.

The acetonide protected triol (5.0 g, 31.5 mmol) from the above step was taken in anhydrous THF (100 mL) under argon atmosphere and cooled to 0 °C. NaH (60% dispersion in mineral oil, 1.51 g, 63.0 mmol) was added portion wise to the stirred reaction mixture. After stirring for 15 min, BnBr (4.12 mL, 34.64 mmol) followed by TBAI (582 mg, 1.57 mmol) was added to the reaction mixture and stirred for 3 h at room temperature prior to quench with slow addition of saturated aqueous solution of NH_4Cl at 0 °C. The reaction mixture was extracted with EtOAc (2×100 mL). The combined organic extract was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 15% EtOAc/hexane) afforded corresponding benzyl protected compound (6.85 g, 87%) as a colorless oil. R_f=0.60 (10% EtOAc in hexane); $[\alpha]_D^{28}$ +6.7 (c 7.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.25 (m, 5H), 4.50 (s, 2H), 4.1 (quint, J=6.2 Hz, 1H), 4.02 (m, 1H), 3.51 (m, 3H), 1.74–1.60 (m, 4H), 1.40 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.7, 128.5, 127.7, 127.6, 108.8, 75.9, 73.0, 70.1, 69.5, 30.4, 27.1, 26.1, 25.8 ppm; HRMS (ESI) m/z calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1467, found 273.1476.

The benzyl protected compound from the above step (5.0 g, 19.97 mmol) was taken in a 100 mL round bottom flask and dissolved in 80% AcOH (60 mL) and stirred for 12 h at room temperature. After completion of the reaction, the AcOH was removed under vacuum and the crude residue was extracted with EtOAc (3×100 mL). The combined organic layers were washed with water, saturated aqueous solution of $NaHCO_3$, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 80% EtOAc/hexane) afforded corresponding acetonide deprotected diol (3.82 g, 91%) as a colorless oil. R_f=0.30 (80% EtOAc/hexane); $[\alpha]_D^{28}$ −1.1 (c 6.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.27 (m, 5H), 4.5 (s, 2H), 3.65 (m, 1H), 3.5 (d, J=11.0 Hz, 1H), 3.50 (m, 2H), 3.39 (m, 1H), 1.76–1.66 (m, 2H), 1.58–1.52 (m, 1H), 1.50–1.43 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.1, 128.5, 127.8, 127.7, 73.1, 72.0, 70.5, 66.7, 30.4, 26.1 ppm; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_3Na$ $[M+Na]^+$ 233.1154, found 233.1154.

To a stirred suspension of NaH (60% dispersion in mineral oil, 560 mg, 23.2 mmol) in anhydrous THF (50 mL) at 0 °C, the diol from the above step (1.94 g, 9.28 mmol) was added under argon atmosphere. Tosyl-imidazole (4.0 g, 18.56 mmol) was then poured to the reaction mixture and stirred for additional 45 min at the same temperature. After completion of reaction, water was added and extracted with EtOAc (2×100 mL). The combined organic extract was washed with water, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed (SiO_2, 10–15% EtOAc/hexane) to purify the epoxide **32** (1.34 g, 75%) as a liquid. R_f=0.50 (10% EtOAc/hexane); data for epoxide **32**: same as Refs. 15 and 17a.

4.3. (*S*)-6-(Benzyloxy)hex-1-en-3-yl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (26)

DCC (7.15 g, 34.66 mmol) and DMAP (222 mg, 2.0 mmol) were added to a solution of acid **27**[18] (5.75 g, 32.0 mmol) and allyl alcohol **28**[17] (5.5 g, 26.67 mmol) in anhydrous CH_2Cl_2 (150 mL) at 0 °C under argon atmosphere. The mixture was stirred at 0 °C for 1 h and then at room temperature for further 19 h. It was then filtered and concentrated under reduced pressure. Flash column chromatography of the crude residue (using SiO_2, 5–10% EtOAc/hexane) gave the ester **26** (7.54 g, 78%) as a colorless oil: R_f=0.50 (20% EtOAc/hexane); $[\alpha]_D^{27}$ −1.4 (c 6.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.27 (m, 5H), 5.76 (m, 1H), 5.21 (m, 3H), 4.49 (s, 2H), 4.11 (m, 1H), 4.03 (m, 1H), 3.53 (t, J=7.4 Hz, 1H), 3.47 (m, 2H), 2.50–2.37 (m, 2H), 1.89–1.84 (m, 2H), 1.74–1.70 (m, 2H), 1.67–1.61 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5, 138.6, 136.5, 128.5, 127.7, 127.6, 116.9, 109.1, 75.0, 74.7, 73.0, 69.9, 69.2, 31.0, 30.7, 28.8, 27.0, 25.7, 25.5 ppm; IR (neat) ν_{max} 2935, 1734, 1251 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{30}O_5Na$ $[M+Na]^+$ 385.1991, found 385.1991.

4.4. (*R,E*)/(*S,E*)-Methyl 8-(benzyloxy)-2-(((*S*)-2, 2-dimethyl-1,3-dioxolan-4-yl)methyl)oct-4-enoate (33, 33a)

LiHMDS (1.0 M in THF, 28.1 mL, 28.1 mmol) was added to a mixture of anhydrous THF (45 mL) and DMPU (15 mL) at −78 °C under argon environment and stirred for 1 h. Then a solution of TBSCl (6.36 g, 42.2 mmol) and the allylester **26** (2.55 g, 7.03 mmol) dissolved in anhydrous THF (15 mL) was cannulated to the reaction. The resulting mixture was stirred for 3.5 h at −78 °C prior to quench with saturated aqueous solution of NH_4Cl at the same temperature. The resulting mixture was stirred vigorously for another 5 min at room temperature and extracted with Et_2O (5×75 mL). The organic layer was then washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo to get a mixture of acids, which was taken forward without further characterizations.

The mixture of the crude acids from above step was next taken in Et_2O (50 mL) and cooled to 0 °C. An ethereal solution of CH_2N_2 (prepared in Et_2O using NMU and 50% aqueous KOH) was added to it until the yellow color persisted and stirred for another 10 min. Solvent was evaporated and the crude reaction mixture was tried to purify by silica gel column chromatography using different solvent systems (EtOAc/hexane, Et_2O/hexane, ^{i}PrOH/hexane) to get **33** and **33a** separately but we ended up with inseparable mixture of esters (dr ~12:1) (2.25 g) as an oil in 85% overall yield after two steps: R_f=0.50 (20% EtOAc/hexane); The major peaks in ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.27 (m, 5H), 5.46 (m, 1H), 5.33 (m, 1H), 4.49 (s, 2H), 4.05 (m, 1H), 4.01–3.98 (m, 1H), 3.66 (s, 3H), 3.49–3.44 (m, 3H), 2.64 (m, 1H), 2.33–2.27 (m, 1H), 2.22–2.17 (m, 1H), 2.07

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(q, J=7.1 Hz, 2H), 1.89–1.83 (m, 1H), 1.69–1.64 (m, 3H), 1.38 (s, 3H), 1.32 (s, 3H). The major signals in ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.8, 138.7, 132.8, 128.4, 127.7, 127.6, 126.8, 109.0, 74.3, 74.1, 73.0, 69.8, 69.5, 51.6, 42.5, 36.1, 35.6, 29.6, 29.2, 27.0, 25.7 ppm; IR (neat) ν_{max} 2937, 1735 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{32}O_5Na$ $[M+Na]^+$ 399.2147, found 399.2147.

4.5. (3*R*,5*S*)/(3*S*,5*S*)-3-((*E*)-6-(Benzyloxy)hex-2-enyl)-dihydro-5-(hydroxymethyl)furan-2(3*H*)-one (34, 34a)

To a stirred solution of mixture of esters **33** and **33a** (250 mg, 0.66 mmol) in MeOH (2 mL) at 0 °C, CSA (8 mg, 0.03 mmol) was added and stirred for 3 h at room temperature. The reaction was then quenched with Et_3N and evaporated in vacuo. The crude residue was purified by column chromatography (SiO_2, 8% EtOAc/hexane) to get separately compounds **34** (168 mg) and **34a** (14 mg) as colorless liquids in 90% combined yield.

*4.5.1. Data for **34**.* R_f=0.2 (30% EtOAc/hexane); $[\alpha]_D^{27}$ +13.8 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.28 (m, 5H), 5.54 (m, 1H), 5.30 (m, 1H), 4.53 (m, 1H), 4.50 (s, 2H), 3.84 (d, J=12.3 Hz, 1H), 3.62 (d, J=12.1 Hz, 1H), 3.46 (t, J=6.4 Hz, 2H), 2.77 (m, 1H), 2.47 (m, 1H), 2.25–2.17 (m, 2H), 2.13–2.09 (m, 2H), 2.04–1.99 (m, 1H), 1.71–1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.2, 138.7, 133.8, 128.5, 127.8, 127.7, 126.0 78.7, 73.0, 69.7, 64.7, 39.8, 34.1, 29.5, 29.2, 28.7 ppm; IR (neat) ν_{max} 3444, 2923, 1741, 1170 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{24}O_4Na$ $[M+Na]^+$ 327.1572, found 327.1575.

*4.5.2. Data for **34a**.* R_f=0.19 (30% EtOAc/hexane); $[\alpha]_D^{27}$ +30.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.27 (m, 5H), 5.57–5.48 (m, 1H), 5.42–5.32 (m, 1H), 4.50–4.43 (m, 3H), 3.88 (m, 1H), 3.64–3.56 (m, 1H), 3.48–3.44 (t, J=6.4 Hz, 2H), 2.76–2.66 (m, 1H), 2.58–2.50 (m, 1H), 2.27–2.16 (m, 2H), 2.15–2.04 (m, 2H), 1.87–1.76 (m, 1H), 1.72–1.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.2, 138.7, 133.4, 128.5, 127.8, 127.6, 126.2, 78.9, 73.0, 69.7, 63.9, 40.8, 33.2, 29.4, 29.2, 28.9 ppm. HRMS (ESI) m/z calcd for $C_{18}H_{24}O_4Na$ $[M+Na]^+$ 327.1572, found 327.1575.

4.6. (3*R*,5*S*)-3-(6-hydroxyhexyl)-5-(hydroxymethyl) dihydrofuran-2(3*H*)-one (35)

The lactone **34** (8 mg, 0.037 mmol) was subjected to hydrogenation in EtOH (1 mL) in the presence of 10% Pd/C (5 mg) using hydrogen-balloon at room temperature. The reaction was continued for 4 h after which it was filtered through a short pad of Celite and the filter cake was washed with EtOAc. The organic layer was evaporated in vacuum and finally passed through a short pad of silica using EtOAc as eluent to furnish the title compound **35** (5.1 mg) in 90% yield. R_f=0.5(EtOAc); $[\alpha]_D^{28}$ +20.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.60 (m, 1H), 3.86 (dd, J=12.3, 2.8 Hz, 1H), 3.66–3.62 (m, 3H), 2.71 (m, 1H), 2.33–2.28 (m, 1H), 2.03–1.97 (m, 1H), 1.87–1.80 (m, 1H), 1.59–1.54 (m, 2H), 1.49–1.34 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.0, 78.6, 64.7, 63.0, 39.6, 32.7, 31.3, 29.7, 29.1, 27.2, 25.6 ppm; IR (neat) ν_{max} 3375, 2929, 1747 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{21}O_4$ $[M+H]^+$ 217.1440, found 217.1436.

4.7. (3*S*,5*S*)-3-(6-Hydroxyhexyl)-5-(hydroxymethyl) dihydrofuran-2(3*H*)-one (35a)

Following the same procedure as described for compound **35**, alcohol **35a** (2.6 mg, 92%) was prepared from compound **34a** (4 mg, 0.02 mmol): R_f=0.48 (EtOAc); $[\alpha]_D^{27}$ +26.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.52–4.47 (m, 1H), 3.92 (dd, J=12.6, 2.6 Hz, 1H), 3.65–3.61 (m, 3H), 2.65 (m, 1H), 2.33 (m, 1H), 1.92 (m, 1H), 1.92–1.77 (m, 1H), 1.57 (m, 2H), 1.47–1.38 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.8, 78.7, 63.9, 63.0, 40.8, 32.7, 30.4, 29.7, 29.2, 27.3, 25.6 ppm; IR (neat) ν_{max} 3375, 2928, 1746 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{21}O_4$ $[M+H]^+$ 217.1440, found 217.1438.

4.8. (*R*,*E*)/(*S*,*E*)-8-(Benzyloxy)-2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)oct-4-en-1-ol (36, 36a)

Diastereomeric mixture of esters **33**, **33a** (4.3 g, 11.42 mmol) was taken in dry CH_2Cl_2 (50 mL), cooled to −78 °C and DIBAL-H (1 M in CH_2Cl_2, 34.26 mL, 34.26 mmol) was added drop wise to it. The reaction mixture was stirred for 15 min at the same temperature. The reaction was then quenched by slow addition of methanol and warmed to room temperature. Saturated aqueous solution of sodium potassium tartrate was then added to the reaction mixture and stirred until the two layers were separated. The reaction mixture was extracted with EtOAc (2×100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 20% EtOAc/hexane) of the resulting residue provided colorless alcohols **36** (3.38 g) as major and **36a** (280 mg) as minor products in 92% combined yield.

*4.8.1. Data for **36**.* R_f=0.33 (20% EtOAc/hexane); $[\alpha]_D^{27}$ +6.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.26 (m, 5H), 5.43–5.36 (m, 2H), 4.49 (s, 2H), 4.18–4.12 (m, 1H), 4.08–4.03 (m, 1H), 3.64–3.58 (m, 1H), 3.51–3.44 (m, 4H), 2.11–2.05 (m, 2H), 2.04–1.94 (m, 2H), 1.71–1.59 (m, 4H), 1.50–1.44 (m, 1H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.7, 132.2, 128.4, 128.3, 127.7, 127.6, 109.4, 75.6, 73.0, 70.1, 69.8, 66.2, 39.9, 36.4, 35.8, 29.6, 29.2, 27.0, 26.0 ppm; IR (neat) ν_{max} 3452, 2931, 1452 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{32}O_4Na$ $[M+Na]^+$ 371.2198, found 371.2195.

*4.8.2. Data for **36a**.* R_f=0.37 (20% EtOAc/hexane); $[\alpha]_D^{27}$ +8.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.26 (m, 5H), 5.48–5.35 (m, 2H), 4.49 (s, 2H), 4.13–4.10 (m, 1H), 4.04–3.92 (s, 2H), 3.63 (dd, J=11.3, 3.7 Hz, 1H), 3.53–3.51 (m, 1H), 3.49–3.43 (m, 2H), 2.11–2.06 (m, 2H), 2.03–1.98 (m, 2H), 1.96–1.90 (m, 1H), 1.71–1.64 (m, 3H), 1.48–1.42 (m, 1H), 1.35–1.33 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 131.9, 128.4, 128.3, 127.7, 127.6, 109.1, 79.9, 72.9, 69.8, 67.8, 66.1, 39.9, 36.6, 35.7, 29.6, 29.2, 26.7, 25.3 ppm; IR (neat) ν_{max} 3461, 2931, 1454 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{32}O_4Na$ $[M+Na]^+$ 371.2198, found 371.2195.

4.9. (*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-7-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)octan-1-ol (37)

Et_3N (1.61 mL, 11.55 mmol) and TBDMSCl (1.40 g, 9.24 mmol) were added sequentially to a solution of alcohol **36** (2.68 g, 7.69 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0 °C. After being stirred for 15 min at the same temperature, DMAP (47 mg, 0.39 mmol) was added and stirring was continued further for 1.5 h at room temperature. The reaction mixture was then quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc (75 mL). The organic extract was washed with water, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, 2% EtOAc/hexane) provided corresponding silyl ether (3.68 g) in quantitative yield: R_f=0.76 (5% EtOAc/hexane); $[\alpha]_D^{27}$ +7.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.26 (m, 5H), 5.45–5.34 (m, 2H), 4.49 (s, 2H), 4.21–4.14 (m, 1H), 4.02 (dd, J=8.0, 5.8 Hz, 1H), 3.53–3.45 (m, 5H), 2.10–1.96 (m, 4H), 1.70–1.61 (m, 3H), 1.56–1.53 (m, 2H), 1.39 (s, 3H), 1.34 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 131.7, 128.6, 128.5, 127.7, 127.6, 108.7, 74.7, 73.0, 70.1, 69.9, 64.7, 38.1, 34.9, 34.8, 29.8, 29.3, 27.2, 26.0, 26.0, 18.4, −5.2 ppm; IR (neat) ν_{max} 2931, 2856, 1469, 1251 cm^{-1}; HRMS (ESI) m/z calcd for $C_{27}H_{46}O_4SiNa$ $[M+Na]^+$ 485.3063, found 485.3064.

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The silyl ether (3.0 g, 6.48 mmol) from the above step, was subjected to hydrogenation in EtOAc (40 mL) in the presence of 10% Pd/C (510 mg) using hydrogen-balloon at room temperature. After 4.5 h the reaction mixture was filtered through a short pad of Celite and the filter cake was washed with EtOAc. The organic layer was concentrated in vacuum and finally passed through a short pad of silica using EtOAc as an eluent to afford the title compound **37** (2.40 g) as a colorless liquid in quantitative yield: R_f=0.22 (20% EtOAc/hexane); $[\alpha]_D^{26}$ +8.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.16 (m, 1H), 4.01 (m, 1H), 3.61 (t, *J*=6.5 Hz, 2H), 3.52–3.44 (m, 3H),1.84 (br s, 1H), 1.56–1.51 (m, 5H), 1.38 (s, 3H), 1.35–1.24 (m, 11H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 108.6, 74.8, 70.1, 65.1, 63.0, 37.7, 35.5, 32.8, 31.7, 29.8, 27.1, 26.9, 26.0, 25.9, 25.8, 18.4, −5.3 ppm; IR (neat) ν_{max} 3452, 3431, 2927, 1585 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{42}O_4SiNa$ $[M+Na]^+$ 397.2750, found 397.2752.

4.10. ((*R*)-2-(((*S*)-2, 2-Dimethyl-1,3-dioxolan-4-yl) methyl)dec-9-ynyloxy)(*tert*-butyl)dimethylsilane (25)

To a cool solution (0 °C) of alcohol **37** (850 mg, 2.27 mmol) in anhydrous toluene (15 mL), Ph_3P (833 mg, 3.18 mmol) was added under argon atmosphere and stirred for 5 min. Then iodine (863 mg, 3.4 mmol) and imidazole (310 mg, 4.54 mmol) were added and kept the reaction mixture at room temperature for 3.5 h prior to extract with Et_2O (50 mL). The organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography of the residue (SiO_2, 4% EtOAc/hexane) afforded corresponding iodide (990 mg, 91%) as a light yellow oil: R_f=0.80 (10% EtOAc/hexane); $[\alpha]_D^{28}$ +6.8 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.20–4.15 (m, 1H), 4.05–4.01(m, 1H), 3.55–3.45 (m, 3H), 3.18 (t, *J*=7.02 Hz, 2H), 1.84–1.77 (m, 2H), 1.58–1.52 (m, 3H), 1.41–1.37 (m, 6H), 1.34 (s, 3H), 1.30–1.25 (m, 5H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 108.7, 74.8, 70.2, 65.1, 37.8, 35.5, 33.6, 31.7, 30.6, 29.0, 27.2, 26.7, 26.0, 26.0, 18.4, 7.2, −5.2 ppm; IR (neat) ν_{max} 2927, 1251 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{41}IO_3SiNa$ $[M+Na]^+$ 507.1767, found 507.1765.

To a solution of TMS-acetylene (0.35 mL, 2.44 mmol) in anhydrous THF (5 mL) under argon atmosphere at −78 °C, ^{n}BuLi (2.5 M in toluene, 0.9 mL, 2.25 mmol) was added drop wise and the reaction mixture was stirred at the same temperature for 45 min. HMPA (1.5 mL) was then added and stirred another 30 min before addition of precursor iodide (910 mg, 1.88 mmol, dissolved in 2.5 mL of dry THF) from above step. The mixture was allowed to warm to room temperature and stirred for 12h. The reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with Et_2O (50 mL). The organic extract was washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 230–400 mesh, 2% EtOAc/hexane) to yield the target compound **25** (580 mg, 81%) as a colorless liquid. The negligible amount of elimination product (terminal alkene) of precursor iodide was also formed, which was discarded during column purification: R_f=0.40 (3% EtOAc/hexane); $[\alpha]_D^{27}$ +2.7 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.17 (m, 1H), 4.03 (m, 1H), 3.55–3.52 (m, 1H), 3.51–3.46 (m, 2H), 2.17 (dt, *J*=7.0, 2.5 Hz, 2H), 1.93 (t, *J*=2.5 Hz, 1H), 1.56–1.48 (m, 5H), 1.39 (br s, 6H), 1.34 (s, 3H), 1.29 (m, 5H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 108.6, 84.8, 74.8, 70.2, 68.2, 65.1, 37.8, 35.5, 31.7, 29.5, 28.8, 28.6, 27.2, 26.8, 26.0, 26.0, 18.5, 18.4, −5.2 ppm; IR (neat) ν_{max} 3313, 2929, 2117, 1471, 1251 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{42}O_3SiNa$ $[M+Na]^+$ 405.2801, found 405.2803.

4.11. (3*R*,5*S*)-Dihydro-5-(hydroxymethyl)-3-(oct-7-ynyl)furan-2(3*H*)-one (23)

Compound **25** (550 mg, 1.44 mmol) was dissolved in anhydrous THF (3 mL) and TBAF (1 M in THF, 1.73 mL, 1.73 mmol) was added to it at 0 °C in argon atmosphere. After 6 h stirring at room temperature, the reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with Et_2O (30 mL). The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue (SiO_2, 8–10% EtOAc/hexane) afforded corresponding alcohol (378 mg, 98%) as a colorless oil: R_f=0.45 (20% EtOAc/hexane); $[\alpha]_D^{26}$ +4.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.25–4.20 (m, 1H), 4.07–4.04 (m, 1H), 3.62 (dd, *J*=11.5, 4.1 Hz, 1H), 3.57–3.49 (m, 2H), 2.20–2.16 (dt, *J*=7.2, 2.5 Hz, 2H), 1.94 (t, *J*=2.5 Hz, 1H), 1.74–1.69 (m, 1H), 1.67–1.59 (m, 2H), 1.55–1.49 (m, 2H), 1.41–1.38 (m, 6H), 1.36 (s, 3H), 1.32–1.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.2, 84.8, 73.5, 70.0, 68.2, 65.5, 37.8, 35.3, 30.9, 29.4, 28.8, 28.5, 27.0, 25.9, 18.5 ppm; IR (neat) ν_{max} 3433, 3307, 2929, 2115 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}O_3Na$ $[M+Na]^+$ 291.1936, found 291.1934.

The alcohol (350 mg, 1.3 mmol) from the above step was taken in anhydrous CH_2Cl_2 (5 mL) under argon atmosphere and cooled to 0 °C. $NaHCO_3$ (546 mg, 6.5 mmol) followed by DMP (830 mg, 1.95 mmol) was added to the reaction mixture and the reaction mixture was allowed to attain the ambient temperature with constant stirring. After 1.5 h, the reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ and diluted with Et_2O (30 mL) and stirred for another 1 h until the two phases were separated. The mixture was then transferred to a separating funnel and the organic extract was washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was passed through a short pad of silica (EtOAc as eluent) to obtain corresponding aldehyde, which was used for the next step without further characterization.

An aqueous solution of $NaClO_2$ (240 mg, 3.25 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (507 mg, 3.25 mmol) was added to a solution of the above aldehyde (1.3 mmol) in ^{t}BuOH (4 mL) and 2-methyl-2-butene (2 mL) at 0 °C. The resultant reaction mixture was left to room temperature and stirred for 5 h. After completion of reaction, the solvent was removed under reduced pressure and extracted with EtOAc (3×20 mL) and the combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to get an acid. The crude acid was directly used in the next step without further purification and characterization.

The crude acid from above step was next dissolved in Et_2O (10 mL) and cooled to 0 °C and chilled ethereal solution of CH_2N_2 was added until the yellow color persisted. After 10 min, the solvent was evaporated and the residue was chromatographed (SiO_2, 3–4% EtOAc/hexane) to afford ester (354 mg, 92%) as a colorless oil: R_f=0.45 (10% EtOAc/hexane); $[\alpha]_D^{27}$ +0.4 (*c* 2.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.07–3.98 (m, 2H), 3.68 (s, 3H), 3.53–3.47 (m, 1H), 2.63–2.56 (m, 1H), 2.17 (dt, *J*=7.0, 2.6 Hz, 2H), 1.93 (t, *J*=2.6 Hz, 1H), 1.92–1.85 (m, 1H), 1.70–1.59 (m, 2H), 1.54–1.46 (m, 3H), 1.39 (m, 5H), 1.32 (s, 3H), 1.31–1.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.4, 109.0, 84.7, 74.4, 69.5, 68.2, 51.6, 42.3, 36.3, 33.1, 29.0, 28.6, 28.4, 27.1, 27.0, 25.7, 18.4 ppm; IR (neat) ν_{max} 3307, 2935, 2115, 1733 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{28}O_4Na$ $[M+Na]^+$ 319.1885, found 319.1887.

Following the same procedure as described for lactone **34**, the title compound **23** (161 mg, 89%) was prepared from the above ester (256 mg, 0.86 mmol) using CSA (20 mg, 0.086 mmol) in MeOH (3 mL): R_f=0.25 (30% EtOAc/hexane); $[\alpha]_D^{27}$ +20.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.61–4.58 (m, 1H), 3.87 (d, *J*=12.2 Hz, 1H), 3.64 (d, *J*=12.2 Hz, 1H), 2.73–2.67 (m, 1H), 2.34–2.28 (m, 1H), 2.20–2.16 (m, 2H), 2.03–1.98 (m, 1H), 1.96–1.94 (m, 1H), 1.87–1.81 (m, 1H), 1.54–1.49 (m, 2H), 1.45–1.35 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.0, 84.6, 78.7, 68.3, 64.6, 39.7, 31.3, 29.7, 28.9, 28.5, 28.4, 27.2, 18.4 ppm; IR (neat) ν_{max} 3446, 3292, 2933, 2113, 1762 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{20}O_3Na$ $[M+Na]^+$ 247.1310, found 247.1313.

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4.12. (*R*)-10-((*tert*-Butyldimethylsilyl)oxy)-9-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)decan-1-ol (38)

To a solution of oxalyl chloride (0.66 mL, 7.6 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C, DMSO (1.15 mL, 16.2 mmol) was added slowly in drop wise manner with constant stirring under argon atmosphere. After 15 min, compound **37** (1.9 g, 5.07 mmol) dissolved in dry CH_2Cl_2 (10 mL) was added to the reaction mixture. After 30 min of stirring at −78 °C, Et_3N (3.54 mL, 25.35 mmol) was added and stirred for another 30 min at same temperature. The reaction mixture was then allowed to warm to room temperature slowly to get an aldehyde. To the crude aldehyde (confirmed through TLC) $Ph_3P{=}CHCO_2Et$ (3.53 g, 10.14 mmol) was added and stirred at ambient temperature for 36 h. The reaction mixture was then quenched with saturated aqueous solution of NH_4Cl and the organic layers were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 5% EtOAc/hexane) furnished corresponding α,β-unsaturated ester (1.99 g, 89%) (mixture of cis/trans isomers) as a colorless liquid: R_f=0.67 (10% EtOAc/hexane). The major peaks in ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98–6.91 (m, 1H), 5.82–5.78 (d, *J*=15.6 Hz, 1H), 4.20–4.13 (m, 3H), 4.04–4.01 (m, 1H), 3.55–3.45 (m, 3H), 2.21–2.15 (m, 2H), 1.55–1.54 (m, 3H), 1.46–1.43 (m, 2H), 1.39 (s, 3H), 1.34 (br s, 4H), 1.29–1.25 (m, 8H), 0.87 (s, 9H), 0.02 (s, 6H). The major signals ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 149.4, 121.4, 108.7, 74.8, 70.2, 65.1, 60.2, 37.8, 35.5, 32.3, 31.7, 29.6, 28.1, 27.2, 26.7, 26.0, 26.0, 18.4, 14.4, −5.3 ppm;; IR (neat) ν_{max} 2929, 1722, 1255 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{46}O_5Si$ Na $[M+Na]^+$ 465.3012, found 465.3010.

Following the same procedure adopted in reduction of ester **31**, the saturated alcohol **38** (1.5 g, 90%) was prepared from the above α,β-unsaturated ester (1.83g, 4.13 mmol) as a colorless oil using LiCl (1.3 g, 30.98 mmol) and $NaBH_4$ (1.17 g, 30.98 mmol) in THF (100 mL) and MeOH (100 mL) in 48 h: R_f=0.25 (10% EtOAc/hexane); $[\alpha]_D^{25}$ +5.9 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.17 (m, 1H), 4.03 (m, 1H), 3.63 (t, *J*=6.6 Hz, 2H), 3.53 (dd, *J*=10.0, 3.6 Hz, 1H), 3.49–3.46 (m, 2H), 1.57–1.54 (m, 5H), 1.39 (s, 3H), 1.34 (s, 3H), 1.32–1.24 (m, 12H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 108.6, 74.8, 70.2, 65.1, 63.2, 37.8, 35.5, 32.9, 31.7, 30.0, 29.6, 29.5, 27.2, 26.9, 26.0, 26.0 25.8, 18.4, −5.3; IR (neat) ν_{max} 3407, 2929, 2856 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{46}O_4SiNa$ $[M+Na]^+$ 425.3063, found 425.3066.

4.13. ((*R*)-2-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)dodec-11-ynyloxy)(*tert*-butyl)dimethylsilane(24)

The corresponding iodide (1.72 g, 92%) was synthesized starting from precursor alcohol **38** (1.47 g, 3.65 mmol) using Ph_3P (1.34 g, 5.11 mmol), imidazole (500 mg, 7.3 mmol) in toluene (20 mL) following the same procedure as described for the shorter homologue above. R_f=0.5 (5% EtOAc/hexane); $[\alpha]_D^{27}$ +4.0 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.16 (m, 1H), 4.03 (m, 1H), 3.53 (m, 1H), 3.49–3.46 (m, 2H), 3.18 (t, *J*=7.0 Hz, 2H), 1.84–1.78 (m, 2H), 1.59–1.55 (m, 3H) (merged with H_2O), 1.39–1.34 (m, 9H), 1.27 (m, 9H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 108.6, 74.8, 70.2, 65.1, 37.8, 35.5, 33.7, 31.7, 30.6, 30.0, 29.5, 28.6, 27.2, 26.9, 26.0, 26.0, 18.4, 7.3, −5.3 ppm; IR (neat) ν_{max} 2927, 2854, 1251 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{45}IO_3SiNa$ $[M+Na]^+$ 535.2080, found 535.2079.

The titled alkyne **24** (859 mg, 80%) was prepared from the above iodide (1.35 g, 2.63 mmol) using TMS alkyne (0.5 mL, 3.42 mmol) and ^{n}BuLi (2.5 M in hexane, 1.26 mL, 3.15 mmol) in THF (10 mL) and HMPA (2 mL) solvent system following the same procedure as describe for compound **25**: R_f=0.50 (5% EtOAc/hexane); $[\alpha]_D^{27}$ +8.2 (*c* 3.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.17 (m, 1H), 4.02 (m, 1H), 3.54 (m, 1H), 3.50–3.46 (m, 2H), 2.17 (dt, *J*=7.1, 2.3 Hz, 2H), 1.92 (m, 1H), 1.55–1.48 (m, 5H), 1.39–1.34 (m, 9H), 1.26 (br, 9H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 108.6, 84.9, 74.8, 70.2, 68.1, 65.1, 37.8, 35.5, 31.7, 30.0, 29.5, 29.2, 28.8, 28.6, 27.2, 26.9, 26.0, 26.0, 18.5, 18.4, −5.3 ppm; IR (neat) ν_{max} 3313, 2929, 2856, 2117, 1251 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{46}O_3SiNa$ $[M+Na]^+$ 433.3114, found 433.3112.

4.14. (3*R*,5*S*)-3-(Dec-9-ynyl)-dihydro-5-(hydroxymethyl)furan-2(3*H*)-one (22)

The desilylated compound (578 mg, 96%) was synthesized from silyl ether **24** (840 mg, 2.04 mmol) using TBAF (1M in THF, 2.45 mL, 2.45 mmol) in THF (6 mL) following the same procedure as described before for the shorter homologue: R_f=0.3 (20% EtOAc/hexane); $[\alpha]_D^{29}$ +2.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.22 (m, 1H), 4.05 (m, 1H), 3.61 (m, 1H), 3.56–3.48 (m, 2H), 2.45 (br s, 1H), 2.17 (dt, *J*=7.0, 2.3 Hz, 2H), 1.94 (m, 1H), 1.71–1.68 (m, 1H), 1.66–1.60 (m, 2H), 1.54–1.49 (m, 2H), 1.41–1.36 (m, 9H), 1.28 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 109.1, 84.8, 73.5, 69.9, 68.2, 65.4, 37.7, 35.3, 30.9, 29.9, 29.5, 29.1, 28.8, 28.5, 27.1, 27.0, 25.9, 18.4 ppm; IR (neat) ν_{max} 3434, 3309, 2927, 2115 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{32}O_3Na$ $[M+Na]^+$ 319.2249, found 319.2251.

Following the same procedure as adopted for shorter homologue, the corresponding ester (552 mg, 92%) was prepared from the alkynyl alcohol (550 mg, 1.85 mmol) obtained from above step: R_f=0.5 (10% EtOAc/hexane); $[\alpha]_D^{27}$ −2.7 (*c* 4.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.06–3.99 (m, 2H), 3.68 (s, 3H), 3.53–3.47 (m, 1H), 2.62–2.56 (m, 1H), 2.17 (dt, *J*=7.0, 2.5 Hz, 2H), 1.93 (t, *J*=2.4 Hz, 1H), 1.91–1.85 (m, 1H), 1.68–1.60 (m, 2H), 1.54–1.47 (m, 3H), 1.39 (m, 5H), 1.32 (s, 3H), 1.27 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.6, 109.0, 84.8, 74.4, 69.5, 68.2, 51.6, 42.3, 36.4, 33.2, 29.5, 29.4, 29.1, 28.8, 28.6, 27.2, 27.1, 25.7, 18.5 ppm; IR (neat) ν_{max} 3290, 2931, 2115, 1735 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{32}O_4Na$ $[M+Na]^+$ 347.2198, found 347.2195.

Following the same procedure as described for lactone **23**, the title compound **22** (171 mg, 88%) was prepared from the above ester (250 mg, 0.77 mmol) using CSA (18 mg, 0.07 mmol) in MeOH (3 mL): R_f=0.25 (30% EtOAc/hexane); $[\alpha]_D^{27}$ +13.9 (*c* 8.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.61–4.57 (m, 1H), 3.89–3.84 (m, 1H), 3.66–3.62 (m, 1H), 2.73–2.67 (m, 1H), 2.51 (br s, 1H), 2.33–2.28 (m, 1H), 2.17 (dt, *J*=7.0, 2.4 Hz, 2H), 2.04–1.97 (m, 1H), 1.94–1.93 (m, 1H), 1.86–1.74 (m, 1H), 1.54–1.49 (m, 2H), 1.47–1.37 (m, 5H), 1.30 (br s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.0, 84.8, 78.7, 68.2, 64.6, 39.7, 31.3, 29.7, 29.3, 29.0, 28.7, 28.5, 27.3, 18.4 ppm; IR (neat) ν_{max} 3294, 3444, 2929, 2856, 2115, 1770 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1623, found 275.1625.

4.15. (3*R*,5*S*)-Dihydro-5-(hydroxymethyl)-3-(octadeca-9,11-diynyl)furan-2(3*H*)-one (39)

To a degassed solution of **22** (25 mg, 0.1 mmol) in Et_3N (0.5 mL) under argon atmosphere CuBr (3 mg, 0.02 mmol) and $NH_2OH{\cdot}HCl$ (2 mg, 0.028 mmol) were added sequentially. Alkynyl bromide **19** (19 mg, 0.1 mmol) dissolved in degassed Et_3N (1 mL) was added drop wise to the reaction mixture and stirred for 12 h at room temperature. The reaction was quenched with water and extracted with Et_2O (10 mL).The organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 30% EtOAc/hexane) furnished the coupled product **39** (26 mg, 72%) as a colorless liquid: R_f=0.56 (30% EtOAc/hexane); $[\alpha]_D^{27}$ +10.8 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.58 (m, 1H), 3.87 (dd, *J*=12.3, 2.8 Hz, 1H), 3.65 (dd, *J*=12.3, 4.7 Hz, 1H), 2.70 (m, 1H), 2.30 (m, 1H), 2.24 (t, *J*=6.9 Hz, 4H), 2.00 (m, 1H), 1.80 (m, 1H), 1.53–1.48 (m, 4H), 1.38 (br s, 7H), 1.29 (br s, 10H), 0.88 (t, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.8, 78.6, 77.7, 77.6, 65.4, 65.3, 64.7, 39.7, 31.4, 31.3, 29.7, 29.3, 29.0, 28.8, 28.6, 28.4, 28.4, 27.3, 22.6, 19.3, 19.3, 14.1 ppm; IR (neat) ν_{max} 3444, 2929, 2254,

2160, 1770, 1458 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{36}O_3Na$ $[M+Na]^+$ 383.2562, found 383.2560.

4.16. (3*R*,5*S*)-Dihydro-5-(methoxymethyl)-3-(octadeca-9,11-diynyl)furan-2(3*H*)-one (4)

Under the minimum exposure of light (covering the reaction flask by carbon paper), to a solution of alcohol **39** (15 mg, 0.042 mmol) in anhydrous CH_2Cl_2 (2 mL), proton sponge (54 mg, 0.25 mmol) and Me_3OBF_4 (31 mg, 0.21 mmol, in two installments) were added sequentially under argon atmosphere at 0 °C. The mixture was warmed to room temperature over 1 h and stirred for 24 h before addition of second installment of Me_3OBF_4. The reaction was continued further for 17 h and quenched with saturated NH_4Cl solution. The reaction mixture was extracted with EtOAc (5 mL) and washed with 1 N HCl, water, brine, dried (Na_2SO_4), and concentrated in vacuum. Purification of the crude residue by column chromatography (SiO_2, 15% EtOAc/hexane) afforded **4** (10 mg, 60%) as a colorless oil : R_f=0.4 (20% EtOAc/hexane); reported $[\alpha]_D^{23}$ +13.3 (*c* 0.206, $CHCl_3$); observed $[\alpha]_D^{23}$ +8.9 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.58 (m, 1H), 3.55 (dd, *J*=10.6, 3.4 Hz, 1H), 3.49 (dd, *J*=10.6, 4.0 Hz, 1H), 3.38 (s, 3H), 2.69 (m, 1H), 2.31–2.26 (m, 1H), 2.24 (t, *J*=6.9 Hz, 4H), 2.02–1.96 (m, 1H), 1.83 (br s, 1H), 1.51 (m, 4H), 1.38 (br s, 7H), 1.29 (br s, 10H), 0.88 (t, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.7, 77.7, 77.6, 76.9, 74.4, 65.4, 65.4, 59.6, 39.3, 31.4, 31.3, 30.5, 29.4, 29.3, 29.1, 28.9, 28.6, 28.4, 28.3, 27.4, 22.6, 19.3, 19.3, 14.1 ppm; IR (neat) ν_{max} 2929, 2856, 2212, 2160, 1772, 1456 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{38}O_3Na$ $[M+Na]^+$ 397.2719, found 397.2716. Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.94; H, 10.25.

4.17. (3*R*,5*S*)-3-((*Z*)-Heptadeca-11,16-dien-9-ynyl)-dihydro-5-(hydroxymethyl)furan-2(3*H*)-one (5)

To a solution of **22** (27 mg, 0.107 mmol) and vinyl iodide **20** (33 mg, 0.14 mmol) in freshly dried and degassed Et_3N (1 mL), $Pd(PPh_3)_2Cl_2$ (7.5 mg, 0.01 mmol) and CuI (6.1 mg, 0.032 mmol) were added and stirred for 20 h at room temperature. The reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ (1 mL) and extracted with EtOAc (5 mL). The organic extract was washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude product was done first by column chromatography (SiO_2, 25% EtOAc/hexanes) and later by preparative TLC (using 4% ^{i}PrOH/hexane as mobile phase) gave compound **5** (26.6 mg, 69%) as a clear yellow oil. The negligible amount of corresponding trans-isomer originated from trans vinyl iodide present as an inseparable impurity in synthesized *cis*-vinyl iodide **20** was discarded during this purification process: R_f=0.3 (25% EtOAc/hexane); reported $[\alpha]_D^{23}$ +14.1 (*c* 0.206, $CHCl_3$); observed $[\alpha]_D^{23}$ +11.3 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.81 (m, 2H), 5.43 (d, *J*=10.6 Hz, 1H), 5.02–4.91 (m, 2H), 4.62–4.55 (m, 1H), 3.91–3.83 (m, 1H), 3.68–3.60 (m, 1H), 2.69 (m, 1H), 2.34–2.24 (m, 5H), 2.07–2.01 (m, 2H), 2.00–1.94 (m, 1H), 1.86–1.80 (m, 1H), 1.50 (quint, *J*=6.2 Hz, 2H), 1.41 (m, 8H), 1.30 (br s, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.8, 142.4, 139.1, 114.4, 109.6, 94.6, 78.6, 77.5, 64.8, 39.7, 33.7, 31.4, 29.9, 29.7, 29.4, 29.4, 29.2, 29.0, 28.5, 28.4, 27.3, 19.6 ppm; IR (neat) ν_{max} 3438, 2927, 2854, 2212, 1768, 1461 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{36}O_3Na$ $[M+Na]^+$ 383.2562, found 383.2564. Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.84; H, 10.10.

4.18. (3*R*,5*S*)-3-((*Z*)-Hexadeca-9,15-dien-7-ynyl)-dihydro-5-(hydroxymethyl)furan-2(3*H*)-one (8)

Experimental procedure and purification process were same as **5**. Compound **8** (20 mg, 67%) was prepared as a clear yellow oil from the lactone **23** (20 mg, 0.09 mmol) using vinyl iodide **20** (27 mg, 0.11 mmol), $Pd(PPh_3)_2Cl_2$ (7.5 mg, 0.01 mmol), and CuI (5.1 mg, 0.03 mmol) in degassed Et_3N (3 mL) in 20 h: R_f=0.27 (25% EtOAc/hexane); reported $[\alpha]_D^{23}$ +14.0 (*c* 0.206, $CHCl_3$); observed $[\alpha]_D^{23}$ +14.7 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 5.87–5.74 (m, 2H), 5.43 (d, *J*=10.6 Hz, 1H), 5.03–4.91 (m, 2H), 4.60 (m, 1H), 3.86 (br d, *J*=12.4 Hz, 1H), 3.46 (dd, *J*=12.3, 4.6 Hz, 1H), 2.7 (m, 1H), 2.35–2.24 (m, 5H), 2.07–2.02 (m, 2H), 2.00–1.95 (m, 1H), 1.83 (m, 1H), 1.56–1.51 (m, 2H), 1.42 (br s, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.7, 142.5, 139.1, 114.1, 109.6, 94.5, 78.5, 77.5, 64.8, 39.7, 33.7, 31.3, 29.9, 29.7, 29.0, 28.9, 28.8, 28.5, 28.4, 27.3, 19.6 ppm; IR (neat) ν_{max} 3417, 2927, 2854, 2208, 1758, 1454 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{32}O_3Na$ $[M+Na]^+$ 355.2249, found 355.2248. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.53; H, 9.73.

4.19. (3*R*,5*S*)-3-((*Z*)-Hexadec-9-en-7-ynyl)-dihydro-5-(hydroxymethyl)furan-2(3*H*)-one (9)

Experimental procedure and purification process were same as **5**. Compound **9** (21 mg, 70%) was prepared from lactone **23** (20.5 mg, 0.09 mmol) as a clear yellow oil using vinyl iodide **21** (26.1 mg, 0.11 mmol), $Pd(PPh_3)_2Cl_2$ (6.3 mg, 0.01 mmol) and CuI (5.14 mg, 0.027 mmol) in degassed Et_3N (3 mL) in 20 h: R_f=0.27 (25% EtOAc/hexane); reported $[\alpha]_D^{23}$ +14.3 (*c* 0.206, $CHCl_3$); observed $[\alpha]_D^{28}$ +10.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.84–5.79 (m, 1H), 5.42 (br d, *J*=10.7 Hz, 1H), 4.60–4.58 (m, 1H), 3.86 (m, 1H), 3.65 (m, 1H), 2.69 (m, 1H), 2.37–2.23 (m, 5H), 2.00 (m, 1H), 1.84 (m, 1H), 1.51–1.29 (m, 17H), 0.88 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.0, 142.8, 109.3, 94.3, 78.5, 77.6, 64.7, 39.7, 31.8, 31.3, 30.1, 29.7, 29.0, 28.9, 28.8, 28.7, 27.3, 22.7, 19.6, 14.2 ppm; IR (neat) ν_{max} 3444, 2927, 2856, 2208, 1770, 1460 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{34}O_3Na$ $[M+Na]^+$ 357.2406, found 357.2404. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.15; H, 10.29.

4.20. (*R*)-2-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl) methyl)icos-19-en-11-yn-1-ol (40)

To a stirred solution of compound **24** (260 mg, 0.63 mmol) in anhydrous THF (1.5 mL) at 0 °C, ^{n}BuLi (2.5 M in hexane, 0.33 mL, 0.82 mmol) was added under argon atmosphere. After stirring for about 30 min at the same temperature, HMPA (0.5 mL) was added. The mixture was stirred for another 30 min at same temperature and the iodide **30** (226 mg, 0.95 mmol, dissolved in 1 mL THF) was cannulated .The mixture was then allowed to warm to room temperature and stirred for further 17 h before it was quenched with saturated aqueous solution of NH_4Cl. The mixture was extracted with Et_2O (25 mL).The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. The inseparable mixture of alkylated product with some unreacted starting material was taken in next step without further characterization.

The crude mixture from above step was dissolved in anhydrous THF (3 mL), cooled to 0 °C, and TBAF (1M in THF, 0.76 mL, 0.76 mmol) was added to it under argon atmosphere. After 2.5 h the reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with Et_2O (30 mL). The organic phase was washed with water, brine, dried (Na_2SO_4), and evaporated in vacuo. Purification of the residue (SiO_2, 10% EtOAc/hexane) afforded title compound **40** {98 mg, 65% overall yield after two steps, based on corresponding silyl deprotected recovered starting material (52 mg)} as a colorless liquid: R_f=0.33 (20% EtOAc/hexane); $[\alpha]_D^{27}$ +1.9 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.80 (m, 1H), 4.98 (dd, *J*=17.1, 1.4 Hz, 1H), 4.92 (d, *J*=10.1 Hz, 1H), 4.22 (m, 1H), 4.05 (m, 1H), 3.62–3.49 (m, 3H), 2.12 (m, 4H), 2.03 (m, 2H), 1.70–1.58 (m, 4H), 1.46 (br s, 4H), 1.41–1.35 (br s, 13H), 1.27 (br s, 11H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.2, 114.3, 109.2, 80.4, 80.3, 73.5, 70.0, 65.5, 37.8, 35.3, 33.8, 31.0, 30.0, 29.6, 29.3, 29.2, 29.0, 28.9, 28.8, 28.7, 27.2,

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27.0, 25.9, 18.9 ppm; IR (neat) ν_{max} 3434, 2927, 2854, 2169, 1369 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{46}O_3H$ $[M+H]^+$ 407.3525, found 407.3522.

4.21. (*R*)-Methyl 2-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl) methyl)icos-19-en-11-ynoate (29)

The ester **29** (56 mg, 88%) was prepared from alcohol **40** (60 mg, 0.15 mmol) following three steps protocol as describe in above: R_f=0.5 (10% EtOAc/hexane); $[\alpha]_D^{27}$ −0.3 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.80 (m, 1H), 4.98 (d, *J*=17.1 Hz, 1H), 4.92 (d, *J*=10.1 Hz, 1H), 4.05–3.98 (m, 2H), 3.68 (s, 3H), 3.48 (t, *J*=6.8 Hz, 1H), 2.58 (m, 1H), 2.12 (m, 4H), 2.03 (q, *J*=6.9 Hz, 2H), 1.87 (m, 1H), 1.68–1.63 (m, 2H), 1.48–1.44 (m, 5H), 1.38–1.29 (m, 13H), 1.25 (br s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.6, 139.2, 114.3, 109.0, 80.3, 80.3, 74.4, 69.5, 51.6, 42.3, 36.3, 33.8, 33.3, 29.5, 29.4, 29.3, 29.2, 29.2, 28.9, 28.8,28.7, 27.3, 27.1, 25.7, 18.9 ppm; IR (neat) ν_{max} 2929, 2856, 2171,1735, 1458,1251 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{46}O_4Na$ $[M+Na]^+$ 457.3294, found 457.3297.

4.22. (3*R*,5*S*)-Dihydro-5-(hydroxymethyl)-3-(octadec-17-en-9-ynyl) furan-2(3*H*)-one (6)

Following the same procedure as described for lactones **34**, the lactone **6** (27 mg, 92%) was prepared from the ester **29** (36 mg, 0.08 mmol) using CSA (2 mg, 0.008 mmol) in MeOH (2 mL): R_f=0.4 (30% EtOAc/hexane); reported $[\alpha]_D^{23}$ +20.4 (*c* 0.206, $CHCl_3$); observed $[\alpha]_D^{23}$ +16.2 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.79 (m, 1H), 4.98 (d, *J*=17.1 Hz, 1H), 4.92 (d, *J*=10.1 Hz, 1H), 4.57 (m, 1H), 3.85 (m, 1H), 3.64 (m, 1H), 2.69 (m, 1H), 2.29 (m, 1H), 2.13 (t, *J*=6.6 Hz, 4H), 2.06–1.93 (m, 3H), 1.82 (m, 1H), 1.46 (m, 4H), 1.36 (m, 8H), 1.29 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.6, 139.2, 114.3, 80.3, 80.3, 78.5, 64.8, 39.7, 33.8, 31.4, 29.7, 29.4, 29.3, 29.2, 29.2, 29.0, 28.8, 28.7, 27.4, 18.9 ppm; IR (neat) ν_{max} 3409, 2929, 2856, 2171, 1766, 1458 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{38}O_3Na$ $[M+Na]^+$ 385.2719, found 385.2716. Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56. Found: C, 76.24; H, 10.52.

4.23. (3*R*,5*S*)-Dihydro-5-(methoxymethyl)-3-(octadec-17-en-9-ynyl)furan-2(3*H*)-one (7)

Following the same procedure as described for lactone **4**, the lactone **7** (12 mg, 65%) was prepared in 48 h from compound **6** (19 mg, 0.05 mmol) using Me_3OBF_4 (39 mg, 0.26 mmol) and proton sponge (67 mg, 0.31 mmol) in CH_2Cl_2 (3 mL): R_f=0.4 (20% EtOAc/hexane); reported $[\alpha]_D^{23}$ +18.0 (*c* 0.206, $CHCl_3$); observed $[\alpha]_D^{27}$ +14.6 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.80 (m, 1H), 4.98 (d, *J*=17.1 Hz, 1H), 4.92 (d, *J*=10.1 Hz, 1H), 4.58 (m, 1H), 3.55 (dd, *J*=10.6, 3.5 Hz, 1H), 3.48 (dd, *J*=10.6, 4.0 Hz, 1H), 3.37 (s, 3H), 2.68 (m, 1H), 2.27 (m, 1H), 2.12 (t, *J*=6.1 Hz, 4H), 2.05–1.95 (m, 3H), 1.82 (m, 1H), 1.48–1.43 (m, 4H), 1.39–1.32 (m, 8H), 1.32–1.24 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.7, 139.2, 114.3, 80.3, 80.3, 76.9,74.4, 59.6, 39.4, 33.8, 31.3, 30.5, 29.4, 29.3, 29.2, 29.2, 29.0, 28.8, 28.7, 27.4, 18.9 ppm; IR (neat) ν_{max} 2929, 2856, 2160,1770, 1456 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{40}O_3Na$ $[M+Na]^+$ 399.2875, found 399.2877. Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.33; H, 10.74.

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Supplementary data

Preparation of compounds **20**, **21** and DFT calculation of model compounds. Copies of NMR (^1H, ^{13}C) and HRMS of representative compounds. NOESY, COSY, HSQC spectrum of compound **35** and **35a**. NOE spectrum of compound **35**. These material can be found in the online version. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.03.028.

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28. Personal communication with the isolation group[2] revealed that there is a typographical mistake in the chemical shift of the olefinic proton of cananginone I (**9**). While it is experimentally observed at δ 5.78 ppm, it has been mistyped as δ 6.03 ppm in the published paper.
29. For preparation of isomerically pure cananginones (E, H, I), we planned to install a sensitive *cis*-enyne system as the last step of the synthetic route to minimize the exposure to light, which, we think, may enhance the rate of isomerization. The Sonogashira reactions of alkynes **22** and **23** with the vinyl iodides **20** and **21** have been carried out in the dark by covering the reaction vessels by aluminum foil or by carbon paper. The purification and data recording have been done very quickly in very low intensity light to minimize the conversion to the trans-isomer.
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