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Synthesis of the C1–C9, C11–C19 Pyran Core and C19–C24 Fragments of Macrolactin 3

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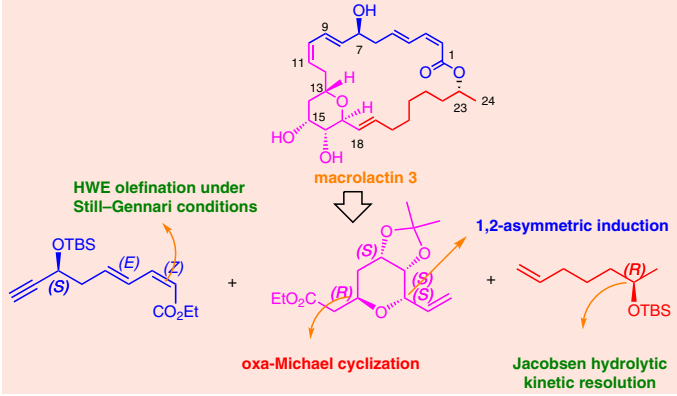

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Abstract We describe herein an efficient synthesis of the C1–C9, C11–C19 pyran moiety and C18–C24 core fragments of macrolactin 3. The prominent features of this work include construction of the *Z*-double bond of the 1,3-(*Z*,*E*)-diene system utilizing Horner–Wadsworth–Emmons reaction under Still–Gennari conditions. A Sharpless asymmetric epoxidation and subsequent epoxide opening under $BF_3{\cdot}OEt_2$ conditions were applied to generate the stereogenic centers at C15 and C16, oxa-Michael addition and Jacobsen resolution facilitate the synthesis of the fragments.

Key words macrolactin **3**, tetrahydropyran, $BF_3{\cdot}OEt_2$, epoxide opening, Jacobsen, oxa-Michael, D-ribose

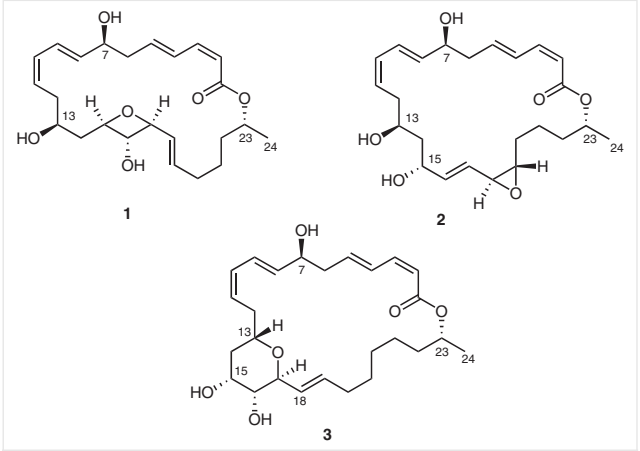


Figure 1 Macrolactins **1**–**3**

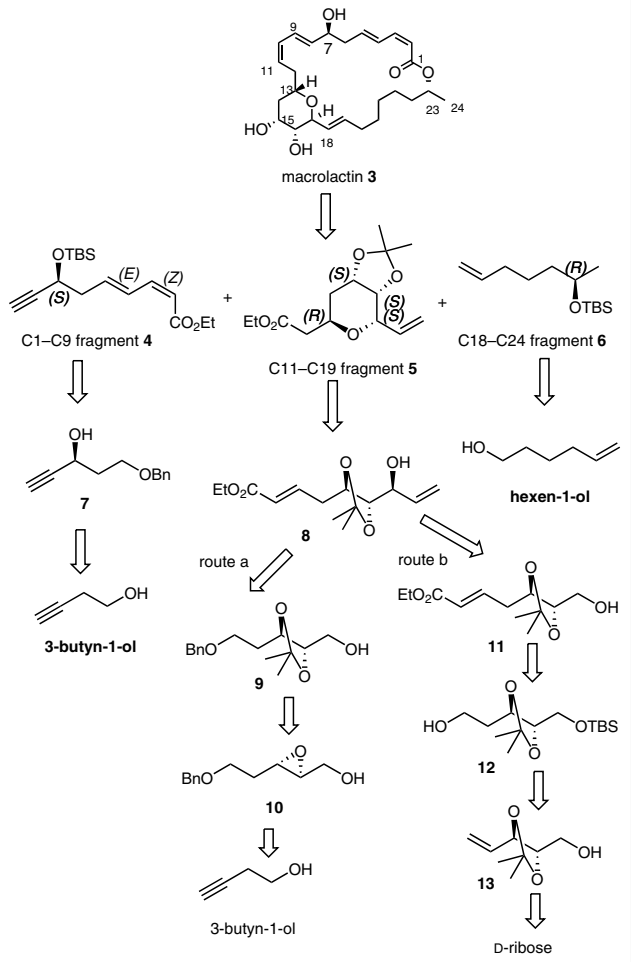
Introduction

Marine microorganisms have proven to be excellent sources of novel, bioactive secondary metabolites, and they attract much attention from chemists, pharmacologists, and molecular biologists. Three novel bioactive 24-membered macrolactones **1**–**3** (Figure 1) were isolated in 2011 from fermentation of a marine microorganism *Bacillus sp.* 09ID194 by Shin and co-workers, and subsequent bio-assay-guided fractionation showed antimicrobial activities against both Gram-positive and Gram-negative pathogens.[1]

ROESY data analysis,[2] coupling constants, and application of the modified Mosher's method[3–5] were used to establish the structures and absolute stereochemistry of macrolactins **1**–**3**. Compounds **1**–**3** exhibit a minimum inhibitory concentration (MIC) of 0.16 µM against *Bacillus subtilis* and *Escherichia coli* in a standard *in vitro* broth dilution assay.[6] Their MICs against *Saccharomyces cerevisiae* were 0.16, 0.02, and 0.16 µM, respectively. As a continuation of our group's interest in the synthesis of tetrahydropyran-containing molecules of complex architecture, the bioactivity of macrolactin **3** prompted us to undertake its synthesis.[7]

Macrolactin **3** is a cyclic ester containing ene diene, tetrahydropyran ring moieties and three -OH groups attached to C7, C15, and C16.

The retrosynthetic analysis of macrolactin is summarized in Scheme 1. Macrolactin can be envisaged to be assembled from three segments, (*E*),(*Z*)-dien-yn-ol ester **4**, vinyl pyran **5**, and hydroxyalkene **6**.



Scheme 1 Retrosynthetic analysis

Synthesis of C1–C9 Fragment 4 (Macrolactins A, C, E, F, N, S and 1–3)

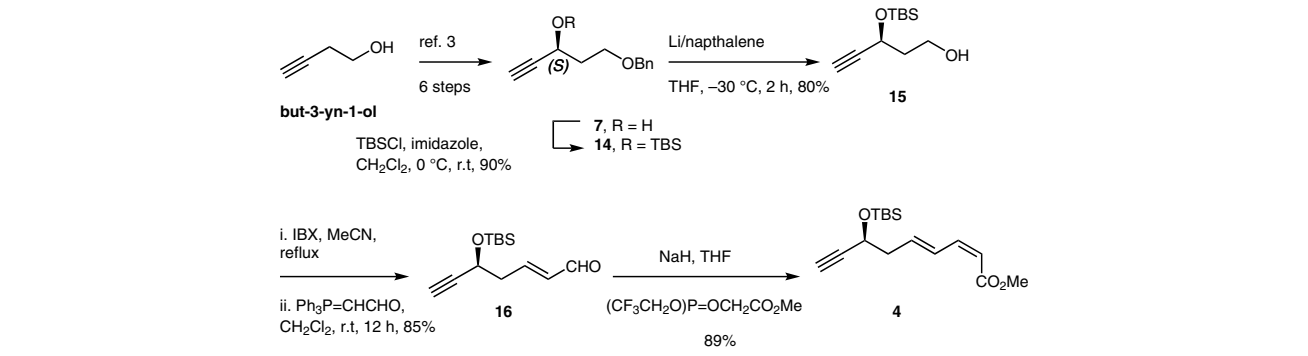
The key building block C1–C9 fragment **4** of macrolactin 3, also present in macrolactins A, C, E, F, N, S and macrolactins **1** and **2**, was derived from commercially available 3-butyn-1-ol (homopropargylic alcohol). The known benzyl protected (*S*)-alcohol **7**[8] was prepared by following a procedure similar to that used for the PMB and THP protected alcohols. The free secondary hydroxyl group was protected as its TBS ether **14**, followed by removal of the benzyl group using Li/naphthalene in THF at –30 °C to furnish alcohol **15** (Scheme 2).

Oxidation of alcohol **15** with 2-(iodooxy)benzoic acid (IBX) furnished the corresponding aldehyde, which was subjected to a two-carbon extension using triphenyl-phosphoranylideneacetaldehyde (Ph_3P=CHCHO) to afford **16** in 85% yield (Scheme 2). Applying Stille–Gennari[9] conditions to compound **16** provided (*E*),(*Z*)-yn-ol ester **4** (C1–C9 fragment) using methyl *P*,*P*′-bis(2,2,2-trifluoroethyl)phosphonoacetate in the presence of NaH in THF at –78 °C with excellent stereoselectivity (*Z*,*E*/*E*,*E* 95:5) in 89% yield.

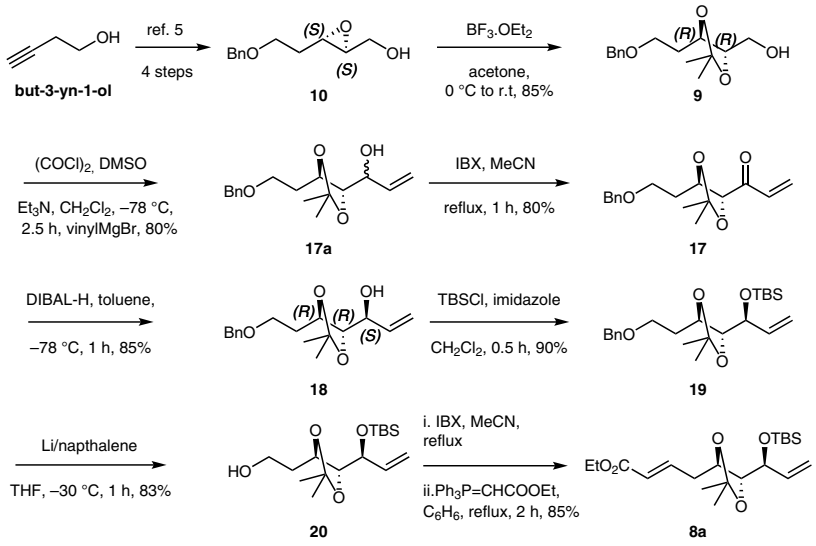
Synthesis of C11–C19 Pyran Core 5

To allow for flexibility in our synthetic plan, we envisaged two pathways to access intermediate **8**. Pathway a (Scheme 3) was based on epoxide opening with BF_3·OEt_2. Accordingly, 3-butyn-1-ol (homopropargyl alcohol) was converted into known benzyl protected 2,3-epoxy alcohol **10** in four steps as reported.[10]

Epoxide **10** was treated with anhydrous acetone in the presence of BF_3·OEt_2 at 0 °C to furnish acetonide **9** in 85% yield.[11] Alcohol **9** was converted into the corresponding aldehyde by Swern oxidation and was used for further reaction without isolation or characterization. To create a third stereogenic center, a Grignard reaction was performed using vinylmagnesium bromide generated *in situ*, which provided allyl alcohol **17a** as a 1:1 mixture of diastereomers. Without separation, the latter was converted into ketone **17**. Stereoselective reduction of the ketone was carried out with diisobutylaluminum hydride (DIBAL-H)[12] in anhydrous CH_2Cl_2 at –78 °C, affording the required (*S*)-alcohol **18** in 90% yield. Alcohol **18**, on treatment with TBSCl and imidazole, provided the corresponding silyl ether **19**, which, on debenzylation with Li/naphthalene in THF at –30 °C, gave



Scheme 2 Synthesis of fragment **4**



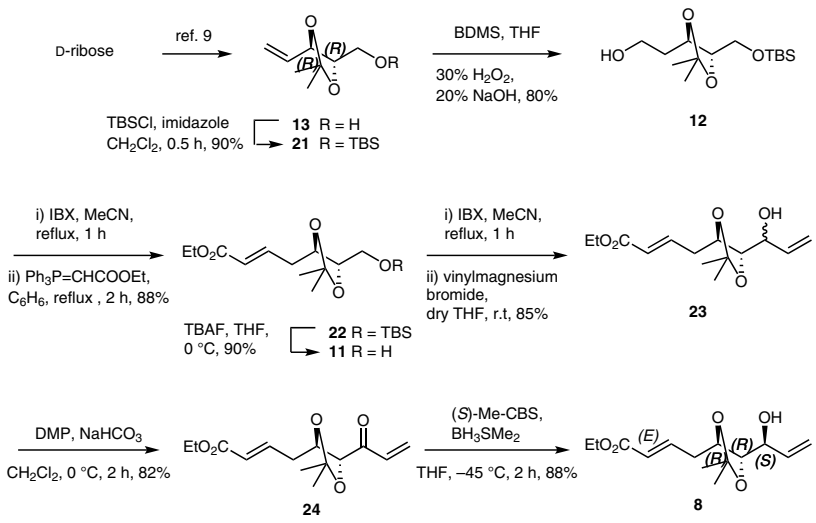
Scheme 3 Pathway a: Synthesis of intermediate **8a**

alcohol **20**. Oxidation of **20** to its corresponding aldehyde with 2-(iodooxy)benzoic acid (IBX), followed by Wittig olefination using the stabilized ylide, Ph_3P=CHCOOEt gave α,β-unsaturated ester **8a**.

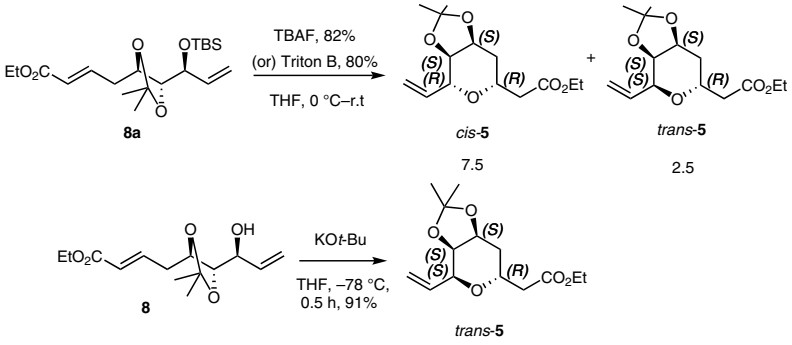
While our manuscript was under preparation, a report appeared[13] in which a similar synthetic scheme was presented for accessing the pyran core. Therefore, we adopted another pathway from D-ribose to access intermediate **8** (Scheme 4).

The synthesis of fragment **8** began with known alcohol **13**, obtained from D-ribose as reported.[14] The hydroxyl group in **13** was protected as its TBDMS ether, followed by hydroboration/oxidation of the terminal alkene with alkaline hydrogen peroxide to produce the corresponding alcohol **12** in 80% yield (over two steps). Swern oxidation of the primary alcohol gave the corresponding aldehyde, which was subjected to Wittig olefination with Ph_3P=CHCOOEt to furnish α,β-unsaturated ester **22** in 90% yield. This was followed by removal of the TBS group with tetrabutylammonium fluoride (TBAF) in THF to obtain alcohol **11** in 90% yield.

Formation of the (*S*)-vinyl alcohol **8** was envisaged by oxidation of alcohol **11** to the aldehyde, followed by Grignard reaction with vinylmagnesium bromide employing an oxidation/selective reduction protocol. Thus, alcohol **11** was treated with IBX to afford the corresponding aldehyde, which, on reaction with vinylmagnesium bromide, furnished both diastereomers of vinyl alcohol **23**. Oxidation of the mixture using Dess–Martin periodinane (DMP) gave



Scheme 4 Pathway b: Synthesis of intermediate **8**



Scheme 5 Synthesis of vinyl tetrahydropyran **5**

ketone **24** in 82% yield and the ketone functionality in **24** was reduced with (*S*)-Me-CBS, BH_3·SMe_2 in THF, affording **8** in 88% yield.

At this stage, intramolecular oxa-Michael addition reactions were studied using substrates **8** and **8a**. Initially, treatment of **8a** either with TBAF or Triton B in THF at 0 °C afforded a mixture of 2,6-*cis*-tetrahydropyran (*cis*-**5**) and 2,6-*trans*-tetrahydropyran (*trans*-**5**) in 82% and 80% yields, respectively in a ratio of 7.5:2.5 (Scheme 5).

The stereochemistry of *cis*-**5** was established by TOCSY and ROESY experiments and that of *trans*-**5** by comparison with literature data.[13] Since macrolactin **3** contains a 2,6-*trans* tetrahydropyran core, we changed the reaction conditions. Thus, intramolecular oxa-Michael cyclization of **8** with KO*t*-Bu[15] (0.05 or 1 equiv) in THF at –78 °C for 30 min gave the required 2,6-*trans*-tetrahydropyran (*trans*-**5**) in 91% yield with excellent diastereoselectivity (dr 19:1). Thus, by simply switching the reaction conditions, either *syn* or *anti* pyran rings could be synthesized from **8** or **8a** in a stereoselective manner.

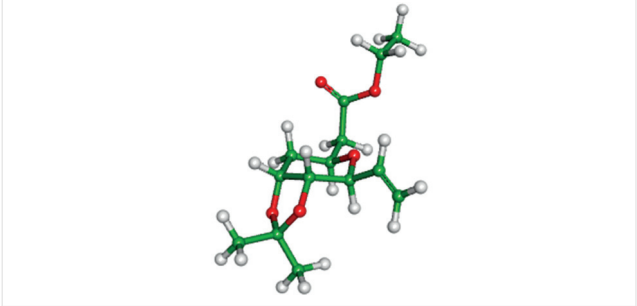
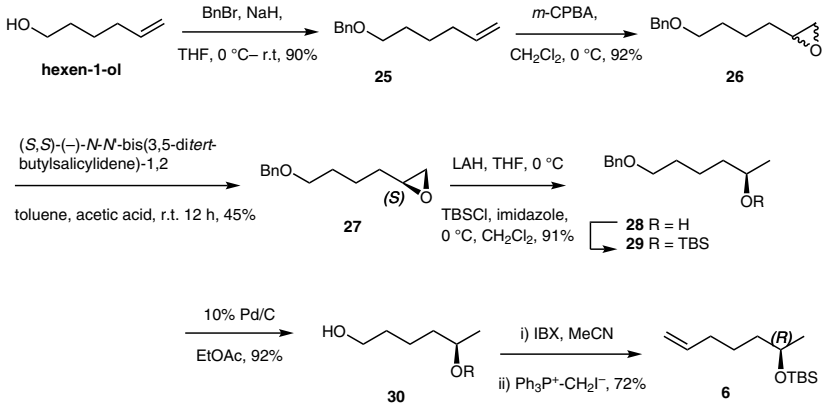


Figure 2 Energy-minimized structure of *cis*-**5**

Synthesis of the C19–C24 Fragment 6

Synthesis of the C19–C24 fragment, hydroxy alkene **6**, began with commercially available hexen-1-ol, which was converted into its corresponding racemic epoxide **26** by reacting with *m*-CPBA after protecting the alcohol as its benzyl ether (Scheme 6). Chiral *S*-epoxide **27** was obtained from **26** by Jacobsen resolution with *S*,*S*-Jacobsen catalyst. Epoxide **27**, on reduction with LAH, furnished *R*-alcohol **28**,



Scheme 6 Synthesis of C19–C24 fragment **6**

which, on silylation with TBSCl and imidazole in CH_2Cl_2, gave **29**. Debenzylation followed by oxidation to the aldehyde and one-carbon Wittig reaction produced alkene **6**.

Conclusion

We have accomplished the asymmetric synthesis of the C1–C9, C11–C19 pyran core, and C19–C24 fragments of macrolatin 3. Key features of this approach include epoxide opening, TEMPO-BAIB oxidation, and oxa-Michael cyclization. Work towards the total synthesis of macrolactin 3 is under way.

Unless otherwise mentioned, all reactions were carried out using standard syringe, septa and cannula techniques. All glassware was flame- or oven-dried and cooled under an atmosphere of nitrogen unless otherwise stated. Column chromatography was performed using silica gel (60–120 mesh) and the column was usually eluted with EtOAc–hexanes. The diastereomeric excess of the products were measured with a chiral-phase HPLC using Chiralpak AS column. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel-60 F254 (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by dipping the plates in sulfuric acid-β-naphthol or to ethanolic anisaldehyde-sulfuric acid-acetic acid and heating the plates at 120 °C. ^{1}H NMR spectra were recorded at 300, 500, 600 MHz and ^{13}C NMR spectra were recorded at 75, 125 MHz in $CDCl_3$ using tetramethylsilane as the reference standard, with s, brs, d, dd, ddd, dt, t, q, qt, and m indicating singlet, broad singlet, doublet, doublet of doublet, doublet of doublet of doublet, doublet of doublet of doublet, doublet of triplet, triplet, quartet, quintet and multiplet, respectively. Infrared spectra were recorded as neat liquids with a Perkin–Elmer infrared–683 spectrophotometer with NaCl optics. Spectra were calibrated against polystyrene absorption at 1610 cm^{-1}. Specific rotations were measured with a JASCO DIP-360 digital polarimeter. Mass spectra were recorded with a Micromass VG-7070H mass spectrometer under ESI or EI. High-resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer

Ethyl (*S*,2*Z*,4*E*)-7-(*tert*-Butyldimethylsilyloxy)nona-2,4-dien-8-ynoate (4)

A solution of ethyl bis(2,2,2-trifluoroethoxy)phosphonoacetate (0.5 g, 1.0 mmol) in anhydrous THF (5 mL) was added slowly to a stirred solution of NaH (0.1 g, 4.1 mmol) in anhydrous THF (10 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min, then cooled to –78 °C, aldehyde **16** in anhydrous THF was added dropwise over 5 min and the resulting mixture was stirred at –78 °C for 30 min. The reaction was quenched with sat. NH_4Cl (2 mL), the product was extracted with EtOAc (3 × 20 mL), and the combined extracts were dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc, 8:2) to afford (*Z*)-olefin ester **4**.

Yield: 0.5 g (89%); colorless liquid; $[\alpha]_D^{25}$ –27.5 (*c* = 0.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.75 (t, *J* = 11.3 Hz, 1 H), 6.18–6.06 (m, 1 H), 5.94–5.88 (m, 1 H), 5.62 (d, *J* = 11.3 Hz, 1 H), 4.42 (dt, *J* = 6.8, 2.3 Hz, 1 H), 3.73 (s, 3 H), 2.59 (t, *J* = 6.8 Hz, 2 H), 2.40 (d, *J* = 2.3 Hz, 1 H), 0.90 (s, 9 H), 0.12–0.09 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 144.8, 139.5, 129.4, 116.0, 72.7, 71.0, 62.2, 51.0, 41.9, 25.6, 18.0, –4.7, –5.1.

IR (neat): 3423, 2954, 2930, 2857, 1732, 1468, 1367, 1248, 1070, 837 cm^{-1}.

ESIMS: *m*/*z* = 331 $[M + Na]^+$.

(2*R*,3*R*)-5-Benzyloxy-2,53-(2,2-dimethyl-1,3-dioxolanyl)pentanol (9)

To a solution of compound **30** (13.63 g, 66.16 mmol) in acetone was added $BF_3{\cdot}Et_2O$ (8.31 mL, 66.16 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 3 h. After completion of reaction, the reaction was quenched by the addition of solid $NaHCO_3$ at 0 °C and the solvent was evaporated under reduced pressure to yield a residue which was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed once with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which, upon column chromatography (EtOAc/hexane, 10%) gave pure **31**.

Yield: 14.84 g (85%); pale-yellow oil; $[\alpha]_D^{25}$ –12.3 (*c* = 0.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.39–7.28 (m, 5 H), 4.53 (s, 2 H), 4.37–4.29 (m, 1 H), 4.21–4.13 (m, 1 H), 3.70–3.53 (m, 4 H), 1.94–1.84 (m, 2 H), 1.71–1.59 (brs, 1 H, OH), 1.45 (s, 3 H), 1.37 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.5, 128.3, 127.5, 127.4, 107.7, 77.7, 74.3, 72.9, 67.5, 61.9, 29.5, 28.1, 25.5; IR (KBr): 3448, 2938, 2856, 1451, 1347, 1253, 1067, 834, 790 cm^{-1}.

EIMS: *m*/*z* = 299 $[M + Na]^+$.

Ethyl (*E*)-(5*R*,6*S*,7*S*)-5,6-(2,2-Dimethyl-1,3-dioxolanyl)-7-(-1-*tert*-butyldimethylsilyl)non-2-enoate (8a)

To an ice-cooled solution of 2-iodoxybenzoic acid (0.5 g, 1.9 mmol) in anhydrous MeCN (50 mL) was added a solution of alcohol **20** (0.5 g, 1.6 mmol). The mixture was heated at reflux for 1 h, and then allowed to cool to r.t. The solvent was removed under reduced pressure and the compound was used directly for the next step without purification by column chromatography.

To a solution of the above aldehyde in C_6H_6 (30 mL) was added Ph_3P=CHCOOEt (0.6 g, 1.7 mmol) and the reaction mixture was stirred for 4 h at reflux condition. After completion of the reaction, monitored by TLC, C_6H_6 was removed under reduced pressure, the residue was dissolved in ether, and petroleum ether was added to it. The triphenylphosphineoxide that crystallized out was filtered off and the filtrate was concentrated to dryness. The crude product was purified by column chromatography (hexane/EtOAc, 8:2) to afford the pure α,β-unsaturated ester **8a**.

Yield: 0.5 g (85%); colorless oil; $[\alpha]_D^{25}$ +9.4 (*c* = 0.4, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.0–6.89 (m, 1 H), 5.88 (dt, *J* = 15.6, 1.3 Hz, 1 H), 5.70 (dd, *J* = 17.3, 10.7, Hz, 1 H), 5.36 (dd, *J* = 17.3, 1.5 Hz, 1 H), 5.25 (dd, *J* = 10.9, 1.5 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, H), 3.99 (t, *J* = 6.7 Hz, 1 H), 3.93–3.83 (m, 2 H), 2.68–2.56 (m, 1 H), 2.52–2.55 (m, 1 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.29 (t, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.4, 145.8, 138.4, 123.1, 117.6, 108.3, 80.1, 76.5, 73.1, 61.0, 32.7, 28.1, 25.7, 18.1, 14.1, –4.5 (2C).

IR (neat): 2927, 2856, 1739, 1383, 1256, 1046, 759 cm^{-1}.

ESIMS: *m*/*z* = 407 $[M + Na]^+$.

Ethyl (*E*)-(5*R*,6*S*,7*S*)-5,6-(2,2-Dimethyl-1,3-dioxolanyl)-7-hydroxyhept-2-enoate (11)

A 1 M solution of TBAF in THF (1.3 mL) was added to a solution of compound **22** (0.5 g, 1.4 mmol) in anhydrous THF (10 mL) at 0 °C. The mixture was stirred at r.t. for 2 h. After completion of the reaction, the mixture was diluted with H_2O (5 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na_2SO_4). Filtration and evaporation of the solvent under reduced pressure, followed by column chromatography (hexane/EtOAc, 6:4) afforded pure **11**.

Yield: 0.3 g (90%); colorless liquid; $[\alpha]_D^{25}$ +9.8 (*c* = 0.3, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.03–6.98 (m, 1 H), 5.92 (dt, *J* = 15.7, 1.5 Hz, 1 H), 4.29–4.26 (m, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.18–4.11 (m, 1 H), 3.60 (dd, *J* = 10.3, 4.6 Hz, 2 H), 2.60–2.55 (m, 1 H), 2.51–2.43 (m, 1 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.2, 144.7, 108.1, 77.5, 76.8, 60.5, 29.5, 28.1, 25.5.

IR (neat): 3447, 2983, 2854, 1736, 1436, 1374, 1152, 1083, 898 cm^{-1}.

ESIMS: *m*/*z* = 267 $[M + Na]^+$.

Ethyl (*E*)-(5*R*,6*S*,7*S*)-5,6-(2,2-Dimethyl-1,3-dioxolanyl)-7-hydroxynon-2,8-dienoate (8)

To a stirred solution of (*S*)-Me-CBS-oxazaborolidine catalyst (1 M in toluene, 0.1 mL) in anhydrous toluene (1 mL), BH_3·DMS (2 M in THF, 0.2 mL) was added at 0 °C and the mixture was stirred for 0.5 h. A solution of compound **24** (0.1 g, 0.34 mmol) in anhydrous toluene (15 mL) was added and the mixture was stirred for 0.5 h at 0 °C. After reaction was complete, monitored by TLC, the reaction was quenched with MeOH (2 mL) and the mixture was warmed to r.t. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 7:3) to afford **8**.

Yield: 85 mg (88%); viscous liquid; $[\alpha]_D^{25}$ +21.7 (*c* = 0.45, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.01–6.88 (m, 1 H), 5.88 (d, *J* = 15.6 Hz, 1 H), 5.70 (dd, *J* = 17.1, 10.7 Hz, 1 H), 5.41 (dd, *J* = 17.3, 1.5 Hz, 1 H), 5.25 (dd, *J* = 10.9, 1.5 Hz, 1 H), 3.92–3.81 (m, 2 H), 2.67–2.58 (m, 1 H), 2.52–2.44 (m, 1 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.5, 145.7, 138.3, 123.1, 117.1, 108.1, 79.8, 76.3, 71.1, 60.3, 32.7, 27.9, 25.6, 14.1.

IR (neat): 2984, 2929, 1456, 1257, 1170, 970 cm^{-1}.

ESIMS: *m*/*z* = 293 $[M + Na]^+$.

Ethyl 2-((3a*S*,4*S*,6*R*,7a*S*)-2,2-Dimethyl-4-vinyltetrahydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-6-yl)acetate (*trans*-5)

To a solution of α,β-unsaturated ester **8** (0.1 g, 0.3 mmol) in THF (10 mL) at –78 °C was added *t*-BuOK (0.04 g, 0.35 mmol). After stirring for 0.5 h at –78 °C, a saturated solution of NH_4Cl (10 mL) was added and the mixture warmed to r.t. Extraction was carried out with Et_2O (3 × 10 mL), the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/EtOAc, 8:2) furnished *trans*-**5**.

Yield: 90 mg (90%); colorless oil; $[\alpha]_D^{25}$ –17.8 (*c* = 0.37, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.91–5.84 (m, 1 H), 5.33 (dt, *J* = 17.4, 1.5 Hz, 1 H), 5.20 (dt, *J* = 10.7, 1.5 Hz, 1 H), 4.41–4.37 (m, 1 H), 4.18–4.10 (m, 3 H), 3.85–3.82 (m, 1 H), 3.77–3.74 (m, 1 H), 2.58 (dd, *J* = 15.1, 7.9 Hz, 1 H), 2.43 (dd, *J* = 15.1, 5.3 Hz, 1 H), 2.18 (dt, *J* = 14.8, 2.1 Hz, 1 H), 1.81–1.75 (m, 1 H), 1.53 (s, 3 H), 1.38 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.6, 135.7, 116.3, 108.1, 78.2, 74.6, 72.2, 69.3, 60.3, 40.8, 32.6, 28.3, 26.1, 14.1.

IR (neat): 2930, 2857, 1738, 1256, 1154, 1047, 836, 775.

ESIMS: *m*/*z* = 293 $[M + Na]^+$.

(*R*)-6-*tert*-Butyldimethylsiloxyhept-1-ene (6)

To an ice-cooled solution of 2-iodoxybenzoic acid (1.17 g, 4.20 mmol) in DMSO (2 mL) and CH_2Cl_2 (6 mL) was added a solution of **30** (0.65 g 2.80 mmol) in anhydrous CH_2Cl_2 (5 mL). The mixture was stirred at r.t. for 5 h and then filtered through a Celite® pad and washed with CH_2Cl_2 (2 × 20 mL). The combined organic filtrates were washed with H_2O (2 × 6 mL), brine (2 × 6 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford the crude aldehyde. This was used for the next step without further purification. In a reaction flask, *n*-BuLi (2.5 M in hexane, 3.36 mL, 8.40 mmol) was added under N_2 atmosphere to a stirred suspension of methyltriphenylphosphonium iodide (6.88 g, 16.81 mmol) in anhydrous THF (50 mL) at –78 °C. The mixture was allowed to warm to r.t., stirred for 1 h, and cooled to –78 °C again. To this mixture, a solution of above crude aldehyde in anhydrous THF (3 mL) was added dropwise, and the resulting mixture was stirred at r.t. for 2 h. The reaction was quenched with aqueous NH_4Cl and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (98:2 hexane/EtOAc) to give compound **6**.

Yield: 0.456 g (72%); liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.89–5.73 (m, 1 H), 5.06–4.90 (m, 2 H), 3.85–3.73 (m, 1 H), 2.09–1.99 (m, 2 H), 1.52–1.31 (m, 4 H), 1.12 (d, *J* = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.9, 114.2, 68.4, 39.1, 33.7, 25.8, 25.0, 23.8, 18.1, –4.4, –4.7.

ESIMS: *m*/*z* = 251 $[M + Na]^+$.

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Supporting Information

Experimental procedures, spectral data, copies of ^{1}H NMR and ^{13}C NMR spectra are available.Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591844.

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