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Enantioselective Total Synthesis of (+)-EBC-23, a Potent Anticancer Agent from the Australian Rainforest

Arun K. Ghosh* and Che-Sheng Hsu

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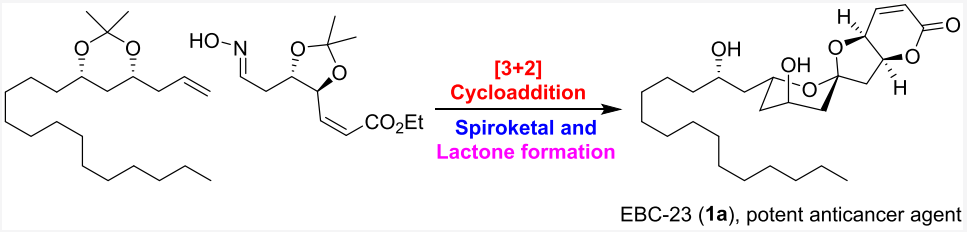

ABSTRACT: We describe here an enantioselective synthesis of (+)-EBC-23, a potent anticancer agent from the Australian rainforest. Our convergent synthesis features a [3+2] dipolar cycloaddition of an olefin-bearing 1,3-*syn* diol unit and an oxime segment containing 1,2-*syn* diol functionality as the key step. The segments were synthesized in a highly enantioselective manner using Noyori asymmetric hydrogenation of a *β*-keto ester and Sharpless asymmetric dihydroxylation of an *α*,*β*-unsaturated ester. Cycloaddition provided isoxazoline derivative which upon hydrogenolysis furnished the *β*-hydroxy ketone expediently. A one-pot, acid-catalyzed reaction removed the isopropylidene group, promoted spirocyclization, constructed the complex spiroketal lactone core, and furnished EBC-23 and its C11 epimer. The C11 epimer was also converted to EBC-23 by chemoselective oxidation and reduction sequence. The present synthesis provides convenient access to this family of natural products in an efficient manner.

INTRODUCTION

Bioactive natural products are an important source of structurally diverse molecules for drug discovery and development.[1,2] Australia is the home to some of the most magnificent rainforests in the world. The great land size, ecosystem, and climate range of this continent have produced a unique and highly diverse flora and fauna. In 2007, as a part of a screening program in search of novel anticancer agents from the Australian tropical rainforests, Reddell and Gordon reported the isolation of an intriguing family of natural products, EBC-23 (**1a**, Figure 1), diacetate of 23 (**1b**), 24 (**1c**), 25 (**1d**), 72 (**1e**), 73 (**1f**), 75 (**1g**), and 76 (**1h**) with spiroketal and fused *α*,*β*-unsaturated *δ*-lactone structural cores from the fruit of *Cinnamonum laubatii* (family Lauraceae).[3,4] These natural products exhibited potent anticancer activity against a number of representative human cancer cell lines. In particular, EBC-23 showed inhibition of cell growth against MM96L (melanoma), MCF7 (breast cancer), and DV145 (prostate cancer) with IC_{50} values of 0.2, 0.45, and 0.48 *μ*g/mL, respectively. In comparison, normal cells are less susceptible to EBC, showing an IC_{50} value of 1.8 *μ*g/mL against NFF (normal fibroblasts) cell lines.[3,4] Furthermore, EBC-23 was evaluated in mouse xenograft models with human prostate tumor cell line, DV-145. EBC-23 inhibited tumor growth with no observable side effects compared to solvent-only controls. This result indicated that EBC-23 and its structural variants have the potential for the treatment of refractory solid tumors in adults.[3,4]

EBC-23 possesses a unique spiroketal with a fused *α*,*β*-unsaturated *δ*-lactone structural feature and six asymmetric centers. The initial structural assignment was carried out by extensive spectroscopic studies and comparison with a natural product, osumundalactone. Subsequently, Williams and co-workers confirmed the structure of EBC-23 and its absolute configuration through enantioselective total synthesis using efficient linchpin strategies.[5−7] The EBC-family of natural products generated much interest in synthesis due to their interesting structural features and potent anticancer activity. Yamamoto and co-workers reported an efficient synthesis of EBC-23 utilizing a supersilyl-aldol reaction as the key step.[8] Yadav and co-workers recently reported the synthesis of EBC-23 utilizing gold-catalyzed spiroketalization of alkylnol as one of the key steps.[9] As part of our interests in exploration of chemistry and biology of EBC-family of natural products, we sought to develop a practical and convergent synthesis of EBC-23 in an effort to facilitate the synthesis of structural variants. Herein, we report an enantioselective synthesis of EBC-23 in a convergent manner employing a [3+2] dipolar cycloaddition as

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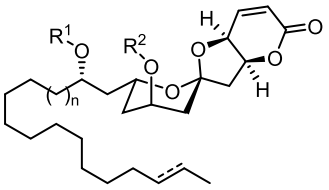
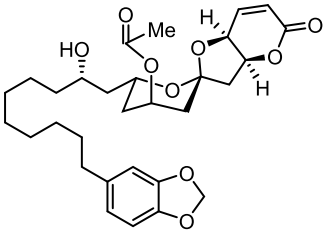


EBC-23 (**1a**) $R^1 = R^2 = H$; n =1
(**1b**) $R^1 = R^2 = Ac$; n =1
EBC-24 (**1c**) $R^1 = R^2 = H$; n = 3; Δ
EBC-25 (**1d**) $R^1 = Ac$; $R^2 = H$; n = 1
EBC-72 (**1e**) $R^1 = Ac$; $R^2 = H$; n = 1; Δ
EBC-75 (**1f**) $R^1 = Ac$; $R^2 = H$; n = 1; Δ
EBC-76 (**1g**) $R^1 = Ac$; $R^2 = H$; n = 1; Δ



EBC-73 (**1h**) $R^1 = R^2 = H$; n =1

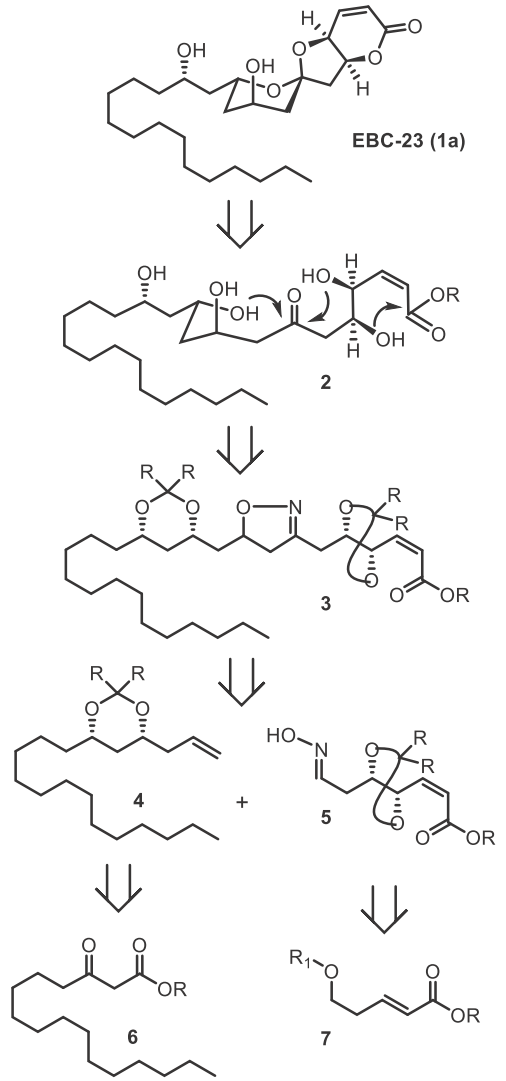
Figure 1. Structures of EBC-23 (**1a**) and related family of natural products.

one of the key reactions. The spiroketal bearing fused *α,β*-unsaturated *δ*-lactone structural core was constructed in a one-pot reaction from the isoxazoline-derived polyhydroxy ketone intermediate. The route is potentially amenable toward the synthesis of structural variants of the EBC-family of natural products for medicinal chemistry optimization.

RESULTS AND DISCUSSION

The EBC-23 family of natural products has shown significant potential for medicinal application. One of our main objectives in the total synthesis is to develop an efficient and practical asymmetric synthesis of (+)-EBC-23 (**1a**) that can be amenable to the synthesis of other members of the EBC-family as well as to the synthesis of structural variants for the structure−activity relationship studies and medicinal chemistry development. Our retrosynthetic analysis is shown in Scheme 1. As depicted, we envisioned that EBC-23 (**1a**) would be obtained from an appropriately protected polyhydroxy ketone intermediate **2**. Presumably, the removal of the protection would affect spiroketal formation as the construction of the *α,β*-unsaturated *δ*-lactone functionality leading to EBC-23 concommitantly. The polyhydroxy ketone intermediate is masked in the isoxazoline derivative **3**, where reductive cleavage of the isoxazoline ring would provide the planned *β*-hydroxy ketone functionality. The isoxazoline heterocycle would be synthesized conveniently by a [3+2] nitrile oxide cycloaddition reaction involving functionalized alkene derivative **4** and aldoxime **5**. The cycloaddition reaction will install the C-11 hydroxyl group necessary for EBC-23 synthesis. While the nitrile oxide cycloaddition of alkene containing allylic stereocenter has been shown to proceed with high diastereoselectivity, the stereocontrol with a homoallylic substrate is likely to be limited.[10−13] However, the formation of a mixture of diastereomers can provide ready access to the C11 epimer of EBC-23. Also, the C11 epimer can be readily

Scheme 1. Retrosynthesis of EBC-23 (1a)



converted to EBC-23 by inversion of configuration. Functionalized alkene **4** can be derived from *β*-keto ester **6** by Noyori asymmetric hydrogenation followed by *syn*-selective reduction of a *β*-hydroxy ketone intermediate. Also, the 1,2-*syn*-hydroxy stereochemistry of oxide **5** can be constructed by Sharpless asymmetric dihydroxylation of an appropriately protected *α,β*-unsaturated ester **7**. All stereocenters of the functionalized alkene and oxime segments will be set by asymmetric synthesis.

Our synthesis of functionalized alkene derivative **4** is shown in Scheme 2. The preparation of *β*-keto ester **9** was accomplished from the commercially available 1-tetradecanal **8**, as reported in the literature.[14,15] Noyori asymmetric hydrogenation[16,17] of *β*-keto ester **9** using $RuCl_2$ [(*S,S*)-BINAP] catalyst (0.5 mol %) in ethanol under 400 psi hydrogen pressure at 50 °C for 3 h provided *β*-hydroxy ester **10** enantioselectively in 87% yield. To determine optical purity, ethyl ester **10** was subject to saponification using aqueous NaOH in tetrahydrofuran (THF) at 23 °C for 8 h. The resulting carboxylic acid was esterified with benzyl bromide and K_2CO_3 in dimethylformamide (DMF) at 70 °C for 2 h to provide benzyl ester **11** in 90% yield over two steps. The enantiomeric excess of **11** was determined to be 95% ee by chiral high-performance liquid chromatography (HPLC)

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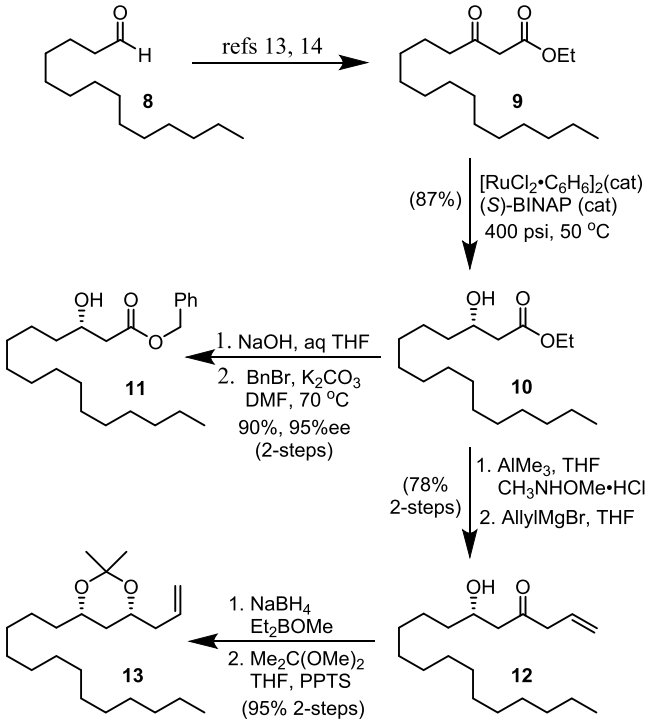
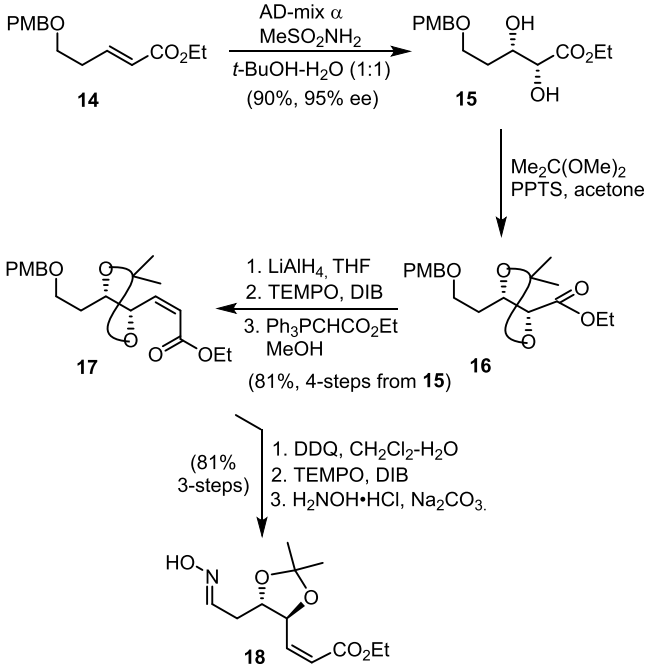
Scheme 2. Synthesis of Functionalized Alkene 13



Scheme 3. Synthesis of Functionalized Aldoxime 18



analysis using chiralpak OD-H column. Ester **10** was converted to the corresponding Weinreb amide,[18,19] by exposure to $AlMe_3$ and MeNHOMe·HCl in THF at −10 to 23 °C for 2 h. The resulting Weinreb amide was reacted with allyl magnesium bromide in THF at 0 °C for 2 h to furnish allyl ketone **12** in 78% yield over two steps. The hydroxyl group directed stereoselective reduction of *β*-hydroxy ketone using the protocol developed by Narasaka and co-workers,[20,21] with $NaBH_4$ in the presence of Et_2BOMe in a mixture (4:1) of THF and methanol at −78 °C to 0 °C for 3 h resulted in the corresponding *syn*-1,3-diol derivative. The resulting diol was protected as an isopropylidene derivative by reaction with dimethoxypropane in the presence of PPTS in CH_2Cl_2 at 23 °C for 4 h to afford the functionalized alkene **13** in only five steps from keto ester **9**. The reaction sequence proved highly efficient, delivering multigram quantities of alkene **13**.

Our synthetic route to functionalized aldoxime segment **5** is shown in Scheme 3. The *α,β*-unsaturated ester **14** was prepared as described previously.[22] Sharpless asymmetric dihydroxylation[23,24] of **14** using AD-mix-*α* in the presence of $MeSO_2NH_2$ and $NaHCO_3$ in aqueous *t*-BuOH at 0 °C for 48 h furnished *syn*-1,2-diol **15** in 90% yield. The optical purity of diol **15** was over 95% ee as determined by chiral HPLC analysis using chiralpak OD-H column. The resulting diol was protected as its isopropylidene derivative using dimethoxypropane and PPTS in acetone at 23 °C for 4 h to provide ester **16**. LAH reduction of the ester at 0 °C in THF for 2 h followed by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) oxidation,[25,26] of the resulting alcohol in the presence of diacetoxyiodobenzene (DIB) at 23 °C for 6 h provided the corresponding aldehyde which was subjected to *Z*-selective[27,28] Wittig olefination with ethoxycarbonyl triphenylphosphorene in MeOH at 23 °C for 12 h to provide a mixture (1:5 ratio by ^1H nuclear magnetic resonance (NMR) analysis) of *E*/*Z*-*α,β*-unsaturated esters, which were separated by silica gel chromatography. The desired *Z*-isomer **17** was obtained in 81% yield from diol **15**.

Ester **17** was converted to oxime **18** in a three-step sequence involving: (1) exposure of **17** to DDQ in aqueous CH_2Cl_2 at 0−23 °C for 2 h to remove the PMB group, (2) TEMPO oxidation,[25,26] of the resulting alcohol to give aldehyde, and (3) reaction of aldehyde with hydroxylamine at 23 °C for 2 h to furnish functionalized oxime **18** in 81% yield over three steps. The overall route to oxime was very efficient and all steps leading to *α,β*-unsaturated ester **18** were carried out on multigram scale.

With the synthesis of the requisite alkene and oxime partners, our focus now shifted to the union of the alkene and oxime segments via intermolecular [3+2] nitrile oxide cycloaddition, as shown in Scheme 4. There are a number of reported methods for the generation of nitrile oxide and the formation of isoxazoline heterocyles under mild conditions.[29,30] However, our initial attempts to merge alkene **13** and aldoxime **18** under various conditions gave unsatisfactory low yields of the target along with unidentified products. As shown in Table 1, known conditions with *t*-BuOCl, NaOCl, or NCS hardly provided any desired cycloadduct **19**.[31,32] The possible reason is that the oxidation of aldoxime **18** forms the linear aliphatic nitrile oxide, which is chemically very reactive and readily undergoes dimerization in an organic solvent or mixed solvent system. We have then examined the generation of nitrile oxide using an environmentally benign condition using oxone.[33−35] As shown, we found that nitrile oxide generated using oxone at 23 °C for 5 h provided cycloadduct **19** in 11% yield as an inseparable mixture (1:1) of diastereomers by ^1H NMR analysis (entry 6). Further optimization using oxone in combination with potassium chloride (1:1 mixture) and addition of aldoxime **19** in portions for 4 h in water at 23 °C improved the result, affording isoxazolines **19** as an inseparable mixture (1:1) of diastereomers in 45% yield (entry 9).[35] Reductive cleavage of the isoxazoline ring was carried out under mild conditions using

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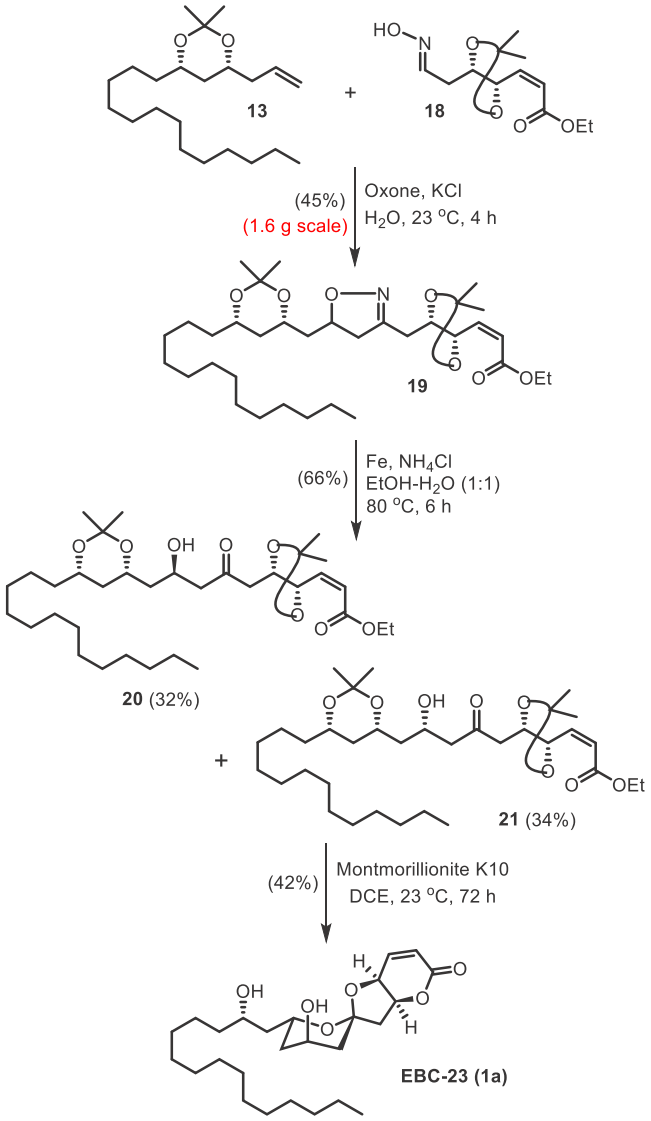
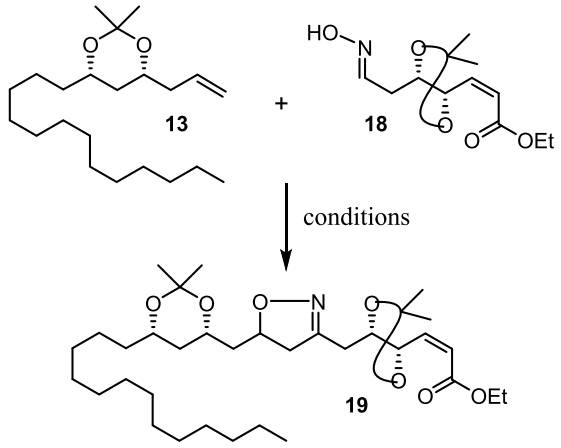
Scheme 4. Convergent Synthesis of EBC-23 (1a)



iron catalyst.[36−38] Treatment of isoxazoline **19** with Fe powder in a mixture of EtOH and water at 23 °C for 6 h resulted in reductive cleavage of the isoxazoline ring and provided β-hydroxyl ketone diasetereomers **20** and **21** in nearly 1:1 ratio with a combined yield of 66%. Both diastereomers were readily separated by column chromatography over silica gel. The configuration of the carbinol carbon in compounds **20** and **21** was assigned after transformation to their respective cyclization products. The (3+2) cycloaddition reaction installed the C11 stereocenter as a 1:1 mixture, thus providing an option to synthesize EBC-23 as well as its C11 epimer. With the polyketide backbone in place, we investigated a sequential deprotection, spirocyclization, and esterification in a one-pot manner to provide the target EBC-23. To this end, as summarized in Table 2, a variety of typical acid conditions led to low yields of the target along with a lot of complex and unidentified products.[39] Fortunately, montmorillonite K10 clay which provides a mild proton source offered encouraging results (entries 8−10). Exposure of diastereomeric β-hydroxy ketone **21** to montmorillonite K10 clay in dichliroethane (DCE) at 15 °C for 72 h removed the isopropylidene group, formed spiroketal and δ-lactone concommitatly, and furnished

Table 1. Cycloaddition of Alkene 13 and Aldoxime 18 Under Various Conditions[a]



entry	conditions (equiv)	solvent	temperature (time)	yield (%)
1	**13** (1) + **18** (1) Et_3N, ^tBuOCl (1.1)	CH_2Cl_2	0 °C (12 h)	<5
2	**13** (1) + **18** (1) Et_3N, ^tBuOCl (slow addition)	CH_2Cl_2	0 °C (12 h)	<5
3	**13** (1) + ^tBuOCl (1:1) Et_3N, **18** (1) slow addition	CH_2Cl_2	0 °C (12 h)	<5
4	**13** (1) + **18** (1) Et_3N, NaOCl (10)	CH_2Cl_2	0 °C (12 h)	NR
5	**13** (1) + **18** (1) Na_2CO_3 (1.5), oxone (3)	CH_3CN-H_2O (20:1)	23 °C (24 h)	NR
6	**13** (1) + **18** (1) KCl (1), oxone (2)	MeOH H_2O (1:3)	23 °C (3 h)	11
7	**13** (1.1) + **18** (1) KCl (1), oxone (2)	H_2O	23 °C (3 h)	28
8	**13** (1.1) + oxone (2); KCl (1); **18** (1), added in five portions, 1 h	H_2O	23 °C (3 h)	34
9	**13** (4), oxone (2), KCl (1); **18** (1) added in four portions, 15 min	H_2O	23 °C (3 h)	45
10	**18** (1) and NCS (1.2); **13** (1.1)	DMF/ CH_2Cl_2	40 °C (1 h) 23 °C (12 h)	<5

[a]The diastereomeric ratio of the cycloaddduct was 1:1 by ^1H NMR analysis.

EBC-23 (**1a**) in 42% yield. The ^1H NMR and ^{13}C NMR spectra of synthetic (+)-EBC-23 (**1a**) {$[\alpha]_D^{20}$ + 15.5 (*c*, 0.75, $CHCl_3$)} are in complete agreement with reported spectra for synthetic and natural (+)-EBC-23 (**1a**).[5−7]

We have converted epimeric β-hydroxy ketone **20** into its C11-epimeric EBC-23 derivative and also transformed it into EBC-23 (**1a**) by an oxidation and reduction sequence. As shown in Scheme 5, montmorillonite K10 clay-promoted spirocyclization and lactonization of hydroxy ketone **20** resulted in C11-epimeric EBC-23 (**22**) in 58% yield. The yield of spirocyclization improved possibly due to the formation of a more stable spiroketal with equatorial C11 hydroxyl group in **22**. Selective epimerization of the C11 alcohol stereocenter in **22** turned out to be a significant problem. When diol **22** was subjected to Mitsunobu conditions, only starting material was recovered. We then planned selective oxidation of the cyclic alcohol over the C15 acyclic alcohol followed by selective reduction to obtain axial alcohol. Swern oxidation or Dess−Martin periodinane

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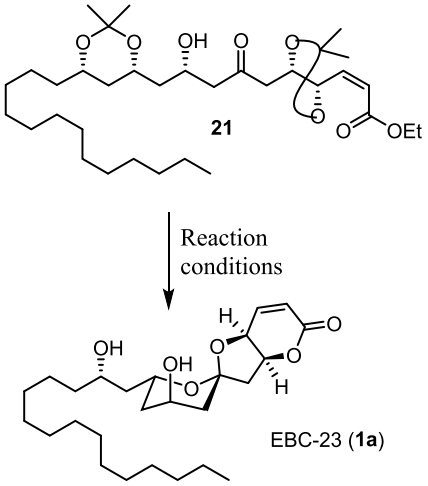
Table 2. Reaction Conditions for Spirocyclization and Lactonization



entry	acid conditions	solvent	temperature (time)	result[a]
1	PTSA	MeOH	23 °C (24 h)	complex[b]
2	PPTS	MeOH	23 °C (24 h)	complex[b]
3	Amberlyst-15 (25% w/w)	MeOH	23 °C (48 h)	<5% yield
4	AcOH-H_2O (1:1)		23 °C (12 h)	complex[b]
5	PTSA	THF-H_2O (10:1)	23 °C (24 h)	complex[b]
6	CSA	MeOH/THF-H_2O (10:5:1)	23 °C (24 h)	complex[b]
7	1 M HCl	THF-H_2O (10:1)	23 °C (48 h)	complex[b]
8	K10 (500% w/w)	CH_2Cl_2	23 °C (48 h)	20% yield
9	K10 (500% w/w)	DCE	23 °C (48 h)	26% yield
10	K10 (500% w/w)	DCE	15 °C (72 h)	42% yield

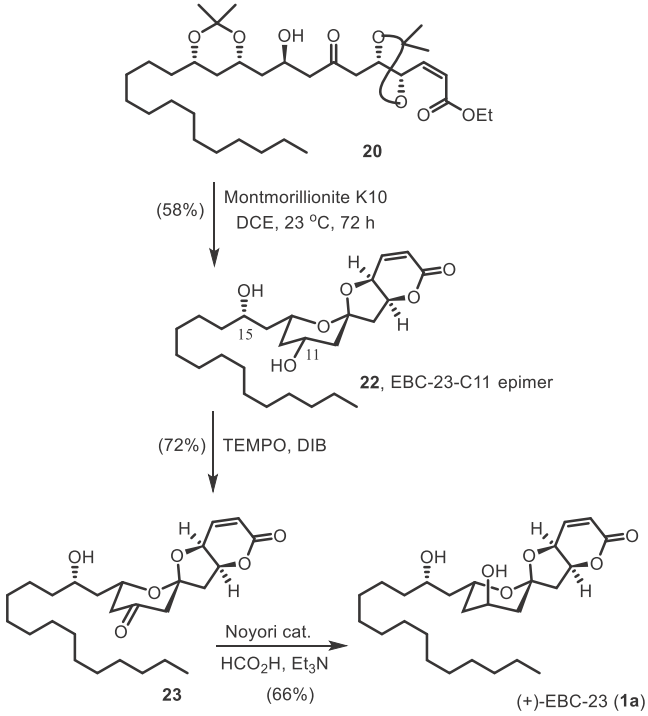
[a]Yield after silica gel chromatography. [b]Unidentified complex mixture of products.

conditions resulted in the oxidation of both alcohols. However, TEMPO oxidation[25,26] turned out to be selective for the cyclic C11 alcohol. Thus, exposure of **22** to TEMPO in the presence of DIB yielded the desired ketone **23** in 72% yield. Selective reduction of **23** using metal hydrides was unsatisfactory due to the presence of the sensitive α,β-unsaturated-δ-lacone functionality.[40] Noyori asymmetric reduction[41,42] of **23** with a catalytic amount (0.5 mol %) of RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] in the presence of HCO_2H and Et_3N in CH_2Cl_2 at 23 °C for 20 h afforded a diastereomeric 3.8:1 mixture of alcohols in 83% combined yield. The major isomer EBC-23 (**1a**) was separated by silica gel chromatography in 66% yield.

CONCLUSIONS

An enantioselective synthesis of EBC-23 has been accomplished. EBC-23 and members of this family of natural products from the Australian rainforest show potent anticancer activity with potential for clinical application. The synthesis involves asymmetric assembly of EBC-23 using highly enantioselective sharpless dihydroxylation and Noyori hydrogenation reactions. One of the key features of the current

Scheme 5. Synthesis of EBC-23 Epimer (22) and Epimerization of C11 Stereochemistry



synthesis is the K-10-mediated formation of spiroketal and osumundalactone core of EBC-23 from the polyketide intermediate that removes protecting group and leads to spiroketalization and lactonization in a one-pot operation. This synthetic route provides EBC-23 in 3.8% overall yield for 11 longest linear steps. The scalable synthesis of isoxazoline as the β-hydroxyl ketone precursor uses environmentally friendly conditions. The synthesis provides access to C11-(*R*)-epimer of EBC-23 and a route to the conversion of the epimer to EBC-23. The present convergent asymmetric synthesis is practical and will provide rapid access to the synthesis of important structural variants for medicinal chemistry optimization.

EXPERIMENTAL SECTION

All reactions were performed in oven-dried round-bottom flasks followed by flame drying in the case of moisture-sensitive reactions. The flasks were fitted with rubber septa and kept under a positive pressure of argon. Cannula was used in the transfer of moisture-sensitive liquids. Heated reactions were allowed to run using an oil bath on a hot plate equipped with a temperature probe. Thin-layer chromatography (TLC) analysis was conducted using glass-backed thin-layer silica gel chromatography plates (60 Å, 250 μm thickness, F-254 indicator). Flash chromatography was done using a 230−400 mesh, a 60 Å pore diameter silica gel. Organic solutions were concentrated at 30−35 °C on a rotary evaporator. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. ^{13}C{^{1}H} NMR spectra were recorded at 100 MHz NMR. Chemical shifts are reported in parts per million and referenced to the deuterated residual solvent peak ($CDCl_3$, 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). NMR data are reported as δ value (chemical shift), *J*-value (Hz), and integration, where s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, dd = doublet doublets, and so on. Optical rotations were recorded on a digital polarimeter. Low-resolution mass spectra (LRMS) spectra were recorded using a quadrupole LCMS under positive electrospray ionization (ESI+). High-resolution mass spectrometry (HRMS) spectra were recorded at

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the Purdue University Department of Chemistry Mass Spectrometry Center. These experiments were performed under ESI+ and positive atmospheric pressure chemical ionization (APCI+) conditions using an Orbitrap XL Instrument.

Ethyl (*S*)-3-hydroxyhexadecanoate (10). A suspension of $[RuCl_2(C_6H_6)]_2$ complex (84 mg, 0.17 mmol) and (*S*)-BINAP (210 mg, 0.34 mmol) in dry DMF (5.7 mL) was heated at 100 °C for 10 min, until complete dissolution, and then cooled down to room temperature. The dark red mixture was then added via cannula to a previously degased solution of α-keto ester **9** (10.0 g, 33.5 mmol) in dry ethanol (19 mL). The resulting solution was placed under a 400 psi hydrogen atmosphere and stirred at 50 °C for 3 h. After evaporation of the solvents, the crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (5−20 (v/v%)) as eluent to afford the desired alcohol **10** (8.75 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.1 Hz, 2H), 3.98 (d, *J* = 3.0 Hz, 1H), 2.97 (br. s., 1H), 2.48 (d, *J* = 16.0 Hz, 1H), 2.38 (dd, *J* = 16.4, 9.3 Hz, 1H), 1.50 (d, *J* = 8.9 Hz, 1H), 1.41 (d, *J* = 8.2 Hz, 2H), 1.37−1.18 (m, 24H), and 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.1, 68.0, 60.6, 41.3, 36.5, 31.9, 29.6 (4C), 29.5, (3C), 29.3, 25.4, 22.7, 14.1, and 14.0; $[\alpha]_D^{20}$ +11.3 (*c* 6.00 $CHCl_3$); IR (neat): ν_{max} 3355, 2970, 2855, 1720,1378, 1302, 1160, 1129, 952, 817, and 757 cm^{-1}; HRMS (ESI) *m*/*z*: $[M+Na]^+$ calcd for $C_{18}H_{36}O_3Na$ 323.2565; found 323.2574.

Benzyl (*S*)-3-hydroxyhexadecanoate (11). To a solution of ester **10** (170 mg, 0.57 mmol) in THF (3.4 mL) were added 2M NaOH (3.4 mL, 6.8 mmol). The solution was stirred at ambient temperature for 8 h. The reaction was quenched by 4M HCl until pH < 7 and extracted with ethyl acetate. The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was without purification to further step.

To a solution of residue in DMF (1.1 mL) was added K_2CO_3 (87 mg, 0.63 mmol), followed by benzyl bromide. The mixture was stirred at 70 °C for 2 h. The reaction was added water and extracted with ethyl acetate. The organic layer was then dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (5−20 (v/v%)) as eluent to afford desired compound **11** (0.18 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.31 (m, 5H), 5.18 (s, 2H), 4.05 (d, *J* = 3.8 Hz, 1H), 2.94 (d, *J* = 4.1 Hz, 1H), 2.63−2.54 (m, 1H), 2.54−2.42 (m, 1H), 1.58−1.49 (m, 1H), 1.45 (d, *J* = 5.1 Hz, 2H), 1.40−1.20 (m, 23H), and 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.9, 135.6, 128.6, 128.4, 128.3, 68.1, 66.5, 41.4, 36.5, 32.0, 29.7, 29.7, 29.6, 29.6, 29.4, 25.5, 22.7, and 14.2; $[\alpha]_D^{20}$ +12.4 (*c* 6.02 $CHCl_3$); IR (neat): ν_{max} 3360, 2970, 2855, 1724,1379, 1216, 1128, 951, 816, 755, and 697 cm^{-1}; HRMS (APCI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{39}O_3$ 363.2894; found 363.2898. Enantiomeric excess of **11** was determined to be 95% ee of the S-enantiomer (^{t}R = 18.03 min) by normal phase chiral HPLC analysis (column: Chiralcel OD-H 4.6 × 250 mm^2, eluent A: hexane; eluent B: *i*-PrOH; 95% A/5% B, flow rate: 0.5 mL/min, detection: UV 220 nm).

(*S*)-6-Hydroxynonadec-1-en-4-one (12). MeONHMe·HCl (4.54 g, 46.5 mmol) was dissolved in THF (20.0 mL) at −10 °C and a solution of $AlMe_3$ (2 M solution, 23.3 mL, 46.5 mmol) was added via syringe over a 30 min period. The reaction mixture was stirred at room temperature for 45 min and then a THF solution (20.0 mL) of ester **10** (6.35 g, 21.2 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The reaction was then quenched by a careful addition of a saturated NH_4Cl aqueous solution followed by an addition of ethyl acetate and by an aqueous saturated solution of Rochelle salt. The resulting mixture was stirred overnight, then the phases were separated and the aqueous phase was extracted twice by ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (40−50 (v/v%)) as eluent to afford desired compound **10′** (6.55 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (br. s., 1H), 3.76 (br. s., 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.62 (m, 1H), 2.43 (m, 1H), 1.59−1.47 (m, 1H), 1.47−1.35 (m, 2H), 1.35−1.15 (m, 21H), and 0.89−0.80 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.9, 67.8, 61.2, 38.1, 36.5, 31.8, 31.7, 29.6, 29.5, 29.3, 25.5, 22.6, and 14.0; $[\alpha]_D^{20}$ +26.3 (*c* 3.76 $CHCl_3$); IR (neat): ν_{max} 3459, 2924, 2853, 1650, and 1387 cm^{-1}; LRMS (ESI) *m*/*z*: 316.3 $(M + H)^+$.

To the above amide dissolved in anhydrous tetrahydrofuran (40 mL) under an argon atmosphere was added allyl magnesium bromide (1 M in ethyl ether, 42.2 mL, 42.2 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C. The reaction was then quenched by an addition of a saturated NH_4Cl aqueous solution followed by addition of ethyl acetate. The resulting mixture was stirred overnight, then the phases were separated and the aqueous phase was extracted twice by ethyl acetate. Combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (20 (v/v%)) as eluent to afford desired compound **12** (4.89 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98−5.84 (m, 1H), 5.31−5.10 (m, 2H), 4.05 (d, *J* = 2.7 Hz, 1H), 3.21 (d, *J* = 7.2 Hz, 2H), 2.94 (d, *J* = 2.4 Hz, 1H), 2.70−2.60 (m, 1H), 2.60−2.50 (m, 1H), 1.58−1.18 (m, 24H), and 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 209.9, 130.0, 119.3, 67.6, 48.7, 48.4, 36.5, 31.9, 29.69, 29.67, 29.59, 29.55, 29.37, 25.5, 22.7, and 14.1; $[\alpha]_D^{20}$ + 22.4 (*c* 8.87 $CHCl_3$); IR (neat): ν_{max} 3380, 2969, 2925, 2855, 1710,1379, 1129, 952, 817, and 757 cm^{-1}; HRMS (ESI) *m*/*z*: $[M +Na]^+$ calcd for $C_{19}H_{36}O_2Na$ 319.2617; found: 319.2625.

(4*R*,6*S*)-4-Allyl-2,2-dimethyl-6-tridecyl-1,3-dioxane (13). To a solution of hydroxy ketone **12** (4.40 g, 14.9 mmol) in anhydrous tetrahydrofuran (102 mL) and anhydrous methanol (27 mL) at −78 °C under argon was added dropwise diethylmethoxyborane (2.3 mL, 16.2 mmol), and the resulting mixture was stirred for 15 min. Then, sodium borohydride (603 mg, 16.2 mmol) was added. The resulting mixture was stirred at 0 °C for 3 h. MeOH (70 mL), aq. NaOH (2 M; 21 mL), and aq. H_2O_2 (30%; 20 mL) were added. The resulting mixture was stirred at ambient temperature for 15 h. The mixture was concentrated. The residue was dissolved in a mixture of CH_2Cl_2 (50 mL) and brine (50 mL). The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic extracts were washed with satd. aq. Na_2SO_3 (30 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude product was used without purification.

To the above diol dissolved in anhydrous dichloromethane (90 mL) under an argon atmosphere were added pyridium *p*-toluenesulfonate (190 mg, 0.7 mmol) and dimethoxypropane (7.3 mL, 59.4 mmol). The mixture was then stirred for 4 h at room temperature. The filtrate was washed with $NaHCO_3$ solution (30 mL, 5%) and brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (4 (v/v%)) as eluent to afford desired compound **13** [4.79 g, 95% (two steps)] as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.70 (m, *J* = 7.2 Hz, 1H), 5.16−4.95 (m, 2H), 3.91−3.82 (m, 1H), 3.82−3.72 (m, 1H), 2.37−2.23 (m, 1H), 2.14 (td, *J* = 14.1, 7.1 Hz, 1H), 1.50 (td, *J* = 12.7, 2.3 Hz, 2H), 1.45−1.40 (m, 3H), 1.39 (s, 4H), 1.33−1.19 (m, 23H), 1.16−1.04 (q, *J* = 12.6 Hz, 1H), and 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 134.2, 116.9, 98.3, 68.9, 68.6, 40.8, 36.4, 36.3, 31.8, 30.2, 29.6, 29.57, 29.52, 29.28, 24.9, 22.6, 19.7, and 14.0; $[\alpha]_D^{20}$ +1.8 (*c* 1.81 $CHCl_3$); IR (neat): ν_{max} 2924, 2854, 1464, 1379, 1199, 1172, and 954 cm^{-1}; HRMS (APCI-Orbitrap) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{43}O_2$; 339.3258; found: 339.3260.

Ethyl (2*R*,3*S*)-2,3-dihydroxy-5-((4-methoxybenzyl)oxy)-pentanoate (15). A solution of AD-mix-α (33.0 g), $NaHCO_3$ (5.70 g, 67.9 mmol), and $MeSO_2NH_2$ (2.20 g, 23.1 mmol) in *t*-BuOH/H_2O 1:1 (230 mL) was stirred at r.t. until both phases were clear and then cooled to 0 °C. Ethyl(E)-5-((4-methoxybenzyl)oxy)-pent-2-enoate **14** (6.00 g, 22.7 mmol) was added and the slurry was stirred at 0 °C for 48 h. Solid $Na_2S_2O_5$ (1 g) was added at 0 °C, and the resulting mixture was warmed to r.t. and stirred for 1 h. Extraction with ethyl acetate and evaporation of the washed (2 N NaOH) org. soln. gave a solid crude residue. The crude product was purified by

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flash chromatography on silica using ethyl acetate/hexane mixtures (40 (v/v%)) as eluent to afford desired compound **15** (6.10 g, 90% yield, 95% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 4.50−4.41 (m, 2H), 4.32−4.21 (m, 2H), 4.18−4.12 (m, 1H), 4.06 (d, J = 1.6 Hz, 1H), 3.79 (s, 3H), 3.72−3.58 (m, 2H), 2.04−1.94 (m, 1H), 1.84 (m, 1H), and 1.30 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.1, 159.2, 129.9, 129.3, 113.8, 73.5, 72.9, 71.4, 67.6, 61.8, 55.2, 33.2, and 14.1; $[\alpha]_D^{28}$ −2.7 (c 3.22 $CHCl_3$); IR (neat): ν_{max} 3471, 2962, 2855, 1734, 1613, 1368, 1247, 1130, 1032, and 821 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{15}H_{22}O_6Na$; 321.1309; found 321.1312. Enantiomeric excess of **15** was determined to be 95% ee of the S-enantiomer (^{t}R = 15.08 min) by normal phase chiral HPLC analysis (column: Chiralcel OD-H 4.6 × 250 mm^2, eluent A: hexane; eluent B: i-PrOH; 80% A/20% B, flow rate: 0.5 mL/min, detection: UV 220 nm).

Ethyl (4*R*,5*S*)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (16). To the above diol **15** (6.10 g, 20.5 mmol) dissolved in acetone (73 mL) were added p-toluenesulfonic acid (28.2 mg, 0.16 mmol) and dimethoxypropane (2.60 g, 24.6 mmol). The mixture was then stirred for 4 h at room temperature. The filtrate was washed with $NaHCO_3$ solution (3 mL, 5%) and brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography on silica using ethyl acetate/hexanes mixtures (10 (v/v%)) as eluent to afford desired compound **16** (6.6 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.42 (s, 2H), 4.33−4.13 (m, 4H), 3.79 (s, 3H), 3.67−3.51 (m, 2H), 2.17−2.02 (m, 1H), 2.01−1.89 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.6, 159.1, 130.3, 129.1, 113.7, 110.6, 79.1, 76.4, 72.6, 66.2, 61.2, 55.2, 33.5, 27.1, 25.7, and 14.1; $[\alpha]_D^{28}$ −18.2 (c 3.81 $CHCl_3$); IR (neat): ν_{max} 2988, 2936, 2855, 1756,1613, 1464, 1212, 1171, 1034, and 820 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{18}H_{27}O_6Na$; 361.1622; found: 361.1624.

Ethyl (*Z*)-3-((4*S*,5*S*)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (17). The ester **16** (5.00 g, 14.8 mmol) dissolved in THF (50 mL) at 0 °C. $LiAlH_4$ (1.12 g, 29.5 mmol) was slowly added to the reaction at 0 °C and stirred for 2 h. The reaction was then quenched by a careful addition of a saturated NH_4Cl aqueous solution followed by an addition of ethyl acetate and an aqueous saturated solution of Rochelle salt. The resulting mixture was stirred until clear, then the phases were separated and the aqueous phase was extracted twice by ethyl acetate. Combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude was used without purification.

To the above alcohol dissolved in CH_2Cl_2 (60 mL) were added 2,2,6,6-tetramethyl-1-piperidinyloxy (463 mg, 2.96 mmol) and (diacetoxyiodo)benzene (7.10 g, 22.2 mmol). The mixture was stirred for 6 h at room temperature. The reaction was quenched by a saturated $Na_2S_2O_3$ aqueous solution followed by an addition of CH_2Cl_2, then the phases were separated and the aqueous phase was extracted twice by CH_2Cl_2. Combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude was used without purification.

To an ice-cooled solution of aldehyde in MeOH (75 mL) was added ethoxycarbonyl triphenylphosphorane (5.67 g, 16.3 mmol) in small portions and the mixture was stirred at room temperature overnight. After the solvent was evaporated in vacuo, The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures (10 (v/v%)) as eluent to afford Z-selectivity olefin **17** (4.47 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.20 (m, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.11 (dd, J = 11.6, 8.9 Hz, 1H), 5.94−5.87 (m, 1H), 5.29 (t, J = 8.5 Hz, 1H), 4.42 (d, J = 1.4 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.93−3.82 (m, 1H), 3.82−3.75 (m, 3H), 3.60−3.51 (m, 2H), 2.04−1.84 (m, 2H), 1.42 (s, 6H), and 1.27 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.4, 159.1, 145.2, 130.5, 129.2, 123.1, 113.7, 109.3, 77.8, 76.1, 72.6, 66.7, 60.4, 55.2, 32.4, 27.3, 27.0, and 14.2; $[\alpha]_D^{20}$ +41.0 (c 6.04 $CHCl_3$); IR (neat): ν_{max} 2983, 2852, 1718,1656, 1587, 1418, 1302, 1165, 1034, 876, and 820 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{29}O_6$ 365.1959; found 365.1963.

Ethyl (2*Z*)-3-((4*S*,5*S*)-5-(2-(hydroxyimino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (18). To a solution of the alkene **17** (7.00 g, 19.2 mmol) in a mixture of CH_2Cl_2/H_2O (17/1, 100 mL), DDQ (6.50 g, 28.6 mmol) was added at 0 °C. After 30 min, the reaction mixture was warmed to room temperature and further stirred for 2 h before it was diluted with CH_2Cl_2 and quenched with sat. aq. $NaHCO_3$. The organic phase was separated, washed with sat. aq. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (30−40 (v/v%)) as eluent to afford desired compound **17′** (4.13 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19−6.06 (m, 1H), 5.93 (d, J = 11.6 Hz, 1H), 5.33 (t, J = 8.4 Hz, 1H), 4.15 (q, J = 6.7 Hz, 2H), 3.87 (dt, J = 7.9, 3.4 Hz, 1H), 3.83−3.68 (m, 2H), 2.27 (br. s., 1H), 2.01−1.84 (m, 2H), 1.53−1.32 (m, 7H), and 1.32−1.18 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.4, 145.2, 123.2, 109.7, 79.6, 76.1, 60.5, 60.4, 34.0, 27.2, 27.0, and 14.1; $[\alpha]_D^{20}$ +46.3 (c 6.86 $CHCl_3$); IR (neat): ν_{max} 3421, 2986, 2850, 1720, 1658, 1418, 1371, 1162, 1067, 1031, 873, 825, and 508 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{12}H_{20}O_5Na$ 267.1203; found 267.1205.

The alcohol (4.15 g, 17.0 mmol) dissolved in CH_2Cl_2 (80 mL) were added 2,2,6,6-tetramethyl-1-piperidinyloxy (530 mg, 3.39 mmol) and (diacetoxyiodo)benzene (8.20 g, 25.5 mmol). The mixture was stirred for 6 h at room temperature. The reaction was quenched by a saturated $Na_2S_2O_3$ aqueous solution followed by an addition of CH_2Cl_2, then the phases were separated and the aqueous phase was extracted twice by CH_2Cl_2. Combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude was used without purification.

To the above aldehyde dissolved in the mixture of EtOH/H_2O 1/1 (52 mL) were added $NH_2OH{\cdot}HCl$ (1.30 g, 18.7 mmol) and Na_2CO_3 (900 mg, 8.50 mmol). The reaction was stirred at room temperature for 2 h. The reaction was then quenched with water followed by an addition of ethyl acetate. The reaction was extracted with ethyl acetate. The organic layer was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (5−20 (v/v%)) as eluent to afford desired diastereomeric mixture of oxime **18** (3.99 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, J = 5.8 Hz, 1H), 6.95−6.81 (m, 1H), 6.23−6.05 (m, 2H), 5.95 (d, J = 11.6 Hz, 2H), 5.33 (t, J = 8.2 Hz, 2H), 4.26−4.07 (m, 4H), 3.89 (dtd, J = 15.5, 7.9, 3.9 Hz, 2H), 2.92−2.79 (m, 1H), 2.75−2.43 (m, 3H), 1.49−1.34 (m, 12H), and 1.34−1.20 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.4 (minor isomer), 165.3, 148.6, 145.0 (minor isomer), 144.6, 123.5, 123.4 (minor isomer), 109.9 (minor isomer), 109.8, 78.3, 77.7, 76.1, 76.0 (minor isomer), 60.6, 32.3, 27.0 (minor isomer), 26.9, and 14.1; $[\alpha]_D^{20}$ + 21.2 (c 4.66 $CHCl_3$); IR (neat): ν_{max} 3339, 2972, 2854, 1722,1381, 1196, 1162, 1129, 951, 817, and 757 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{12}H_{20}NO_5$ 258.1336; found: 258.1335.

Ethyl (*Z*)-3-((4*S*,5*S*)-5-((5-(((4*S*,6*S*)-2,2-dimethyl-6-tridecyl-1,3-dioxan-4-yl)methyl)-4,5-dihydroisoxazol-3-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (19). To a solution of alkene **13** (5.28 g, 15.6 mmol) and a solution of potassium chloride (0.46 g, 6.22 mmol) and oxone (1.90 g, 12.5 mmol) in H_2O (56 mL) was added aldoxime **18** (1.60 g, 6.22 mmol) in four portions in 1 h intervals. After the last addition, the solution was stirred at room temperature for additional 3 h until the completion of reaction, monitored by TLC and NMR. The reaction mixture was diluted with ethyl acetate (50 mL), washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo to give the crude product. The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (10−20 (v/v%)) as eluent to provide the corresponding isoxazoline **19**, diasterisomers ratio: 1:1 (1.56 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21−6.12 (m, 2H), 5.96 (d, J = 11.6 Hz, 2H), 5.35 (d, J = 3.1 Hz, 2H), 4.78−4.61 (m, 2H), 4.17 (q, J = 7.2 Hz, 4H), 4.10−3.99 (m, 2H), 3.95 (d, J = 2.0 Hz, 2H), 3.85−3.73 (m, 2H), 3.18−2.98 (m, 2H), 2.87−2.76

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(m, 3H), 2.63 (d, J = 7.9 Hz, 3H), 1.98−1.88 (m, 1H), 1.78−1.53 (m, 9H), 1.51−1.46 (m, 4H), 1.46−1.38 (m, 18H), 1.38−1.33 (m, 8H), 1.33−1.05 (m, 46H), and 0.88 (t, J = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.4, 156.8, 145.2 (minor isomer), 145.1, 123.3, 110.0 (minor isomer), 109.9, 98.4, 98.2, 78.4, 77.7, 77.5, 76.4, 68.9, 66.1, 66.0 (minor isomer), 60.5, 43.5, 42.9, 42.5, 41.1, 37.4, 36.5 (minor isomer), 36.4, 31.9, 31.1 (minor isomer), 31.0, 30.2, 29.6, 29.5, 29.3, 29.2, 27.3, 27.0, 24.9, 22.6, 19.9, 19.7, 14.1, and 14.0 (minor isomer); $[\alpha]_D^{20}$ +28.6 (c 1.68 $CHCl_3$); IR (neat): ν_{max} 2925, 2855, 1720, 1380, 1196, 1057, 1024, and 855 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{60}NO_7$ 594.4364; found: 594.4355.

Ethyl (*Z*)-3-((4*S*,5*S*)-5-((*R*)-5-((4*R*,6*S*)-2,2-dimethyl-6-tridecyl-1,3-dioxan-4-yl)-4-hydroxy-2-oxopentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (20) and ethyl (*Z*)-3-((4*S*,5*S*)-5-((*S*)-5-((4*R*,6*S*)-2,2-dimethyl-6-tridecyl-1,3-dioxan-4-yl)-4-hydroxy-2-oxopentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (21). To a stirred degassed solution of 2-isoxazoline **19** (1.00 g, 1.69 mmol) and NH_4Cl (2.24 g, 42.3 mmol) in ethanol and water (1:1, 34 mL) was added Fe powder (2.36 g, 42.3 mmol). The mixture was heated to 80 °C and was allowed to stir at this temperature for 6 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a silica pad. The filtrate was washed with brine and the organic layer was separated, dried over $MgSO_4$, and evaporated in vacuo. The residue was then purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (10−20 (v/v%)) as eluent to give two isomers.

*Hydroxy Ketone **20**.* (322 mg, 32%), ^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (dd, J = 11.6, 8.5 Hz, 1H), 5.95 (dd, J = 11.6, 1.0 Hz, 1H), 5.27 (t, J = 7.9 Hz, 1H), 4.39−4.27 (m, 1H), 4.24−4.07 (m, 4H), 3.87−3.71 (m, 1H), 3.29 (d, J = 3.8 Hz, 1H), 2.95−2.76 (m, 2H), 2.62 (d, J = 5.8 Hz, 2H), 1.64−1.45 (m, 7H), 1.45−1.39 (m, 10H), 1.39−1.33 (m, 6H), 1.33−1.16 (m, 20H), and 0.87 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.8, 165.6, 145.5, 123.0, 109.7, 98.5, 76.2, 76.0, 69.0, 66.2, 64.2, 60.5, 50.6, 46.0, 42.4, 36.9, 36.4, 31.9, 30.2, 29.6, 29.5, 29.3, 27.1, 26.9, 24.9, 22.6, 19.8, 14.1, and 14.0; $[\alpha]_D^{20}$ +21.1 (c 4.78 $CHCl_3$); IR (neat): ν_{max} 3403, 2925, 2855, 1718,1381, 1198, 1100, 1048, and 860 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{61}O_8$ 597.4361; found: 597.4350.

*Hydroxy Ketone **21**.* (343 mg, 34%), ^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (dd, J = 11.8, 8.4 Hz, 1H), 5.94 (dd, J = 11.6, 1.0 Hz, 1H), 5.25 (t, J = 7.9 Hz, 1H), 4.29−4.06 (m, 5H), 3.86−3.75 (m, 1H), 3.56 (d, J = 1.4 Hz, 1H), 2.95−2.79 (m, 2H), 2.75−2.52 (m, 2H), 1.68−1.44 (m, 10H), 1.42 (br. s., 3H), 1.41 (br. s., 3H), 1.37 (s, 3H), 1.31−1.22 (m, 22H), 1.21−1.09 (m, 2H), and 0.87 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 207.9, 165.6, 145.5, 123.0, 109.7, 98.5, 76.2, 75.9, 69.0, 68.8, 66.7, 60.5, 50.2, 46.1, 42.5, 36.9, 36.3, 31.9, 30.2, 29.7, 29.6, 29.5, 29.5, 29.3, 27.2, 26.9, 24.9, 22.6, 19.9, 14.1, and 14.0; $[\alpha]_D^{20}$ +25.9 (c 4.36 $CHCl_3$); IR (neat): ν_{max} 3403, 2927, 2854, 1718,1396, 1260, 1196, and 862 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{34}H_{60}O_8Na$ 619.4180; found 619.4172.

(2*R*,3a*S*,4′*R*,6′*S*,7a*S*)-4′-Hydroxy-6′-((*S*)-2-hydroxypentadecyl)-3a,3′,4′,5′,6′,7a-hexahydrospiro [furo[3,2-*b*]pyran-2,2′-pyran]-5(3H)-one (22). To a solution of ketone **20** (100 mg, 0.168 mmol) dissolved in 1,2-dichloroethane was added montmorillionite K10 (500 mg, 500 w/w%). The mixture was stirred for 3 days at room temperature. The reaction mixture was filtered through a Celite to remove the K10. The Celite was washed with MeOH (3 × 20 mL) and the solvent removed from the combined filtrates under reduced pressure to give a yellow residue. The residue was then purified by flash chromatography on silica gel to give the **22** (44.0 mg, 58% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (dd, J = 9.9, 5.1 Hz, 1H), 6.20 (d, J = 9.9 Hz, 1H), 5.04 (td, J = 4.4, 2.2 Hz, 1H), 4.41 (t, J = 4.8 Hz, 1H), 4.06 (dd, J = 10.9, 4.4 Hz, 2H), 3.83−3.70 (m, 1H), 2.55 (dd, J = 15.0, 6.8 Hz, 1H), 2.33 (dd, J = 14.9, 1.9 Hz, 1H), 2.23−2.13 (m, 1H), 2.02−1.91 (m, 1H), 1.73−1.56 (m, 5H), 1.46−1.36 (m, 4H), 1.36−1.19 (m, 21H), and 0.87 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3, 139.0, 124.3, 106.7, 79.3, 71.7, 71.1, 68.2, 64.4, 47.2, 42.8, 42.3, 40.2, 37.7, 31.9, 29.7, 29.6, 29.5, 29.3, 25.4, 22.7, and 14.1; $[\alpha]_D^{20}$ +11.5 (c 0.75 $CHCl_3$); IR (neat): ν_{max} 3462, 2920, 2850, 1749,1387, 1254, 1120, 1041, and 863 cm^{-1}; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{26}H_{44}O_6Na$; 475.3048; found 475.3055.

(2*S*,3a*S*,6′*S*,7a*S*)-6′-((*S*)-2-Hydroxypentadecyl)-3a,5′,6′,7a-tetrahydrospiro[furo[3,2-*b*]pyran-2,2′-pyran]-4′,5(3H,3′H)-dione (23). To a solution of diol **22** (23 mg, 0.051 mmol) dissolved in dichloromethane (2.0 mL) were added 2,2,6,6-tetramethyl-1-piperidinyloxy (1.6 mg, 0.010 mmol) and (diacetoxyiodo)benzene (18 mg, 0.061 mmol) at 0 °C. The mixture was stirred for 8 h at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$. The organic phase was separated, washed with sat. aq. $NaHCO_3$, dried with Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (30−40 (v/v%)) as eluent to afford desired compound **23** (16.5 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (dd, J = 9.9, 5.1 Hz, 1H), 6.21 (d, J = 9.9 Hz, 1H), 5.12 (dt, J = 4.4, 2.2 Hz, 1H), 4.47 (t, J = 5.0 Hz, 1H), 4.35 (m, J = 4.1 Hz, 1H), 3.79 (br. s., 1H), 2.68−2.82 (m, 2H), 2.68−2.60 (m, 1H), 2.55−2.25 (m, 4H), 1.85−1.73 (m, 1H), 1.73−1.65 (m, 1H), 1.51−1.38 (m, 3H), 1.37−1.17 (m, 21H), and 0.88 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.7, 160.9, 138.6, 124.4, 107.3, 79.0, 70.8, 70.6, 68.6, 49.5, 47.1, 46.5, 42.6, 37.7, 31.9, 29.6, 29.5, 29.3, 25.4, 22.7, and 14.1; $[\alpha]_D^{20}$ +50.2 (c 0.24 $CHCl_3$); IR (neat): ν_{max} 3552, 2919, 2851, 1742, 1716, 1468, 1334, 1279, 1104, 1068, and 817 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{43}O_6$ 451.3054; found 451.3058.

(2*R*,3a*S*,4′*S*,6′*S*,7a*S*)-4′-Hydroxy-6′-((*S*)-2-hydroxypentadecyl)-3a,3′,4′,5′,6′,7a-hexahydrospiro[furo[3,2-*b*]pyran-2,2′-pyran]-5(3H)-one (EBC-23, 1a). To a solution of ketone **23** (20 mg, 0.044 mmol) in CH_2Cl_2 (0.5 mL) were added RuCl(*p*-cymene)-[(S,S)-Ts-DPEN] (0.14 mg, 0.5 mol %), HCO2H (16 μL, 0.44 mmol), and Et_3N (60 μL, 0.44 mmol). The reaction mixture was stirred at room temperature for 20 h. After being diluted with water (1 mL), the organic layer was collected, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (0.5 mL) and brine (0.2 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (70−90 (v/v%)) as eluent to give the EBC-23 (**1a**) (13.1 mg, 66% yield) and the **22** (3.4 mg, 17% yield) in 83% total yield with a diastereomeric ratio of 3.8:1.

(2*R*,3a*S*,4′*S*,6′*S*,7a*S*)-4′-Hydroxy-6′-((*S*)-2-hydroxypentadecyl)-3a,3′,4′,5′,6′,7a-hexahydrospiro[furo[3,2-*b*]pyran-2,2′-pyran]-5(3H)-one (EBC-23, 1a). To a solution of ketone **21** (100 mg, 0.17 mmol) dissolved in 1,2-dichloroethane was added montmorillionite K10 (500 mg, 500 w/w%). The mixture was stirred for 2 days at 15°. The reaction mixture was filtered through a Celite to remove the K10 clay. The Celite was washed with MeOH (3 × 5 mL) and the solvent removed from the combined filtrates under reduced pressure to give a yellow residue. The residue was then purified by flash chromatography on silica using ethyl acetate/hexane mixtures of increasing polarity (70−90 (v/v%)) as eluent to give the EBC-23 (**1a**) (32.3 mg, 42%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (dd, J = 9.9, 5.1 Hz, 1H), 6.22 (d, J = 9.9 Hz, 1H), 5.05 (ddd, J = 7.0, 4.6, 2.5 Hz, 1H), 4.52 (t, J = 5.0 Hz, 1H), 4.43−4.33 (m, 1H), 4.12 (br. s., 1H), 3.80 (d, J = 3.4 Hz, 1H), 2.55 (dd, J = 15.0, 6.8 Hz, 1H), 2.31 (dd, J = 14.9, 2.2 Hz, 1H), 2.08−1.97 (m, 2H), 1.79 (d, J = 14.0 Hz, 1H), 1.68−1.56 (m, 3H), 1.56−1.36 (m, 5H), 1.36−1.17 (m, 21H), and 0.87 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0, 138.6, 124.6, 106.6, 78.8, 71.8, 68.9, 67.7, 64.2, 47.7, 42.2, 38.7, 37.7, 31.9, 29.7, 29.3, 25.4, 22.7, and 14.1; $[\alpha]_D^{20}$ +15.5 (c 0.75 $CHCl_3$); IR (neat): ν_{max} 3448, 2924, 2854, 1729,1396, 1260, 1100, 1024, and 800 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{45}O_6$ 453.3211; found 453.3208.

■ ASSOCIATED CONTENT

Supporting Information

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^{1}H and ^{13}C NMR spectra for all new compounds; chiral HPLC data; and comparison of ^{1}H NMR data for EBC-23 (PDF)

AUTHOR INFORMATION

Corresponding Author

Arun K. Ghosh − *Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States;* orcid.org/0000-0003-2472-1841; Email: akghosh@purdue.edu

Author

Che-Sheng Hsu − *Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00172

Notes

The authors declare no competing financial interest.

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