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FULL PAPER

A Concise Synthesis of the Key Tetrahydrofuran Moieties of Caruifolin A and EBC-342

Rodney A. Fernandes,*[a] and Venkati Bethi[a]

Dedication ((optional))

Abstract: A common strategy for the concise synthesis of the key tetrahydrofuran moieties of caruifolin A and EBC-342 is presented. Asymmetric dihydroxylation and intramolecular S_N2-cyclization are key strategic reactions for the synthesis of the furan fragments.

Introduction

Caruifolin A (**1a**, Figure 1), a germacranolide was isolated from the aerial part of *Artemisia caruifolia* Buch.-Ham. ex Roxb. (Asteraceae) by Hattori and co-workers.[1] This herb is one of the botanical sources of the Chinese herbal drug "Qing Hao", that has been used for the treatment of infectious diseases.[2] Caruifolin A showed 22-46% HIV-1 protease inhibition at 100 μg/mL concentration.[1] The structure of caruifolin A (**1a**) features the 10-membered carbocyclic skeleton, which includes a tetrahydrofuran (THF) moiety with three asymmetric centers. A α-methyl-γ-butyrolactone is appended through the C7–C8 bond and adds three more asymmetric centers. The relative stereochemistry was established by NOESY and molecular modelling studies. Recently, a related THF containing casbane, EBC-342 (**1b**, Figure 1) has been isolated by Williams and co-workers[3] from the Australian rain forest plant *Croton insularis*. The structure was established through extensive NMR studies and the configurational assignment has been proposed based on measured CD spectra and comparison with the quantum chemical calculations-based spectrum. The THF moiety present in **1b** is diastereomeric to that in **1a**, but has a similar substitution pattern. Compound **1b** also features gem-dimethyl containing cyclopropane ring adding two chiral centres. The 14-membered macrocycle also contain a conjugated enone with α-hydroxy group. There are no reports on the synthetic studies of these molecules.[4] Thus, we took up the preparation of the key THF moieties **3a** and **3b** based on asymmetric dihydroxylation and intramolecular S_N2-cyclization for THF synthesis.

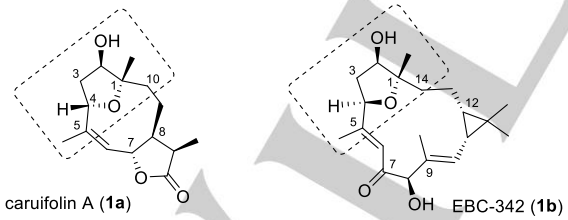
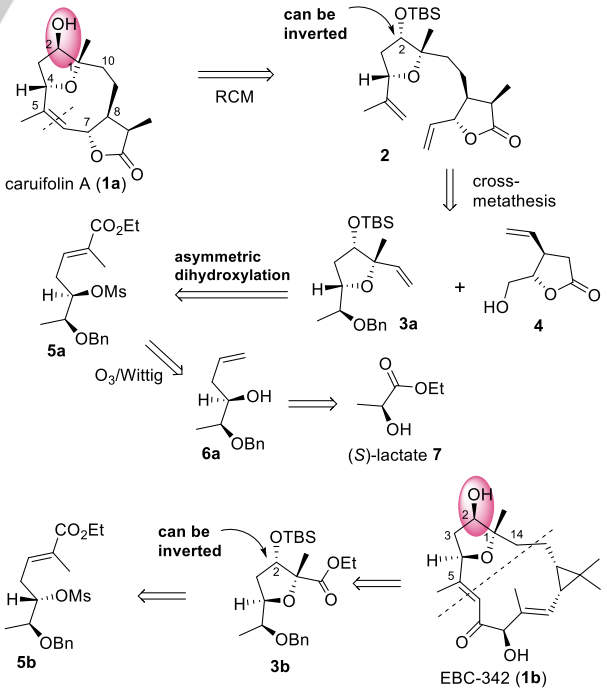


Figure 1. Caruifolin A (**1a**) with substituted tetrahydrofuran and α-methyl-γ-lactone units and related molecule EBC-342 (**1b**).

Results and Discussion

The envisaged retrosynthetic strategy for caruifolin A (**1a**) and EBC-342 (**1b**) is depicted in Scheme 1. A ring-closing metathesis[5] of **2** and C-2 inversion would lead to **1a**. The THF unit **3a** and the γ-lactone **4** can be combined through cross-metathesis[6] toward the synthesis of **2**. The THF **3a** was planned through asymmetric dihydroxylation[7] of **5a** with intramolecular S_N2 displacement of correctly placed mesyl group. Compound **5a** can be traced back to intermediate **6a** that can be obtained by diastereoselective allylation of the aldehyde from benzyl protected (*S*)-lactate **7**. The diastereomer **3b** would be an intermediate toward the synthesis of recently isolated EBC-342 (**1b**), also requiring the inversion of configuration at the C-2 hydroxy group. The former can be traced similarly to **5b** and then to the diastereomer of **6a** that will be formed during allylation. The relative configuration at C-1 and C-2 positions in the THF moieties



Scheme 1. Retrosynthetic analysis.

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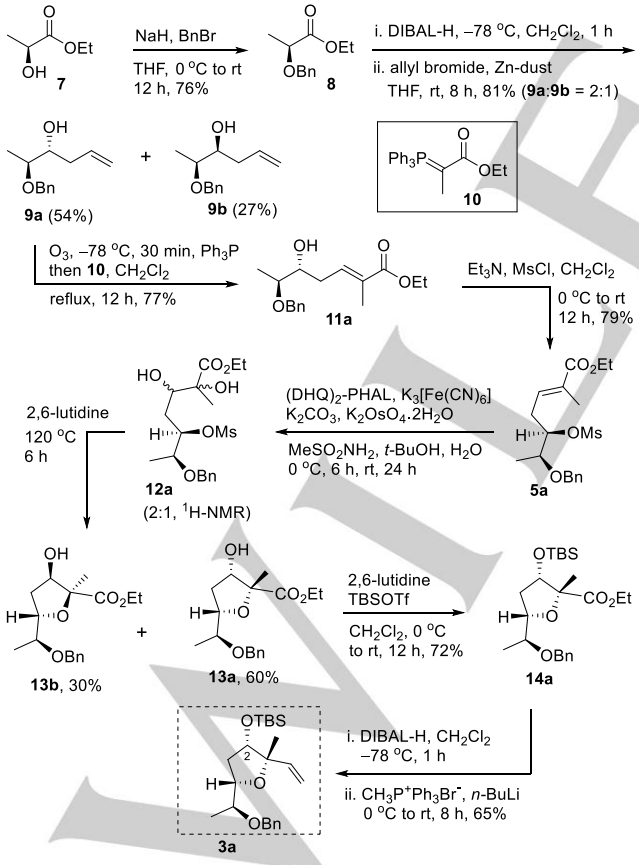
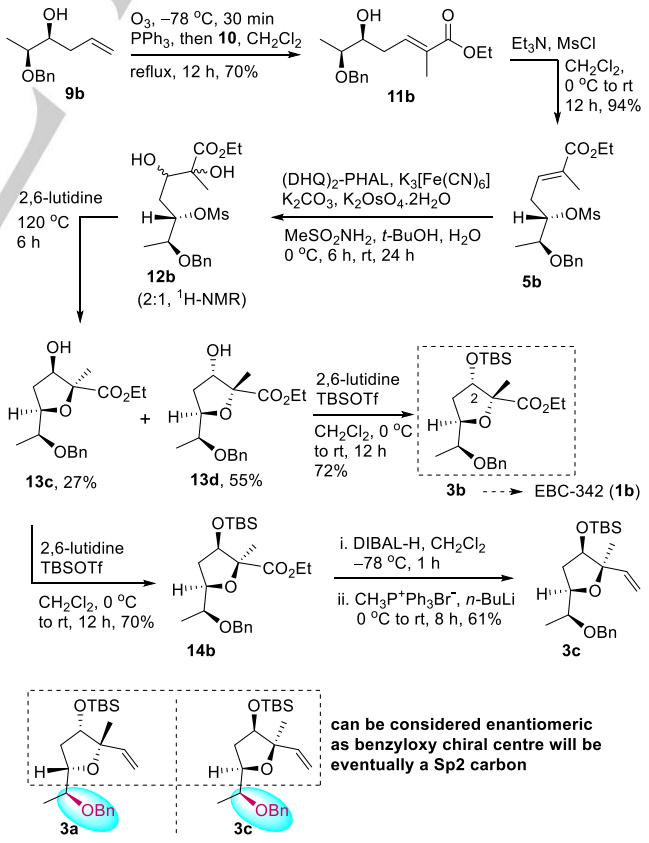
of both **1a** and **1b** are identical and have *anti*-placement of the oxygen atoms, while they differ at the C-4 position (and hence are diastereomeric). It also infers from this analysis and the retrosynthesis (Scheme 1) that these configurations can be directly set if a *cis*-olefin corresponding to **5a** or **5b** is used in asymmetric dihydroxylation. However, *cis*-olefins and that too trisubstituted and electron deficient are sluggish and known to give lower enantio- or diastereoselectivity in asymmetric dihydroxylation.[7b] Since the absolute stereochemistry of **1a** and **1b** is not established by synthesis and that the C-2 position can be easily inverted under Mitsunobu conditions,[8] we planned at this stage to execute the asymmetric dihydroxylation and S_N2-cyclization strategy as depicted in Scheme 1.

The synthesis of THF moiety **3a** commenced from ethyl (*S*)-lactate **7** (Scheme 2) that was first protected as benzyl ether **8** (76% yield). Further, the partial reduction of ester to aldehyde and subsequent zinc-mediated allylation[9] gave a separable mixture of homoallyl alcohols *anti*-**9a** (54%) and *syn*-**9b** (27%) in 2:1 ratio. The latter *syn*-compound is normally obtained as major product in other allylation reactions (9:1 to 97:3, *syn*/*anti*).[10] The *anti*-alcohol **9a** was subjected to ozonolysis followed by Wittig olefination of the aldehyde with stable ylide **10** to afford the (*E*)-α,β-unsaturated ester **11a** in 77% yield. The later on treatment with methanesulfonyl chloride furnished the mesylate **5a** in 79% yield. Subsequent asymmetric dihydroxylation using the $(DHQ)_2$-PHAL ligand provided the diastereomeric mixture of diols **12a** in 2:1 ratio (^{1}H NMR), which on further intramolecular cyclization through S_N2 displacement of mesylate gave a separable mixture of THF diastereomers **13a** (60%) and **13b** (30%). The stereochemical assignment is based on conversion to compound **3a** and NMR studies (see further below). Thus, major compound **13a** was protected as TBS ether **14a** (72%) and then DIBAL-H reduction of ester to aldehyde and one carbon Wittig olefination led to the THF-moiety **3a** in 65% yield over two steps. The C-2 hydroxy in caruifolin A (**1a**) has opposite stereochemistry with respect to that in compound **3a**. Inversion of this center at latter part of the synthesis could be envisaged.

Following a similar strategy, the minor diastereomer *syn*-**9b** was carried forward to the synthesis of an intermediate **3b** (for EBC-342) and also to the diastereomer of **3a**, i.e. **3c** (**3c** can be considered as enantiomer to **3a**, as the benzyloxy chirality will be eventually a double bond or Sp2 carbon and hence is inconsequential) (Scheme 3). Ozonolytic cleavage of **9b** to aldehyde and Wittig olefination led to the ester **11b** (70%). Conversion of free hydroxy to mesylate (**5b**, 94%), asymmetric dihydroxylation (to **12b**) and S_N2-cyclization led to two diastereomers **13c** (27%) and **13d** (55%) that were easily separated by column chromatography. The minor diastereomer **13c** on TBS protection to **14b** (70%) and further ester reduction/Wittig olefination provided compound **3c** (61%). The major diastereomer **13d** on TBS protection gave the intermediate **3b** (72%) representing the THF core of EBC-342 (**1b**), considering a possible C-2 hydroxy inversion later.[11] The minor diastereomer **13b** (Scheme 2) and the major diastereomer **3b** (Scheme 3) are available to be carried forward if need be while establishing the absolute stereochemistry for the natural product **1a**. The strategy is



Scheme 2. Synthesis of tetrahydrofuran moiety **3a**.



Scheme 3. Synthesis of tetrahydrofuran moieties **3b** and **3c**.

also flexible to shift the diastereoselectivity by changing ligand to $(DHQD)_2$-PHAL in asymmetric dihydroxylation in Schemes 2 and 3.

The stereochemical assignment for compounds **3a** and **3c** was considered by ^{1}H NMR study (Figure 2). The stereochemical relationship among H_a, H_b, H_c, Me and olefin C-H is ascertained by $J_{H\text{-}H}$ coupling constants, ^{1}H-^{1}H-COSY and NOE experiments on **3a** and **3c** as depicted in Figure 2. ^{1}H-^{1}H-COSY experiment shows the relationship between the adjacent protons in compound **3a** and **3c**.[12] Whereas, NOE experiment study accomplished the spacial relationship of assigned protons with others. For example, in compound **3a**, irradiation of H_a shows Me and H_b are in same plane and there is no relation with H_c. Whereas irradiation of H_b proton in **3c** shows H_a, H_b, H_c are in same plane and also with one of the olefin C-H (J = 17.5, 2.0 Hz). Similarly, the irradiation of H_c shows special relationship with H_b. Thus, the stereochemistry for compounds **3a** and **3c** is as depicted. This also establishes the stereochemistry in other isomers **13b** and **3b**, working backward.

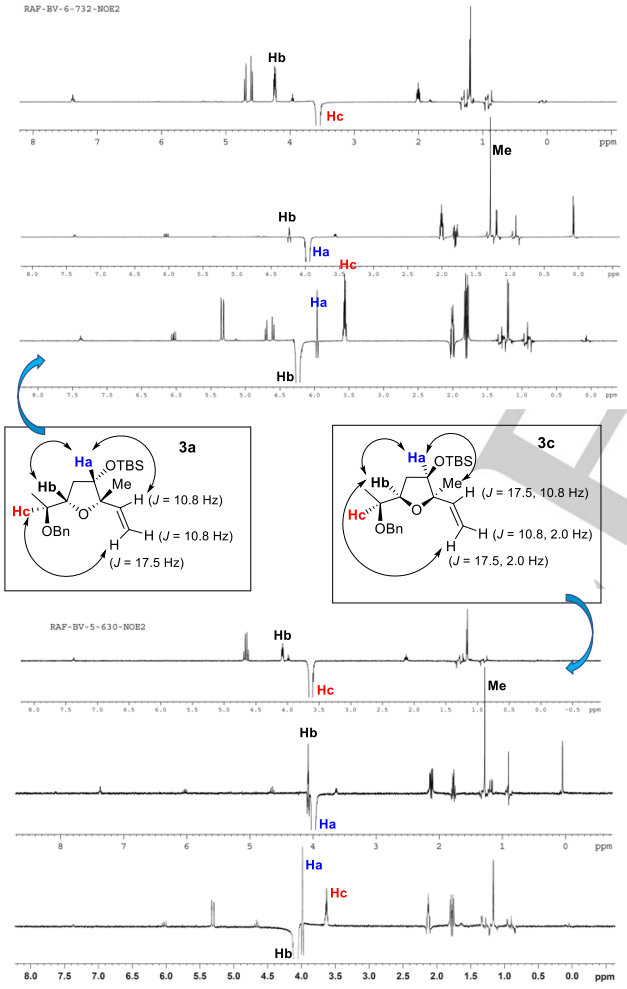


Figure 2. NOE experiments for **3a** and **3c**.

Conclusion

In summary, we have synthesized the tetrahydrofuran moieties **3a**, **3b** and **3c** from (*S*)-lactate **7** using Sharpless asymmetric dihydroxylation and intramolecular S_N2-cyclization as key steps. The strategy is flexible and diastereoselectivity can be reversed based on change in stereochemistry at the asymmetric dihydroxylation step. This will help in establishing the absolute stereochemistry of the natural product. Further synthesis of compound **4** for the cross-metathesis toward the total synthesis of caruifolin A is underway in our laboratory.

Experimental section

General Information

Flasks were oven or flame dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed with EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or under UV lamp. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker, AVANCE III 400 spectrometer and the chemical shifts are calculated relative to the tetramethylsilane peak at δ = 0.00 pm for ^{1}H NMR and $CDCl_3$ peak at δ = 77.00 ppm (t) for ^{13}C NMR spectra. IR spectra were obtained with a Perkin–Elmer Spectrum One FT–IR spectrometer and samples were prepared by evaporation from $CHCl_3$ on CsBr plates. Optical rotations were measured with a Jasco P-2000 digital polarimeter. High-resolution mass spectra (HRMS) were obtained by using positive electrospray ionization and by TOF method.

(*S*)-Ethyl 2-(benzyloxy)propanoate (8):

To a stirred solution of (*S*)-ethyl lactate **7** (2.0 g, 16.93 mmol) in dry THF (50 mL), was added oil free NaH (0.487 mg, 20.32 mmol, 1.2 equiv.) at 0 °C, and the mixture was stirred for 20 min. BnBr (2.4 mL, 20.316 mmol, 1.2 eqiuv.) was added and the reaction mixture was slowly warmed to room temperature and stirred for 12 h. It was then quenched with water (10 mL) and the solution extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography with petroleum ether/EtOAc (95:5) as eluent to give **8**[13] (2.68 g, 76%) as a colorless oil. $[\alpha]_D^{25}$ = −5.8 (*c* = 10.0, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3088, 3064, 3031, 2984, 2938, 2873, 1746, 1496, 1454, 1396, 1372, 1301, 1271, 1200, 1143, 1065, 1025, 907, 860, 698, 609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39−7.27 (m, 5H), 4.69 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 4.25−4.19 (m, 2H), 4.05 (q, J = 6.8 Hz, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 173.2, 137.6, 128.4, 127.9, 127.8, 74.0, 71.9, 60.8, 18.7, 14.2 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{16}O_3Na$ 231.0992, found 231.0981.

(2*S*,3*R*)-2-(Benzyloxy)hex-5-en-3-ol (9a) and (2*S*,3*S*)-2-(Benzyloxy)hex-5-en-3-ol (9b)[9]:

To a stirred solution of **8** (2.0 g, 9.60 mmol) in dry CH_2Cl_2 (30 mL) at –78 °C was added DIBAL-H (8.3 mL, 14.41 mmol, 1.5 equiv., 1.75 M solution in toluene) drop wise over 25 min under a N_2 atmosphere. The reaction mixture was stirred for

1 h and then quenched with saturated aq. Rochelle's salt solution (4.0 mL) and stirred vigorously at room temperature for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated to give the corresponding aldehyde (1.58 g), which was used directly in the next reaction.

To a stirred suspension of zinc dust (942.3 mg, 14.41 mmol, 1.5 equiv.) in THF (20 mL) was added allylbromide (1.3 mL, 14.41 mmol, 1.5 equiv.) at 0 °C followed by 4 drops of saturated aq. NH_4Cl. The mixture was stirred for 20 min and a solution of the above aldehyde (1.58 g) in THF (3 mL) was added. It was warmed to room temperature and stirred for 8 h and then quenched with saturated aq. NH_4Cl solution. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography with petroleum ether/EtOAc (9:1) as an eluent to afford the *syn*-**9b** (534 mg, 27%) and further elution gave *anti*-**9a** (1.07 g, 54%) as colorless oils.

Characteristic data for compound *anti*-9a: $[\alpha]_D^{25}$ = +3.9 (*c* = 2.3, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3457, 3067, 3030, 2979, 2933, 2874, 1641, 1496, 1454, 1382, 1330, 1284, 1090, 1073, 1028, 995, 916, 871, 698, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.27 (m, 5H), 5.89−5.78 (m, 1H), 5.17−5.10 (m, 2H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 3.81−3.76 (m, 1H), 3.58−3.50 (m, 1H), 2.30−2.22 (m, 2H), 1.96 (br s, 1H, *OH*), 1.20 (d, *J* = 6.3 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 138.4, 134.9, 128.3, 127.7, 127.6, 117.4, 77.3, 72.5, 70.6, 36.9, 13.7 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{13}H_{18}O_2Na$ 229.1199, found 229.1191.

Characteristic data for compound *syn*-9b[10]**:** $[\alpha]_D^{25}$ = +2.2 (*c* = 3.25, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3442, 3067, 3030, 2976, 2932, 2872, 1641, 1497, 1454, 1394, 1375, 1333, 1281, 1261, 1207, 1071, 1028, 992, 914, 870, 608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.27 (m, 5H), 5.93−5.83 (m, 1H), 5.13−5.07 (m, 2H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.59−3.51 (m, 1H), 3.45 (q, *J* = 6.1 Hz, 1H), 2.39−2.32 (m, 1H), 2.25−2.17 (m, 1H), 2.08 (br s, 1H, *OH*), 1.20 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 134.8, 128.5, 127.8, 127.7, 117.2, 77.5, 74.2, 71.0, 37.5, 15.4 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{13}H_{18}O_2Na$ 229.1199, found 229.1186.

(5*R*,6*S*,*E*)-Ethyl 6-(benzyloxy)-5-hydroxy-2-methylhept-2-enoate (11a)

Ozone in oxygen gas was bubbled through a stirred and cooled (−78 °C) solution of homoallyl alcohol **9a** (100 mg, 0.485 mmol, 1.0 eqiuv.) in CH_2Cl_2 (5 mL) until blue color persisted (30 min). Nitrogen gas was then passed through the solution for 15 min at −78 °C to remove any excess ozone. Then, PPh_3 (190.8 mg, 0.727 mmol, 1.5 equiv.) was added, and the solution was stirred at room temperature for 30 min. To the reaction mixture was added triphenylphosphorane **10** (211 mg, 0.582 mmol, 1.2 equiv.) and refluxed for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with petroleum ether/EtOAc (4:1) as an eluent to afford the compound **11a** (109 mg, 77%) as colorless oil. $[\alpha]_D^{25}$ = +1.5 (*c* = 1.0, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3469, 3064, 2981, 2933, 2873, 1705, 1651, 1496, 1454, 1390, 1369, 1326, 1279, 1205, 1095, 1029, 915, 869, 699, 667, 608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51−7.28 (m, 5H), 6.83 (td, *J* = 7.1, 1.4 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.18 (q, *J* = 5.2 Hz, 2H), 3.88−3.84 (m, 1H), 3.56−3.54 (m, 1H), 2.39−2.33 (m, 2H), 2.11 (s, 1H, *OH*), 1.85 (d, *J* = 1.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 6.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.9, 138.3, 138.0, 129.7, 128.4, 127.7, 127.6, 77.3, 72.6, 70.8, 60.5, 31.7, 14.2, 13.8, 12.6 ppm; HRMS (ESI-TOF) *m/z*: [M + K]$^+$ calcd for $C_{17}H_{24}O_4K$ 331.1306, found 331.1304.

(5*R*,6*S*,*E*)-Ethyl 6-(benzyloxy)-2-methyl-5-(methylsulfonyloxy)hept-2-enoate (5a):

To a stirred solution of **11a** (1.0 g, 3.42 mmol) in dry CH_2Cl_2 (15 mL), was added triethylamine (0.95 mL, 6.841 mmol, 2.0 equiv.) and methanesulfonyl chloride (0.4 mL, 5.13 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 12 h. It was then quenched with water (5 mL) and the solution extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography with petroleum ether/EtOAc (85:15) as eluent to give **5a** (1.0 g, 79%) as a colorless oil. $[\alpha]_D^{25}$ = +0.2 (*c* = 5.0, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3031, 2982, 2938, 1709, 1653, 1455, 1353, 1280, 1219, 1174, 1133, 1101, 1028, 956, 921, 795, 700, 529 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.28 (m, 5H), 6.72 (t, *J* = 7.3 Hz, 1H), 4.86−4.82 (m, 1H), 4.58 (d, *J* = 6.0 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.73−3.69 (m, 1H), 3.0 (s, 3H), 2.74−2.66 (m, 1H), 2.56−2.49 (m, 1H), 1.86 (s, 3H), 1.31−1.24 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.5, 137.7, 134.8, 131.2, 128.4, 127.8, 127.76, 83.4, 75.2, 71.3, 60.7, 38.7, 30.2, 14.7, 14.2, 12.7 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{18}H_{26}O_6SNa$ 393.1342, found 393.1343.

(2*R*,3*S*,5*S*)-Ethyl 5-[(*S*)-1-(benzyloxy)ethyl]-3-hydroxy-2-methyltetrahydrofuran-2-carboxylate (13a) and (2*S*,3*R*,5*S*)-Ethyl 5-[(*S*)-1-(benzyloxy)ethyl]-3-hydroxy-2-methyltetrahydrofuran-2-carboxylate (13b):

To a mixture of $K_3Fe(CN)_6$ (1.33 g, 4.05 mmol, 3.0 equiv.), K_2CO_3 (0.56 g, 4.050 mmol, 3.0 equiv.), $MeSO_2NH_2$ (0.257 g, 2.7 mmol, 2.0 equiv.), $(DHQ)_2$-PHAL (10.5 mg, 0.0135 mmol, 1.0 mol%) and $K_2OsO_4{\cdot}2H_2O$ (2.0 mg, 0.0054 mmol, 0.4 mol%), *t*-BuOH (4 mL) and water (5 mL) were added. The mixture was stirred for 5 min and cooled to 0 °C in an ice bath. To the cooled mixture, a solution of the α,β-unsaturated ester **5a** (0.5 g, 1.35 mmol) in *t*-BuOH (1 mL) was added. The reaction mixture was stirred at 0 °C for 6 h and at room temperature for 24 h and then quenched with solid Na_2SO_3 (1.0 g) and stirred for 30 min. The solution was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with 1M KOH (50 mL), water (50 mL), brine, dried (Na_2SO_4) and concentrated to give the corresponding inseparable diastereomeric mixture of diol **12a** (437 mg) which was used directly in the next reaction.

To the above crude diol **12a** (437 mg), was added 2,6-lutidine (2 mL) and the resulting mixture was heated at 120 °C for 6 h. It was then concentrated under reduced pressure and the residue was purified by silica gel column chromatography with CH_2Cl_2/EtOAc (95:5) as an eluent to afford the compound **13b** (125 mg, 30%) as colorless oil. Further elution gave compound **13a** (250 mg, 60%) as colorless oil.

Characteristic data for compound 13a: $[\alpha]_D^{25}$ = +1.5 (*c* = 4.0, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3458, 3065, 2981, 2935, 1732, 1496, 1455, 1390, 1373, 1300, 1283, 1112, 1069, 1025, 964, 914, 861, 698, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.24 (m, 5H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.46−4.40 (m, 1H), 4.30−4.18 (m, 3H), 3.63−3.55 (m, 1H), 2.14−2.03 (m, 1H), 1.99−1.90 (m, 1H), 1.45 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 173.5, 138.6, 128.1, 127.5, 127.3, 87.1, 81.4, 78.1, 75.8, 71.0, 61.1, 34.9, 23.4, 15.1, 14.0 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{24}O_5Na$ 331.1516, found 331.1514.

Characteristic data for compound 13b: $[\alpha]_D^{25}$ = +2.8 (*c* = 3.4, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3461, 3067, 2986, 2937, 1735, 1498, 1460, 1395, 1367, 1312, 1285, 1118, 1071, 1035, 974, 924, 867, 687, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.27 (m, 5H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.28−4.10 (m, 3H), 4.06 (dd, *J* = 5.5, 1.2 Hz, 1H), 3.50 (qd, *J* = 9.5, 2.8 Hz, 1H), 2.46−2.35 (m, 1H), 1.84 (dd, *J* = 3.2, 1.3 Hz, 1H), 1.39−1.34 (m, 6H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 171.9, 137.4, 128.4, 128.2, 127.9, 88.6, 81.0, 77.3, 75.5, 70.9, 60.8, 35.3, 22.0, 15.3, 14.1 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd $C_{17}H_{24}O_5Na$ 331.1516, found 331.1516.

(2*R*,3*S*,5*S*)-Ethyl 5-[(*S*)-1-(benzyloxy)ethyl]-3-(*tert*-butyldimethylsilyloxy)-2-methyltetrahydrofuran-2-carboxylate (14a):

To a stirred solution of **13a** (0.27 g, 0.875 mmol) in dry CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.2 mL, 1.75 mmol, 2.0 eqiuv.) and TBDMSOTf (0.347 g, 1.314 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. It was then diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The solution was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography with petroleum ether/EtOAc (95:5) as eluent to afford **14a** (0.266 g, 72%) as a colorless oil. $[\alpha]_D^{25}$ = +1.8 (*c* = 1.45, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3065, 3030, 2955, 2931, 2858, 2899, 1738, 1496, 1471, 1463, 1455, 1372, 1252, 1193, 1127, 1066, 1028, 939, 914, 862, 837, 777, 698, 672, 597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.27 (m, 5H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.60−4.49 (m, 2H), 4.29−4.18 (m, 1H), 4.14 (t, *J* = 5.5 Hz, 1H), 4.11−4.01 (m, 1H), 3.56 (q, *J* = 5.6 Hz, 1H), 2.06−1.92 (m, 2H), 1.43 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 172.9, 138.9, 128.3, 127.6, 127.4, 87.3, 81.4, 79.2, 76.0, 71.2, 60.6, 35.9, 25.6, 23.0, 17.8, 15.1, 14.2, −4.8, −5.1 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{38}O_5SiNa$ 445.2381, found 445.2381.

[(2*S*,3*S*,5*S*)-5-[(*S*)-1-(Benzyloxy)ethyl]-2-methyl-2-vinyltetrahydrofuran-3-yloxy](*tert*-butyl)dimethylsilane 3a:

To a stirred solution of **14a** (100 mg, 0.237 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added DIBAL-H (0.2 mL, 0.355 mmol, 1.5 equiv., 1.75M solution in toluene) dropwise under N_2 atmosphere. The reaction mixture was stirred for 1 h and then quenched with saturated aq. Rochelle's salt solution (3 mL) and stirred vigorously at room temperature for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated to give the corresponding aldehyde (80 mg), which was used directly in the next reaction.

To a stirred suspension of methyltriphenylphosphonium bromide (169.3 mg, 0.474 mmol, 2.0 equiv.) in dry THF (10 mL) was added *n*-BuLi (0.3 mL, 0.474 mmol, 2.0 equiv., 1.6M solution in hexane) at 0 °C. The mixture was stirred for 1 h and a solution of the above aldehyde (80 mg) in THF (3 mL) was added. It was warmed to room temperature and stirred for 8 h and then quenched with saturated aq. NH_4Cl solution. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography with petroleum ether/EtOAc (9:1) as an eluent to afford olefin **3a** (58 mg, 65%) as a colorless oil. $[\alpha]_D^{25}$ = +2.3 (*c* = 2.5, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 2933, 2861, 2328, 1612, 1462, 1375, 1256, 1188, 1134, 1027, 839, 776, 758, 666, 607, 551, 499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.25 (m, 5H), 6.00 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.30 (dd, *J* = 17.5, 2.0 Hz, 1H), 5.11 (dd, J = 10.8, 2.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz,1H), 4.23−4.18 (m, 1H), 3.93 (t, *J* = 7.0 Hz, 1H), 3.55−3.52 (m, 1H), 2.00−1.94 (m, 1H), 1.81−1.74 (m, 1H), 1.26 (s, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 139.7, 139.0, 128.2, 127.6, 127.4, 112.5, 84.0, 78.6, 78.1, 76.4, 71.2, 35.3, 25.7, 25.0, 18.0, 15.1, −4.7, −5.03 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{36}O_3SiNa$ 399.2326, found 399.2323.

(5*S*,6*S*,*E*)-Ethyl 6-(benzyloxy)-5-hydroxy-2-methylhept-2-enoate (11b):

The titled compound was prepared from **9b** (100 mg, 0.485 mmol, 1.0 eqiuv.) following similar procedure as described for **11a** to give **11b** (99.2 mg, 70%) as a colorless oil. $[\alpha]_D^{25}$ = +1.6 (*c* = 2.5, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3472, 3064, 3031, 2979, 2932, 2903, 1707, 1649, 1496, 1454, 1391, 1369, 1278, 1205, 1129, 1094, 1029, 916, 871, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 5H), 6.85 (td, *J* = 7.2, 1.1 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.61 (q, *J* = 6.0 Hz, 1H), 3.45 (q, *J* = 6.0 Hz, 1H), 2.45−2.32 (m, 2H), 1.85 (s, 3H), 1.75 (br s, 1H, *OH*), 1.28 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.9, 138.1, 137.8, 129.4, 128.4, 127.7 (2C), 77.3, 74.0, 70.9, 60.4, 32.4, 15.5, 14.2, 12.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{24}O_4Na$ 315.1567, found 315.1569.

(5*S*,6*S*,*E*)-Ethyl 6-(benzyloxy)-2-methyl-5-(methylsulfonyloxy)hept-2-enoate (5b)

The titled compound was prepared from **11b** (0.6 g, 2.052 mmol, 1.0 eqiuv.) following similar procedure as described for **5a** to give **5b** (0.715 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ = +0.6 (*c* = 3.45, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3030, 2982, 2938, 2902, 2875, 1709, 1455, 1355, 1281, 1255, 1218, 1175, 1135, 1099, 1028, 966, 923, 862, 802, 700, 528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.27 (m, 5H), 6.73 (t, *J* = 7.0 Hz, 1H), 4.69 (q, *J* = 5.8 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.77 (q, *J* = 6.1 Hz, 1H), 2.93 (s, 3H), 2.77−2.62 (m, 1H), 2.61−2.2.54 (m, 1H), 1.86 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.5, 137.7, 134.8, 131.2, 128.4, 127.84, 127.8, 83.1, 74.8, 71.5, 60.7, 38.4, 29.7, 15.0, 14.2, 12.7 ppm; HRMS (ESI-TOF)) *m/z*: [M + Na]$^+$ calcd for $C_{18}H_{26}O_6SNa$ 393.1342, found 393.1338.

(2*S*,3*R*,5*R*)-Ethyl 5-[(*S*)-1-(benzyloxy)ethyl]-3-hydroxy-2-methyltetrahydrofuran-2-carboxylate (13c) and (2*R*,3*S*,5*R*)-Ethyl 5-[(*S*)-1-(benzyloxy)ethyl]-3-hydroxy-2-methyltetrahydrofuran-2-carboxylate (13d):

The titled compounds were prepared from **5b** (0.5 g, 1.35 mmol, 1.0 eqiuv.) following similar procedure as described for **13a** and **13b** to give **13c** (112.4 mg, 27%) and **13d** (229 mg, 55%) as colorless oils.

Characteristic data for compound 13c: $[\alpha]_D^{25}$ = +1.4 (*c* = 2.5, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3454, 3061, 2978, 2931, 1736, 1485, 1465, 1385, 1383, 1305, 1284, 1112, 1055, 1023, 970, 917, 872, 698, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.19 (m, 5H), 4.61 (dd, *J* = 15.0, 11.8 Hz, 2H), 4.36−4.31 (m, 1H), 4.29−4.19 (m, 3H), 3.79−3.74 (m, 1H), 2.33−2.26 (m, 1H), 1.96−1.90 (m, 1H), 1.45 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 173.7, 138.9, 128.2, 127.5, 127.4, 87.2, 82.8, 78.3, 75.4, 71.9, 61.3, 33.3, 23.5, 16.6, 14.2 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{24}O_5Na$ 331.1516, found 331.1515.

Characteristic data for compound 13d: $[\alpha]_D^{25}$ = –1.9 (*c* = 2.2, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3455, 3068, 2983, 2938, 1735, 1491, 1460, 1393, 1375, 1303, 1273, 1115, 1063, 1033, 961, 698, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32−7.16 (m, 5H), 4.69 (dd, *J* = 17.2, 11.3 Hz, 2H), 4.36−4.29 (m, 1H), 4.26−4.14 (m, 2H), 4.13−4.06 (m, 1H), 4.04−3.97 (m, 1H), 3.85 (qd, *J* = 6.5, 2.2 Hz, 1H), 2.38−2.26 (m, 1H), 1.95 (dd, *J* = 14.2, 2.8 Hz, 1H), 1.29 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 171.6, 137.4, 128.4, 128.1, 127.8, 89.1, 81.3, 76.5, 75.9, 72.4, 60.9, 32.4, 21.8, 16.5, 14.2 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{24}O_5Na$ 331.1516, found 331.1516.

(2*S*,3*R*,5*R*)-Ethyl 5-[(*S*)-1-(Benzyloxy)ethyl]-3-(*tert*-butyldimethylsilyloxy)-2-methyltetrahydrofuran-2-carboxylate (14b):

The titled compound was prepared from **13c** (0.160 g, 0.52 mmol, 1.0 eqiuv.) following similar procedure as described for **14a** to give **14b** (0.154 g, 70%) as a colorless oil. $[\alpha]_D^{25}$ = −1.7 (*c* = 2.2, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3058, 3032, 2968, 2928, 2874, 1743, 1486, 1466, 1373, 1343, 1280, 1090, 1073, 1030, 997, 869, 698, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.25 (m, 5H), 4.62 (d, *J* = 7.0 Hz, 2H), 4.41 (td, *J* = 7.2, 3.2 Hz, 1H), 4.28−4.21 (m, 1H), 4.19−4.14 (m, 1H), 4.09−4.01 (m, 1H), 3.78−3.71 (m, 1H), 2.25−2.16 (m, 1H), 1.95−1.87 (m, 1H), 1.43 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 172.9, 139.1, 128.3, 128.25, 127.7, 127.5, 127.3, 87.5, 83.0, 79.2, 75.8, 71.9, 60.7, 34.3, 25.6, 23.2, 17.9, 16.7, 14.2, –4.8, –5.1; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{23}H_{38}O_5SiNa$ 445.2381, found 445.2383.

[(2*R*,3*R*,5*R*)-5-[(*S*)-1-(Benzyloxy)ethyl]-2-methyl-2-vinyltetrahydrofuran-3-yloxy](*tert*-butyl)dimethylsilane 3c:

The titled compound was prepared from **14b** (100 mg, 0.237 mmol, 1.0 eqiuv.) following similar procedure as described for **3a** to give **3c** (54.4 mg, 61%) as a colorless oil. $[\alpha]_D^{25}$ = −1.7 (*c* = 2.2, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3064, 3028, 2955, 2929, 2887, 2858, 1734, 1710, 1471, 1463, 1454, 1404, 1369, 1258, 1216, 1121, 1071, 1036, 997, 920, 902, 871, 837, 777, 753, 734, 697, 668, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.27 (m, 5H), 6.01 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.30 (dd, *J* = 17.5, 2.0 Hz, 1H), 5.10 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.08−4.03 (m, 1H), 3.96 (t, *J* = 7.1 Hz, 1H), 3.64−3.58 (m, 1H), 2.13−2.07 (m, 1H), 1.79−1.72 (m, 1H), 1.26 (s, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 139.7, 139.2, 128.2, 127.5, 127.3, 112.5, 83.8, 79.5, 78.5, 76.7, 71.7, 34.2, 25.7, 24.9, 18.0, 16.6, –4.7, –5.0 ppm; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{22}H_{36}O_3SiNa$ 399.2326, found 399.2325.

(2*R*,3*S*,5*R*)-Ethyl 5-[(*S*)-1-(benzyloxy)ethyl]-3-(*tert*-butyldimethylsilyloxy)-2-methyltetrahydrofuran-2-carboxylate 3b:

The titled compound was prepared from **13d** (80 mg, 0.259 mmol, 1.0 eqiuv.) following similar procedure as described for **14a** to give **3b** (79 mg, 72%) as a colorless oil. $[\alpha]_D^{25}$ = −1.7 (*c* = 2.2, $CHCl_3$); IR ($CHCl_3$): υ_{max} = 3030, 2956, 2931, 2886, 2858, 1737, 1496, 1472, 1463, 1454, 1370, 1254, 1193, 1072, 1028, 964, 914, 838, 777, 698, 671, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.24 (m, 5H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.28−4.13 (m, 2H), 4.09−3.99 (m, 1H), 3.95 (q, *J* = 7.0 Hz, 1H), 3.85−3.76 (m, 1H), 2.31 (q, *J* = 6.5 Hz, 1H), 2.16−2.08 (m, 1H), 1.42 (s, 3H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 138.9, 128.2, 127.7, 127.4, 87.2, 81.5, 79.8, 77.3, 70.9, 60.6, 37.0, 25.6, 22.7, 17.8, 16.9, 14.1, –4.7, –5.2; HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{23}H_{38}O_5SiNa$ 445.2381, found 445.2383.

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Keywords: Allylation • chiral pool • germacranolide • asymmetric dihydroxylation • cyclization • natural products

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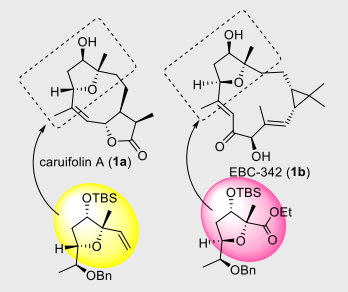
FULL PAPER

A common strategy for the synthesis of substituted tetrahydrofuran moieties of caruifolin A and EBC-342 has been developed based on asymmetric dihydroxylation and intramolecular S_N2-cyclization



Tetrahydrofuran

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A Concise Synthesis of the Key Tetrahydrofuran Moieties of Caruifolin A and EBC-342

*Diastereoselective synthesis