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Asymmetric Total Synthesis of Amphirionin-2

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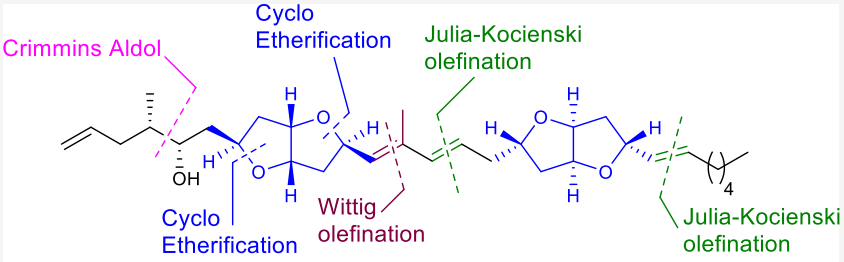

Amphirionin-2

ABSTRACT: A convergent route for the asymmetric total synthesis of potent anticancer polyketide natural product amphirionin-2 has been developed. Our initial synthetic trials revealed that the proposed structures of amphirionin-2 need to be revised consistent with a recent report of Fuwa et al., where the actual structure of amphirionin-2 was established. The key features of our synthesis comprised Sharpless asymmetric dihydroxylation, followed by cycloetherification, Wittig olefination, Julia−Kocienski olefination, and Crimmins propionate aldol reaction.

INTRODUCTION

Amphirionin-2 was isolated by Tsuda and co-workers in 2014 from the KCA09051strain of laboratory-cultured marine dinoflagellates *Amphidinium* sp.[1] It showed promising in vitro anticancer activities against Caco-2 (human colon carcinoma) and A549 (human nonsmall cell lung adenocarcinoma) cell lines as well as in vivo antitumor efficacy against murine tumor P388 cells.[1] The discovery of amphirionin-2 may play a significant role in deciphering cancer biology. The chemical structures (**1a** and **1b**, Figure 1) of amphirionin-2 were proposed initially based on detailed NMR and Mosher's ester analysis. Architecturally, it is a linear polyketide embedded with two unique hexahydrofuro[3,2-*b*] furan moieties, 10 stereogenic centers, a conjugated olefin, and two isolated olefins. The relative stereochemistry of the asymmetric centers present on left and right halves of the molecule was speculated based on *J* values and NOESY correlation, but the stereochemical correlation between hexahydrofuro[3,2-*b*] furan units remained undisclosed during its isolation. Our continued interest[2] in chemical synthesis of bioactive natural products prompted us to embark on the total synthesis of structurally complex and potential anticancer polyketide natural product amphirionin-2. During our ongoing synthetic study, an elegant synthetic route was reported by Fuwa et al., where the actual structure[3] (**1c**, Figure 1) of amphirionin-2 was established. Herein, we report a convergent and flexible stereoselective synthetic route for the proposed structures of amphirionin-2 (**1a** and **1b**, Figure 1). The spectroscopic data of the synthesized proposed structures of amphirionin-2 indicated discrepancies, which suggested that the proposed structures need to be revised as also observed by Fuwa et al. Later, this developed strategy was employed to achieve the total synthesis of the actual structure (**1c**, Figure 1) of amphirionin-2. The developed route is quite different compared to the recent report,[3] where a different set of reactions was adopted to install the different functional moieties and asymmetric centers embedded in the molecule.

RESULTS AND DISCUSSION

Retrosynthetic analysis of the proposed structure (**1a**) of amphirionin-2 is delineated in Scheme 1. The target molecule could be assembled from the two major segments **2** and **3** using Julia−Kocienski olefination as the key reaction. Left segment **2** could be constructed from compound **5** via compound **4** adopting Sharpless asymmetric dihydroxylation, followed by subsequent in situ cycloetherification and Crimmins propionate aldol and Wittig olefination as the pivotal steps, whereas right segment **3** could be synthesized from ***ent*-5** through ***ent*-4** in a similar way to compound **2** except the use of Julia−Kocienski olefination in place of the Wittig olefination.

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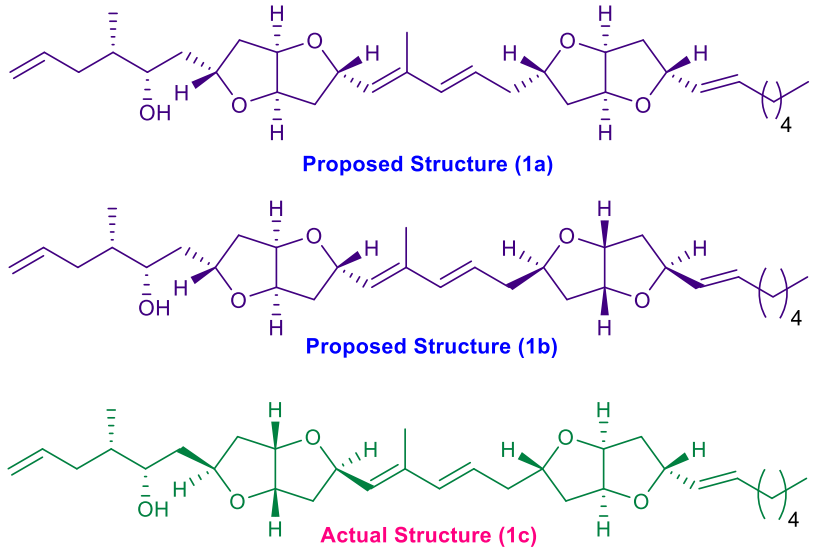
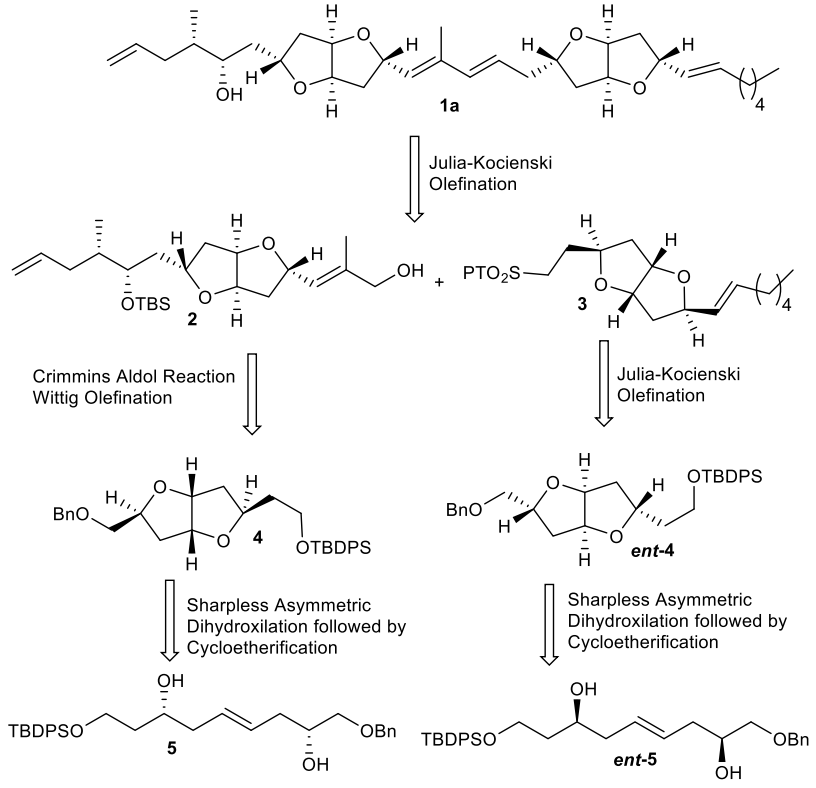


Figure 1. Chemical structures of amphirionin-2.

Scheme 1. Retrosynthetic Analysis of the Proposed Structure of Amphirionin-2 (1a)



The synthesis of compound **4** is described in Scheme 2. The known compound **6**, prepared in four steps from D-aspartic acid following a literature procedure,[4] was treated with TESCl/Et_3N/DMAP to get the corresponding TES ether. Our initial effort for oxidative cleavage of the olefin moiety using OsO_4/$NaIO_4$/$NaHCO_3$ was not effective. The reaction was sluggish, where in situ deprotection of TES ether took place. Thus, a two-step protocol was followed. First dihydroxylation was performed using OsO_4/NMO. The resultant mixture of diol was then subjected to oxidative cleavage using $NaIO_4$/$NaHCO_3$ to get the corresponding aldehyde without having any TES-deprotected compound, which was further reduced to alcohol **7** by $NaBH_4$. Alcohol **7** was then reacted with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) in the presence of Ph_3P/DIAD following the Mitsunobu protocol[5] to produce the corresponding sulfide, which was further oxidized[6] to sulfone **8** using mCPBA. On the other hand, the known alcohol **9**, obtained from *R*-glycidyl benzyl ether in one step following the literature procedure,[7] was treated with TESCl/Et_3N, followed by OsO_4/NMO and $NaIO_4$/$NaHCO_3$ to obtain the required aldehyde **10**. The stage was set for Julia−Kocienski olefination[8] to couple aldehyde **10** and sulfone **8**. Our initial trial with NaHMDS provided compound **11** with 75% yield with an *E*/*Z* ratio of 4:1. Delightfully, the use of KHMDS resulted the

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Scheme 2. Synthesis of Compound 4

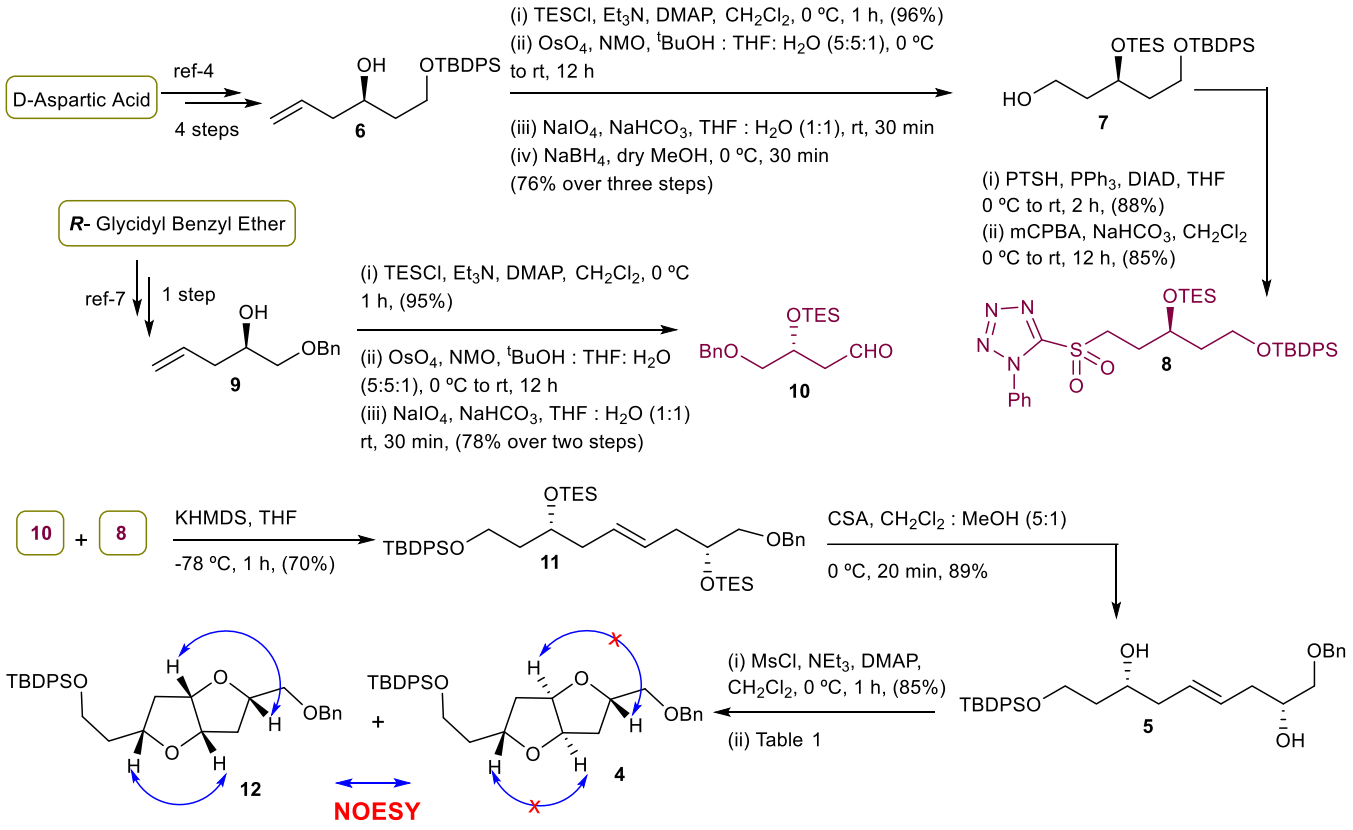

Table 1. Optimization of Dihydroxylation and Cycloetherification for Compound 4

entry	reagents	solvent	temperature	time (h)	yield (%)	*dr* (4:12)
1	OsO_4 (0.01 equiv)/NMO (2 equiv)/K_2CO_3 (3 equiv)	THF/^{t}BuOH: H_2O (4:4:1)	0 °C to rt	12	55	1.5:2
2	AD-mix-α (1.4 g/mmol)/$MeSO_2NH_2$ (2 equiv)	H_2O/^{t}BuOH (1:1)	0 °C to rt	36	50	1:1
3	AD-mix-β (1.4 g/mmol)/$MeSO_2NH_2$ (2 equiv)	H_2O/^{t}BuOH (1:1)	0 °C to rt	36	60	3:1
4	AD-mix-β (14 g/mmol)/$MeSO_2NH_2$ (2 equiv)	H_2O/^{t}BuOH (1:1)	0 °C to rt	28	59	2.9:1
5	AD-mix-β (1.4 g/mmol)/OsO_4 (0.5 equiv)/$MeSO_2NH_2$ (2 equiv)	H_2O/^{t}BuOH (1:1)	0 °C to rt	12	65	3.5:1

required compound exclusively in *E* geometry with 70% yield. Compound **11** was then treated with CSA to get diol **5**, which was mesylated further to access the corresponding dimesylated compound. Next, dihydroxylation, followed by the cycloetherification strategy[9] was adopted to prepare a hexahydrofuro[3,2-*b*] furan moiety. A number of conditions were screened (Table 1). The use of a catalytic amount of OsO_4 (entry 1) or AD-mix-α (entry 2) provided compounds **4** and **12** almost in a 1:1 ratio, whereas AD-mix-β (entry 3) elevated that ratio to 3:1. A tenfold increase in the amount of AD-mix-β (entry 4) provided almost similar results compared to the entry 3 but the reaction time reduced considerably. The increase of the OsO_4 concentration in the AD-mix-β reaction (entry 5) by addition of an excess amount of it provided a faster result with a further increase of selectivity to 3.5:1. However, in our case, the selectivity was still lower compared to the literature report,[9a] where the substrate for dihydroxylation, followed by cycloetherification, bears two benzyl ethers in the tris-homoallylic position. In contrast, the dimesylated counterpart of compound **5** possesses one bis-homoallylic benzyl ether and one tris-homoallylic TBDPS ether. It is most likely the steric influence,[10a,b] of benzyl ether in the bis-homoallylic position opposed the Sharpless facial selectivity model to some extent. It was conceived further from our trial with the corresponding substrate, where the benzyl ether was replaced with bulky TBS ether. The reaction in that case was too sluggish following the condition in entry 5, where the selectivity reduced to ~2:1. It is noteworthy that the reaction functioned better toward a stoichiometric amount of OsO_4 in the presence of chiral amine (entry 5) compared to its catalytic variation (entry 3), which might be due to the probability factor. Both the compounds were separated using column chromatography. Analysis of mass spectrometry as well as NMR spectroscopy especially NOESY correlation revealed their structural identities. It is noteworthy that the identification of expected NOESY interactions between H-2 and H-7 of compound **4** was difficult in this stage as those protons were resonating in close proximity as a multiplet.

The synthesis of the left segment **2** is depicted in Scheme 3. Compound **4** was treated with TBAF to get the corresponding primary alcohol, which was oxidized to the corresponding aldehyde using DMP/$NaHCO_3$ and finally subjected to the Crimmins propionate aldol reaction,[11a,b] using the known thiazolidinethione **13**[11c] in the presence of $TiCl_4$/DIPEA to achieve compound **14** exclusively. Initially, our exhaustive trials to install the required terminal allyl group of compound **2** via opening of oxetane, prepared from compound **14**,[12] using vinyl Grignard did not work. Next, the free hydroxyl of compound

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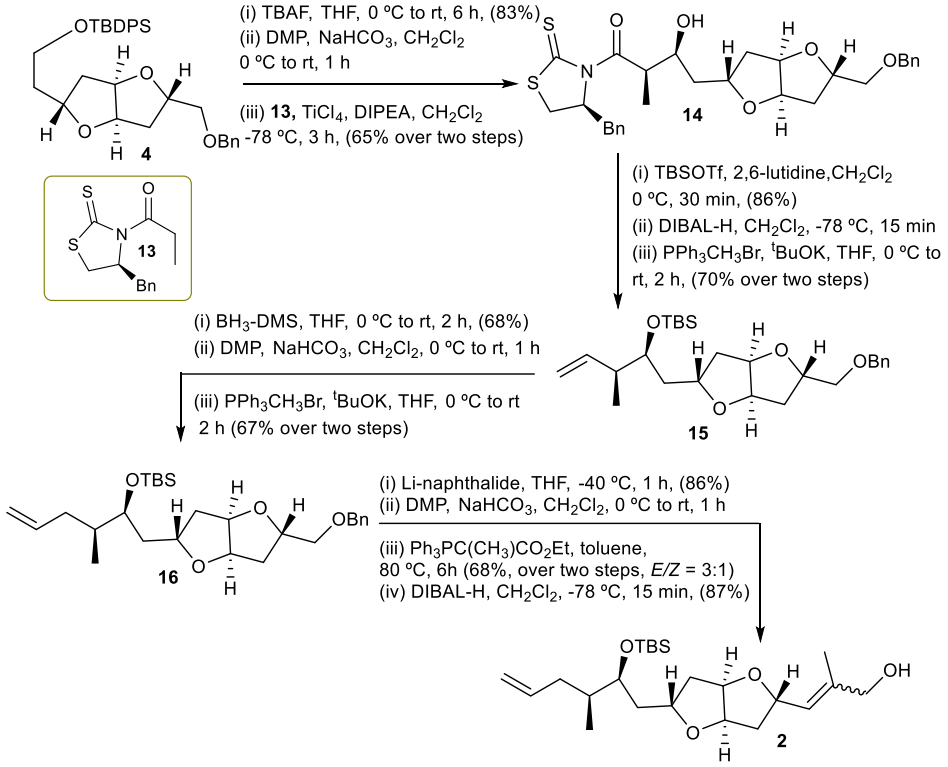
Scheme 3. Synthesis of Compound 2



14 was protected as TBS ether using TBSOTf/2,6-lutidine and reduced further to the corresponding primary alcohol, which was then transformed into the corresponding iodo compound. It was quite unfortunate to observe that substitution of iodo by the vinyl group following Gilman's protocol[13] did not proceed and the iodo compound remained unreactive. Thus, the TBS ether obtained from compound **14** was reacted cautiously with DIBAL-H to generate the corresponding aldehyde, which was then treated with $Ph_3PCH_3Br/^tBuOK$ to produce compound **15** in good overall yield. It was further subjected to hydroboration using BH_3-DMS. The resultant alcohol was oxidized to the corresponding aldehyde using DMP/$NaHCO_3$ and subsequently exposed to olefination in the presence of $Ph_3PCH_3Br/^tBuOK$ to obtain compound **16**. Benzyl ether of compound **16** was removed by Li-naphthalide and the resultant alcohol was oxidized to the corresponding aldehyde using DMP/$NaHCO_3$, which was finally subjected to Wittig olefination[14] using $Ph_3PC(CH_3)CO_2Et$ to get the corresponding α,β-unsaturated esters (E/Z = 3:1) as an inseparable mixture. The ester group was then reduced with DIBAL-H to get alcohol **2** along with its corresponding *Z*-counterpart, which remained inseparable in this stage too.

The synthesis of compound **3** is shown in Scheme 4. The known compound ***ent*-6**, synthesized from L-aspartic acid following the literature procedure,[15] was converted to sulfone ***ent*-8** via the intermediate ***ent*-7** following exactly the same chemistry of sulfone **8**. On the other hand, the known compound ***ent*-9**,[16] prepared from *S*-glycidyl benzyl ether, was transformed into aldehyde ***ent*-10** mimicking the synthesis of aldehyde **10**. Next, compounds ***ent*-8** and ***ent*-10** were stitched together following Julia−Kocienski olefination to produce ***ent*-11** in good yield. The formation of the corresponding *Z*-counterpart was not observed. Compound ***ent*-11** was then transmuted to its corresponding dimesylated compound in two steps following the same chemistry described in Scheme 2. The crucial dihydroxylation followed by cycloetherification was carried out under different dihydroxylation conditions (Table 2). AD-mix-α (entry 1) and AD-mix-β (entry 2) produced the desired compound ***ent*-4** and the undesired compound ***ent*-12** in a ratio of 1:1.2 and 1:2, respectively. However, the reaction proceeded in a favorable direction with a slight increase of the ratio to 1.2:1 in the presence of a catalytic amount of OsO_4 (entry 3). The use of excess OsO_4 in association with AD-mix-α (entry 3) improved the required selectivity further to 1.6:1 (entry 4). Both compounds were separated using column chromatography. Compound ***ent*-4** was then subjected to debenzylation, followed by oxidation to obtain the corresponding aldehyde, which further reacted with the known sulfone **17**[6] in the presence of NaHMDS to get compound **18** (E/Z = 2.5:1). Later KHMDS was tested but the result was similar to NaHMDS. The minor *Z*-isomer was inseparable at this stage. TBDPS ether of compound **18** mixed with its corresponding *Z*-counterpart was then removed using TBAF and the resultant alcohols were converted to their corresponding sulfides. These were further oxidized[17] using $H_2O_2/(NH_4)_6MoO_4{\cdot}6H_2O$ to get sulfone **18** and its corresponding *Z*-counterpart, which were separated completely by column chromatography.

The completion of total synthesis of one of the proposed structures (**1a**) of amphirionin-2 is described in Scheme 5. Alcohol **2** mixed with its inseparable *Z*-counterpart was oxidized to aldehyde **19** mixed with its corresponding minor isomer and subjected further to Julia−Kocienski olefination using sulfone **3** in the presence of NaHMDS. However, the required product remained inseparable in this stage with the minor counterpart generated from the *Z*-isomer of reacting aldehyde **19**. Next, this inseparable mixture was treated with TBAF. Compound **1a** was isolated in the pure form and the corresponding *Z*-counterpart originated from inseparable

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Scheme 4. Synthesis of Compound 3

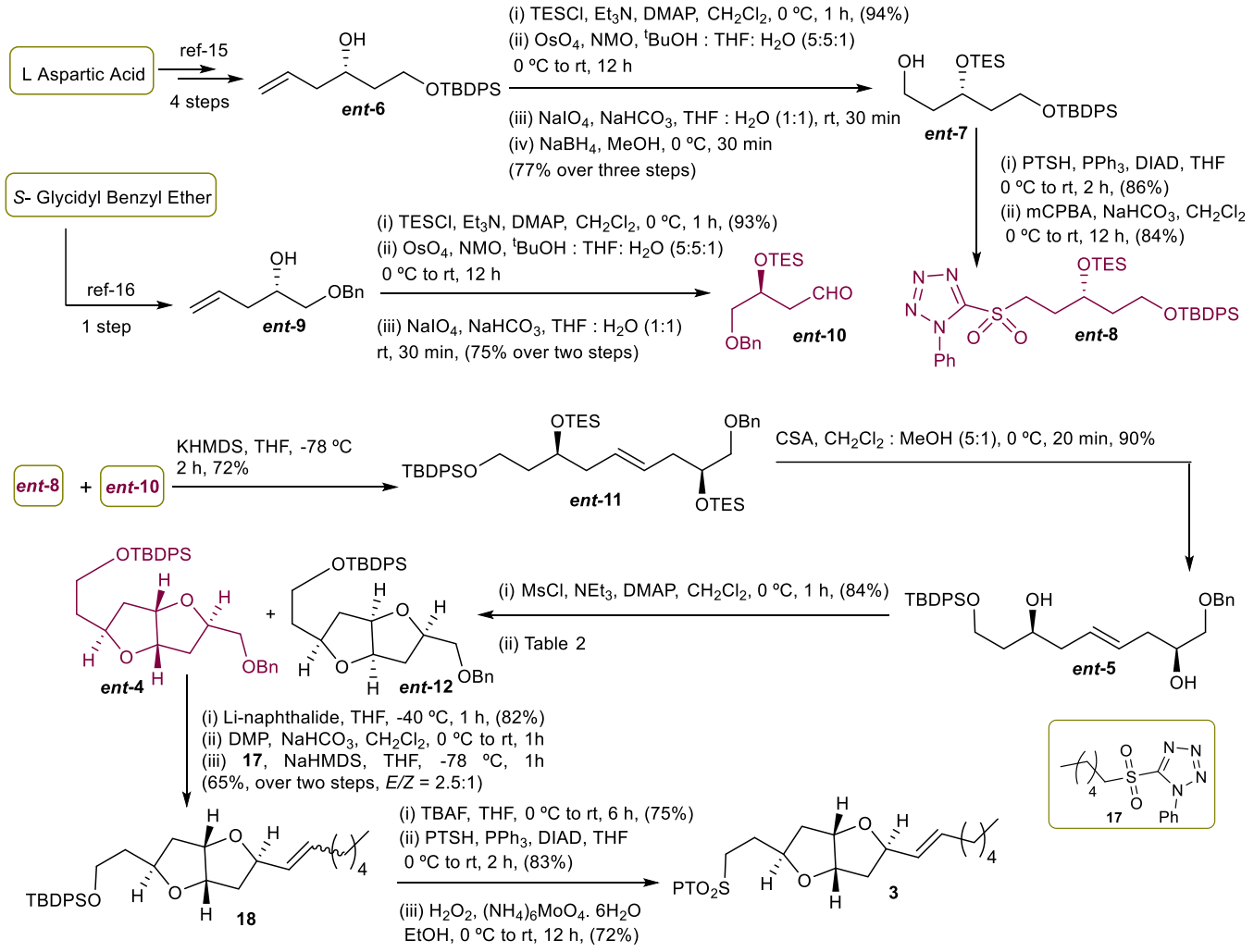

Table 2. Optimization of Dihydroxylation and Cycloetherification for Compound *ent*-4

entry	reagents	solvent	temperature	time (h)	yield (%)	*dr* (*ent*-4/*ent*-12)
1	AD-mix-α (1.4 g/mmol)/$MeSO_2NH_2$ (2 equiv)	H_2O/^{t}BuOH (1:1)	0 °C to rt	48	52	1:1.2
2	AD-mix-β (1.4 g/mmol)/$MeSO_2NH_2$ (2 equiv)	H_2O/^{t}BuOH (1:1)	0 °C to rt	48	55	1:2
3	OsO_4 (0.01 equiv)/NMO (2 equiv)/K_2CO_3 (3 equiv)	THF/^{t}BuOH: H_2O (4:4:1)	0 °C to rt	12	57	1.2:1
4	AD-mix-α (1.4 g/mmol), OsO_4 (0.5 equiv), $MeSO_2NH_2$ (2 equiv)	H_2O/^{t}BuOH (1:1)	0 °C to rt	12	60	1.6:1

minor aldehyde counterpart was discarded during column purification. It is noteworthy that Julia−Kocienski olefination proceeded in a complete *E*-regioselective fashion in this case. The configuration of the conjugated diene moiety of compound **1a** was confirmed unambiguously as *E*, *E* from the observed NOESY correlation between H_{13}−H_{15} and H_{32}−H_{16} and also from the large coupling constant values of H-15 and H-16 ($J_{H_{15}}$ = 15.6 Hz and $J_{H_{16}}$ = 15.1, 7.2 Hz). The observed NOESY interactions between H-7 and H-12 as well as H-18 and H-23 have confirmed further the stereochemistry of hexahydrofuro[3,2-*b*] furan moieties of compound **1a**.

Completion of the total synthesis of other proposed structure (**1b**) of amphirionin-2 is depicted in Scheme 6. Following the similar chemistry of sulfone **3**, compound **4** was debenzylated and the resultant alcohol was oxidized to the corresponding aldehyde, which was further reacted with sulfone **17** to obtain ***ent*-18** along with its inseparable minor *Z*-isomer (*E*/*Z* = 3:1). Next, ***ent*-18** mixed with its minor counterpart was treated with TBAF, followed by PTSH under Mitsunobu conditions and the resultant sulfide was oxidized to achieve sulfone ***ent*-3** in its pure form along with its separable corresponding *Z*-isomer. Next, sulfone ***ent*-3** and aldehyde **19** were subjected to Julia−Kocienski olefination to obtain the corresponding coupled products with complete *E*-selectivity, which was further desilylated to produce compound **1b** in good yield. The minor isomer carried over from aldehyde **19** was discarded at this step during column chromatographic purification.

The spectroscopic data of both compounds **1a** and **1b** were analyzed and compared to the reported data of the isolated amphirionin-2. It is noteworthy that the ^{13}C spectra of both compounds **1a** and **1b** were almost identical but a minor mismatch in the ^1H spectra between them was observed at H-18 and H-12, which might be due to the difference in a long-

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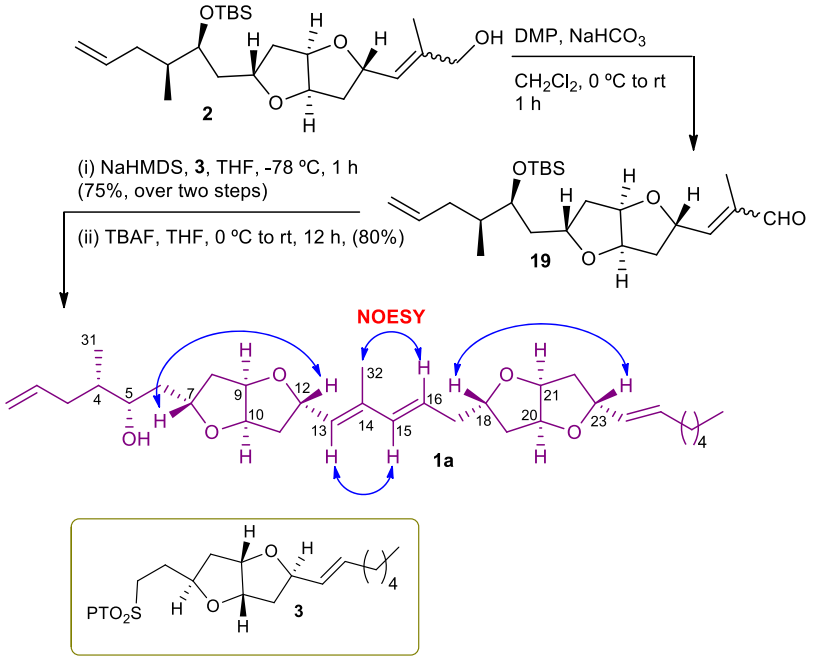
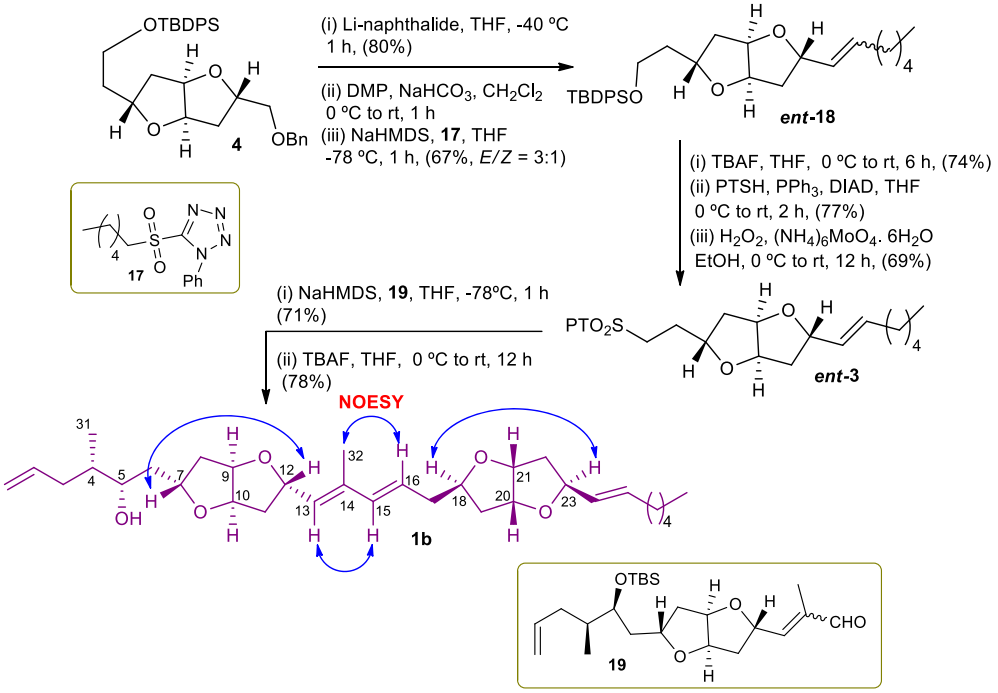
Scheme 5. Completion of Total Synthesis of the Proposed Structure (1a) of Amphirionin-2



Scheme 6. Completion of Total Synthesis of Compound 1b



range interaction between the C-12 and C-18 centers. However, it was quite unfortunate that considerable mismatches were observed in the ^{1}H NMR data of the synthesized compounds (**1a** and **1b**) with respect to the reported data[1] of the isolated natural product especially for H-2, H-3, H-4, H-6, H-7, H-8, H-10, H-11, and H-12 (Table S1). Anomalies in the ^{13}C spectra were also observed (Table S2). The chemical shifts of C-5 to C-10 of both compounds **1a** and **1b** were recorded at δ 74.4, 40.1, 81.5, 42.2, 83.0, and 84.6 ppm, respectively, whereas those signals were observed at δ 71.2, 39.2, 78.3, 41.2, 84.0, and 83.8 ppm, respectively, for the isolated amphirionin-2. Moreover, the optical rotations of compounds **1a** {observed $[\alpha]_D^{20}$ = −26.6 (*c* 0.3, $CHCl_3$)} and **1b** {observed $[\alpha]_D^{20}$ = −13.3 (*c* 0.6, $CHCl_3$)} differed significantly from the data[1] of the isolated natural product {reported $[\alpha]_D^{20}$ = +5 (*c* 0.8, $CHCl_3$)}. These findings clearly indicated that the proposed structures of amphirionin-2 might not be right. At this stage, we were looking for synthesizing other analogues by changing the relative stereochemistry of the fused ring system embedded on the left segment with respect to the stereochemistry of hexahydrofuro[3,2-*b*] furan on the right part of isomers **1a** and **1b** as the absolute stereochemistry of the C-5 center was established by the isolation group according to Mosher's ester analysis. Coincidentally, an elegant synthetic study at this

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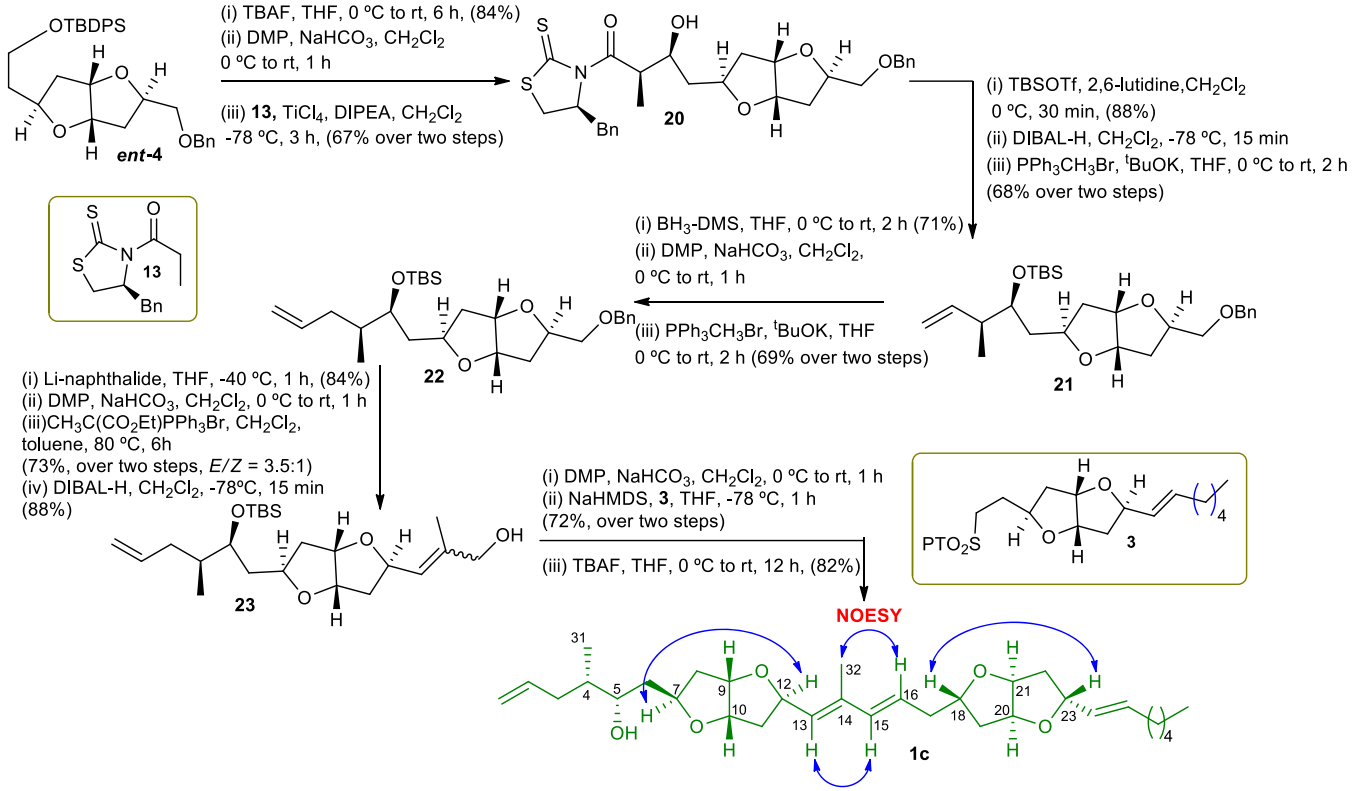
Scheme 7. Completion of Total Synthesis of Compound 1c



juncture was disclosed by Fuwa et al.,[3] where the actual structure (**1c**, Figure 1) of amphirionin-2 was established unambiguously. We were happy to observe that our ongoing investigations were in good alignment with the reported study. Thus, we decided to explore our developed strategy to achieve the total synthesis of the actual natural product (Scheme 7). Compound ***ent*-4** was desilylated, following that it was oxidized and subsequently subjected to Crimmins propionate aldol to get compound **20**, which was later transformed into compound **22** via intermediate **21**. Benzyl ether of compound **22** was deprotected and the resultant alcohol was oxidized to the corresponding aldehyde, which was then exposed to Wittig olefination, followed by DIBAL-H reduction to obtain major compound **23** mixed with its inseparable *Z*-counterpart with an improved ratio (E/Z = 3.5:1) compared to compound **2**. The mixture of alcohols was then oxidized to the corresponding aldehydes and subjected to Julia−Kocienski olefination with sulfone **3** to get the corresponding coupled products, which were finally desilylated. Compound **1c** was separated easily from its minor counterpart. The NMR data of synthesized compound **1c** were in accordance with the reported data (Table S3) of the isolated natural product. The optical rotation of compound **1c** {observed $[\alpha]_D^{20}$ = +6.65 (*c* 0.6, $CHCl_3$)} was in agreement with the literature value of amphirionin-2, which clearly demonstrates its total synthesis.

CONCLUSIONS

In summary, we have achieved the total synthesis of amphirionin-2 from L-aspartic acid in 30 longest linear steps with 0.3% overall yield. Our initial efforts resulted in the total synthesis of the proposed structures of the natural product too, which eventually revealed that the structural revision of the reported structure was essential. The conclusions arrived at are in line with the results from Fuwa et al., which appeared when these investigations were underway. Dihydroxylation followed by the cycloetherification approach was used to build the fused ring system, whereas Julia−Kocienski olefination was adopted to stitch the major halves together. The developed synthetic route is quite flexible, which creates an opportunity to explore the structure−activity relationship of this potent molecule.

EXPERIMENTAL

General Experimental Procedure. All moisture sensitive reactions were performed in an oven or flame-dried glassware with a Teflon-coated magnetic stirring bar under an argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless-steel needle. Reactions were monitored by thin layer chromatography (TLC, Silica gel 60 F254) plates with UV light, ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4) with heat and aqueous $KMnO_4$ (with K_2CO_3 and 10% aqueous NaOH solution) as developing agents. All workup and purification procedures were carried out with reagent-grade solvents under an ambient atmosphere unless otherwise stated. Column chromatography was performed using silica gel 60−120 mesh, 100−200 mesh, and 230−400 mesh. Yields were mentioned as chromatographically and spectroscopically homogeneous materials unless otherwise stated. Optical rotations were measured only for pure compounds and not for mixtures using a sodium (589, D line; Anton paar MCP 200 system) lamp and are reported as follows: $[\alpha]_D^{25}$ = (*c* = *g*/100 mL, solvent). IR spectra were recorded as neat (for liquids). HRMS were recorded using a Quadruple-TOF (Q-TOF) micro-MS system using the electrospray ionization (ESI) technique. ^{1}H NMR spectra were recorded on 300 and 600 MHz spectrometers in appropriate solvents and calibrated using a residual undeuterated solvent as an internal reference, and the chemical shifts are shown on ppm scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), and so forth. ^{13}C and 2D NMR spectra were

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recorded on a 75 MHz spectrometer. Structural assignments were made with additional information from gCOSY, gHSQC, gNOESY, gTOCSY, and gHMBC experiments.

*(R)-5-((Tert-butyldiphenylsilyl)oxy)-3-((triethylsilyl)oxy)pentan-1-ol (**7**).* To an ice-cold solution of compound **6** (9.5 g, 26.8 mmol) in anhydrous CH_2Cl_2 (60 mL) under argon, Et_3N (5.6 mL, 40.3 mmol) was added. After 10 min stirring at 0 °C, TESCl (5.4 mL, 32.2 mmol) and DMAP (327 mg, 2.7 mmol) were added sequentially and the reaction mixture was stirred for another 40 min at the same temperature prior to quenching with a saturated solution of NH_4Cl (5 mL). The resultant mixture was extracted with CH_2Cl_2 (3 × 50 mL), washed with H_2O, brine, dried over Na_2SO_4, and finally concentrated in vacuo. Column chromatographic (SiO_2 60−120 mesh, 5% EtOAc in hexane as the eluent) purification gave the corresponding TES ether (12.1 g, 96%) as a colorless oil; R_f = 0.9 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = −10.4 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (ddd, *J* = 6.3, 4.1, 2.0 Hz, 4H), 7.39 (ddt, *J* = 7.6, 5.2, 2.5 Hz, 6H), 5.81 (ddt, *J* = 19.2, 9.5, 7.1 Hz, 1H), 5.10−4.94 (m, 2H), 3.96 (p, *J* = 5.9 Hz, 1H), 3.72 (q, *J* = 6.4 Hz, 2H), 2.21 (q, *J* = 6.7 Hz, 2H), 1.69 (p, *J* = 6.4 Hz, 2H), 1.05 (s, 9H), 0.93 (t, *J* = 7.8 Hz, 9H), 0.58 (q, *J* = 8.1 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 135.7, 135.2, 134.1, 129.6, 127.7, 116.9, 69.0, 60.9, 42.2, 39.8, 29.8, 27.0, 7.0, 5.1 ppm; IR(neat) ν_{max}: 2964, 2929, 1428, 1109, 1080,735, 699 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{28}H_{45}O_2Si_2$, $[M + H]^+$ 469.2958; found, 469.2956.

To a stirred solution of the above compound (12 g, 25.6 mmol) in THF (50 mL), ^{t}BuOH (50 mL) and H_2O (10 mL) at 0 °C, OsO_4 (0.2 M solution in ^{t}BuOH, 0.3 mL), and NMO (6.0 g, 51.2 mmol) were added, and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was then cooled to 0 °C and quenched with saturated solution of $NaHSO_3$ (10 mL). The resultant mixture was extracted with EtOAc (3 × 50 mL), washed with water, and concentrated in vacuo. The corresponding diol was taken for the next step without further purification and characterization.

To a stirred solution of the above diol (25.6 mmol) in THF (40 mL) and H_2O (40 mL) at 0 °C, $NaHCO_3$ (4.3 g, 51.2 mmol) and $NaIO_4$ (10.9 g, 51.2 mmol) were added. The reaction mixture was slowly warmed to the room temperature and stirred further for 1 h. The reaction mixture was then passed through a small bed of Celite, and the THF solvent was evaporated under reduced pressure and extracted with EtOAc (4 × 50 mL). The filtrate was washed with water then brine and dried over Na_2SO_4, and concentrated in vacuo to obtain the crude aldehyde. It was then passed through a short silica pad to get the corresponding aldehyde, which was used in the next reaction without further purification or characterization.

To a stirred solution of the above aldehyde (25.6 mmol) in anhydrous methanol (60 mL) under argon at 0 °C, $NaBH_4$ (1.45 g, 38.4 mmol) was added portion wise. The reaction mixture was stirred at the same temperature for 1 h and then quenched with saturated aqueous NH_4Cl (10 mL) solution. The methanol solvent was evaporated under reduced pressure and the mixture was extracted with EtOAc (3 × 50 mL), washed with H_2O, brine, dried over Na_2SO_4, and finally concentrated in vacuo. Column chromatographic (SiO_2 60−120 mesh, 7% EtOAc in hexane as the eluent) purification resulted alcohol **7** (9.2 g, 76%) as a colorless oil; R_f = 0.35 (10% EtOAc/hexane); $[\alpha]D^{25}$ = −3.0 (*c* 2.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73−7.62 (m, 4H), 7.44−7.35 (m, 6H), 4.26−4.07 (m, 1H), 3.86−3.62 (m, 4H), 2.55 (t, *J* = 5.2 Hz, 1H), 1.92−1.71 (m, 3H), 1.67−1.55 (m, 1H), 1.06 (s, 9H), 0.97 (t, *J* = 4.5 Hz, 9H), 0.62 (q, *J* = 7.35, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 135.6, 133.8, 129.7, 127.7, 69.4, 60.8, 60.5, 39.7, 37.9, 26.9, 19.2, 6.9, 5.0 ppm; IR (neat) ν_{max}: 3440, 2937, 2874, 1465, 1107, 1036, 855 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{27}H_{45}O_3Si_2$, $[M + H]^+$ 473.2907; found, 473.2905.

*(S)-5-((5-((Tert-butyldiphenylsilyl)oxy)-3-((triethylsilyl)oxy)-pentyl)sulfonyl)-1-phenyl-1H-tetrazole (**8**).* To a mixture of alcohol **7** (8.75 g, 18.51 mmol), Ph_3P (9.71 g, 37.0 mmol), and 1-phenyl-1*H*-tetrazol-5-thiol (PTSH) (4.95 g, 27.76 mmol) in anhydrous THF (60 mL) at 0 °C under argon, DIAD (7.3 mL, 37.0 mmol) was added in dropwise and the reaction mixture was stirred for 2 h at ambient temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with EtOAc (3 × 50 mL), washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, 100−200 mesh, 5% EtOAc in hexane as the eluent) to afford the corresponding sulfide (10.3 g, 88%) as a thick oil. R_f = 0.45 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = −11.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69−7.60 (m, 4H), 7.59−7.50 (m, 5H), 7.44−7.31 (m, 6H), 4.10 (qd, *J* = 6.4, 4.6 Hz, 1H), 3.72 (td, *J* = 6.2, 1.6 Hz, 2H), 3.51−3.36 (m, 2H), 2.12−1.88 (m, 2H), 1.85−1.67 (m, 2H), 1.02 (s, 9H), 0.93 (t, *J* = 8.3, 9H), 0.58 (q, *J* = 7.2, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 135.6, 130.1, 129.8, 129.7, 129.7, 127.8, 127.7, 123.9, 68.2, 60.5, 39.9, 36.3, 29.6, 26.9, 19.2, 7.0, 5.1 ppm; IR (neat) ν_{max}: 2956, 2929, 1500, 1427, 1250, 1111, 836 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{34}H_{48}N_4NaO_2SSi_2$, $[M + Na]^+$ 655.2934; found, 655.2936.

To an ice-cold solution of the above sulfide (10.2 g, 16.11 mmol) and $NaHCO_3$ (8.12 g, 96.68 mmol) in anhydrous CH_2Cl_2 (80 mL) under argon, mCPBA (11.11 g, 64.38 mmol) was added portion wise. The reaction was stirred for 12 h at room temperature. The reaction mixture was then quenched with saturated aqueous $Na_2S_2O_3$ solution (20 mL) at 0 °C and extracted with CH_2Cl_2 (3 × 50 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography (SiO_2, 100−200 mesh, 5% EtOAc in hexane as eluant) to yield sulfone **8** (9.1 g, 85%) as a pale-yellow oil. R_f = 0.42 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = −10.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72−7.56 (m, 9H), 7.40 (dtd, *J* = 8.8, 5.6, 5.0, 2.0 Hz, 6H), 4.16 (qd, *J* = 6.4, 4.6 Hz, 1H), 3.88−3.68 (m, 4H), 2.27−2.12 (m, 1H), 2.10−1.99 (m, 1H), 1.86−1.73 (m, 1H), 1.71−1.58 (m, 1H), 1.05 (s, 9H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.8 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.6, 135.6, 133.6, 131.5, 129.8, 129.8, 127.8, 127.8, 125.1, 67.2, 60.3, 52.5, 39.6, 29.1, 26.9, 19.2, 7.0, 5.0 ppm; IR (neat) ν_{max}: 2955, 2857, 1468, 1428, 1111, 701 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{34}H_{48}N_4NaO_4SSi_2$, $[M + Na]^+$ 687.2832; found, 687.2834.

*(R)-4-(Benzyloxy)-3-((triethylsilyl)oxy)butanal (**10**).* Following the same experimental procedure as described in the preparation of compound **7**, compound **9** (4.0 g, 20.8 mmol) was converted to the corresponding TES ether. Column chromatographic (SiO_2 60−120 mesh, 5% EtOAc in hexane as the eluent) purification gave the compound (6.0 g, 95%) as a colorless oil; R_f = 0.8 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = −8.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.28 (m, 5H), 5.83 (ddt, *J* = 17.3, 10.1, 7.2 Hz, 1H), 5.10−4.98 (m, 2H), 4.52 (s, 2H), 3.88 (p, *J* = 5.6 Hz, 1H), 3.39 (d, *J* = 5.5 Hz, 2H), 2.42−2.31 (m, 1H), 2.28−2.18 (m, 1H), 0.94 (q, *J* = 7.5 Hz, 6H), 0.61 (t, *J* = 7.8 Hz, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 135.0, 128.5, 128.4, 127.7, 127.6, 117.1, 74.3, 73.4, 71.2, 39.5, 6.9, 5.0 ppm; IR (neat) ν_{max}: 2910, 2876, 1455, 1111, 1004, 731 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{18}H_{30}NaO_2Si$, $[M + Na]^+$ 329.1913; found, 329.1914.

Following the same experimental procedure as described in the preparation of compound **7**, the above compound (6.0 g, 19.6 mmol) was converted to the corresponding diol (6.6 g, quantitative) as a light yellowish oil using OsO_4 (0.2 M solution in *t*-BuOH, 0.2 mL) and NMO (4.58 g, 39.1 mmol), which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **7**, the above diol (19.6 mmol) was converted to the corresponding aldehyde **10**. Purification by flash column chromatography (SiO_2, 60−120 mesh, 10−20% EtOAc in hexane as the eluent) provided a pure compound (4.68 g, 78% over two steps) as a colorless liquid, which was taken for the next step without further characterization.

*(5R,10R,E)-5-((Benzyloxy)methyl)-3,3-diethyl-15,15-dimethyl-14,14-diphenyl-10-((triethylsilyl)oxy)-4,13-dioxa-3,14-disilahexadec-7-ene (**11**).* Sulfone **8** (3.0 g, 4.51 mmol) was dissolved in anhydrous THF (15 mL) under argon and cooled to −78 °C. KHMDS (0.5 M in THF, 9.8 mL, 4.88 mmol) solution was added to it and stirred for 10 min. A solution of aldehyde **10** (1.16 g, 3.76 mmol) in THF (7 mL) was cannulated into the reaction mixture and stirred for 2 h. The reaction was then quenched with saturated

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aqueous NH_4Cl solution (3 mL) at the same temperature. The resultant mixture was extracted with EtOAc (2 × 30 mL), washed with water and brine, dried over Na_2SO_4, and finally concentrated in vacuo. Purification by flash column chromatography (SiO_2, 100−200 mesh, 2% EtOAc in hexane as the eluent) of the resultant crude residue provided compound **11** (1.96 g, 70%) as a colorless liquid. R_f = 0.45 (5% EtOAc/hexane); $[\alpha]_D^{25}$ = −2.35 (*c* 8.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (ddd, *J* = 7.8, 4.4, 1.8 Hz, 4H), 7.45−7.34 (m, 6H), 7.32 (d, *J* = 4.5 Hz, 4H), 5.51−5.39 (m, 2H), 4.51 (s, 2H), 3.97−3.80 (m, 2H), 3.71 (td, *J* = 6.4, 3.8 Hz, 2H), 3.38 (d, *J* = 5.4 Hz, 2H), 2.37−2.25 (m, 1H), 2.22−2.08 (m, 3H), 1.72−1.59 (m, 2H), 1.04 (s, 9H), 1.00−0.84 (m, 18H), 0.65−0.49 (m, 12H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 138.6, 135.7, 134.1, 134.1, 129.6, 129.1, 128.7, 128.4, 127.7, 127.5, 74.4, 73.4, 71.6, 69.3, 61.0, 41.2, 39.8, 38.3, 27.0, 19.3, 7.0, 7.0, 5.1, 5.1 ppm; IR (neat) ν_{max}: 2930, 2875, 1457, 1110, 1090, 1006, 736, 700 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{44}H_{70}NaO_4Si_3$, $[M + Na]^+$ 769.4480; found, 769.4477. The same reaction was performed batchwise.

*(2R,7R,E)-1-(Benzyloxy)-9-((tert-butyldiphenylsilyl)oxy)non-4-ene-2,7-diol (**5**).* To an ice cold solution of compound **11** (5.9 g, 7.9 mmol) in anhydrous CH_2Cl_2 (20 mL) and MeOH (4 mL), CSA (96 mg, 0.43 mmol) was added and stirred for 45 min. The reaction was then quenched with Et_3N (5 mL) and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 60−120 mesh, 20% EtOAc in hexane as the eluent) to obtain diol **5** (3.64 g, 89%) as a colorless oil. R_f = 0.4 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = −16.65 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (ddt, *J* = 6.6, 2.1, 0.8 Hz, 4H), 7.48−7.37 (m, 6H), 7.37−7.27 (m, 5H), 5.62−5.45 (m, 2H), 4.55 (s, 2H), 3.96−3.79 (m, 4H), 3.50 (dd, *J* = 9.5, 3.4 Hz, 1H), 3.37 (dd, *J* = 9.5, 7.3 Hz, 1H), 2.30 (d, *J* = 5.9 Hz, 1H), 2.27−2.18 (m, 3H), 1.69 (dq, *J* = 9.5, 4.9 Hz, 2H), 1.06 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 138.1, 135.6, 135.6, 133.2, 133.1, 129.9, 128.7, 128.5, 127.9, 127.8, 74.0, 73.5, 71.0, 70.0, 63.3, 40.9, 38.0, 36.9, 26.9, 19.1 ppm; IR (neat) ν_{max}: 3421, 3064, 2930, 2857, 1472, 1427, 1106, 822, 737, 700 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{32}H_{43}O_4Si$, $[M + H]^+$ 519.2931; found, 519.2923.

*(2-((2R,3aR,5S,6aR)-5-((Benzyloxy)methyl)hexahydrofuro[3,2-b]-furan-2-yl)ethoxy)(tert-butyl)diphenylsilane (**4**).* To a stirred solution of diol **5** (3.5 g, 6.74 mmol) in anhydrous CH_2Cl_2 (20 mL), Et_3N (4.7 mL, 33.7 mmol) at 0 °C under argon, MsCl (1.56 mL, 20.22 mmol), followed by DMAP (0.17 g, 1.4 mmol) were added. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) solution at 0 °C after 1 h and extracted with CH_2Cl_2 (3 × 15 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by column chromatography (SiO_2, 60−120 mesh, 30−40% EtOAc in hexane as the eluent) to obtain the corresponding mesylated compound (3.86 g, 85%) as a pale-yellow oil. R_f = 0.45 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = −10.67 (*c* 3.37, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (ddd, *J* = 7.5, 5.3, 1.8 Hz, 4H), 7.48−7.38 (m, 6H), 7.37−7.29 (m, 5H), 5.66−5.45 (m, 2H), 4.97 (dq, *J* = 6.9, 5.4 Hz, 1H), 4.87−4.75 (m, 1H), 4.62−4.49 (m, 2H), 3.84−3.70 (m, 2H), 3.65−3.57 (m, 2H), 3.00 (s, 3H), 2.92 (s, 3H), 2.59−2.35 (m, 4H), 1.94−1.77 (m, 2H), 1.07 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 137.5, 135.6, 133.4, 133.3, 129.9, 128.5, 128.0, 127.8, 127.8, 127.2, 81.3, 79.8, 73.4, 71.0, 59.5, 38.6, 38.3, 38.3, 38.1, 36.6, 35.3, 26.9, 19.2 ppm; IR (neat) ν_{max}: 2932, 2858, 1472, 1428, 1352, 1178, 913, 702 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{34}H_{46}NaO_8S_2Si$, $[M + Na]^+$ 697.2301; found, 697.2304.

To a stirred solution of ^{t}BuOH/H_2O (1:1, 50 mL) at room temperature, AD-mix-β (7.71 g, 1.4 g/mmol) and methanesulfonamide (1.05 g, 11 mmol) were added. The solution was further stirred well for 15 min. A solution of the above mesylated compound (3.7 g, 5.51 mmol) in ^{t}BuOH/H_2O (1:1, 15 mL) was added to the reaction mixture at 0 °C and then it was warmed to room temperature and stirred for 36 h. The mixture was quenched with a saturated solution of Na_2SO_3 and the resultant mixture was stirred further for 1 h. The aqueous layer was extracted with EtOAc (4 × 30 mL), washed with water and brine, dried over Na_2SO_4, and finally concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 230−400 mesh, 10% EtOAc in hexane as the eluent) to separate the two diastereomers with 60% total yield (*dr* = 3:1). The isolated major compound **4** (1.28 g, 45%) was obtained as a colorless oil. R_f = 0.8 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = +4.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72−7.62 (m, 4H), 7.48−7.26 (m, 11H), 4.72 (t, *J* = 4.5 Hz, 1H), 4.66 (t, *J* = 4.8 Hz, 1H), 4.63−4.51 (m, 2H), 4.34−4.17 (m, 2H), 3.75 (dd, *J* = 7.3, 5.8 Hz, 2H), 3.53 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.42 (dd, *J* = 10.2, 5.8 Hz, 1H), 2.23 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.07 (dd, *J* = 13.4, 5.8 Hz, 1H), 1.88−1.71 (m, 3H), 1.66−1.59 (m, 1H), 1.04 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 138.3, 135.6, 133.9, 129.6, 128.4, 127.8, 127.7, 127.7, 84.5, 83.2, 79.1, 77.0, 73.5, 72.6, 61.3, 41.4, 38.5, 37.5, 26.9, 19.3 ppm; IR (neat) ν_{max}: 2962, 2832, 1466, 1235, 1031 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{32}H_{40}NaO_4Si$, $[M + Na]^+$ 539.2594; found, 539.2592.

Minor compound **12** (0.43 g, 15%) was obtained as a colorless liquid. R_f = 0.75 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = −3.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70−7.62 (m, 4H), 7.46−7.27 (m, 11H), 4.61−4.50 (m, 3H), 4.41 (ddd, *J* = 6.5, 4.5, 2.0 Hz, 1H), 4.20 (qd, *J* = 7.3, 4.4 Hz, 1H), 4.14−4.04 (m, 1H), 3.79−3.66 (m, 2H), 3.61−3.52 (m, 1H), 3.48 (dd, *J* = 9.9, 4.4 Hz, 1H), 2.28−2.12 (m, 2H), 2.00−1.87 (m, 1H), 1.85−1.70 (m, 3H), 1.04 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 138.3, 135.7, 134.0, 129.7, 128.4, 127.9, 127.7, 127.7, 85.4, 84.0, 80.2, 78.6, 73.4, 73.1, 61.4, 39.5, 39.0, 35.9, 27.0, 19.3 ppm; IR (neat) ν_{max}: 2935, 2823, 1472, 1135, 953 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{32}H_{40}NaO_4Si$, $[M + Na]^+$ 539.2594; found, 539.2597.

Improved Procedure for Dihydroxylation Followed by Cycloetherification. To a stirred solution of ^{t}BuOH/H_2O (1:1, 3 mL) at room temperature, AD-mix-β (38 mg, 1.4 g/mmol), OsO_4 (0.2 M solution in ^{t}BuOH, 60 μL), and methanesulfonamide (6 mg, 0.06 mmol) were added. The solution was further stirred well for 15 min and then the above dimesylated compound (18 mg, 0.03 mmol) in ^{t}BuOH (1 mL) was cannulated and stirred for 12 h. The mixture was quenched with a saturated solution of Na_2SO_3 and the resultant mixture was stirred further for 1 h. The aqueous layer was extracted with EtOAc (4 × 10 mL), washed with water and brine, dried over Na_2SO_4, and finally concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 230−400 mesh, 10% EtOAc in hexane as the eluent) to separate the two diastereomers with 60% overall yield (*dr* = 3.5:1). Isolated major compound **4** (8 mg, 46%) and minor compound **12** (2 mg, 14%) were obtained as a colorless oil.

*(2R,3S)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-4-((2R,3aR,5S,6aR)-5-((benzyloxy)methyl) hexahydrofuro[3,2-b]-furan-2-yl)-3-hydroxy-2-methylbutan-1-one (**14**).* To the solution of compound **4** (1.0 g, 1.93 mmol) in anhydrous THF (10 mL) at 0 °C under argon, TBAF (1.0 M in THF, 2.9 mL, 2.90 mmol) was added. The reaction was stirred at room temperature for 6 h and then quenched with saturated NH_4Cl (5 mL) solution. The aqueous layer was extracted with EtOAc (3 × 20 mL), the combined organic layer was washed with water and brine, and then dried over Na_2SO_4 and concentrated in vacuo. Column chromatography (SiO_2, 60−120 mesh, 20% EtOAc in hexane as the eluent) produces the desire alcohol (0.45 g, 83%) as a colorless oil. R_f = 0.2 (50% EtOAc/hexane); $[\alpha]_D^{25}$ = + 40.0 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.26 (m, 5H), 4.78−4.69 (m, 2H), 4.64−4.51 (m, 2H), 4.35−4.17 (m, 2H), 3.76 (dd, *J* = 6.4, 5.1 Hz, 2H), 3.52 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.41 (dd, *J* = 10.2, 5.8 Hz, 1H), 2.23 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.14−2.04 (m, 1H), 1.87−1.77 (m, 2H), 1.75−1.69 (m, 1H), 1.68−1.60 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 138.2, 128.4, 127.7, 127.7, 83.9, 83.8, 79.6, 79.2, 73.5, 72.5, 61.4, 41.3, 37.4, 37.3 ppm; IR (neat) ν_{max}: 3422, 3032, 2937, 2867, 1453, 1354, 1173, 1072, 1051, 910, 737 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{22}NaO_4$, $[M + Na]^+$ 301.1416; found, 301.1417.

To an ice-cold solution of the above alcohol (0.44 g, 1.58 mmol) in anhydrous CH_2Cl_2 (15 mL), $NaHCO_3$ (0.53 g, 6.32 mmol) and DMP (1.34 g, 3.16 mmol) were added sequentially. The reaction mixture was warmed gradually to room temperature and stirred further for 1 h. The reaction was then quenched with saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL) and then diluted with CH_2Cl_2

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(10 mL) and stirred further until the two phases were separated. The resultant mixture was extracted with CH_2Cl_2 (2 × 20 mL), washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was subjected to flash column chromatography (using a short pad of 60−120 silica and EtOAc as the eluent) to get the corresponding aldehyde as a colorless liquid, which was taken for the next reaction without further characterization.

To a solution of thiazolidinethione **13** (0.5 g, 1.89 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C under argon, freshly distilled $TiCl_4$ (216 μL, 1.98 mmol) was added dropwise. The orange slurry was stirred for 10 min at the same temperature, and DIPEA (0.7 mL, 3.95 mmol) was added dropwise. The deep brown solution was stirred for another 30 min at 0 °C before being cooled to −78 °C, and the above aldehyde (1.58 mmol dissolved in 5 mL of CH_2Cl_2) was cannulated. Stirring was continued at −78 °C for 2 h and then quenched by water (5 mL). The resultant mixture was extracted with CH_2Cl_2 (2 × 25), washed with water, brine and saturated aqueous $NaHCO_3$ then dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 230−400 mesh, 15−20% EtOAc in hexane) to obtain isomer **14** (0.55 g, 65%) exclusively as a yellowish liquid; R_f = 0.6 (40% EtOAc in hexane); $[\alpha]_D^{25}$ = +66.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.26 (m, 10H), 5.46−5.37 (m, 1H), 4.78−4.66 (m, 3H), 4.63−4.52 (m, 2H), 4.34−4.20 (m, 3H), 3.53 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.44−3.33 (m, 2H), 3.25 (dd, *J* = 13.2, 3.9 Hz, 1H), 3.09−2.98 (m, 1H), 2.88 (dd, *J* = 11.6, 1.0 Hz, 1H), 2.28 (dd, *J* = 13.2, 4.9 Hz, 1H), 2.10 (dd, *J* = 13.5, 5.7 Hz, 1H), 1.87−1.78 (m, 1H), 1.72−1.66 (m, 2H), 1.65−1.59 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 201.4, 177.0, 138.2, 136.6, 129.5, 129.0, 128.5, 127.8, 127.7, 127.3, 84.0, 83.8, 79.2, 77.3, 73.5, 72.5, 71.0, 69.1, 43.6, 41.6, 39.5, 37.4, 37.1, 31.9, 11.4 ppm; IR (neat) ν_{max}: 3482, 2925, 2857, 1725, 1700, 1495, 1454, 1078, 743 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{29}H_{35}NNaO_5S_2$, $[M + Na]^+$ 564.1854; found, 564.1855.

*(((2S,3S)-1-((2S,3aR,5S,6aR)-5-((Benzyloxy)methyl)-hexahydrofuro[3,2-b]furan-2-yl)-3-methylpent-4-en-2-yl)oxy)(tert-butyl)dimethylsilane (**15**).* To an ice-cold solution of compound **14** (510 mg, 0.94 mmol) in anhydrous CH_2Cl_2 (8 mL) under argon, 2,6-lutidine (0.22 mL, 1.88 mmol) and TBSOTf (0.32 mL, 1.41 mmol) were added sequentially. The reaction mixture was stirred at 0 °C for 30 min and was then quenched by saturated aqueous $NaHCO_3$ solution (2 mL). The solvent was evaporated under reduced pressure and the resulting mixture was extracted with EtOAc (3 × 10 mL). The organic extracts were washed with aqueous $CuSO_4$, water, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 60−120 mesh, 5−10% EtOAc in hexane) furnished the corresponding TBS protected compound (530 mg, 86%) as a yellowish liquid; R_f = 0.85 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = +79.9 (c 0.1 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.32 (m, 5H), 7.32−7.26 (m, 5H), 5.38 (ddd, *J* = 10.4, 7.0, 3.3 Hz, 1H), 4.84 (p, *J* = 7.0 Hz, 1H), 4.63 (dt, *J* = 13.6, 4.4 Hz, 2H), 4.57 (d, *J* = 2.0 Hz, 2H), 4.28−4.18 (m, 3H), 3.53 (dd, *J* = 10.4, 3.1 Hz, 1H), 3.39 (dd, *J* = 10.4, 5.7 Hz, 1H), 3.36−3.28 (m, 1H), 3.22 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.98 (dd, *J* = 13.2, 10.9 Hz, 1H), 2.81 (dd, *J* = 11.5, 0.9 Hz, 1H), 2.15 (td, *J* = 13.0, 5.3 Hz, 2H), 1.95 (ddd, *J* = 14.6, 8.0, 4.0 Hz, 1H), 1.81−1.69 (m, 2H), 1.54−1.45 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 200.2, 176.6, 138.4, 137.0, 129.5, 129.0, 128.4, 127.8, 127.6, 127.3, 100.1, 84.0, 83.5, 79.3, 75.2, 73.5, 72.6, 71.5, 69.0, 43.5, 42.1, 41.0, 37.3, 36.8, 31.1, 26.1, 18.2, 15.3, −4.0, −4.4 ppm; IR (neat) ν_{max}: 2951, 2856, 1711, 1693, 1455, 1255, 1091, 835 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{35}H_{49}NNaO_5S_2Si$, $[M + Na]^+$ 678.2719; found, 678.2718.

To a cold solution (−78 °C) of the above TBS protected compound (0.5 g, 0.76 mmol) in anhydrous CH_2Cl_2 (10 mL) under argon, DIBAL-H (1.52 mL, 1.52 mmol, 1.0 M in hexane) was added slowly. The reaction was quenched immediately with MeOH (0.5 mL) at the same temperature when the color of the reaction mixture was changed from yellow to colorless. A saturated solution of sodium potassium tartrate (5 mL) was added into it. After 1 h of vigorous stirring at room temperature, the resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 60−120 mesh, 30% EtOAc in hexane as the eluent) to obtain the corresponding aldehyde; R_f = 0.3 (30% EtOAc in hexane), which was taken for the next step without further characterization.

To a suspension of Ph_3PCH_3Br (542 mg, 1.52 mmol) in anhydrous THF (6 mL) at 0 °C under argon, ^{t}BuOK (153 mg, 1.36 mmol) was added and stirred for 30 min at the same temperature. The above aldehyde (0.76 mmol, dissolved in 5 mL of anhydrous THF) was cannulated into it at the same temperature. The reaction mixture was allowed to stir for another 2 h at room temperature and then quenched with saturated aqueous NH_4Cl solution (2 mL). The resultant mixture was extracted with EtOAc (3 × 10 mL), washed with water, brine, dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (SiO_2, 60−120 mesh, 10% EtOAc in hexane as the eluent) of the crude residue gave compound **15** (235 mg, 70%) as a yellowish oil. R_f = 0.7 (15% EtOAc/hexane); $[\alpha]_D^{25}$ = +5.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.27 (m, 5H), 5.97−5.79 (m, 1H), 5.05−4.95 (m, 2H), 4.75−4.66 (m, 2H), 4.63−4.52 (m, 2H), 4.31−4.22 (m, 1H), 4.19−4.10 (m, 1H), 3.68−3.62 (m, 1H), 3.52 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.42 (dd, *J* = 10.3, 5.8 Hz, 1H), 2.45−2.29 (m, 1H), 2.23 (dd, *J* = 13.2, 4.9 Hz, 1H), 2.07 (dd, *J* = 13.4, 5.8 Hz, 1H), 1.89−1.72 (m, 2H), 1.58−1.46 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (d, *J* = 2.7 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 141.2, 138.3, 128.4, 127.7, 127.7, 114.3, 84.3, 83.1, 79.1, 76.8, 73.6, 73.4, 72.6, 42.5, 41.6, 39.8, 37.5, 26.0, 18.2, 14.4, −4.2, −4.3 ppm; IR (neat) ν_{max}: 2957, 2929, 2857, 1456, 1472, 1253, 1090, 835 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{42}NaO_4Si$, $[M + Na]^+$ 469.2750; found, 469.2752.

*(((2S,3S)-1-((2S,3aR,5S,6aR)-5-((Benzyloxy)methyl)-hexahydrofuro[3,2-b]furan-2-yl)-3-methylhex-5-en-2-yl)oxy)(tert-butyl)dimethylsilane (**16**).* To a stirred solution of alkene **15** (220 mg, 0.49 mmol) in anhydrous THF (5 mL) at 0 °C under argon, BH_3-DMS (0.73 mL, 1.47 mmol, 2 M in THF) was added and the reaction was continued for 1 h at the same temperature. The cooling bath was then removed and the mixture was stirred for another 1 h at room temperature. The mixture was cooled to 0 °C. Water (0.1 mL) and K_2CO_3 (200 mg) were added slowly. The resultant mixture was then filtered and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography (SiO_2, 60−120 mesh, 40% EtOAc in hexane as the eluent) resulted the corresponding alcohol (154 mg, 68%) as a light yellowish oil. R_f = 0.2 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = +6.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.27 (m, 5H), 4.66−4.55 (m, 2H), 4.51 (tt, *J* = 4.4, 2.4 Hz, 1H), 4.47−4.35 (m, 1H), 4.20 (tt, *J* = 7.3, 3.7 Hz, 1H), 4.00 (dt, *J* = 12.3, 6.4 Hz, 1H), 3.83 (td, *J* = 7.2, 6.2, 3.7 Hz, 1H), 3.77−3.57 (m, 3H), 3.51 (ddd, *J* = 9.6, 4.4, 2.0 Hz, 1H), 2.30−2.12 (m, 2H), 1.96−1.80 (m, 2H), 1.70 (dddd, *J* = 14.0, 8.7, 5.6, 3.6 Hz, 4H), 1.40−1.27 (m, 1H), 0.87 (s, 9H), 0.04 (dd, *J* = 7.9, 3.4 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.3, 128.4, 127.9, 127.7, 85.2, 84.1, 80.3, 78.8, 73.8, 73.4, 73.2, 61.7, 39.5, 35.8, 35.6, 29.8, 26.0, 18.1, 16.1, −4.2, −4.4 ppm; IR (neat) ν_{max}: 3409, 2934, 2843, 1501, 1251, 1086, 763 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{44}O_5SiNa$, $[M + Na]^+$ 487.2856; found, 487.2854.

Following the same DMP oxidation conditions as described in the preparation of compound **14**, the above alcohol (140 mg, 0.3 mmol) was transformed into the corresponding aldehyde (purified by flash column chromatography using a short pad of 60−120 silica with 10% EtOAc in hexane as the eluent) as a yellowish liquid, which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **15**, the above aldehyde (0.3 mmol) was converted to the corresponding alkene **16** (92 mg, 67%, purification by flash column chromatography, SiO_2, 60−120 mesh, 10% EtOAc in hexane as the eluent) as a colorless oil. R_f = 0.8 (20% EtOAc/hexane); $[\alpha]_D^{25}$ = +13.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.27 (m, 5H), 5.85−5.70 (m, 1H), 5.07−4.94 (m, 2H), 4.72 (p, *J* = 4.4 Hz, 2H), 4.63−4.50 (m, 2H), 4.31−4.23 (m, 1H), 4.15−4.05 (m, 1H), 3.68 (td, *J* = 6.4, 3.1 Hz, 1H), 3.53 (dd, *J* = 10.2, 3.3 Hz,

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1H), 3.42 (dd, J = 10.2, 5.8 Hz, 1H), 2.33−2.25 (m, 1H), 2.25−2.18 (m, 1H), 2.11−2.03 (m, 1H), 1.89−1.78 (m, 2H), 1.77−1.64 (m, 2H), 1.57−1.47 (m, 2H), 0.89 (s, 9H), 0.81 (d, J = 6.7 Hz, 3H), 0.05 (d, J = 3.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 138.3, 138.1, 128.4, 127.7, 127.7, 115.6, 84.3, 83.2, 79.1, 73.4, 73.1, 72.6, 41.6, 39.5, 37.7, 37.5, 37.0, 29.8, 26.0, 18.2, 13.8, −4.1, −4.3 ppm; IR (neat) ν_{max}: 2957, 2928, 2856, 1472, 1459, 1436, 1102, 1090, 835, 695 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{27}H_{44}O_4SiNa$, $[M + Na]^+$ 483.2907; found, 483.2904.

3-((2S,3aR,5S,6aR)-5-((2S,3S)-2-((Tert-butyldimethylsilyl)oxy)-3-methylhex-5-en-1-yl)hexa Hydrofuro[3,2-b]furan-2-yl)-2-methyl-prop-2-en-1-ol (**2**). To a solution of naphthalene (100 mg, 0.8 mmol) in anhydrous THF (5 mL) under argon, Li was added (7 mg, 1 mmol) as small pieces. After 1 h stirring at room temperature, the reaction mixture was cooled to −40 °C and subsequently a solution of compound **16** (90 mg, 0.19 mmol, dissolved in 3 mL of anhydrous THF) was cannulated into it. The reaction was continued further for 1 h at the same temperature and then quenched with saturated aqueous solution of NH_4Cl (2 mL). The resultant mixture was extracted with EtOAc (2 × 15 mL), washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 60−120 mesh,20% EtOAc in hexane as the eluent) to get the corresponding alcohol (60 mg, 86%) as a colorless oil; R_f = 0.2 (35% EtOAc/hexane); $[\alpha]_D^{25}$ = +39.95 (c 0.1, $CHCl_3$);^1H NMR (300 MHz, $CDCl_3$): δ 5.76 (dddd, J = 16.7, 10.1, 7.7, 6.2 Hz, 1H), 5.08−4.93 (m, 2H), 4.53 (ddd, J = 6.5, 4.1, 2.2 Hz, 1H), 4.37 (ddd, J = 5.8, 4.1, 1.4 Hz, 1H), 4.22 (dtd, J = 8.6, 5.4, 3.1 Hz, 1H), 3.99 (dq, J = 8.2, 6.8 Hz, 1H), 3.72−3.59 (m, 3H), 2.33−2.24 (m, 2H), 2.19 (dd, J = 8.5, 5.8 Hz, 1H), 1.99 (ddd, J = 14.0, 5.3, 1.5 Hz, 1H), 1.91−1.81 (m, 2H), 1.76−1.63 (m, 3H), 0.88 (s, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.04 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 138.1, 115.6, 85.2, 84.3, 81.6, 78.9, 73.1, 65.3, 39.8, 37.9, 36.8, 34.1, 29.8, 26.0, 18.2, 14.0, −4.3 ppm; IR (neat) ν_{max}: 3418, 2948, 2929, 2857, 1463, 1440, 1081, 836,774 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{20}H_{39}O_4Si$, $[M + H]^+$ 371.2618; found, 371.2613.

Following the same DMP oxidation procedure as compound **14**, the above alcohol (55 mg, 0.15 mmol) was converted to the corresponding aldehyde (purification by flash column chromatography, SiO_2, 60−120 mesh, 5% EtOAc in hexane as the eluent) as a colorless oil. It was taken for the next step without further characterization.

To a solution of the above aldehyde (0.15 mmol) in anhydrous toluene, ethyl 2-(triphenylphosphoranylidene) propionate (163 mg, 0.45 mmol) was added at 80 °C under argon. The reaction was continued for 6 h. Then, toluene was evaporated in vacuum and the resultant residue was purified by column chromatography (SiO_2, 230−400 mesh, 2% EtOAc in hexane as the eluent) to get the corresponding α, β-unsaturated ester (46 mg, 68% over two steps, E/Z = 3:1) as a colorless liquid, which remained inseparable. R_f = 0.6 (15% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 6.87 (d, J = 7.9 Hz, 1H), 5.76 (ddt, J = 17.2, 10.5, 7.0 Hz, 1H), 5.05−4.90 (m, 2H), 4.74 (q, J = 7.4 Hz, 1H), 4.56−4.43 (m, 2H), 4.18 (dd, J = 8.0, 6.3 Hz, 2H), 4.03 (q, J = 7.0 Hz, 1H), 3.66 (td, J = 8.4, 7.9, 4.3 Hz, 1H), 2.34 (ddt, J = 30.8, 13.4, 6.8 Hz, 3H), 1.91 (d, J = 6.5 Hz, 1H), 1.85 (s, 3H), 1.75 (dd, J = 12.7, 6.9 Hz, 2H), 1.68 (d, J = 4.6 Hz, 2H), 1.31−1.27 (m, 3H), 0.88 (s, 9H), 0.83 (d, J = 6.8 Hz, 3H), 0.04 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.8, 141.6, 138.1, 132.3, 128.7, 115.5, 85.3, 84.4, 79.1, 73.3, 60.8, 39.7, 39.5, 39.3, 38.1, 36.7, 26.0, 18.2, 14.4, 14.2, 12.9, −4.2, −4.3 ppm; IR (neat) ν_{max}: 2948, 2811, 1561, 1421, 1246, 986 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{25}H_{44}NaO_5Si$, $[M + Na]^+$ 475.2856; found, 475.2854.

Following the same experimental procedure as described in the preparation of compound **15**, the above α, β-unsaturated ester (40 mg, 0.09 mmol) was converted to the alcohol **2** along with its Z-counterpart using DIBAL-H (0.14 mL, 0.23 mmol, 1.6 M in toluene). Purification by flash column chromatography (SiO_2, 60−120 mesh, 20% EtOAc in hexane as the eluent) provided compound **2** along with its inseparable minor counterpart (32 mg, 87%) as a colorless liquid. R_f = 0.3 (30% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 5.86−5.67 (m, 1H), 5.39 (dd, J = 8.3, 1.4 Hz, 1H), 5.07−4.92 (m, 2H), 4.81−4.74 (m, 1H), 4.73 (dd, J = 4.6, 3.3 Hz, 2H), 4.17 (tt, J = 8.6, 4.4 Hz, 1H), 4.06−3.97 (m, 2H), 3.83 (dt, J = 8.8, 3.3 Hz, 1H), 2.43−2.29 (m, 1H), 2.24−2.13 (m, 2H), 1.72 (s, 3H), 1.70−1.62 (m, 4H), 1.49 (td, J = 8.7, 3.7 Hz, 2H), 0.90 (s, 9H), 0.83 (d, J = 6.6 Hz, 3H), 0.12−0.03 (m, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 139.3, 138.1, 126.0, 124.9, 115.6, 83.7, 83.6, 77.8, 75.9, 73.4, 68.0, 42.0, 41.6, 39.2, 38.4, 36.3, 29.8, 26.0, 18.2, 14.4, 14.1, −4.2, −4.2 ppm; IR (neat)ν_{max}: 3388, 2925, 2854, 1457, 1440, 1184, 1074, 776 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{23}H_{43}O_4Si$, $[M + H]^+$ 411.2931; found, 411.2923.

(S)-5-((Tert-butyldiphenylsilyl)oxy)-3-((triethylsilyl)oxy)pentan-1-ol (***ent*-7**). Following the same experimental procedure as described in the preparation of compound **7**, alcohol ***ent*-6** (8 g, 22.6 mmol) was converted to the corresponding TES ether. Purification by column chromatography (SiO_2, 60−120 mesh, 5% EtOAc in hexane as the eluent) provides a pure compound (9.9 g, 94%) as a colorless oil. R_f = 0.9 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = +15.0 (c 0.8, $CHCl_3$); ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of TES ether obtained from compound **6**.

Following the same experimental procedure as described in the preparation of compound **7**, the above compound (9.8 g, 20.9 mmol) was converted to the corresponding diol (10.5 g, quantitative) as a yellowish oil using OsO_4 and NMO, which was taken for the next step without further purification.

Following the same experimental procedure as that used for compound **7**, the above diol (20.9 mmol) was treated with $NaHCO_3$ (3.5 g, 41.8 mmol) and $NaIO_4$ (8.9 g, 41.8 mmol) to get the corresponding aldehyde (purification by flash column chromatography, SiO_2, 60−120 mesh, 25% EtOAc in hexane as the eluent) as a light yellowish oil, which was taken for the next step without further purification.

The above aldehyde (20.9 mmol) was reduced to alcohol ***ent*-7** using $NaBH_4$ (1.6 g, 41.8 mmol) in anhydrous MeOH following the same experimental procedure as compound **7**. Purification by flash column chromatography (SiO_2, 60−120 mesh, 8% EtOAc in hexane as the eluent) provided a pure compound (7.6 g, 77% over three steps) as a colorless liquid. R_f = 0.35 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = +7.26 (c 1.1, $CHCl_3$); ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of compound **7**.

(R)-5-((5-((Tert-butyldiphenylsilyl)oxy)-3-((triethylsilyl)oxy)-pentyl)sulfonyl)-1-phenyl-1H-tetrazole (***ent*-8**). Following the same experimental procedure as described in the preparation of compound **8**, compound ***ent*-7** (7.3 g, 15.5 mmol) was converted to corresponding sulfide (8.4 g, 86%, purification by column chromatography, SiO_2, 230−400 mesh, 5% EtOAc in hexane as the eluent) as a light yellowish oil. R_f = 0.45 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = +15.98 (c 0.5, $CHCl_3$); the ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of sulfide compound obtained from **7**.

The above sulfide (8.3 g, 13.1 mmol) was oxidized to sulfone ***ent*-8** (7.37 g, 84%) following the same experimental procedure as compound. Purification by flash column chromatography (SiO_2, 60−120 mesh, 5% EtOAc in hexane as the eluent) provided a pure compound as a colorless liquid. R_f = 0.42 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = +8.07 (c 1.98, $CHCl_3$); the ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of compound **8.**

(S)-4-(Benzyloxy)-3-((triethylsilyl)oxy)butanal (***ent*-10**). Following the same experimental procedure as described in the preparation of compound **7**, compound ***ent*-9** (4.0 g, 20.8 mmol) was converted to the corresponding TES ether. Purification by flash column chromatography (SiO_2, 60−120 mesh, 5% EtOAc in hexane as the eluent) provided a pure compound (5.9 g, 93%) as a colorless liquid. R_f = 0.8 (10% EtOAc/hexane); $[\alpha]_D^{25}$ = + 6.0 (c 0.6, $CHCl_3$); the ^1H NMR, ^{13}C NMR, IR, and HRMS data are exactly the same as those of the TES ether compound obtained from **9**.

Following the same experimental procedure as described in the preparation of compound **7**, the above compound (5.8 g, 18.9 mmol) was converted to the corresponding diol as a light yellowish oil using OsO_4 (5% solution in t-BuOH, 0.5 mL), and NMO (4.4 g, 37.8

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mmol), which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **7**, the above diol (18.9 mmol) was converted to the aldehyde ***ent*-10** using $NaHCO_3$ (3.2 g, 37.8 mmol) and $NaIO_4$ (8 g, 37.8 mmol). Purification by flash column chromatography (SiO_2, 60−120 mesh, 20% EtOAc in hexane as the eluent) provided pure aldehyde (3.8 g, 75%) as a colorless liquid, which was taken for the next step without further characterization.

*(5S,10S,E)-5-((Benzyloxy)methyl)-3,3-diethyl-15,15-dimethyl-14,14-diphenyl-10-((triethyl Silyl)oxy)-4,13-dioxa-3,14-disilahexadec-7-ene (**ent-11**).* Following the same experimental procedure as described in the preparation of compound **11**, aldehyde ***ent*-10** (3 g, 9.7 mmol) and sulfone ***ent*-8** (7.1 g, 10.7 mmol) were converted to the corresponding coupled product. Purification by flash column chromatography (SiO_2, 60−120 mesh, 2% EtOAc in hexane as the eluent) provided a pure compound (5.2 g, 72%) as a colorless liquid. R_f = 0.45 (5% EtOAc/hexane); $[\alpha]_D^{25}$ = +6.7 (*c* 1.2, $CHCl_3$); the ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of compound **11**.

*(2S,7S,E)-1-(Benzyloxy)-9-((tert-butyldiphenylsilyl)oxy)non-4-ene-2,7-diol (**ent-5**).* Following the same experimental procedure as described in the preparation of compound **5**, the TES ether ***ent*-11** (5.0 g, 6.7 mmol)was converted to the corresponding diol by using CSA (3.1 g, 2.784 mmol). Purification by flash column chromatography (SiO_2, 60−120 mesh, 15−20% EtOAc in hexane as the eluent) provided a pure compound (3.12 g, 90%) as a colorless liquid. R_f = 0.4 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = + 14.0 (*c* 0.6, $CHCl_3$); the ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of compound **5**.

*(2-((2S,3aS,5R,6aS)-5-((Benzyloxy)methyl)hexahydrofuro[3,2-b]-furan-2-yl)ethoxy)(tert-butyl)diphenylsilane (**ent-4**).* Following the same experimental procedure as described in the preparation of compound **4**, the above diol (3.0 g, 5.8 mmol) was converted to the corresponding dimesylated compound. Purification by flash column chromatography (SiO_2, 60−120 mesh, 30−40% EtOAc in hexane as the eluent) provided a pure compound (3.3 g, 84%) as a colorless liquid. R_f = 0.45 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = +14.7 (*c* 0.3, $CHCl_3$); the ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of the mesylated compound obtained from compound **5**.

To a stirred solution of the above compound (3.2 g, 4.7 mmol) in THF (20 mL), ^{t}BuOH (20 mL) and H_2O (4 mL) at 0 °C, OsO_4 (0.2 M solution in ^{t}BuOH, 0.3 mL), and NMO (1.01 g, 9.4 mmol) were added, and the reaction mixture was stirred for 12 h at room temperature. K_2CO_3 (1.95 g, 14.1 mmol) was then added and the reaction mixture was stirred for another 6 h. The reaction mixture was then cooled to 0 °C and quenched with saturated solution of $NaHSO_3$ (5 mL). The resultant mixture was extracted with EtOAc (3 × 50 mL), washed with water and brine, and concentrated in vacuo, and purification by flash column chromatography (SiO_2, 230−400 mesh, 5−20% EtOAc in hexane as the eluent) was carried out to separate the two diastereomers with 57% overall yield (*dr* = 1.2:1). Isolated major isomer ***ent*-4** (0.754 g, 31%) was obtained as a colorless liquid. R_f = 0.8 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = −7.1 (*c* 0.4, $CHCl_3$); the ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly same as those of compound **4**.

Minor isomer ***ent*-12** (343 mg, 26%) was obtained as a colorless liquid with R_f = 0.75 (30% EtOAc/hexane). $[\alpha]_D^{25}$ = +5.5 (*c* 0.7, $CHCl_3$); the ^1H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of compound **12**.

Improved Procedure for Dihydroxylation Followed by Cycloetherification. To a stirred solution of ^{t}BuOH/H_2O (1:1, 3 mL) at room temperature, AD-mix-α (42 mg, 1.4 g/mmol), OsO_4 (0.2 M solution in ^{t}BuOH, 0.07 mL), and methanesulfonamide (6 mg, 0.06 mmol) were added. The solution was further stirred well for 15 min and then the above dimesylated compound (20 mg, 0.03 mmol) in ^{t}BuOH (1 mL) was cannulated and stirred for 12 h. The mixture was quenched with a saturated solution of Na_2SO_3 and the resultant mixture was stirred further for 1 h. The aqueous layer was extracted with EtOAc (4 × 5 mL), washed with water and brine, dried over Na_2SO_4, and finally concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 230−400 mesh, 10% EtOAc in hexane as the eluent) to separate the two diastereomers with 60% total yield (*dr* = 1.6:1). Isolated major compound ***ent*-4** (6 mg, 37%) and minor compound ***ent*-12** (4 mg, 23%) were obtained as a colorless oil.

*Tert-butyl(2-((2S,3aS,5R,6aS)-5-(hept-1-en-1-yl)hexahydrofuro-[3,2-b]furan-2-yl)ethoxy) Diphenylsilane (**18**).* Following the same experimental procedure as described in the preparation of compound **2**, compound ***ent*-4** (400 mg, 0.8 mmol) was treated with Li-naphthalide to get the corresponding benzyl-deprotected alcohol (280 mg, 82%, purification by column chromatography, SiO_2, 100−200 mesh, 40% EtOAc in hexane as the eluent) as a colorless oil. R_f = 0.15 (40% EtOAc/hexane); $[\alpha]_D^{25}$ = −12.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.71−7.64 (m, 4H), 7.44−7.35 (m, 6H), 4.76−4.58 (m, 2H), 4.19 (dddd, *J* = 14.9, 8.3, 6.0, 3.9 Hz, 2H), 3.80−3.72 (m, 3H), 3.53−3.42 (m, 1H), 2.20 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.03 (dd, *J* = 13.6, 5.5 Hz, 1H), 1.96−1.85 (m, 2H), 1.84−1.72 (m, 2H), 1.05 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 135.6, 133.9, 129.7, 127.7, 84.4, 83.5, 80.4, 64.3, 61.2, 41.4, 38.5, 36.3, 26.9, 19.3 ppm; IR (neat) ν_{max}: 3416, 2933, 2857, 1428, 1111, 1041, 702 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{34}NaO_4Si$, $[M + Na]^+$ 449.2124; found, 449.2126.

Following the same experimental procedure as described in the preparation of compound **14**, the above alcohol (250 mg, 0.6 mmol) was oxidized using DMP (500 mg, 1.1 mmol) and $NaHCO_3$ (0.1 g, 1.1 mmol) to get the corresponding aldehyde (purification by flash column chromatography, SiO_2, 60−120 mesh, 40% EtOAc in hexane as the eluent) as a colorless oil, which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **11**, the above aldehyde (0.6 mmol) and sulfone **17** (520 mg, 1.8 mmol) were converted to coupled product **18** along with its inseparable minor *Z*-isomer. Purification by flash column chromatography (SiO_2, 60−120 mesh, 2% EtOAc in hexane as the eluent) provided an inseparable mixture of *E*/*Z* (2.5:1) isomers (190 mg, 65%) as a colorless liquid. R_f = 0.7 (20% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (ddd, *J* = 6.2, 3.3, 1.7 Hz, 4H), 7.39 (dtd, *J* = 7.4, 5.9, 5.2, 3.6 Hz, 6H), 5.75−5.50 (m, 1H), 5.44−5.23 (m, 1H), 4.83−4.57 (m, 2H), 4.50−4.35 (m, 1H), 4.35−4.09 (m, 1H), 3.83−3.69 (m, 2H), 2.33−2.15 (m, 2H), 2.07−1.99 (m, 2H), 1.77 (dt, *J* = 13.4, 6.6 Hz, 2H), 1.67−1.63 (m, 1H), 1.41−1.28 (m, 7H), 1.05 (s, 9H), 0.87 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 135.7, 134.2, 134.0, 134.0, 129.8, 129.7, 127.7, 83.9, 83.6, 81.0, 61.3, 42.0, 41.6, 38.6, 32.3, 31.5, 29.8, 28.8, 27.0, 22.6, 19.3, 14.1 ppm; IR (neat) ν_{max}: 2926, 2853, 1497, 1409, 1290, 1072, 762 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{44}NaO_3Si$, $[M + Na]^+$ 515.2957; found, 515.2954.

*5-((2-((2R,3aS,5R,6aS)-5-((E)-Hept-1-en-1-yl)hexahydrofuro[3,2-b]furan-2-yl)ethyl)sulfonyl)-1-Phenyl-1H-tetrazole (**3**).* Following the same experimental procedure as described in the preparation of compound **14**, compound **18** mixed with its corresponding *Z*-isomer (180 mg, 0.37 mmol) was treated with TBAF (0.7 mL, 1 M in THF) to get the corresponding silyl deprotected alcohols (70 mg, 75%). Purification by column chromatography (SiO_2, 100−200 mesh, 30% EtOAc in hexane as the eluent) afforded an inseparable *E*/*Z*-mixture as a colorless oil. R_f = 0.25 (30% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$): δ 5.80−5.52 (m, 1H), 5.45−5.22 (m, 1H), 4.73 (tt, *J* = 8.4, 4.5 Hz, 2H), 4.56−4.38 (m, 1H), 4.36−4.11 (m, 1H), 3.87−3.69 (m, 2H), 2.30−2.16 (m, 2H), 2.02 (tdd, *J* = 8.1, 5.5, 1.5 Hz, 2H), 1.92−1.78 (m, 2H), 1.76−1.65 (m, 2H), 1.44−1.27 (m, 6H), 0.91−0.85 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 134.4, 133.7, 129.5, 119.6, 84.2, 83.3, 81.1, 80.0, 75.6, 61.4, 42.0, 41.8, 41.5, 37.4, 37.4, 32.2, 31.4, 29.4, 28.7, 27.8, 22.6, 14.1 ppm; IR (neat) ν_{max}: 3421, 2927, 2825, 1457, 1079 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{15}H_{26}NaO_3$, $[M + Na]^+$ 277.1780; found, 277.1782.

Following the same experimental procedure as described in the preparation of compound **8**, the above mixture of alcohols (65 mg, 0.26 mmol) was converted to the corresponding sulfides (87 mg, 83%). Purification by column chromatography (SiO_2, 60−120 mesh,

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20% EtOAc in hexane as the eluent) resulted a mixture of compounds (*E*/*Z*) as a light yellowish oil. R_f = 0.6 (30% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (tt, *J* = 4.7, 2.1 Hz, 5H), 5.80−5.49 (m, 1H), 5.42−5.27 (m, 1H), 4.72 (tt, *J* = 8.8, 4.4 Hz, 2H), 4.53−4.35 (m, 1H), 4.29−4.10 (m, 1H), 3.54−3.40 (m, 2H), 2.25−1.99 (m, 6H), 1.75−1.67 (m, 1H), 1.41−1.28 (m, 7H), 0.91−0.84 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 154.3, 134.3, 130.2, 129.9, 129.5, 123.9, 83.6, 80.9, 78.5, 78.4, 41.8, 41.0, 35.1, 32.2, 31.5, 30.1, 29.4, 28.8, 22.6, 14.1 ppm; IR (neat) ν_{max}: 2957, 2857, 1732, 1498, 1343, 1153, 1074, 764 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{22}H_{31}N_4O_2S$, $[M + H]^+$ 415.2168; found, 415.2165.

To EtOH (5 mL) solution of the above sulfides (70 mg, 0.17 mmol), H_2O_2 (0.1 mL) and ammonium molybdate hexahydrate (42 mg, 0.034 mmol) were added at 0 °C. After 12 h, EtOH was evaporated and the mixture was extracted with EtOAc (3 × 15 mL), washed with saturated solution of $Na_2S_2O_3$, brine, dried over Na_2SO_4, and concentrated. The crude material was purified by column chromatography (SiO_2, 230−400 mesh, 5% EtOAc in hexane as the eluent) to provide two geometric isomers (55 mg, 72%). Major isomer **3** (39 mg, 51%) was isolated as a colorless oil. R_f = 0.45 (20% EtOAc/hexane); $[\alpha]_D^{25}$ = −27.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 7.8, 2.1 Hz, 2H), 7.65−7.56 (m, 3H), 5.80−5.67 (m, 1H), 5.36 (ddt, *J* = 15.3, 7.4, 1.5 Hz, 1H), 4.71 (dt, *J* = 12.4, 4.3 Hz, 2H), 4.40 (ddd, *J* = 10.2, 7.4, 5.2 Hz, 1H), 4.18 (td, *J* = 8.8, 3.9 Hz, 1H), 3.94 (ddd, *J* = 14.7, 10.5, 5.2 Hz, 1H), 3.80 (ddd, *J* = 14.8, 10.4, 5.3 Hz, 1H), 2.29−2.10 (m, 3H), 2.10−1.95 (m, 3H), 1.69 (dddd, *J* = 13.4, 9.7, 8.9, 4.8 Hz, 2H), 1.43−1.31 (m, 3H), 1.27 (dd, *J* = 5.0, 1.7 Hz, 3H), 0.90−0.82 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.6, 134.5, 133.1, 131.6, 129.8, 129.4, 125.2, 84.3, 83.5, 81.0, 77.3, 53.6, 41.6, 41.0, 32.2, 31.5, 28.8, 28.2, 22.6, 14.1 ppm; IR (neat) ν_{max}: 2932, 2860, 1740, 1500, 1327, 1162, 1088 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{30}N_4NaO_4S$, $[M + Na]^+$ 469.1885; found, 469.1887.

Minor *Z* isomer of compound **3** (16 mg, 21%) as a colorless oil. R_f = 0.42 (20% EtOAc/hexane); $[\alpha]_D^{25}$ = −41.3 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76−7.65 (m, 2H), 7.61 (td, *J* = 4.5, 2.3 Hz, 3H), 5.62−5.47 (m, 1H), 5.35−5.26 (m, 1H), 4.74 (ddt, *J* = 13.9, 8.7, 4.7 Hz, 3H), 4.29−4.13 (m, 1H), 3.95 (ddd, *J* = 14.7, 10.7, 5.2 Hz, 1H), 3.82 (ddd, *J* = 15.0, 10.5, 5.3 Hz, 1H), 2.30−2.21 (m, 2H), 2.14−2.05 (m, 3H), 1.75−1.63 (m, 2H), 1.34−1.27 (m, 7H), 0.90 (d, *J* = 5.5 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.5, 133.8, 133.1, 131.6, 129.8, 129.3, 125.2, 84.3, 83.5, 75.5, 53.6, 41.8, 41.0, 31.5, 29.8, 29.4, 28.2, 27.8, 22.6, 14.1 ppm; IR (neat) ν_{max}: 2927, 2855, 1731, 1492, 1343, 1129, 1088 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{30}N_4NaO_4S$, $[M + Na]^+$ 469.1885; found, 469.1887.

*3-((2S,3aR,5S,6aR)-5-((2S,3S)-2-((Tert-butyldimethylsilyl)oxy)-3-methylhex-5-en-1-yl)hexa Hydrofuro[3,2-b]furan-2-yl)-2-methylacrylaldehyde (**19**).* Following the same experimental procedure as described in the preparation of compound **14**, alcohol **2** mixed with its inseparable minor Z-isomer (15 mg, 0.04 mmol) was oxidized using DMP (33 mg, 0.08 mmol) and $NaHCO_3$ (7 mg, 0.08 mmol) to get aldehyde **19** mixed with its minor counterpart (purification by column flash chromatography, SiO_2, 60−120 mesh, 20% EtOAc in hexane as the eluent) as a colorless oil, which was taken for the next step without further characterization.

*(2S,3S)-1-((2R,3aR,5S,6aR)-5-((1E,3E)-5-((2S,3aS,5R,6aS)-5-((E)-Hept-1-en-1-yl)hexahydro furo[3,2-b]furan-2-yl)-2-methylpenta-1,3-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)-3-methylhex-5-en-2-ol (**1a**).* Following the same experimental procedure as described in the preparation of compound **11**, aldehyde **2** mixed with its minor *Z*-isomer (0.04 mmol) and sulfone **3** (21 mg, 0.05 mmol) were converted to the corresponding Julia−Kocienski olefination products. Purification by flash column chromatography (SiO_2, 60−120 mesh, 10% EtOAc in hexane as the eluent) provided an inseparable mixture of diastereomers (14 mg, 75%) as a colorless liquid, which was generated from the regioisomeric mixture of reacting aldehydes. R_f = 0.6 (20% EtOAc/hexane); R_f = 0.6 (20% EtOAc/hexane); δ ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (d, *J* = 15.7 Hz, 1H), 5.79−5.48 (m, 3H), 5.35 (dd, *J* = 22.9, 7.7 Hz, 2H), 5.07−4.93 (m, 2H), 4.81 (dd, *J* = 9.5, 5.2 Hz, 1H), 4.75−4.61 (m, 4H), 4.41 (d, *J* = 14.4 Hz, 1H), 4.23−4.08 (m, 2H), 3.89−3.79 (m, 1H), 2.36 (tt, *J* = 14.8, 7.3 Hz, 3H), 2.26−2.08 (m, 5H), 2.01 (q, *J* = 7.2, 6.8 Hz, 2H), 1.79 (s, 3H), 1.66 (td, *J* = 10.0, 3.8 Hz, 5H), 1.49 (d, *J* = 3.8 Hz, 2H), 1.40−1.29 (m, 4H), 1.26 (d, *J* = 4.0 Hz, 2H), 0.90 (d, *J* = 2.8 Hz, 12H), 0.82 (s, 3H), 0.09 (d, *J* = 11.3 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.4, 136.6, 134.3, 133.5, 130.4, 129.7, 125.3, 115.4, 84.1, 83.9, 83.7, 81.0, 79.8, 77.3, 76.5, 75.5, 73.0, 42.2, 41.9, 40.7, 39.3, 39.0, 35.6, 32.3, 31.5, 29.4, 28.8, 27.8, 26.1, 22.6, 18.3, 14.9, 14.1, 13.1, −4.1, −4.3 ppm; IR (neat) ν_{max}: 2961, 2928, 2857, 1459, 1252, 1161, 1093 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{38}H_{64}O_5SiNa$, $[M + Na]^+$651.4421; found, 651.4422.

Following the same experimental procedure as described in the preparation of compound **14**, the above coupled compound (12 mg, 0.02 mmol) was treated with TBAF (1 M) (0.2 mL) to get corresponding silyl deprotected alcohol. Purification by column chromatography, SiO_2, 100−200 mesh, 5% EtOAc in hexane as the eluent, afforded a pure major compound **1a** (8 mg, 80%) as a colorless oil, which was separated from its minor isomer. R_f = 0.35 (30% EtOAc/hexane); $[\alpha]_D^{20}$ = −26.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, benzene-d_6): δ 6.21 (d, *J* = 15.6 Hz, 1H), 5.92 (ddt, *J* = 17.1, 10.0, 7.3 Hz, 1H), 5.78 (dt, *J* = 15.1, 7.2 Hz, 1H), 5.70 (dt, *J* = 14.3, 6.8 Hz, 1H), 5.54−5.49 (m, 2H), 5.21−5.15 (m, 1H), 5.14−5.09 (m, 1H), 4.95−4.86 (m, 1H), 4.59 (dd, *J* = 10.7, 5.6 Hz, 1H), 4.56 (t, *J* = 4.3 Hz, 1H), 4.53 (t, *J* = 4.5 Hz, 1H), 4.43 (t, *J* = 4.5 Hz, 1H), 4.34−4.30 (m, 1H), 4.18 (dq, *J* = 11.1, 5.7 Hz, 1H), 4.15−4.07 (m, 1H), 3.83 (d, *J* = 10.4 Hz, 1H), 2.54 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.41−2.35 (m, 1H), 2.27−2.22 (m, 1H), 2.21 (dd, *J* = 13.0, 5.1 Hz, 1H), 2.12 (dd, *J* = 13.4, 5.3 Hz, 1H), 2.09−2.06 (m, 1H), 2.05−2.02 (m, 1H), 1.99 (p, *J* = 7.1 Hz, 3H), 1.74 (d, *J* = 1.2 Hz, 3H), 1.61 (s, 1H), 1.57−1.52 (m, 1H), 1.44 (d, *J* = 4.2 Hz, 1H), 1.41−1.39 (m, 2H), 1.33 (d, *J* = 7.6 Hz, 3H), 1.27 (d, *J* = 7.4 Hz, 2H), 1.23 (dd, *J* = 9.7, 3.8 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, C_6D6): δ 138.3, 136.7, 135.9, 132.5, 131.4, 131.1, 126.0, 115.9, 84.6, 84.1, 83.9, 83.0, 81.5, 80.9, 80.0, 76.6, 74.4, 42.5, 42.4, 42.2, 41.2, 40.1, 39.4, 39.3, 38.1, 32.5, 31.6, 29.2, 28.0, 22.9, 14.2, 14.1, 13.1 ppm; IR (neat) ν_{max}: 3445, 2925, 2854, 1456, 1372, 970 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{32}H_{50}O_5Na$, $[M + Na]^+$ 537.3556; found, 537.3555.

*Tert-butyl(2-((2R,3aR,5S,6aR)-5-(hept-1-en-1-yl)hexahydrofuro-[3,2-b]furan-2-yl)ethoxy) Diphenylsilane (**ent-18**).* Following the same experimental procedure as described in the preparation of compound **2**, compound **4** (280 g, 0.54 mmol) was reacted with lithium naphthalide. Purification by flash column chromatography (SiO_2, 100−200 mesh, 40% EtOAc in hexane as the eluent) provided the corresponding benzyl-deprotected compound (184 mg, 80%). R_f = 0.15 (40% EtOAc/hexane); $[\alpha]_D^{25}$ = +13.3 (*c* 0.9, $CHCl_3$); the ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of alcohol obtain from compound ***ent*-4**.

Following the same experimental procedure as described in the preparation of compound **14**, the above alcohol (180 mg, 0.4 mmol) was oxidized using DMP (340 mg, 0.8 mmol) and $NaHCO_3$ (67 mg, 0.8 mmol) to get corresponding aldehyde, and purification by column flash chromatography (SiO_2, 60−120 mesh, 40% EtOAc in hexane as the eluent) afforded a pure compound as a colorless oil, which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **11**, the above aldehyde (0.4 mmol) and sulfone **17** (360 mg, 1.2 mmol) were converted to the corresponding coupled products. Purification by flash column chromatography (SiO_2, 60−120 mesh, 2% EtOAc in hexane as the eluent) provided an inseparable mixture of *E*/*Z* (3:1) isomers (135 mg, 67%) as a colorless liquid. R_f = 0.7 (15% EtOAc/hexane); the ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of compound **18**.

*5-((2-((2S,3aR,5S,6aR)-5-((E)-But-1-en-1-yl)hexahydrofuro[3,2-b]furan-2-yl)ethyl)sulfonyl)-1-Phenyl-1H-tetrazole (**ent-3**).* Following the same experimental procedure as described in the preparation of compound **14**, compound ***ent*-18** (120 mg, 0.24 mmol) mixed with its minor *Z*-isomer was treated with TBAF (0.75 mL, 0.75 mmol) to get the corresponding inseparable mixture of alcohols. Purification by

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flash column chromatography (SiO_2, 100−200 mesh, 40% EtOAc in hexane as the eluent) provided the corresponding mixture of *E*/*Z* isomers (45 mg, 74%). R_f = 0.25 (30% EtOAc/hexane); the ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of alcohol obtained from compound **18**.

Following the same experimental procedure as described in the preparation of compound **8**, the above mixture of alcohols (42 mg, 0.12 mmol) was converted to the corresponding inseparable sulfides (37 mg, 77%, purification by column chromatography, SiO_2, 230−400 mesh, 5% EtOAc in hexane as the eluent) as a light yellowish oil. R_f = 0.6 (30% EtOAc/hexane); ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of the sulfide compound obtained from compound **18**.

Following the same experimental procedure as described in the preparation of compound **3**, the above mixture of sulfides (35 mg, 0.08 mmol) was converted to the corresponding sulfones. The crude material was purified by column chromatography (SiO_2, 230−400 mesh, 5% EtOAc in hexane as the eluent) provided two geometric isomers (24 mg, 69%). Major isomer ***ent*-3** (18 mg, 52%) was isolated as a colorless oil. R_f = 0.45 (20% EtOAc/hexane); $[\alpha]_D^{25}$ = +24.2 (*c* 0.5, $CHCl_3$); the ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of compound **3**.

The *Z* isomer of compound ***ent*-3** (6 mg, 17%) was isolated as a colorless oil. R_f = 0.42 (20% EtOAc/hexane); $[\alpha]_D^{25}$ = +38.6 (*c* 0.2, $CHCl_3$); the ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were exactly the same as those of the *Z* isomer of compound **3**.

*(2S,3S)-1-((2R,3aR,5S,6aR)-5-((1E,3E)-5-((2R,3aR,5S,6aR)-5-((E)-Hept-1-en-1-yl)hexa Hydrofuro[3,2-b]furan-2-yl)-2-methylpenta-1,3-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)-3-methylhex-5-en-2-ol (**1b**).* Following the same experimental procedure as described in the preparation of compound **11**, aldehyde **19** mixed with its minor *Z*-counterpart (12 mg, 0.03 mmol) and sulfone ***ent*-3** (17 mg, 0.036 mmol) were coupled to get the corresponding coupled products. Purification by flash column chromatography (SiO_2, 230−400 mesh, 20% EtOAc in hexane as the eluent) provided an inseparable mixture of diastereomers (13 mg, 71%) as a colorless liquid. R_f = 0.6 (20% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (d, *J* = 15.6 Hz, 1H), 5.84−5.58 (m, 3H), 5.35 (dd, *J* = 22.5, 7.1 Hz, 2H), 5.06−4.94 (m, 2H), 4.86−4.79 (m, 1H), 4.74 (dt, *J* = 16.3, 5.8 Hz, 4H), 4.47−4.38 (m, 1H), 4.12 (h, *J* = 6.1 Hz, 2H), 3.66 (t, *J* = 4.1 Hz, 1H), 2.34 (dq, *J* = 12.9, 7.2, 6.6 Hz, 3H), 2.17 (ddd, *J* = 18.4, 9.1, 4.9 Hz, 4H), 2.06−1.97 (m, 3H), 1.79 (d, *J* = 1.1 Hz, 3H), 1.68−1.61 (m, 3H), 1.52−1.44 (m 3H), 1.34−1.27 (m, 8H), 0.89 (d, *J* = 2.4 Hz, 9H), 0.87−0.79 (m, 7H), 0.11−0.03 (m, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.4, 138.2, 136.6, 134.3, 132.4, 129.7, 125.5, 115.4, 84.1, 83.9, 83.7, 83.6, 81.0, 79.8, 77.3, 76.3, 73.0, 42.2, 42.0, 40.8, 39.2, 39.0, 32.3, 31.5, 29.8, 29.5, 28.8, 26.0, 22.8, 22.6, 18.2, 14.4, 14.1, 13.1, −4.2, −4.2 ppm; IR (neat) ν_{max}: 2935, 2844, 1475, 1352, 1237, 1104, 956, 742 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{38}H_{64}O_5SiNa$, $[M + Na]^+$ 651.4421; found, 651.4423.

Following the same experimental procedure as described in the preparation of compound **14**, the mixture of the above coupled products (10 mg, 0.015 mmol) was treated with TBAF (40 μL, 1 M in THF) to get the corresponding silyl-deprotected alcohol. Purification by column chromatography (SiO_2, 100−200 mesh, 5% EtOAc in hexane as the eluent) afforded pure major compound **1b** (6 mg, 78%) as a colorless oil, which was separated from its minor isomer. R_f = 0.35 (30% EtOAc/hexane); $[\alpha]_D^{20}$ = −13.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ 6.21 (d, *J* = 15.6 Hz, 1H), 5.97−5.87 (m, 1H), 5.76 (dt, *J* = 15.1, 7.2 Hz, 1H), 5.70 (dt, *J* = 14.2, 6.8 Hz, 1H), 5.51 (dd, *J* = 15.4, 7.2 Hz, 2H), 5.17 (d, *J* = 17.0 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.91 (td, *J* = 9.1, 5.6 Hz, 1H), 4.60−4.57 (m, 1H), 4.57−4.54 (m, 1H), 4.54−4.51 (m, 1H), 4.43 (t, *J* = 4.6 Hz, 1H), 4.34−4.32 (m, 1H), 4.17 (dd, *J* = 10.4, 5.4 Hz, 1H), 4.16−4.09 (m, 1H), 3.83 (d, *J* = 9.7 Hz, 1H), 2.54 (dt, *J* = 13.0, 6.0 Hz, 1H), 2.37 (dt, *J* = 13.7, 6.9 Hz, 1H), 2.27−2.22 (m, 1H), 2.20 (dd, *J* = 13.3, 5.4 Hz, 1H), 2.13−2.10 (m, 1H), 2.09−2.07 (m, 1H), 2.07−2.04 (m, 1H), 2.02−1.97 (m, 3H), 1.74 (s, 3H), 1.62−1.60 (m, 1H), 1.55 (dd, *J* = 8.6, 4.7 Hz, 1H), 1.45−1.43 (m, 1H), 1.43−1.40 (d, *J* = 4.3 Hz, 2H), 1.36−1.34 (m, 3H), 1.27−1.23 (m, 5H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): δ 138.3, 136.7, 135.8, 132.5, 131.4, 131.1, 126.0, 115.9, 84.6, 84.1, 83.9, 83.0, 81.5, 80.9, 79.9, 76.6, 74.4, 42.5, 42.4, 42.2, 41.3, 40.2, 39.5, 39.3, 38.1, 32.5, 31.6, 29.2, 22.9, 14.2, 14.1, 13.1 ppm; IR (neat) ν_{max}: 3446, 2918, 2836, 1442, 1393, 1146, 1063, 923, 841 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{32}H_{50}O_5Na$, $[M + Na]^+$ 537.3556; found, 537.3557.

*(2R,3S)-1-((S)-4-Benzyl-2-thioxothiazolidin-3-yl)-4-((2S,3aS,5R,6aS)-5-((benzyloxy)methyl) hexahydrofuro[3,2-b]-furan-2-yl)-3-hydroxy-2-methylbutan-1-one (**20**).* Following the same experimental procedure as described in the preparation of compound **14**, the above compound (350 mg, 0.67 mmol) was treated with TBAF (1 mL, 1 mmol, 1 M in THF) to get the corresponding alcohol. Purification by flash column chromatography (SiO_2, 60−120 mesh, 40% EtOAc in hexane as the eluent) provided the corresponding silyl-deprotected compound (153 mg, 84%). R_f = 0.2 (50% EtOAc/hexane); $[\alpha]_D^{25}$ = −37.0 (*c* 0.2, $CHCl_3$); the ^{1}H NMR, ^{13}C NMR, IR, and HRMS data are exactly the same as those of alcohol obtained from compound **6**.

Following the same DMP oxidation conditions as described in the preparation of compound **14**, the above alcohol (150 mg, 0.54 mmol) was transformed into the corresponding aldehyde (146 mg, quantitative, purified by flash column chromatography using a short pad of 60−120 silica, 40% EtOAc in hexane as the eluent) as a yellowish liquid, which was taken for the next step without further characterization.

Following the same aldol conditions as described in the preparation of compound **14**, the above aldehyde (0.54 mmol) was converted to aldol product **20**. Purification by column chromatography (SiO_2, 230−400 mesh, 20% EtOAc in hexane as the eluent) provided a pure compound (195 mg, 67%) as a yellowish oil. R_f = 0.6 (40% EtOAc/hexane); $[\alpha]_D^{25}$ = +33.5 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.26 (m, 10H), 5.37 (ddd, *J* = 10.7, 7.0, 4.0 Hz, 1H), 4.75 (dq, *J* = 10.8, 3.8 Hz, 3H), 4.58 (d, *J* = 2.3 Hz, 2H), 4.30 (ddq, *J* = 16.0, 9.0, 3.0 Hz, 3H), 3.53 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.42 (dd, *J* = 10.3, 5.7 Hz, 1H), 3.36 (ddd, *J* = 11.5, 7.2, 1.0 Hz, 1H), 3.22 (dd, *J* = 13.2, 4.1 Hz, 1H), 3.13−3.04 (m, 1H), 2.87 (dd, *J* = 11.6, 0.8 Hz, 1H), 2.22 (dd, *J* = 13.4, 5.1 Hz, 1H), 2.11 (dd, *J* = 13.4, 5.9 Hz, 1H), 1.84 (dddd, *J* = 14.8, 9.4, 4.8, 1.8 Hz, 2H), 1.74−1.65 (m, 1H), 1.60−1.53 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 201.5, 177.9, 138.3, 136.5, 129.5, 129.0, 128.4, 127.7, 127.7, 127.3, 84.2, 83.5, 79.1, 77.3, 73.5, 72.6, 69.1, 69.0, 43.2, 41.2, 38.8, 37.4, 37.1, 31.8, 11.6 ppm; IR (neat) ν_{max}: 3405, 2943, 2861, 1722, 1682, 1459, 1376, 1237, 1104, 767 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{29}H_{35}NNaO_5S_2$, $[M + Na]^+$ 564.1854; found, 564.1856.

*(((2S,3S)-1-((2R,3aS,5R,6aS)-5-((Benzyloxy)methyl)-hexahydrofuro[3,2-b]furan-2-yl)-3-methylpent-4-en-2-yl)oxy)(Tert-butyl)dimethylsilane (**21**).* Following the same experimental procedure as described in the preparation of compound **15**, compound **20** (180 mg, 0.33 mmol) was converted to the corresponding TBS-ether. Purification by flash column chromatography (SiO_2, 60−120 mesh, 15% EtOAc in hexane as the eluent) provided a pure compound (190 mg, 88%). R_f = 0.8 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = +51.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.26 (m, 10H), 5.29 (dddd, *J* = 10.8, 7.1, 3.7, 2.0 Hz, 1H), 4.72 (t, *J* = 5.8 Hz, 3H), 4.56 (d, *J* = 1.3 Hz, 2H), 4.28 (dddd, *J* = 8.9, 7.1, 4.9, 2.4 Hz, 2H), 4.22−4.13 (m, 1H), 3.51 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.41 (dd, *J* = 10.3, 5.6 Hz, 1H), 3.34−3.24 (m, 2H), 3.06−2.96 (m, 1H), 2.86 (dd, *J* = 11.5, 2.0 Hz, 1H), 2.21 (dd, *J* = 13.3, 5.1 Hz, 1H), 2.14−2.04 (m, 1H), 1.92−1.78 (m, 2H), 1.75−1.66 (m, 1H), 1.58 (dd, *J* = 9.1, 4.0 Hz, 1H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H), 0.12 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 201.1, 176.8, 138.4, 136.8, 129.5, 129.0, 128.4, 127.7, 127.6, 127.3, 84.4, 83.4, 79.0, 75.7, 73.4, 72.6, 71.3, 69.4, 44.9, 41.8, 41.5, 37.4, 37.3, 31.9, 26.2, 18.3, 14.0, −4.0, −4.1 ppm; IR (neat) ν_{max}: 2968, 2860, 1718, 1684, 1435, 1285, 1121, 925 cm^{-1};HRMS (ESI) *m*/*z*: calcd for $C_{35}H_{49}NNaO_5S_2Si$, $[M + Na]^+$ 678.2719; found, 678.2718.

Following the same DIBAL oxidation conditions as described in the preparation of compound **15**, the above compound (170 mg, 0.26 mmol) was transformed into the corresponding aldehyde (purified by

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flash column chromatography using a short pad of 60−120 silica and 20% EtOAc in hexane as the eluent) as a liquid oil, which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **15**, the above aldehyde (0.26 mmol) was converted to alkene **21** (80 mg, 68%, purification by flash column chromatography, SiO_2, 60−120 mesh, 5% EtOAc in hexane as the eluent) as a colorless liquid. R_f = 0.7 (15% EtOAc/hexane); $[\alpha]_D^{25}$ = 12.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.27 (m, 5H), 5.93 (ddd, *J* = 17.1, 10.7, 6.3 Hz, 1H), 5.11−4.94 (m, 2H), 4.70 (p, *J* = 4.5 Hz, 2H), 4.58 (t, *J* = 2.7 Hz, 2H), 4.29 (dtd, *J* = 9.3, 5.8, 3.5 Hz, 1H), 4.15 (ddd, *J* = 10.1, 8.0, 5.0 Hz, 1H), 3.81 (dt, *J* = 8.3, 4.3 Hz, 1H), 3.52 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.42 (dd, *J* = 10.3, 5.6 Hz, 1H), 2.41−2.29 (m, 1H), 2.18 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.12−2.05 (m, 1H), 1.89−1.76 (m, 1H), 1.62−1.52 (m, 1H), 1.51−1.43 (m, 2H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.08 (d, *J* = 5.2 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 140.6, 138.3, 128.4, 127.7, 127.6, 114.3, 84.4, 83.4, 79.1, 75.9, 73.4, 73.2, 72.6, 43.2, 41.8, 39.3, 37.5, 26.1, 18.2, 14.5, −4.1, −4.4 ppm; IR (neat) ν_{max}: 2958, 2927, 1462, 1253, 1102, 1055, 775 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{42}NaO_4Si$, $[M + Na]^+$ 469.2750; found, 469.2751.

*(((2S,3S)-1-((2R,3aS,5R,6aS)-5-((Benzyloxy)methyl)-hexahydrofuro[3,2-b]furan-2-yl)-3-methylhex-5-en-2-yl)oxy) (Tert-butyl)dimethylsilane (**22**).* Following the same experimental procedure as described in the preparation of compound **16**, the above olefin (80 mg, 0.18 mmol) was reduced using BH_3-DMS (0.5 mL, 0.5 mmol) to the corresponding terminal alcohol (59 mg, 71%, purified by flash column chromatography using a short pad of 60−120 silica, 50% EtOAc in hexane as the eluent) as a colorless liquid. R_f = 0.2 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = +4.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.24 (m, 5H), 4.71 (h, *J* = 4.4, 3.6 Hz, 2H), 4.57 (t, *J* = 2.7 Hz, 2H), 4.28 (dddd, *J* = 14.9, 9.3, 5.4, 2.8 Hz, 1H), 4.20−4.07 (m, 1H), 3.89−3.72 (m, 2H), 3.69−3.59 (m, 1H), 3.51 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.46−3.37 (m, 1H), 2.18 (dt, *J* = 13.2, 5.6 Hz, 1H), 2.08−2.02 (m, 1H), 1.91−1.72 (m, 3H), 1.55 (dq, *J* = 14.1, 5.5, 4.7 Hz, 4H), 0.92−0.84 (m, 12H), 0.05 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.3, 128.4, 127.7, 127.6, 84.4, 83.4, 79.1, 76.3, 73.4, 72.5, 41.7, 37.5, 34.1, 32.0, 29.7, 26.0, 22.7, 18.1, 15.5, 14.2, −4.2, −4.6 ppm; IR (neat) ν_{max}: 3463, 2981, 2869, 1475, 1220, 1088, 932, 750 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{26}H_{44}O_5SiNa$, $[M + Na]^+$ 487.2856; found, 487.2853.

Following the same DMP oxidation conditions as described in the preparation of compound **14**, the above alcohol (58 mg, 0.13 mmol) was transformed into the corresponding aldehyde (55 mg, quantitative, purified by flash column chromatography using a short pad of 60−120 silica, 20% EtOAc in hexane as the eluent) as a yellowish liquid, which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **15**, the above aldehyde of **21** (55 mg, 0.12 mmol) was converted to the corresponding alkene **22** (38 mg, 69%, purification by flash column chromatography, SiO_2, 60−120 mesh, 10% EtOAc in hexane as the eluent) as a colorless oil. R_f = 0.8 (20% EtOAc/hexane); $[\alpha]_D^{25}$ = +11.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.26 (m, 5H), 5.85−5.69 (m, 1H), 5.07−4.93 (m, 2H), 4.71 (p, *J* = 4.4 Hz, 2H), 4.64−4.51 (m, 2H), 4.35−4.24 (m, 1H), 4.13 (dq, *J* = 12.6, 5.6 Hz, 1H), 3.79 (ddd, *J* = 7.5, 5.2, 3.0 Hz, 1H), 3.52 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.41 (dd, *J* = 10.3, 5.7 Hz, 1H), 2.40−2.27 (m, 1H), 2.18 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.11−2.03 (m, 1H), 1.82 (ddd, *J* = 14.2, 9.4, 5.2 Hz, 2H), 1.75−1.57 (m, 3H), 1.58−1.53 (m, 1H), 0.90 (s, 9H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.06 (d, *J* = 5.6 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.4, 128.4, 127.8, 127.7, 127.7, 115.4, 84.4, 83.3, 79.1, 76.2, 73.4, 73.0, 72.6, 41.8, 39.1, 38.9, 37.5, 36.0, 26.1, 18.2, 14.6, −4.2, −4.3 ppm; IR (neat) ν_{max}: 2927, 2869, 1451, 1385, 1253, 1096, 824, 758 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{27}H_{44}O_4SiNa$, $[M + Na]^+$ 483.2907; found, 483.2906.

*3-((2R,3aS,5R,6aS)-5-((2S,3S)-2-((Tert-butyldimethylsilyl)oxy)-3-methylhex-5-en-1-yl)hexa Hydrofuro[3,2-b]furan-2-yl)-2-methyl-prop-2-en-1-ol (**23**).* Following the same experimental procedure as described in the preparation of compound **2**, compound **22** (36 mg, 0.08 mmol) was reacted with lithium naphthalide. Purification by flash column chromatography (SiO_2, 60−120 mesh, 25% EtOAc in hexane as the eluent) provided the corresponding benzyl-deprotected compound (24 mg, 84%). R_f = 0.15 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = +29.6 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.77 (dddd, *J* = 19.3, 10.2, 7.5, 6.3 Hz, 1H), 5.05−4.92 (m, 2H), 4.71 (t, *J* = 3.4 Hz, 2H), 4.18 (ddt, *J* = 12.4, 5.1, 2.9 Hz, 1H), 3.85−3.79 (m, 1H), 3.78−3.71 (m, 1H), 3.68 (dt, *J* = 6.3, 3.2 Hz, 1H), 3.46 (dd, *J* = 11.8, 5.0 Hz, 1H), 2.43−2.28 (m, 2H), 2.16 (dd, *J* = 13.3, 5.0 Hz, 1H), 2.03 (d, *J* = 7.0 Hz, 1H), 1.93−1.79 (m, 2H), 1.74−1.61 (m, 3H), 0.90 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.07 (d, *J* = 4.3 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.4, 115.5, 84.4, 83.6, 80.5, 76.4, 73.0, 64.3, 41.9, 39.2, 38.8, 36.4, 35.8, 26.0, 18.2, 14.7, −4.2, −4.3 ppm; IR (neat) ν_{max}: 3512, 2927, 2869, 1435, 1319, 1154, 1031, 906 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{39}O_4Si$, $[M + H]^+$ 371.2618; found, 371.2615.

Following the same DMP oxidation conditions as described in the preparation of compound **14**, the above alcohol (22 mg, 0.06 mmol) was transformed into the corresponding aldehyde (purified by flash column chromatography using a short pad of 60−120 silica, 10% EtOAc in hexane as the eluent) as a yellowish liquid, which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **2**, the above aldehyde (0.06 mmol) was converted to the α, β-unsaturated ester using ethyl 2-(triphenylphosphoranylidene) propionate (65 mg, 0.18 mmol) in dry toluene. Purification by flash column chromatography (SiO_2, 60−120 mesh, 10% EtOAc in hexane as the eluent) provided a pure compound (18 mg, 73%, *E*/*Z* = 3.5:1) as a colorless liquid. R_f = 0.4 (20% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.63 (dq, *J* = 7.9, 1.5 Hz, 1H), 5.75 (dtd, *J* = 17.3, 7.6, 3.8 Hz, 1H), 5.07−4.94 (m, 2H), 4.87−4.70 (m, 3H), 4.19 (qd, *J* = 7.1, 6.6, 1.5 Hz, 3H), 3.83 (dd, *J* = 8.7, 3.4 Hz, 1H), 2.37 (dtd, *J* = 7.6, 4.2, 1.9 Hz, 1H), 2.31−2.24 (m, 1H), 2.19 (dd, *J* = 13.5, 5.0 Hz, 1H), 1.87 (s, 3H), 1.79−1.72 (m, 1H), 1.67 (ddd, *J* = 12.0, 6.0, 3.3 Hz, 3H), 1.51 (dd, *J* = 8.7, 4.0 Hz, 2H), 1.28 (s, 3H), 0.90 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.12−0.05 (m, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.7, 140.8, 138.4, 129.4, 115.5, 84.4, 83.6, 76.7, 76.5, 73.0, 60.8, 42.0, 41.3, 39.3, 38.9, 35.6, 26.1, 18.2, 14.9, 14.3, 13.0, −4.2, −4.2 ppm; IR (neat) ν_{max} 2960, 2852, 1698, 1459, 1360, 1245.1104, 1037 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{44}NaO_5Si$, $[M + Na]^+$ 475.2856; found, 475.2854.

Following the same experimental procedure as described in the preparation of compound **2**, the above α, β-unsaturated ester (18 mg, 0.04 mmol) was converted to the alcohol **23** using DIBAL-H (80 μL, 0.12 mmol, 1.6 M in hexane). Purification by flash column chromatography (SiO_2, 60−120 mesh, 30% EtOAc in hexane as the eluent) provided a pure compound (14 mg, 88%) as a colorless liquid. R_f = 0.3 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86−5.67 (m, 1H), 5.39 (dt, *J* = 8.3, 1.4 Hz, 1H), 5.05−4.93 (m, 2H), 4.83−4.66 (m, 3H), 4.25−4.11 (m, 1H), 4.01 (d, *J* = 1.4 Hz, 2H), 3.83 (dd, *J* = 8.8, 3.4 Hz, 1H), 2.42−2.29 (m, 1H), 2.25−2.11 (m, 2H), 2.10−1.99 (m, 1H), 1.72 (s, 3H), 1.66 (dq, *J* = 3.6, 2.4 Hz, 2H), 1.60−1.55 (m, 1H), 1.49 (td, *J* = 8.5, 3.7 Hz, 2H), 0.90 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.09 (d, *J* = 10.9 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 139.0, 138.4, 125.3, 115.4, 83.9, 76.1, 73.0, 68.1, 42.2, 42.0, 39.3, 38.9, 35.6, 29.8, 26.1, 22.8, 18.3, 14.9, 14.1, −4.2, −4.2 ppm; IR (neat) ν_{max}: 3479, 2968, 2852, 1451, 1376, 1237, 1088, 1047, 767 cm^{-1}; HRMS (ESI) *m*/*z*: calcd for $C_{23}H_{42}O_4SiNa$, $[M + Na]^+$ 433.2750; found, 433.2752.

*(2S,3S)-1-((3aS,6aS)-5-((1E,3E)-5-((2S,3aS,5R,6aS)-5-((E)-Hept-1-en-1-yl)hexahydrofuro [3,2-b]furan-2-yl)-2-methylpenta-1,3-dien-1-yl)hexahydrofuro[3,2-b]furan-2-yl)-3-methyl Hex-5-en-2-ol (**1c**).* Following the same DMP oxidation conditions as described in the preparation of compound **14**, the above alcohol **23** (12 mg, 0.03 mmol) was transformed into the corresponding aldehyde (purified by flash column chromatography using a short pad of 60−120 mesh silica gel, 20% EtOAc in hexane as the eluent) as a yellowish liquid, which was taken for the next step without further characterization.

Following the same experimental procedure as described in the preparation of compound **11**, the above aldehyde (0.03 mmol) and

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sulfone **3** (15 mg, 0.036 mmol) were coupled to get the corresponding product. Purification by flash column chromatography (SiO_2, 230−400 mesh, 20% EtOAc in hexane as the eluent) provided an inseparable mixture of diastereomers (13 mg, 72%) as a colorless liquid. R_f = 0.6 (20% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (d, J = 15.7 Hz, 1H), 5.84−5.57 (m, 3H), 5.44−5.27 (m, 2H), 5.07−4.94 (m, 2H), 4.88−4.77 (m, 1H), 4.76−4.65 (m, 4H), 4.42 (dt, J = 11.9, 6.4 Hz, 1H), 4.15 (ddd, J = 15.3, 11.4, 4.8 Hz, 2H), 3.90−3.78 (m, 1H), 2.43−2.28 (m, 3H), 2.24−2.12 (m, 4H), 2.01 (q, J = 7.0 Hz, 2H), 1.79 (d, J = 1.2 Hz, 3H), 1.75−1.59 (m, 6H), 1.49 (td, J = 8.1, 3.8 Hz, 2H), 1.38 (q, J = 6.2 Hz, 2H), 1.33−1.27 (m, 4H), 0.92−0.87 (m, 12H), 0.83 (d, J = 6.5 Hz, 3H), 0.09 (d, J = 11.2 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.4, 136.6, 136.3, 134.2, 130.4, 129.7, 125.4, 115.4, 84.1, 83.9, 83.7, 81.0, 79.8, 78.6, 77.3, 76.5, 73.0, 42.2, 42.0, 40.8, 39.3, 39.0, 35.7, 32.3, 31.5, 29.8, 28.8, 26.1, 26.0, 22.6, 18.3, 14.9, 14.1, 13.1, −4.1, −4.2 ppm; IR (neat) ν_{max}: 2943, 2869, 1475, 1369, 1237, 1121, 981, 725 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{38}H_{64}O_5SiNa$, $[M + Na]^+$ 651.4421; found, 651.4423.

Following the same experimental procedure as described in the preparation of compound **14**, the above coupled compound (10 mg, 0.02 mmol) was treated with TBAF (1 M) (40 μL) to get corresponding silyl deprotected alcohol. Purification by column chromatography, SiO_2, 100−200 mesh, 5% EtOAc in hexane as the eluent, afforded pure major compound **1c** (8 mg, 82%) as a colorless oil, which was separated from its minor isomer. R_f = 0.35 (30% EtOAc/hexane); $[\alpha]_D^{25}$ = +6.65 (c 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6): δ 6.22 (d, J = 15.5 Hz, 1H), 5.85−5.79 (m, 1H), 5.79−5.74 (m, 1H), 5.74−5.67 (m, 1H), 5.56 (d, J = 8.3 Hz, 1H), 5.54−5.49 (m, 1H), 5.08 (d, J = 17.2 Hz, 1H), 5.06 (d, J = 11.0 Hz, 1H), 5.00 (ddd, J = 10.1, 8.0, 5.3 Hz, 1H), 4.59 (dd, J = 10.6, 5.6 Hz, 1H), 4.56−4.51 (m, 3H), 4.42 (d, J = 4.6 Hz, 1H), 4.40 (d, J = 7.6 Hz, 1H), 4.18 (dq, J = 11.2, 5.8 Hz, 1H), 3.83 (d, J = 9.7 Hz, 1H), 2.38 (dt, J = 13.8, 6.7 Hz, 1H), 2.29 (dt, J = 13.9, 6.0 Hz, 1H), 2.22 (dd, J = 8.8, 6.0 Hz, 1H), 2.20−2.17 (m, 1H), 2.17−2.14 (m, 1H), 2.12 (dd, J = 13.3, 5.1 Hz, 1H), 2.09−2.06 (m, 1H), 1.99 (q, J = 7.4 Hz, 2H), 1.93 (dt, J = 14.8, 8.0 Hz, 1H), 1.74 (s, 3H), 1.70−1.67 (m, 1H), 1.57−1.51 (m, 2H), 1.48 (ddd, J = 10.1, 8.6, 5.0 Hz, 2H), 1.43−1.41 (m, 1H), 1.39−1.38 (m, 1H), 1.34 (d, J = 7.4 Hz, 2H), 1.28−1.22 (m, 4H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6): δ 137.9, 136.8, 135.7, 132.5, 131.6, 131.1, 125.8, 115.9, 84.1, 84.0, 83.9, 83.8, 80.9, 79.9, 78.3, 76.8, 71.2, 42.5, 42.4, 41.3, 41.1, 39.5, 39.1, 39.1, 38.2, 32.5, 31.6, 29.2, 22.9, 14.2, 14.0, 13.1 ppm; IR (neat) ν_{max}: 3459, 2924, 2855, 1457, 1436, 1375, 1155, 1078, 1031, 915 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{32}H_{50}O_5Na$, $[M + Na]^+$ 537.3556; found, 537.3555.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00686.

Copies of NMR (^{1}H and ^{13}C{^{1}H}), HRMS, and 2D NMR (COSY, NOESY, HSQC, HMBC, and TOCSY) of some representative compounds and comparison of the NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kumagai, K.; Minamida, M.; Akakabe, M.; Tsuda, M.; Konishi, Y.; Tominaga, A.; Tsuda, M.; Fukushi, E.; Kawabata, J. Amphirionin-2, a Novel Linear Polyketide with Potent Cytotoxic Activity from a Marine Dinoflagellate Amphidinium Species. *Bioorg. Med. Chem. Lett* **2015**, *25*, 635−638.

(2) (a) Paul, D.; Saha, S.; Goswami, R. K. Total Synthesis of Pestalotioprolide e and Structural Revision of Pestalotioprolide F. *Org. Lett.* **2018**, *20*, 4606−4609. (b) Saha, D.; Guchhait, S.; Goswami, R. K. Total Synthesis and Stereochemical Assignment of Penicitide A. *Org. Lett.* **2020**, *22*, 745−749. (c) Paul, D.; Kundu, A.; Saha, S.; Goswami, R. K. Total Synthesis : The Structural Confirmation of Natural Products. *ChemComm* **2021**, *57*, 3307−3322. (d) Mondal, J.; Sarkar, R.; Sen, P.; Goswami, R. K. Total Synthesis and Stereochemical Assignment of Sunshinamide and Its Anticancer Activity. *Org. Lett.* **2020**, *22*, 1188−1192.

(3) Kato, S.; Mizukami, D.; Sugai, T.; Tsuda, M.; Fuwa, H. Total Synthesis and Complete Configurational Assignment of Amphirionin-2. *Chem. Sci.* **2021**, *12*, 872−879.

(4) Zurwerra, D.; Gertsch, J.; Altmann, K.-H. Synthesis of (-)-Dactylolide and 13-Desmethylene-(-)-Dactylolide and Their Effects on Tubulin. *Org. Lett.* **2010**, *12*, 2302−2305.

(5) (a) Candy, M.; Audran, G.; Bienaymé, H.; Bressy, C.; Pons, J.-M. Total Synthesis of (+)-Crocacin C Using Hidden Symmetry. *J. Org. Chem.* **2010**, *75*, 1354−1359. (b) Das, S.; Kuilya, T. K.; Goswami, R. K. Asymmetric Total Synthesis of Bioactive Natural Lipid Mycalol. *J. Org. Chem.* **2015**, *80*, 6467−6489.

(6) Nakayama, A.; Sato, H.; Karanjit, S.; Hayashi, N.; Oda, M.; Namba, K. Asymmetric Total Syntheses and Structure Revisions of Eurotiumide A and Eurotiumide B, and Their Evaluation as Natural Fluorescent Probes. *Eur. J. Org Chem.* **2018**, *2018*, 4013−4017.

(7) Taylor, C. A.; Zhang, Y.-A.; Snyder, S. A. The Enantioselective Total Synthesis of Laurendecumallene B. *Chem. Sci.* **2020**, *11*, 3036−3041.

(8) (a) Julia, M.; Paris, J.-M. Syntheses a l'aide de Sulfones v(+)-Methode de Synthese Generale de Doubles Liaisons. *Tetrahedron Lett.* **1973**, *14*, 4833−4836. (b) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. A Stereoselective Synthesis of Trans-1,2-Disubstituted Alkenes Based on the Condensation of Aldehydes with Metallated 1-Phenyl-1H-Tetrazol-5-Yl Sulfones. *Synlett* **1998**, *1998*, 26−28. (c) Mandal, G. H.; Saha, D.; Goswami, R. K. Total Synthesis of Nafuredin B. *Org. Biomol. Chem.* **2020**, *18*, 2346−2359.

(9) (a) Marshall, J. A.; Sabatini, J. J. Synthesis of Cis- and Trans-2,5-Disubstituted Tetrahydrofurans by a Tandem Dihydroxylation-SN2 Cyclization Sequence. *Org. Lett.* **2005**, *7*, 4819−4822. (b) Srinivas, B.; Reddy, D. S.; Mallampudi, N. A.; Mohapatra, D. K. A General Diastereoselective Strategy for Both Cis- and Trans-2,6-Disubstituted Tetrahydropyrans: Formal Total Synthesis of (+)-Muconin. *Org. Lett.* **2018**, *20*, 6910−6914.

(10) (a) Gill, D. M.; Male, L.; Jones, A. M. A Structure-Reactivity Relationship of the Tandem Asymmetric Dihydroxylation on a Biologically Relevant Diene: Influence of Remote Stereocenters on Diastereofacial Selectivity. *Eur. J. Org Chem.* **2019**, *2019*, 7568−7577. (b) Hale, K. J.; Manaviazar, S.; Peak, S. A. Anomalous Enantioselectivity in the Sharpless Catalytic Asymmetric Dihydroxylation Reaction of 1,1-Disubstituted Allyl Alcohol Derivatives. *Tetrahedron Lett.* **1994**, *35*, 425−428.
(11) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. Asymmetric Aldol Additions: Use of Titanium Tetrachloride and (-)-Sparteine for the Soft Enolization of N-Acyl Oxazolidinones, Oxazolidinethiones, and Thiazolidinethiones. *J. Org. Chem.* **2001**, *66*, 894−902. (b) Saha, S.; Paul, D.; Goswami, R. K. Cyclodepsipeptide Alveolaride C: Total Synthesis and Structural Assignment. *Chem. Sci.* **2020**, *11*, 11259−11265. (c) Venkatesham, A.; Nagaiah, K. Stereoselective Total Synthesis of Stagonolide-C. *Tetrahedron: Asymmetry* **2012**, *23*, 1186−1197.
(12) (a) Trost, B. M.; Wrobleski, S. T.; Chisholm, J. D.; Harrington, P. E.; Jung, M. Total Synthesis of (+)-Amphidinolide A. Assembly of the Fragments. *J. Am. Chem. Soc.* **2005**, *127*, 13589−13597. (b) Sharma, G. V. M.; Venkateshwarlu, G.; Katukuri, S.; Ramakrishna, K. V. S.; Sarma, A. V. S. Design and Synthesis of Novel Oxetane B3-Amino Acids and α,β-Peptides. *Tetrahedron* **2015**, *71*, 2158−2167.
(13) (a) Karabiyikoglu, S.; Boon, B. A.; Merlic, C. A. Cycloaddition Reactions of Cobalt-Complexed Macrocyclic Alkynes: The Transannular Pauson-Khand Reaction. *J. Org. Chem.* **2017**, *82*, 7732−7744. (b) Ma, R.; White, M. C. C-H to C-N Cross-Coupling of Sulfonamides with Olefins. *J. Am. Chem. Soc.* **2018**, *140*, 3202−3205.
(14) Das, S.; Paul, D.; Goswami, R. K. Stereoselective Total Synthesis of Bioactive Marine Natural Product Biselyngbyolide B. *Org. Lett.* **2016**, *18*, 1908−1911.
(15) Grove, C. I.; Fettinger, J. C.; Shaw, J. T. Second-Generation Synthesis of (-)-Viriditoxin. *Synthesis* **2012**, *2012*, 362−371.
(16) Chen, W.; Xiong, F.; Liu, Q.; Xu, L.; Wua, Y.; Chen, F. Substrate stereocontrol in bromine-induced intermolecular cyclization: asymmetric synthesis of pitavastatin calcium. *Tetrahedron* **2015**, *71*, 4730−4737.
(17) Cichowicz, N. R.; Nagorny, P. Synthesis of Conjugated Polyenes via Sequential Condensation of Sulfonylphosphonates and Aldehydes. *Org. Lett.* **2012**, *14*, 1058−1061.

https://doi.org/10.1021/acs.joc.1c00686
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